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

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Lecture - 19
Common Observations During Submission of C T/B A/B E Protocol

Course Current Regulatory Requirement for Conducting Clinical Trial in India Version 2. This is our lecture number 19 and here we are going to address the common things that is the Common Observations During Submission of Clinical Trial or the BA BE Protocol, that is the bioequivalence and bioavailability protocol.

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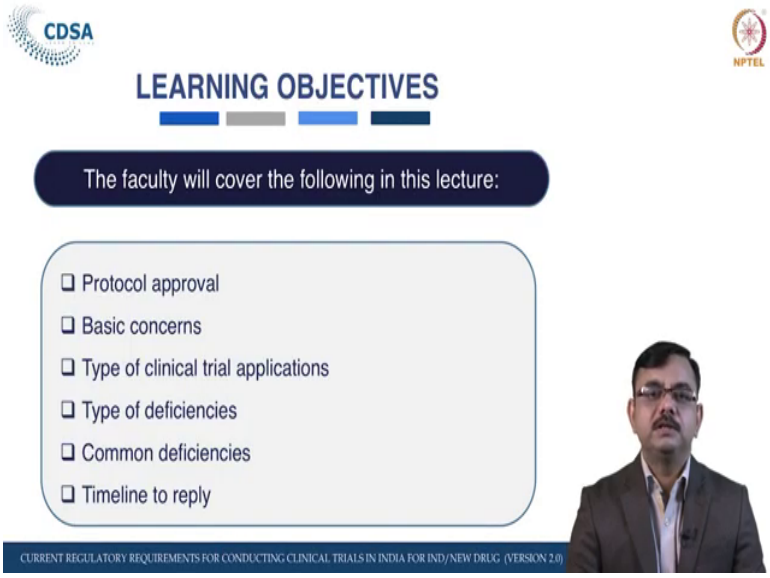

The learning objective from this lecture, the learners will come to know after the lecture; whether the protocol approval is mandatory or not, what are the basic concerns while submitting the protocol, then types of the clinical trial applications, the deficiencies, what is

the our main objective of this lecture. So, you will see the major deficiencies and the timeline to reply and what could be happen if it is not addressed properly.

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So, let us start with the introduction of this lecture; the major concern in any clinical trial are the production, protection of study participants safety and right and ensuring the accuracy and validity of the data being collected. To ensure that these concerns are adequately addressed in a study.

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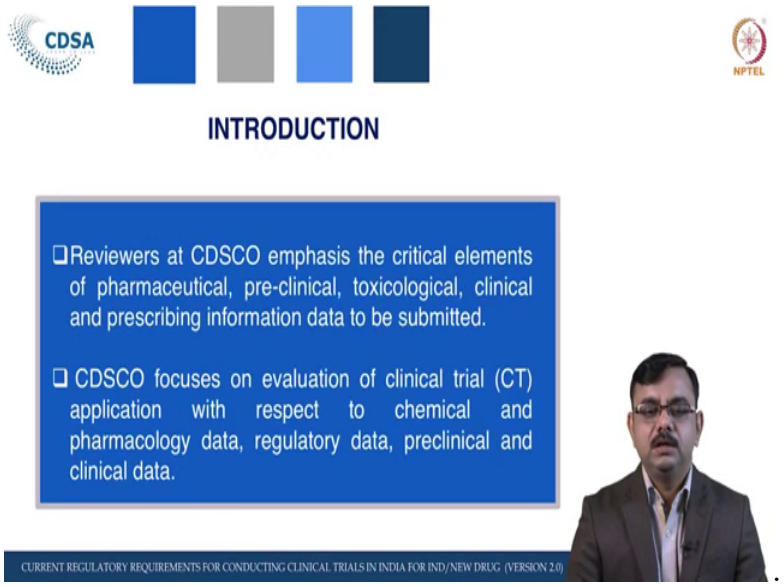

Reviewers at CDSCO emphasize the critical elements of pharmaceutical, pre-clinical, toxicological, clinical regulatory aspects and some other aspects. CDSCO while dealing with the applications focuses on evaluation of clinical trial application with respect to chemical and pharmaceutical information of active pharmaceutical ingredient as well as the formulation; then the regulatory status in country and outside the county, then data with respect to the preclinical study and the clinical trial studies.

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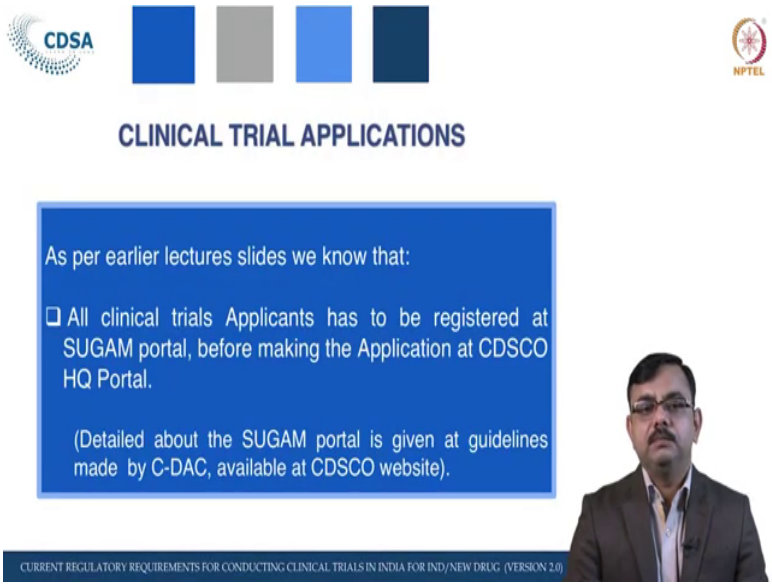

We have seen in our earlier lecture that, all clinical trial applicants has to be registered at SUGAM portal. We are having a online submission and I am going to give a detail lecture on how to submit the online application is our subsequent lectures.

So, before making the application at CDSCO HQ headquarter, the applicant has to register on the SUGAM portal. Detail about this SUGAM portal is given in the guideline by C DAC and it is available at our website CDSCO dot gov dot in.

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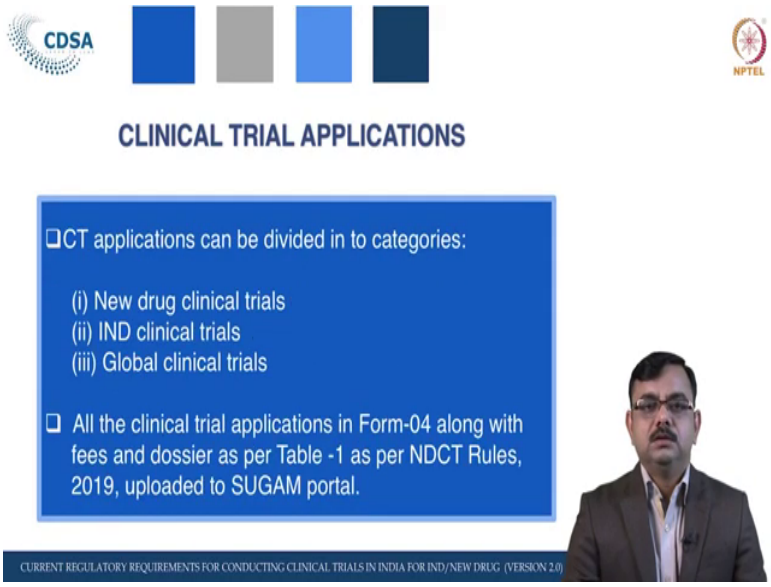

We can divide the CT applications type in the category like new drug application, then the investigational new drug application, global clinical trial or subsequent new application and other. So, these types of categories are given there. All the clinical trial applications in form 4 along with the fees and dossier as the requirement has been given in the Table 1 as per the New Drug and Clinical Trial Rules, it has to be uploaded onto the SUGAM portal.

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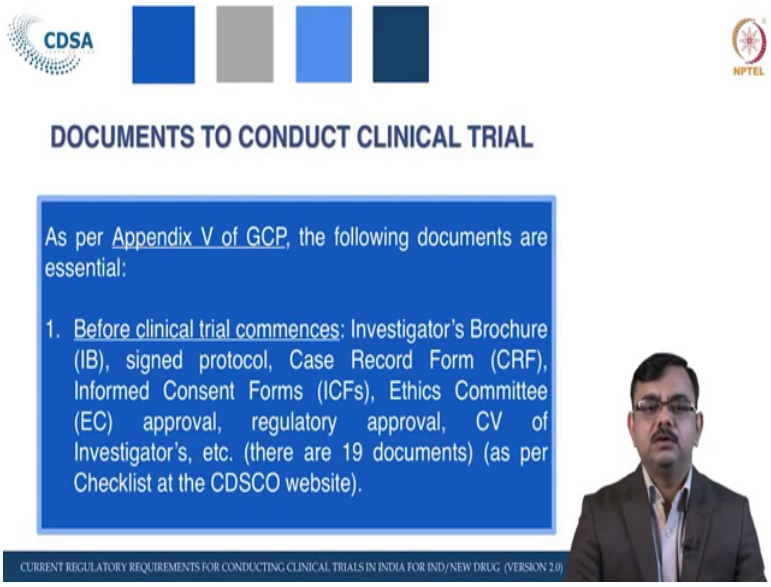

We know that as per appendix V of good clinical practices; the document essential to upload that before clinical trial of commencements are Investigators Brochure, then signed protocol, CRF, ICF format, Ethics Committee approval. Then the regulatory approval, whether it has been banned, withdrawn or approved in country or any of the country; along with this the series of investigator and other related documents.

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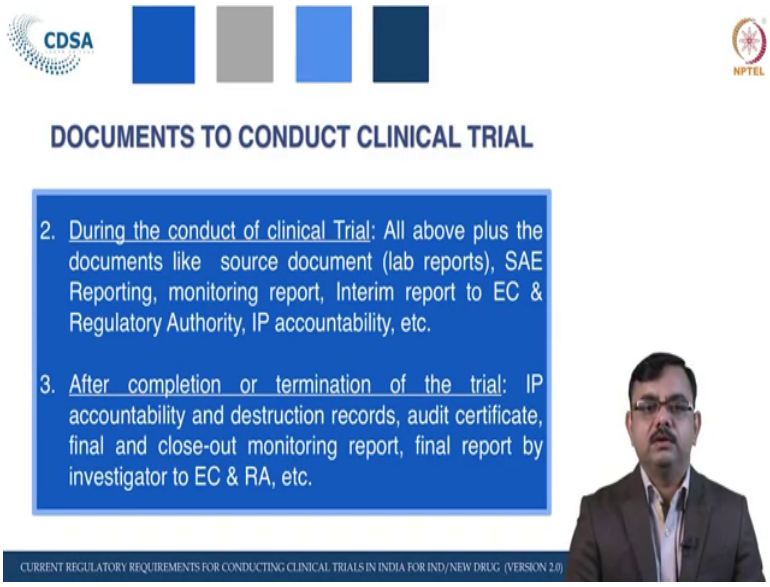

In addition to the all the source document, SAE reporting, monitoring report by the monitor, then interim report and the I P accountability at the side these documents also required to submit.

CDSCO has a clinical trial and global clinical trial division and also it is having subsequent new drug division IND division, FDC division. And they examine the application along with the dossiers and fee for administrative requirement; and if found the document submitted they are not adequate, they raise the query and this is also online. So, they raise the query through SUGAM portal and it will reaches to the applicants mail ID.

Similarly, in all the division like global clinical trial IND these all divisions are online nowadays. Regarding IND applications, all applications along with dossier and fees evaluated by IND committee at ICMR both scientifically, technically and also at the CSSCO

headquarter. And if found it is not compliant with, then the CDSCO in consultation with the IND committee and gives the query letter. The applicant has to reply to this query letter and after receiving the satisfactory reply for administrative query; CDSCO then refer this application to the subject expert committee. And the subject expert committee after detail deliberation in presence of the applicant and his representative if found satisfactory, then they recommend to give the clinical trial permission and accordingly the licensing authority issues the permission.

So, this is the overview of how to submit the application and how to how the query is raised by the central licensing authority and the procedure to be followed. Now, let us see, what is means by actually clinical trial protocol.

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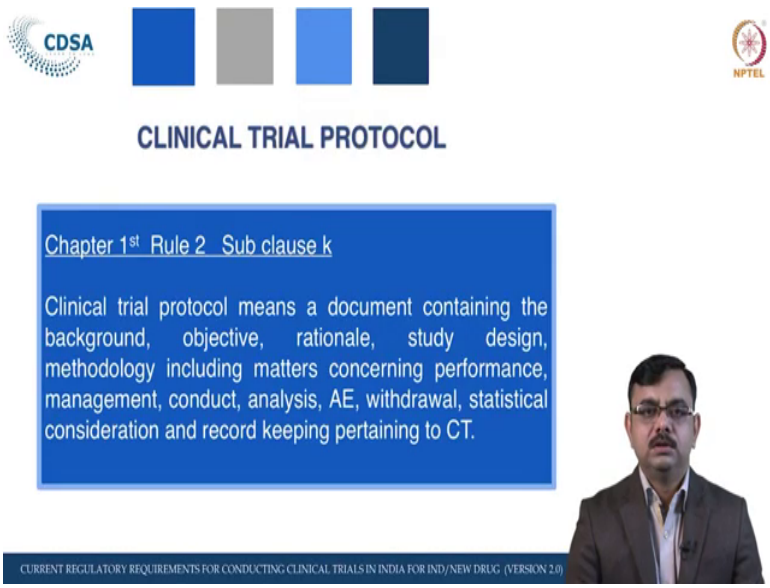

So, the definition of the clinical trial protocol it was not there in previous rules and regulation. Now it has been given in the chapter first of new drug and clinical trial rule, that is the rule 2 and subclass k. So, according to the this rules, the clinical trial protocol means document containing the background, objective, rationale, design, methodology including the matters concerning performance, management, conduct, analysis, then adverse event, withdrawal, statistical consideration, and record keeping pertaining to the clinical trial. So, this is a comprehensive document definition given in the chapter 1st rule second, subclass k.

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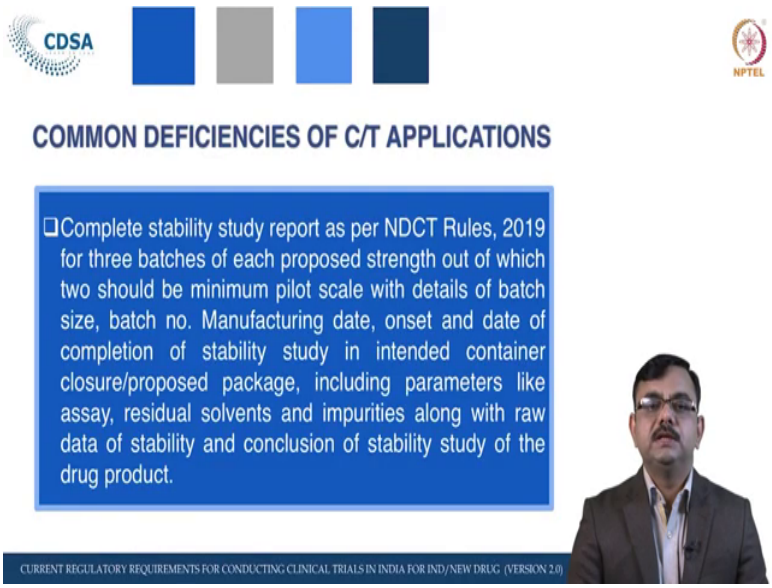

Now, let us see what are the common deficiencies. So, these deficiencies maybe related to the administrative deficiencies, this may be related to the regulatory deficiencies, this may be related to the non-submission of some information and this may be related to the safety concern and the scientific point of view. So, when we receive the application. So, these are the common deficiencies what I am going to mention here; most of the time we observe that along

with the application, the complete stabilities study report as per new drug and clinical trial rule 2019 has not been enclosed and for that we issue the query.

As per this rules, this complete stability data for the duration of the period of the clinical trial is required. And it is generally we know the for development and other things it takes around 3 months; so at least 3 months data should be there. And this data should be on three batches of each proposed strength; if the strength is proposed for 50 milligram, 100 milligram, 200 milligram the stability study data require for each strength. Sometimes the applicant applies for the apply for the two strength, but submit the data only for the one strength; then in that case, again the query is issued.

And these batches the, here it is clearly mentioned the batches the two should be minimum pilot scale with and that has to be submitted with proper batch size, then what was the batch number, manufacturing date, the onset and date of completion of the stability study in an intended container. So, that everything has to be submitted, but most of the time it is not submitted and the CDSCO then issues the query.

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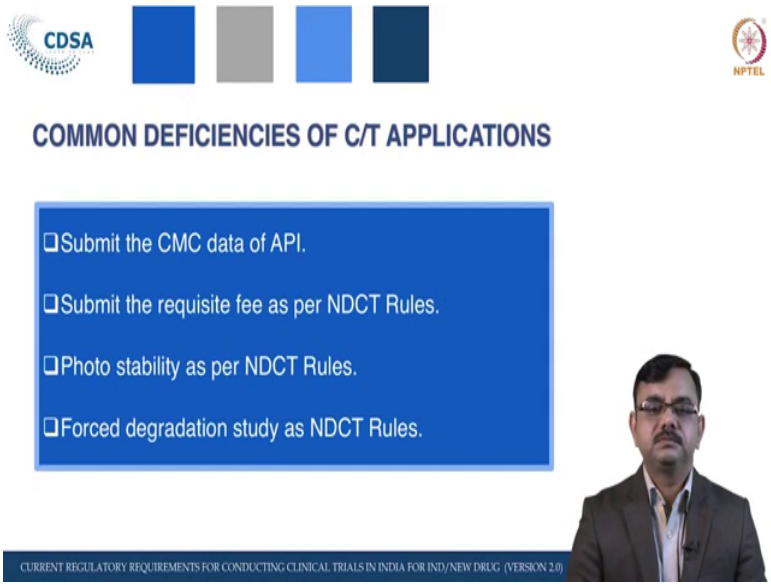

Then many of the time it has been found that the application is for the formulation; but the address has not been given and the CMC data has not been addressed properly, so for that also the CDSCO issues a query.

The most of the time with the changes in the fees, the adequate fees has not been paid and this is very important as is a government office. So, the proper fees that is for phase 1 we have seen it is a 3 lakh; and subsequently for 2 and 3, it is 2 lakhs. So, whatever the fees given in our schedule that has to be paid completely; if it is not paid, then the application is incomplete and the applicant has to submit that fees properly.

Then sometimes if the drug is for, drug is not enough sensitive the drug is enough sensitive and it there may be a chances of getting it degraded by the light. Then in that case along with

the stability that is a routine stability study real time accelerated; then the photo stability study also require to be submitted and if it is not submitted, then again there is a query.

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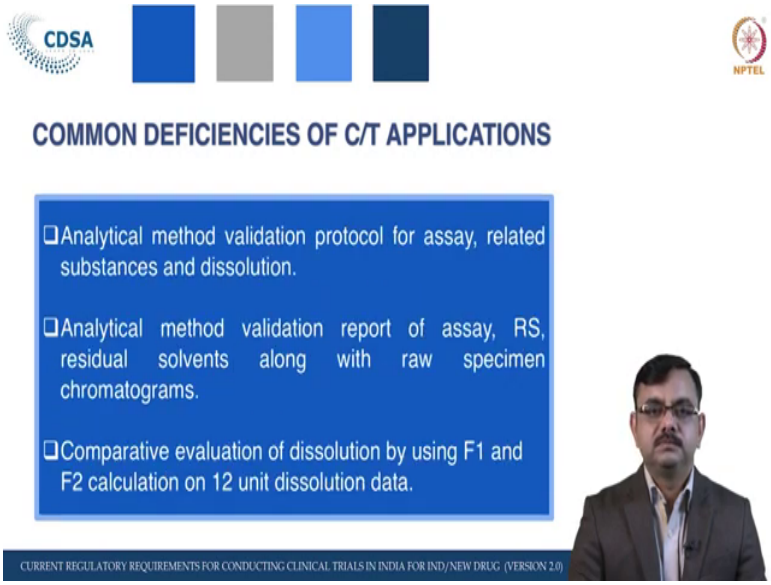

Accelerated stability study like forced degradation study that is also required to be submitted. Then whatever the method developed for the analysis of this samples that, detail analytical method developed and whether that method has been validated or not; that validation protocol assay, related substance, then the data about the dissolution that is found not submitted into the along with the application, for that also the CDSCO raise the query.

Then one of the important thing that is a dissolution data, which specifies the release of the drug. So, that is also required to submit and it should be a comparative evaluation of dissolution by using F 1 and F 2 calculation on 12 units dissolution data or 6 unit data, whatever that is mentioned in the official books.

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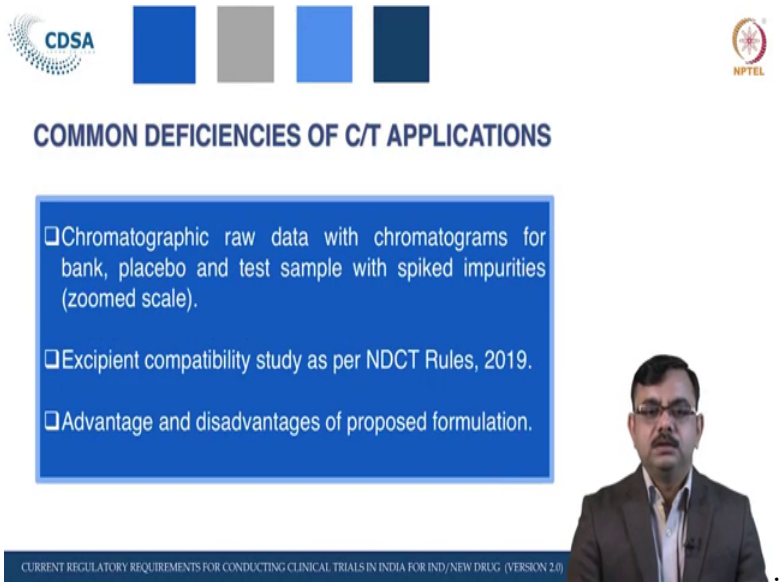

Then the chromatographic raw data; if the method has been developed and method validation report has been submitted with respect to the accuracy precison LOD, LOQ of the data; then in that case to verify whether the really the method has been developed and whether the method has been validated or not. To the regulator the chromatographic data is also require; the chromatogram, then the chromatogram of the bank, then what is the test of placebo and test sample spiked with the impurities that everything should be attached with the application.

Then excipient compad compatibility studies also require while submitting the application as per our new drug and clinical trial rule. Sometimes the application is for the fixed dose combination drug. So, particularly in the type of such type of application or whenever there is a change in the dosage form or any route of administration or indication.

Then particularly in this type of case, in this type of application the advantage and disadvantage of the proposed formulation require to be submitted. It is not like that, you have just submitted the application; but whatever the advantage and disadvantage as compared to the molecule or drug which is existing in market that is also required to be submitted along with the rationale and justification.

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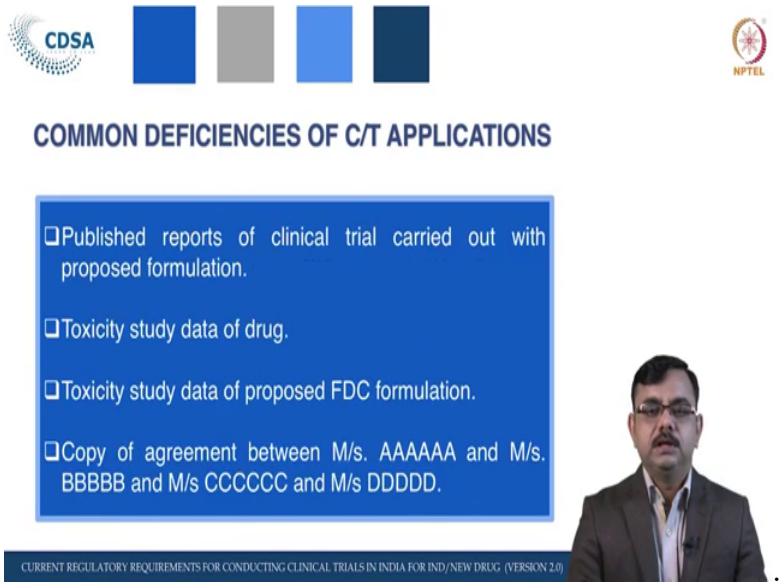

Then if the application is for the clinical trial phase 3, phase 2 which is and if the applica if the drug is already approved in some of the countries or some work has been done on that drug; then the published report of clinical trial carried out with the proposed formulation that is also required to be submitted.

Then for phase 3 before actually reviewing the phase 3 or the phase 1 data; the CDSCO expect to submit the toxicity data and preclinical data. It is also required for FDC proposed FDC, the toxicity data and most of the time the applicant do not submit the preclinical data.

Then material safety data sheet, then the finished product standard testing procedure; how they are going to evaluate that is also require. So, along with this, the certificate of analysis of three batches; particularly to know what are the impurities, the routine impurities, any specific impurities, whether they are within limit or not limit for that the certificate of analysis of three batches required to be submitted.

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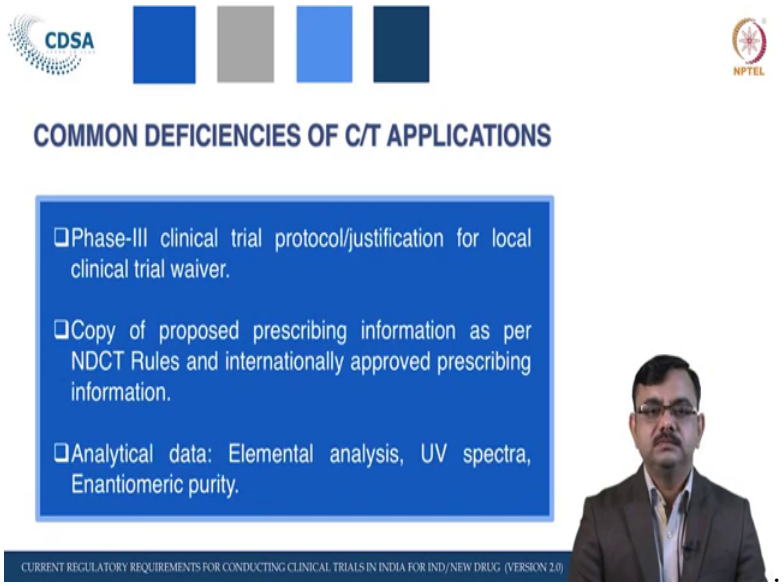

Then phase III clinical trial protocol, justification for local clinical trial waiver. Many of the times we have seen in our previous lectures also; the applicant can request for the clinical trial waiver, if the drug is already existing in the stringent regulatory countries. In that case, the

justification for the clinical trial waiver required to be submitted by the applicant. So, that based on that the application can be considered by the subject expert committee and by the regulator.

Then copy of proposed prescribing information's as per new drug and clinical trial requirement; what is the prescribing information which is approved internationally, and if it is available in the India, then what is the what is that prescribing and formation, the copy of that has to be submitted. If it is not existing, then the proposed prescribing information and proposed packages label has to be get approved from the DCJ office.

With respect to the analytical data and the elemental analysis, then UV spectra, Enantiomeric purity these all these tests are very important; and the whether that test have been performed and what are the results, whether they are within the limit that has also required to be submitted by the applicant.

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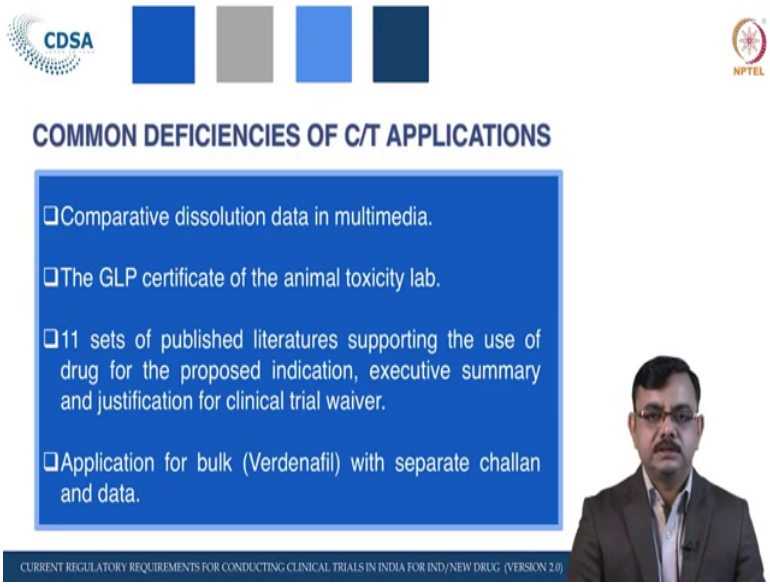

Comparative dissolution data in multimedia we have already covered. So, that should be in a multimedia; like in acidic condition, like in basic conditions that that is required to be submitted.

And with respect to the animal toxic course study, whether the study has been done; then whether that laboratory where the study has been performed is complaint with the GLP or not, so it has been you know that, we have seen it is in GLP accreditation is mandatory. And the data generated should be in the lab, which is a compliance with the GLP norms that is good laboratory practices. So, that certificate also required to be submitted.

Then we have the procedure that before sending it to the subject expert committee, we require to send the literature data to the different experts. So, in this regard, so we require the 11 set of the published literature supporting the use of drug for the proposed indication; then we

forward this literature data for the prev for the study purpose to the different experts, so that they have the basic knowledge of the proposed drug and they can deliver it thoroughly into the subject expert committee. So, before actually having the subject expert committee, these 11 sets of the literature data should be submitted to the CDSCO.

Then application for bulk with separate challan and data; if the there are different application, like application for the API application, for the formulation, then the different type of challan and the forms are required.

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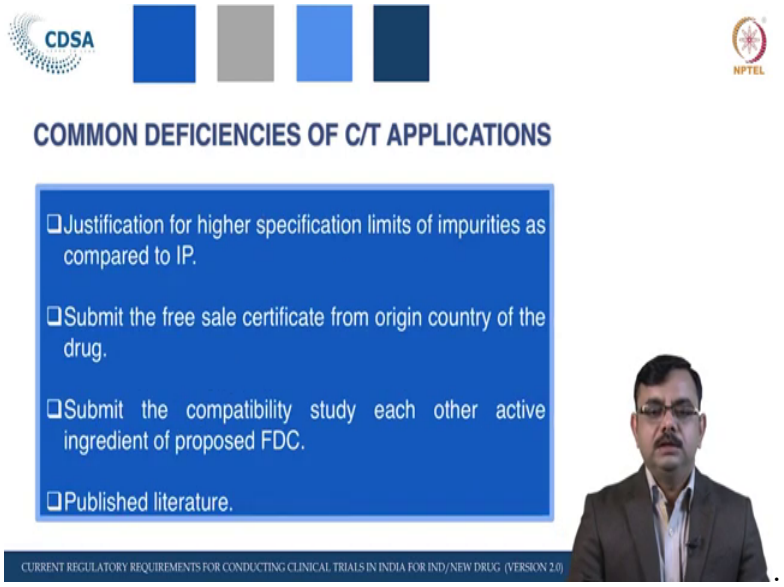

In case of the certificate of analysis I as I have mentioned the, certificate of analysis from three batches are required. So, if the impurity is higher than the specification limit; then justification for higher specification limit of impurities as compared to the Indian pharmacopia or any other pharmacopia that is required to submit.

Then in case of the import of the drug from other countries, the applicant has to submit a free sale certificate from the country of origin. Whether that this free sale certificate ensure that, the drug whether it is available in the market or not in that country, so for that purpose we require a free sale certificate.

Then compatibility study of each ingredient in case of the FDC is required to be submitted. Then if the protocol is for the bioavailability and bio bioequivalence, the inclusion criteria, exclusion criteria, investigator undertaking, objective, rationale of study, study design everything require to be submit; not only for the BAP protocol, but for the clinical trial protocol also.

Once it is in the subject expert committee; what we have found the many of the times, the application is not complete and the design whatever they have given for the clinical trial that design is not appropriate. Sometimes the subject expert committee found that the sample size calculation that is not matching with the number of the points they have taken for the evaluation and it is not matching with the primary and secondary objective. So, in that case the subject expert committee may has to change the size of the samples and they can also ask to revise the design of the protocol.

Then sometime the data submitted with respect to the safety of the drug that is not adequate. So, sometimes the applicants they are submitting only one or two published literature available in the market and that is also not adequately addressing the concern regarding the safety, and sometimes they are not from the reputed journals also and there is no authenticity. So, that required to be changed by the applicants before submitting the application.

Then the applicant required to submit the any safety concern raised by the US FDA or any other countries. If the drug is already approved in the US or any other countries, whether that that country has raised any safety concern, whether any serious adverse event or the adverse events are associated with that drug that is also required to submit with the application. So, these were some of the common observations to be found during the clinical trial protocol submissions.

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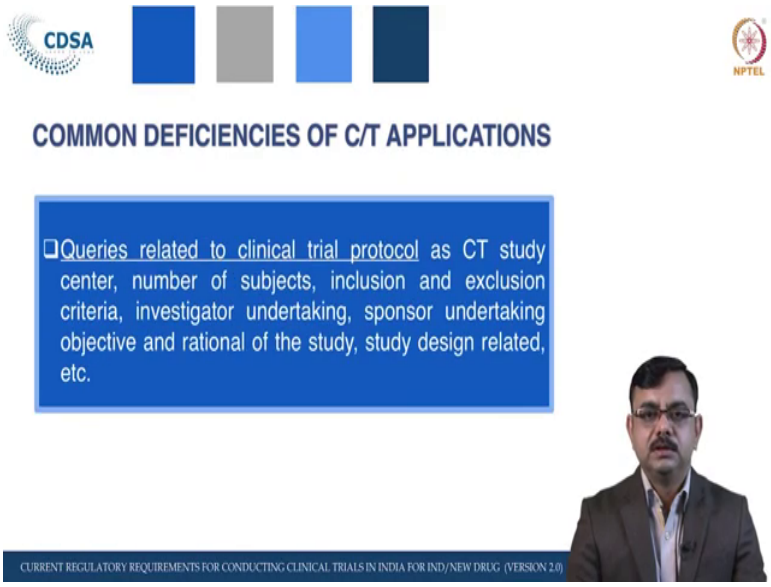

And these are not the limited to this; just we are giving the example. So, the most important the things applicant has to be keep into the mind that, first he has to go through the checklist and we have given the detailed checklist. So, the first part is he has to submit all the applications whatever mentioned into the checklist, then the regulatory status of the drug, then publish clinical trial. And that published clinical trial should be adequate into the number and with the proper justification and from the well reputed journals; then only it can considered and this should address the safety concerns.

The other important thing we have seen that is the preclinical data, that is also that data should be generated and the data generated should be as per the new drug and clinical trial rules.

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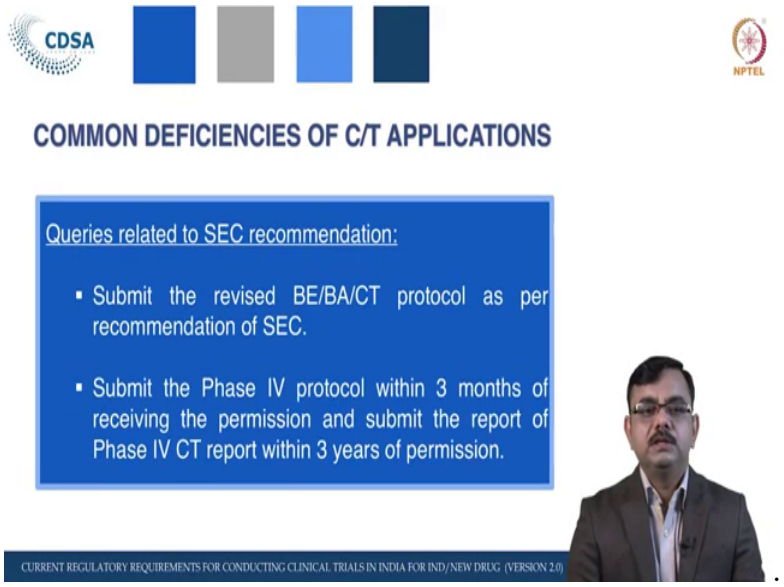

Now, let us see what happens if the protocol has not been submitted or the application is not complete in all respect or sometimes you know the applicants, they generate the data and then fabricate the data. Like we have many of the time, we have seen the stability data what they submit; in that stability report they mentions that, the batch has manufactured in the month of say for example, January 2019 and they are submitting the application in the March of 2019.

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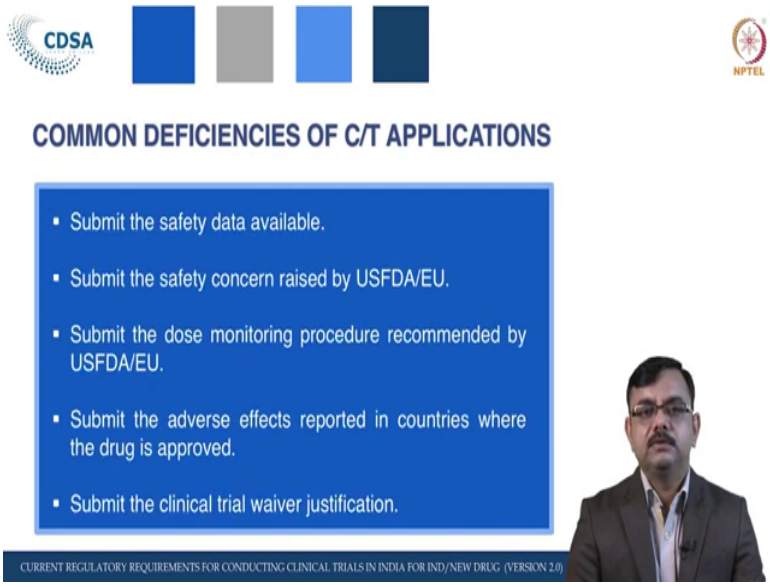

And the data what they are giving that data is of the 6 months, 6 months stability; from that we can you know, we can smell that the data has been fabricated, because it is not possible to generate the 6 month data within the 3 months. So, from that dates we can find out that data has been fabricated and managed to submit to the CDSCO.

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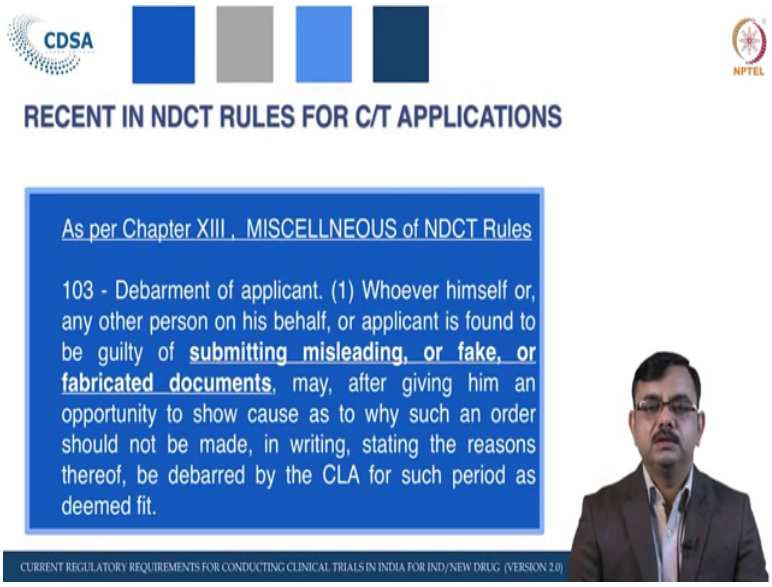

In such cases now, in the new drug and clinical trial rule, in the last chapter the it has been given that; whoever are any other person on his behalf of the applicant is found to be guilty of submitting such data, which is a misleading or fake or fabricated document, then the licensing authority may after giving him an opportunity to show cause.

So, the licensing authority first will give the chance; because sometimes what I have mention the date of the January and the date of the March has been given, but sometimes there may be a typographical errors also and it is not a intentionally, but this is without an intention that can be happen. So, considering that it is not intentional, so the licensing authority issues a show cause notice and asks as to why such an order should not be made to debarred the applicant.

And if applicant is unable to provide the satisfactory justification, sometimes the if the licensing authority feels that there is a need for the verification of the data at the site where the

data has been generated that; the licensing authority can send a auditor or the drug inspector to verify whether really they have generated the data or not generated, whether they have fabricated the data or whether they have generated the data, but they have not submitted it properly and there is a there may be a type of graphical error of something.

So, after reviewing all these the justification or the inspection the; if it is found guilty and if it understood that the data has been fabricated, the licensing authority may debarred the applicant for such a period as if deem fit. So, this action can be taken by the licensing authority. So, this is all about the observations; these are not limited, but only these are these can be the examples.

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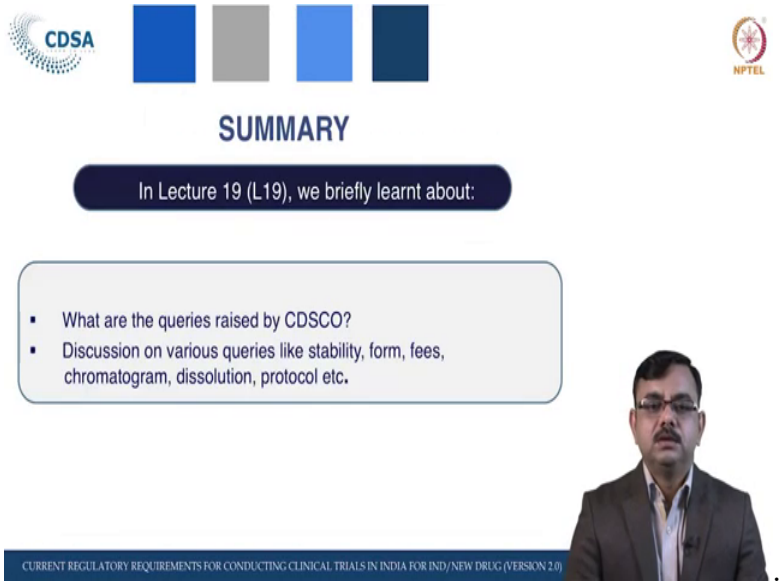

So, what we have learned from this topic let us have the summary. So, we have seen what is means the protocol, what type of applications, what type of CT applications are there; like a

new drug, subsequent drug, FDC, global clinical trial. Then we have seen whether it is approval is mandatory or not, further we have seen the different types of the deficiencies which are observed into the CDSCO expert committee or by the officers of the CDSCO.

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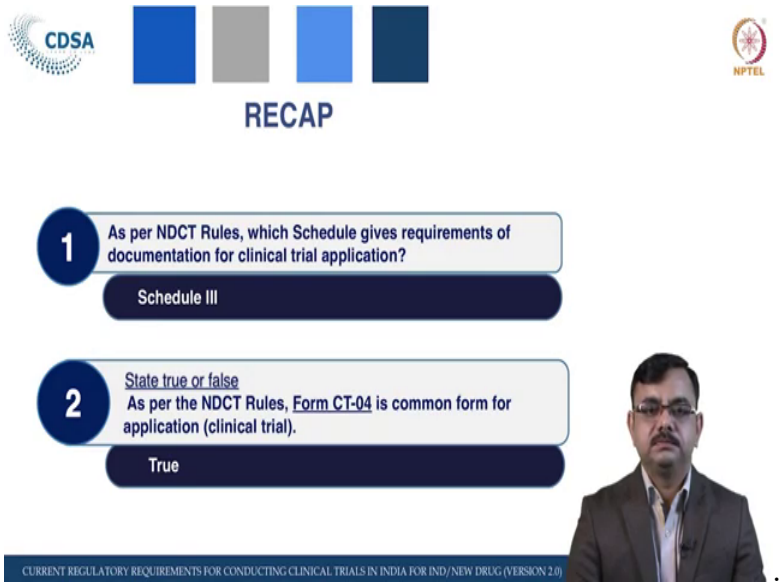

Now, it is time for you to give some reply to the questions to check whether you have attended it properly, whether you your attentions was there or not. So, the question for you is as per new drug and clinical trial rule; which schedule gives the requirement of documentation for clinical trial application? So, you have to mention the schedule. So, it is the schedule III which gives the requirement of document for clinical trial application.

The next question is, as per new drug and clinical trial rule, CT 4 is a common form of application for clinical trial. You have to answer it into the yes or no; so yes, it is a common

application, be it is a application for FDC, new drug or IND it is a common application. So, this is the quick recap.

And this is about the clinical trial protocol deficiencies. In our next lecture we are going to see what are the deficiencies or anomalies which the regulator generally find out at the clinical trial site or at the bioequivalence and bioavailability study center.

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So, till then take care and bye, we will see in next lecture.

Thank you.