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

Prof. Y. K. Gupta
Department of Biotechnology
Indian Institute of Technology, Madras

Lecture - 22
Salient Features of NDCT 2019 (WHAT'S NEW IN NDCT?)

[FL] Good morning, this is Prof. Y. K Gupta, former dean and head of department of Pharmacology, All India Institute Medical Sciences talking to you on Salient Features of New Drug Clinical Trial Rule 2019. And we will be highlighting what is new in this. I will be talking to you on the Salient Features through this presentation which has been prepared in consultation with CDSEO.

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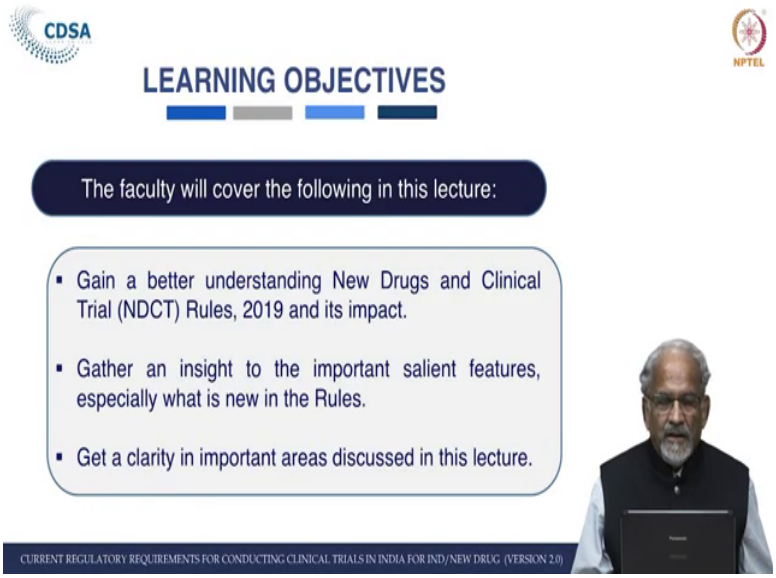

The primary learning objective of this nearly 1 hour session would be a: to gain better understanding of New Drug and Clinical Trial Rule 2019 and what has been it is impact on the new drug discovery process and medicine safety in general. And also to gather an insight to an important salient features, especially what are the new features which did not exist earlier in this rule and also to get clarity in some important areas.

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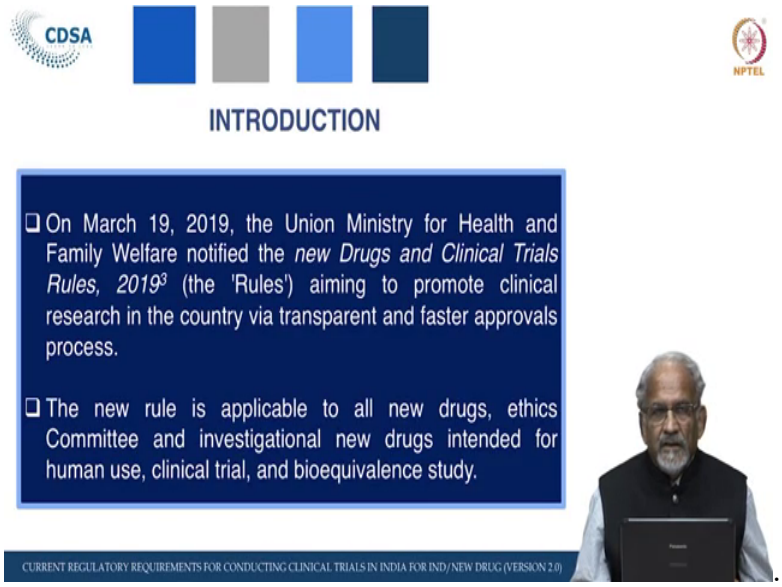

To begin with the important thing is what is new drug and if you just see the difference for in the new drug is for humans earlier it was called as a regulation and schedule Y, but now schedule Y is a non entity as far as for human is concerned which is replaced by New Drug and Clinical Trial Rule 2019.

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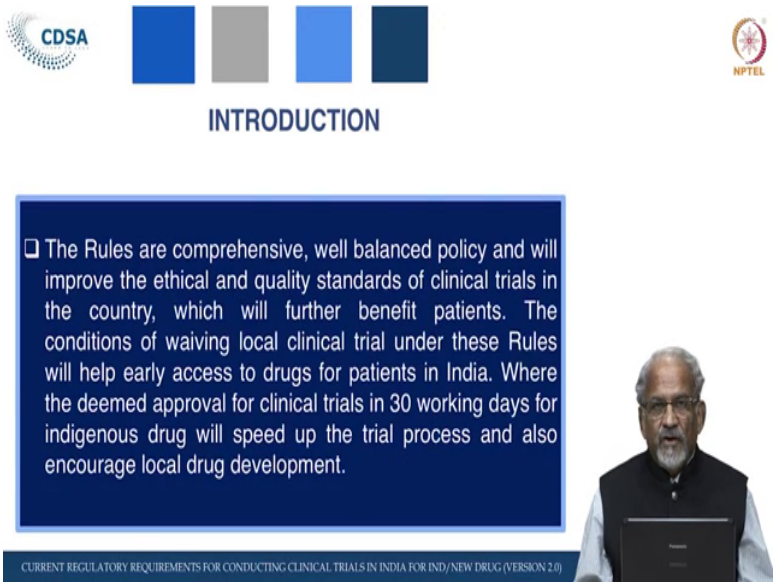

However, for veterinary use still the earlier regulations and schedule Y is in place.

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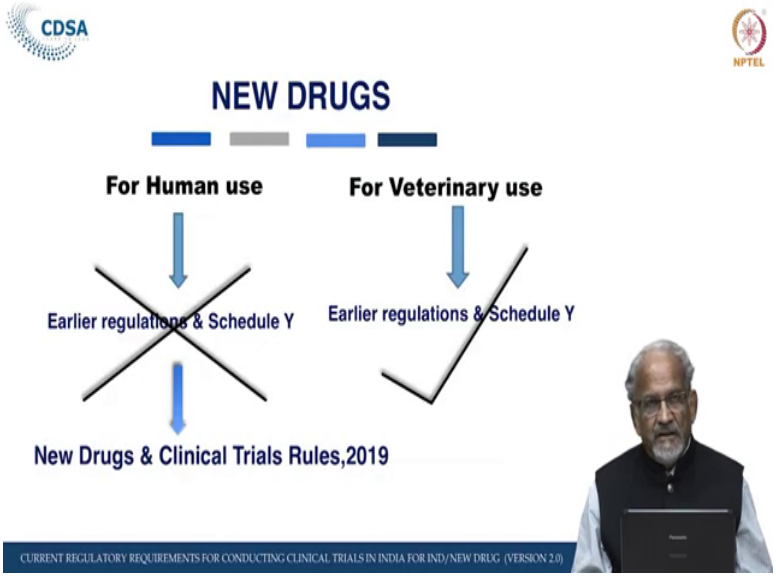

Important thing to remember which even now very senior regulators, teachers, students, industry people make a mistake that they still say that this is the schedule Y. We remember keep this in mind that schedule Y has been replaced by New Drug and Clinical Trial Rules 2019. So, do not call a schedule Y in present context.

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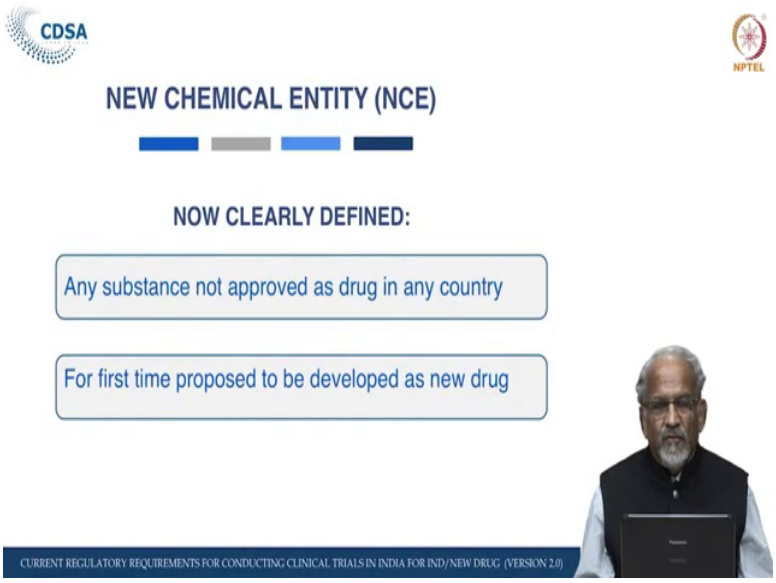

Now, it is clearly defined what is new chemical entity. This is any substance which is not approved as drug in any country in any country that is a NCE and for the first time proposed to be developed as new drug. Clearly, any drug which is not any substance, substance mean it can be a molecule or it can be a molecules it can be anything which gives a delivery, but which comes into the definition and is being for the first time that is important. The another term which is often used is Investigational New Drug, IND.

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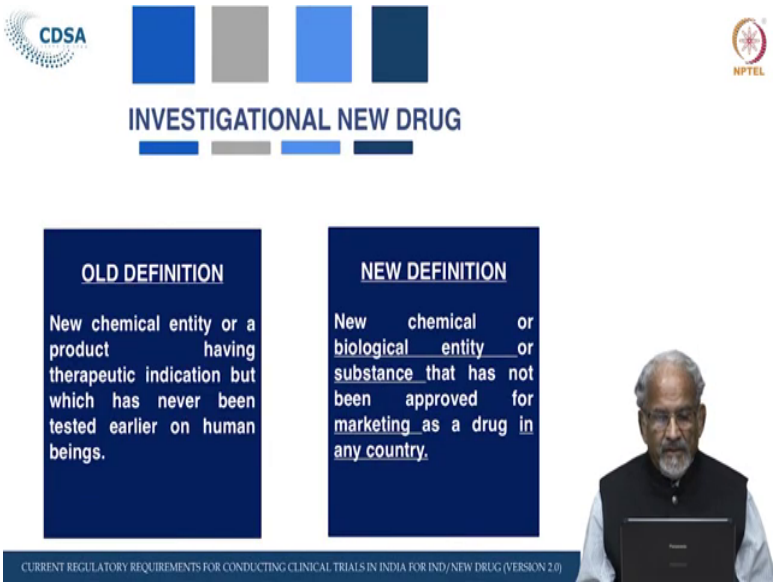

The old definition was new chemical entity or a product having therapeutic indication, but which has never been tested earlier on human being. However, if you just see the red part here that is the new definition it says new chemical or biological entity or substance that has not been approved for marketing as a drug in any country. Take home messages, the any country remains the same not approved for marketing is an important thing, but the most important thing is new chemical or biological entity or substance.

Now this will means it includes all biosimilars, it includes all other substances which have a drug or which has not approved in any country.

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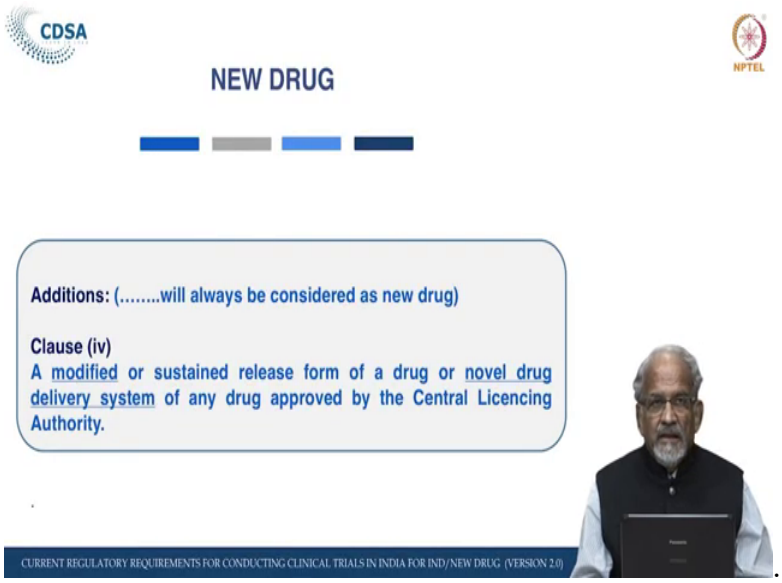

The definition of new drug; there is an addition that will always be considered a new drug means, a modified or sustained release form of a drug or a novel drug delivery system, this has been added. Now modified drug or sustained release or novel drug delivery system and a clause 5 has been added where vaccine and recombinant derived product, monoclonal antibody, stem cell derived product, gene therapeutic product, geno graphs, which are intended to be used as a drug. So, all these things will now be called as a new drug.

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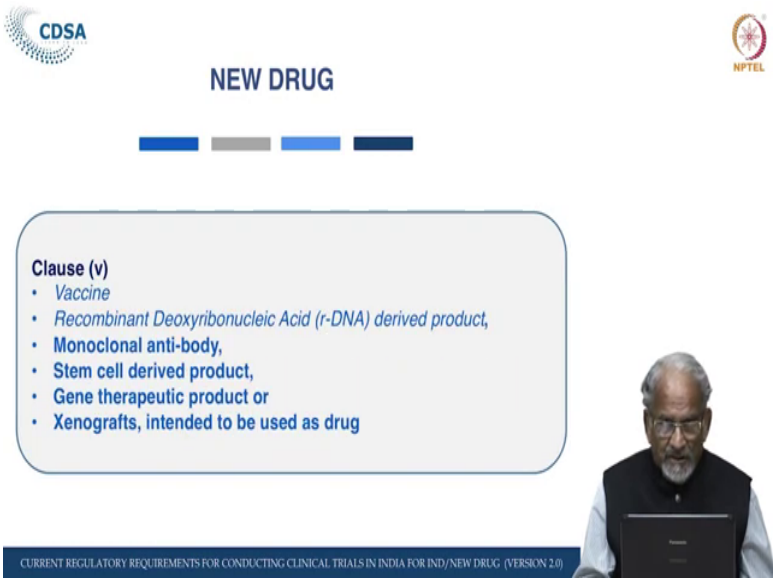

Important is any vaccine which is introduced and produced by a person, a place or different technology will be called as a new drug. And this if you just see that this will always be remaining as a new drug.

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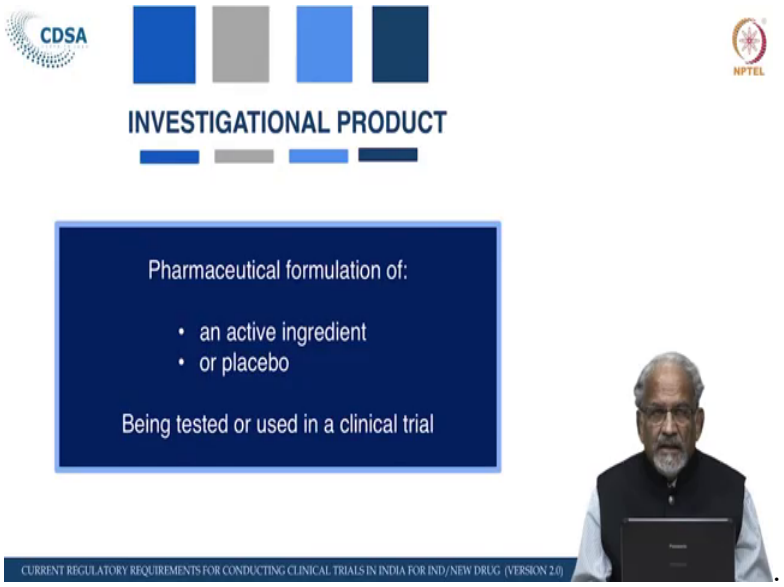

Now, investigational product, what is the investigational product? Investigational product is the pharmaceutical formulation of an active ingredient, but this is also placebo which is being tested for the purpose.

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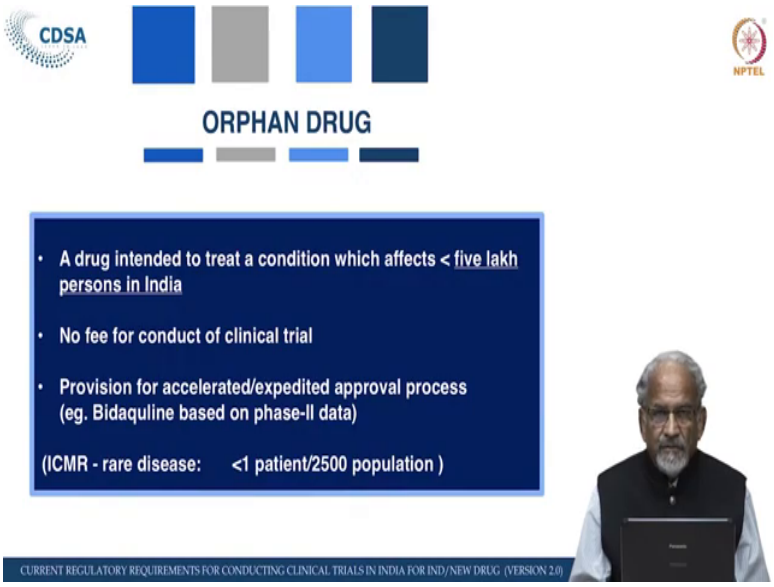

In new drug; for the first time we have added the definition of orphan drug, which was not defined earlier and the orphan drug has been defined as a drug intended to treat a condition which affects less than 5 lakh person in India. There was a no uniformity of definition of orphan drug in literature where different people have used. In India for this rule we have defined as a new drug intended to treat less than 5.

And if you just see the red part, the ICMR rare disease is that which is less than one patient per 2500 population. And if you convert this to our population of the country today nearly the same ratio will lead to 5 lakhs in India. One may argue that 5 lakhs were maybe more or it may we become more if the population increases, then we are opened to change this at a later date. But as on date this is a 5 lakhs person less than that.

Advantage or to promote the drug discovery in orphan drug, there is a no fee for clinical trial. Also there is a provision of accelerated or expedited review process. An example, it will same like bedaquiline which was used which was given permission even after phase 2 data because this was required for the patient in India for a problem which is a national problem that is a multi drug resistant or resistant tuberculosis.

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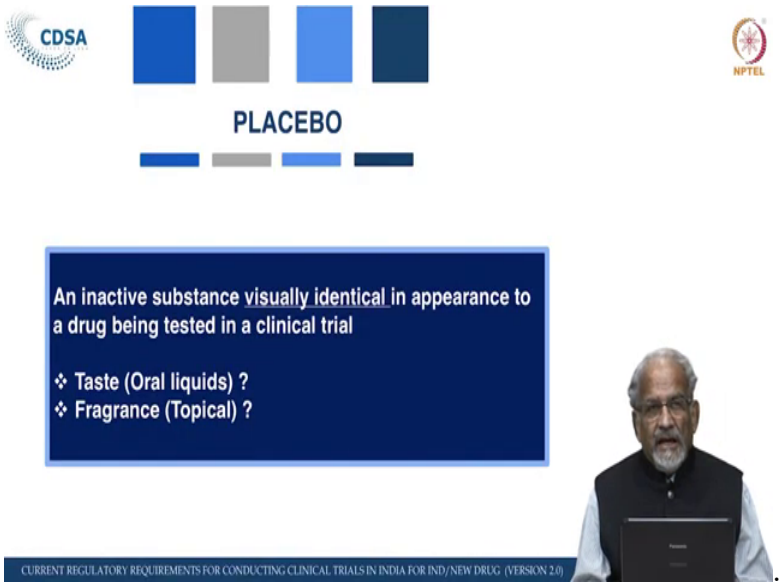

Placebo has been defined now is that an inactive substance visually identical in appearance to a drug being tested in clinical trial. We are still debating and this will be included maybe in the next time, because some placebo can be identically has to be identical in taste particularly when you are using liquid or oral substance or it may have a fragrance for topical application particularly.

And therefore, making placebo which is a liquid or oral preparation which can give you a taste that whether use a taste masking agent or if a specific fragrance then masking agent for fragrance has to be added though this is not been in the has been defined in the regulation, but the procedure has to be there for taking care of these two things as well.

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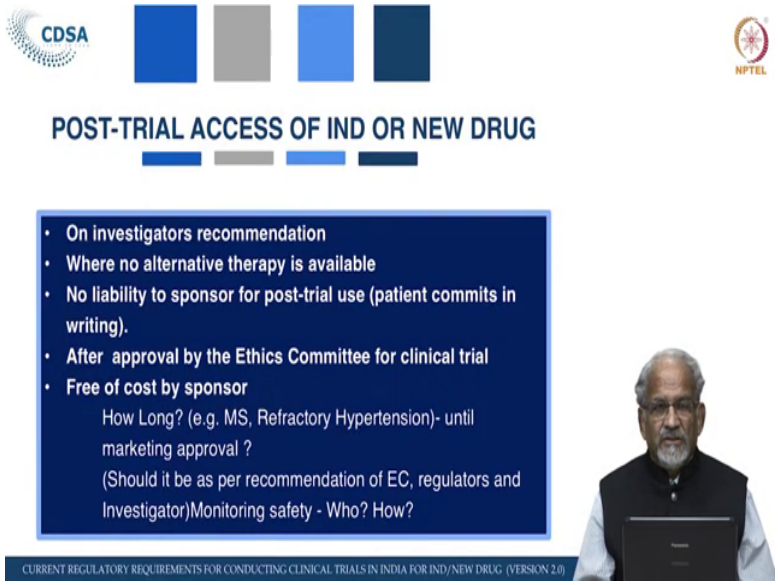

This has been a new addition. What is the post trial access of IND drugs or new drug? After the trial is over it is ethically required and now regulatory requirement that the post trial drug should be I mean available. This is we have provided the guidelines that this type,] this is to be given on the recommendation of the investigator. Only when then there is a no alternative therapy available to the patient only then the person can have the post trial access.

In this case the important thing is there is a no liability to sponsor for post trial access and for that the patient has to give an specific undertaking in writing that he is asking this and the

doctor or the investigator is recommending this, there is a no liability of the company and after approval by Ethics Committee this can be done.

This is important to know that the post trial access the cost is 0 to the patient. And this is to be provided free of cost by sponsor. Now the question which is yet to be settled for how long, particularly in cases like multiple sclerosis MS or Refractory Hypertension suppose there is a drug when the patient is not responding to any drug, but this is and the he has been termed as a refractory hypertension or any other condition which requires a long term. The question is for how long.

Should it be as per recommendation of Ethics Committee, it should be on the regulator or the investigator? And, important issue which needs to be deliberated that who will report the safety of these drugs and who and how? But this is also the responsibility of the investigator who is recommending the minimum reporting of this is also important.

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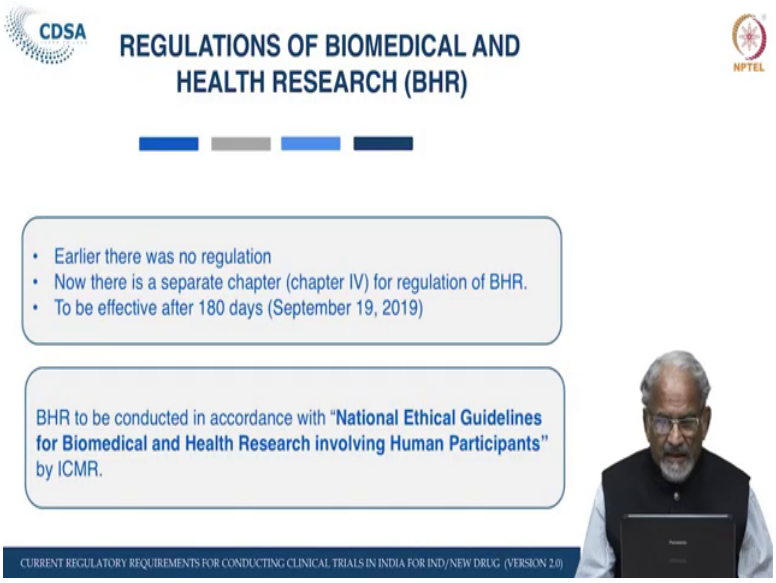

We have now Biomedical and Health Research regulations. This called as a BHR, Regulations for Biomedical and Health Research; there was no such regulation earlier. Now there is a separate chapter, chapter 6, chapter 4 for regulation of BHR and this will be effective after 180 days; that means, from the September 19 later and BHR to be conducted in accordance with National Ethics Guideline for Biomedical and Health Research involving Human Participants by ICMR.

For BHR or say regulations of Biomedical and Health Research, Ethics Committee is required to be registered with Department of Health Research, Ministry of Health and Family Welfare. And this deals with non regulatory studies and Ethics Committee to supervise this study. The SAE, Serious Adverse Events and compensation dealt by Ethics Committee as per BHR guidelines.

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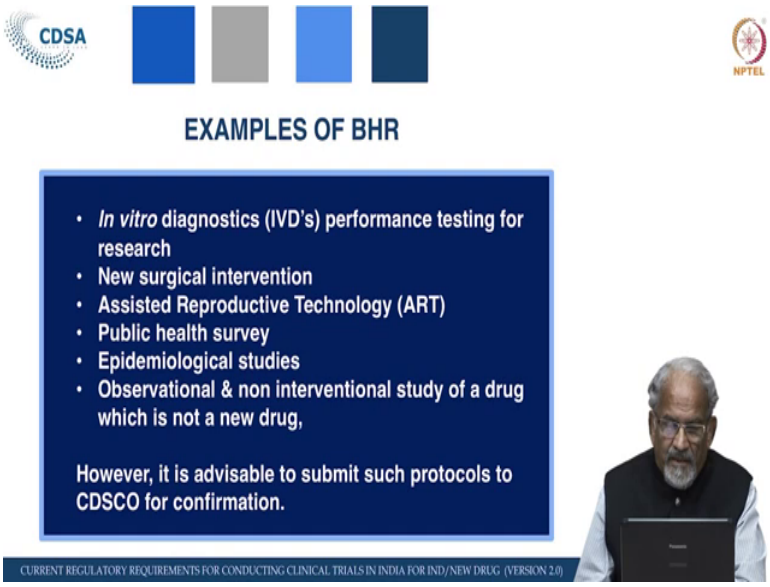

For example, Biomedical Health Research will take care of studies such as in vitro diagnostics IVDs performing testing of research. There is a no surgical new surgical intervention, for example there is a Assisted Reproductive Technology, public health survey maybe epidemiological studies, observational and non interventional history of a drug which is not a new drug. However, in it is advisable that when you are doing observational or non interventional study, it is advisable that you submit such protocol to CDSEO and gets a confirmation from that otherwise this is acceptable.

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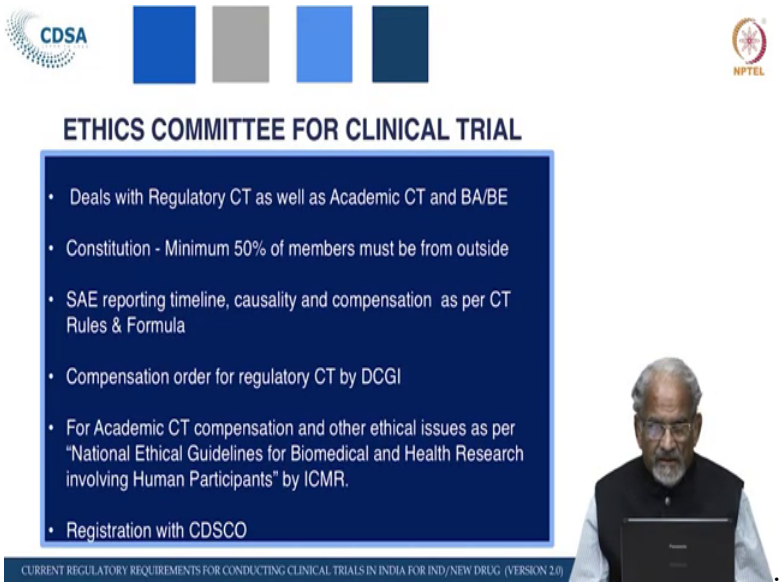

Now, Ethics Committee for Clinical Trial; there are some changes. This deals with the Regulatory Clinical Trial as well as academic clinical trial and also BA BE studies. The constitution is now changed that it should have minimum 50 percent members from outside. Remember, minimum 50 members from outside. SAE timeline reporting, causality in compensation CT rules is the same which was earlier. Compensation order which was there earlier remains the same, but now this has become an order by regulatory process.

For clinical trial compensation for academy clinical trial and other ethical issues would be as per National Ethical Guidelines for Biomedical and Health Research involving human participants which is given in the ICMR booklet. And this has to be registered with CDSEO. So, Ethics Committee for Clinical Trial it has to be registered with CDSEO, it will give

approval for clinical trial as well as Regulatory Clinical Trial as well as academic clinical trial, it can also give for BA BE studies, it should have minimum 50 percent members from outside.

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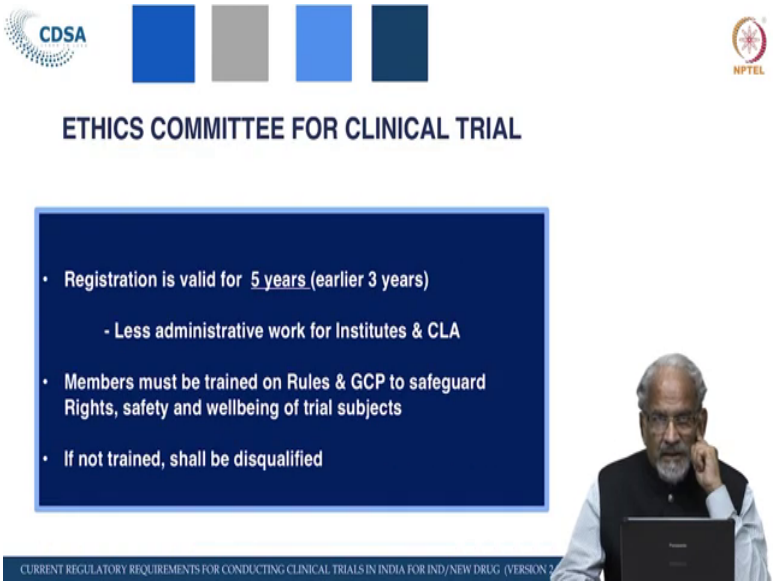

The change in the regulatory framework is the registration for Ethics Committee is valid for 5 years, earlier it was 3 years. And this will reduce the administrative work for the institute and also the administrative work of Central Licensing Authority. Members of the Ethics Committee it is now mandatory that they should be trained on rules and good clinical practice GCP to safeguard the rights safety and well being of the subjects and if not trained the Central Licensing Authority or the Ethics Committee chairman, this Ethics Committee or the member can be disqualified.

And this creates a challenge. Challenge means; a nationwide training how to organize and that is what we are trying to do that organizing a training mechanism by E learning offered by

CDSA or the face to face training program nationwide and we are looking for the modalities how we can find out across the country.

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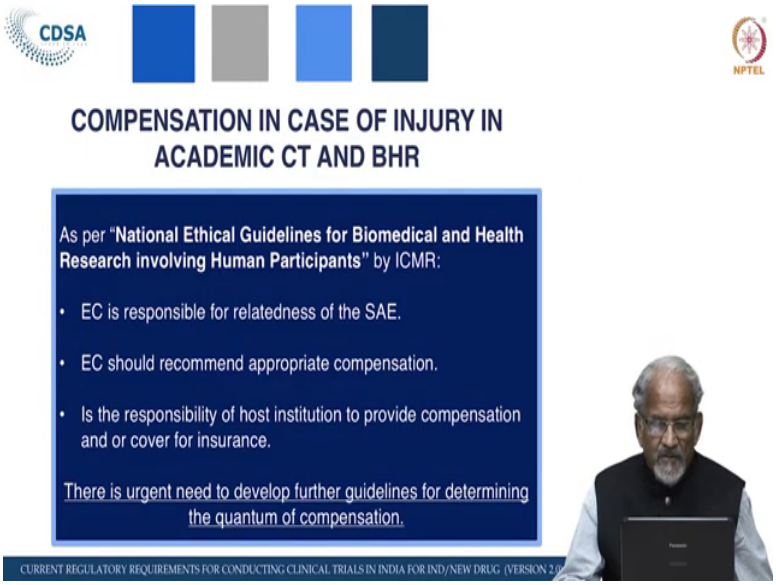

The issue of compensation in case of injury in academic trial or where the trial are governed by Biomedical Health Research is as per National Ethics Guideline for Biomedical Research involving human participant. In academic trial also Ethics Committee is responsible for deciding relatedness of SAE. If you understand in a regulatory trial the Ethics Committee decides SAE, but final decision would be by an Apex Committee set up by regulator.

In Academic Trial Ethics Committee should recommend appropriate compensation. This is written as appropriates the decision of fixing the amount of the compensation largely depends upon the Ethics Committee. It is responsibility of the host institution to provide compensation and to cover for insurance, this is important thing. It is not that the Ethics Committee will

recommend to regulator who will order compensation to the industry. In Academic Clinical Trial, the institution has to make arrangement either through a pool or through the insurance coverage.

Now, there is a need today for developing the guidelines for determining the quantum of compensation in academic trial. In absence of that the clinical trial academic trial majority of the Ethics Committee used the compensation regulation process which is followed by the regulatory clinical trial also. There are now required clarity on the Ethics Committee. One is called as the independent Ethics Committee.

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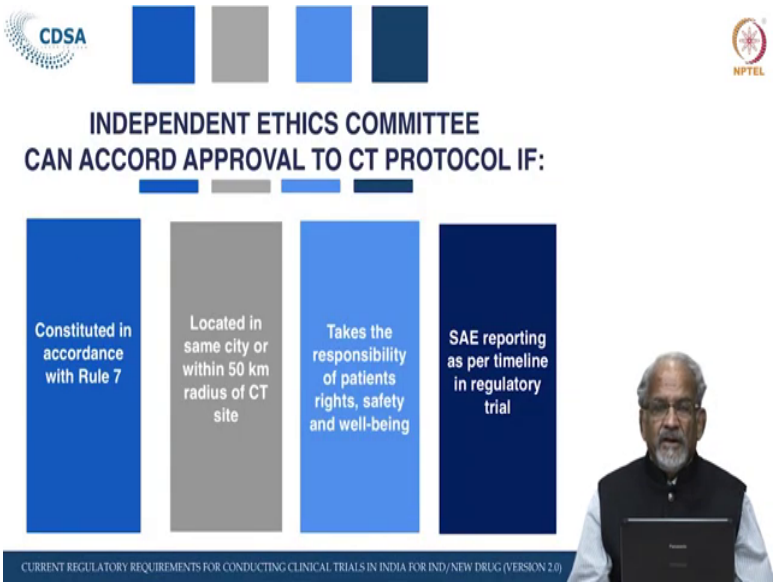

Independent Ethics Committee in addition to the institutional Ethics Committee can approve or can accord approval of clinical trial protocol if it is constituted in accordance with rule 7 which gives the constitution. If it is located in the same city or within 50 kilometres of radius

of clinical trial site that means, to ensure the quick accessibility of the Ethics Committee members to the clinical trial site.

The 50 kilometre is a notional and should not be taken as that 51 kilometres or 49 kilometre will be the border area. And this should take the responsibility of the patient right, safety and well being. SAE reporting is as per timeline of the regulatory trial. Now to take home messages independent Ethics Committee were earlier only permitted to do BA BE studies. But now if the Independent Ethics Committee is trained competent formed as per rule 7, they can accord permission of the trial site provided they are within 50 kilometres. There are two important things; one is the Ethics Committee which is approving for Biomedical Health Research as per and it is also approving clinical trial and it is also approving BA BE studies.

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The question would be where they should get registered. If you remember for doing a clinical trial which is a Regulatory Clinical Trial, we mentioned that they have to be registered with CDSEO whereas, for BHR for an academic clinical trial they have to be registered with the Department of Health Research.

Now if they are doing both then they have to be registered at both the places in Ministry of Health, the Health Research as well as in CDSEO. There are some new timelines for applications of new drug and IND which has been now in place.

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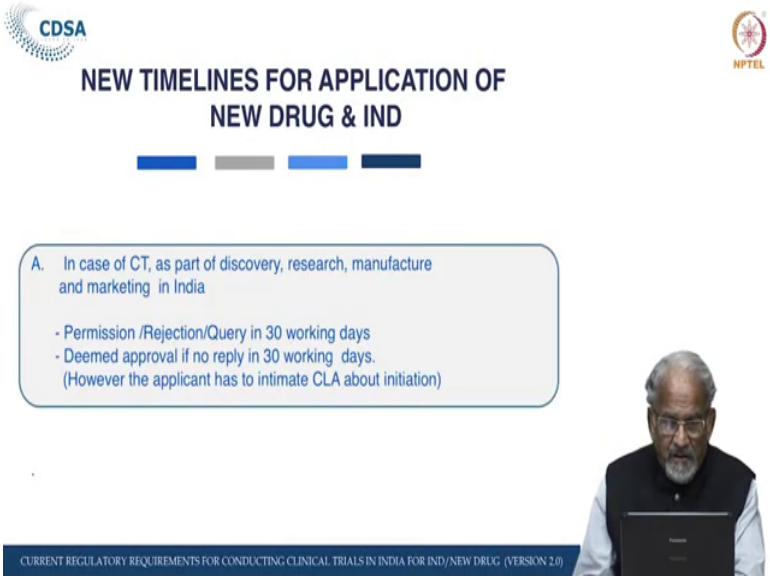

That is; in case of clinical trial as part of discovery and research or manufacturer in India, if this is primarily promote clinical trial drug discovery for India by Indian industry. And this case permission rejection query must be given by the regulator within 30 days. If in 30 days, the

applicant of new drug application or IND is not received response it will be deemed as approved which is an important challenging development.

However, the applicant has to intimate CLA for initiation; that means, after even after 30 days response is not received from CLA, Center License Authority will be deemed as approved, but when you enroll the first subject it has to be informed.

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For other applications for clinical trial or new drugs, permission, rejection or query for 90 days; if the drug is developed outside the country, then the time period is 90 days and if you do not receive the response it is not a deemed to be approved. So, you have to wait for the response. The primary aim is to promote clinical research and drug development in India.

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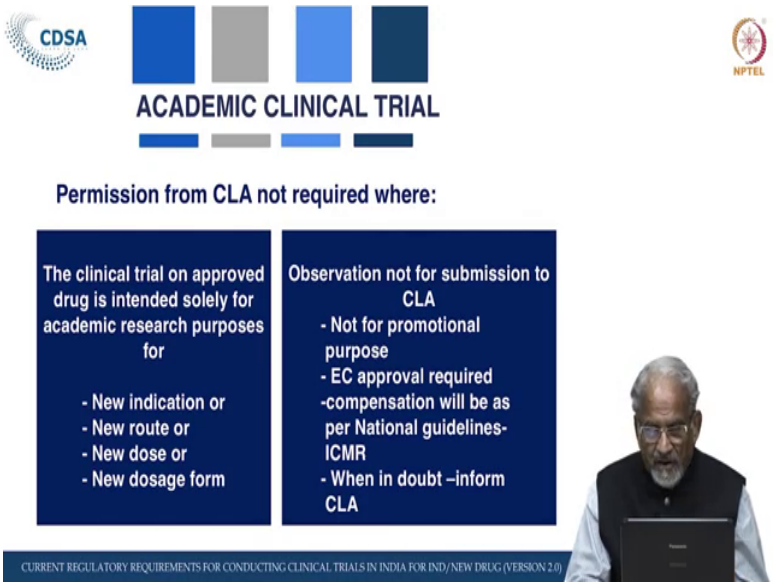

Now for academic clinical trial; the clinical trial on approved drug is intended solely for academic research purpose that is called as an academic. In this case, permission for central licensing authority is not required. And this is usually for new indication may be for new route or for new dose or dosage form, this will become academic. The important thing is the observation cannot be submitted for are not meant for submission to Central Licensing Authority. And not for promotional purpose and Ethics Committee only can approve it, compensation here will be as per National Guidelines of ICMR, but whenever there is a doubt you must inform Central Licensing Authority.

So, that is a new development of academic clinical trial. The primary intent is that this is to identify the proof of concept establishing and not for bringing new drug into the market.

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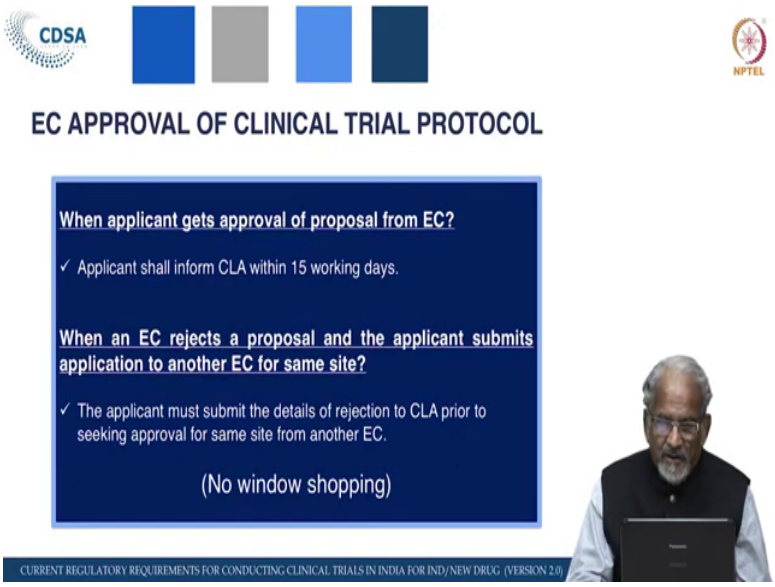

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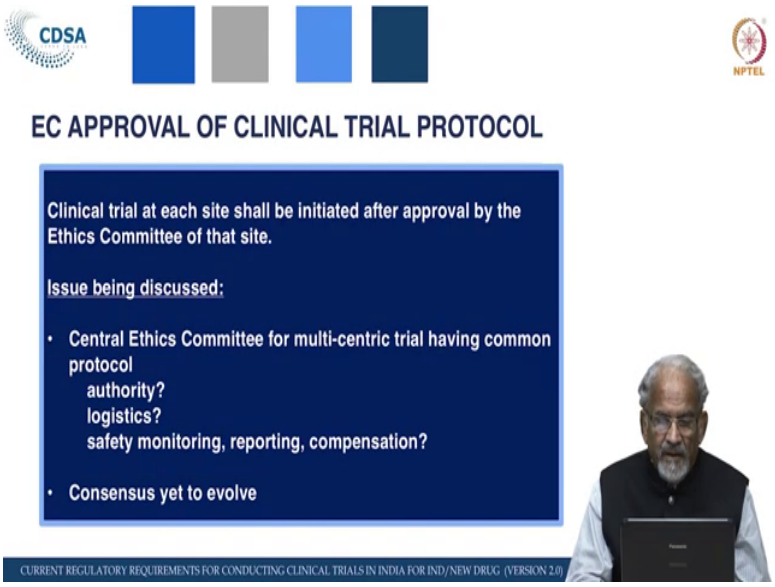

In Ethics Committee approval for clinical trial protocol, the clinical trial at each site shall be initiated after approval by Ethics Committee of that site. That means the ethics each Ethics Committee has to give approval. We are now discussing can there be a mechanism of Central Ethics Committee for trial which are multicentric, but there is a common protocol. But logistics and who will be the competent authority, this is still being worked out. So, this is not part of the regulatory process, but this is what we would like to have your feedback on this and we are working on that and the consensus yet to evolve.

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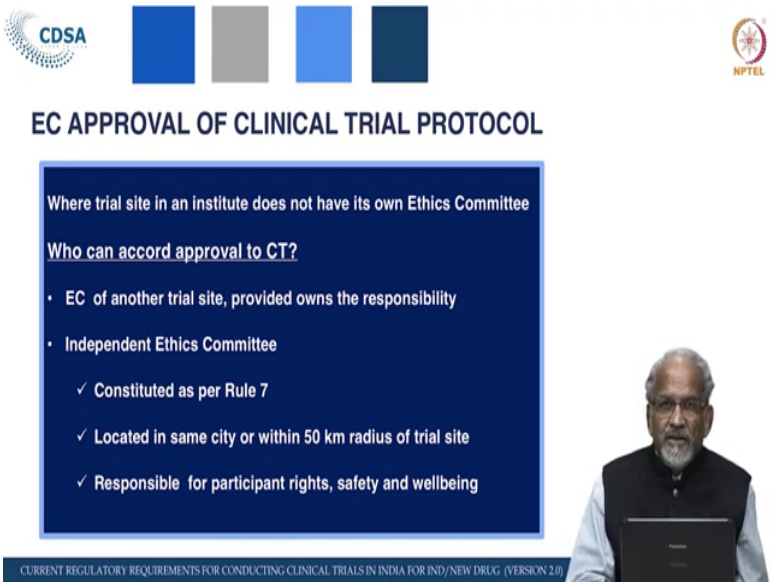

Where trial site is an institute does not have it is own Ethics Committee. Many times the a trial site may not have it is own Ethics Committee. The question is who can accord approval. Ethics Committee of another site can approve now, provided it owns the responsibility of safety and any consequences and it can be done by Independent Ethics Committee also, provided it is constituted as per rule 7. And as I mentioned earlie,r located in the same city within 50 kilometres radius and responsible for safety and well being.

When an applicant gets approval for of proposal from EC, that the applicant shall inform CLA within 15 working days, this is a new change. When Ethics Committee rejects a proposal and the applicant submits the application to other EC which happens that I have submitted proposal to one Ethics Committee, it rejects and because of some reasons I submit it to another Ethics Committee. But when you do so, you have to submit the application and then you have to give must submit the details of rejection to Central Licensing Authority and that is

primarily because that you do not do window shopping, that this has rejected. So, I let us try on this shop, I have this Ethics Committee and may get approved. So, when you approach other Ethics Committee this is important that you give the reasons for the rejection.

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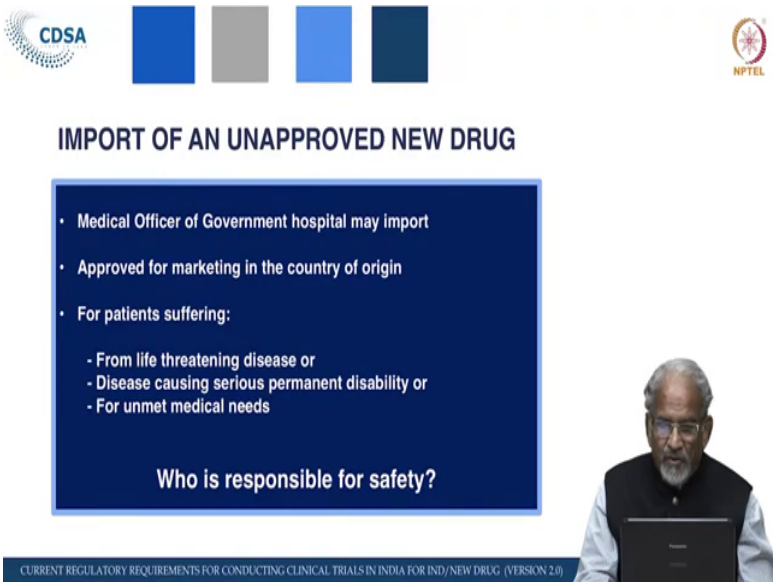

A new development in this rule is import of unapproved new drug. The drug which has not been approved in India, in that case the medical officer of as on date on the government hospital may import it. And approved for marketing in country of origin that is it has to be and the patient is suffering from life threatening disease, disease causing serious permanent disability or an unmet need.

So, if a patient suffering from the life threatening disease, unmet need and causing serious illness in that case if the medical officer or the indenting person from the government hospital thinks that this drug will be useful there is a provision to import such unapproved new drug.

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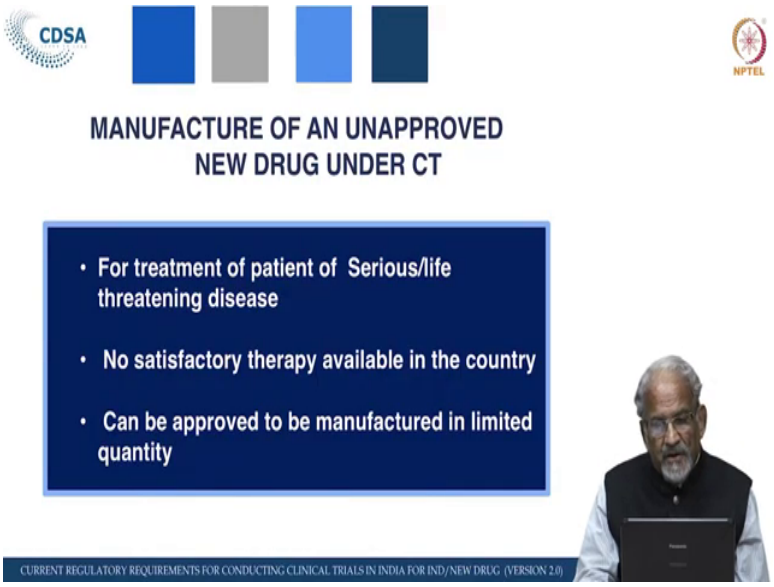

Also there is a provision now for manufacturing on a unapproved drug under an which is under an clinical trial, but not approved otherwise. For treatment of patient from serious life threatening disease, no satisfactory therapy available in the country can be approved for manufacturing limited quantity not more than 100.

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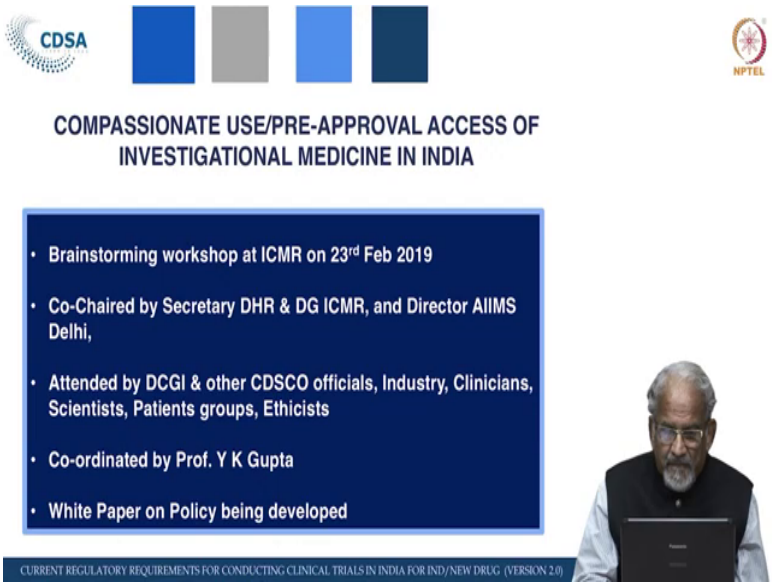

We are today we are also discussing, but this is not part of the rule that compassionate use or which is called as a pre approval axis of investigational drug in India. The drug which has not been approved in any country including India, how and under what provision with what guidelines this drug can be made available to the patient in India. This is a no rule for this and a white paper on this is being developed, but soon this may find acceptance in the regulatory process.

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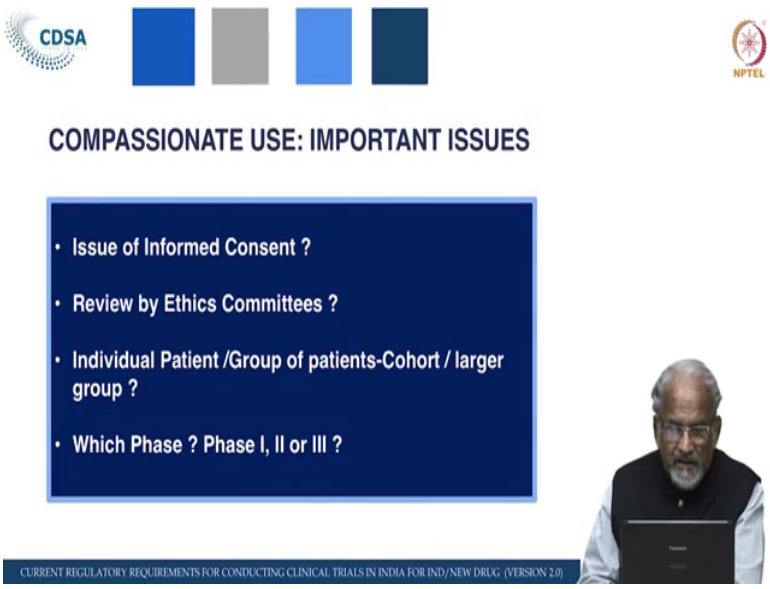

This is called as an compassionate use. And in this we need your suggestions and views what would be the informed consent in this, whether this should be reviewed by Ethics Committee and what points Ethics Committee will review, individual patient if it is required or maybe a few patients require. Whether the drug which is under phase 1, phase 2 or phase 3 in any part of the word, but it is not approved anywhere, how this can be indented and who pays the cost.

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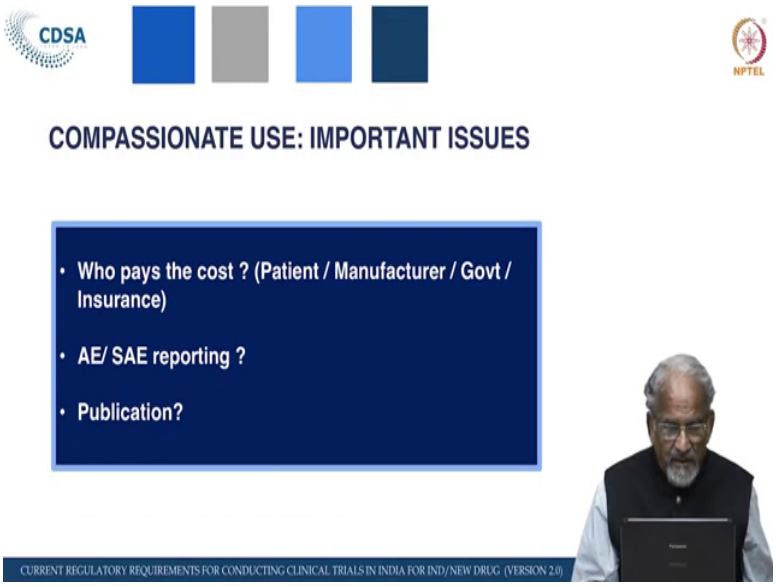

We have in couple of meetings have of one opinion that the patient should not pay, there must be a mechanism for SAE or AE reporting and this cannot be published because this has not been the research mode and this should not also be part of the clinical trial dossier submission.

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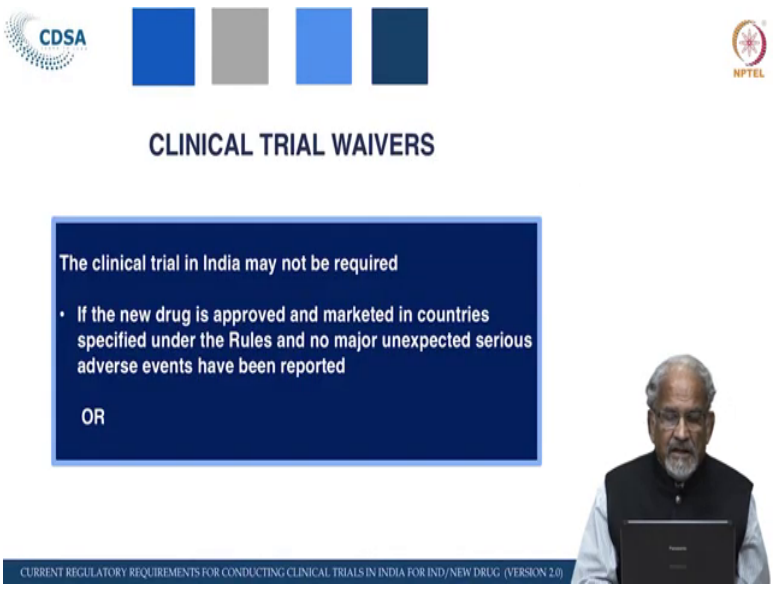

There are now provision of clinical trial waivers in some situation; that is a clinical trial in India may be may not be required in case if the drug is approved and marketed in countries is specified under the Rules and these countries are primarily the well regulated countries. And therefore, this has not been named, because the list can increase when the regulator thinks that these are the main regulatory countries but as on day this is USA, UK, Japan. And no major unexpected serious events have been reported.

In that case, the trial can be waived off or there is a global clinical trial in which India is a partner, part and there is no evidence that there is a difference of enzyme or gene involve in metabolism which affect the PK PD, safety and efficacy of the new drug.

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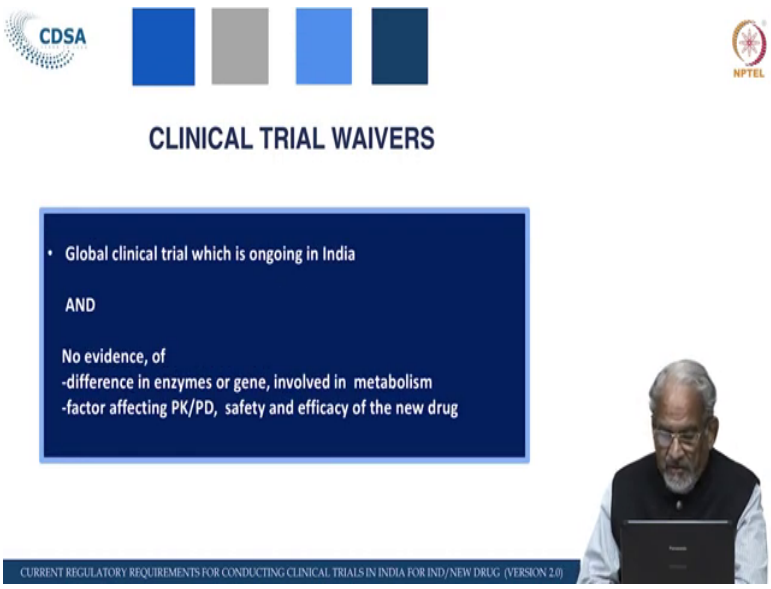

So, if there is an unmet need, if there is a serious concern, if there is a drug which is approved outside and there is a no reason to believe that there is a genetic difference, then case by case examination the clinical trial waiver can be considered by the regulator.

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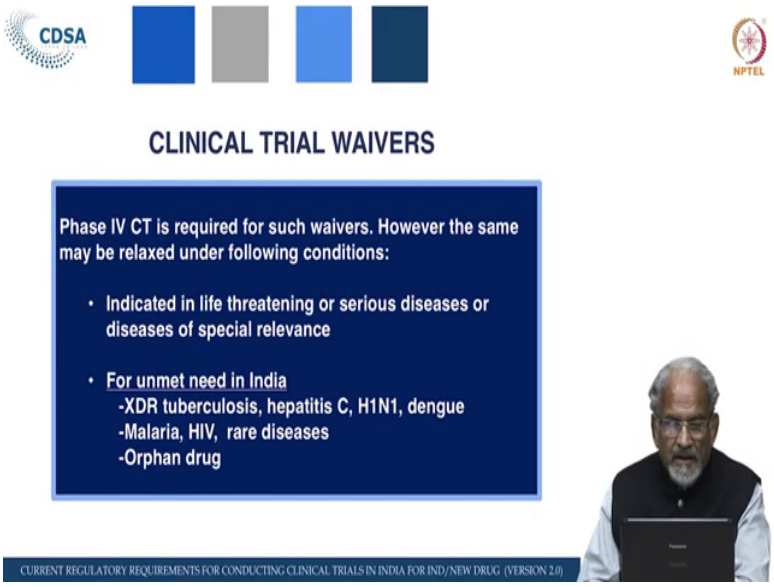

Phase IV CT is required for such waivers; however, the same may be relaxed under following condition: Indicated in life threatening or serious or serious special relevance for unmet need like tuberculosis, hepatitis, H1N1, dengue, malaria, HIV and rare disease and drugs for orphan drugs disease. There is now process of accelerated approval to a new drug.

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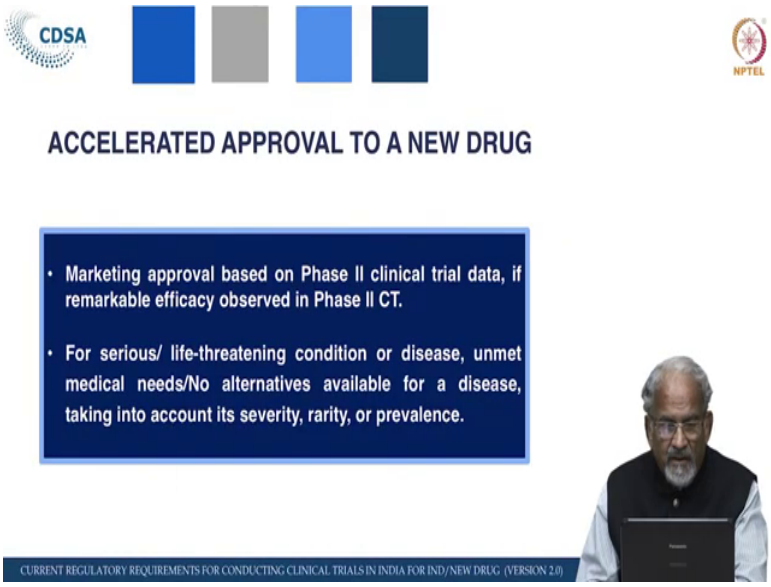

Now, this marketing approval faced on, based on phase 2 clinical trial data, if remarkable efficacy observed in phase 2 clinical trial then there is a reason to have an accelerated process. For serious and life threatening conditions or disease unmet medical needs when there is no alternative treatment available and consideration taking into account severity, rarity or prevalence, there can be accelerated approval process.

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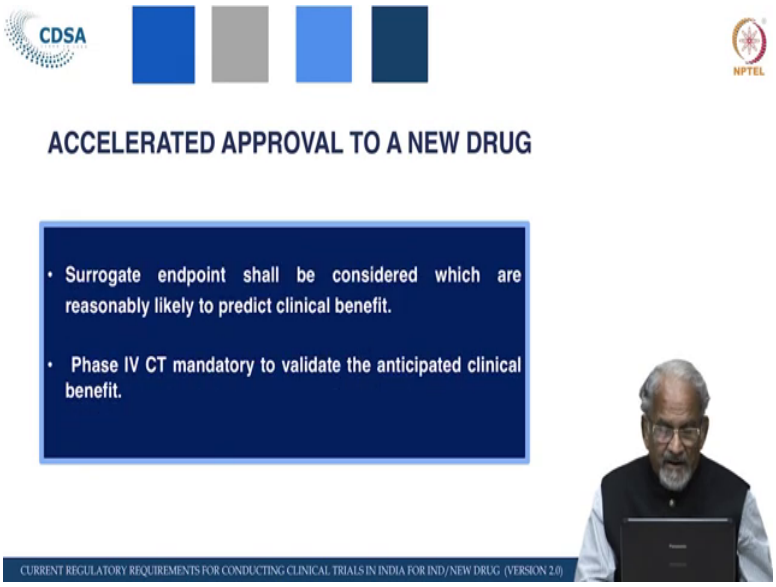

Surrogate endpoints shall be considered which are reasonably likely to predict clinical benefit. In many cases you have no certain endpoints, in that case surrogate endpoints can be considered. Expert committees now included in CT rules, you may be going through SEC Committees, many SEC Committees this is called a Subject Expert Committee. Now these expert committees is now has been defined in rule earlier this was an administrative decision only.

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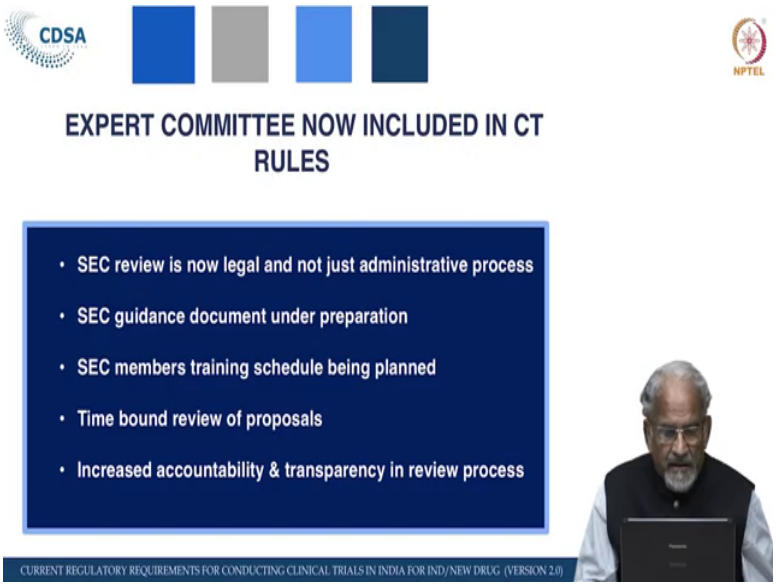

What we are doing now also the SEC review is now legal and not just an administrative process. SEC guidelines document under we are preparing a guideline document and members are being trained and time bound review of the process. This is the all these read are the agenda which is being worked upon.

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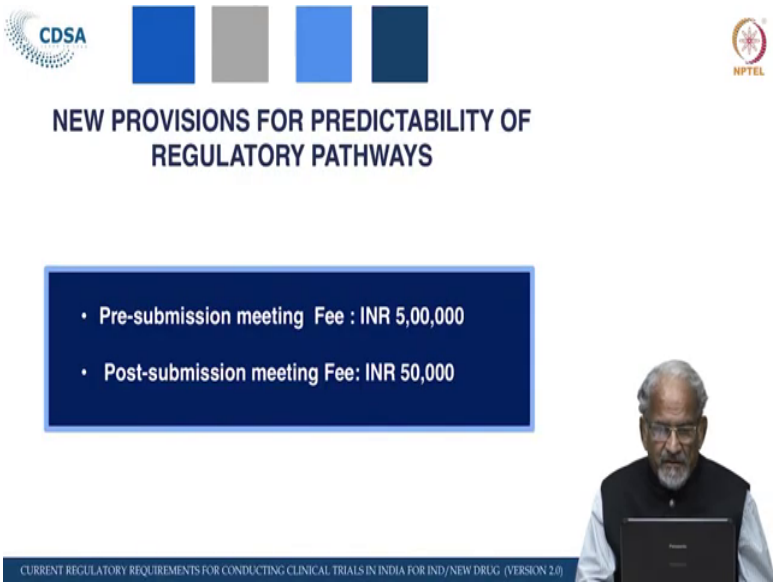

Fees for new for pre submission meeting now, there is a provision of pre IND submission meeting which was not earlier. And this guideline detailed guidelines for this has been worked out and the fee have to pay to 5 lakh rupees and there will be a an expert or a body of expert regulator will meet the person who is pre IND meeting seeker, pre submission and will provide the guidance. There is also provision of having a post submission meeting and the fee is 50000.

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To promote research by small scale industry and academic research, the fees is 50 percent and for the government and autonomous institution there is no fee. So, there is a reason to smile by the academic institution that the government has waived off complete fee for academic institution to promote research in India.

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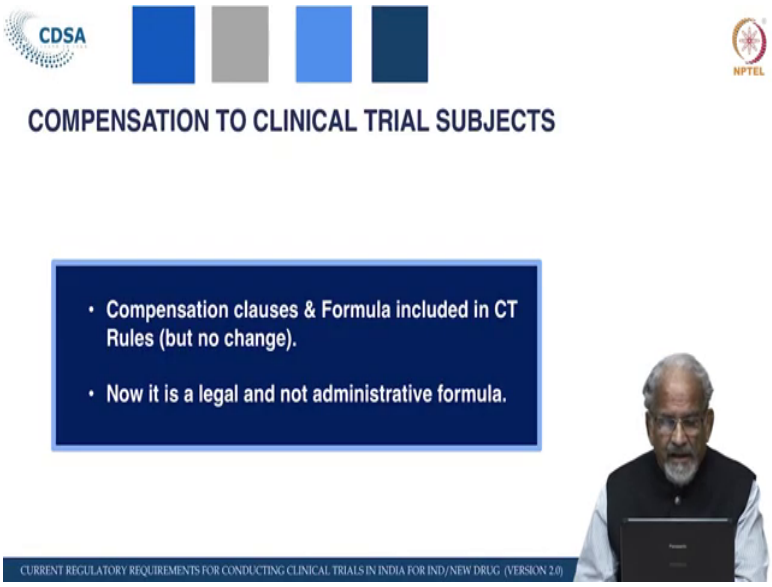

Compensation of clinical trial, there is no change. However, now this formula which we introduced much earlier is now a regulatory status. Some change or ease has been there in animal toxicology requirement.

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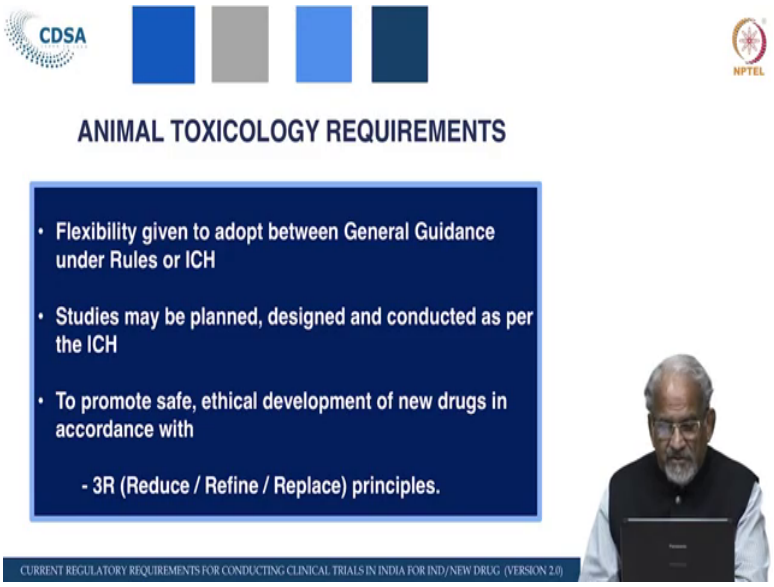

And that is flexibility given to adopt between general guidance under rules or ICH and studies may be planned designed and conducted as per ICH which will be acceptable. And the important thing is to promote safe ethical environment of new drugs which is in accordance with rule of 3R. A reduced number of animals as much as possible, wherever possible, refine your technology. So, that with a minimum experimental process you give maximum information; replace the animal wherever possible with the non animal means in vitro or in silico models and therefore, government is also promoting replacement of animals with other alternatives for which they require validation process.

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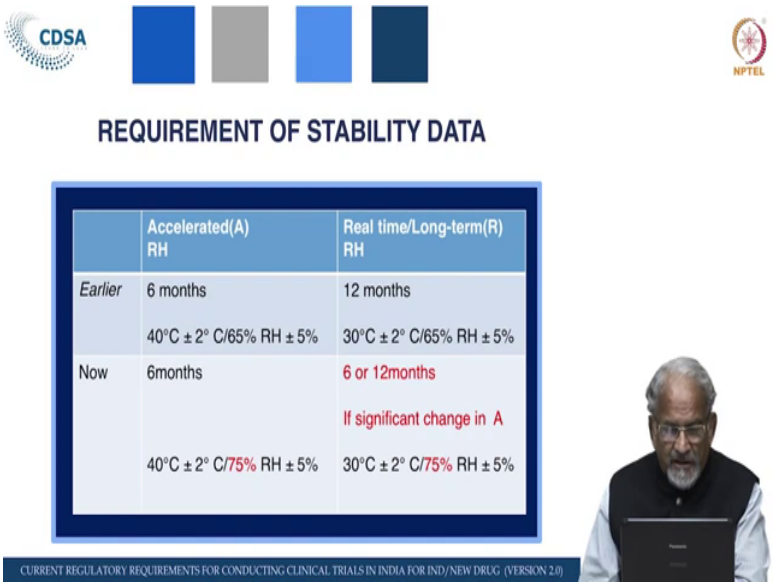

Stability data; there is now clarity on a stability data. If you just see the earlier it was 6 months accelerated data and there was a real time data was 12 months. But now the accelerated the relative humidity and the temp is now 75 percent which is this slightly more and the significant change is that from 6 or 12 months. So, the real time and the accelerated time; that means, even if you do the real time for 6 months it is acceptable. And so, this is the difference in requirement of this safety data.

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Post marketing safety assessment; detailed guidelines in the fifth schedule post marketing safety assistant may be carried out in the different ways that is phase 4. Post marketing trial is a DCGI directs them and as per approved protocol by Central Licensing Authority and all regulations of clinical trial guidelines compensation will apply and this is called as a phase 4 trial.

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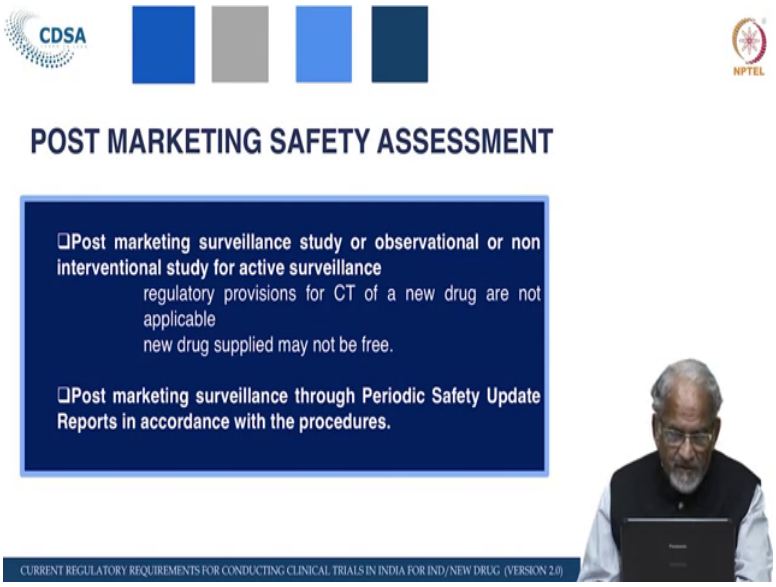

The second thing is post marketing surveillance or observational or non interventional study for active surveillance. That is, there is a regulatory provision of CT of new drug this is not available, not applicable; that means, no compensation and the new drugs supplied may not be free. So, the priority is now phase 4 trial where there is a DCGI direction to do it. There is a protocol which has been approved.

In this case, all rules of clinical trial will follow including compensation and the drugs have to be free of cost. Whereas, another category is the post marketing surveillance study; where this is not a regulatory directed, no protocol approval required and this case the drug is also not free. The third is what you conventionally say or know is the PSUR. That is what you do every 6 months for 2 years and for every year for next 2 years; that means, for 4 years.

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Now, the post marketing surveillance study or observational or non interventional study for active surveillance. A non interventional observational study means a study in which the investigator does not assign the participants any specific intervention or treatment that is an observation does not assign. Whatever the physician has prescribed, that is what it is.

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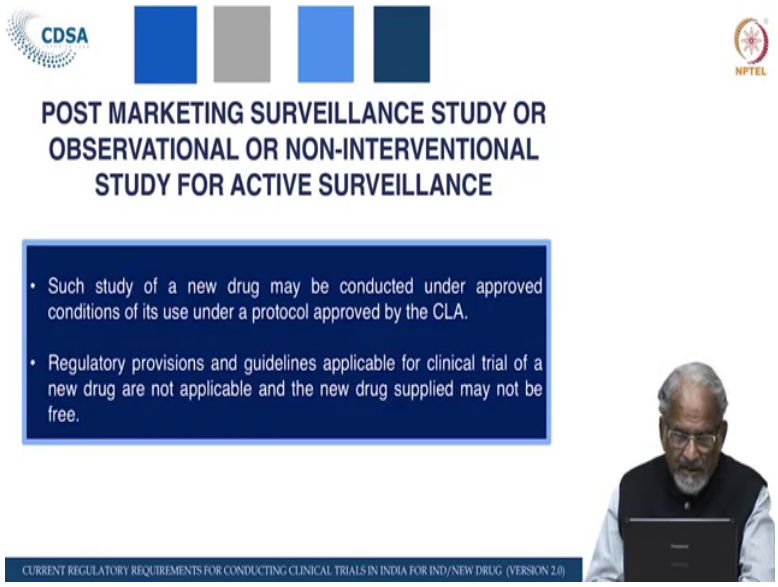

Such study of a new drug may be conducted under approver approved conditions and it is used under protocol approved by CLA. Regulatory provisions and guidance applicable for clinical trial of a new drug are not applicable and the new drug supplied may not be free in this case.

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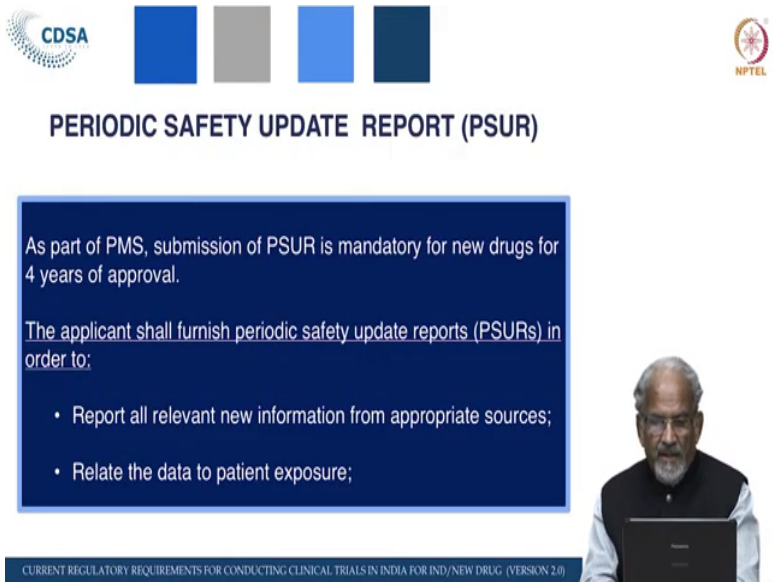

So, PSUR as part of PMS, submission to PSUR is mandatory for drug for 4 years and in the sense for first 2 years every 6 months and next 2 years every year.

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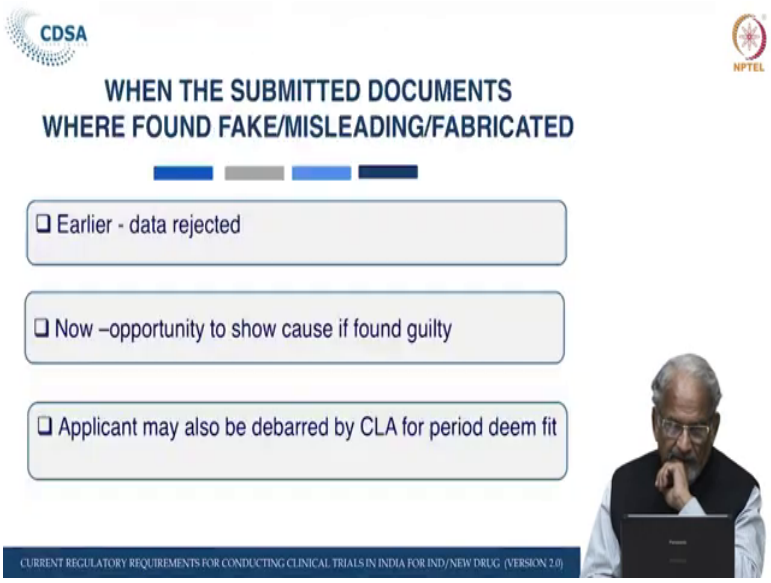

When the submitted document found fake, misleading or fabricated; earlier it was only the data was rejected, but now there is an opportunity to show cause if found guilty, applicant may also be debarred by CLA for period as they deem fit. So, this is now slightly stricter.

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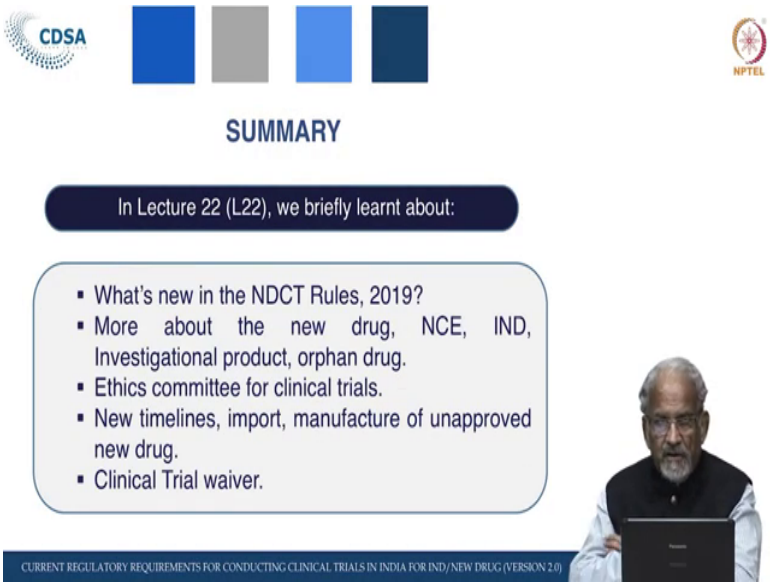

Now, in this, I would just like to add few things that what are the points which you would like to highlight. A: starting from the beginning the Clinical Trial Rules are to simplify the regulatory process. B: it has become more clarity, C: the compensation for academic trial and for clinical trial for regulatory purpose have been defined the timelines have been defined.

So, this is the purpose of this. I hope that you have understood the salient features of clinical trial rules which have been now called as a Clinical Trial Rules 2019.

Thank you very much. We expect some feedback from you. We will be happy to answer questions through email or interactive forum.

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Thank you.