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

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Lecture – 24
Tables Given in NDCT 2019 and it is Content

Hello friends, I am good to see you at the last stage and to the last lectures. So, this last lecture is about the tables given in New Drug and Clinical Trial Rule 2019 and its Content.

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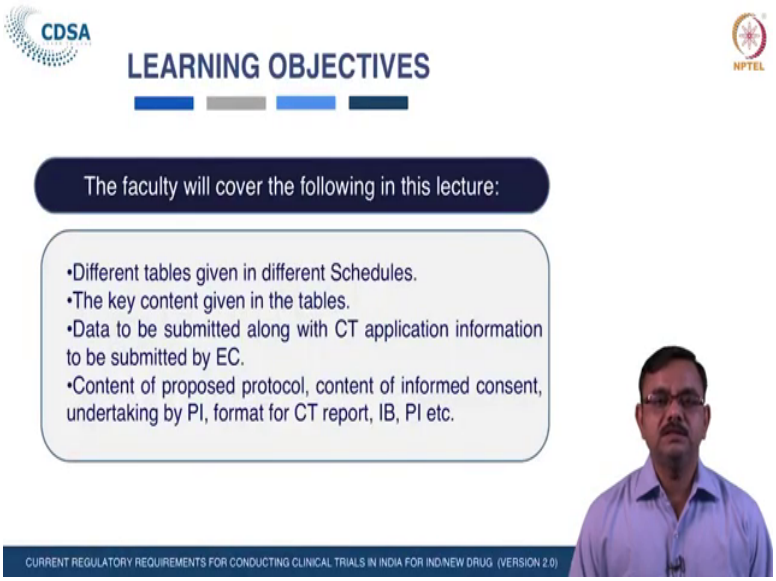

This is the most important lecture of our course because, if you have gone through all these lectures you might have seen that all the requirements like data to be submitted for the clinical trial, manufacture, import, all this data requirement has been given in these tables. And these

are these are the table which actually gives the requirement for submission of the any application. So, it is you know the we are giving the summary of all this.

So, that it would be at one place and you could identify the which document require for the which type of applications. So, the expected outcome from this lecture, you would be knowing that what are the different tables given in different schedules and which are these schedules, what are the different key contents in the tables.

Further those which we have not covered earlier for example, the data requirement for the phyto pharmaceutical, what are the content of the ICF, what are the content of the information brochure, what are the content of PI that is undertaking by the PI.

So, those which I have not covered we are going to cover in detail in this lecture and you will you would be knowing that. Then what are the data to be submitted along with clinical trial application ethics committee that though we have seen it in our earlier lecture, but again we will see here.

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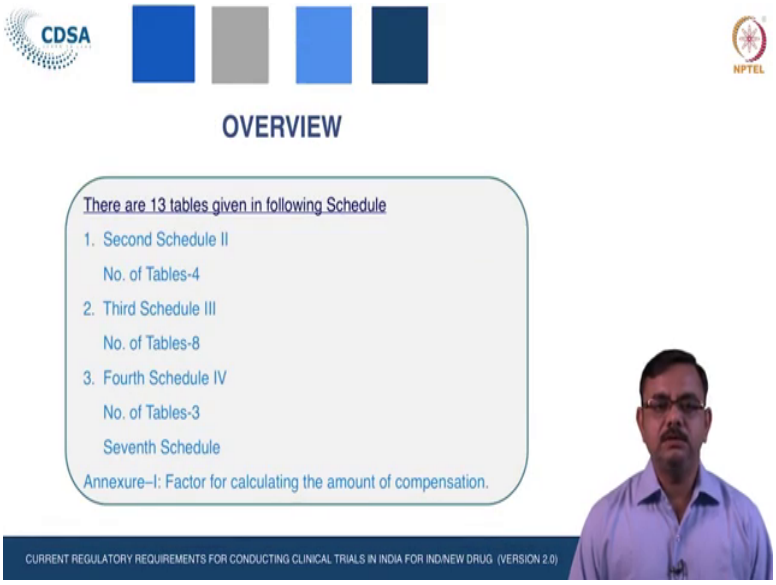

So, let us start with lecture 24. So, I would like to brief about this. So, there are 15 tables given in the 4 schedule of the New Drug and Clinical Trial Rules and these schedules are the second schedule as we know there are around 8 schedules, but the tables are given in only few of the schedules and these schedules has been enlisted here.

The second schedule it has total number of tables there are 4 numbers of tables, in the third schedule; there are around 8 different types of tables and the requirement given in the fourth schedule the number of tables given are 3. There is one more schedule that is the 7 schedule where in there is a no table, but one annexure has been given and then that annexure is related to the factor for calculation the amount of compensation, that will also.

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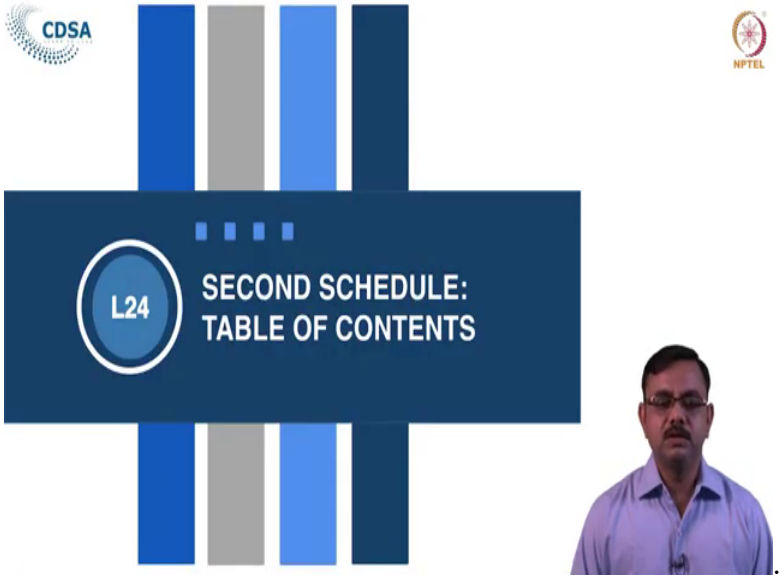

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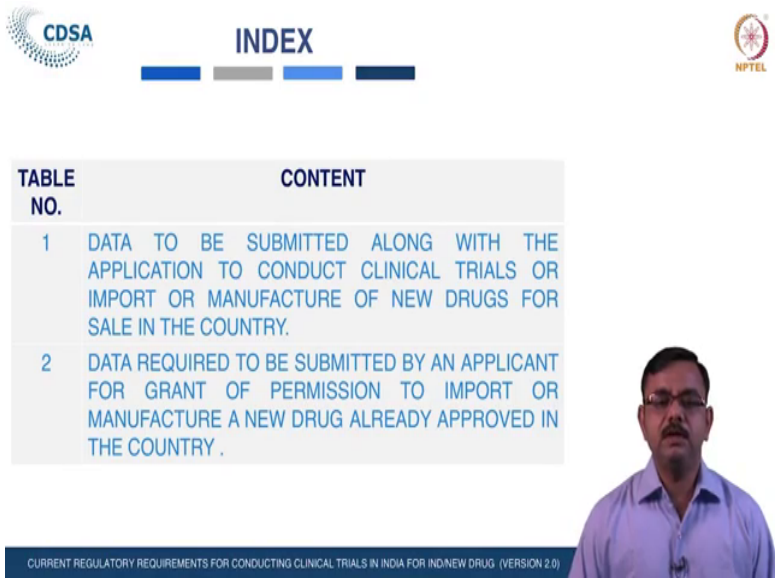

So, let us start with the first schedule of table of content and here it is a second schedule, which is related to the requirement and guideline for permission to import or manufacture of new drug for sale or to undertake clinical trial.

So, this is regarding the permission to import or manufacture or to undertake a clinical trial. So, in this schedule there are 4 tables; the first table is related to the data to be submitted along with the applicant application to conduct clinical trial or import or manufacture of new drug for sale in the country.

So, import and manufacture there is a separate lecture, we have seen that the second table is related to the data to be submitted by an applicant for grant of permission to import or manufacture a new drug already approved in the country that is we called as a subsequent new drug. So, this also has been covered in our previous lecture. The third is regarding data

required to be submitted by an applicant for conduct of clinical trial of an approved new drug with the new claim, new route of administration, new indication or nutrients.

So, what are the data to be submitted data required to be submitted by an application while conducting clinical trial for the drug which is already approved in the country that we will see in this schedule. The fourth table is related to the data to be submitted along with the application to conduct clinical trial or import or manufacture of a phyto pharmaceutical drug. So, this will see in detail. So, the first as I have mentioned data to be submitted by the applicant for the conduct of clinical trials study and which is for the import or manufacture.

So, we have a separate lecture on this so, I am not going to read all this if you wish you can see this, the introduction chemical pharmaceutical information related information related to the drug, information related to it is testing, then information related to the specification, validation, then data related to the formulation if it is a fixed those formulation then data related to the FDC then (Refer Time: 05:53) and compatibility comparative elevation, then stability study including photo stability first degradation, that is required to be submitted.

Then with respect to the preclinical animal pharmacological study animal toxicological study that are required to be submitted. Then if it is a phase three study, then data with respect to the phase one phase two study, that is also required to be submitted along with the published literature.

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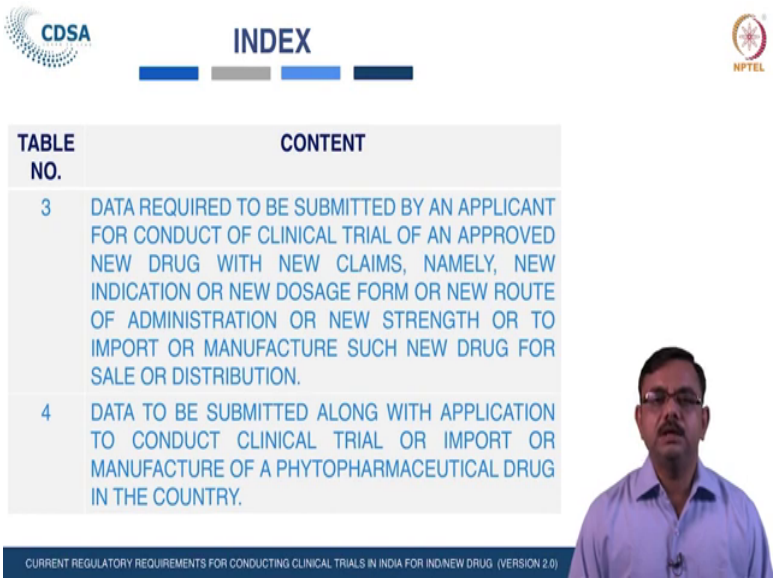

So, that is about the first table, I am not going in depth because we have already covered in another lecture. The table number 2; it is also covered in the other lecture and it is the data required to be submitted by an application for grant of permission to import or manufacture of new drug already approved into the country, means; we call it as a subsequent new drug.

So, in this case also the detail about the drug chemical pharmaceutical information detail about the dosage form and it is composition that is the stability data then what would be the package insert and the promotional literature, the specimen copy of that package insert and that required to be submitted. Here the BAB study and the dissolution study is required for the oral dosage form because the drug is already approved.

Now, it has just to establish whether it is efficacious or not. Then subacute animal toxicity studies also require if the dosage form is intravenous or in future and the injectables. Now

moving towards the table number 3; it is a data requirement and data required to be submitted by an applicant for conduct of clinical trial of an approved new drug with new claims.

As I have mentioned new dosage form, new route of administration and other for the purpose of import or manufacture of such new drug for sale in sale or distribution. So, in this case, the number and date of permission or license approved granted for the approved new drug. As this is the data to be submitted for the subsequent new drug it means that drug has already been approved.

So, details of the approval that has to be submitted, then why the new dosage form or new route of indication that therapeutic justification has to be given. Then again they have to the applicant have to give the chemical and pharmaceutical information to verify whether that is same or not including the chemical name, code name or any number proprietor name, generic name, the structure of the drug.

Then detail about the dosage form and it is composition is required to be given this test specification for active inactive moieties further the specification of finished product is also required to be given. And if it is a modified dosage form then as I have said the therapeutic justification. Why they are going for the modified dosage form that is required to be given.

The clinical trial data as referred in our clause one of the schedule and the regulatory status of the modified dosage form either in others in other countries. If it is a for example, if it is the tablet is approved and applicant is desired to manufacture a capsule then whether that type of that kind of you know dosage form or if it is a different strain then that different kind of strain whether it is available in the international market or not, that regulatory status has to be given.

Then propose package insert for that particular modified drug that is required to be given. Then we are moving towards a table number 4 of this schedule. It is related to the data requirement for the phyto pharmaceutical drugs.

So, we have seen the definition of the phyto pharmaceutical in our very initial lectures. So, it is a drug which is having a minimum 4 bio active ingredient. So, in this data requirement it has

been you know divided into the two part; the part a is a data to be submitted by the applicant is whatever the data the applicant is having and he has to submit that has been given into the part 1 and part 2 is related to the data generated by the applicant, means the information which is not available, but it has been generated by the applicant for the regulatory approval.

So, let us see the part first. Here the applicant is required to give the brief description or the summary of the phyto pharmaceutical drug for which he has applied then the published literature if any available that has to be provided with the application. Information on any contract indication or any side effects in the published scientific report irrespect of safety and pharmacological studies that is required to be submitted.

Where the process and uses are similar or same to the product known in traditional medicine or ethno medicine and where you know the where the process or usage is different from that known in traditional medicine. In such cases also the published literature is required.

Then if any side effect or adverse events for that drug known into the another market, that is also required to be submitted. Then what is the present usage of the phyto pharmaceutical drug to establish the history of usage the details of the product manufacturer then the quantity sold and extent of exposure on human population.

What we have what we are doing in case of the drug like PSUR that is periodic safety update the exposure we are getting from the applicant. The same here the applicant has to submit the quantum of the drug sold and the extent of the exposure. Then in this case also though it is a phyto pharmaceutical the human or clinical pharmacology information is required.

Then the pharmaco dynamic information if it is available, if it is the drug is already existing then the pharmacodynamic information. Then the monograph if published on the on the plant or product or extract of pharma phyto pharmaceutical, then the copies of all this publication with English translation has to be submitted.

In addition to this, the data generated by the applicant like identification of the authentication, source of the plant or it is a taxonomical identity which is given in the authorized the book or

which is you know it is approved by some well known taxonomies. So, name and the species of that plant is required to be given. Then morphological and anatomical description giving diagnostic features and photograph of the plant or part of further confirmation identity that is also required to be given.

See this is a something you know, different from the our new chemical entity where we do not ask for the photographs. Here the plant photograph is also required because that should be the real plant and that should be match with it is taxonomical drug taxonomical identity and the code and it is species also should have to be matched for it is correct identification.

So, the photo of photograph of that plant and that should be you know approved by the some known taxonomies. Then it is a natural habitat and geographical distribution of the plant also has to be mentioned whether the part of the plant used is renewal or destructive and the source whether the whether it is cultivated or whether it is wild. Then the season or time of collection, when it is a plant so, unlike the chemical entity it would grow in some certain specific season. So, the what is that season that the information regarding that season has to be given.

Source of the plant including it is a geographical location, season and also the time of collection. Then a statement indicating whether the species is any of the following where what I have mentioned here in this slide that has to be given in the undertaking or in the statement form the, the determined to be endangered or threatened under the endangered species act whether that plant is mentioned in this act or not. Or there is one you know CITS so, we call it as a CITS Convention or International Trade in endangered species of wild fauna and flora. So, whether that enlisted in the CITS or not that has to be given.

Whether it has entitled a special protection under the Biological Diversity Act 2002, so that also has to be mentioned. If the species is having any genotypic or chemotypic ecotypic variability of the species, that is required to be given. Further, the list of grower or supplier that required to be given who are the supplier who are the cultivator of the plant, then the harvest location growth conditions stage of plant growth, harvesting times, collection, washing after the harvesting and for the processing the collection, washing, drying, storage

condition, how to handle the drug and how to handle it while transportation the precaution to be taken that has to be submitted.

Then when it is in to the manufacturing procedure, then what are the processes or manufacturing procedure the applicant is going to follow that with respect to grinding polarization of the plant material and saving for getting uniform particle size the details of the slew and the slew number that is required to be submitted along with application. Further with respect to the chemical and analytical testing the details about the specification like the foreign matters the total ash contained in the powder then ICD insoluble, ash pesticide residue heavy metals and other chromatographic detail is required to be submitted.

The applicant is required to give an undertaking to supply the specimen sample of plant duly labored and photocopy of the certificate of identity confirmation issued by qualified taxonomies along with drawing of the photographs. As I have mentioned he has to ensure the continue, supply of this same specimen sample. And that sample has to be approved by the qualified taxonomist.

Then in the manufacturing the process of extraction and subsequent fraction nation if they are there, the detail of that required to be given. And detail processes involved and the steps involved, that is also required to be given like a extraction then solvent residue test, physico chemical test, microbial test or the chromatographic finger profile, phytochemical reference markers. So, that everything regarding the testing that has to be submitted.

Characterization of the purified extraction, then test for identification what are the tests implied for the identification of the drug that also has to be covered. Further here also we required the animal toxicity and the safety data that is as per the as per given in this table number 4. Regulatory status; as we like as we see it in to the in case of the chemical entity, the same here is also required. And in case if the phyto pharmaceutical is already available in the market, then the data related to the post marketing surveillance that is also required to be submitted.

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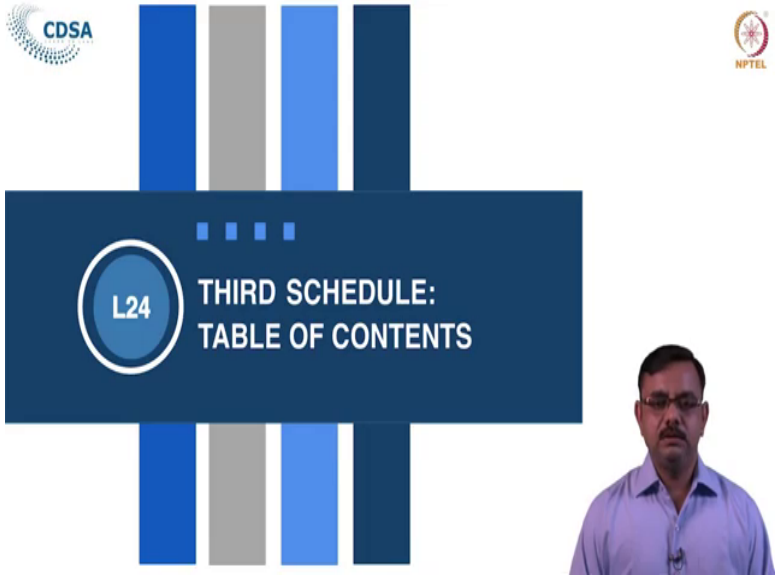

Let us move toward the third schedule and the third schedule it is a conduct of clinical trial.

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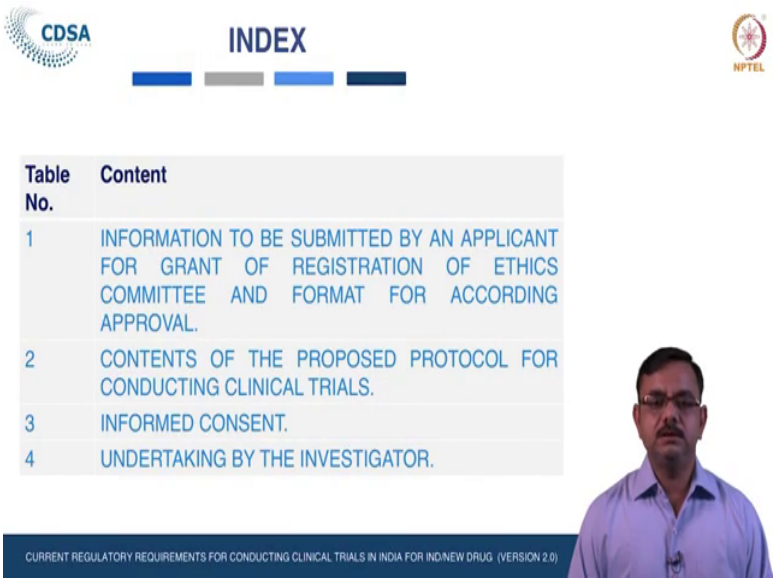

So, it contains around 8 tables. This is the schedule which is having the large number of tables. The table 1 is related to the information to be submitted by an applicant for registration of the ethics committee.

So, the ethics committee registration we have seen in detail in our other lecture. The second table related to the content of proposed protocol for conducting the clinical trial this also we have seen in our previous lecture. Informed consent is in table number 3, we will see it in detail, then table number 4 undertaking by the investigator this is also not covered anywhere.

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So, this will also see in detail data element for reporting SAE in a clinical trial or in a BAB study. Then table number 6 is structure content and format for clinical trial report. This is also covered in one of the separate lecture. Table number 7 is the elements for the investigator brochure and table number 8 for the prescribing information. So, table number 1, table number 2 and the table number 6 we have already covered in another lecture. So, we will just see we will not go into the detail.

So, this is our table number 1 data requirement and the data to be submitted for the registration of the ethics committee. So, detail about the Ethics Committee, detail about the Ethics Committee member and details about the composition details about the procedure what they are going to follow. And the series of all the employees their contact number their detail

the site specification that everything has to be given that we have seen in our previous lecture. So, I am going to skip this.

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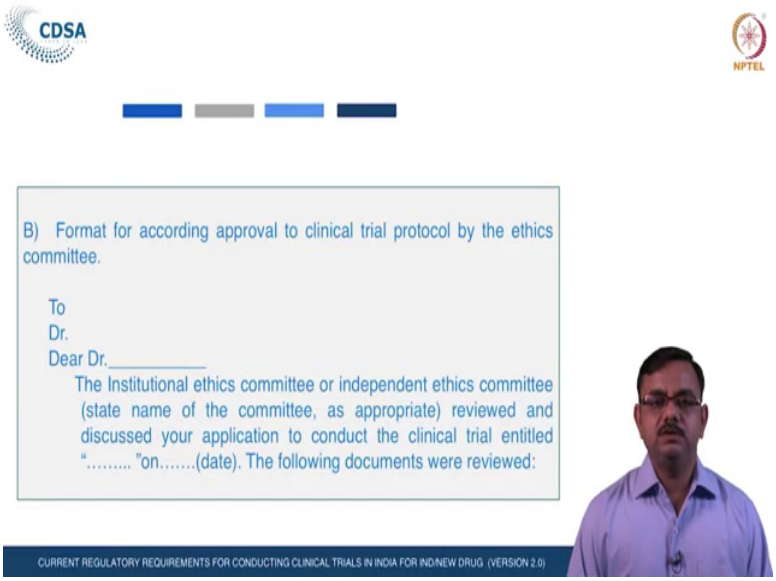

And also we have seen in this the format for according approval to clinical trial protocol by Ethics Committee. So, this is the format this also we have seen. The table number 2 is the content of the proposed protocol for conducting a clinical trial. So, we are having separate lecture, we have seen in one of the separate lecture what are the content of the proposed protocol.

So, this is with respect to study the details of the drug detail of the study including it is protocol, design and the background, the preclinical data, then the study population inclusion exclusion criteria, how to assess the study who would be the principle investigator that has been given in that schedule.

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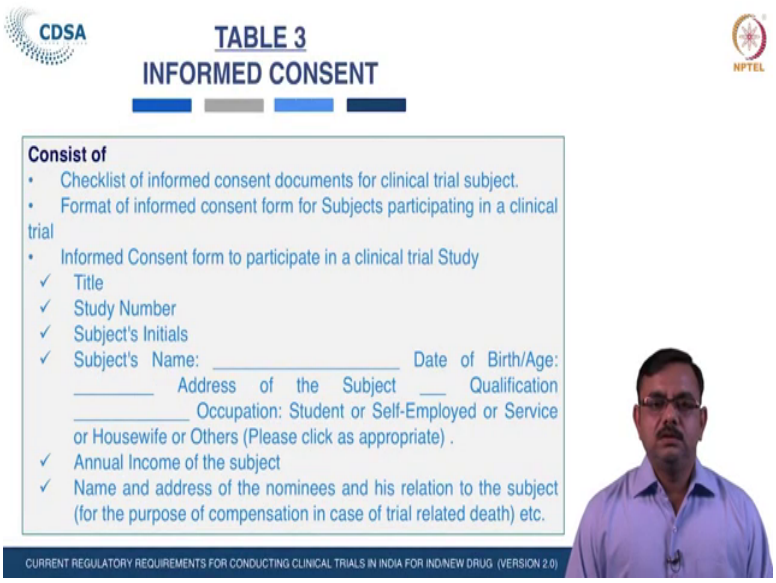

Now, let us move towards the table number 3, which is a very important document and it is the informed consent document it is in the two form that is informed consent form and informed consent patient information. So, here in the table number 3, it has been actually divided into 2 parts; the first is checklist of informed consent document for clinical trial subjects. So, here in the some essential elements has been given I would just read this essential elements.

So, these are there is a requirement of statement that the study involves the research and explanation of the purpose of the research. So, that statement should be there that study is involved only the research and it is explanation for the purpose of the research. Then the next element is expected duration of the participation whether it is fifteen days 10 days that has to be mentioned into the informed consent form.

Then description about the procedure to be followed, description of any reasonable foreseeable risk or risk compared to the subject that is also required to be given. And what are the benefit the subject would likely get that is also required to be given. Then disclosure of specific appropriate alternative procedure in case of if it is a phase three clinical trial or if it is a trial with the patient and then what are the alternative procedure there are having that is also required to be given.

Statement describing extent to which confidentially record identified subject will be maintained that should be also the part of the informed consent form. Then trial treatment schedule. So, how many times he is going undergoing the treatment that that schedule is required to be mentioned. Statement describing Financial Compensation, Medical Management. So, in case of any injury or any SAE or in case of the death so, the what would be the policy and whether the financial compensation management medical management.

So, regarding that the statement has to be given. Then the explanation about whom to contact. So, in case of any injury or in case of any SAE so, whom to contact the detail information like a phone number, fax number that is required to be given. Then responsibility of subject on participation. What the subject has to be cooperated with and what is his responsibility that should be given in ICR.

The statement that participation is voluntary this is very important that statement has to be given and it should not be the undue influence to the subject and he has to give the that should be a voluntary and freely obtain informed consent form. Statement that there is a possibility of failure of the investigational product. The PI has to clearly mention and it has to be clarified that there may be a possibility of the failure of the investigational product.

Then a statement that in the case of placebo control trial, placebo administered that shall not have any therapeutic effect that statement has to be given or any other information pertinent to the study that is required to be given to the ICR. There are some additional elements, additional elements which may be the statement may be required for foreseeable circumstances

under which the participation of the subject may be determined by the investigator without his or her concern.

So, additional cost to the subject that may result from the participation in the study in or the consequences of the subject decision to withdraw from the research and the procedure for you know for the termination of participation by the subject. Or the statement that the study subject representative will be notified in timely manner if significant new findings developed during the course of the research which may affect the subject willingness to continue participation that is that will be provided. Then approximate number of subjects enrolled in the subject that can also be disclosed.

So, the second part of this informed consent is the format of informed consent form. For subject participating into the clinical trial. So, this is the format it has been given into the New Drug and Clinical Trial Rule. So, this format has to be followed by every CRO site and pi while giving the informed consent form. So, here it is informed consent form to participate in clinical trial study, the title study number, subject initial and this details has to be given.

The annual income of the subject is also very you know significant and essential as there should be no exploitation of the poor people that is why these annual income column has been mentioned here, then these details where the study is going to conduct what is the name of the PI detail of the pi to whom to contact. So, these things has to be covered.

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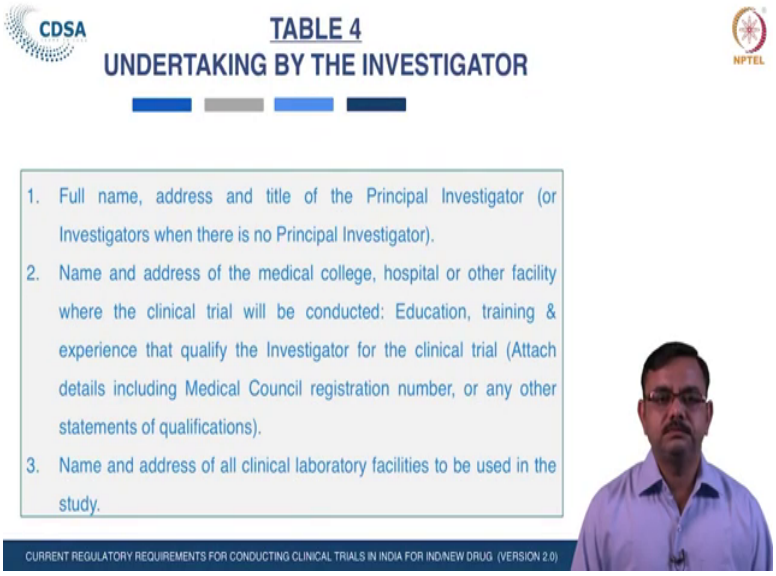

The table number 4 it is related to the undertaking by the investigator. So, in the undertaking by the investigator the full name address title of the PI or it is investigator when there is a no PI. So, that detail has to be mentioned, then where the conduct is to be conducted the details of the medical college, hospital that is required to be provided. Through the undertaking, then name and address of all clinical laboratory facilities to be used in the study then name and address of the Ethics Committee which is going to continue the approval name of other members who are the co or sub investigators.

Protocol title and study number that is to be mentioned. The commitment has to be given by the investigator that he has reviewed the clinical protocol and now he is agreeing that it can is agreeing with the content of the protocol. And further the commitment regarding with the

agreement of the content he is agreed to conduct the study in accordance with the current protocol and the GCP guidelines

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Further the commitment has to be given that is he will personally conduct and supervise the clinical trial site clinical trial at his site, then he should agree to inform all the trials subject that the drugs are being used for the investigational purpose and he has to ensure that the requirement relating to the obtaining informed consent Ethics Committee, review approval as you know specified in our New Drug and Clinical Trial Rule.

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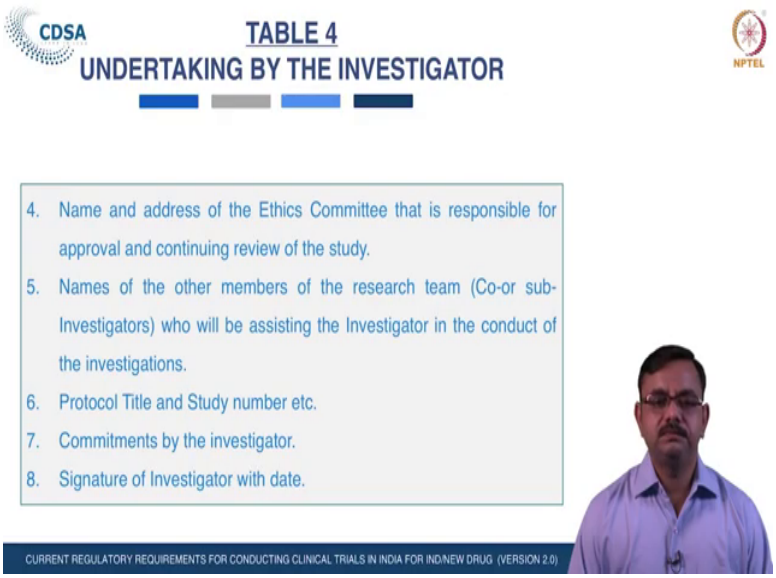

He should agree to report the sponsor all the adverse experience that occur during the trial finally, he has to give you in writing that he has read and understood the information in the

investigator brochure including potential risks and the side effect and he is agreed to ensure that all the associate colleague employee assisting in the conduct of the study are you know qualified and well experience. He has to give the agreement and he has to give the consent that he will maintain adequate and accurate record of all the audit inspection which is done by the sponsor or Ethics Committee or Central Licensing Authority. Further the commitment with respect to the promptly report of all the adverse event and SAEs that has to be given.

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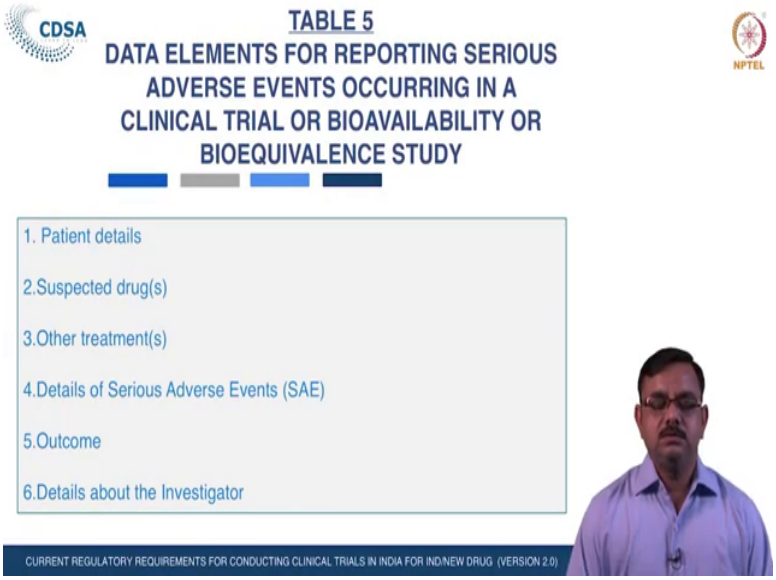

So, let us move toward the table number 5, data elements for reporting SAE. So, this we have I think not covered in any of our lecture. So, these are the content of reporting the serious adverse event. The patient details including the initial and other relevant identifier that is that has to be given like a hospital or out patient OPD patient and then his gender age height that is required to be given. Then what was the suspected drug the generic name of that drug the

dose dosage form indication route of administration by using the drugs which have adversely affected. The details of that drug has to be given.

Apart from this, whatever the other treatment provided that the details of that other treatment provided as is required to be submitted and the important is detail of the SAE like a full description of the event including the body sight and the severity as well as the criteria for considering the report as a serious why it is a serious that is required to be given. And in addition to these description of the reported sign and symptoms whenever possible describe a specific diagnosis for the event that is the start date or onset of event and the stop date the de challenge and re challenged information.

So, that should be then while conducting the trial the who was the investigator and the detail of the investigator that is also required to be given.

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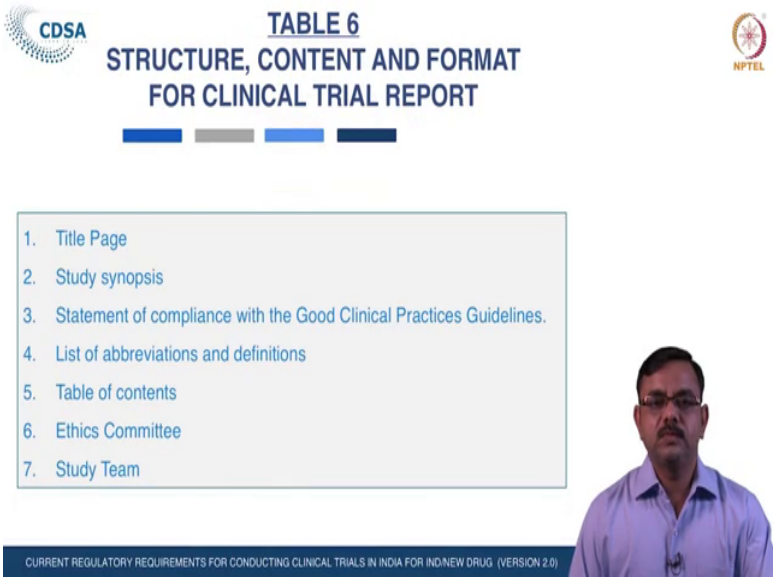

Now, let us move towards the table number 6; it is a structure content and format for clinical trial report. So, as I have mentioned this has been covered in one of our lecture which is exclusively for how to report a clinical trial.

So, in the report the detail of the study the detail of the protocol what was approved, then what was the investigational plan, how they have evaluated the study, what are the result, what are the references they have made then what was the investigator brochure then brief summary has to be given highlighting the significant, physical, chemical, pharmaceutical, pharmacological, all this summary has to be submitted along with the along with the protocol. The protocol also should have this non clinical information what they have conducted.

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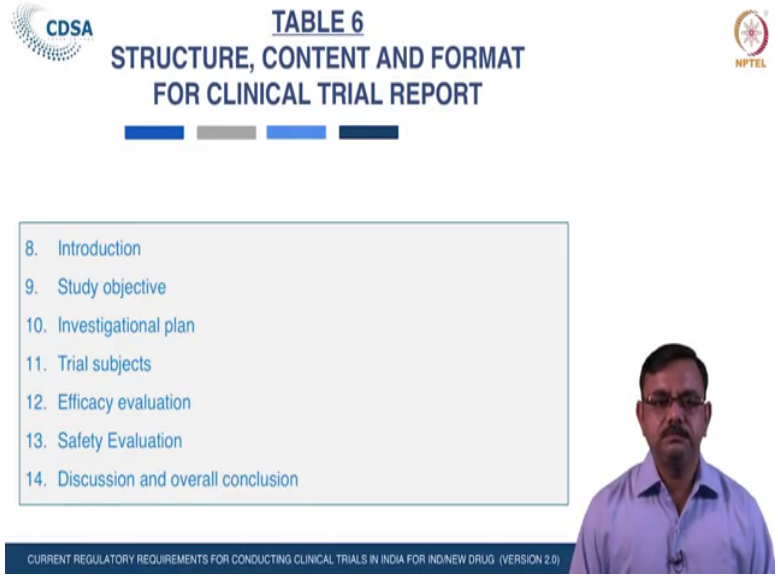

So, this we have already seen in one of our lecture and now we will see the table number 8 which is for the prescribing information.

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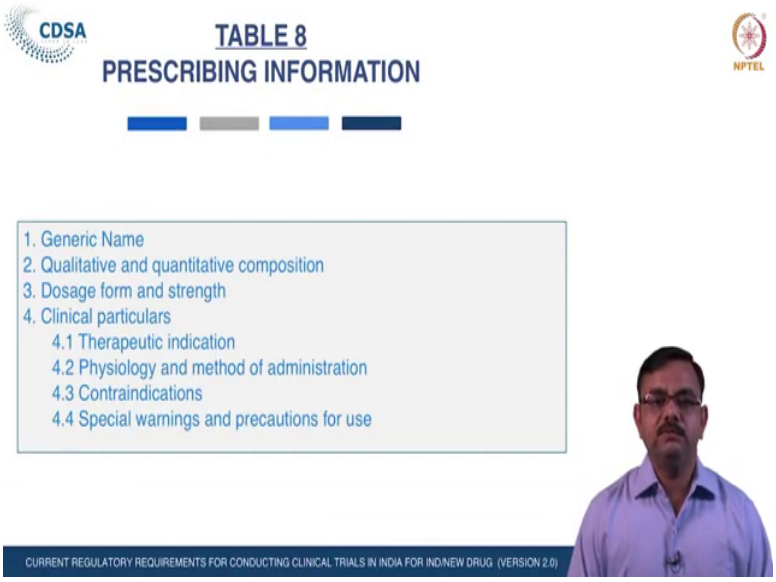

What should be the content of the prescribing information? So, in the prescribing information there should be a generic name then qualitative and quantitative composition of the drug, dosage forms strength, the clinical particulars like therapeutic indication the contraindication, physiology, drug interaction is required to be given.

Then the pharmacological properties including mechanism of action pharmacodynamics pharmacokinetic, then non clinical properties like animal toxicology, pharmacology, pharmaceutical particulars like incompatibility if it is there on the shelf life that is also given in this table.

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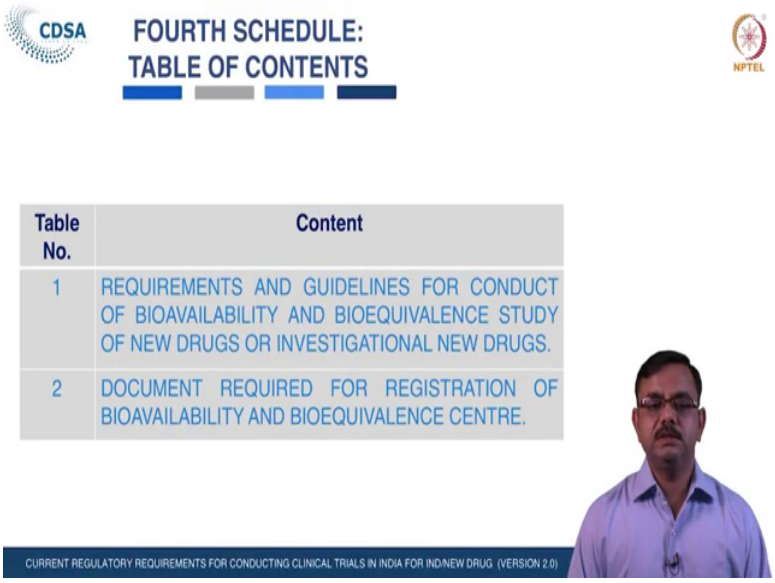

The fourth schedule it is the requirement and guideline for conduct of BAB study of new drug or investigational new drug. So, here there are again 3 tables; the first is for the registration of BAB study centre, second is data information for grant of permission to conduct BAB study and third is data information required for grant of permission to conduct BAB study of new drug already approved in the country that we call subsequent new drug.

So, these are the content and these are the information required to be submitted for the registration of the BAB study centre. So, I think I have covered these in one of the lecture which is related to the BAB study centre. We can have a look of this the name and address of the organization then document regarding legal identity then list of sops and the list of employees the infrastructure related documents and details of the ethics committee they are going to have the registration from that then facility maintenance record that is required to be

submitted. The table 2 is the data and information required for grant of permission to conduct BAB study of new drug or investigational new drug.

So, this is the regarding you know, the chemical and pharmaceutical information detailed introduction, then permission for the permission it is required to submit the published report regulatory status as what we have seen in the case of the clinical trial it is also more some more somehow it is more or less you know it is a similar. Because, BAB is also one of the clinical trial.

So, here also you are required to give the regulatory status what is in the other countries then prescribing information undertaking by the pi study synopsis of the BAB, then certificate of analysis from the 3 branches of the subject and for conducting the bioequivalence study with the with reference to you know cytotoxic drug or the special type of drug.

For example, hormonal preparation, narcotic and psychotropic substances in healthy humans. Scientific justification with a special emphasis on safety of subject with proper risk mitigation strategies should be submitted when there are special type of a drug. And in case if regulatory guidance is available that the that they have to provide a copy of the same.

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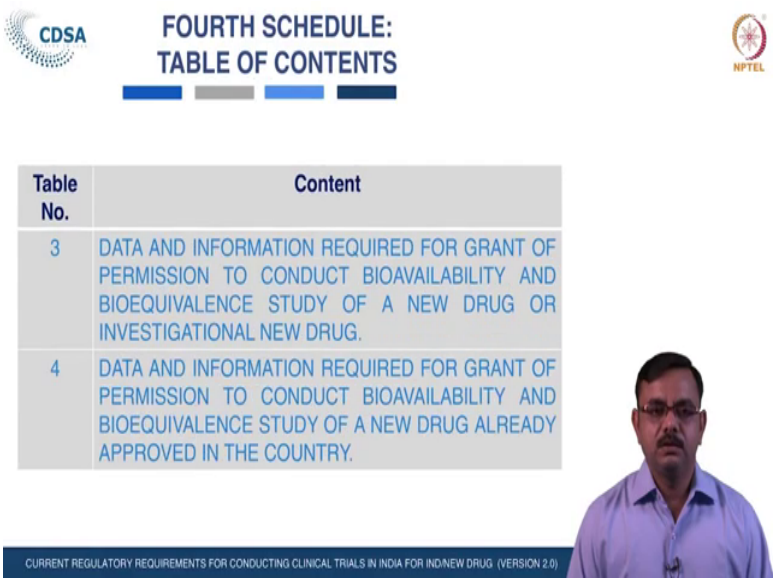

Table number 3 is data and information required for grant of permission to conduct BAB study of new drug already approved in the country.

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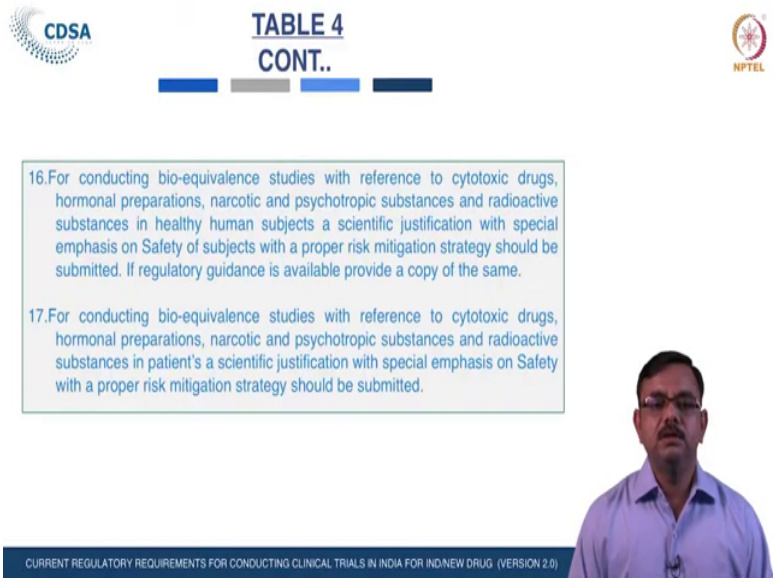

So, if the drug is already approved, then some data can be abbreviated or omitted, otherwise the whatever the data we have seen in previous slide it is it will be the same data. So, you can see this is COA and details of the drug details of the study conducted.

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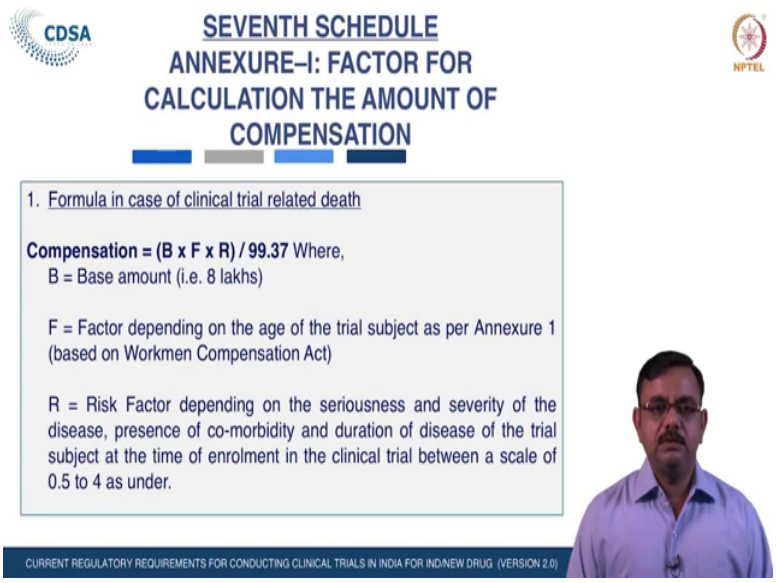

The last we are having the 7th schedule and it does not have any tables and the data requirement. But this is also important and it has not been covered in our previous lecture, that so it has been captured here. It is actually annexure and this annexure contains a factor for calculation of the amount of the compensation.

So, various formulas has been given like a formula you can see here formula in case of clinical trial related, That is B into F into R divided by 99.37 a B is the base amount factor. And the risk factor and the risk factor how to calculate that has also within the grading scale has been given in this annexure this grading scale is from 0.5 to 0.4. 0.5 in case of the terminally ill patient and terminally ill is expected survival is not more than the 6 months so.

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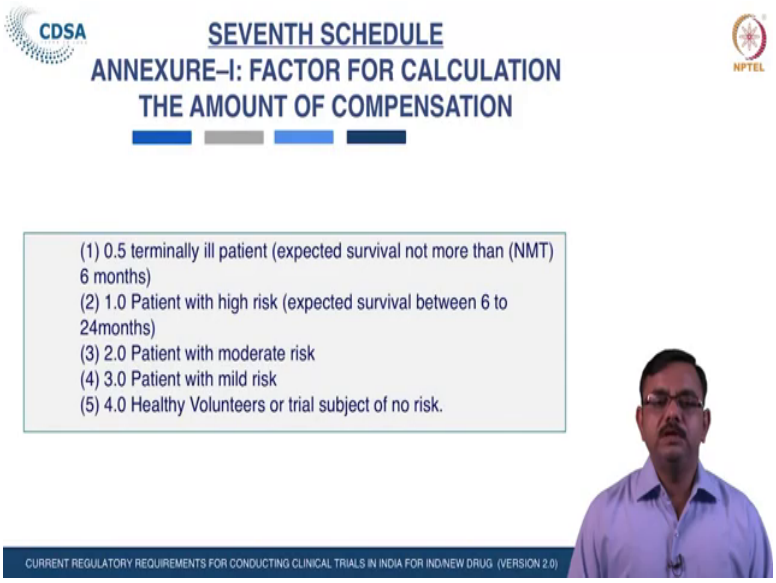

In this case what are the factors to be considered that is a 0.5 is the factor to be considered. The second is the factor one when patient with a high risk and as there is you know the if the expected survival between the 6 to 24 months, then we can say it is with the higher risk and the factor to be considered is a when subsequently it has given factor 2, 3 and 4. If the subject is healthy volunteer or trial subject then there is a more risk and the factor is high.

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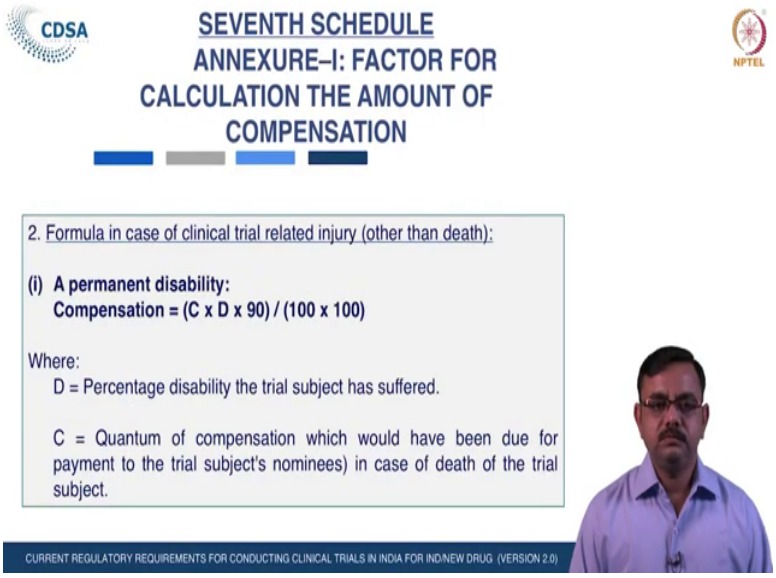

Similarly, the formulas has been given for the injury or death related to the clinical trial. When it is a permanent disability, when it is congenital anomaly or if it is a life threatening disease or if it is a reverse SAE, then different formula as I have shown in this slide that has to be taken into consideration while calculating the compensation.

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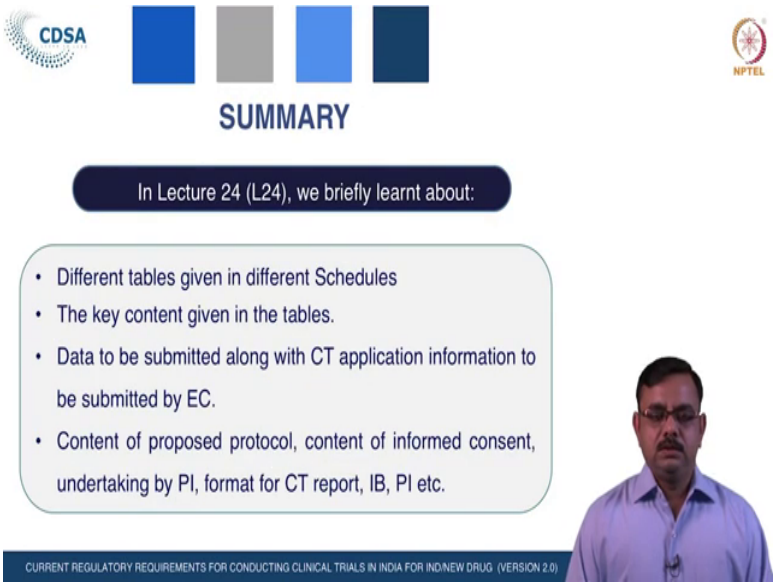

So, this is about the tables given in the New Drug and Clinical Trial Rule. Let us have a recap. So, what we have seen in this very lengthy lecture that different tables given and the different requirement with respect to the application with respect to the submission of data for the BAB study protocol with respect to the BAB study centre protocol with respect to the conduct of clinical trial for new drug conduct of drug which is already approved with respect to the Ethics Committee.

Then further we have seen that what are the elements in the undertaking by the PI what are the elements into the informed consent form then the informed investigator brochure and the other things.

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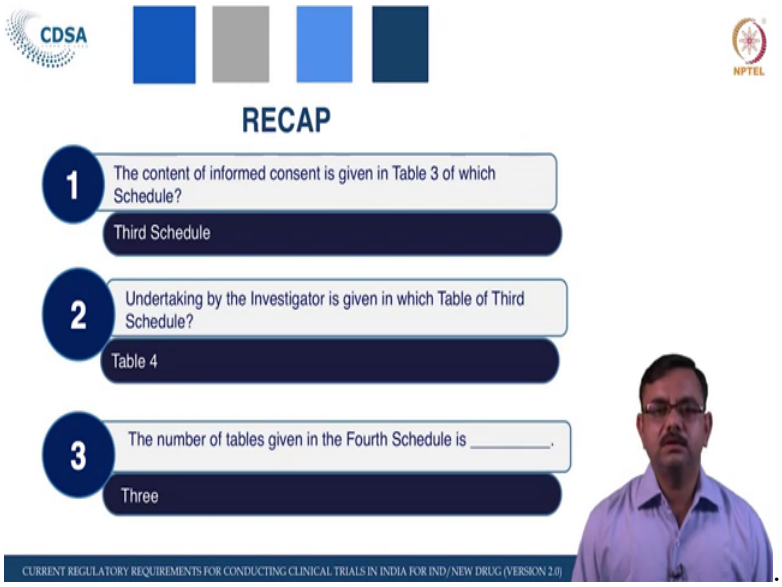

So, let us have questions for you. So, the first question the content of informed consent given in table 3 of which schedule. So, you have to you have to answer the which schedule is there for the content of informed consent. So, it is the it is a third schedule. The next question is the undertaking by the investigator given in which table of third schedule. So, the first you have been asked the schedule now here the table you have to mention. So, it is a table number 4 of the third schedule. The number of table given in fourth schedule. So, you have to answer how many numbers of tables are given.

So, there are three tables. So, this is what about our all the course. And I hope you have enjoyed all the lectures and if you have any queries with respect to any of the lecture then you can give it into the feedback or we can share it to the forum and certainly we will try to

address your query in a very proper way and in a regulatory manner and as per the New Drug and Clinical Trial Rule.

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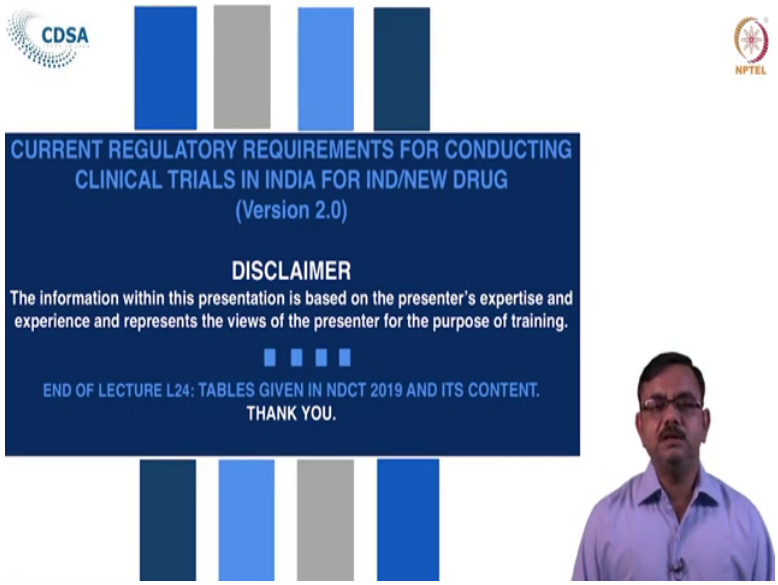

So, enjoy this all the topics and take care and bye.

Thank you.