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

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Lecture - 20
Common observations during CT/BA/ BE centre inspections

Hello friends, welcome back once again to the course Current Regulatory Requirement for Conducting Clinical Trial in India for New Drug and the Investigational New Drug. So, this is our lecture number 20; Common observations during clinical trial or BA-BE study center sites.

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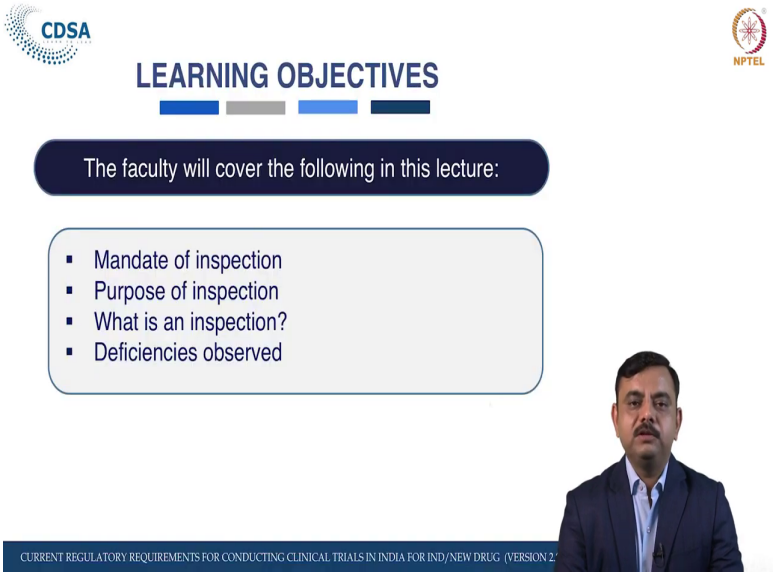

In our previous lecture, that is lecture 19; we have seen the common observations and the common deficiencies which are at the submission of the protocols. So, in this lecture the

learning objective is we will see what is the mandate of inspection, which is the rule, which says the inspection and what is the purpose of the inspection, what are the types of inspection, what are the types of deficiencies and what is inspection what could be the obligations of this inspection and what could be the punishment.

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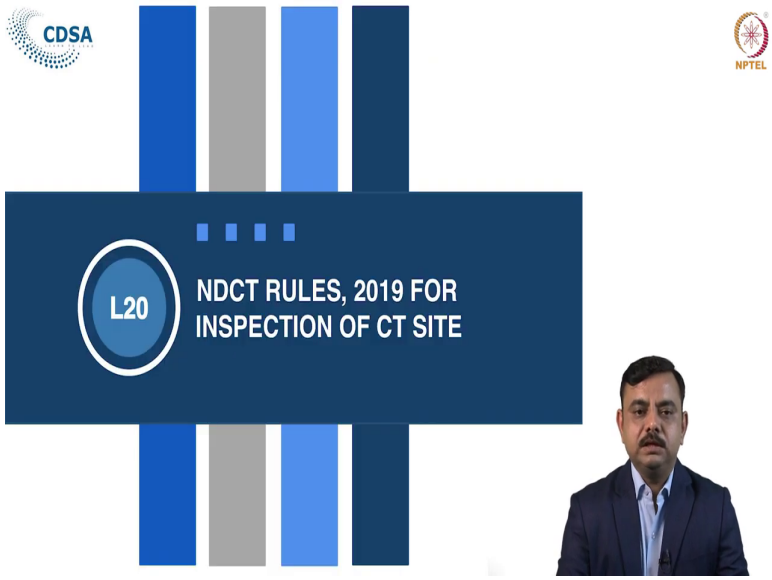

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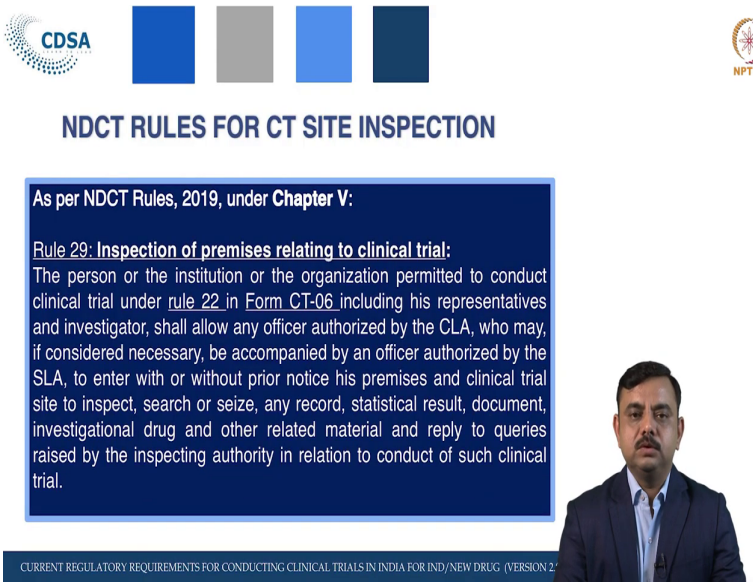

So, let us see as we know that in the New Drug and Clinical Trial Rule, there is a rule number 29 which is related to the inspection of premises, relating to the clinical trial. And one more rule is there which is related to the inspection of the premises of the BA-BE study centers. So, as per these rules, the applicant maybe it is a organization or institution any person who has taken the permission who has obtained permission from the licensing authority to conduct the clinical trial; or to conduct the bioavailability and bioequivalence at study center and those the applicant who have granted the study center permissions.

So, they shall allow any officer authorized by the Centre Licensing Authority, that licensing authority or that officer designated he may accompany with the state licensing authorities and he may with or without notice he may enter into the premises where the study center has been granted, or proposed to be granted, or the clinical trial site where the permission has been

granted. And he may inspect search or seize any record related to the clinical trial or related to the study centers.

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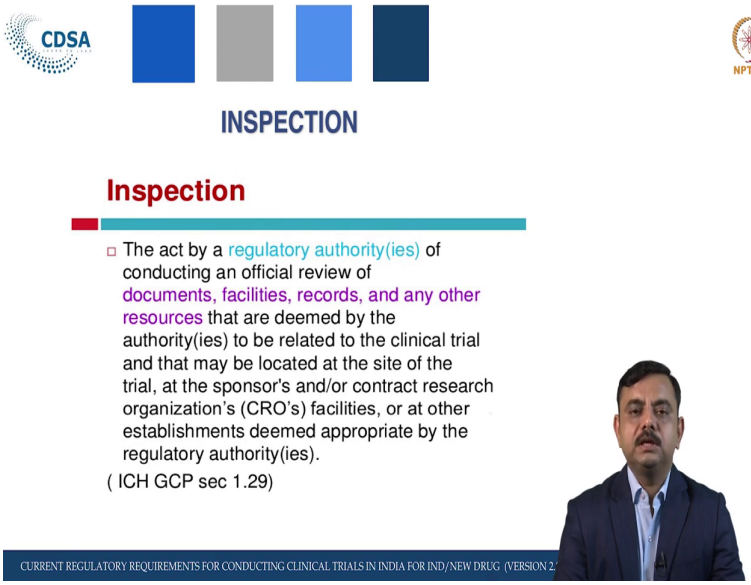

Now, what is means by inspection? So, actually inspection it has not been defined or in our New Drug and Clinical Trial Rule, but this is the definition I have taken it from the ICH GCP section 1.29. As per this definition it is the inspection is act by regulatory authorities in case of India it is a state licensing authority or the CDSCO that is Central Licensing Authority.

Of conducting an official review of document facilities record and any other resources that are deemed by the authority to be related to the clinical trial and that may be located at the site of the trial at the site of the sponsor CRO at the facility of the sponsor or at any other establishment deemed appropriate by the regulatory authority.

So, a regulatory authority is empowered to search and have the inspection of the sites. So, this is the inspection let us see in which cases the inspection is done. So, in general there are three types of the inspection for example, if it is a application for the grant of the BA-BE study centre. Then once, the applicant apply to the Centre Licensing Authority with all the regulatory documents and requisite fees what we have seen in our previous lecture as per the New Drug and Clinical Trial Rule 2019.

Then the licensing authority and his officer they scrutinize the application, and before giving the a final nod, they may conduct a inspection to see whether the actual facility is there or not; whether the adequate infrastructure, manpower resources has been provided or not. So, for that purpose also they can cause the inspection. Then after having the satisfactory compliance, they may give them the permissions; or the grant of the study centers.

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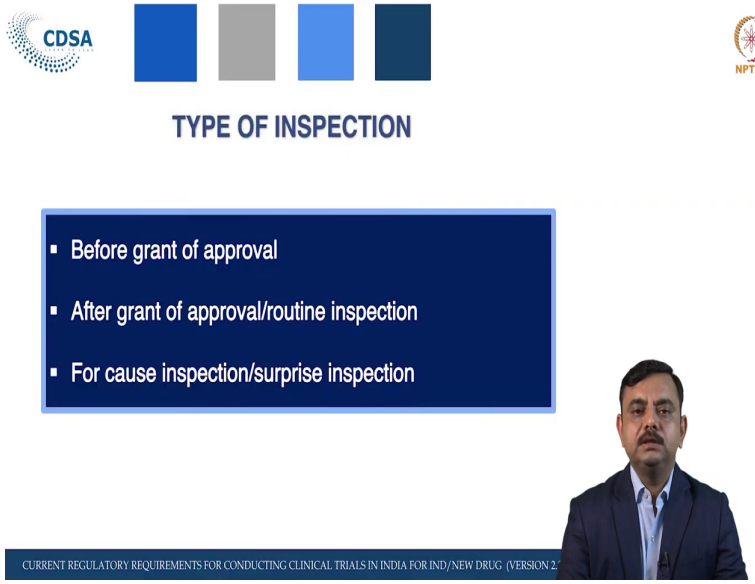

The next type of the inspection may be after granting the approval or the permissions. So, once the in case of the clinical trial if it has been given the clinical trial NOC. Then, whether that that study site or the center is complying with the conditions given in this CT site. To verify that there can be a routine inspection and for the in the case of the BA-BE study center there is also provision to have routine inspection of such a study center to verify whether the study center is complying with the conditions of the license, and as per the compliance as per the New Drug and Clinical Trial.

Then one more type of inspection we can say that is a for cause inspection whenever there is a in the knowledge of the licensing authority that there is a violations of some conditions, or there are some complaints regarding the not conducting the trial in accordance with the GCP guideline or not complying with the condition of the permission by the BA-BE study center. In that case also with or without prior notice the licensing authority can cause the inspection, in such cases mostly it is without notice and we call it as a surprise inspection.

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So, what is expected by the inspector? So, this is these are my personal views what we mostly focus on the inspection. So, actually we have to keep in mind the three the three things and that are three P's we can say the first P is Personnel, then Premises and the Processes. So, these three things we have to look in to the; we have to keep into the mind while having the inspection. We will see it in detail in our next slides.

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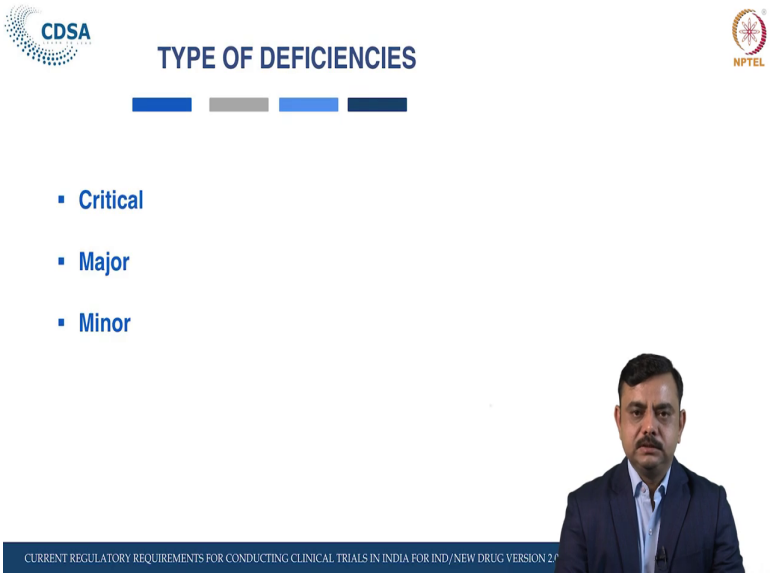

Then what are the type of deficiencies? So, there are there are three types of deficiencies which can be categorized as a critical, major and minor deficiencies. The critical deficiencies are those deficiencies which certainly affect the quality of the procedure and the quality of the results and the integrity of the results. Certainly, it will affect the safety of the subjects involved in the participations and based on such critical observations that permissions or the study centre approval that can be cancelled.

The major deficiencies we can say they may or may not you know affect the quality of the trial or they may or may not affect the safety of the subject participating into the study, whether it is a clinical trial study or whether it is a BA-BE study. But we cannot ignore all these majors also and minor also; because sometimes this major that can become a critical if we do not take into the consideration all this major observations.

The minor observations that that are required to prevent and that may not harm to the subject and they not that may not impact on the quality of the trial, but certainly as I have said for the major sometimes the many minor observation and it may affect and cause the major and many of the major observation that can cause a critical observation. So, we have to take care of all these critical, major and even the minor observations.

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Let us see what is the procedure of inspection and when the regulatory authorities, when and how they conduct the inspection. So, whenever there is application for the this is particularly related to the BA-BE study center. Whenever there is applications for the BA-BE study center the regulatory authorities and his officers they review the applications, and accordingly then propose the inspections.

Within certain time period they have to submit the report. The auditor has to submit the report to the licensing authority and the licensing authority after reviewing the report, the observations and the recommendation given by the auditor, in this case the drug inspectors, they may grant the permission to have the study center of bioavailability and bioequivalence.

In some cases, if there is a there is no clear cut recommendation and if the things can be improved, then in that case the licensing authority can issue them the query letter, to improve the deficiencies. And once that deficiencies has been rectified by the applicant it has to be submitted to the licensing authority; licensing authority having the satisfaction that the applicant has rectified all the deficiencies to the satisfactory level of the licensing authority, the licensing authority may grant the permission to the BA-BE study center.

In this case, it is important to know that if these deficiencies to be rectified, if it is related to the infrastructure, then after having the submission of the report of from the applicant; again the licensing authority can cause a inspection to verify whether they have rectified all the deficiencies or not. In case if these deficiencies are related to the for example, for the SOP's are not there; or any other things are there, or the SOP's are not clear.

So, these deficiencies the applicant can applicant can solve at their end and they can submit the rectified deficiencies along with the proper document to the licensing authority. In such cases most of the time there will be no inspections. So, this is about the inspection procedure.

Now, let us move towards our actual part, that is the deficiencies. So, these are certain deficiencies; there may be a variety of deficiencies and different types of deficiencies; that may vary from the inspector to inspector, auditor to auditor and site to site.

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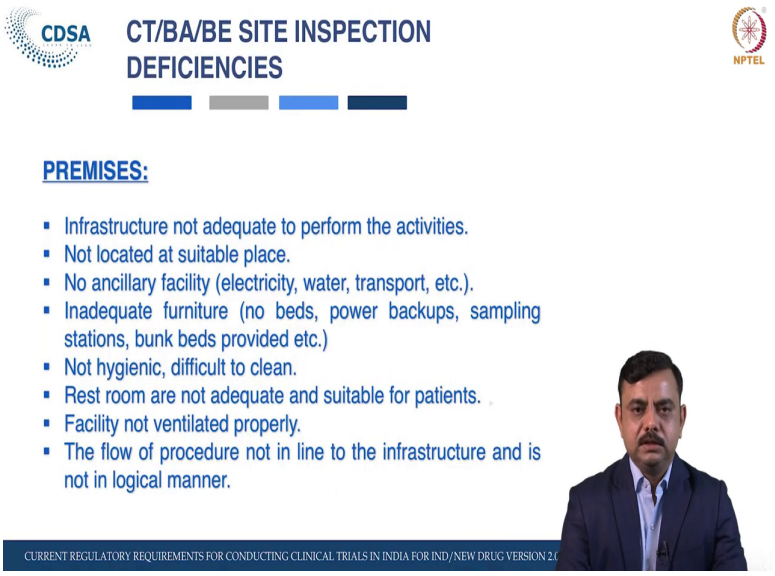

So, mainly these are the deficiencies with respect to the BA-BE study centers. As I have mentioned, we have to focus on three P's. So, the deficiencies related with the premises are mainly the infrastructure provided is not adequate to perform the perform the all the activities related to the bioequivalence and bioavailability studies. That may not be located at suitable place. There may be no roads, there may be no transportation available.

So, they may not handle the properly the BA-BE study center; in case of the emergency. So, that should be located at easily accessible place; and also from the little bit away from the noise and the drainage systems. That should have to see.

Further, there may be the adequacy of the ancillary facilities for example, electricity, water or transportation; as I have mentioned. If electricity failure is there, or if you know there in some rural places still there exist a load shedding what we call, the power cut is there. So, this is

actually directly related to the that may affect the quality of the product which has been stored if it has to be stored into the freezer refrigerator and if there is often power cut or the load shedding; then, that may affect the quality of the product.

So, these things also required to be taken into the consideration. Easily accessible and the easily accessible water should be there. Then there should be inadequate furniture to seat properly the subjects and to raise them. There should be a properly power backup in case of the power shedding, then, for the testing and the drawing this bloods from the subjects, there should be adequate sampling stations.

In most of the centres, with the inadequate space they provide the bunk beds. So, it depends upon the study if the study is in the patients in such cases the bunk bed should be avoided; or even if it is provided then the measure should be taken to go to that bed very safely and there should be no harm to the subject participant or to the patient in case of the clinical trials.

Sometimes we found there is no hygienicity in the premises and outside also the premises sometimes there are some drainage or there if it is in remote area. So, that is also not good and it may affect the health of the subjects sometimes the infrastructure is made is in a such a way that it is not possible to clean it and there may be some cobwebs or the ceiling problem.

So, that is also not good for the premises in most of the time we have seen that the rest rooms provided are not adequate and the patient the subjects they have to be in queue and in our guideline it is clearly given how the restroom should be there should be a restroom for handicapped people also if they are they are and that should be easily accessible and that can be easily open then some alarm should be there in case something happens that that all the facilities and this should be provided there.

As it is not mentioned that how the facility it should be for the BA BE study center, but that should have some you know logical flow. For example, if the subject is coming for giving the ICF and he has submitted the ICF then again he has to go somewhere for very long to approach the next stage and again after this next stage again he has to return back to the first stage. So, that logical flow should be there to avoid any you know it should be hassle free and

should be convenient to all. So, this these are few of the observations with related to the premises.

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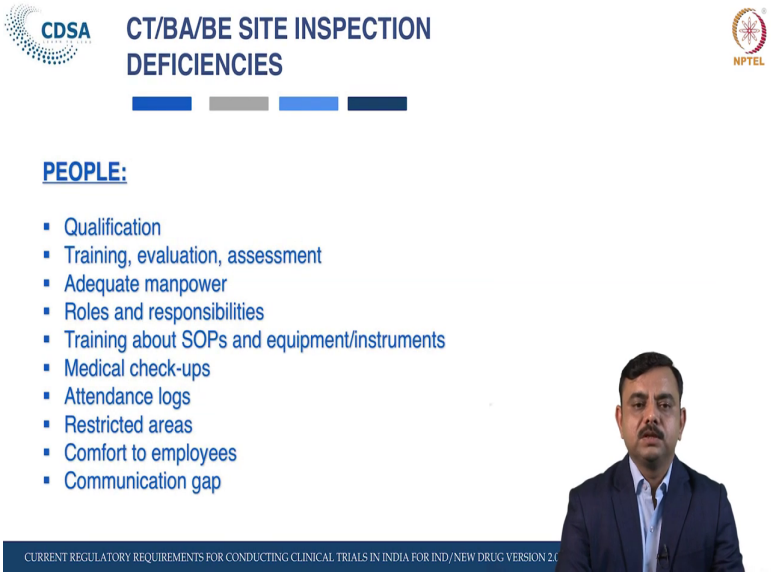

Then with related to the peoples that the observations there may not be a qualified staff and in this regard the investigator it is very important to have the proper qualification and subject knowledge and it should not be like that in case of the clinical trial the trial is going on for the oncology product and the investigator who has been looking after he is not having any knowledge of the oncology product and he may be from the different streamline. So, that is also that is also not actually allowed and that should be avoided

And be it is a investigator or any other staff member who are directly looking after the trial like nursing staff or the analyst and the other staff they should be properly trained as per the SOP and the SOP should be developed for their training. And after training the how much

they have understood how much they could figure out from the training that should be evaluated it. .

It should not be just a verbal training and the people are listening and nobody is understanding, but you have taken the signature and to show to the inspector and the licensing authority that you have conducted the training that should not be there should be a proper you know procedure for giving the training to the employees and whatever the training has been given whether they have understood or not that should be verified through the evaluation there should be a proper SOP.

Then adequate manpower should be there otherwise if for example, the trial is with the 100 of the subject or the 100 of the patients and only few of the staffs they are attending then though it has not been mentioned in the New Drug Clinical Trial Rule, but that should be adequate to avoid this hassling and to have the convenient and pleasant atmosphere.

Then the role and responsibilities that should be clearly identified and SOPs for them should be provided and it should be given to the individual worker individual employee of the institution. So, that it should be well conversant with his roles and responsibilities the training about SOPs equipment that I have mentioned. So, the related to the equipment the training should be given to all the employees. Then all the employees they should be checked before joining they should there should be a their medical checkup and they should be healthy.

Then the attendance log most of the time they are not maintaining at the site. So, whether the employee has attended or not attended whether he or she was on the leave. So, that should be; that should be maintained properly there should be some restricted area for the restricted people. For example, in case of the pharmacy only the pharmacists or investigator they should be allowed no other people should be allowed to avoid the misuse or the mismanagement in the pharmacy area. So, that should be identified.

There should be there should be no communication gap between all the employees otherwise there may be a duplicacy of the work for example, there are 3 or 4 staff of the nurse and everybody is withdrawing the sample and there is no communication whether they have they

have taken the samples or not that or there may be a possibility of taking the samples again and again. So, there should be a proper communication.

And the most important there should be comfort to all the employees proper ventilation should be there proper water system should be there. So, that the atmosphere would be very pleasant and the efficiency should be increased.

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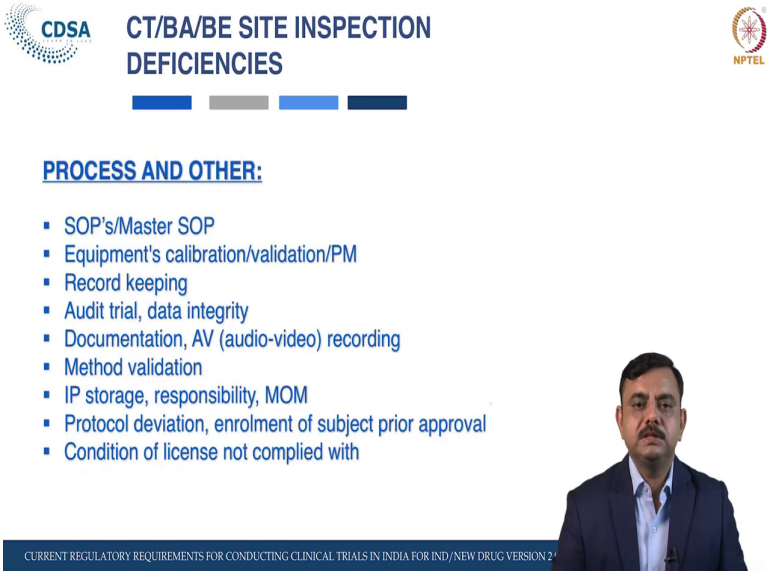

The processes are most important and in this I would like to say there should be a first SOP of SOP we call it as a master SOP that should be there and this SOP should specify how to prepare other SOPs where when should be the version change what should be the title in what format it has to be written who has to written it who has to approve it who has to sign it one clear cut master SOP should be there and accordingly other SOP should be prepare.

Then whatever the equipments where equipments and the instruments provided that should have the proper preventive maintenance and that tag should be there. And again they should be properly validated and calibrated where it is a necessary and that should also carry your tag. So, that if it is every after 6 months then where is when is the due date then they have when they have you know calibrated or validated previously that date should be there and whether and as and when there is a there is a due date due date it should be calibrated properly.

The record should be kept in a proper archival system. So, that there would be no loss of the record and it should be kept for the time as what is mentioned in our new drug and clinical trial role for BA BE study the data should be maintained for the 5 years. So, the people should be aware about all these audit trial data integrity now a days data integrity is the biggest problem. So, that policy should be there how to avoid this in integrative problem.

Then heavy recording that should be also the audio and video recording should be also properly audible otherwise you would you would record it and if it is not audible to the auditor whenever comes in it has no use again. The method whatever applied for example, for centrifugation or any other for method analysis that should be validated. So, that the correct results come out.

The important thing is the IP should be stored properly and into the pharmacy the storage condition should be mentioned on the label and that should be verified it is most of the time we have seen that the in the storage condition is different and it is stored at the different places and by the different people it is having no label. So, that should be avoided.

Protocol deviation enrolment of subject prior the approval of the license in them many of times we have seen and it is a critical it can be considered as a critical observation that without having a permission from the licensing authority. Sometimes what the sponsor do that assuming that today or tomorrow we are going to get permission they start the clinical trial and this is the big violation they should not big we can say this is a critical violation they should not do this they should not you know initiate the clinical trial or bio bioavailability

bioequivalence study before the approval by the ethics committee as well as the licensing authority.

And once permission has been issued the applicant should read all the conditions. Most of the time we have seen they have been issued permission or the grant of license in certain condition, but most of the time they are ignoring this condition and they are not reading properly the conditions and whenever the inspector goes there and read the condition then he find out they have not followed the conditions that may be a major violation

So, these are the some of the my personal observations and opinion at the last I would like to I would like to say that with respect to sSOP and procedure and premises to avoid any major and critical deficiencies.

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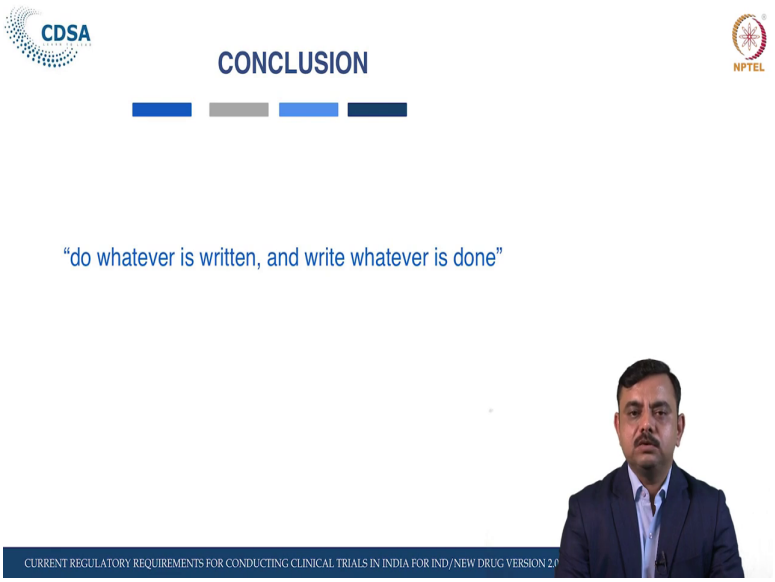

The firm should have the policy and they should all the employee should do whatever it is written in the documents whatever it is written in the SOP and whatever they are doing that should be written to avoid any further non compliances.

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If there are some non compliances then what would be the consequences of these inspections. So, if it is as I have mentioned if it is for the BA BE study centre and if it is a inspection prior to the approval then if there are many deficiencies then that could delay the approval process of the permission or of the study centers. If the study has been conducted and if there are some major or critical observation that study may be invalidated or the results may not be considered appropriate.

In certain cases if there are critical observations and these observations they are not rectified within time and keep continuing continue doing this malpractices in that cases if it is all; if it is

all the unethical practices in that cases the investigator maybe disqualified or restricted for conducting in future studies. So, these are the observations and procedures.

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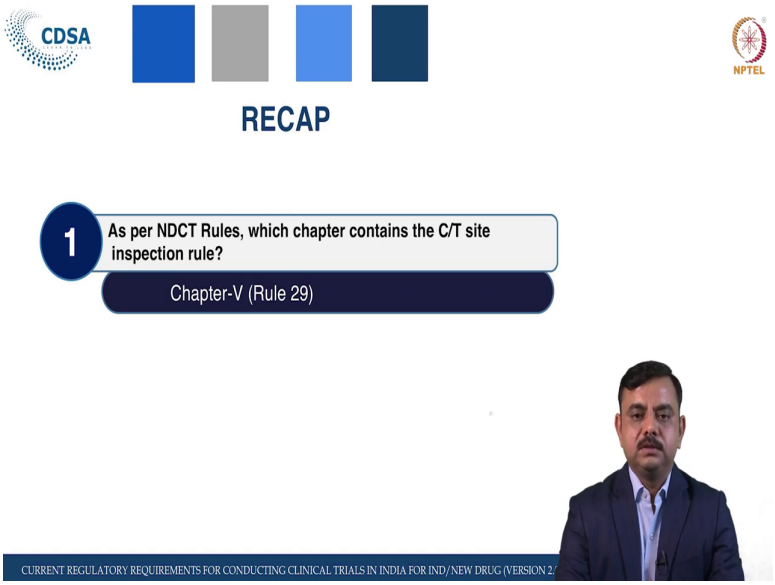

Now, it is time for you to answer some of the questions. So, the first question for you as per New Drug and Clinical Trial Rule which chapter contains the clinical trial C T inspection rule. I have mentioned it in the very first slides. So, this is the chapter 1st and rule 29.

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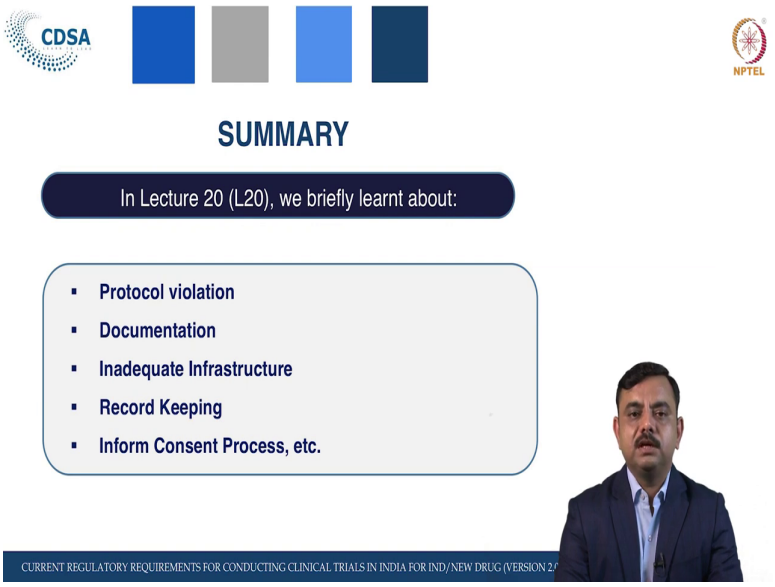

So, let us summarize what we have learnt from this lecture. So, we have seen in this lecture what is means by inspection what are the types of the deficiencies what are the types of the inspection what is the objective of the inspection and what are the different types of the deficiencies commonly observed with respect to the personal premises and the procedures. So, this is all about lecture 20 and we will meet in our next lecture till then you take care.

Thank you and bye.