

Current Regulatory Requirements for Conducting Clinical Trials in India for IND/New Drug Version 2.0
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Lecture – 08
Regulatory Pathway & Data Requirements for NDCT, 2019

Hello everyone, I hope you have enjoyed the previous lectures and I hope that you are improving your knowledge about the New Drug and Clinical Trial Rules, 2019. In this lecture that is lecture 6B we are going to see Regulatory Pathway and the Data Requirement for New Drug and Clinical Trial, 2019. This is very important lecture for you those who require or those who are willing to apply for the clinical trials.

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LEARNING OBJECTIVES

WHAT WILL WE LEARN IN LECTURE 6B?

- Legal provisions
- Committees for evaluation
- Regulatory process
- Data requirement for new drugs
- Data requirement for phytopharmaceuticals



So, we are going to cover the; what are the documents and requirements let us see one by one. So, the expected outcome from this lecture that the learners will be able to know what are the rules under which they have to apply for the application to the clinical trials; that is rules associated with the clinical trials. Then what are the different types of committees like IND committees, then New Drug Advisory committees. Which are the committees which evaluate your applications; those year that we are going to see. Then what are the actual process where the scrutiny is completed, then at which stage the committees the see the; those years and applications and when we get the approval.

So, that the regulatory process will see, then data requirement of new drug; what are the data you require to submit while applying to the application for the new drug approval. Then again we are going to see the data requirement for phytopharmaceuticals; the first is the data requirement for new drug and the data requirement for the phytopharmaceuticals.

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So, let us start with the our first slide that is legal provision for regulation of clinical trial. So, before applying to the application for the new drug or the clinical trial one must know what are the rules under which they are going to apply and what are the rules under which they are going to get a permission approval.

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CDSA **LEGAL PROVISIONS FOR REGULATION OF CLINICAL TRIAL** **NPTEL**

New Drugs & Clinical Trials Rules (NDCT), 2019

Rule 21
Application for permission to conduct clinical trial of a new drug or Investigational new drug

Rule 22
Grant of permission to conduct clinical trial

Rule 23
Permission to conduct clinical trial of a new drug or investigational new drug as part of discovery, research and manufacture in India

Rule 24
Permission to conduct clinical trial of a new drug already approved outside India

CURRENT REGULATORY REQUIREMENTS FOR CONDUCTING CLINICAL TRIALS IN INDIA FOR IND/NEW DRUG (VERSION 2.0)

The rule 21st of the New Drug and Clinical Trial; this is regarding the application for permission to conduct clinical trial of new drug or the investigational new drug.

So, under this rule that is rule 21, you can apply to the licensing authority that is state Central Licensing Authority. Then rule 22 is a grant of permission to conduct a clinical trial, so under rule 22 you will obtain a permission to conduct phase 1, 2 or 3; whatever your application.

Then rule 23 is permission to conduct clinical trial of new drug or investigational new drug as a part of discovery research and manufacture in India. Then the next rule that is rule 24, it is regarding permission to conduct clinical trial of new drug already approved outside India.

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CDSA **LEGAL PROVISIONS FOR REGULATION OF CLINICAL TRIAL** **NPTEL**

New Drugs & Clinical Trials Rules (NDCT), 2019

Rule 25
Conditions of permission for conduct of clinical trial

Rule 26
Validity period of permission to initiate a clinical trial

Rule 27
Post-trial access of investigational new drug or new drug

Rule 28
Academic clinical trial

CURRENT REGULATORY REQUIREMENTS FOR CONDUCTING CLINICAL TRIALS IN INDIA FOR IND/NEW DRUG (VERSION 2.0)

The previous is for the manufacture in India and the next is for the drug which is approved outside the India. Rule 25, it is related to the conditions of permission for conduct of clinical trial; once you have obtained the clinical trial permission the permission under this rule 25, it gives some certain conditions which require to be complied while conducting the clinical trials.

Rule 26 is the validity period; so under this rule 26; the validity period for conducting or initiating the clinical trial that has been given. Rule 26 is the post trial access of investigational drug or the new drug; after completion of the trial whether to give the patients or subject the post trial access or not that is mentioned in this rules. Rule 28, it is related to the academic clinical trial; we have seen that academic clinical trial, it is not for the commercial market and it should be initiated by the investigator and it is for only for the academic purpose.

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CDSA **LEGAL PROVISIONS FOR REGULATION OF CLINICAL TRIAL** **NPTEL**

New Drugs & Clinical Trials Rules (NDCT), 2019

Rule 29
Inspection of premises related to clinical trial

Rule 30
Suspension or cancellation of permission to conduct CT

CURRENT REGULATORY REQUIREMENTS FOR CONDUCTING CLINICAL TRIALS IN INDIA FOR IND/NEW DRUG (VERSION 2.0)

Rule 29, it is inspection of premises related to the clinical trial; under this rule it has been mentioned that the sites or the CROs, where the clinical trial is going on that should be open for the open regulator or the auditor those who have been appointed by the Central Licensing Authority.

Rule 30 is the suspension or cancellation of permission; once you get the permission of for conducting the clinical trial or B; B studying; so if the condition stipulated in that permission is not complied with or if there is any violation of this conditions or rules regulation, then under the rule 30 licensing authority can suspend or cancel the permission.

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CDSA **IMPORT OR MANUFACTURE OF
NEW DRUG FOR SALE OR FOR DISTRIBUTION**

New Drugs & Clinical Trials Rules (NDCT), 2019

Rule 75
Application for permission to import new drug for sale or distribution

Rule 76
Grant of permission for import of new drugs for sale or distribution

Rule 77
Condition of permission for import of new drugs for sale or distribution

Rule 78
Suspension or cancellation of import permission for new drug

CURRENT REGULATORY REQUIREMENTS FOR CONDUCTING CLINICAL TRIALS IN INDIA FOR IND/NEW DRUG (VERSION 2.0)

Rule 75 is application for permission to import new drug for sale or distribution; once the trial has been completed then for the import under rule 75 has to apply. Rule 76 grant of permission for import; once you have applied and the data is complete in all respect, then you will get the permission to import that new drug for sale and distribution under rule 76.

Rule 77 is the condition of permission for import of new drug for sale and distribution. So, the 77 it also stipulate the conditions after importing. So, while importing and after importing; what are the conditions like it has to be stored in to the proper conditions, it has to be imported from a authentic weight source that conditions has stipulated under the rule 77.

Rule 78 is the suspension or cancellation of import for a new drug. So, if there is any violation of the condition stipulated into the import permission of or the drug which are imported into the Indian market found to be sub standard or not of quality standard; then the import

permission can be cancelled or suspended after giving a short notice, it is mentioned in the rule 78.

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CDSA **IMPORT OR MANUFACTURE OF
NEW DRUG FOR SALE OR FOR DISTRIBUTION**

New Drugs & Clinical Trials Rules (NDCT), 2019

Rule 79
Licence to import new drug for sale or for distribution under the
Drugs and Cosmetics Rules, 1945

Rule 80
Application for permission to manufacture new drug for sale or
distribution

Rule 81
Grant of permission for manufacture of new drug for sale or
distribution

Rule 82
Condition of permission for manufacture of new drugs for sale or
distribution

CURRENT REGULATORY REQUIREMENTS FOR CONDUCTING CLINICAL TRIALS IN INDIA FOR IND/NEW DRUG (VERSION 2.0)

Then next rule that is rule 79; this is license to import new drug for sale or distribution under drug and cosmetic rules; so this is under this 79; so this can be issued. Rule 80 is the application for permission to manufacture new drug for sale and distribution. So, first we have seen the application for the import, then license for the import and under this rule it is application for manufacture.

Rule 81 is the grant of permission; so the first is the application and under rule 81; it is the grant of permission to manufacture new drug for sale and distribution that is for the marketing purpose. Rule 82 it is a condition of permission for manufacture new drug. So, under this drug

82 rule; what are the condition the applicant and the applicant who has obtain a permission to manufacture, what the condition they have to complied with given under rule 82.

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CDSA **IMPORT OR MANUFACTURE OF
NEW DRUG FOR SALE OR FOR DISTRIBUTION**

New Drugs & Clinical Trials Rules (NDCT), 2019

Rule 83
Licence to manufacture a new drug for sale or for distribution under Drugs and Cosmetics Rules, 1945

Rule 84
Suspension or cancellation of permission

Rule 85
Responsibility of importers or manufacturers in marketing of new drugs

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Rule 83 is license to manufacture new drug for sale and distribution, then rule 84 is the suspension or cancellation of the permission; in case of the violation. Rule 85, the responsibility of importer or manufacturer marketing of new drug. So, what are the responsibilities that has been given under rule 85.

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The slide features a central dark blue rectangular box with a white circle on the left containing the text 'L6B'. To the right of the circle, the text 'COMMITTEES FOR EVALUATION OF APPLICATIONS' is written in white. Above the box, there are four vertical bars: two blue, one grey, and one dark blue. In the top left corner, there is a logo for 'CDSA' (Central Drugs Standardization Authority) and in the top right corner, there is a logo for 'NPTEL' (National Programme on Technology Enhanced Learning). A small inset video of a man in a suit sitting at a desk is visible in the bottom right corner of the slide area.

Now, moving towards the next slide that is which are the committees for the evaluation of application; whereas, the application is with the licensing authority there is a procedure we will see in our next slide what is the procedure. So, before that we will just have the brief about the committees.

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COMMITTEES FOR EVALUATION OF APPLICATIONS

- **IND Committee** – Evaluation of Investigational New Drugs (new molecules discovered in India). Chaired by Director General (DG), Indian Council of Medical Research (ICMR) & Secretary, Department of Health Research (DHR).
- **Subject Expert Committees (SEC)** – 25 panels of about 350 medical experts in various therapeutic areas for evaluation of applications of clinical trial and new drug approvals except IND.



CURRENT REGULATORY REQUIREMENTS FOR CONDUCTING CLINICAL TRIALS IN INDIA FOR IND/NEW DRUG (VERSION 2.0)

So, the first committees for approval for the application is the IND committee; this committee is for the evaluation of investigational new drugs, that is a new molecules. We have seen the investigational new drugs which is not approved elsewhere in the world and first time it has to be administered to the subject or patient that is new molecules discovered in the India.

So, such type of applications are evaluated under the IND committee which is a chaired by DG, ICMR and Secretary Department of Health and Research along with the experts from different fields and from the representative from the CDSE; that is Central Licensing Authority. The next committee is subject expert committee, this committee comprises of 25 panels of and it is having around 350 medical expert across the country and there are different types of classes of these committee based on the therapeutic areas.

For example, the committee is for the anti diabetic drug, oncology committee or for the anti microbial committee. So, depending upon the nature and the indication of the drug there are different committees and such type of 25 panels are there. And this panels they mainly look after the new drug those which are approved outside and not approved in to the India.

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COMMITTEES FOR EVALUATION OF APPLICATIONS

- ❑ **Technical Committee (TC)** – Separate committee of experts chaired by Director General Health Services to assist Apex Committee in supervision of clinical trial.
- ❑ **Apex Committee** : Reviews recommendations of TC.



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Then we are having Technical Committee; this is a separate committee of experts chaired by Director General Health Services, DGHS to assist Apex Committee in supervision of a clinical trial. If the applicant is agreed by the decision of the subject expert committee, then he can approach to the technical committee which is chaired by the DGHS and along with the some experts.

In that committee also if he is not satisfied with the decision, then again there is a next level committee that is we called apex committee and it reviews the recommendation of the technical committee and the subject expert committee and then it gives its own opinion.

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Let us see what is the timeline and the automatic approval of clinical trial, what is this automatic approval.

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TIMELINE AND AUTOMATIC APPROVAL OF CLINICAL TRIAL

□ **Timeline:** 30 working days.

□ **Under the provision to sub-rule (1)** where no communication has been received from the Central Licensing Authority to the applicant within the said period, the permission to conduct clinical trial shall be deemed to have been granted by the Central Licensing Authority and such permission shall be deemed to be legally valid for all purposes and the applicant shall be authorised to initiate clinical trial in accordance with these rules.



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So, the timeline mention in the New Drug and Clinical Trial is 30 working days; if the drug is discovered into the India. Under the provision to sub rule where no communication has been received from Central Licensing Authority to the applicant within the said period that is the 30 days for this drug which is discovered in India and 90 which is not discovered in India.

The permission to conduct clinical trials shall be deemed to have been granted by Central Licensing Authority and such permission shall be deemed to be legally valid for all purposes and the applicant shall be authorized to initiate clinical trial in accordance with these rules. If within this 30 days time period; if there is no communication from the licensing authority to the applicant; then that can be consider as a deemed approval.

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TIMELINE AND AUTOMATIC APPROVAL OF CLINICAL TRIAL

- **Under Rule 23 sub rule 2** The applicant who has taken deemed approval under the proviso to sub-rule (1) shall before initiating the clinical trial, inform the Central Licencing Authority in Form CT-4A and the Central Licencing Authority shall on the basis of the said information, take on record the Form CT-4A which shall become part of the official record and shall be called automatic approval of the Central Licencing Authority.

- **Validity period of permission to initiate a clinical trial:**
Two years from the date of its issue, unless extended by the Central Licencing Authority.



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Provided that he has to inform in to form CT-4A to the licensing authority that he has not received in any communication from the Central Licencing Authority within 30 days and the drug is discovered into the India and the R and D has also been carried out into the India and the drug is proposed for the manufacture marketing into the India; in such cases, if we has not received any communication, it is considered in approval.

Then validity period of permission to initiate a clinical trial; so earlier there was no validity period mentioned. Now, with this New Drug and Clinical Trial rule; this provision has been made to include the validity period and the validity period is two years from the date of its issue.

Once the permission or approval has been obtained from the licensing authority, then the applicant has to initiate clinical trial within period of two years. And if it is not initiated then

that can also be extended provided that the applicant has to give a reason; why they have not conducted the clinical trial study and after satisfying the Central Licensing Authority can extend it.

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The slide displays the following text:

L6B NEW DRUG APPLICATION:
DATA REQUIREMENT IN BRIEF

Now, we will switch toward the data requirement. So, while applying we have seen the various committees, we have seen various rules under which the applicant has to file the application; now we will see what is the data the applicant supposed to submit while applying to the clinical trial.

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NEW DRUG APPLICATION DATA REQUIREMENT IN BRIEF

- Chemical and pharmaceutical information
- Animal Pharmacology
- Animal Toxicology
- Phase I, II, III clinical trials



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So, this is the data which are required the chemical and pharmaceutical information about the drugs. So, in detail the applicant has to submit the chemical and pharmaceutical information. Chemical information like related to the chemistry of the drug molecular formula, empirical formula, the structure of that drug, what is the name of the API.

Then regarding pharmaceutical formulation the dosage form, dose, strength which is proposed; all parameters related to the analytical validation, then the parameter related to the solubility dissolution integrate integration this parameters have to be submitted. Then detail about the animal pharmacology conducted, then animal toxicology conducted; then phase I, II and III clinical trials. So, if the drug has been discovered in to the India or outside the India; the studies which are conducted for the phase I, II and III that data has to be submitted.

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NEW DRUG APPLICATION DATA REQUIREMENT IN BRIEF

- Regulatory status in other country
- COPP/FSC (in case of import)
- Label, prescribing information



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Then the regulatory status of that drug in other countries; if the drug is already approved in other countries then whether that drug is continued to be market; marketed in that country or whether it has been prohibited, withdrawn or the cancel or if any side effect or adverse effect associated with that drug because of which the drug has been banned in that country that detailed information has to be submitted.

Then COPP that is a Certificate of Pharmaceutical Product or finish sale certificate in case of the import. If the applicant would like to import the drug, then whether that drug is freely available in the market or not, whether that has been manufactured in compliance with the GMP or not; the certificate of pharmaceutical product issued by the concern NRA, National Regulatory Authority or licensing authority has to be submitted.

Then apart from this the labels and the prescribing information including the dosage form, the precaution, warnings to be taken; whether it is scheduled drug H 1 drug etcetera. What are the precaution to be taken; how the drug has to be taken that that prescribing information including label has to be submitted.

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Data for conduct of clinical trial or import or manufacture new drug.

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DATA FOR CONDUCT OF CLINICAL TRIAL OR IMPORT OR MANUFACTURE OF NEW DRUG

1. Introduction: Description and therapeutic class.

2. Chemical and pharmaceutical information: For API and FPP.

Data on API:

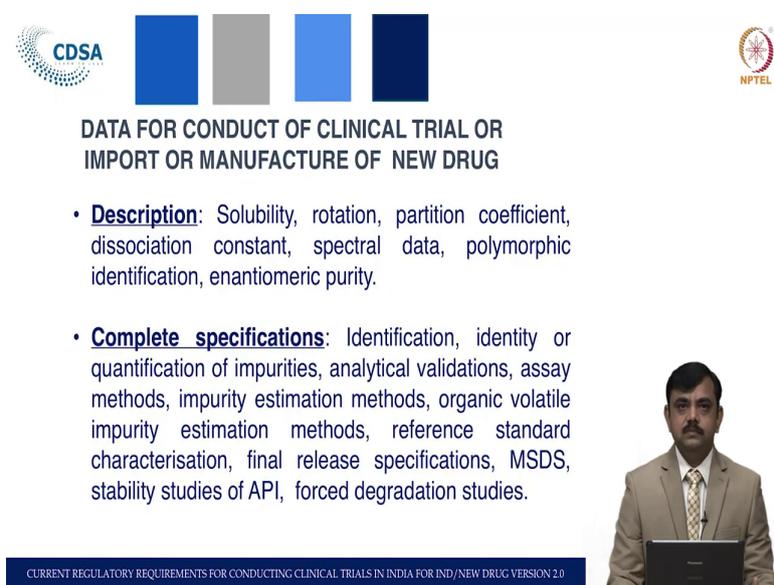
- Physicochemical characterisation: Empirical formula and molecular formula.



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So, data for conduct of clinical trial; this is the data introduction I have to give has to be given that is the description and therapeutic class of the drug, then chemical, pharmaceutical information for API and finish formulation, then data on the active pharmaceutical ingredient that is physicochemical characteristic including empirical formula and molecular formula that has to be given.

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DATA FOR CONDUCT OF CLINICAL TRIAL OR IMPORT OR MANUFACTURE OF NEW DRUG

- **Description:** Solubility, rotation, partition coefficient, dissociation constant, spectral data, polymorphic identification, enantiomeric purity.
- **Complete specifications:** Identification, identity or quantification of impurities, analytical validations, assay methods, impurity estimation methods, organic volatile impurity estimation methods, reference standard characterisation, final release specifications, MSDS, stability studies of API, forced degradation studies.

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Then data with respect to the description like a solubility, then partition coefficient, dissociation constant, then rotation, polymorphism, identification, enantiomerism all this data related to the purity, impurity profile has to be submitted.

Then complete specification including; its identification identity, then impurity profile analytical method validations; the method of assay, the method of determination of the impurity including organic volatile impurity, then reference standard characterization, final release specification, the its material safety, data sheet how to handle the material what precaution has to be taken.

Then stability studies of the API as mentioned in the New Drug and Clinical Trial rule for 30 degree Celsius, for 45 degree Celsius for the 6 months that has to be submitted. Then the

forced degradation studies carried out to see the effect of the accelerated conditions on the drug that is also required to be submitted.

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**DATA FOR CONDUCT OF CLINICAL TRIAL OR
IMPORT OR MANUFACTURE OF NEW DRUG**

Data on formulation:
Dosage form, composition, excipient compatibility study, validation of analytical methods, master manufacturing formula, in process quality control check, finished product specification, comparative evaluation with international brand or approved brand in India where applicable, pack presentation, dissolution studies, assay, stability studies in intended pack at proposed storage conditions, packing specifications, impurities, content uniformity, PH where applicable, process validation



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Data on formulation; the data on formulation is the data with respect to the dosage form if it is a tablet, capsule, injections, what are the dosage form that has to be given; then what are the excipient use; the detail composition winder, then again diluents, the quantity added for the compression that everything the quantity and the excipient name has to be given. Then whether that is compatible with the excipient or not that study has to be conducted and the result of the excipient excipient compatibility study has to be submitted.

Then validation of analytical method; the method which are used for the determination whether that method has been previously validated or not that validation report has to be submitted. Then the master formula for the manufacturing of the dosage form that master

formula required to be submitted. Further, in process quality control check, then finish products specifications; we have seen that APS specification has to be given; here again the finish products specification has also required to be given. Then comparative evaluation with the international brand; if the drug is available outside the India, then what is the comparison with the approved brand that is also required to be submitted.

In India where applicable; pack presentation then dissolution study we know that dissolution in (Refer Time: 19:08) dissolution study to see the drug release that is also required to submit. Then assay, stability studies in intended pack; if it is a blister pack then the stability study is required to be conducted in the same panel packaging material and that is; that is required to be submitted, then packing specification, impurities, content uniformity, PH wherever applicable. Then whatever the validation has been done for the process that process validation also for the three batches; it has also required to be submitted.

So, in the that was a related to the API and the dosage form; if it is the application for the phase I trial, then the preclinical studies like animal pharmacology, animal toxicology that is also required to be submitted.

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DATA FOR CONDUCT OF CLINICAL TRIAL OR IMPORT OR MANUFACTURE OF NEW DRUG

3. Animal Pharmacology: Provide summary, specific pharmacological actions, general pharmacological actions PK, ADME, follow up and supplemental pharmacological studies.

4. Animal Toxicology: Systemic toxicity studies, male fertility Studies, female reproduction and developmental toxicity studies, local toxicity: dermal toxicity allergenicity/hypersensitivity Studies: GMPT, local lymph node assay, ocular toxicity, inhalational toxicity studies etc. genotoxicity, carcinogenicity studies*.



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In the animal pharmacology, the applicant require to provide summary of the study which is conducted with the animals. Then specific pharmacological action, general pharmacological action then pharmacokinetic data like ADME data of sale and distribution metabolism and excretion in animals. Then the study conducted for the follow up and supplemental pharmacological studies that is also required to be submitted.

Then animal toxicology data including systematic toxicity study, male fertility study, female reproduction developmental studies, then local toxicity study. If the product for the external use, then dermal toxicity study, allergenicity, then hypersensitivity studies; this studies required to be submitted. Some this studies are required to be carried out in animal and this studies may include (Refer Time: 20:59) maximization, dose maximization study, then Local Lymph Node; what we call it is LLNA study, ocular toxicity study if the product is to be used for the

treatment of the eyes, then inhalation toxicity study; all this studies required to be submitted depending upon the nature of the drug and the intention of the treatment of the drug.

For certain drug and genotoxicity study, carcinogenicity study; those drug which are having the long exposure for particular for those drugs this studies are required to be submitted; where animal toxicity data has been submitted and the same is consider by the regulatory authority on the country which has earlier approved the drug; the animal toxicity study shall not be required to be conducted, in India except in case where there are specific concerns recorded in writing.

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DATA FOR CONDUCT OF CLINICAL TRIAL OR IMPORT OR MANUFACTURE OF NEW DRUG

*where animal toxicity data has been submitted and the same considered by the regulatory authority of the country which had earlier approved the drug, the animal toxicity studies shall not be required to be conducted in India except in cases where there are specific concerns recorded in writing.

5. Human or Clinical Pharmacology (Phase I): Provide summary, specific pharmacological effects, general pharmacological effects, PK/ADME, pharmacodynamics/early measurement of drug activity.



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If the animal pharmacology, animal toxicity study has already be conducted in other countries; then that is now that is not required to be repeated in the Indian animals or the pre clinical studies; unless there is a particular or special concern if the data is not satisfactory, something

is wrong happen with the animals; if the deaths are more, if the toxicity is more then it require to repeat the data.

Then human or clinical pharmacological study after the pre clinical study that is the clinical pharmacological study phase 1; we have seen what is the phase I study. So, phase I the they has to submit the protocol first and after the study, then has to give the summary of the study, specific pharmacological effect, general pharmacological effect then PKPD study; it is require for the those which are required to be conducted for the phase I study and for the early measurement of the drug.

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DATA FOR CONDUCT OF CLINICAL TRIAL OR IMPORT OR MANUFACTURE OF NEW DRUG

6. Therapeutic exploratory trials (Phase II): Provide summary, study report as given in Table 6 of Third Schedule.

7. Therapeutic Confirmatory trials (Phase III): Provide summary, study report as given in Table 6 of Third Schedule.

8. Special Studies: Provide summary, BA/BE study data if applicable, other studies e.g. geriatrics, paediatrics, pregnant or nursing women.



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Then phase II study same it has to be provided the summary; then study report as given in the table 6 of the third schedule. So, third schedule of the New Drug and Clinical Trial rule, it mentions about the particulars to be submitted for phase II study. Phase III data also require

to be submitted after completion of phase II, here also the summary then study report as given in table 6 of the third schedule that is required to be submitted.

If the drug is of particular nature; then the special study is required to be conducted and the data required to be submitted. The special studies may be if the drug is particularly for the geriatric patient or the for the children's, then the studies you know like behavioral studies data and the studies conducted in the geriatric pediatrics or the pregnant or nursing women; that is also required to be carried out and required to be submitted to the licensing authority.

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DATA FOR CONDUCT OF CLINICAL TRIAL OR IMPORT OR MANUFACTURE OF NEW DRUG

9. Regulatory status in other countries: Countries where the drug is marketed/approved, withdrawn if any with reasons, restrictions on use, if any in countries where marketed, free sales certificate or COA, where appropriate.

10. Prescribing Information: Proposed full prescribing Information, draft of labels and cartons.

11. Samples and Testing Protocols: Samples of pure drug substance and finished product (50 clinical doses or more) with testing protocols, full impurity profile and release specifications.



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Regulatory status in other countries; we have seen whether the drug is released so available in the market of other countries or whether it has been withdrawn or suspended prohibited; if so, the reason of that that is required to be submitted.

Then prescribing information proposed full prescribing information draft of label and carton. So, whatever the information the applicant or manufacturer is going to propose on the draft label or the information; that label prescribing information also require to be get approved from the licensing authority. Samples and test sample and testing protocol samples of pure drug substance and finish product, at least 50 clinical dose with testing protocol fully impurity profile and release specification.

So, this full impurity profile release specification are required to be submitted along with the testing sample this; this licensing authority and they send this sample to the concern laboratory and once the result of satisfactory result from that laboratory comes, then the permission can be granted.

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DATA FOR CONDUCT OF CLINICAL TRIAL OR IMPORT OR MANUFACTURE OF NEW DRUG

12. New Chemical Entity and Global Clinical Trial.

Assessment of risk vs benefit to the patients, Innovation vis a vis existing therapeutic option, unmet medical need in the country.

13. Copy of Drug License to manufacture any drug for sale granted by SLA in case the application is for manufacture for sale of new drug.



Then new chemical entity and the global clinical trial if any; assessment of risk versus benefit to the patient, innovation visa vis existing therapeutic option, unmet medical need in the country; if it is there the reason that has to be submitted. And then copy of drug license to manufacture any drug for sale granted by SLA in case the application is for manufacture or sale of new drug. So, this was about the; the new drug that are the chemical entity.

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Again we have in we have incorporated in our new drug definition; we have seen the phytopharmaceuticals. So, we will see what are the data requirement for the phytopharmaceuticals.

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PHYTOPHARMACETICALS

Phytopharmaceutical drug means:

- drug of purified standardized fraction.
- assessed qualitatively and quantitatively with defined minimum four bio-active or phytochemical compound of an extract of plant or its part.



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Let us see first what is the phytopharmaceuticals; phytopharmaceutical drug means a drug it is of purified standardized fraction. Assessed qualitatively and quantitatively with defined four bio active or phytochemical compound of an extract of plant or its part; so, there is a requirement of it should contain the minimum four bio active phytochemical compound. Further, we will add to this that this drug supposed to not being given in the parenteral dosage forms, then we call it as the phytopharmaceutical.

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DATA TO BE SUBMITTED ALONG WITH APPLICATION TO
CONDUCT CLINICAL TRIAL OR IMPORT OR MANUFACTURE
OF A PHYTOPHARMACEUTICAL DRUG IN THE COUNTRY

Second Schedule

**Table 4: Data To Be Submitted Along With Application To
Conduct Clinical Trial Or Import Or Manufacture Of A
Phytopharmaceutical Drug In The Country**

- Part A
- Part B

Part A: Data to be submitted by the applicant human or
clinical pharmacology information.



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Let us see what is the data requirement for the application of the manufacture of import of the phytopharmaceutical. So, it is given in the second schedule table 4 data to be submitted along with application to conduct clinical trial or import or manufacture of a pharmaceutical drug in the country.

So, this data requirement has been given in the two parts that is part A and part B; we will see first the part A. Part A is related to the data to be submitted by the applicant and it is related to the human clinical data like human or clinical pharmacology information.

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SECOND SCHEDULE

Part B: Data generated by applicant

- Identification, authentication and source of plant used for extraction and fractionation
- Process for extraction and subsequent fractionation and purification
- Formulation of phytopharmaceutical drug applied for
- Manufacturing process of formulation
- Stability data



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Then part B data generated by the applicant; first is the data submitted by the applicant and part B. Data generated by the applicant data submitted by the applicant it means that whatever the data available like publish literature or data from other countries; data generated means this may be from the R and D of the applicant.

So, in this B part identification, authentication, source of plant used for extraction and fractionation that is required to be submitted, then what are the processes used for the extraction and subsequent fractionation and purification. Formulation of phytopharmaceutical drug applied and for the manufacturing process of formulation, then again here it is required to submit the stability data.

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SECOND SCHEDULE

- Safety and pharmacological information
- Human studies
- Confirmatory clinical trials
- Regulatory status
- Marketing information
- Post marketing surveillance (PMS)
- Any other relevant information



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Safety and pharmacological information, then human studies, confirmatory clinical trial, regulatory studies we have seen in case of the chemical entities that is in case of the drugs also the regulatory status whether it is prohibited banned approved. Then marketing information, post marketing surveillance and any other relevant information.

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The slide features a central dark blue rectangular box with the text "L6B REQUIREMENTS OF LOCAL CLINICAL TRIAL" in white. To the left of the text is a white circle containing "L6B". Above the box are four vertical bars: blue, grey, light blue, and dark blue. Above the slide are the logos for CDSA (Central Drug Safety Authority) and NPTEL (National Programme on Technology Enhanced Learning). In the bottom right corner, there is a small inset image of a man in a suit sitting at a desk with a laptop.

So, we have seen the phase III is mandatory to conduct before marketing approval has been obtained, but there are certain cases where in the clinical trial can be; phase III clinical trial can be waved off.

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REQUIREMENTS OF LOCAL CLINICAL TRIAL

For new drug substance discovered in India clinical trial is required to be conducted right from Phase I.

For new drugs approved outside India, Phase III studies need to be carried out to generate evidence of efficacy and safety of drug in Indian patients when used as recommended in the prescribing information.



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For new drug substance discovered in India; these are some important things which we are required to be know. Now, for new drug substance discovered in India clinical trial is required to be conducted right from phase I. For new drug approved outside India, phase III studies need to be carried out to generate evidence of safety efficacy in Indian population that we have seen.

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Four vertical bars of varying heights and colors (blue, grey, blue, dark blue) are positioned behind the central slide content.

L6B WAIVER OF LOCAL CLINICAL TRIAL REQUIREMENT



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WAIVER OF LOCAL CLINICAL TRIAL REQUIREMENT

Rule 24

new drug which is already approved and marketed in a country, as specified under rule 101, the application, shall be disposed of within a period of ninety working days from the date of the receipt of the application by the said Authority.



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So, as per the rule 24; not with the standing anything containing these rules what we have seen in the in our previous slides the rules, where any person or institution or organization makes as application under rule 21 to conduct clinical trial of new drug which is already approved and marketed in country; as specified under rule 101.

So, the countries for the consideration that would be notified under the rule 101, the application shall be disposal of by way of grant of permission or rejection or processed by way of communication to rectify any deficiencies; as the case may be as specified in rule 22 by Central Licensing Authority within a period of 90 working days from the receipt of the application. So, if it is for the import; if it is a import case within 90 days the application required to be disposed of either by rejection or the either by query or other by the approval.

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WAIVER OF LOCAL CLINICAL TRIAL REQUIREMENT

Rule 101

The Central Licensing Authority, with the approval of the Central Government, may specify, by an order, the name of the countries, from time to time, for considering waiver of local clinical trial for approval of new drugs.

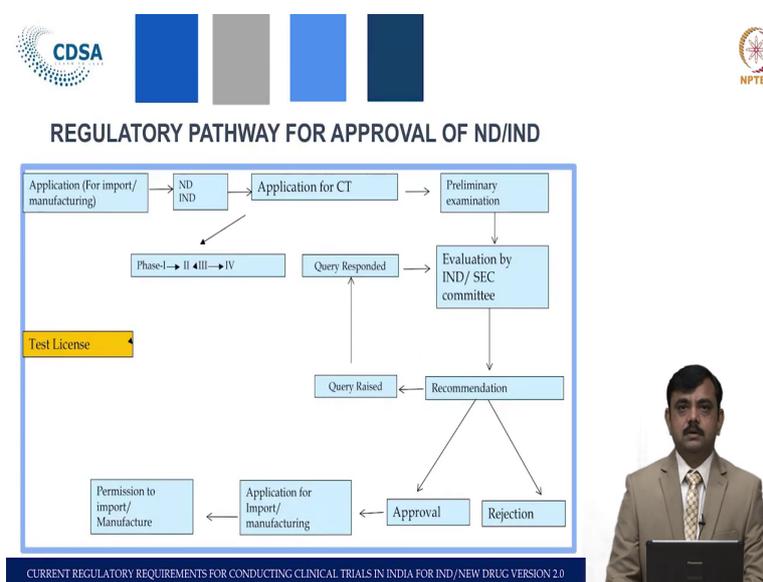


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So, the rule 101 mention that the Central Licensing Authority with the approval of the Central Government may specify by an order the name of the countries from time to time for considering the waiver of local clinical trial for approval of new drug under chapter 10 and for grant of permission for conduct of clinical trial under chapter 5.

So, this rule mentions the notification of the countries; the Central Government that is Central Licensing Authority with the approval of Central Government will specify the name of the countries which are Indian regulatory authorities; if the drug is available in that countries and the applicant desired to import that drugs. So, that can be waived of the phase phases of the clinical trial that is phase III can be waive of.

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So, you can see the slide wherein the diagram has been given for the regulatory pathway for approval of the new drug or the IND. So, this is the actually the procedure what the applicant and the regulators has to be followed; you can see the slide.

The application for import or the manufacturing; so, there can be two type of application. The drug can may available in to the India by the import or by the manufacturing and also the drug can be a new drug or the drug can be a investigational new drug. For both of this; this application has to submitted, we have seen the application forms and the fees.

Irrespective of whether the application is for import or manufacture; if it is not approved, then application for CT has to be given. The CT protocol with respect to the design, population that is that undergoes the preliminary examination at the CDSO that is Central Licensing

Authority. And after the preliminary examination with respect to the chemical pharmaceutical data and some administrative like a forms, fees these goes to the evaluation committee.

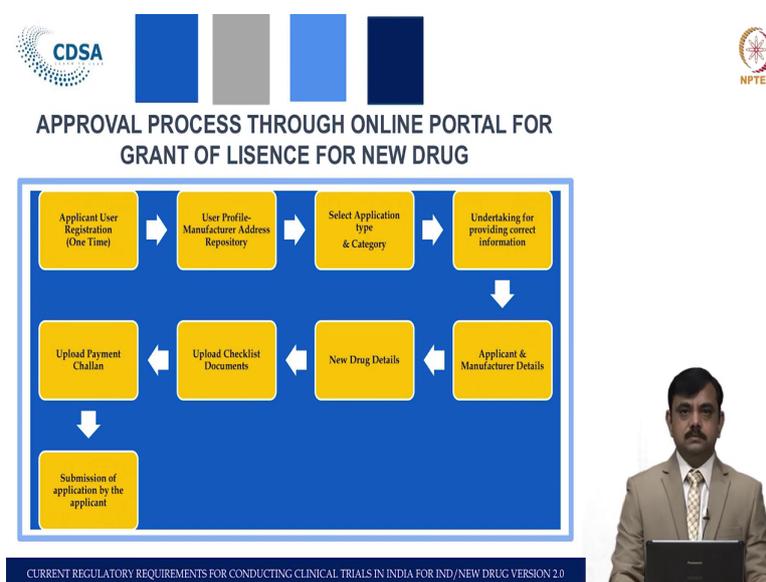
We have seen the evaluation committee, IND committee; if it is the new molecule, then it goes to the IND committee. If it is a new drug, then it goes to the subject expert committee and after evaluation by this committee; the committee gives the recommendation either they may they may ask the applicant to modify or amend the protocol, in that regard they may issue the query to the applicant. Once the applicant receives the [query/query] query; he has to respond to that query and once that has been responded that query whether they have amended the protocol as per the SEC committees recommendation or not

That is again evaluated by the SEC committee and in case of the IND by the IND committee. After that again this SEC committee after detailed deliberation give its opinion and that opinion may be approval of the rejection. If the query raised by the SEC committee or the central licensing authority; if it is not satisfied, then application can be rejected or if it is to the satisfactory level; then approval can be given to conduct the clinical trials.

Then once the clinical trial has been approved, the applicant require to conduct the clinical trial and after conducting clinical trial; it require to submit the detailed report that the study report and the outcome of the clinical trial; that is again evaluated by the SEC committee or the IND committee. And if that results are satisfactory and if it is or the benefit of the patient; then that committee gives not to the applicant and after that if the applicant would like to import that drug, then he has to apply for the import.

If it is the case of the manufacture, then he has to apply through the manufacturing pathway. Then after seeing all this if it is for the manufacturing, he has to he has to submit all the details of the manufacturing premises. If it is a case of the import, then details of the manufacturing country or that country they have to submit. And after satisfactory submission of this; the permission can be granted for the manufacture of the import of the drug. So, this is the regulatory pathway.

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So, the applicant has to apply through the online portal. The approval process through online portal for grant of license for new drug; we will see in brief how to how to apply and how it goes to the panel conclusion. The applicant user has to register on onto the portal that we call the Sugam portal.

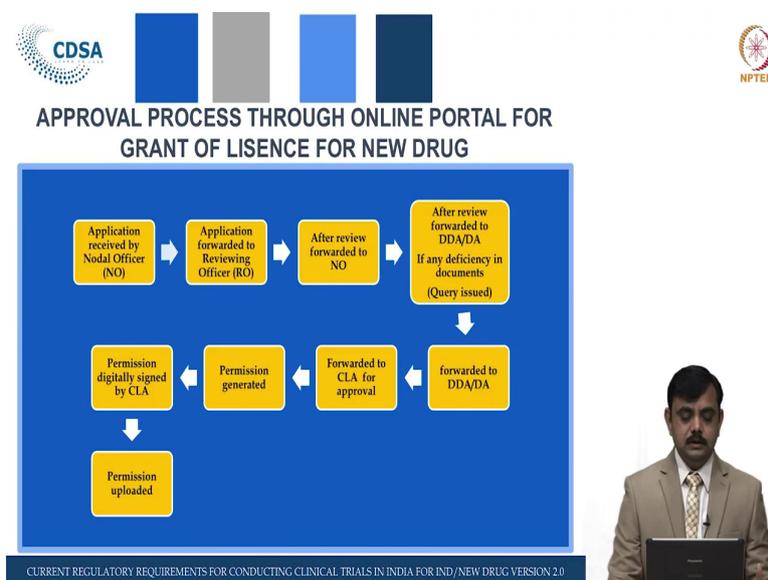
Then it will generate the user profile and manufacturer address repository, then the applicant has to select application type and category whether it is new drug, IND, veterinary, vaccine that we have to select. Then the applicant has to upload the undertaking for providing correct information. The undertaking which will specify that the whatever the information they are submitting that is true that undertaking has to be submitted or up uploaded on the Sugam portal.

Then the applicant required to upload the information regarding the manufacturer detailing; if it is the manufacturing; then manufacturer detail, if it is import then importers detail. After that the applicant required to submit the details of the new drug; what we have seen in our earlier slides regarding pharmaceutical, chemical information, regarding the new drug detail we have to submit.

Then there is a check list check list has been given on the Sugam portal for the different categories of the drug and different type of the drug; we have to select the category. If it is for the manufacturer, then there is different check list; if it is for the import purpose different check list. If it is for the clinical trial, then what are the data requirement that has been mention in the check list; the applicant required to fill up that check list.

Then upload payment challan; so this payment can be whatever the fees; we have seen in earlier slides that fees has to be uploaded. This fees in case; this fees in like a receipt they have to upload. If it is paid through the Bharat Kosh, then in that Bharat Kosh receipt or if it is paid into the Bank of Baroda where to pay the fees that has also to be mention in our rule and that; so that fees paid challan or receipt has to be uploaded. Then submission of application by the applicant, then after uploading all this they have to submit it.

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Once the part from the application is over, then it is the; it is on the side of the regulatory side that is application received by the nodal officer; so it goes to the nodal officer. Application then forwarded to the reviewing officer. So, after the scrutiny whether the application is completed in all manner that will be looked after by the nodal officers and if it is they will forward it to the reviewing officer.

Reviewing officer after scrutinizing and reviewing the application, it forward to the nodal officers. Then nodal officer giving its a recommendation and after reviewing, forward it to the decision taking authority or the decision authority. If any deficiency in document, then at this level the query would be raised on and this query would go directly in the mail of the applicant.

Then after satisfactory response from the applicant, it is again forwarded to the DDA or DA. Then this DDA and that is a decision taking authority; it will forward the application to the Central Licensing Authority for the approval purpose. And once the Central Licensing Authority sees it that the application is in complete in all manner, it may grant the license and the permission is generated online.

Then after generation of this permission; that is digitally signed by the Central Licensing Authority and that permission then is uploaded onto; uploaded on to the website that can be seen or downloaded by the applicant. So, this is the online procedure.

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SUMMARY

In lecture 6B (L6B), we briefly learnt about:

- Various Rules under the legal provisions for regulation of clinical trials with new drugs, phytopharmaceuticals, etc.
- Various Rules related to import or manufacture of new drug for sale or for distribution
- Various committees engaged in the evaluation of applications at CDSCO
- Data requirements for submission of online application for the conduct of clinical trials/new drugs/INDs.
- Timeline, automatic approval and validity of clinical trials
- Requirements of local clinical trials, and waivers.



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So, this is about all about our lecture and we will have the summary what we have seen in this lecture. So, we have seen various rules under the legal provision for regulation of clinical trial.

Then we have seen the various rules related to the import related to the manufacture related to the test license.

Then we have seen the various committee like if the drug is for the investigational new drug; then IND committee. If it is a new drug then Subject Expert committee, then we have seen the Technical committee, Apex committee in case of the applicant; if it is a aggrieve by the decision of the previous committee. Then we have seen the data requirement; what are the document required for the new drug and what are the document required for the phytopharmaceuticals that we have seen. We have also seen that the phase III is the mandatory for before the marketing of the drug into the country. But we have also seen that there are some conditions wherein the phase III can be waived of; then we have seen the requirement of local clinical trials.

And further we have seen the procedure, regulatory pathways and the how to apply to the portal and how it moves from the reviewing officer to the Central Licensing Authority on the Sugam online portal. So, the last we will take recap of this by checking your memory and attention.

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RECAP

- 1** State true or false:
For new drug application, data from animal pharmacology is necessary.
True
- 2** Fill in the blank:
IND Committee is chaired by _____
DG, ICMR & Secretary, Department of Health Research
- 3** Permission to conduct clinical trial of a new drug already approved outside India is stated under which rule?
Rule 24



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So, the first question for you; you have two state true or false; for new drug application data from animal pharmacology is necessary. Yes, it is a required; if it is a phase I and then the data is 1, 2, 3; the data from the animal pharmacology is necessary. The next question is the fill in the blank the IND committee is chaired by?

So, the IND committee is chaired by DG, ICMR and Secretary, Department of Health and Research. Permission to conduct clinical trial of new drug already approved outside India is stated under which rule? So, this is a rule 24.

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RECAP

4

Minimum how many bio-active phytochemical compounds are required to be assessed in a phytopharmaceutical drug?

Four Bio-active phytochemical compounds



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Next question, minimum how many bio active phytophar[maceuticals]- phytochemical compound are required to be assessed in a phytopharmaceutical drug? So, you have to recall the definition of phytopharmaceutical and the answer is minimum four bio active phytochemical compounds. So, this is about the lecture 6; we will, we will see the next provisions and the; what is there in again in the New Drug and Clinical Trial rules in our next lecture. Till then; you take care, all the best.

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The information within this presentation is based on the presenter's expertise and
experience and represents the views of the presenter for the purpose of training.

■ ■ ■ ■

END OF LECTURE L6(B) - REGULATORY PATHWAY & DATA REQUIREMENT FOR NDCT, 2019
THANK YOU.



And thank you for watching this video.