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

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Lecture – 07
Phases of Clinical Trial, Forms and Fees

Hello friends, hope you are doing well. Welcome once again to the course that is a regulatory Current Regulatory Requirement for Conducting Clinical Trial in India for New Drug Version 2 0. So, today we are going to discuss about the Phases of Clinical Trial, the forms given in that rules and the fees in our lecture 6 A.

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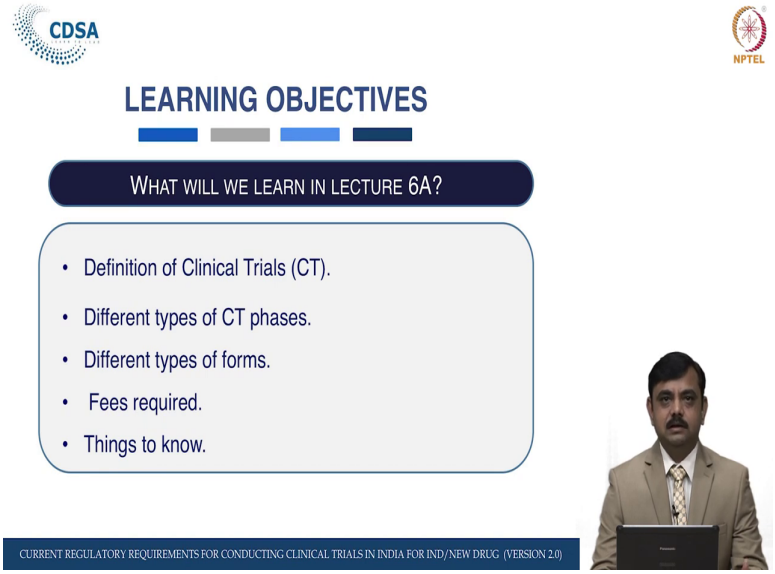

So, the expected outcome from this lecture, the learners will come to know the definition of clinical trial as we have seen earlier also; then the different phases of clinical trials; the different

forms require for the application to the central licensing authority and the different forms in which the permission is to be granted. Then the fees required and some important things which is required to be known while applying to the central licensing authority.

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So, let us start one by one with the definition of clinical trial.

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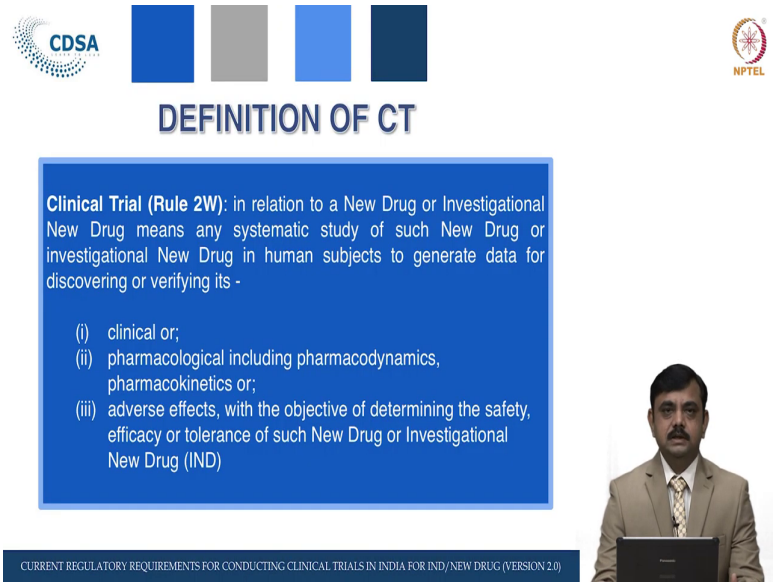

We have seen earlier also in our lecture 3 the definition of clinical trial. So, the definition of clinical trial is given in the rule 2 W; the clinical trial in relation to a new drug or investigational new drug means any systematic study of such new dug or investigational new drug in human subject to generate data for discovering or verifying its clinical, pharmacological including pharmacodynamics and pharmacokinetics.

Also it covers the determination of adverse effect with the objective of determining safety, efficacy or tolerability of such new drug or the investigational new drug.

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Moving towards the phases of clinical trial.

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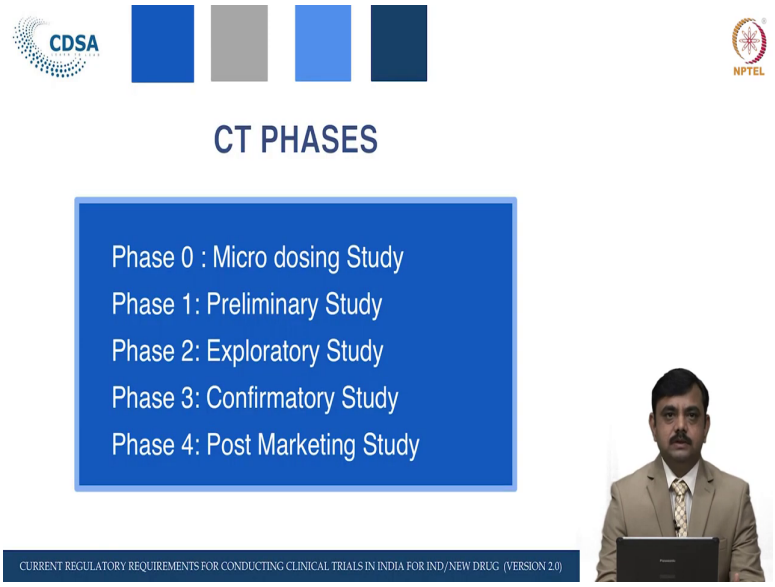

So, there are around five phases starts from phase 0 to phase 4; phase 0 is called micro dosing study or micro dose phase; phase 1 is human or clinical pharmacological trial; phase 2 is therapeutic exploratory trial; phase 3 is therapeutic confirmatory trial and phase 4 is the last phase which is a post marketing trials. We will see one by one this all these phases.

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So, the phase 0 study; the phase 0 study it is also called a micro dosing study. Phase 0 studies are done in a small sample size population; the small size that is in comparison to the phase 1. The purpose of this phase is to help speed up and streamline the drug approval process. Phase 0 studies often use few small doses of a new drug. So, the dose use in this phase 0 is very small that is why it is called as a micro dosing. And as such there is no requirement of this phase in India.

So, India it is start from the phase 1 after completion of the pre-clinical study; but in some regulatory authorities like USA and other countries the phase 0 is also required to avoid the unnecessary exposure of the large population.

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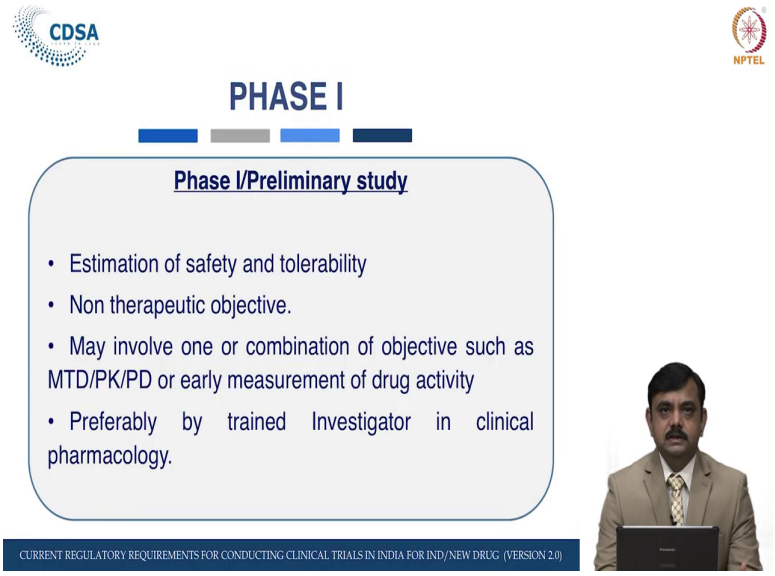

The next phase is phase I; phase I study it is also called as human or clinical pharmacological trial. The objective of this phase I study is the estimation of safety and tolerability of the drug. This phase is not having any therapeutic objective, as it is the determination of safety and tolerability of the drug in the human subject. This may involve one or combination of objective such as maximum tolerated dose, then pharmacokinetic, pharmacodynamics or early measurement of the drug activity.

The phase I study what we call it as human or clinical pharmacological trials, it is preferably done by trained investigator in a clinical pharmacology.

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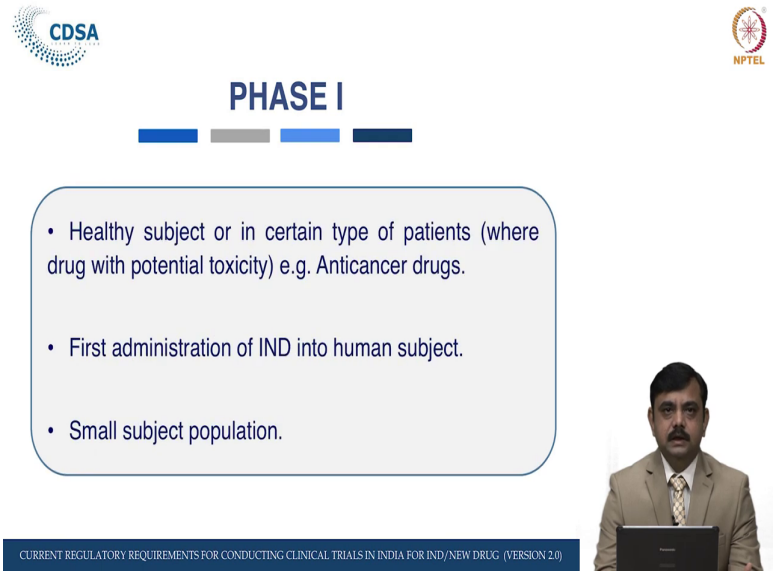

And in this phase healthy subjects are mostly use; unless there is a specific requirement to use the patients. In certain type of cases like if the drug is having potential toxicity, like drug for anticancer use or any other drug which are used in the life threating cases and if there is no alternative; then the healthy subject are not unnecessary expose to the this toxic or potential toxic drugs. So, that is why the patients are also use.

This is the phase in which the first administration of IND into human subject is carried out. So, this drug when it is investigational new drug, if you are if it has not been use elsewhere in the world; so this would be the first administration, because before this phase I, if it is not a phase 0, then it is a pre-clinical studies. So, that is why we call it as first administration of IND into human subject. As compare to other phases phase II, phase III; this phase is also having a small subject population.

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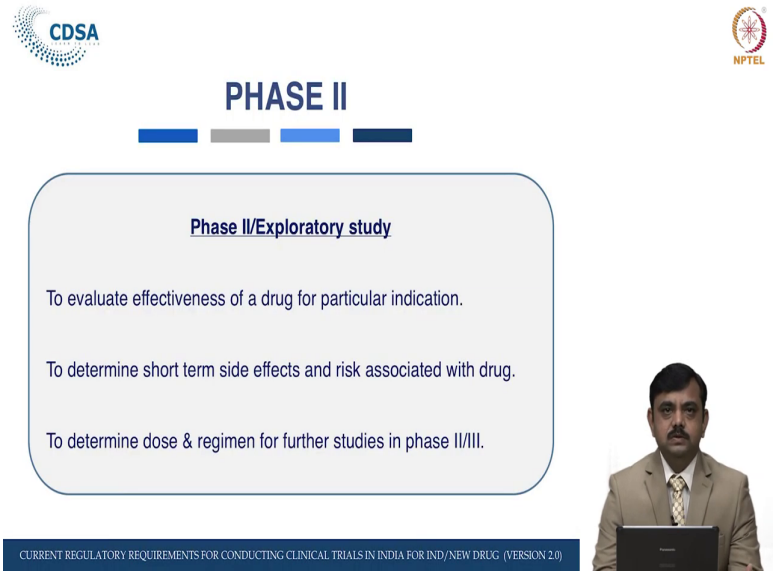

Let us see phase II study; the phase II study it is also called as the therapeutic exploratory trials. And the objective of this study is to evaluate effectiveness of a drug for a particular indication. This study is also involve the determination of short term side effects and the risk associated with the drug. To determine dose and regimen for further studies in phase II or phase III. So, in this study the dose also has been determined the dose and the regimen which will be useful for conducting the phase III study.

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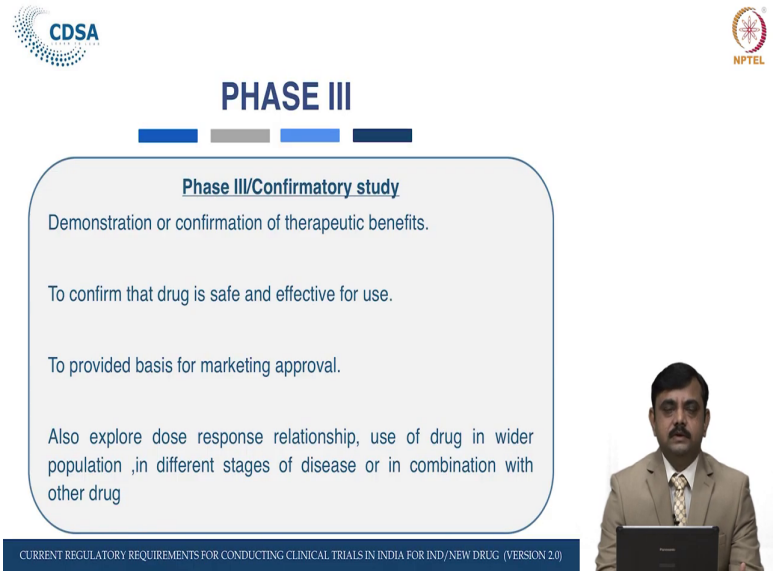

Let us see phase III study; phase III study is also called as a therapeutic confirmatory trial, because whatever the indication or the therapeutic activity that has been asserted into the phase II study that has to be confirmed through the phase III study, that is why this phase III study is conducted. So, the purpose is demonstration or confirmation of the therapeutic benefit. To confirm that drug is safe and effective for you for use. So, already the safety and efficacy establish in phase I, phase II; but here again to confirm that the drug is safe and effective in a larger population this phase III is conducted.

This phase III is required to provide the bases for marketing approval. So, in India before marketing the drug, the phase III is mandatory; even though the drug is manufactured into the country or if it has to be imported from the another country, then the phase III conduct is mandatory and it will provide the basis for marketing approval. As the population involve in

the phase III clinical trial is little bit more than the phase I and phase II study. It is to also to explore the dose response relationship.

So, what is the dose and response that is also ascertain in this phase III study. Then use of drug in wider population as I have mentioned; in different stages of diseases or in combination with other drug. So, after the satisfactory result of the phase III studies, then it comes the phase IV study.

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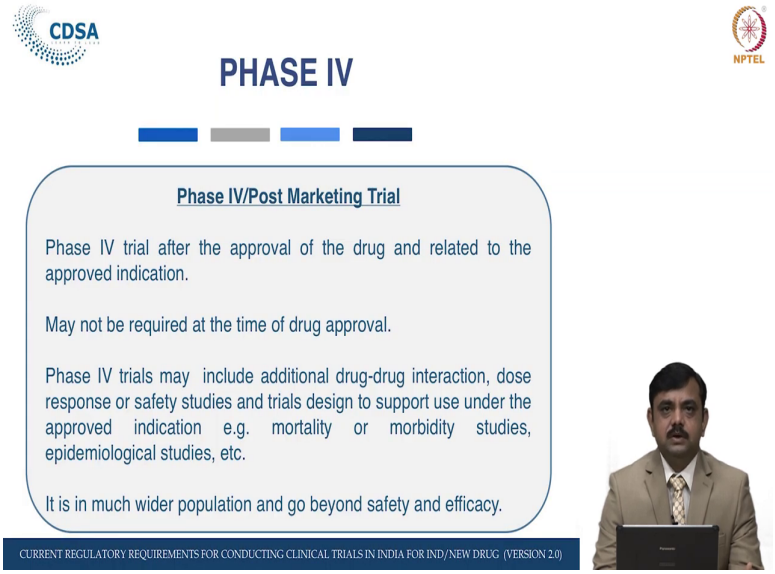

Let us see what is means by the phase IV study. Phase IV study is also called as a post marketing study or PMS study. Phase IV trial is after the approval of the drug and related to the approved indication. So, as I have mentioned, the phase III is mandatory for getting the approval from the licensing authority. So, once their approval has been obtained, that approval

may be with the condition of the phase IV trial or it may not require at the time of drug approval.

Phase IV trial may include additional drug-drug interaction, dose response or safety studies and trial design to support use under the approved indication. Once the indication has been approved, then this study goes beyond the dose response relationship and it is in the wider population after marketing the drug.

For example, to see the mortality or morbidity studies, then to see the epidemiological studies etcetera; it is in much wider population and go beyond safety and efficacy study which is not seen earlier in the phase III, II and I with respect to the dose and food action with respect to the climate action with respect to the genetic variation and the dose. So, all these study to be carried out in this phase.

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Post marketing assessment of new drug may be carried out in different ways. So, there are ways to carried out the phase IV or post marketing trial; first is the phase IV post marketing trial. So, this post marketing trial, if the condition has been mentioned in the approval after the phase III; then the phase IV with the permission of the central licensing authority it has to be carried out with the design protocol, with the approval of the licensing authority, with the permission of the ethics committee, and having defined number of subject, and with the proper scientific design.

Then post marketing surveillance or observational or non-interventional study for the active surveillance. To find out the adverse effect or to find out how the drug is behaving in the wider population, the post marketing surveillance also can be carried out. The last is the post marketing surveillance through periodic safety update report; means wherever the drug has been distributed and given to the patients, the surveillance what happens with that patients, in accordance to the physician those who have prescribed the drug.

That survey has to be carried out whether the drug has caused any toxicity or whether it has not been tolerated or any unwanted side effects which have not been estimated in the phase I, II and III that has to be ascertained. And the periodic safety update report it is required to be submitted to the licensing authority. Now which are the forms which require to be submitted to the licensing authority if the applicant require the permission or approval to conduct a clinical trials and the associated fees.

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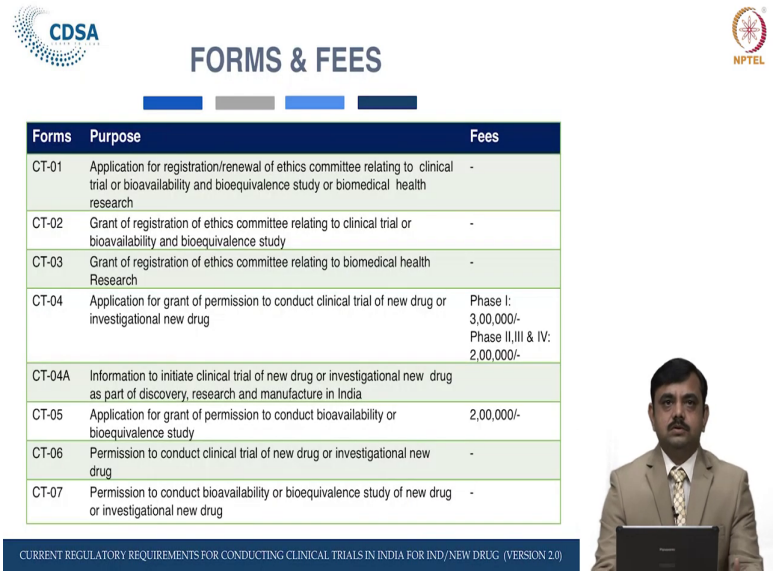

So, you can see this slides there are many forms, I have already mentioned in our lecture 1st and 2nd that earlier only the Form 44 was there; now there are around 27 forms. We can see the slides; the CT 01 form it is the form application for registration or renewal of ethics committee relating to clinical trial or bioavailability, bioequivalence study or biomedical health research.

So, this is the form which is required in which the applicant has to be apply for the registration or renewal for both of ethics committee. Here it is only the form which is required for the registration of ethics committee which has to be registered with the CDSCO and the registration of the ethics committee for biomedical and health research, which is to be applied into the Ministry Department of DHR. Next is the CT 02 form, it is for the grant of

registration of ethics committee relating to clinical trial or bioavailability and bioequivalence study.

So, this is when you apply in the CT 01 form; then if your documents are all satisfactory, then the registration of ethics committee can be given in the CT 02 forms. CT 03 is the grant of registration of ethics committee relating to biomedical health research. So, for the biomedical health research the ethics committee should be there, and form for this application form is CT 01; but the permission or registration in two different form, if it is related to the clinical trial then CT 02 and if it is related to the biomedical health then it is CT 03.

You can see in the slide there is no fees for the application and for the registration of the ethics committee. Next is the CT 04 form, it is for the application for grant of permission to conduct clinical trial of new drug or the investigational new drug. So, this is the important form which you require to file to the licensing authority for the grant of permission to conduct clinical trial.

So, if it is for phase I, then the fees is rupees 3,00,000; then if it is for phase II, III and phase IV, the fees is 2,00,000 for each trial. CT 04 A it is related to the information to initiate clinical trial of new drug or IND as a part of discovery, research and manufacture in India. So, we have seen in our other lecture, if the licensing authority do not communicate anything within the timeline prescribed; then it is considered as a deemed approval and if the applicant has obtained such deemed approval, then he has to inform into the form 04 A. So, in this case also there is no fee.

The next form is CT 05 it is application for grant of permission to conduct bioavailability or bioequivalence study. So, this is earlier it was not there; the bioavailability, bioequivalence and clinical trial it was the same form. Now this forms has been separated, CT 05 is particularly for the conduct of bioavailability or bioequivalence study. And the fee associated with this is 2,00,000 rupees. The CT 06 it is the form for permission to conduct clinical trial of new drug or investigational new drug.

When you apply for the clinical trial, you will obtain the permission in CT 06 form. CT 07 is the permission to conduct bioavailability or bioequivalence study of new drug or the IND. We have seen there is a separate form for the application and there is a separate form for the obtaining the permission of bioequivalence.

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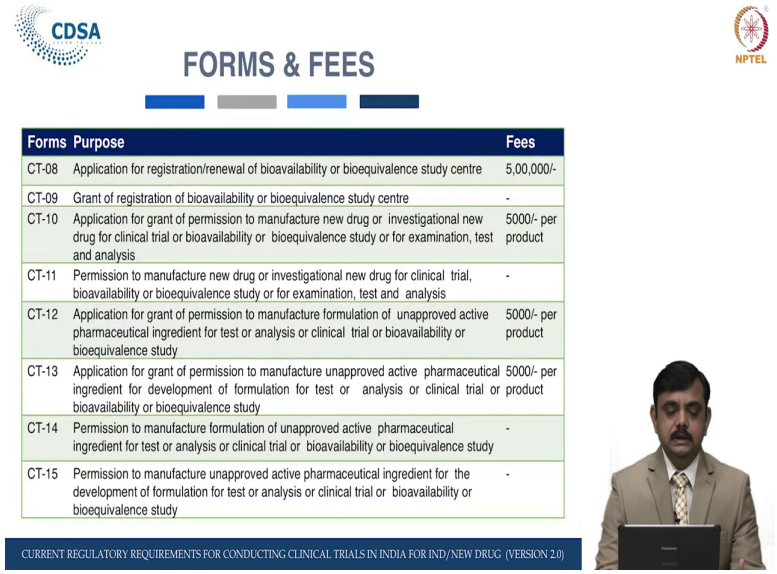

Forms	Purpose	Fees
CT-08	Application for registration/renewal of bioavailability or bioequivalence study centre	5,00,000/-
CT-09	Grant of registration of bioavailability or bioequivalence study centre	-
CT-10	Application for grant of permission to manufacture new drug or investigational new drug for clinical trial or bioavailability or bioequivalence study or for examination, test and analysis	5000/- per product
CT-11	Permission to manufacture new drug or investigational new drug for clinical trial, bioavailability or bioequivalence study or for examination, test and analysis	-
CT-12	Application for grant of permission to manufacture formulation of unapproved active pharmaceutical ingredient for test or analysis or clinical trial or bioavailability or bioequivalence study	5000/- per product
CT-13	Application for grant of permission to manufacture unapproved active pharmaceutical ingredient for development of formulation for test or analysis or clinical trial or bioavailability or bioequivalence study	5000/- per product
CT-14	Permission to manufacture formulation of unapproved active pharmaceutical ingredient for test or analysis or clinical trial or bioavailability or bioequivalence study	-
CT-15	Permission to manufacture unapproved active pharmaceutical ingredient for the development of formulation for test or analysis or clinical trial or bioavailability or bioequivalence study	-

CT 08 form is the application for registration or renewal of BA BE study center. So, earlier we have seen that is for the bioavailability and bioequivalence study, and this is the application for the BA BE study center and the fees associated with this is 5,00,000 rupees per study center. CT 09 is a grant of registration of bioavailability or bioequivalence study center.

So, after satisfactory document submission, you will get the registration of study center in CT 09 form. CT 10 is the application for grant of permission to manufacture new drug or IND for clinical trial or BA BE study or for examination test and analysis. So, this is actually form to

manufacture a small quantities of the drug for clinical trial or for the bioavailability study or the any other test and analysis, we can call it as a application for the test license.

The fees for this is 5000 per product. And CT 11 is the permission to manufacture new drug or IND for clinical trial, BA BE study or for examination test and analysis. So, once you apply for this test license, you will get that test license to manufacture small quantities of the drug which is not approved so you will get a permission in CT 11.

CT 12 is application for grant of permission to manufacture, formulation of unapproved active pharmaceutical ingredient for test or analysis or clinical trial or BA BE study. If it is not approved and if you would like to have a test license to manufacture small quantities, then you have to apply into the CT 12; the fees is again same 5000 rupees per product. CT 13 is the form for application for grant of permission to manufacture unapproved active pharmaceutical ingredient for development of formulation for test or product for test and analysis or clinical trial or BA BE study.

Again this is for the unapproved manufacture for the unapproved drug. And the fees is also the same that is a 5000 per product. CT 14 is the permission for this application that is permission to manufacture formulation of unapproved API for test or analysis or clinical trial or bioavailability or bioequivalence study. CT 15 is permission to manufacture unapproved API for the development of formulation for test or analysis or clinical trial or BA BE study.

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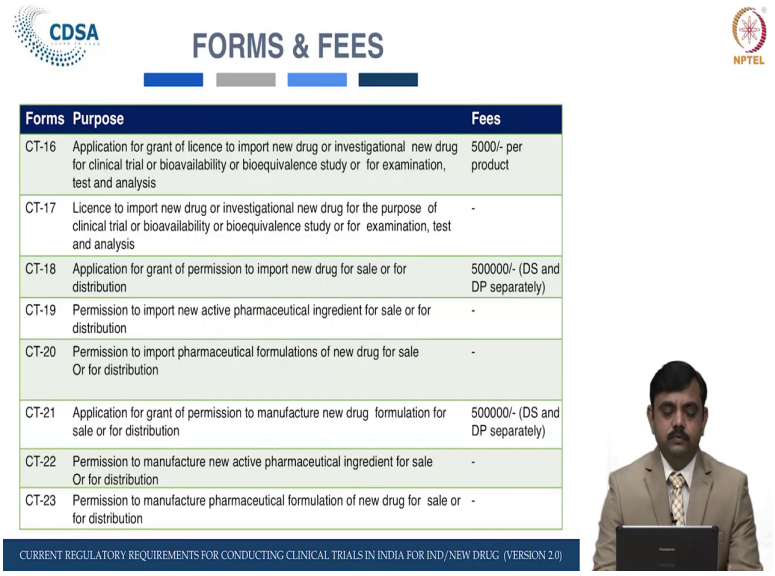

Moving to the next form that is the CT 16, it is application for grant of license to import new drugs or IND for clinical trial or BA BE study for examination test and analysis. So, this is also test license, but in case of the import of small quantities of the drug; then you have to apply in the CT 16, the fees is the same that is 5000 per product. CT 17 is a license to import new drug or IND for the purpose of clinical trial or BA BE study for examination test and analysis.

So, this is the test license you will obtain from the licensing authority to import small quantities of the drug for the purpose of clinical trial or the bioavailability and the bioequivalence study. CT 18 is the application for grant of permission to import new drug for sale or for distribution. So, this is the application for grant of permission to import new drug and it is for the sale or for the distribution; the fees is 5,00,000 rupees. Then CT 19 it is

permission to import new API for sale or distribution. So, you will get the permission to import new API for the sale and distribution.

Next is CT 19 permission to import new API we have seen this. CT 20 is the permission to import pharmaceutical formulations of new drug for sale or for distribution. So, earlier we have seen this is for the active pharmaceutical ingredient that is API, we can call it bulk drug also. CT 20 is particularly permission to import pharmaceutical formulation that is a dosage form and it is for the purpose of sale and distribution. CT 21 is application for grant of permission to manufacture new drug formulation for sale or for distribution; the fees is again it is a 5,00,000 rupees.

So, this is the application for manufacture; earlier we have seen the form is for the import. Then CT 22 you will get the permission to manufacture new API for sale or for distribution. So, this CT 22 it is a permission to manufacture new API. CT 23 is a permission to manufacture pharmaceutical formulation of new drug for sale or distribution.

So, this is a for the dosage form that is a final dosage form permission to manufacture. So, we can keep in mind, they this forms are particularly for the conduct of the CT different form, then conduct of the BA BE study is different form, then for the manufacture of the small quantities for the test and analysis there is a different form. And for the import of the small quantities, again there is different form; import of the small quantities of API and import of the quantities for sale and distribution, again it is given that manufacture of the quantities for the sale and distribution, likewise this forms have been separated.

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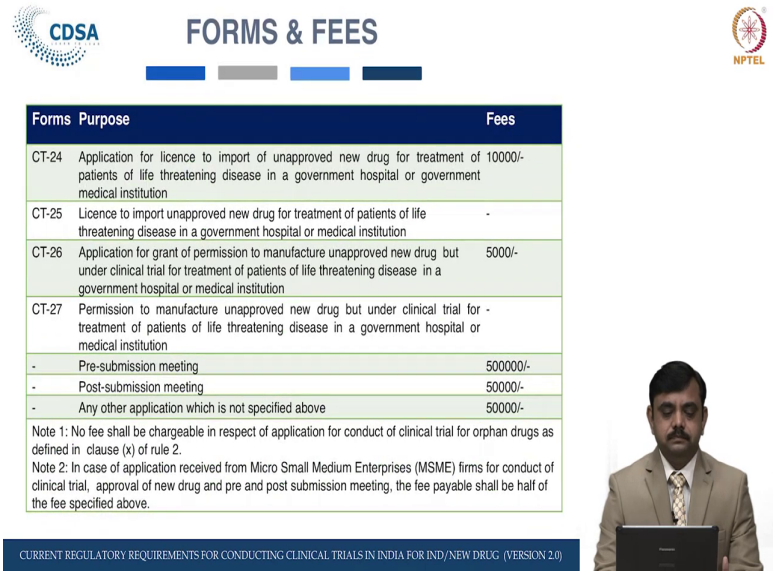

CT 24 is application for license to import unapproved new drug for treatment of patient of life threatening disease in government hospital or government medical institutions. So, this CT 24 it is the application; if the institution or any hospital or medical college, if they would like to import a small quantity for the treatment for the patient who is suffering from life threatening disease or any other diseases and if the drug is not available in the India, then for the small quantity they can apply into the CT 24 and the fees associated is given here.

The CT 25 is a license to import unapproved new drug for treatment of patient of life threatening disease in government hospital or medical institution. So, you will get a license to import such drug for the purpose of treatment of the patient in the CT 25. So, these are the provision made to avoid the what we can say, to avoid the lengthy procedure of getting the drug imported or getting the drug manufactured and to avoid the fees which is huge in. So,

you can import the small quantity for the patient that is why they have it has been given the separate forms.

CT 26 is the application for grant of permission to manufacture unapproved new drug; but under clinical trial for treatment of patient of life threatening disease in government hospital or medical institutions, so this provision has also been made. Then CT 27 is the permission to manufacture unapproved new drug, but under clinical trial for treatment of patient of life threatening disease in government hospital. Even the drug is not approved in the outside country, but it has shown some results in the clinical trial that also can be imported under the permission in CT 27.

Then you have seen in our last chapter of the new drug and clinical trial; the provision for pre submission meeting, post submission meeting has been given to guide applicant; and the fees given is for the pre submission meeting it is 500000 rupees and for the post submission once the application has been submitted to the license authority. And if it require some guidance suggestion, then the fees is 50000.

Any other application which is not specified about, so if anything has not been covered in this applications; then the you can apply in the applications and fees associated with this is a 50000. So, the load is given here that low fees shall be chargeable in respect of application for conduct of clinical trial for orphan drug as defined clause 10 of rule 2. So, if it is the application for the orphan drug, then there would be no fees for the clinical trial.

Further in case of publication receive from MSME that is from micro small medium enterprises firms for conduct of clinical trial, approval of new drug and pre and post submission meeting; the fee payable shall be half of the fee specified above. So, to motivate this small companies, medium companies fees has been given half of the fees whatever mentioned above. So, something's we required to know and this are important while applying for the clinical trial; what are these things let us see.

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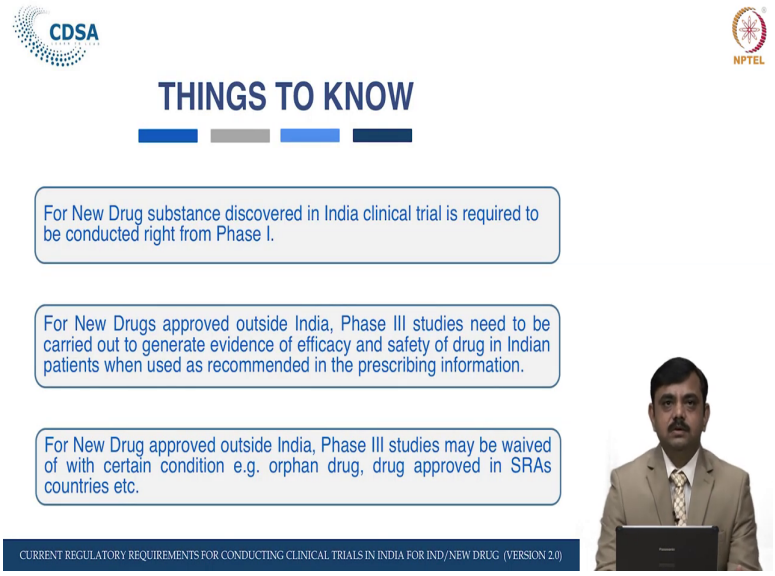

For new drug substances discovered in India, clinical trial is required to be conducted right from the phase I. So, if the drug product has discovered in India; after the pre-clinical the applicant has to conduct the phase 1 study, then he can go further. For a new drugs which is approved outside the India, that are which has not approved in the India and it has been approved discovered outside the India; the phase III studies need to be carried put to generate evidence of safety and efficacy of drug in Indian patient when used as recommended in the prescribing information.

We have seen our earlier slides also the phase III is mandatory; even though the drug is available in the market outside the country, to confirm the therapeutic indications and whether it is a suitable for the Indian patients or not, the applicant required to conduct the phase III

study. For a new drug approved outside India phase III studies may be waived of with certain condition like post marketing studies.

If the drug is approved outside the India and if it is for example, for the life threatening diseases or for the orphan if it is a orphan drug in such cases, case to case basis it can be phase 3 can be waived of; but with the condition to conduct a post marketing study.

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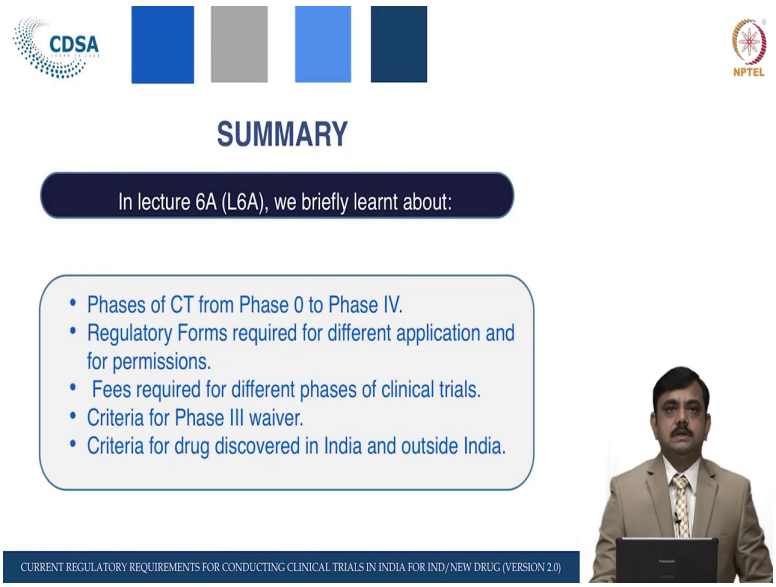

So, this is about lecture 6 A. Let us have the summary of this lecture what we have seen. So, in this lecture we have seen first the what is meant by clinical trial, then phases of clinical trial we have seen from phase 0 to phase IV; phase 0 is micro dosing which is not available in India, phase IV is post marketing after the approval of the drug for the marketing.

Then we have seen various forms required for different application. The forms required for the conduct of the clinical trial, the forms that require for the manufacture, the forms require for the test license, the forms require for the import and the forms which are required for import of that drug for the patient by government institutions. Then we have seen this fees required for different phases of clinical trials and for the different applications.

Then we have seen the criteria for phase II waiver; if it is the drug is available in the well regulated country and if the drug is for life threatening diseases, if there is no alternative in India, then in such cases with the phases IV condition it may or may not be phase IV conditions, so that phase III can be waived off. Then we have seen criteria for drug discovered in India and outside India. So, this is about the our lecture 6 A.

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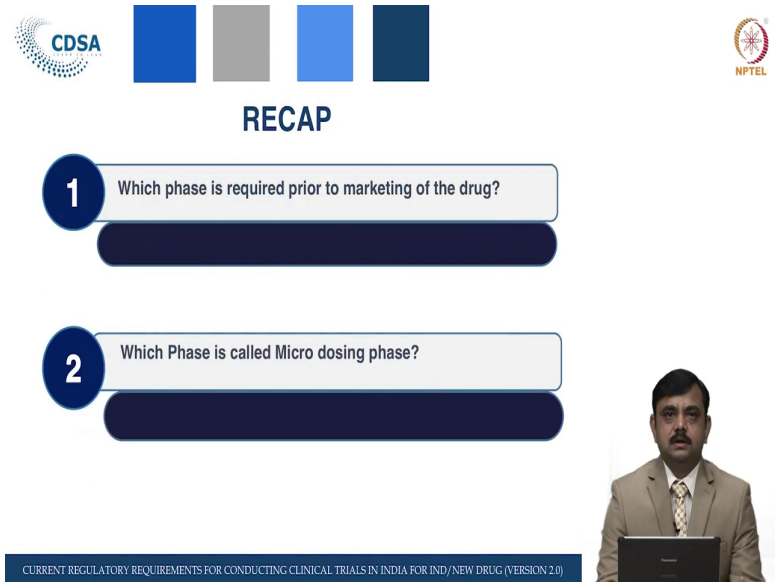

Now, it is the time for the question; just to check your memory. The question first is which phase of clinical trial is required prior to marketing of the drug in India? I have mentioned many of the times. So, it is the phase III; phase III is mandatory before the marketing. Which phase is called micro dosing phase? So, as the name indicate, it is a micro, it is a phase 0.

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So, this is about lecture 6 A, we will again see you in our next lecture. Till then you take care, bye and all the best.

Thank you.