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

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Lecture - 06
Rules Governing Clinical Trials

Hello friends, hope you are enjoying the lecture and doing well. I will come once again all of you to the course Current Regulatory Requirement for conducting Clinical Trials in India for New Drug and the Investigational New Drug Version 2. Today we are going to see lecture 5 in which, we are going to see the different rules. This lecture is about Rules Governing Clinical Trials.

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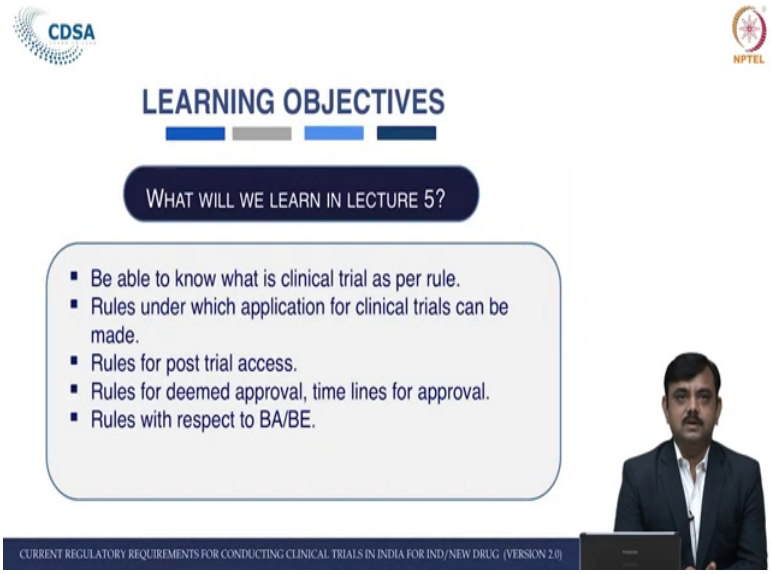

So, we are going to focus more on the rules which are related to the clinical trials. After completion of this lecture, the learners, the trainees, they will be able to know what is clinical trial as per rule. Then rules under which application for clinical trial can be made. Then what are the rules under which there has been given the mention of post trial access, then what are the rules for the deemed approval in which rules the timelines have been given and which are the rules with respect to bioavailability and bioequivalence study center.

So, let us start one by one, dear friends, before going to see actual, the what are the rules, which govern the Clinical Trials in India, we must know what is means by the clinical trial, and the definition of the clinical trial as per this new drug and clinical trial rule. So, the definition of clinical trial has been given under the rule 2 J of new drug and Clinical Trial Rule 2019.

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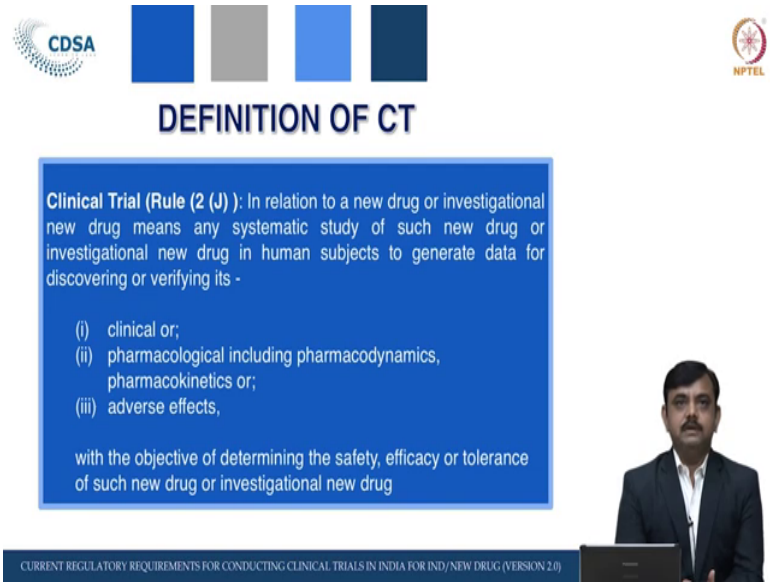

As per this definition clinical trial in relation to a new drug or investigational new drug means, any systematic study of such new drug or investigational new drug in human subjects to generate data for discovering or verifying its clinical or, pharmacological including pharmacodynamics and pharmacokinetics or adverse effect and, the objective of this study, should be to determine the safety efficacy or tolerance of such new drugs or investigational new drug.

So, this is the definition as per the new drug and clinical trial rules, which is mentioned in the 2 J. Let us see one by one the what is the meaning of this definition. So, this definition mentions about the new drug and investigational see the 1st line in relation to new drug or investigational new drug. It means it does not cover the all drugs. So, whatever the trials with the old drug that does not come under the purview of this definition, then it is mentioning; that means, any systematic studying.

So, the meaning of the systematic study means, the study which is properly designed the study which is having the prior approval of the central licensing authority the study which is having the approval of the ethics committee. It has, it is as per the new drug and clinical trial rules. Study of such new drug and investigational new drug, yes we will see the what is new drug and what is the IND in our other chapters.

Just I will tell you the new drug which has not been completed 4 years or if it has completed 4 year and, if it is modified with relation to the dose, then strength, dosage form, then we call it is a new drug and IND is when it is an no where it is approved in the world, and this study in human subjects. So, the study should be in the human subject if it is in animal, we call it as a Preclinical study, to generate a data for discovering or verifying.

If applicant would like to discover the data means, the data is nowhere there in the globe and, if he would like to discover the data then we call it as a clinical trial or verifying if the data is available somewhere. For example, in the country like U.S Japan and this data has to be verified into the Indian population then, the study is required for that verifying of the data and

this study is also called as a clinical trial study. Here, below it is given that clinical or pharmacological including pharmacodynamic and pharmacokinetic parameter.

If the drug is already available somewhere else in the world, and if in relation to the Indian population the if the applicant would like to know what are the pharmacodynamic effects or what is the pharmacokinetic in our population, that studies also called as a clinical trial. If the study is related to find out the adverse effects that also comes under the clinical trial. The objective of all these study is to determine the safety efficacy and tolerance.

So, this is about the clinical trial. If any study which falls under this criteria we can say this is a clinical trial and that clinical trial required the permission. So, the studies and research which are not following under this clinical trial that comes under the Biomedical and Health Research, we are seen in our lecture 3 the detail of this is given in the different chapters. Now, let us see what are these Legal Provisions for Regulation of Clinical Trial and which are the rules governing the clinical trial in India.

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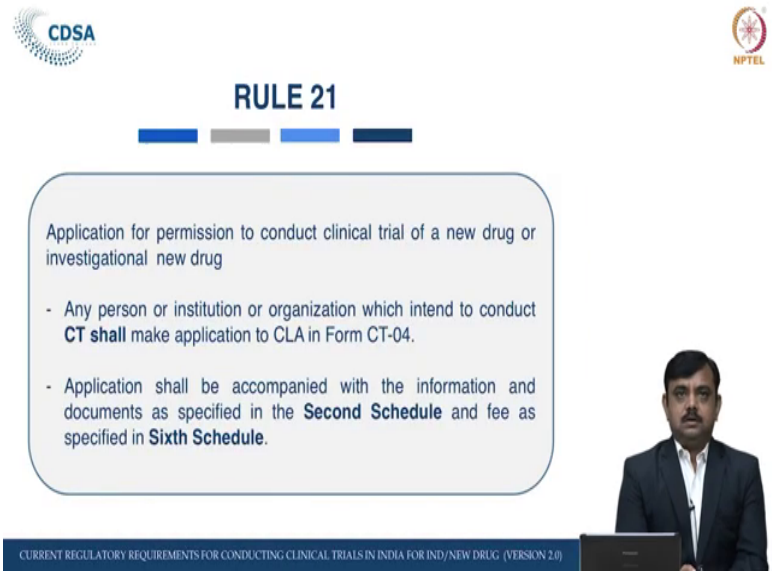

Rule 21 it is related to the application for permission to conduct clinical trial of a new drug or the investigational new drug. So, under this rule the application has to be proceed to the Central Licensing Authority and the applicant has to apply under this rule for the clinical trial. So, any person institution or organization, which intend to conduct clinical trial he or she has to make a application to Central Licensing Authority in form CT 04.

So, earlier there was a Form 44 that has been now replaced with the CT 04. The application shall be accompanied with the information and document as specified in the Second Schedule. So, whatever the data which has which is required to conduct a clinical trial or to take the permission from the Central Licensing Authority to conduct a clinical trial the data like a preclinical study, chemical structure, then the detail details about the new molecule the

preclinical data, what are these data required that has to be submitted and that data should be as per the Second Schedule.

The fees as specified in the Sixth Schedule. So, if it is a phase 1, phase 2, phase 3, then the different fees are given and, whatever the fees that has to be paid along with this application the fees required is given in the Six Schedule under rule 21. Rule 22 it is about to grant a permission to conduct a clinical trial. So, under this rule the central licensing authority grant permission for the conduct of clinical trial.

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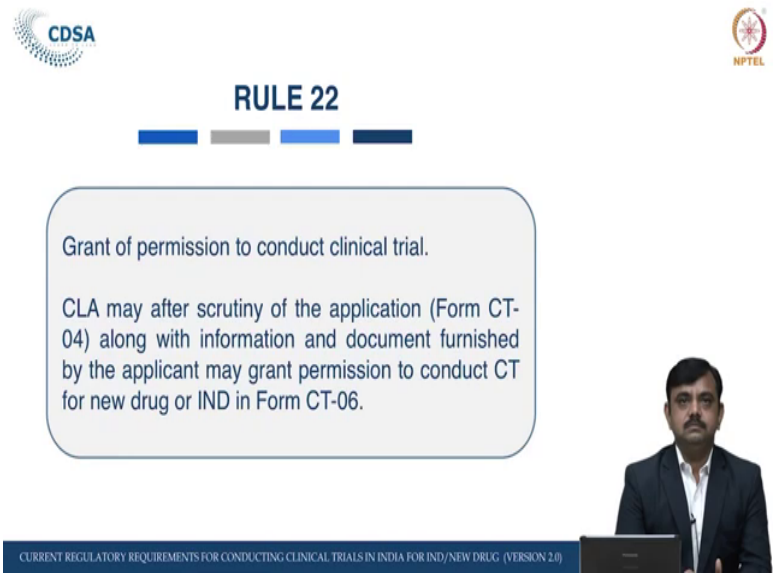

So, once the application from the applicant is with the Central Licensing Authority then the Central Licensing Authorities officer, they review the applications and after having the satisfaction that the applicant has submitted all the data and document as mentioned in the consent schedule. If the licensing authorities satisfied, then the applicant may grant permission

to clinical trial for new drug or IND in Form CT 06. Rule 23 says permission to conduct clinical trial of new drug or investigational new drug as part of discovery research and manufacturer in India.

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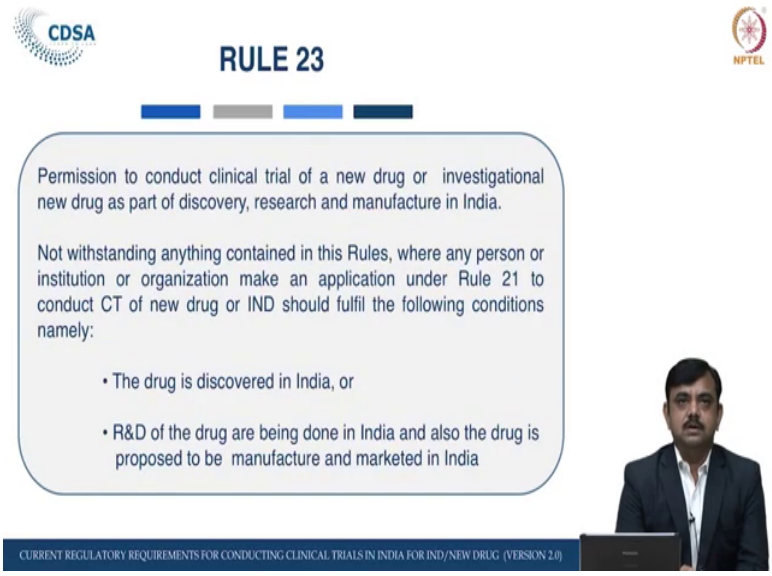

So, this is a special rule it was not there earlier and this is about the timelines the within how much time period the Central Licensing Authority has to give the permission or has to dispose of the; dispose of the application. So, the conditions are this is actually related to the drug which is discovered in India and the R and D of the drug is being done in India and also the drug if it is proposed to be manufactured and marketed into the India.

For such kind of a drug which is discovered in India and there India has been made into the India and which is for the manufacturer and market in India the licensing authority, after reviewing all the documents has to dispose of the application within 30 working days.

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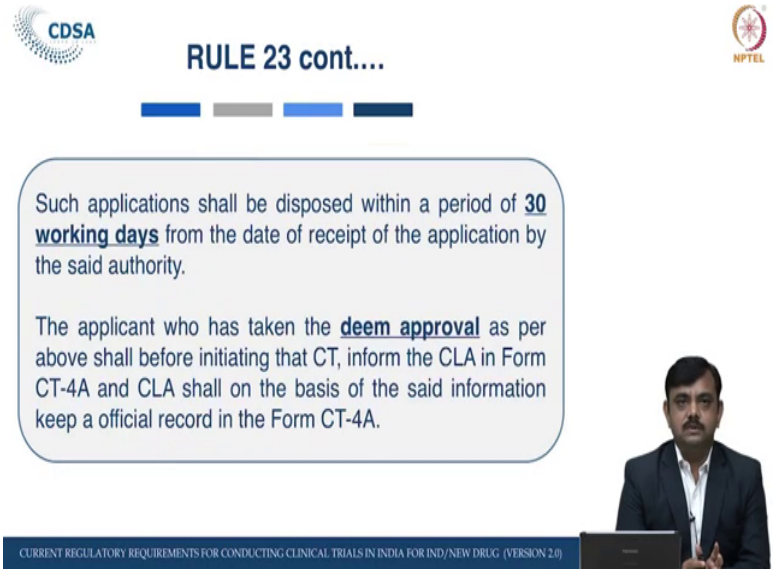

So, this is a mandatory for the regulators or the license approving authority, to dispose of this application within 30 working days and this is as per Rule 23. If there is a no communication from the licensing authority to the applicant, then that is consider as a deem approval. The applicant can initiate the clinical trial study irrespective of the his communication irrespective of the deficiency or whether he has submitted full document or not.

So, if he does not receive any communication from licensing authority within 30 working days, then it is consider as a deem approval for such type of approval, the applicant who has taken the deem approval as per above rule, he shall before initiating that clinical trial inform to the central licensing authority in form CT 4A.

So, there is a separate Form CT 4A in which he has to inform that he has applied to the central licensing authority and there has been more than 30 working days he has not received any

communication, and he has started the; study in the form CT 4A, and central licensing authority upon deceiving this CT 4A shall on the basis of the said information keep this form as official record in the form CT 4A. The rule 24 permission to conduct clinical trial of new drug already approved outside the India.

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So, the previous rule which was related to the drug which is approved in the country, and the discovery and R and D all for the all from the India and the drug also proposed to be marketed in the for the Indian population for that the rule 23 was there. This is in case of the import of the drug if the drug is already approved outside the India and, if the applicant is desirous to import that drug into the country.

So, within a period of ninety working days, the licensing authority or, the officer's subsidy so they have to response to the applicant, and within if within a period of 90 working days, he

does not receive any response from the licensing authority again this is considered as deem approval. So, this is according to the Rule 24. Rule 25 it is related to the conditions of permission for conduct of clinical trial. Once the applicant has obtained clinical trial permission he has to follow the conditions, and these conditions are.

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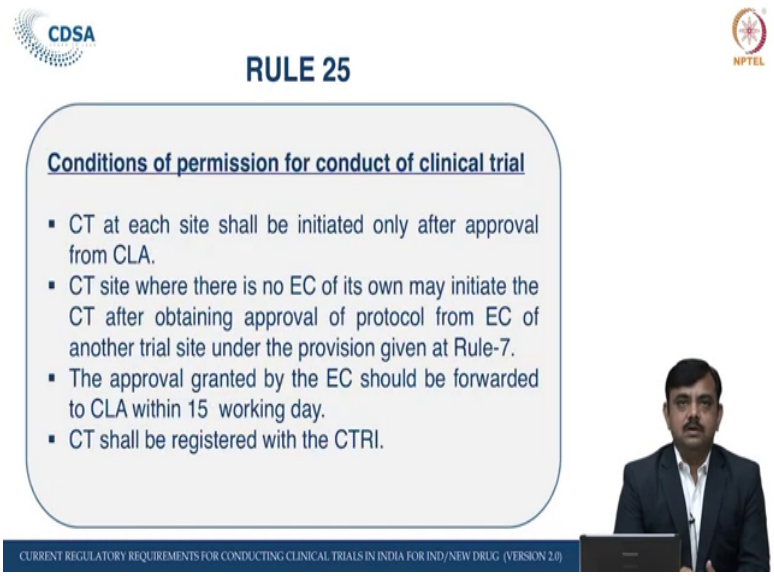

The clinical trial at each site shall be initiated only after approval from the central licensing authority. Clinical trial site where there is no this committee of its own may initiate the clinical trial after obtaining approval of protocol from Ethics Committee of another trial.

If there is another trial site and the 1st site if does not have any Ethics Committee you can take the approve from the Ethics Committee of the another trials site which is given under the provision Rule 7. The approval granted by Ethics Committee then once the approval has been

granted by that another Ethics Committee that should be forwarded to the Central Licensing Authority within a 15 working days.

Then as we know that every clinical trial, it shell be registered with the clinical trial registry of India that is a CTRI. Then clinical trial shall be conducted in accordance with the requirement of GCP guidelines. The clinical trial permission once it has been obtained then the applicant has to follow all the good clinical practices guideline. What are the Good Clinical Practices guideline? That has been given into our 1st chapter we have seen in the chapter our lecture 3 the definition of GCP guideline.

Then the applicant has to submit 6 monthly status report of each trial, whether it is ongoing whether it has been completed or, whether it has been terminated that shall be submitted to the central licensing authority electronically in the SUGAM portal the CDSCO is having the SUGAM portal and the every application has to be made online and the status report also, the applicant can submit online, through the SUGAM portal.

The other condition that any SAE Serious Adverse Event occurring during the clinical trial after due analysis may be forwarded to the, Central Licensing Authority chair person of Ethics Committee and institute, where the clinical trial has been conducted and this has to be forwarded within 14 day of its occurrence. In case of injury during the trial, suppose any injury happens or death happen. In case of the injury the complete management has to be given. Along with the compensation as the formula prescribed in chapter 4. Then premises or sponsor including clinical trials site shall be open for the inspection by officer of CLA.

So, whenever the auditor or the authority from the Central Licensing Authority would like to, inspect the facility or, the CT site it should be open to them. The clinical trial Central Licensing Authority may if considered necessary impose any other conditions. So, while scrutinizing the application and the clinical trial protocol, if the licensing authority and its committee finds that there is a need to change some study design, or objective, or the study population, or subject eligibility assessment, that condition also they can impose according to the Rule 25 conditions.

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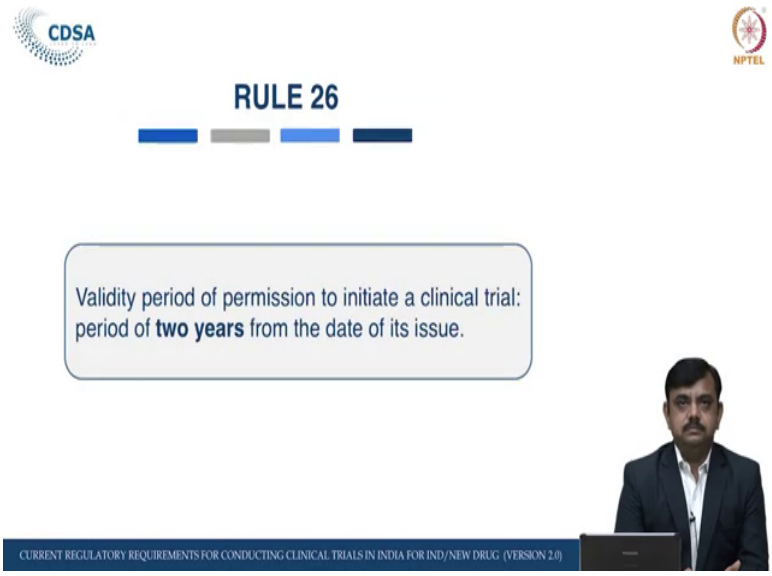

Rule 26 it is about the validity period of permission to initiate a clinical trial under Rule 22 in form CT 06. We have seen the permission is in CT 06 form or sometimes, if it is automatic approval what we are seeing that is deemed approval, and the applicant has to submit the information for 4A. So, this permission it shall remain valid for a period of two years from the date of issue.

So, early in our old clinical trial rule, this type of validity provision was not there now it is a two years from the date of its issue. Rule 27 we have seen that there is a new provision regarding the post trial access of investigational new drug, or the new drug. After completion of clinical trial any trial subject required any IND or new drug which has been approved by the Ethics Committee the post trial access shall be provided by the sponsor free of cost.

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If the ethics committee and the sponsor thinks that the, drug which is tried on the subject which is beneficial for the subject and the drug is not available in the market there is no alternative therapy then with the permission, and with the consent of the subject that can be provided free from the cost. That is called the post trial assists and it is according to Rule 27. Rule 28 it is related to the Academic Clinical Trial.

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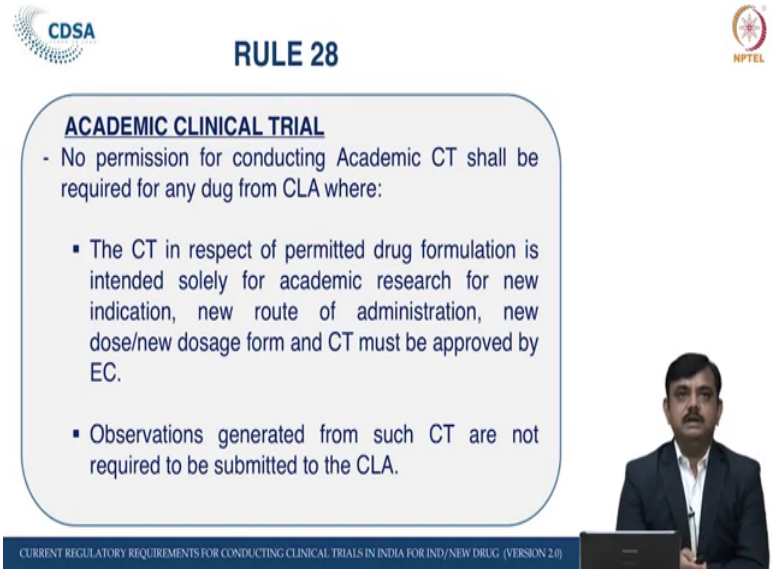

So, there was a lot of confusion regarding the Academic Clinical trial. So, there was lot of confusion regarding academic clinical trial whether it required the permission or not require the permission. So, as per this rule it has been clarified that, for the academic clinical trial that no permission for conducting academic clinical trial shall be required for any drug for, from the Central Licensing Authority. But certain conditions has been stipulated according to these rules and these conditions are the clinical trial in respect of permitted drug formulation is intended solely for the academic research.

For new indication, new route of administration, new dosage form and CT must be approved by the Ethics Committee. So, for having that this academic clinical trial the drug should be approved one the molecule should be approved one and there is and it should be purely for the research purposes and that may include; the that may include the research or new indication,

new route of administration, dosage form or the strength. Observation generated from such clinical trial are not required to be submitted to the Central Licensing Authority.

So, these observation whatever the outcome from this academic clinical trial that is not required to be submitted from the submitted to the central licensing authority; however, it require the Ethics Committee approval we have seen earlier. The observation of such clinical trial are not used for any promotional purposes as it is a academy clinical trial, the observation or the outcome it should not be used for any promotional purposes, or it should not be used for any commercial purpose.

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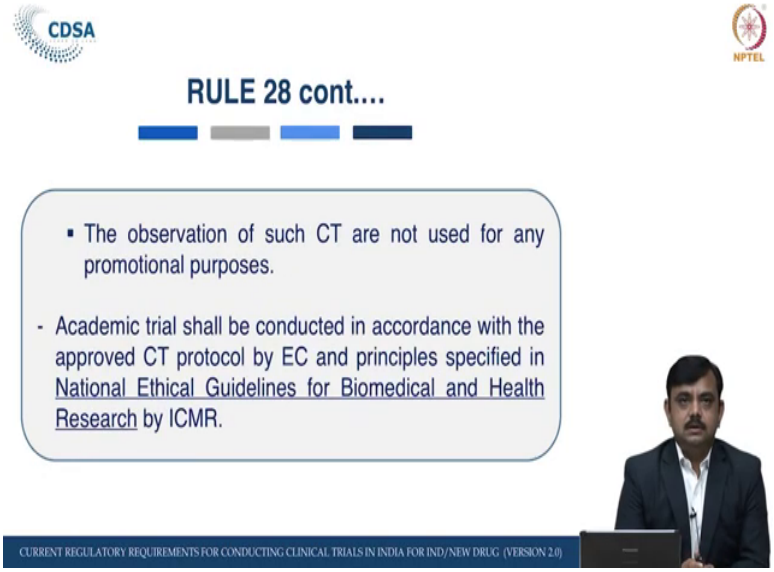

This, these are the conditions then academic trial shall be conducted in accordance with the approved clinical trial protocol by ethics committee. So, as I have mentioned the ethics committee has to approve this and most it has been approved by the ethics committee in the

protocol whatever the protocol approved by the ethics committee the same has to be followed by the researcher. Ethics Committee and principles specified in National Ethical Guidance for Biomedical and Health Research.

So, he has we will see in the, our subsequent lectures these National Guideline on Biomedical and Health Research. So, if it is a academic clinical trial then the protocol approved by this committee that has also to be followed by the applicant and, the guidelines which are given by the Biomedical and Health Research that is from the ICMR that also has to be followed while conducting the Academic Clinical trial this is mentioned in the rule 28.

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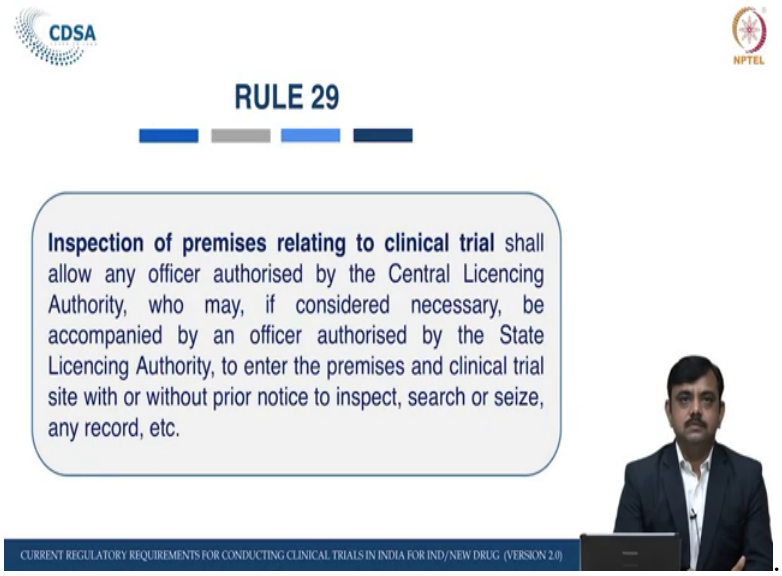

Rule 29 it is inspection of premises relating to the clinical trial. The person or the institution or the organization permitted to conduct clinical trial under Rule 22 in form CT 06. We have seen the permission in C to 06 or Rule 23 in Form CT 4 in case of the deem approval.

Including his representative and investigator shall allow any officer authorized by the Central Licensing Authority, who may if considered necessary, he can be accompanied by an officer authorized by the State Licensing Authority.

He can enter the premises and clinical trial site with or without prior notice to inspect, search or seize, it in case of any violation if he found then the inspector or the authorized officer they can search anywhere in the clinical trial site or they can seize the document which are in objection, they can seize any record or the statistical, results or the any document, which are related to the clinical trial for the further investigation. So, this is mentioned and that should be allowed by the sponsor and the clinical trial site.

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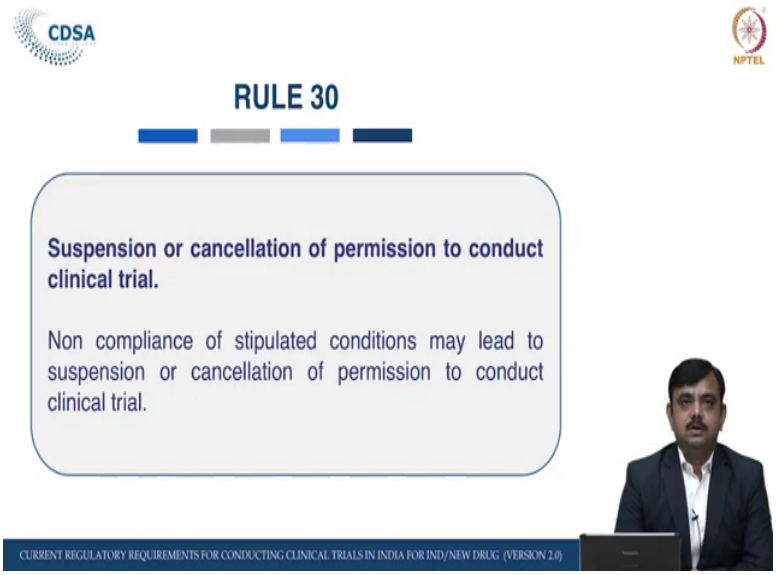

Rule 30 is related to the suspension or cancellation of permission to conduct clinical trial, we are seeing the permission is granted in CT 06 and form CT 4A, which deem approval. So,

during the inspection or if the licensing authority came to know that there is a violation of the clinical trial and the subject is not protected properly or the protocol which is approved by the committee has not been followed by the clinical trial site and principal investigator. Then in such cases if there is a non compliance of the stipulated conditions that may lead to the suspension or cancellation of permission to conduct a clinical trial.

So, once the regulator or the licensing authority they observe the non compliances, they issue a show cause notice to the clinical trials site principal investigator or the sponsor and, after getting the reply for that show cause notice if it is not satisfactory, then under Rule 30 the licensing authority and suspend or cancel the permission of conduct of clinical trial. Rule 31 it is a bioavailability or bioequivalence study of new drug or investigational new drug.

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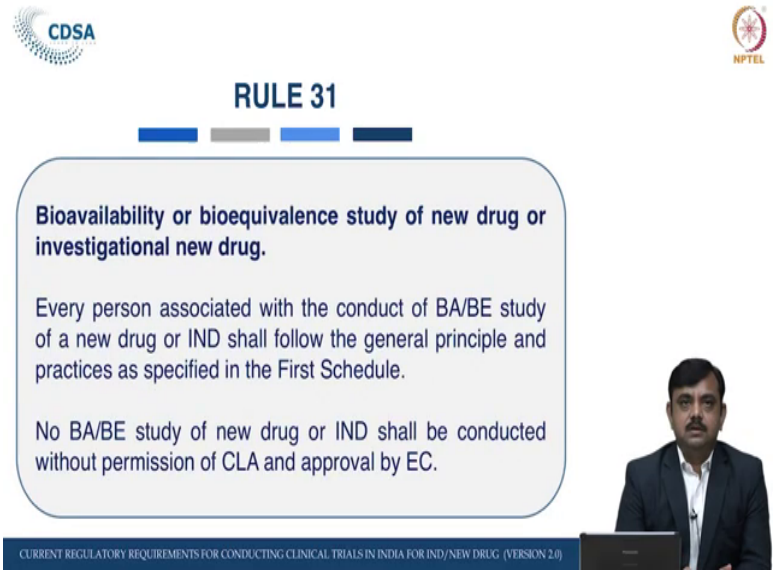

So, as per this rule every person associated with the conduct of BA BE study of new drug or IND shall follow the general principle and practices. As specified in the First Schedule. We have seen in our lecture 3rd the there are 8 schedule and in the 1st schedule and the principles and guidelines for the conduct of this clinical trial has been given. So, the applicant has to follow this First Schedule.

No person or institution or organization shall conduct BA BE study of new drug or IND in human subject except in accordance with the permission granted by CLA. So, according to this rule no one can conduct the Bioavailability or Bioequivalence study unless it is having a permission from the Central Licensing Authority, and subsequently or simultaneously they should have the, permission and the approval from the Ethics Committee the Ethics company which is already registered with the Central Licensing Authority as per Rule 8.

Rule 32 it is the oversight of bioavailability bioequivalence study center. The work of every BA BE study center shall be overseen by Ethics Committee, before initiation and throughout the duration of the conduct of the study.

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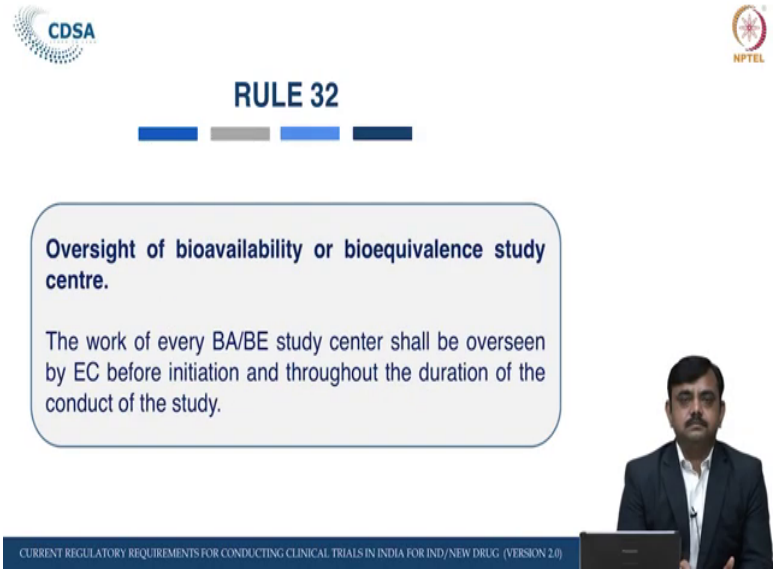

As what we have seen in the clinical trial also the sponsor has to, required to allow to the licensing authority or the designated officer to conduct the audit of the site. In the case of the BA BE study also. The BA BE study center they can be overseen by the licensing authority and that should be allowed as per the Rule 32. Rule 33 it is application for permission to conduct bioavailability or bioequivalence study. So, there is there are separate application for clinical trial and for the conduct of bioavailability and bioequivalence study.

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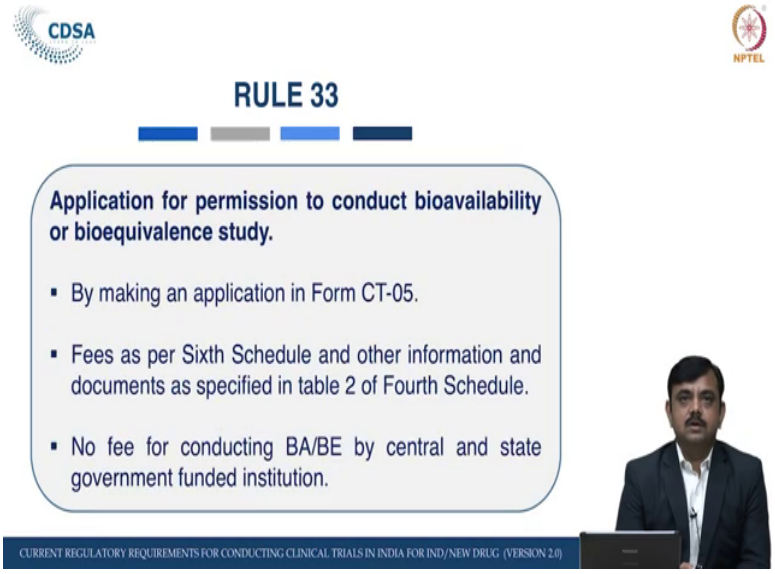

Also there are separate application for registration of the BA BE study centers. So, as per this rule by making an application in form CT 5 applicant has to apply in form CT 5 shall be accompanied by fees as mentioned in the Sixth Schedule and other information and document as specified in table 2 of the Fourth Schedule. So, what are the documents required that has been given in the Four Schedule of Four Schedule and in that schedule the various tables have been given.

So, according to the table 2 the information document has to be submitted, for the BA BE study then, no fee for conducting BA BE by central and state government funded institutions. If the central government agencies or state government agency like the government agencies, if they are involved in the BA BE study conduct or the trial conduct then the fees is not require as per the Rule 33.

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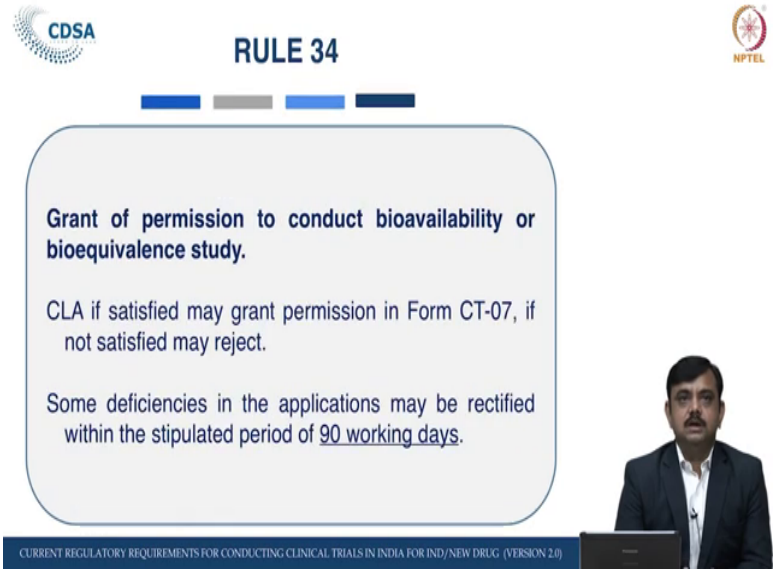

Rule 34 grant of permission to conduct bioavailability study and the bioequivalence study. We have seen the conditions for the Clinical Trial also these are also more or less similar conditions, the applicant has to follow after getting the permission from the Central Licensing Authority. So, central Licensing Authority after scrutiny of document furnished in application for CT 5 if satisfied grant permission in form CT 7. So, if it is a related to the bioavailability and bioequivalence study then the permission in from CT 7, if it is related to the Clinical Trial it is in CT 6.

If the licensing authority is not satisfied then they may reject the application. Some deficiencies in the application may be rectified within the stipulated period of 90 working days. If there are some deficiencies then the query later is issued from the Central Licensing Authority and that has to be rectified. In case of rejection application applicant may request Central Licensing

Authority to reconsider their application within period of 60 working days from the date of the rejection.

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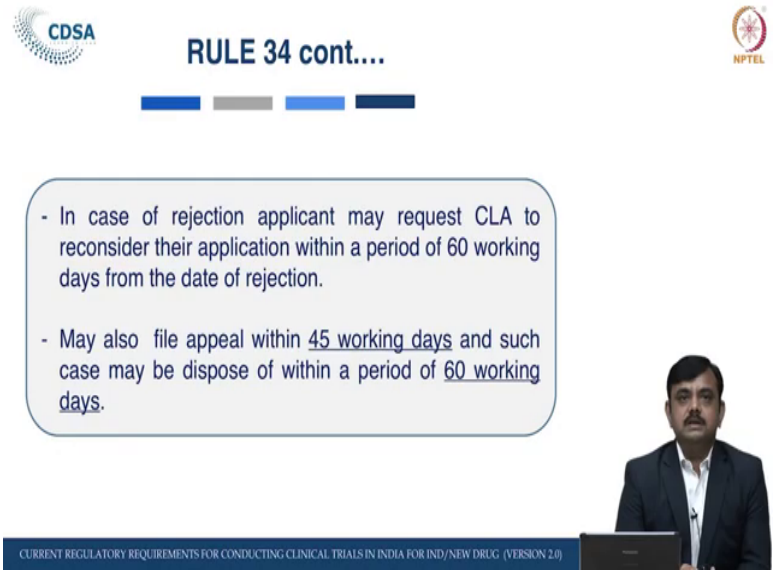

So, there is a scope for the application even after the rejection of this application. The applicant can again apply and, can again request to the Licensing Authority, but that is within a 60 working days period, he can apply and request. Applicant who is agreed you by the decision of Central Licensing Authority in case if it is not considered by the Central Licensing Authority then again he can go to the further states that, he may file appeal within a 45 working days and that appeal also would be consider

And, after having the after having the satisfactory report or the satisfactory justification within 45 working days and such case. In such case the Licensing Authority and the government they may dispose of the application within period of 60 working days.

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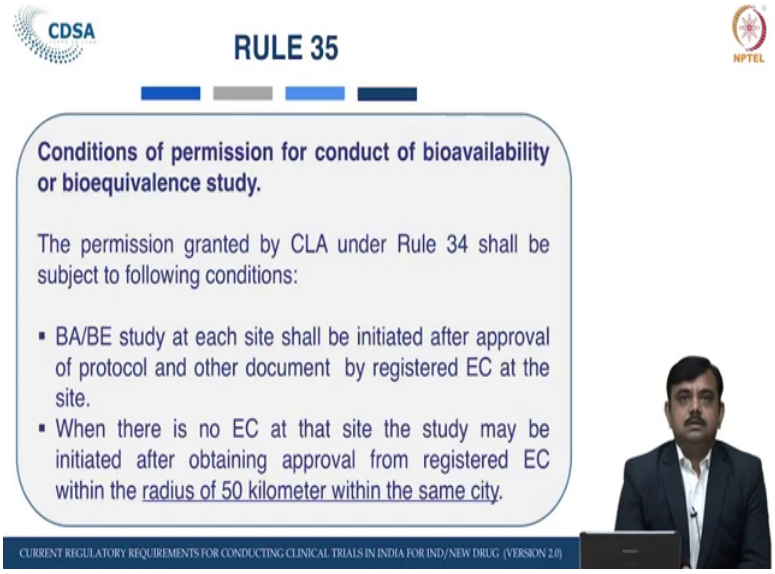

Rule 35 condition of permission for conductor for BA BE study center we have seen for the clinical trial that each site shall be initiated shall initiate the study for BA BE only after the approval of the protocol. Then if there is a no Ethics Community approval from that site other sites can be taken. So, these conditions we have seen earlier these are same like a clinical trial.

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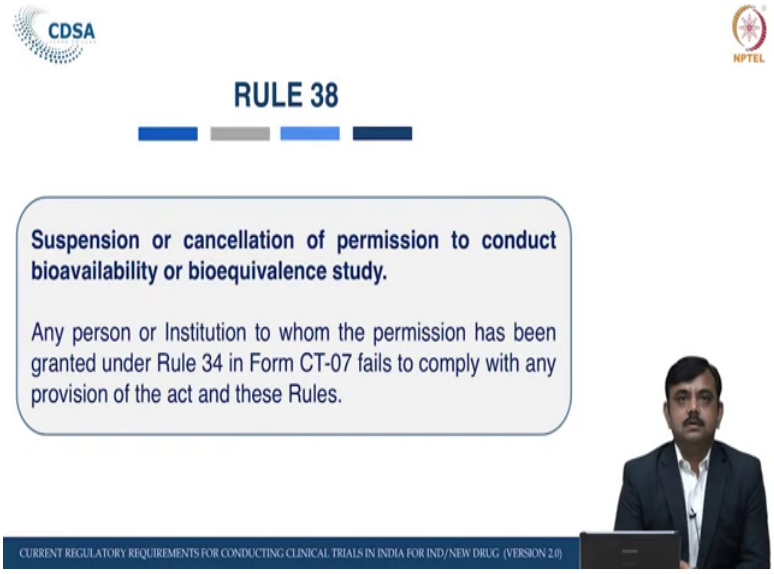

Inspection we have seen then the Rule 38 it is a suspension or cancellation of permission to conduct a bioavailability or bioequivalence study any person or institution to whom the permission has been granted under Rule 34 in Form CT 7 fails to comply with the any provision then in such case that permission can be canceled if there is a violation of the protocol deviation from the protocol then. If the licensing authority considered that the condition imposed has not been followed and that can cancel or suspend the permission.

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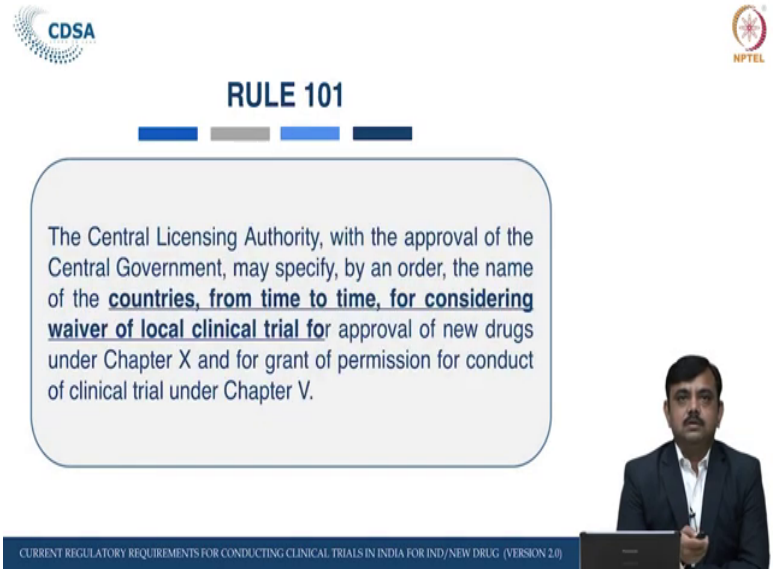

Rule 101 it is related to the waiver of the clinical trial. So, the central licensing authority with the approval of central government may specify by an order the name of the countries from time to time for considering waiver of local clinical trial for approval of new drug under Chapter X.

So, the meaning of this is that if the drug is already approved in some Stringent Regulatory Authorities the name would be specified by the name of the countries would be specified by the Central Government Authority by the Gadget notification and, if in that country the drug is already approved for more than 2 years 3 years and there is no data regarding the adverse effect or side effect of that drug. So, in such cases after deliberating the proposal the committee and a central licensing authority can give the clinical trial waiver.

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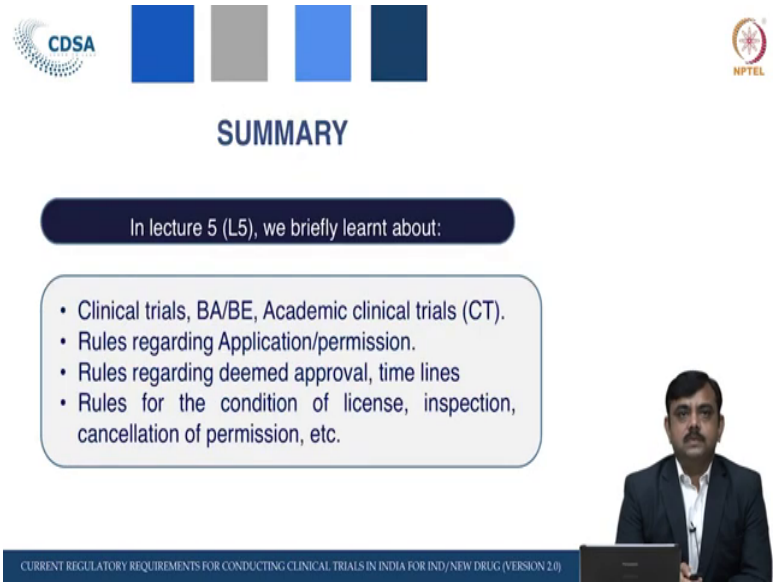

So, this is about all, the chapter 5. Let us have the quick look about the summary. So, in this lecture 5 we briefly learn about the clinical trial we have seen the Rule 2 J where in we have seen the definition of clinical trial which is a systematic study for new drug and the IND.

Then we have seen the bioavailability and bio equivalence related rules. We have seen the Academic clinical trial what is academic clinical trial whether the permission from the CLA is required or not. Then we have seen the rules regarding applications and the permission the various forms required for the application and in which form the permission is granted by the Central Licensing Authority

We have seen the rules regarding deemed approval, the timeline that it 30 working days, if it is the drug in the discovered in the India and, it is 90 days if it is to be imported and approved

somewhere else. Then rules for the conditions of license we have seen the after obtaining the clinical trial permission, what are the conditions the applicant has to be followed?

Then what are the conditions for the inspections, central licensing authority can inspect the facilities can inspect the trial side BA BE study and in case of the violation, the central licensing authority can cancel the permission, and under which rule that cancel the permission that rules we have seen.

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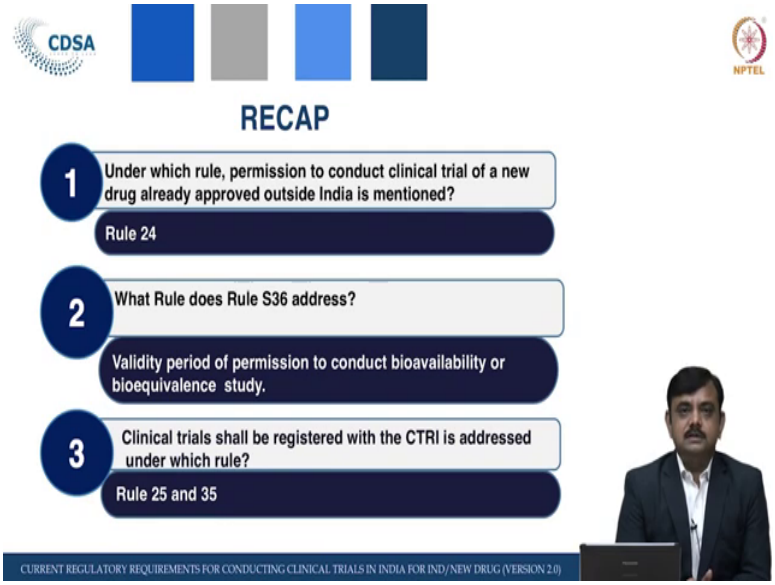

So, let us have the quick recap, you have to answer the question as usual, the 1st question for you. Under which rule permission to conduct clinical trial of new drug already approved outside India is mentioned? So, this is a Rule 24. The next question, what does Rule 36 address?

So, in the Rule 36 the validity period of permission to conduct BA BE study has been given. The next question, clinical trial shall be registered with the CTRI is addressed under which rule? So, you have to mention which rule under which the CTRI has to be even registered.

So, answer is Rule 25 and Rule 35 we have seen it is mentioned under the Rule 25 and somewhere in the conditions also it is mentioned, to register under the CTRI. So, this is about the lecture 5 we will come with the next lecture. I hope you have enjoyed this lecture. So, till the next lecture take care.

Thank you. All the best and bye bye.