Current Regulatory Requirements for Conducting Clinical Trials In India

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Lecture – L8
Schedule Y & Related Rules- Overview

Hello friends, welcome back once again to the course Current Regulatory Requirement for Conducting Clinical Trials in India, lecture 8 schedule Y and Related Rules its Overview.

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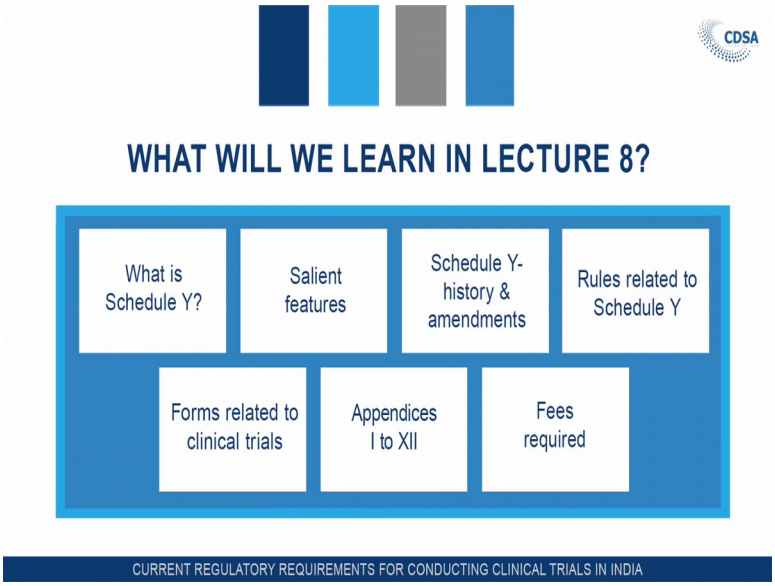

What will we learn in lecture 8? So, we will learn, what is schedule Y? Its salient features then, schedule Y related rules, fees required, appendices that is I to XII related forms and related rules. So, this is the outline of lecture 8.

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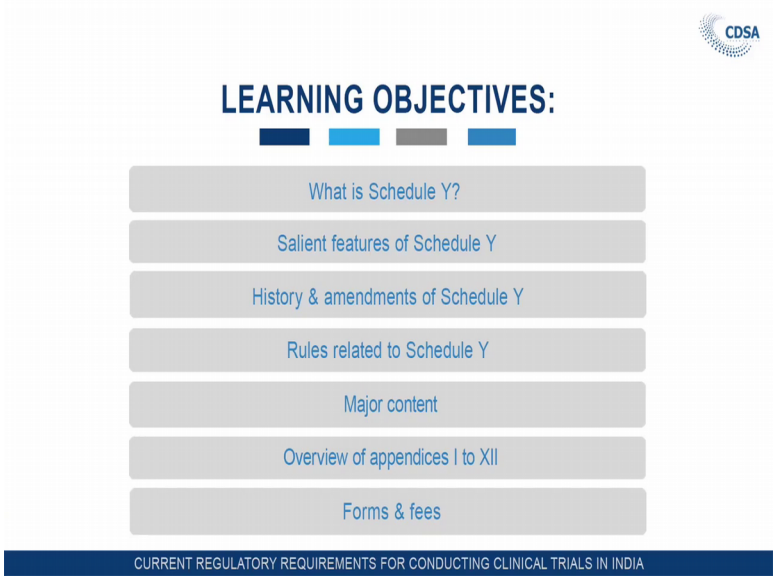

It is related to schedule Y and related rules. So, as I have said first we will see, what is schedule Y? Then, salient feature; schedule Y, its history and amendment rules related to schedule Y then, what are the major content of the schedule Y then, overview of this appendices that is appendices I to XII and related forms require for the clinical trial application and permission and the relevant fees.

Dear friends, in almost all the lectures we have seen somewhere or other mentioning the schedule Y. Schedule Y, is required for conducting clinical trial; the data required to be submitted as per the schedule Y, the forms mentioned in schedule Y. So, now, it is the time to see, what exactly the schedule Y means and where it is given? Whether it is in drug and cosmetic act or whether it is in the rules. So, let us see, what actually the schedule Y is.

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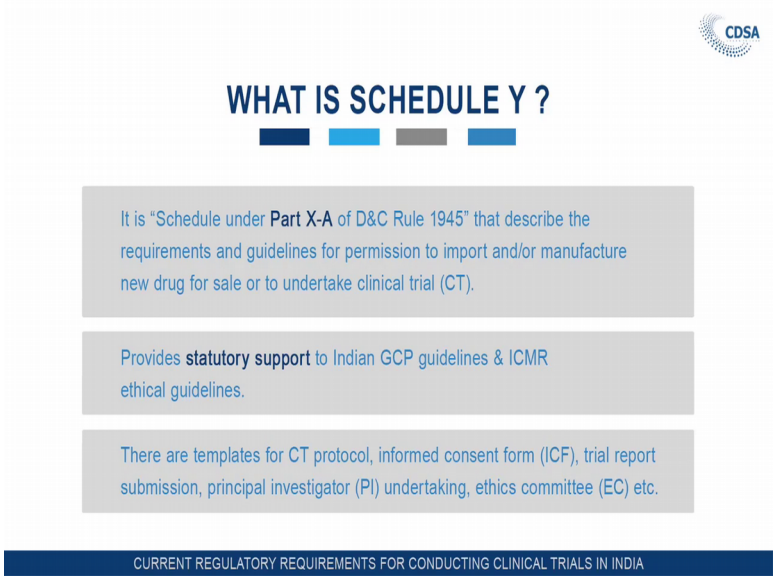

We have seen in our previous lecture that, act and rules. The rules are divided into 19 parts. Schedule Y is under part 10 A of drug and cosmetic rules 1945. What it is? It describes the requirement and guideline for permission to import and or manufacture new drug for sale or to undertake clinical trial. Means, we have seen that before the manufacture applicant has require to undertake a clinical trial for the new drug. Similarly, for the import of the new drug; it has to be undergo first to first, to the clinical trials. So, schedule Y it provides statutory support to Indian good clinical practice guideline and ICMR bioethics guideline. As this is in rule; it is the statutory. Guidelines are for the better clarification and the rules these are somehow mandatory.

So, in this schedule Y, there are templates are given for propose a clinical trial protocol. How to submit the proposed protocol? Then, how to report the protocol then, what is ICF? What are the contents of ICF? Then, trail reports, submission, package insert, ethics committee, the composition that are given in the schedule Y. Let us see, the salient feature of the schedule Y.

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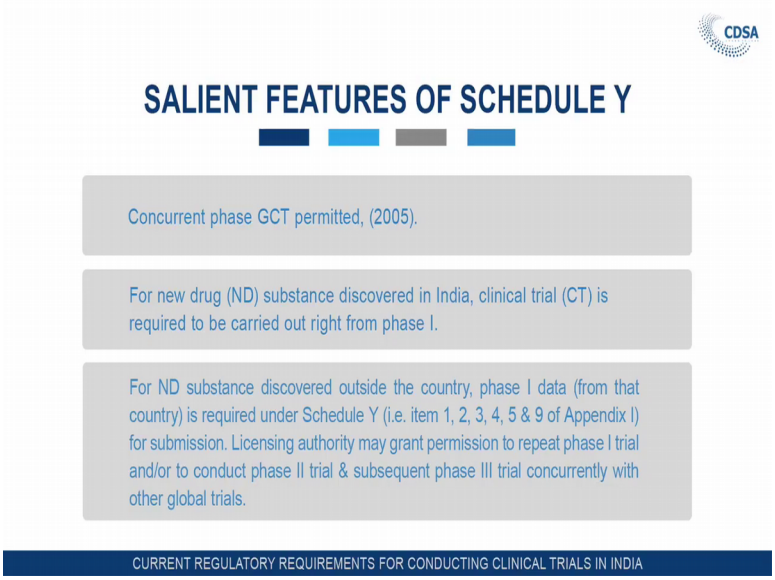

So, the things which are not covered under the appendices given in schedule Y, we try to summarize all these things here in the schedule Y salient feature. So, the concurrent phase GCT permitted, under the schedule Y. So, this was the amendment in 2005 that one can go for the concurrent phase of the global clinical trial. For new drug substance discovered in India, clinical trial required to be carried out right from phase I. See, if the drug is discovered in India after pre clinical trial, it require to conduct all the phases of clinical trial that is from phase I to phase III and subsequently phase IV.

What is the status for the drug, which is not discovered in India? So, the new drug substance discovered outside the country that is not in India. Phase I data, phase I data from that country where it has been discovered as required under schedule Y has to be submitted. That data is as per the schedule Y and; what is that data? It is mentioned under the schedule Y at 1, 2, 3, 4, 5 and 9 of appendix. Licensing authority after seeing that, the data may grant permission to repeat phase I trial.

So, it is very important to repeat phase I trial and or to conduct phase II trial. And then, subsequently phase III trial and if require phase IV trial concurrently with other global trials. So, it means for the drug substance to be marketed in Indian market the phase III trial are required to be conducted.

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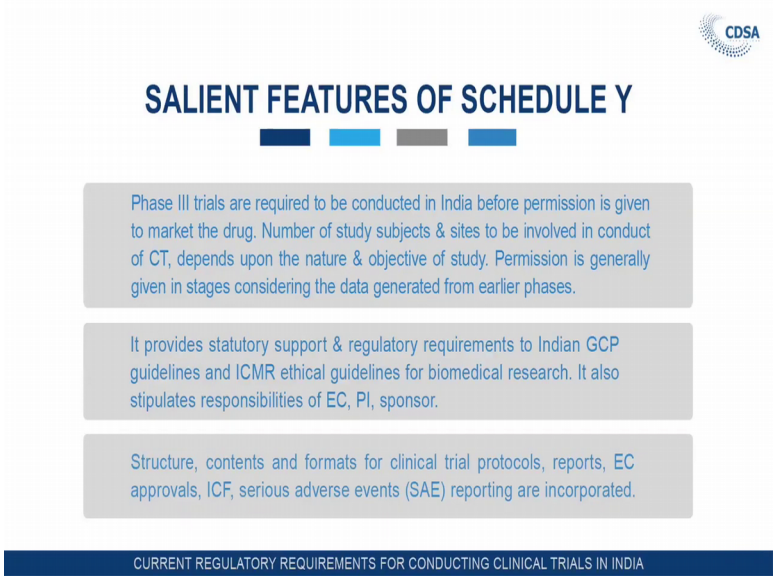

The number of subject and the number of sites involved in these phases are not mentioned here and it is depend upon the nature and objective of the study of clinical trials. The permissions for the phase I, phase II and phase III these are generally given in stages considering the data generated from earlier phases.

If the phase I is successful with the positive result then, they are allowed to go for phase II and then, subsequently phase III and phase IV. We have seen that schedule Y it is a, it gives a statutory support and regulatory requirement to Indian good clinical practice guidelines and ICMR ethics guidelines for biomedical research. Stipulate; it also stipulate responsibilities of ethics committee then, PI then, sponsor. It also gives the structure content and format for clinical trial proposed protocol then, the report then, the format for ICF then, how to report SAE? Then its time period, ethics committee approval, its composition, that have been given in the schedule Y.

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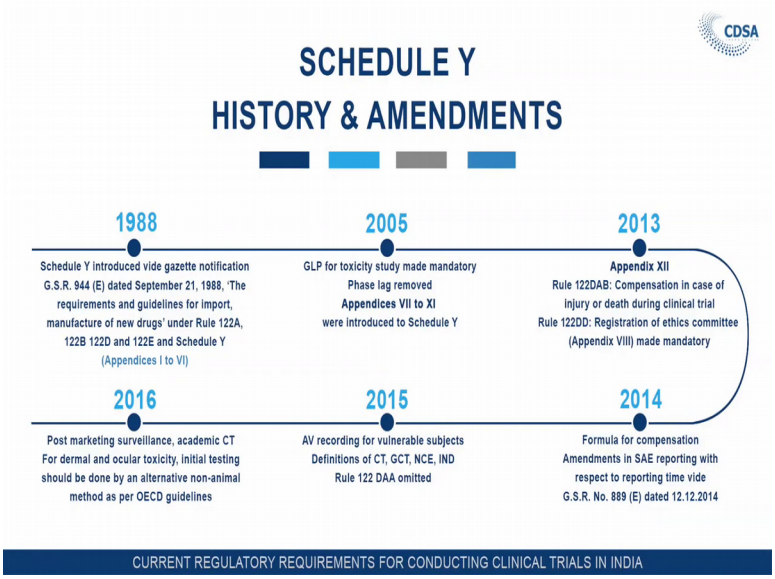

Let us see, where from it has started? So, the schedule Y history and amendment; before 1988, we have seen earlier in our lecture also. Before 1988, there were no rules and regulation for the new drugs. There were no schedule Y and no new drug definitions. So, in 1988, government of India, ministry of health and family welfare introduced schedule Y via gadget notification that is GSR 944 E dated 21st September, 1988. And as we have seen it is related to the requirement and guideline for import manufacture of new drug under rule 122 A B D and 122 E.

We will see these rules in our subsequent slides. At that time the appendices I to VI were present; subsequently, in 2005 some amendments made in this schedule Y. So, for example, GLP for toxicity has made mandatory for animal toxicity studies. Then, phase lag was earlier there; means, we cannot do the concurrent phase that was removed. Then, appendices further VII to XI were introduced to the schedule Y. In 2013, appendix XII was added. Side by side rule 122 DAB that is for compensation, in case of injury or death during clinical trial was added. Then, rule 122DD that is registration of ethics committee, which is given in appendix VIII; that is also made mandatory.

In 2014, formula for compensation has been devised. Though, it is not in the schedule Y, it is available in our CDSCO website. And there are two three formulas for the compensation. Then, amendment in SAE reporting with respect to reporting time vide G.S.R number 889 dated 12.12.2014. So, earlier there were the SAE reporting, but the timelines not mentions. It means the within how much time the ethics committee has to report the SAE to the sponsor to the licensing authority. Within how much time the

sponsor has to report the same SAE to the licensing authority, that has been revised and that is mention according to this amendment.

In 2015 audio video recording for vulnerable subjects made mandatory. Then, rule 122 DAA omitted and in the 1 rule 122DA, the definitions of Clinical Trial, Global Clinical trial, IND, NCE that has been given under the explanation. In 2016, post marketing surveillance was added. We have seen in our lecture first and second that academic clinical trial is non-regulatory and does not require permission from the regulatory authority. That has been given in 2016 in the same rule. For dermal and ocular toxicity, initial testing should be done by alternative non-animal method as per OECD guidelines.

This has been added like a dress test and other where, there is alternative method animal should not be used. So, this is about the schedule Y history and its amendments. Now, we will see, what are the rules which are related to it?

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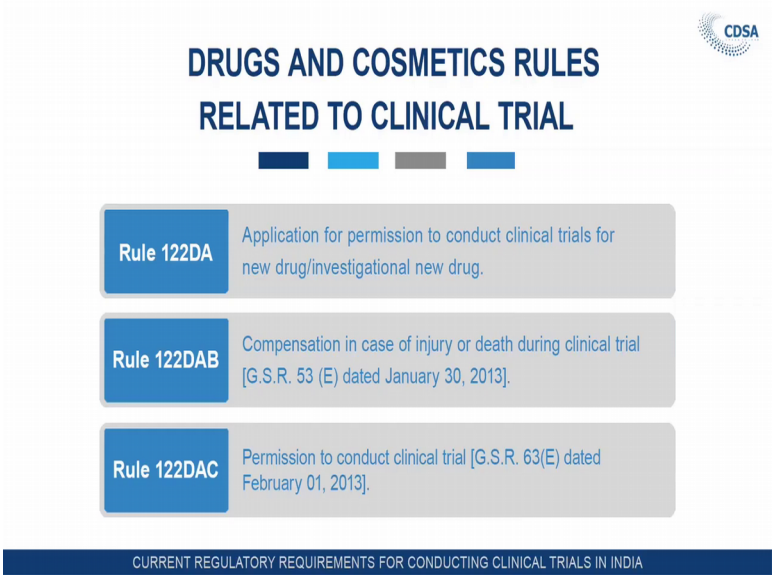

Rule 122DA, application for permission to conduct clinical trial for new drug or IND. So, as per this rules were to apply for the clinical trial permission. Then, rule 122DAB, it is related to the compensation in case of injury or death during clinical trial. This has been added vide G.S.R. 53 in 2013. Rule 122DAC is permission to conduct clinical trial according to G.S.R. 63 in 2013.

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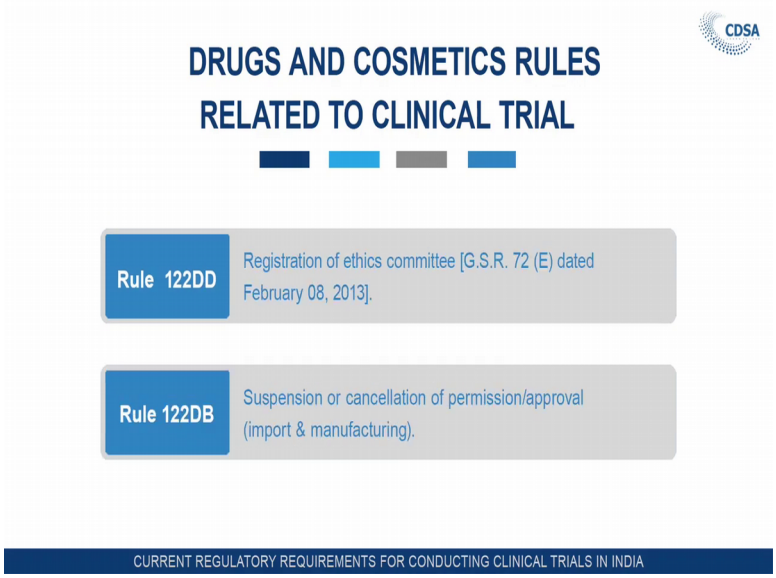

Rule 22DD is a registration of ethics committee G.S.R. 72 dated 8th February, 2013. rule 122DB, suspension or cancellation of permission or approval for the import and manufacturing. If the licensee fail to comply with the conditions or fail to comply with the schedule M or the schedule Y conditions; then, suspension can happen or cancellation is also possible according to the rule 122DB. Now, let us see, what are the content of the schedule Y?

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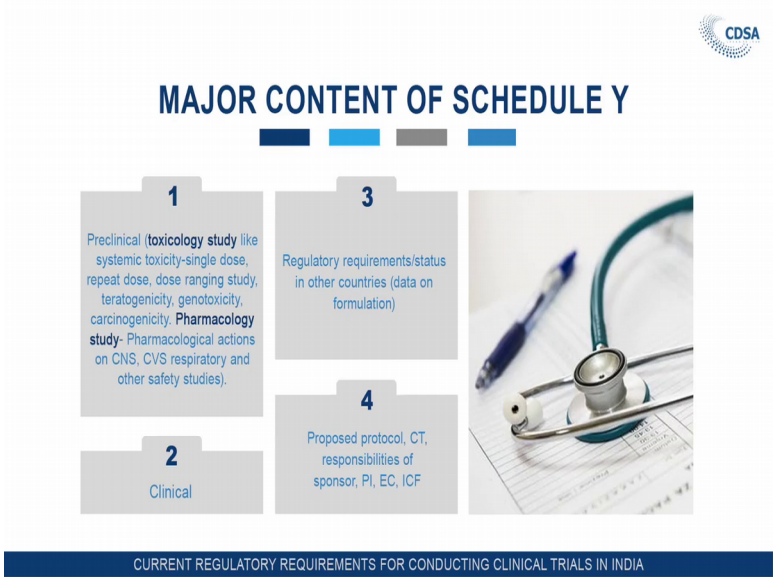

Schedule Y, it gives a comprehensive content of whatever require for the permission of the clinical trial. So, what we require for the clinical trial and what we require for the application of new drug? The first we require, the pre clinical chemical and formulation data. Then, in pre clinical, in the schedule Y, it is mention in two aspect that is toxicological study like a systematic toxicity study, single dose study, repeat dose study, dose ranging study then, teratogenicity study, genotoxicity, carcinogenicity; all these study, all these studies are mentioned in the clinical.

Then, the second part that is pharmacological safety study in the animal; the safety study that is pharmacological action on the CNS, CVS respiratory and other safety studies are have been mentioned. After, the pre clinical then, the clinical trial that is as we know the clinical trial phase I, II, III; so, these are also mentioned in the schedule Y. Then, the next regulatory requirement that is whatever the data related to the drug and dosage pump that is extra dose, strain, propose indication.

Then, chemistry point of view; its molecular weight, molecular formula then, identification of these drugs; that data also have to be given in form 44. That form 44, we will see in our subsequent slides. Then, as I have mentioned propose protocol of clinical trial, how to submit this protocol? How to make this protocol? Then, the responsibilities of ethics committee then, responsibilities of the sponsor then, responsibilities of the principal investigator than format of the ICF; these are all the major content of schedule Y.

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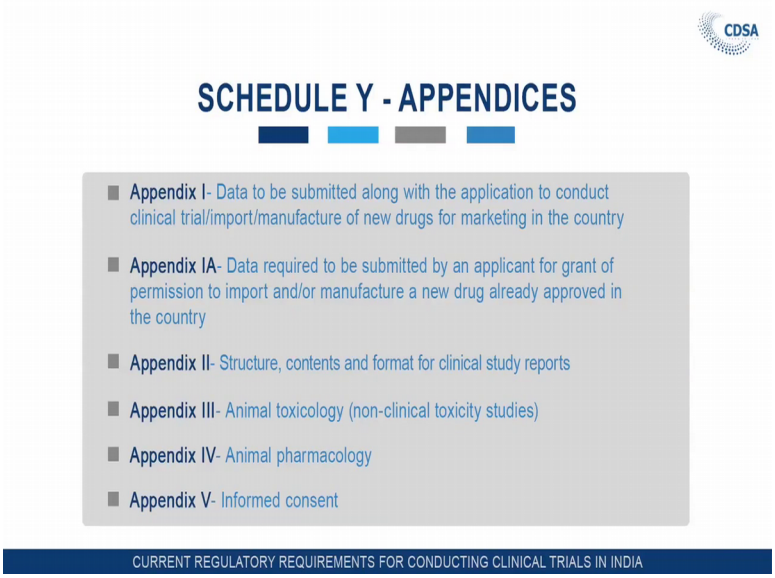

Now, let us see, what are the appendices given in the schedule Y? So, in schedule Y contains twelve appendices. Let us see one by one. appendix I is a data to be submitted along with the application to conduct clinical trial for import or manufacture of new drug for marketing in the country. Means, the data whatever required for the import of manufacture of the drug, which is a new drug that has to be submitted according to the appendix I.

In this appendix, it is also mention that the data is required; if you say for example, the data is required with respect to the animal toxicology. Then, it is mentioned that data is required as per the appendix III. If it is a pharmacology then, appendix IV; likewise it has been mentioned. So, this is the brief about all, the appendix I and it is require for the new drug.

Appendix IA, it has been added lately. Then, it is a data required to be submitted by an applicant for grant of permission to import and or manufacture new drug already approved in the country. So, the difference is only that the data is required for the drug which is already approved in the country. Some data has been abbreviated because the drug is already approved in the country; for example, pre-clinical studies, animal safety animal toxicity; these data may be abbreviated. And the data required for the approved drug is as per appendix IA.

Appendix II, it is a structure content and format for clinical study report. Means, how to propose a study? In what format, how the design should be there? Then, what are the content? That structure and content everything has been given in appendix II. Then, appendix III, it is animal toxicology non clinical toxico studies. As we have seen the animal toxicology studies that is systemic toxicity and dose ranging, all the studies and the number of animals, the number of the species that is given in the appendix III. Appendix IV, is animal pharmacology is about the safety of the drug in animals. Then, appendix IV is informed consent in case informed consent form, what are the elements that is given in the appendix V?

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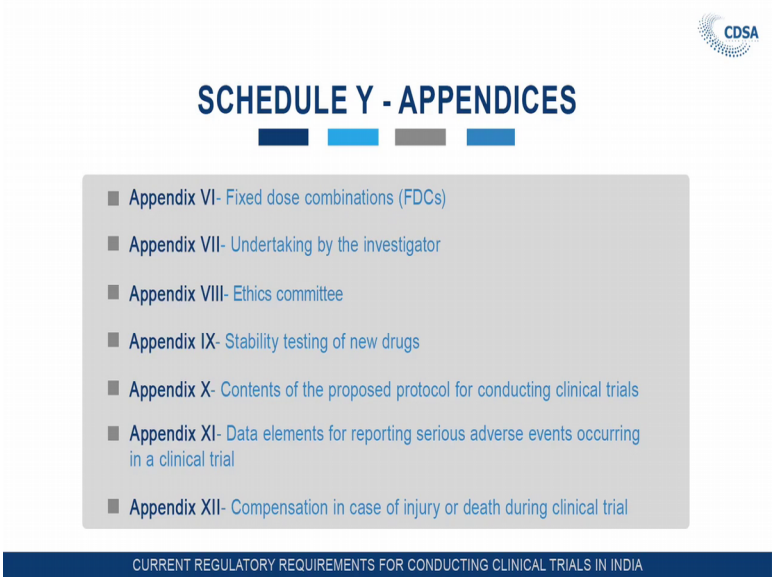

Appendix VI, is the fixed dose combination drug. So, here are the types of FDC has been given. It has been divided into the four. We will see in detail in our next lecture all these appendices. This is the overview of the appendices. appendix VII, it is undertaking by the investigator. So, what are the elements that have been given in this undertaking? How the in the undertaking has to be given by the principal investigator or his subordinate investigator that is given in the appendix VIII?

Appendix VIII is about ethics committee. So, the composition of the ethics committee than the responsibility how much should be the quorum? And everything about the ethics committee given in the appendix VIII; appendix IX is regarding the stability testing of a new drug. What should be the criteria for stability? The accelerated stability study, real

time study, what are the condition of the temperature? What are the condition of the humidity? That has been given in this appendix IX. appendix X is a content of the proposed protocol for conducting clinical trial that is the proposed protocol for conducting clinical trial. In the appendix II, we have seen that is the structure and content for the reporting the trial. This one is the study has been completed; then, they have to report according to appendix II in that format. This is the appendix X; it is for the proposed protocol.

Appendix XI is data elements for reporting SAE offering in a clinical trial. So, what are the data to be captured, while reporting the SAE? That has been given in the appendix XI. appendix XII is compensation in case of injury or death during clinical trial; so, how to and where to report this SAE? It has been given in the appendix XII.

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Now, let us see the, how to apply, where to apply for the application for clinical trial import or manufacture of a new drug? So, here is our site.

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That is a cdscoonline.gov.in; it is a SUGAM website; that is an e-governance solution for the CDSCO. The web link is given here. So, once you open this page, it will gives you the option application for submission then, the track of status of the application then, grant of NOC. So, under these headings you can see where your application after applying lies. So, first of all you have to register yourself on this site. You have to create your login id, username. Then, after creating then, you have to apply for your application. Once apply; then, you can see the status of your application.

The stages are given here that is after submission. Then, there is a review and after the review the grant of NOC may be given. If there is a query then, the applicant will get a query online. So, this is our site; you can apply here. Now, let us while applying on these sites, which forms require to be uploaded.

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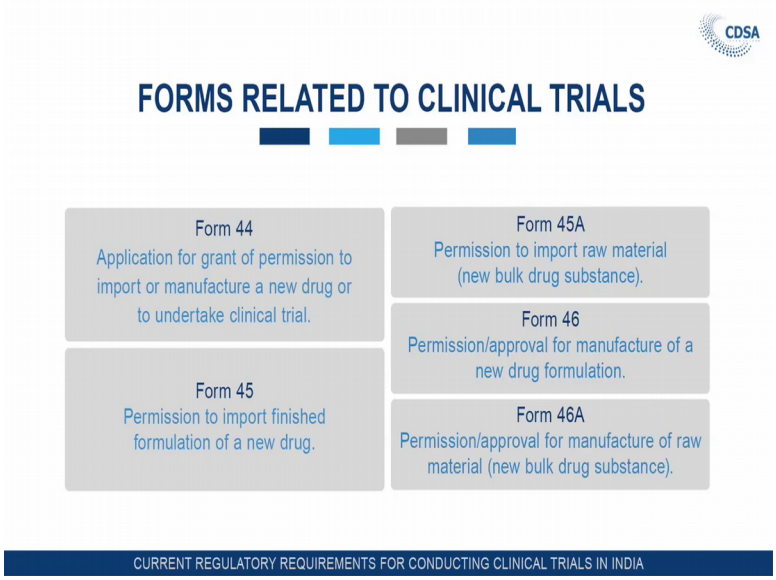

So, the first is Form 44, which is application for grant of permission to import or manufacture a new drug or to undertake clinical trial. This is the form in which, you have to apply the; it is the legal form. The content and everything we will see in the subsequent slides. Then, Form 45 is a permission to import finished formulation of a new drug. In Form 45, you will obtain permission to import finished formulation. Form 45A is permission to import raw material. If you would like to import raw material that is API or bulk drug; then, you get a permission in Form 45A.

If it is A; then, it is a; you can understand or remember it is for the API. Form 46 is a permission approval for manufacture of new drug formulation. So, the Form 46 is for the related to the manufacture of new drug. You have seen Form 45, it is for permission to import finish formulation, Form 46 is a permission for the manufacture of new drug formulation. Form 46A is a permission or approval for manufacture of raw material that is API or new bulk drug substances. These are some of the other forms for the testing and analysis purposes.

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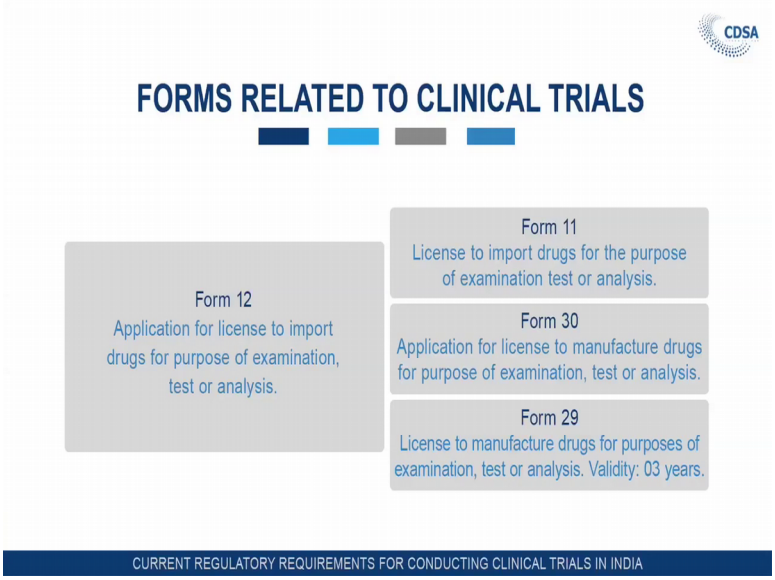

Form12 is a application for license to import drug for purpose of examination test or analysis. This also includes the clinical trial purpose. So, if somebody would like to import that drug for the clinical trial purposes. Then, he has to take permission and he has to apply in form 12. It is called the test license. In form 11, you will get the license to import a drug for the purpose of examination test or analysis. Form 12, you have to apply; you will get the Form 11. Form 30, application for license to manufacture drug for the purpose of examination test or analysis.

So, form 12 and form 11 these are related to imports. And form 30 is application for the manufacture. If somebody would like to manufacture; this test drug to be used in the clinical trials study or preclinical study. Then, he has to apply in this form. form 29, you will get the license to manufacture; that is a test license we call it. Test license to manufacture drugs for the purpose of examination test and analysis. The validity of these licenses that is from Form 12, 11, 30 form. Form 11 and Form 29 is three years; 12 and 30 are the applications. So, now I am coming to the next slide.

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Let us see the, application its format. So, this is as per the rule 122 A, B, D, DA, DAB and these rules are applicable. This form 44 is application for grant of permission to import or manufacture new drug or to undertake clinical trial; we have seen it. So, these are the content. First, you have to mention the name or the company whatever it may be along with the date. Hereby, apply for grant of permission for import and or clinical trial or for approval to manufacture new drug or fixed dose combination or subsequent permission of already approved new drug. So, you have to click, you have to strike through whichever is not applicable.

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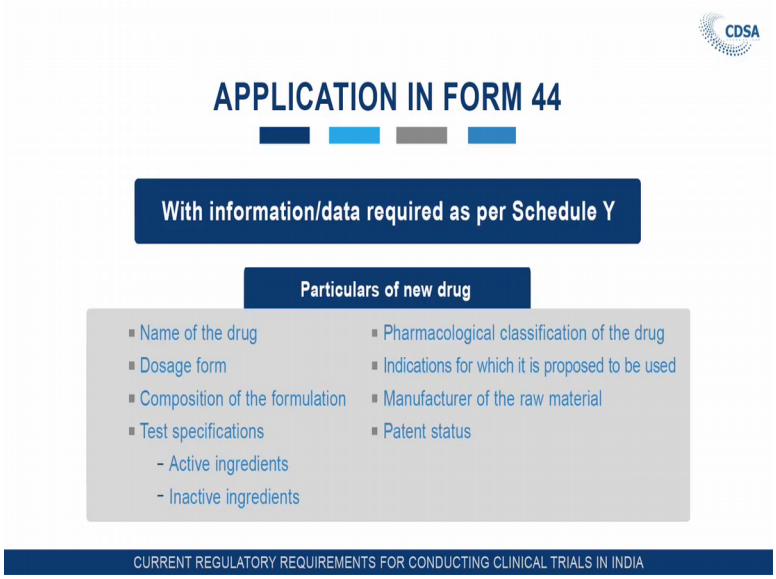

And the necessary information required is given here; that particular of the drug. That is name of drug, its generic name then, dosage form that whether it is in the form of tablet, capsule, suspension. Then, composition of the formulation; what are the excipients? What are the diluents and the active constituent?

That you have to mention; test specification, what I have said? Active ingredient, inactive ingredient that also I have to be submitted; then, pharmacological classification of the drug, indication for which proposed to be used; for which indication the trial is proposed or the drug is to be reported; that also has to be given. Then, manufacturer of the raw material, if the application is for the manufacturing of the formulation; then, who is the manufacturer of raw material that also has to be given.

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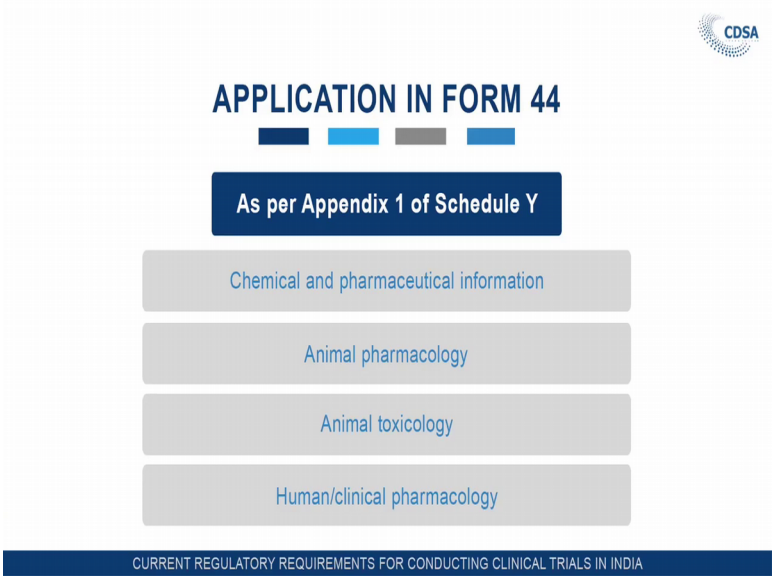

Then, data as per appendix I of schedule Y, we have seen the appendix I data required to be submitted for the new drug. Then, chemical and pharmaceutical information regarding the structure, molecular, weight and other things; then, animal pharmacology that is a safety in animals, animal toxicology we have seen. That has to be submitted.

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Then, human clinical pharmacology that is phase I, II, III exploratory clinical trials, confirmatory clinical trials phases I, II, III whatever the data. Then, some special studies bioavailability, bioequivalance, dissolution and stability data that also required to be submitted.

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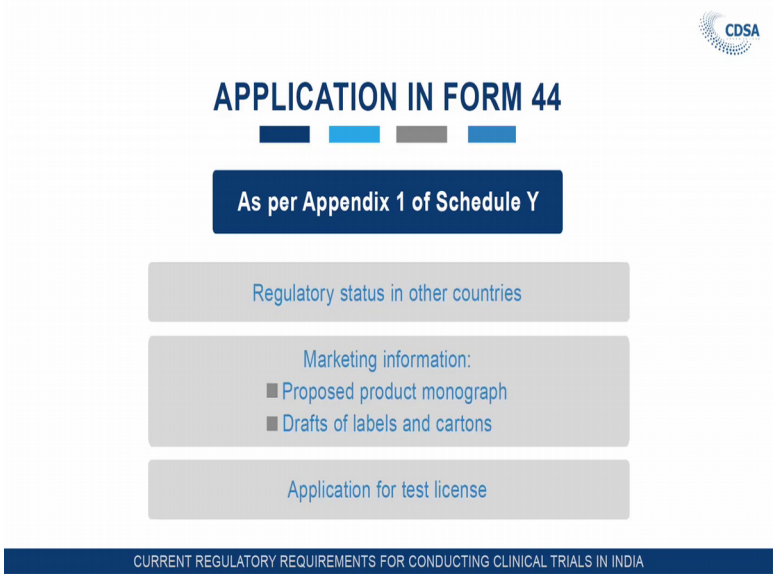

Then, the regulatory status in other countries; whether the drug is approved in other countries, whether it has been manufacture, whether after the approval whether it has

been banned, whether it has been prohibited or withdrawn that regulatory status also will help the regulator for its convenience.

Then, marketing information like a proposed product monograph then, draft of label and cartoons; propose a product monograph and draft of label. That label will also be approved by the licensing authority. That should contain whatever the propose indication dose, how to take it in guidance for the physician. That draft label also, how to be submitted? Application for the test license; so, if somebody would like to manufacture or import then, application for test license is to be submitted.

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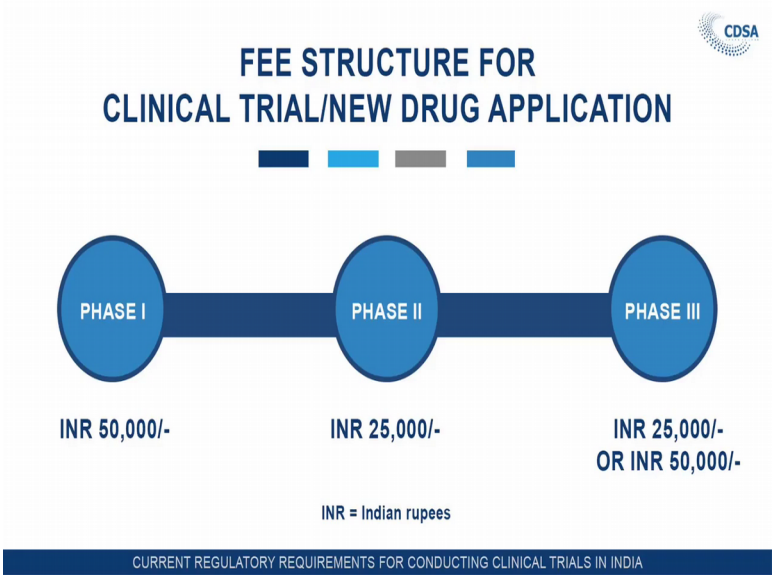

Now, let us see, what are the fees requirement as per the drug and cosmetic act and rules there under? So, this is the fees structure for clinical trial new drug application. If the drug has been discovered in India, it has to be go through phase I and the fees for the phase I is 50,000. Then, phase II, it is a 25,000 and phase III is also twenty five 25,000.

But in case, if the drug has been manufactured or approved in other countries. And now, somebody would like to import it and conduct the phase III; then, the fees required is 50,000. So, this is about all the schedule Y and related rules. Now, is the time for the questions and to check the memory.

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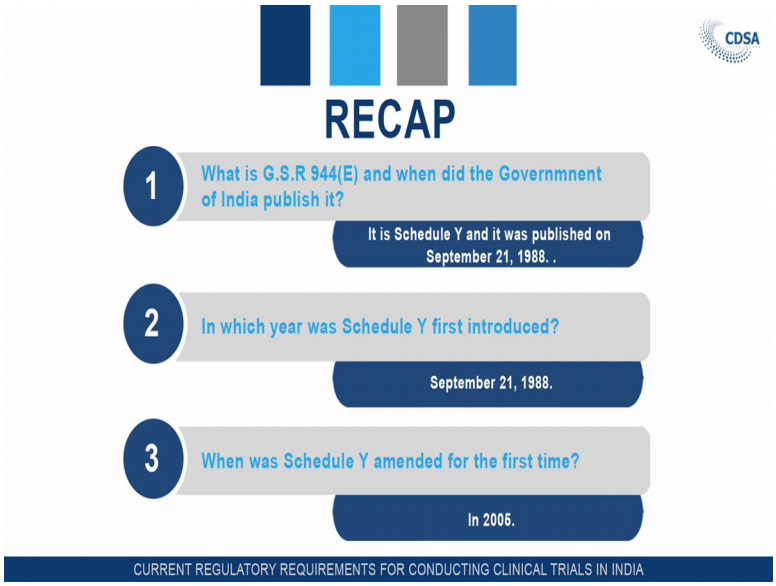

So, let us have some questions for you. Question 1, when government of India published gazette notification that is G.S.R 944 E and; what is it? What it deals with? We have seen it in the history and other thing. So, the answer is 21st September, 1988 and it is a schedule Y. Question 2, in which year schedule Y was first introduced? We have seen it in history. So, in year 1988, it has been first introduced before that there were no rules.

Question 3, when is schedule Y amended version introduced for the first time? When the schedule Y has been introduced and amended first time? In year 2005, it has been amended first time.

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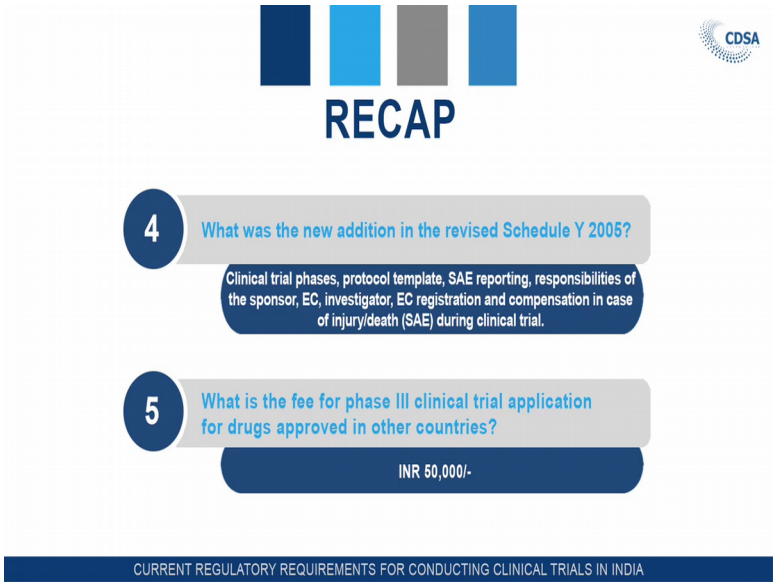

Question 4, what is new addition in revised schedule Y 2005? So, we have seen, there were many editions that is clinical trial phases, protocol template, SAE reporting and others. Question 5, what is fee for phase III clinical trial application for the drug which is approved outside the country? So, the fee requirement is a 50,000 for the drug which is approved outside the country and somebody would like to import it. So, let us summarize now what we have seen in our lecture 8.

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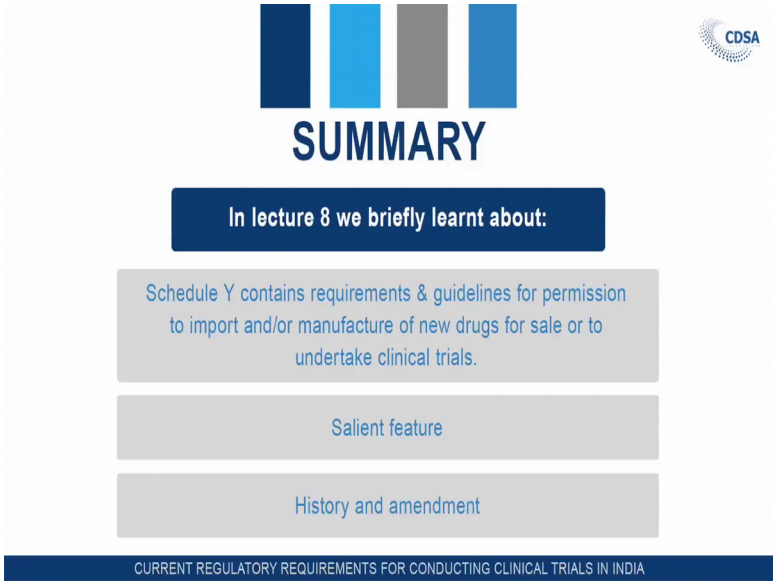

So, briefly we have seen the schedule Y. It is a requirement and guideline for permission to import and or manufacture of new drug for sale to undertake clinical trials. Then, we have seen the salient feature that the phase lag has been removed, concurrent phase has been allowed. Then, phase III is required to market the drug. Then, we have seen the history and amendment; it has started from the 1988. Then, first there was amendment 2005. Then, lot of amendment has happened until the 2016.

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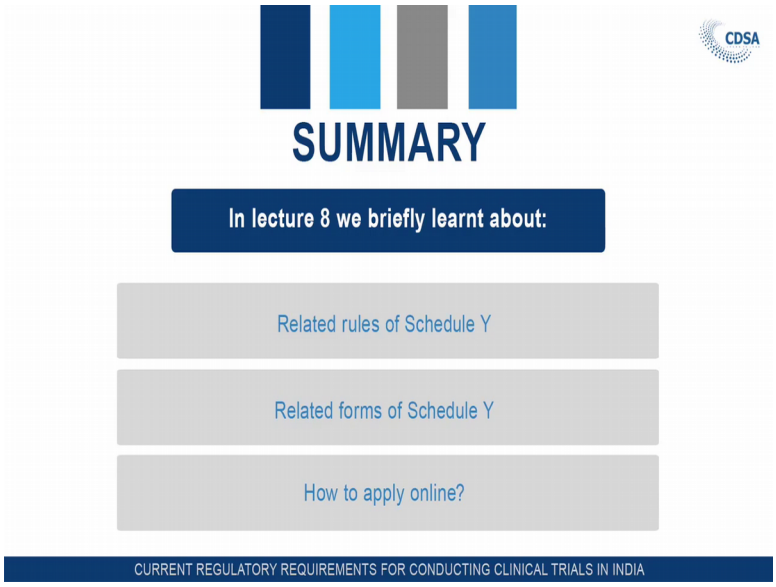

Then, we have seen the related rules. These rules were 122 DA, DAC, DAB and others. Then, related forms we have seen. Form 44 is the most important that is a application for the conduct of clinical trial or import or manufacture and new drug. Then, we have seen the fees requirement and then, we have seen how to apply online and other things; we have to apply online on the SUGAM portal. So, this is about the lecture 8. We will see the next lecture soon.

Thank you; take care and bye bye.