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

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Lecture – 10
Guidelines to Conduct BA/BE Studies

Hello friends, welcome back to the course Current Regulatory Requirement for Conducting Clinical Trial in India for New Drug and the Investigational New Drug. So, today, we are going to see the lecture 8 which is related to the guidelines to conduct BA BE studies. In previous lecture, we have seen the rules related to the bioavailability and bioequivalence study. In this lecture, we are going to see guidelines to conduct BA be studies.

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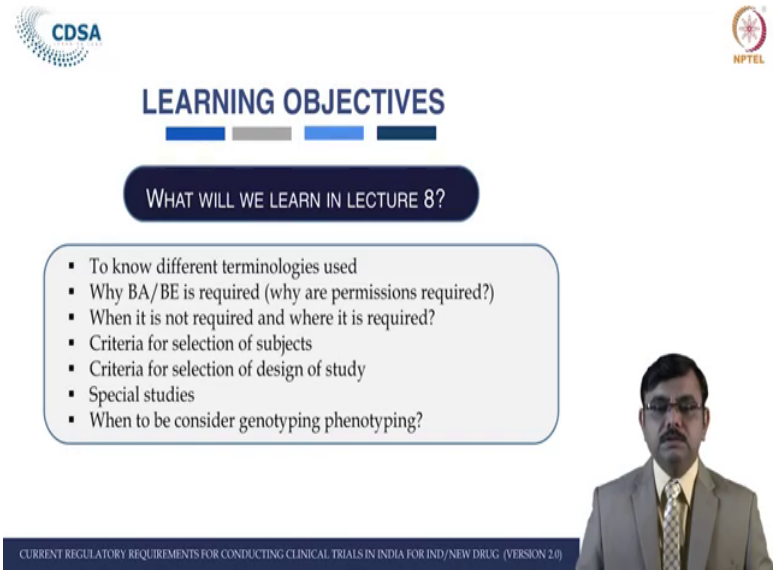

So, the expected outcome from this lecture, the learners will come to know the different terminologies like a pharmaceutical alternative, bioequivalence and other terminologies. Then, why BA be is required? When it is not required and in what cases it is required? Then, criteria for selection of the subject; how to select the subject, which are the things to be consider? Criteria for selection of the design of study, then, special studies food effect and when to consider genetic phenotyping.

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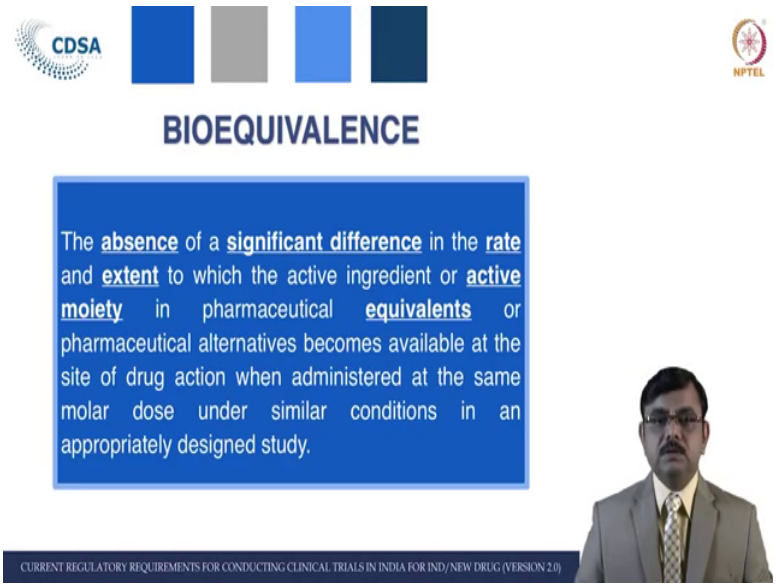

So, let us see one by one. We will start with the definition of the bioequivalence. Bioavailability definition we have seen in our previous lecture. So, the bioequivalence is can be achieved and it can be said that it has been achieved when there is absence of a significance difference in the rate and extent that is bioavailability to which the active ingredient or active moiety in pharmaceutical equivalent or pharmaceutical alternatives. The definition of this we

will see in the next slides. Become available at the site of drug action when administered at the same molar dose under similar condition in an appropriately designed study.

So, when there is a absence of significant difference in the bioavailability from a two different molecules having the same active ingredient, then it is called the bioequivalence has been achieved.

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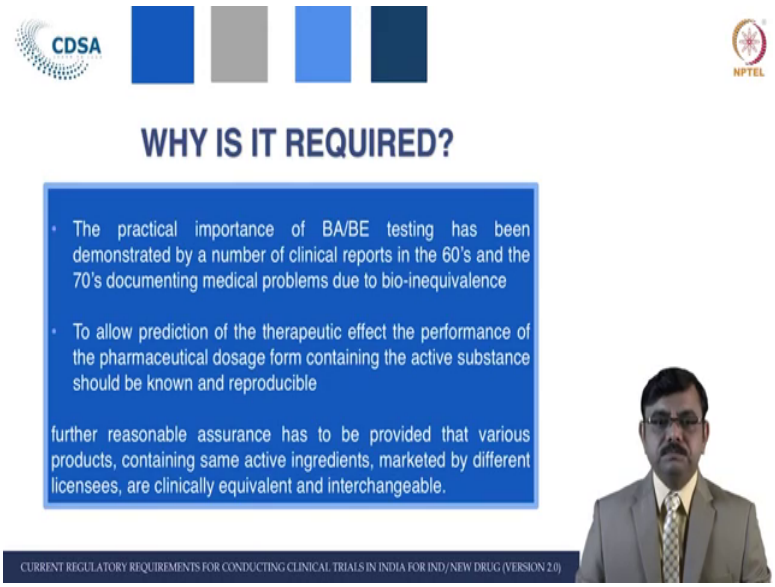

So, why the bioequivalence study is required? As we know the practical importance of BA BE testing has been demonstrated by a number of clinical report in the 60's and 70's documenting medical problem due to bio-inequivalence. Because of the lack of equivalence, there was a problem in achieving the targeted therapeutic effect that has been shown by the different published literature in 60's and 70's.

To allow the prediction of the therapeutic effect, the performance of the pharmaceutical dosage form containing the active substance should be known and reproducible. Further to give the reasonable assurance and it has to be provided that various products continuing same active ingredient marketed by same different licenses are clinically equivalent and interchangeable.

If it is a bioequivalent, then the different product which are marketed and manufactured by the different manufacturer with a same moiety can be interchangeable. Further, bioequivalence study; this study should be conducted for the comparison of two medicinal product containing same active substances.

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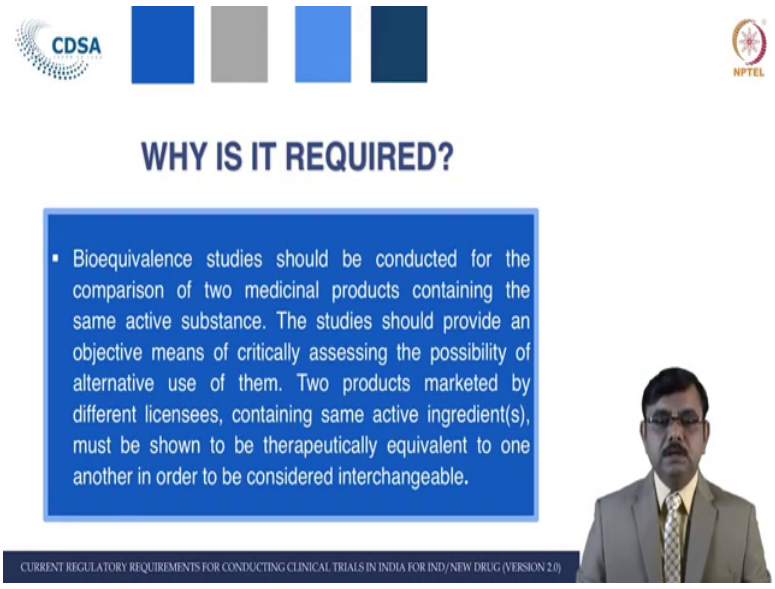

The study should provide an objective means of critically assessing the possibility of alternative use of them. Two products marketed by different licensing containing same active

ingredient must be shown to be therapeutically equivalent to one another in order to be considered interchangeably. There are many methods to see the whether these two different products, they are actually equivalent or not this methods are enumerated here.

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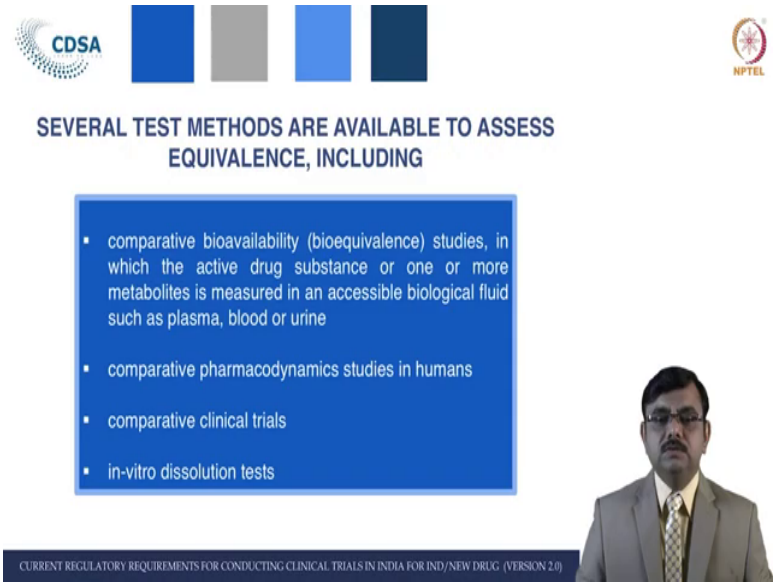

Comparative bioavailability, that is bioequivalence studies in which the active drug substance or one or more metabolites is measured, in an accessible biological fluids such as plasma, blood or urine; so, this is one of the method. Then, comparative pharmacodynamics studies in humans this the pharmacodynamics studies can also be done to see the bioequivalence; comparative clinical trials and in vitro dissolution test.

So, in-vitro dissolution test when there is no need of the co relation between the in-vivo and the in-vitro. The in-vitro dissolution test with the apparatus mentioned in the USP or IP using the apparatus, it can be done.

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Let us move toward the some important definitions. The bioavailability, it is the rate and extent to which drug is available in the systemic circulation means whatever the fraction of the drug which is available in the blood circulation that is called the bio available drug. Clinical trial site it is the site means any hospital or institute or any other clinical establishment having the required facilities to conduct a clinical trial.

So, it can anything, it can be anything like a hospital institute, but it should be provided with the facilities to conduct such a trials. Then, good clinical practices guideline; it means the guideline for conduct of clinical studies in India and which is formulated by the CDSCO and adopted by the DTAB that is the Drug Technical Advisory Board.

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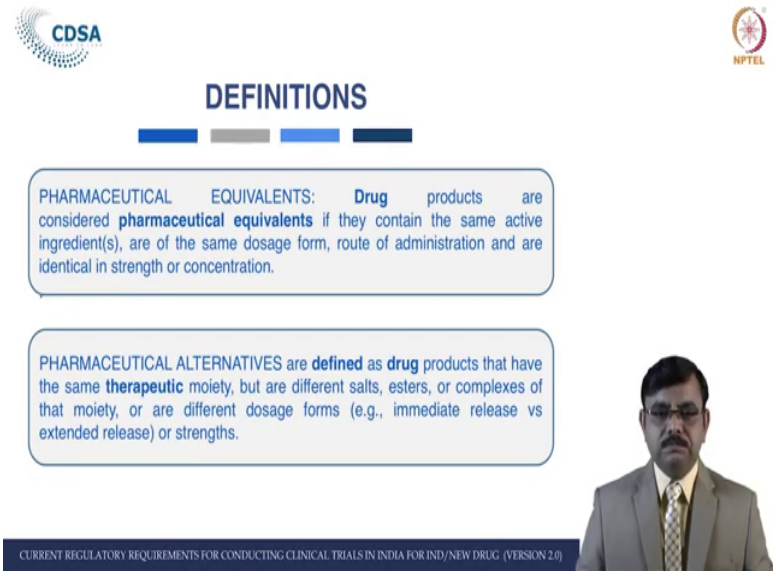

Pharmaceutical equivalent; it is drug product are considered pharmaceutical equivalent, if they contain the same active ingredient, are of the same dosage from route of administration and at identical in strength or the concentration. Then, it is called a pharmaceutical equivalent.

Let us see what is mean by a pharmaceutical alternatives. The pharmaceutical alternatives are defined as the drug product that have the same therapeutic moiety, but are different salt ester or complexes of that moiety or are different dosage form. For example, immediate release dosage form, extended release dosage form, control release dosage form or that that may be a different in a strength then, it is called as a pharmaceutical alternatives.

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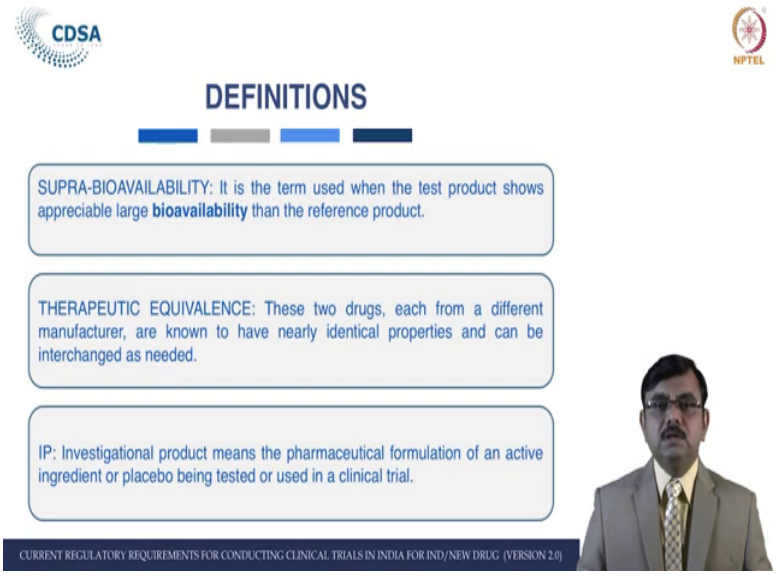

What is supra bioavailability? We have seen the bioavailability that is rate and extent now let us see what is mean by supra bioavailability. Supra bioavailability it is the term used when the test product shows appreciable large bioavailability than the reference product. As we know there is a comparison of the reference product with the test product for the bioequivalence and when the test product shows larger and appreciable bioavailability than the reference product, then it is called a supra bioavailability.

Let us see what is means by therapeutic equivalence, when these two drugs each from a different manufacturer are known to have nearly identical properties and can be interchanged as a needed. Then, it is called it is having therapeutic equivalence. So, in this bioavailability bioequivalence study clinical trial, we are using the drug which is called investigational

product. So, as per rule the investigational product means in the pharmaceutical formulation of an active ingredient or placebo being tested or used in clinical trial.

Now, let us move towards the bioavailability study, when it is required and when it is not required.

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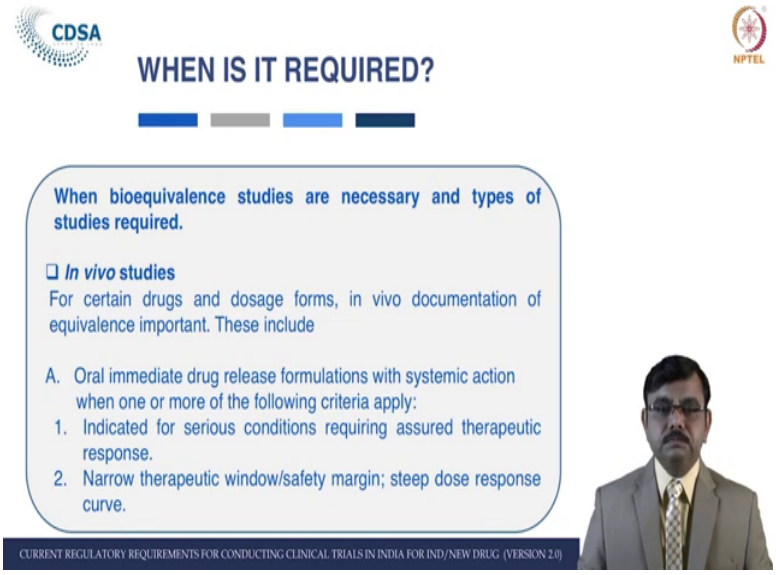

So, there are actually two types in vivo and in vitro. In vivo that is in the animal or in the human body; in vitro it is a outside the body. So, where it is required and where it is not required, we will see one by one.

So, the first when it is required, when bioequivalence studies are necessary and type of studies required. So, first is the in vivo studies; for certain drugs and dosage form in vivo documentation of equivalence through either a bioequivalence study or a comparative clinical

pharmacodynamics study or comparative clinical trial study is regarded as a specially important.

For example, if it is a oral immediate drug release; in case of oral immediate drug release formulation, which is having a systemic action and when one or more of this criteria mentioning here are to be applied. When this oral immediate drug release formulation are indicated for serious conditions requiring assured therapeutic responses, in that case it is required to have the in vivo bioequivalence studies.

When such a such type of oral immediate drug release formulation is having narrow therepeutical window or the narrow safety margin or steep dose response curve, then in that case also it is required to have the bioequivalence study. Because if there is a no bioequivalence study and even in a small difference, even in a small difference which is observed and it is found that the drug is not available in the blood circulation, then it is very difficult to treat that disease condition.

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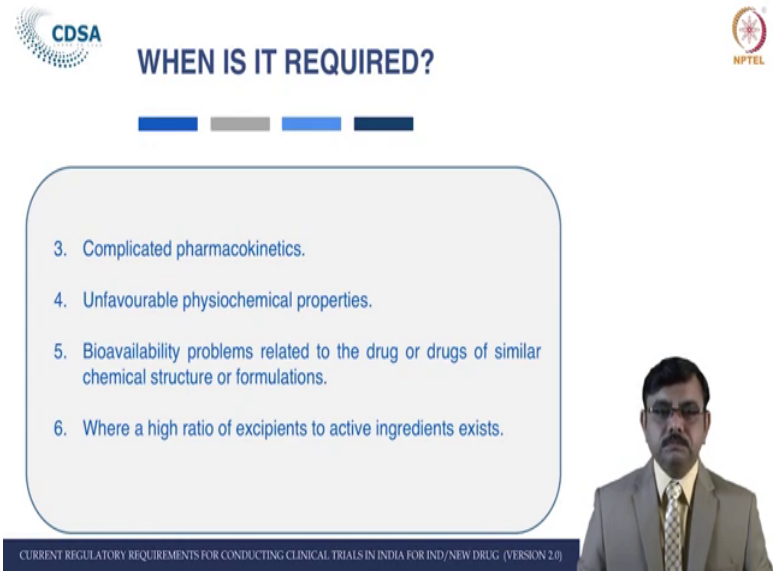

When the pharmacokinetics complicated by a variable or in complete absorption or absorption window non-linear pharmacokinetic, pre systematic elimination or when the drug is having high first pass metabolism that is more than 70 percent. In such cases also in vivo bioequivalence study is recommended. When there is a unfavorable physiochemical properties, we have seen in last lecture if it is low solubility low permeability, then it will require a bioequivalence study.

For example, if there is a instability in the product or the metastable modifications are there; poor solubility, poor permeability are there, then in that case the in vivo study of the bioequivalence is required. When the documented evidence for bioavailability problems related to the drug or drug of similar chemicals structure or formulation, when it is documented from the published literature where there is a problem with the bioavailability or solubility, in that

case also it is required. Next is where there is a high ratio of excipient to active ingredient exist. So, in such cases also it is required to demonstrate a in vivo bioequivalence.

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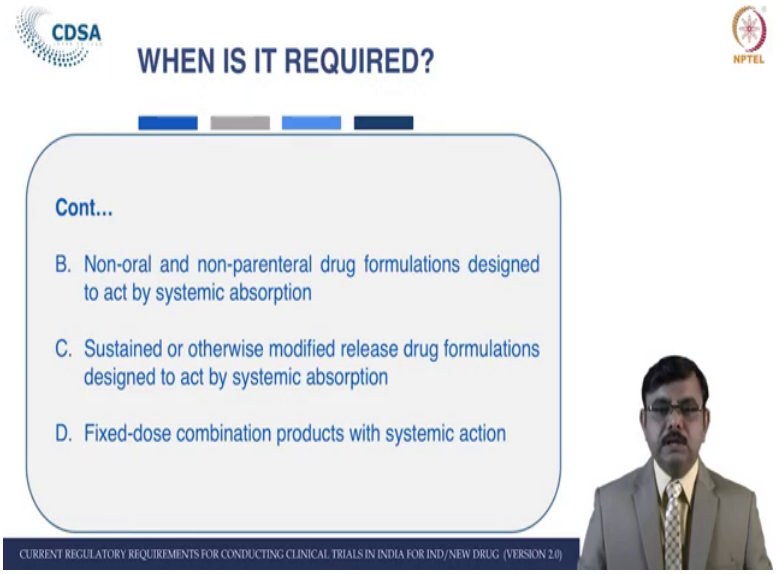

So, all these were for the oral formulation. Now, the next is for the non oral and non parenteral drug formulation designed to act by systemic absorption, even if it is a non-oral and non-parenteral; but if it is designed to act by systemic circulation or systemic absorption, then in that case is also required.

In case of sustained or otherwise modified released drug formulation designed to act by systemic absorption. Then, in case of fixed dose combination product with the systemic action. So, wherever there is a expected systemic action or the systemic absorption drugs is required to be act through the systemic circulation, then in that case it is required.

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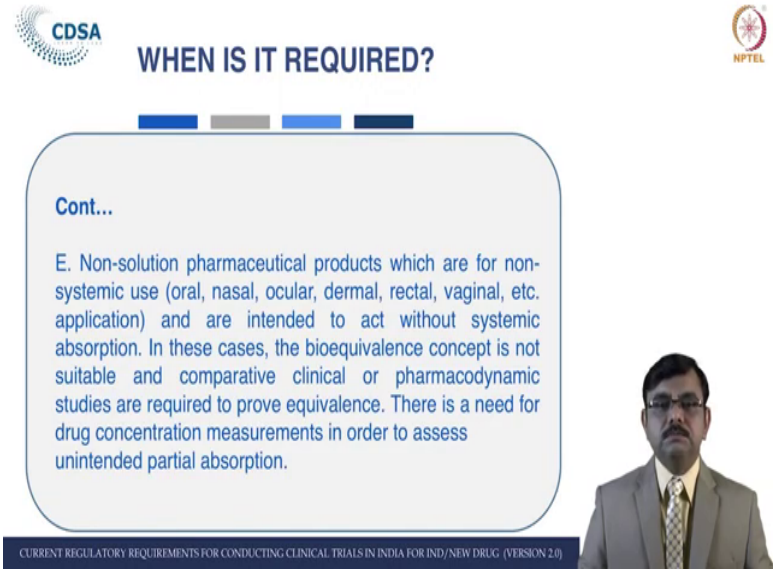

In case of the non solution pharmaceutical product which are for non-systemic use; for example, oral, nasal or ocular, dermal product, rectal product. If like this applications are there and are intended to act without systemic absorption; for example, the dermal product and does not have any systemic absorption.

In this case, the bioequivalence concept is not suitable and in this case comparative clinical or pharmacodynamics studies are required to prove the equivalence. So, in this case it is not is possible to have the an in vivo bioequivalence. There is a need for a drug concentration measurement in order to assess unintended partial absorption.

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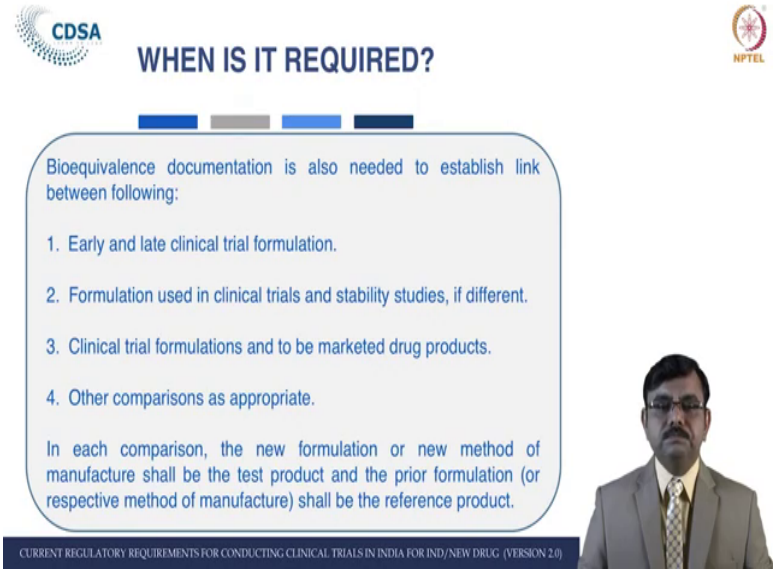

Bioequivalence documentation is also needed to establish link between the early and late clinical trial formulations. It is also required for the formulation used in clinical trial and stability studies are different. If the formulations used in clinical trial are those different from the used in the stability studies, then in that case also it is required.

The bioequivalence documentation establishing a link is also required in case of the clinical trial formulation and to be marketed drug product, they are the different one. Then, other comparison has a appropriate. In each of this comparison, the new formulation or new method of manufacture shall be the test product and the prior formulation that is a respective method of manufacture shall be the reference product.

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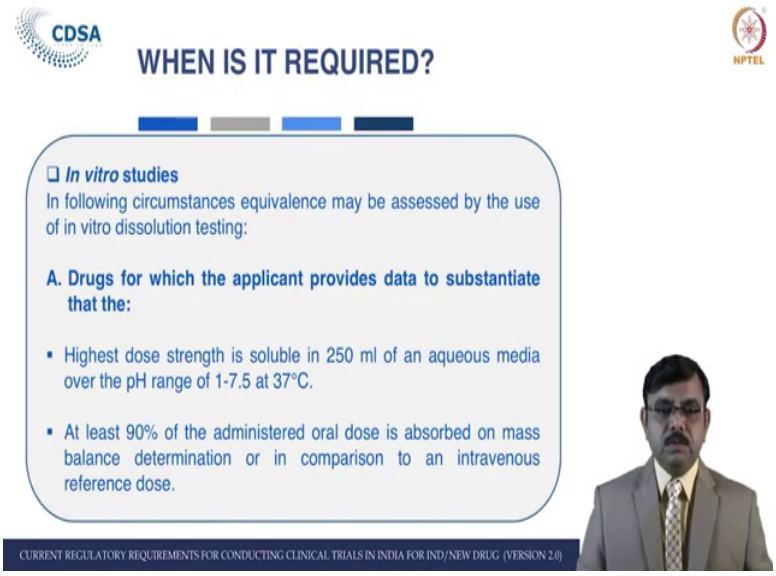

Let us see where the in vitro studies are useful? So, these are the following some circumstances given here for the equivalence that may be assessed by the use of in vitro dissolution testing. So, the first is drug for which the applicant provides data to the substantiate that the highest dose strength is soluble in 250 ml of aqueous media over the pH range of 1 to 7.5 at 37 degree Celsius.

So, in such cases if the applicant shows that the highest dose strength, if the paracetamol dose if it is available in 3 doses for example, 250, 500 and 650 milligram. Then, if it has been shown that the highest dose strength that is 650 milligram is soluble in 250 ml at this pH range 1 to 7.5 and at 37 degree Celsius, then in such cases the in vitro studies can be suffice.

In case where there is at least 90 percent of the administered oral dose is absorbed or mass balance determination or in comparison to an intravenous reference dose. So, in such cases also in vitro studies can be ok.

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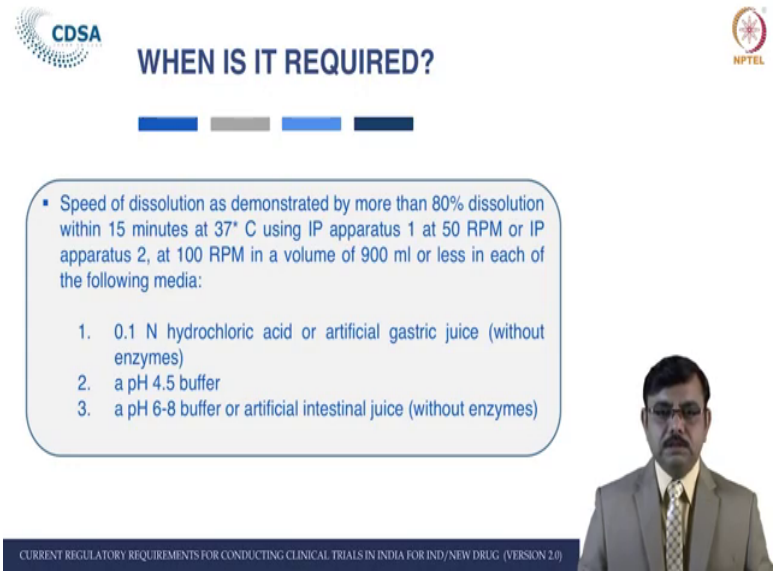

Speed of dissolution as demonstrated by more than 80 percent dissolution within 15 minute at 37 degree Celsius using IP apparatus 1 at 50 rotation per minute or IP apparatus 2 at 100 rotation per minute in volume 900 ml or less in each of the media like your 0.1 normal hydrochloric acid or artificial gastric juice or a pH 4.5 buffer or a buffer with the pH 6 to 8 that is intestinal juice. So, in such cases also in vitro design is adequate.

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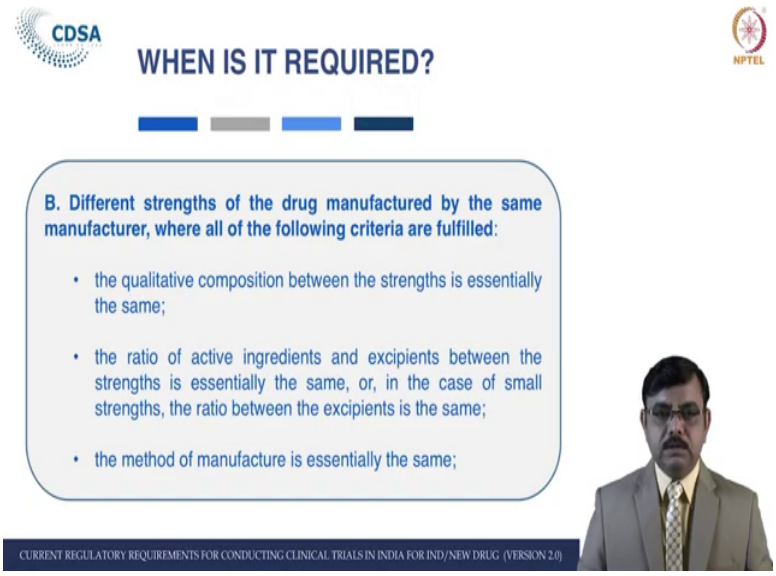

Let us see the different strength of the drug manufactured by the same manufacturer where all of the following criteria are fulfilled. So, in the case, in this case the qualitative composition between the strength is essentially the same. When the ratio of active ingredient and excipient between the strength is essentially same or in case of small strength, the ratio between excipient is the same, if the method of manufacture is essentially the same or an appropriate equivalence study has been performed on at least one of the strength of the formulation.

Usually, this is a highest strength unless a lower strength is chosen for specific reason of the safety and in case of systemic availability, pharmacokinetics have been shown to be linear over the therapeutic dose range.

In vitro dissolution testing may also be suitable to confirm unchanged product quality and performance characteristic with minor formulation or manufacturing changes after approval.

So, these are the cases, where the where the in vivo and in vitro dissolution and bioequivalence studies require. Let us see where this bioequivalence studies are not required.

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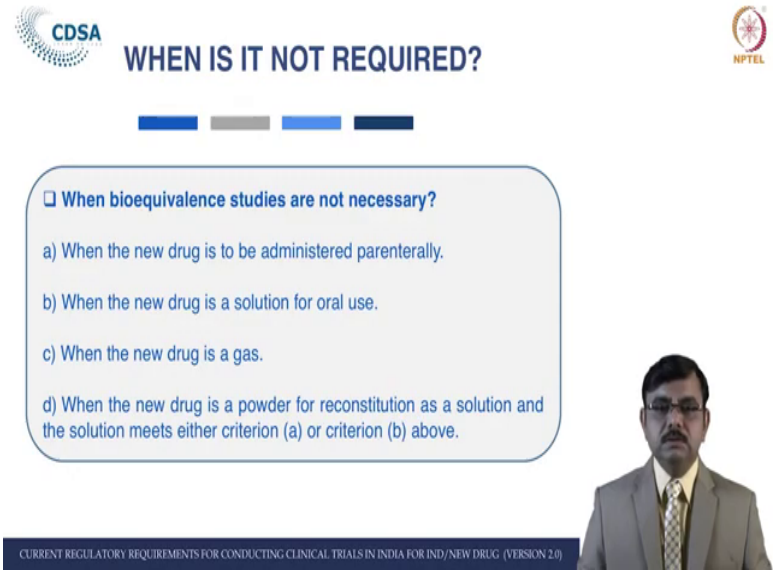

So, when new drugs are to be administered parenterally; in these case the bioequivalence study is not required because as we know bioequivalence study is to know that whatever the dose or how much is the dose available in the systemic circulation or the blood circulation. And if the drug is to be administered parenterally like a intravenous muscular subcutaneous, so we know the intravenous it is a hundred percent bioavailable dose.

So, when new drugs are to be administered parenterally as aqueous solution and contain the same active substance in the same concentration with the same excipient in comparable concentration. So, in this case the bioequivalence studies may not be necessary. When the new drug is a solution for overall use and contains the active substance in the same concentration

and does not contain an excipient that is known or suspect to effect gastro intestinal transit or absorption of the active substance.

In case, when the new drug is a gas. So, the availability and absorption of the gas is also having no doubt. So, in this case also bioequivalence studies may not be required. When the new drug is a powder for reconstitution as a solution and the solution meets the criteria as I have mentioned in a and b, when it is there to be administered parenterally or when the drug is in a solution form for oral use. So, in such cases also it is not required.

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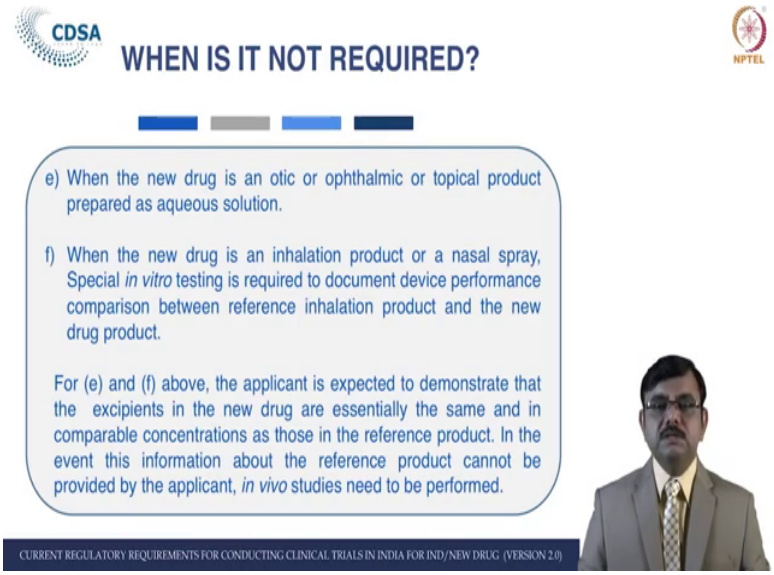

When the new drug is an otic or ophthalmic or tropical product prepared as aqueous solution and contains the same active substance in the same concentration, essentially the same excipient in comparable concentrations. When the new drug is an inhalation product or the nasal spray tested to be administered with or without essentially the same device as the

reference product prepared as aqueous solution and contain the same active substances in the same concentration and essentially the same excipient in comparable concentration, in such cases also it is not required.

Special in vitro testing, in this case special in vitro testing is required to document device for farmers, comparison between reference in a inhalation product and the new drug product. For these conditions what I have mentioned in e and f, the applicant is expected to demonstrate that the excipient in the new drug are essentially the same and in comparable concentration as those in the reference product.

In the event this information about the reference product cannot be provided by the applicant, then in vivo studies need to be performed. Let us move to the design and conduct of studies.

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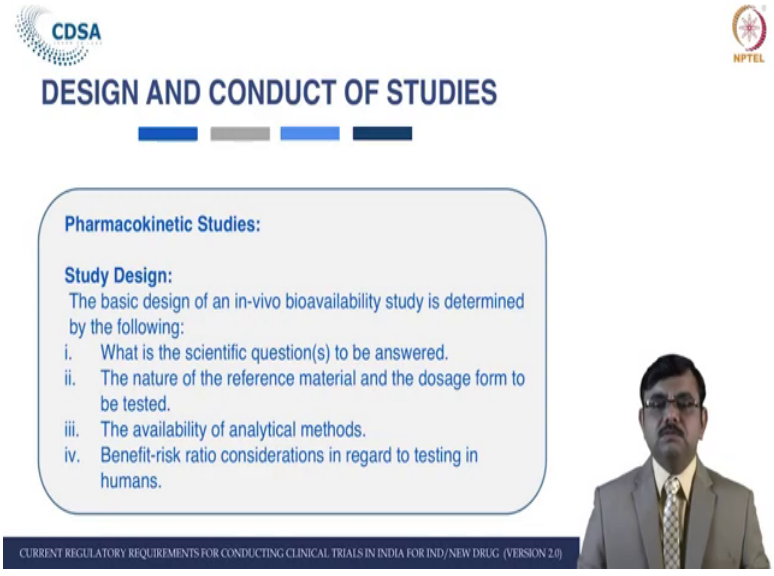

So, we will see the pharmacokinetic studies and design the basic design of an in vivo bioavailability study is determined with the criteria like what is the scientific question to be answered, then the nature of the reference material and the dosage form to be used, the availability of analytical method, benefit risk ratio consideration in regard to the testing in human.

So, these questions have to be answered by your study design and based on this question the study design should be established. The study what we have designed should be designed in such a manner that the formulation effect can be distinguished from other effects. Typically, if two formulations are to be compared or two period two sequence cross over design is the design of the choice with the two phases of treatment separated by an adequate wash out period which should ideally be equal to or more than 5 half lives of the moiety is to be measured.

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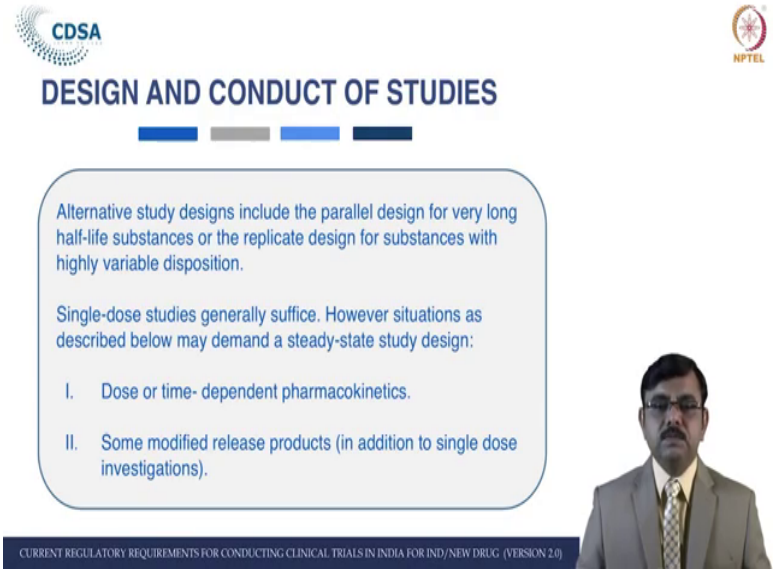

We can try the alternative study design and that that may include the parallel design, when the substance is having a very long half-life substance or the replicate design for substances with the highly variable dispositions. Single dose studies generally suffice or however, situations as described here if it demand a study state study design, dose or time dependent pharmacokinetic is there.

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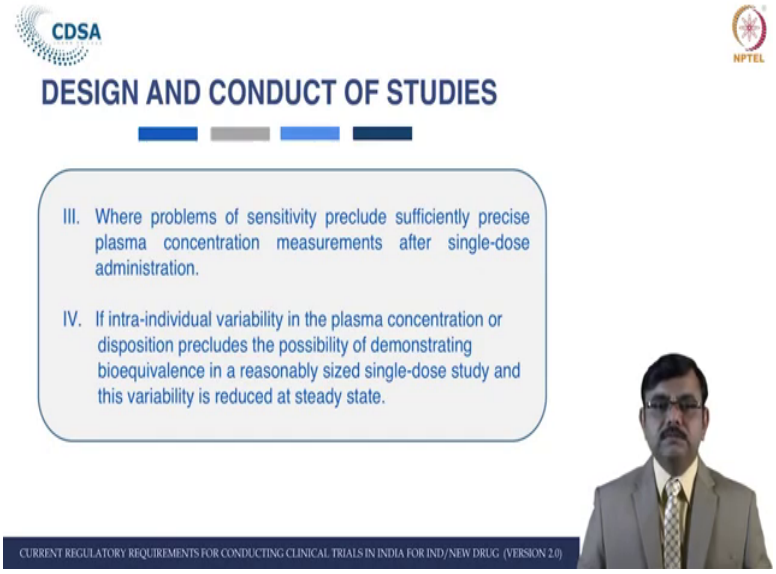

Or some modified release products are there or where a problem of sensitivity preclude the sufficient precise plasma concentration measurement after single dose.

So, in this case also single dose studies is a preferable. If intra individual variability in the plasma concentration or the disposition precludes the possibility of demonstrating bioequivalence in reasonably sized single dose study and the variability is reduced at steady state, in such cases the single dose generally suffice.

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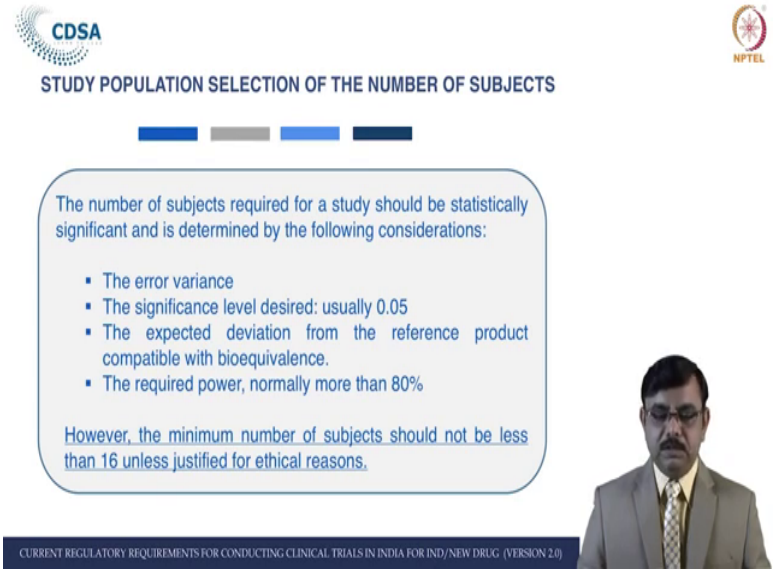

Let us see the study population and how to select the number of subjects; what are the things to be considered while selecting the subject for the bioequivalence and bioavailability studies. The number of subjects required for a study should be statistically significant and is determined with the consideration.

So, here I have given 3-4 consideration. It is based on the error variance. We called it as a coefficient of variance. So, the error variance associated with the primary characteristic to be studied as estimated from a pilot experiment from previous studies or from a published data, the coefficient of variance has to be taken in to the consideration. The significance level desired usually should be 0.05 and the expected deviation from the reference product should be compatible with the bioequivalence.

The required power that is the what we called statistical power or discriminatory power, it should be normally more than 80 percent to detect the maximum allowable differences usually plus or minus 20 percent in a primary characteristic to be studied. However, it is the it is the rule or we can say it has been mentioned in the guideline of the CDSCO that the minimum number of subject should not be less than 16 unless justified for the ethical reason and two subject should be kept as a standby in case of the withdrawal.

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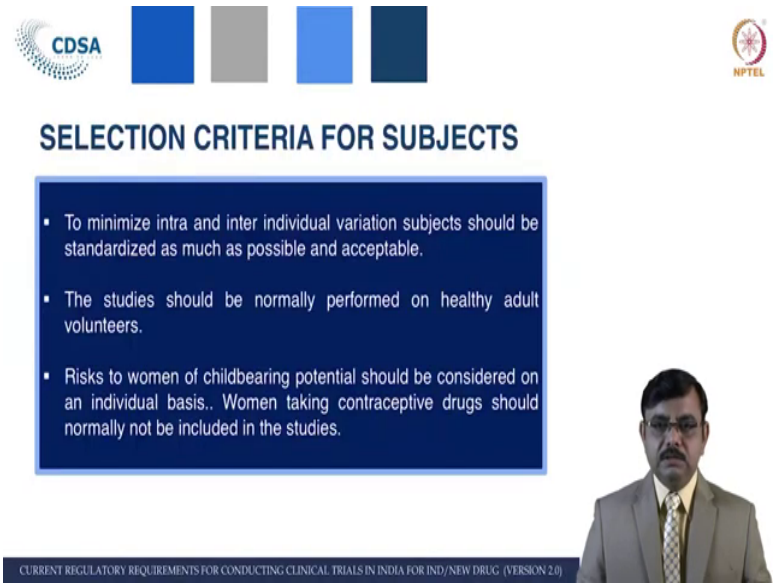

To minimize intra and inter individual variations subject, it should it should be standardized as much as possible and the acceptable. The studies should be normally performed on healthy adult volunteer with the aim to minimize variability, if the disease condition is there, they may respond to the drug in a different manner and there may not be appropriate bioequivalence.

Subjects may be male or females; however, the choice of gender should be consistent with usage and the safety criteria. The risk to women of child bearing potential should be considered on individual basis and women taking contraceptive drug should normally not to be included in the study.

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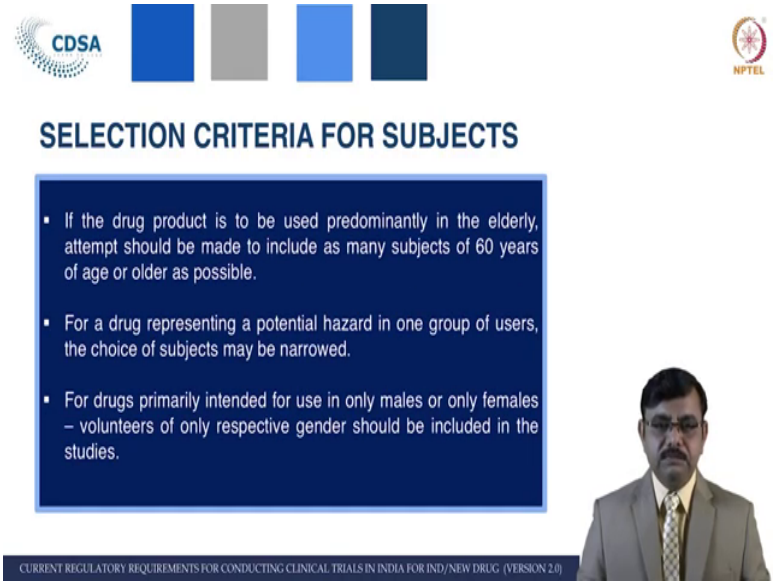

If the drug product is to be used predominantly in the elderly, then the elderly patient a sorry elderly subject of 60 years of age or older as possible can be considered. For a drug representing potential hazard in one group of users, the choice of subject may be narrowed. Example studies on teratogenic drug should be conducted only on males. For a drug primarily intended for use in only males or only females, then in such cases volunteers of only respective gender should be included in the studies.

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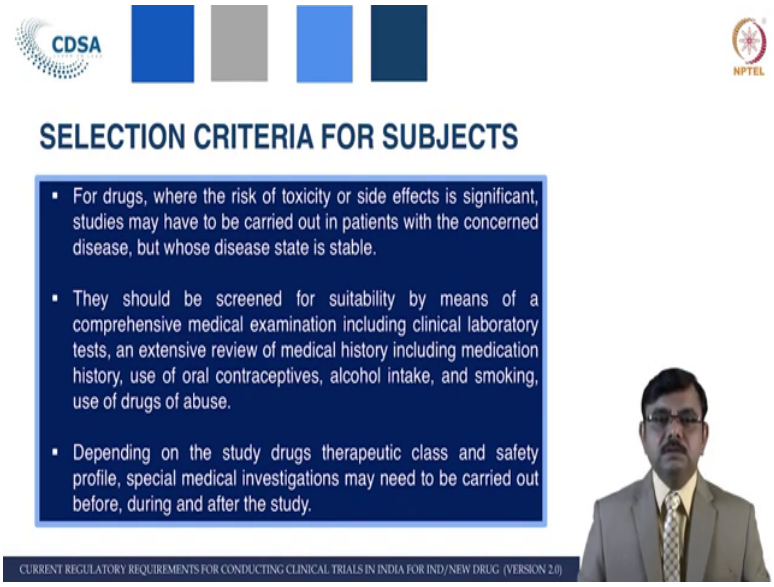

For a drug, where there is a risk of toxicity or side effect is significant, then the studies may have to be carried out in patient with the concerned disease. But whose disease state should be stable, the disease state should not be stable to give the appropriate results.

And these they should be screened for suitability, where means of comprehensive medical examination including clinical laboratory test or exchange review of the medical history, medication history, use of oral contraceptive alcohol intakes, smoking; this has to be reviewed and depending on the study drugs theoretic class and safety profile, special medical investigation may need to be carried out before during and after the study.

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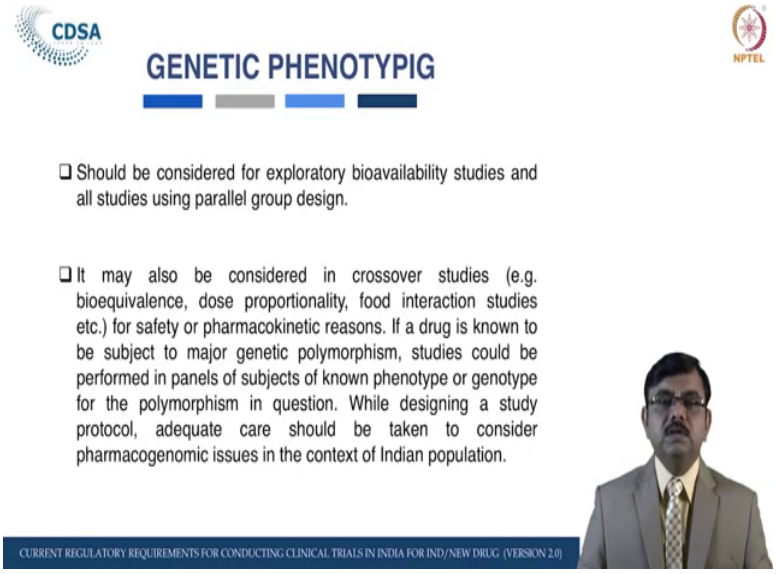

Let us see when to be consider the genetic phenotyping. The phenotyping or genotyping of subject should be considered for explorative bioavailability studies and all studies using parallel group design. When there is a exploratory bioavailability studies or the parallel group design studies, then in that case genetic phenotyping is considered.

It may also be considered in some cross over studies. For example, bioequivalence dose proportionality or if there is a food interaction studies, in this case also it has to give the consideration for a safety or pharmacokinetic reasons.

If a drug is known to be subject to major genetic polymorphism, then the studies could be performed in panels of subject of known phenotype or genotype for the polymorphism in a

question. While designing such a study the protocol adequate care should be taken to consider pharmacogenomic issues in the context of Indian population.

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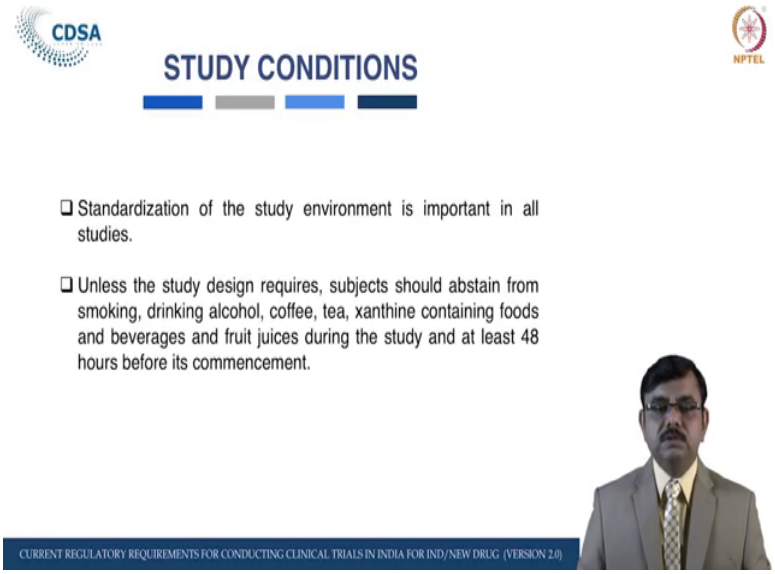

Let us see the study conditions the standardization of the study environment diet, fluid, intake, then pose dosing posture question exercise sampling this is all having the important consideration in all the studies. And unless the study design requires subject should abstain from smoking, drinking alcohol, coffee intake or tea, xanthine containing foods and beverages and fruit juices during the study and at least 48 hours before its commencement.

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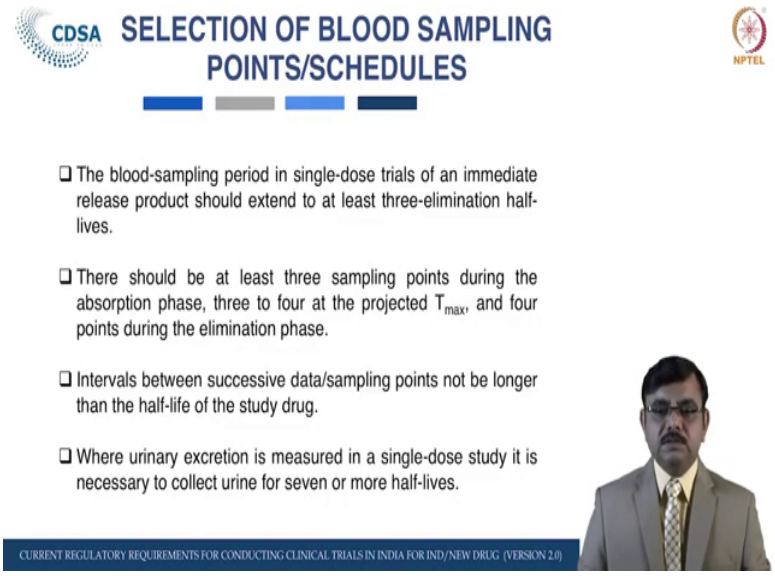

Let us move toward the selection of blood sampling points; how to be select a blood sampling points. The blood sampling period in a single dose trial of an immediate release product should extended to at least three elimination half-life and there should be at least three sampling points during the absorption phase, three to four sampling point at the projected T max and four point during the elimination phase.

Interval between successive data, sampling points not be longer than the half-life of the study drugs. Where in case of the urinary excretion and urine sample is to be used; where urinary excretion is measured in the single dose study, it is necessary to collect urine for seven or more half-lives. Generally, a single dose study should be conducted after an overnight fasting.

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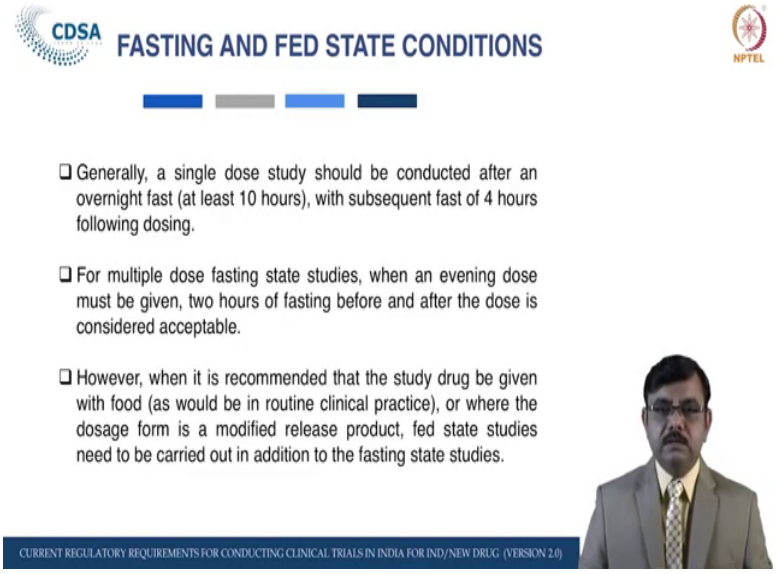

So, this is about the fasting and the feds; fed conditions. So, generally a single dose study should be conducted after an overnight fast that overnight fast means at least 10 hours; at least 10 hours has to be fast, with the subsequent fast of 4 hours following the dosage. And for the multiple dose fasting state studies, when an evening dose must be given, it should be 2 hours are of fasting before and after the dose is considered acceptable.

However, when it is recommended that the study drug be given with food and as would in our routine clinical practice, or where the dosage form is a modified release product fed state studies need to be carried out in addition to the fasting state studies. Let us see what is study state studies and when it require.

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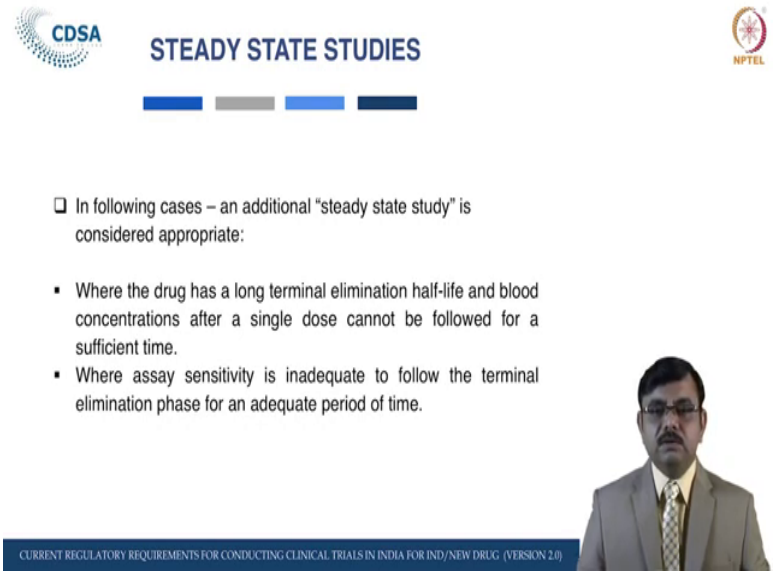

So, the study state studies, it is an additional study state studies which is considered appropriate, where the drug has a long terminal or we can say the long elimination half-life and the blood concentration after a single dose cannot be followed for a sufficient time.

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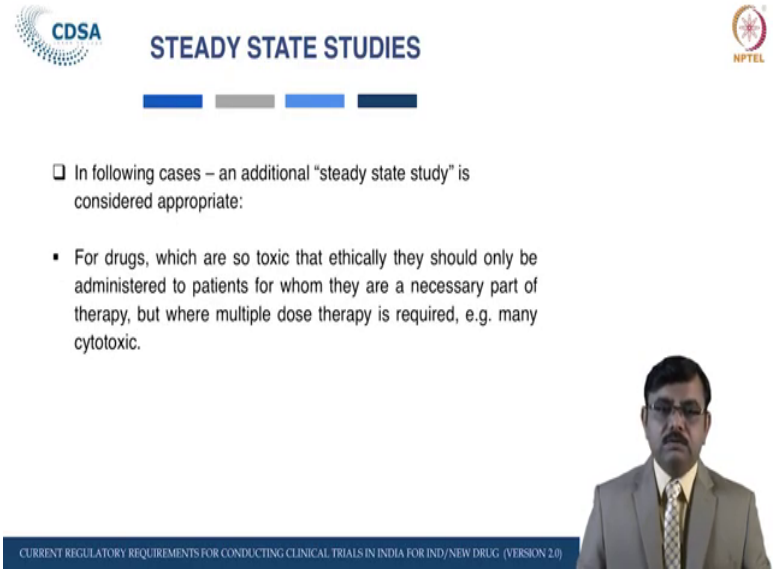

Or where assay sensitivity is inadequate to follow the terminal elimination phase, for an adequate period of time; in these cases an additional studies study is required.

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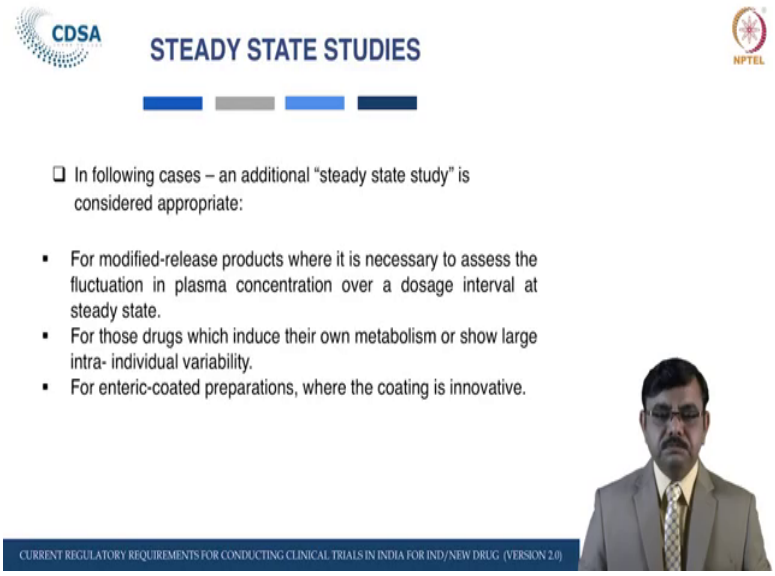

In case for a drug which are so toxic that ethically they should only be administered to patient for whom they are necessary part of therapy; but where multiple dose therapy is required. For example, in many of the cancer drug or many of the cytotoxic drug; so, in such cases also this type of study is required.

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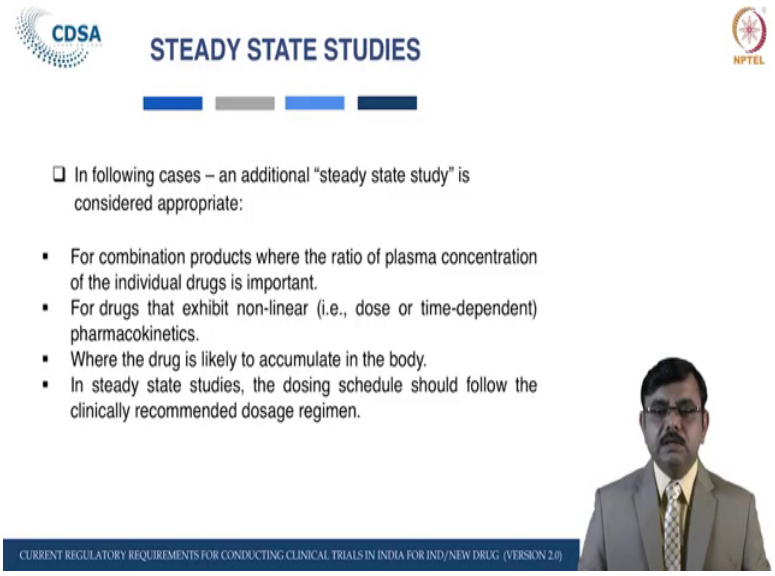

In case of modified release product, where it is necessary to assess the fluctuation in plasma concentration over dosing interval at a study state. So, in this case also study state study which is an additional is required. For those drug which induced their own metabolism or show large intra individual variability and for enteric coated preparation, where the coating is innovative; if the coating is new, in that case also the study is required.

For the combination product where the ratio of plasma concentration of the individual drug is important and for the drugs that exhibit non-linear pharmacokinetic, if it is non-linear pharmacokinetic, then also this additional study is required. In this study state studies, the dosing schedule should follow the clinically recommended dosage regimen.

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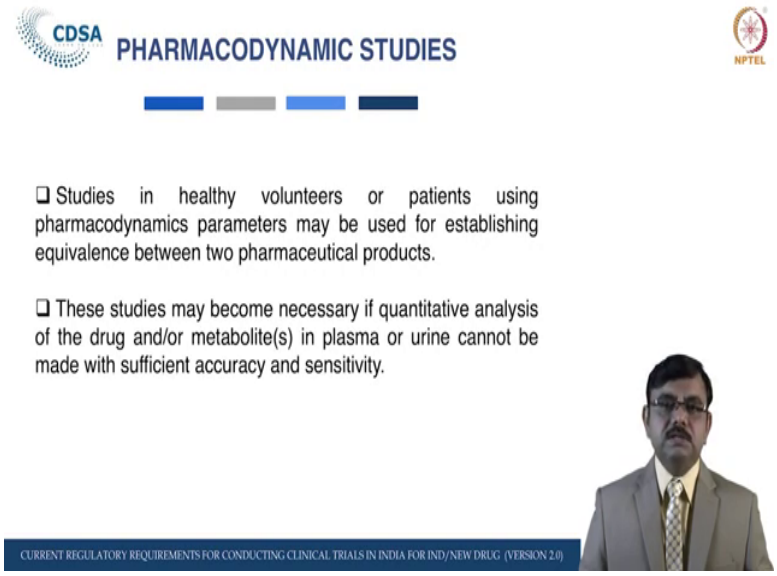

Now, let us see where the Pharmaco dynamic studies are required in the bioequivalence. So, these studies are in healthy volunteers or patient using pharmacodynamic parameter. So, it can be in a patient when there is cytotoxic drug and it may be used for establishing equivalence between two pharmaceutical product. This study is may become necessary if quantitative analysis of the drug or metabolite in plasma or urine cannot be made with sufficient accuracy and the sensitivity.

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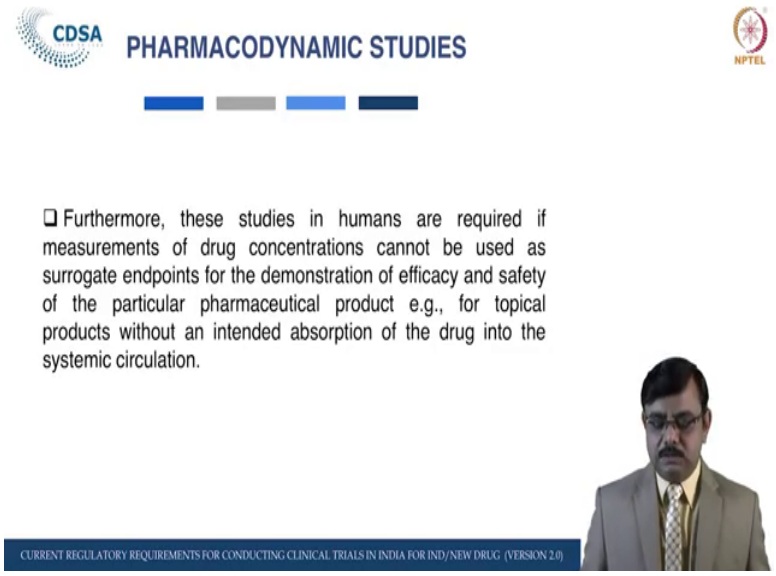

Furthermore, we can say this studies in humans are required if measurement of a drug concentration cannot be used as a surrogate end point for the demonstration of efficacy and safety of the particular pharmaceutical product. For example, for tropical product without an intended absorption of the drug in to the systemic circulation.

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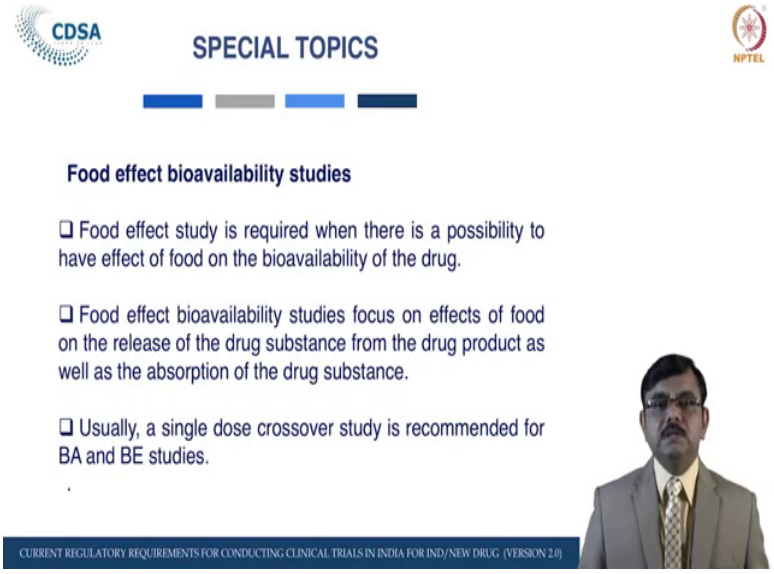

We will see now some special topics, like what is of effect of food; what are the consideration to be given. The food effect bioavailability study, this type of study is required when there is a possibility to have effect of food on the bioavailability of the drug. And when the food effect bioavailability studies focus on effect of food on the release of the drug substance from the drug product as well as the absorption of the drug substance. Usually, a single dose crossover study is recommended for BA BE and bioequivalence studies, when there is a food effect.

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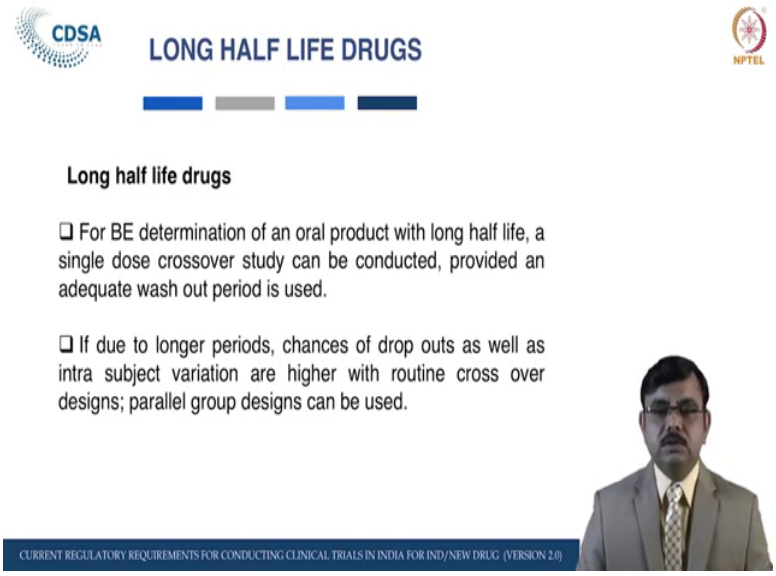

In case of long half-life of the drug for the bioequivalence determination of oral product with such type of product, a single dose cross over study can be conducted, provided an adequate washout period has to be provided. If due to a longer period because there is a chances of the drop out as well as intra subject variation with this routine cross over studies, in that case the parallel group design can be used. So, this is about the guideline of bioavailability and bioequivalence.

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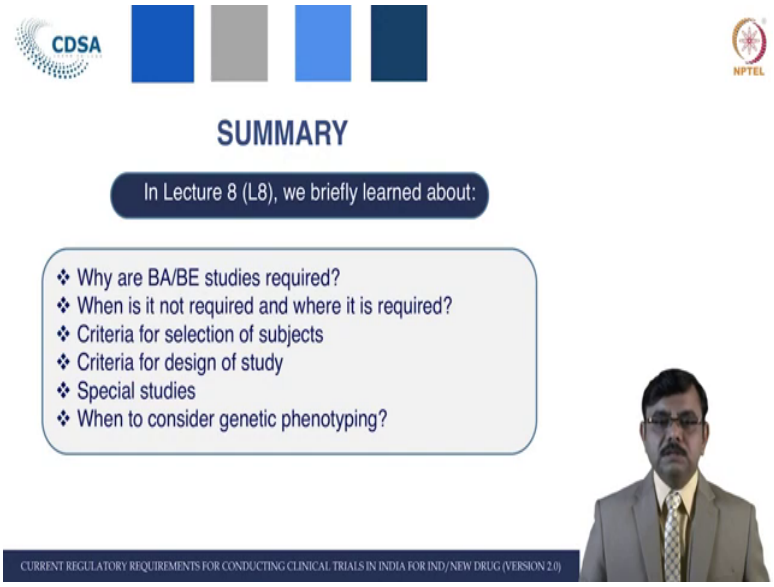

Let us have the look of summary of this lecture. So, in this lecture, what we learnt? We have learned about what is bioavailability; what is bioequivalence; what is supra bioavailability and many other different terminologies like pharmaceutical alternative therapeutic equivalence. Then, we have seen where the bioequivalence study is required; where it is required in vivo, where it is required in vitro.

Then, further we have seen that where the bioavailability and bioequivalence studies are not required; how to select the subject; what is the criteria for selection of subjects. Then, criteria for selection of the study design and the special studies like a food effect and other studies. We have also seen in this lecture, when to consider the genetic phenotyping.

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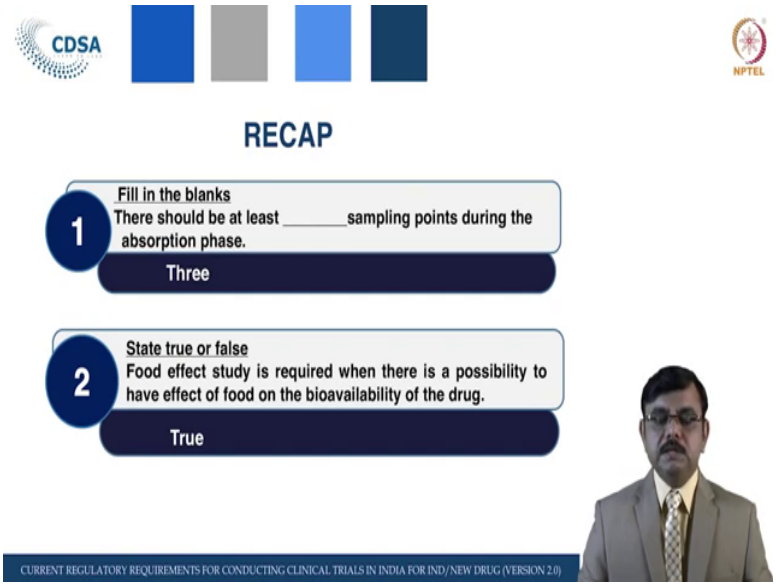

So, now it is the time for you to answer some questions. So, the first question for you is you have to fill in the blanks. There should be at least dash sampling points during the absorption phase. So, you have to answer how many sampling point should be there in the absorption phase.

So, there are at least three sampling point should be there. We have seen at the absorption phase, there should be three sampling point; at the T max three to four and so, the next question food effect study is required when there is a possibility to have effect of food on the bioavailability of the drug. You have to answer whether it is a true or false. So, yes, this is a true. The food effect study is required when there is possibility of food and drug interaction.

So, here we have completed the lecture which is a related to the bioavailability guideline and the previous lecture, we have completed with the rules and regulation of the bioavailability and bioequivalence.

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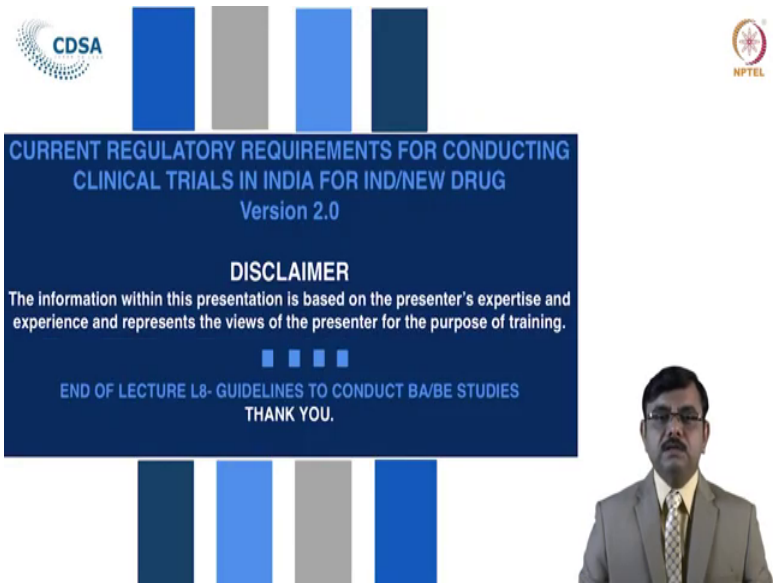

We will we will come back in the next lecture soon. Till, then you take care. Bye, bye and thank you for watching the lecture.