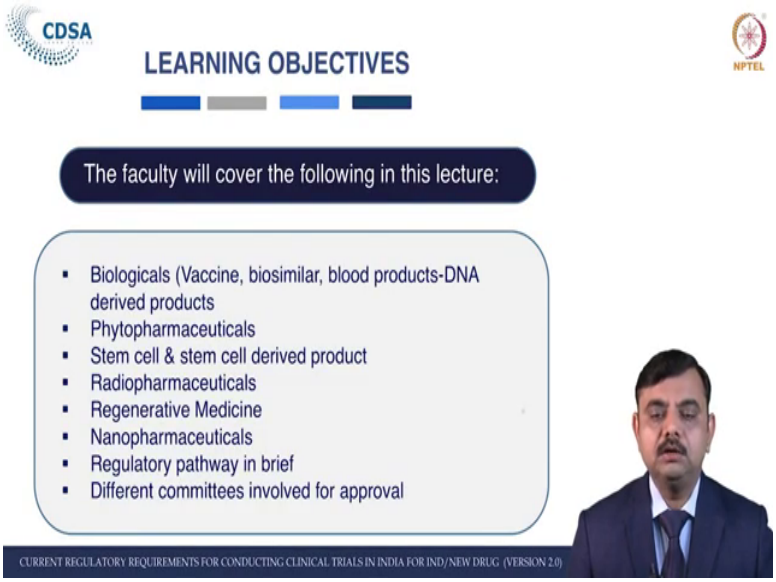
Current Regulatory Requirements for Conducting Clinical Trials in India for IND/New Drug Version 2.0

Dr. Dhananjay K. Sable
Department of Biotechnology
Indian Institute of Technology, Madras

Lecture – 14
Special concern

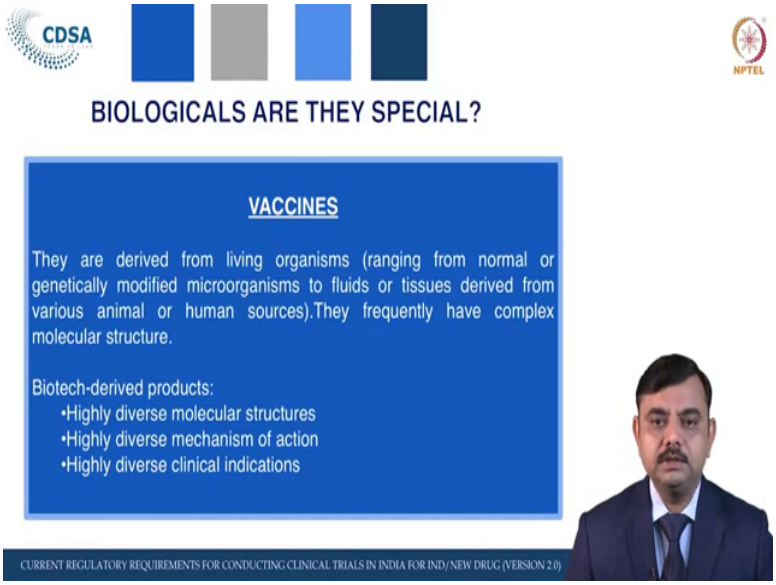
Hello friends, welcome back to the course Current Regulatory Requirement for Conducting Clinical Trial in India for Investigational New Drug and New Drug Version 2.0. This is our lecture 14 and this is a Special Concern lecture and daily this lecture covers all the special concern which require a special attention as it involves a different committees and other than the regular our product that is a new chemical entity, it require certain special attention to be given.

(Refer Slide Time: 00:54)



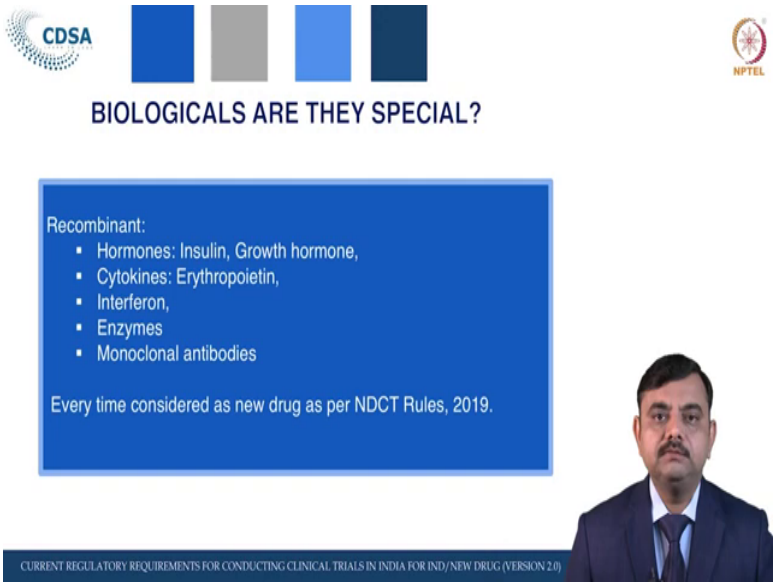
So, the learning objective from this lecture, upon completion of this session, the trainee will learn in brief about the biologicals; why they are special; then, phytopharmaceuticals, stem cell and stem cell derived product; radiopharmaceuticals; regenerative medicines; nanopharmaceuticals and the different committees involved for the approval of this product.

(Refer Slide Time: 01:25)



So, let us begin with the biologicals are they special? Certainly, these are the specials biologicals; it the biologicals, it covers vaccines, biotech derived product, hormones, enzymes and other. Let us see why they are special in nature.

(Refer Slide Time: 01:47)



If we see for the vaccine, they are derived from living organism and that could be ranging from normal or genetically modified organism to fluids or tissue derived from various animals or human sources. They frequently have a complex molecular structure that is why they are special.

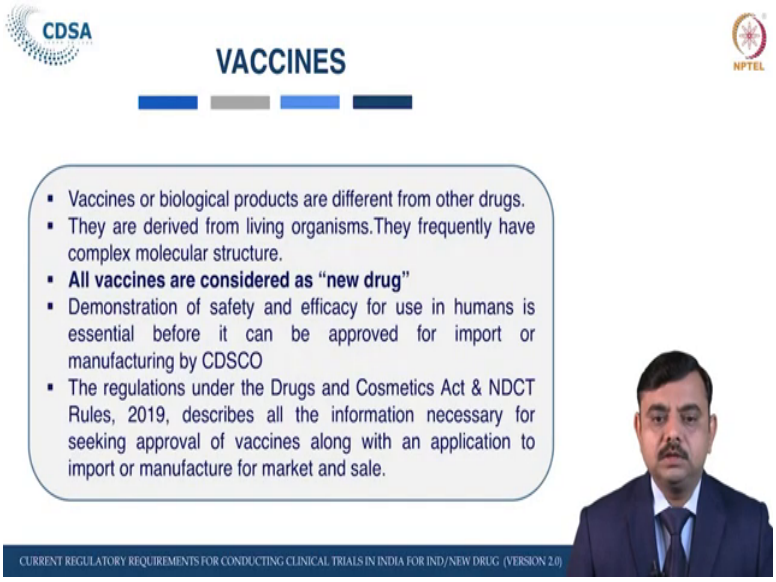
(Refer Slide Time: 00:19)

Then, the biotech derived product as we know, they are having highly diverse molecular structure, highly diverse mechanism of action and the highly diverse clinical indications. The other product like a recombinant, hormones, insulin, growth hormone, cytokines, erythropoietin, interferon, enzymes and the monoclonal antibodies; these all are the biological products.

And the special thing in this that for the regulatory approval, it required to take a new drug permission every time. So, as per the New Drug and Clinical Trial Rule 2019, these are the special product and there may be a change in the quality, safety and efficacy of this product whenever the new manufacturing process is there or whenever there is a new manufacturer and that is why these product are always considered as a new drug product.

Unlike our routine drug, what we have seen once the drug has been approved that drug remain new for only 4 years and after that the applicant need not have to take the new drug permissions and they have to take the permission from the State Licensing Authority to manufacture it. In case of this biological product, these are always a new drug product and required to take a new drug permission every time.

(Refer Slide Time: 03:43)

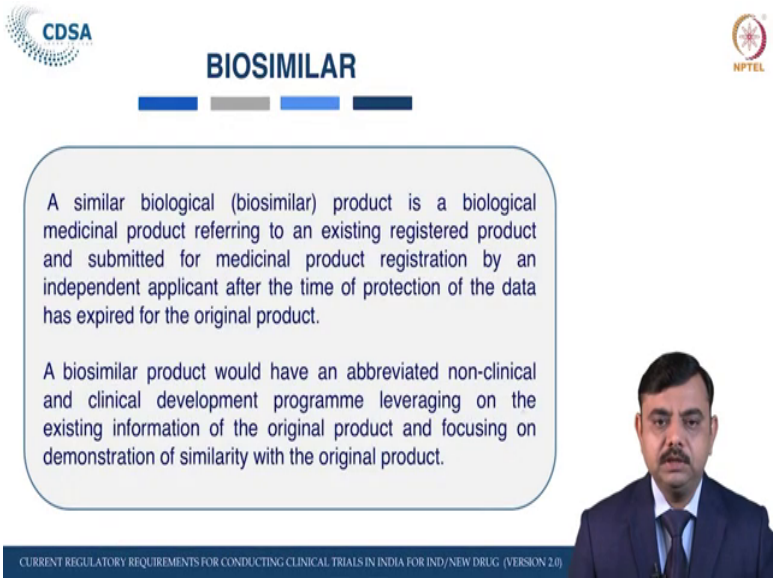


So, let us begin with one by one. First, we will see the vaccine. So, as I have mentioned vaccines or these biological product are different from other drugs. As they are derived from the living organisms and they frequently have a complex molecular structure, that is why they are vaccines are also considered as a new drug every time. And the demonstration of safety and efficacy for use in human is essential before it can be approved for import or

manufacturing and this permission is given by the CDSCO that is National Regulatory Authority.

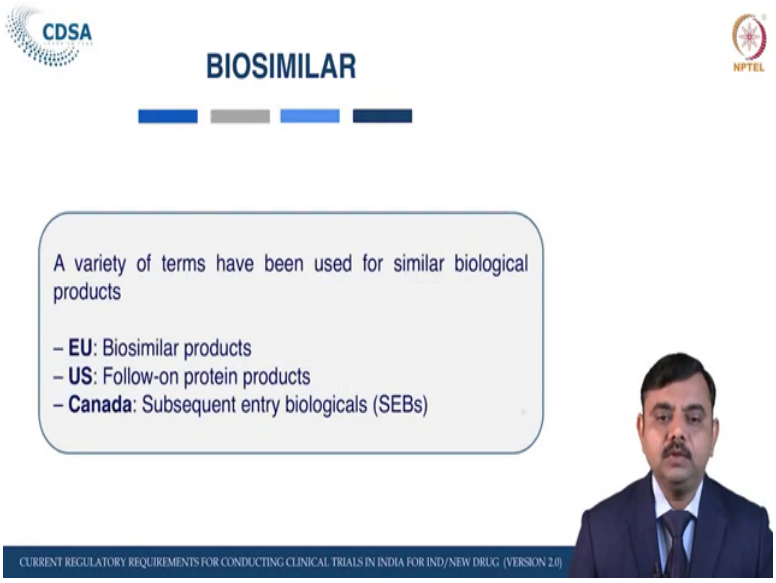
The regulation under the Drug and Cosmetic Act and New Drug and Clinical Trial Rule, 2019, describes all the information necessary for seeking approval of vaccines along with an application to import or manufacture for market and sale.

(Refer Slide Time: 04:49)



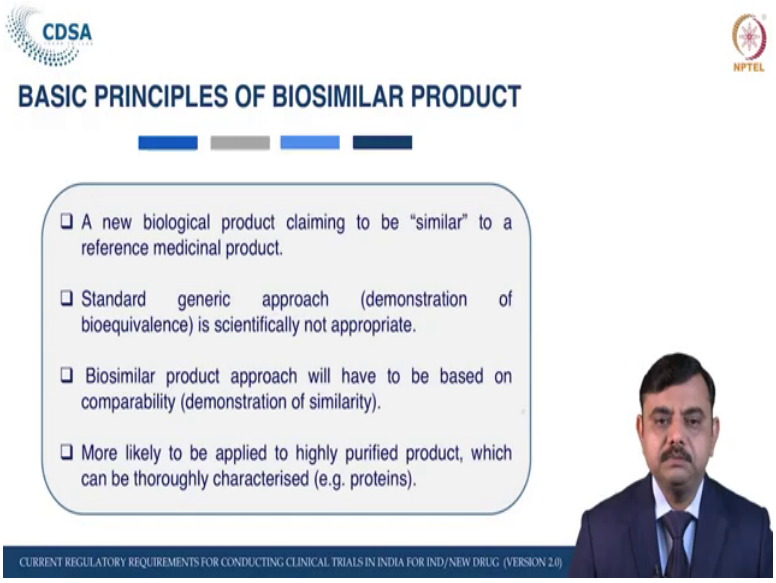
Let us see what is the Biosimilar. The biosimilar is the similar biological or the similar product and it is a biological medical product referring to an existing registered product and submitted for medicinal product registration by an independent applicant, after the time of protection of the data has expired for the original product. A biosimilar product would have an abbreviated, nonclinical and clinical development; leveraging on the existing information of the original product and focusing on demonstration of similarity with the original product.

(Refer Slide Time: 05:29)



Different terminologies has been used for this a similar biological or biological like in EU, it is a Biosimilar product; in the US, it is a Follow-on protein product; in Canada, it is Subsequent entry biologicals and likewise.

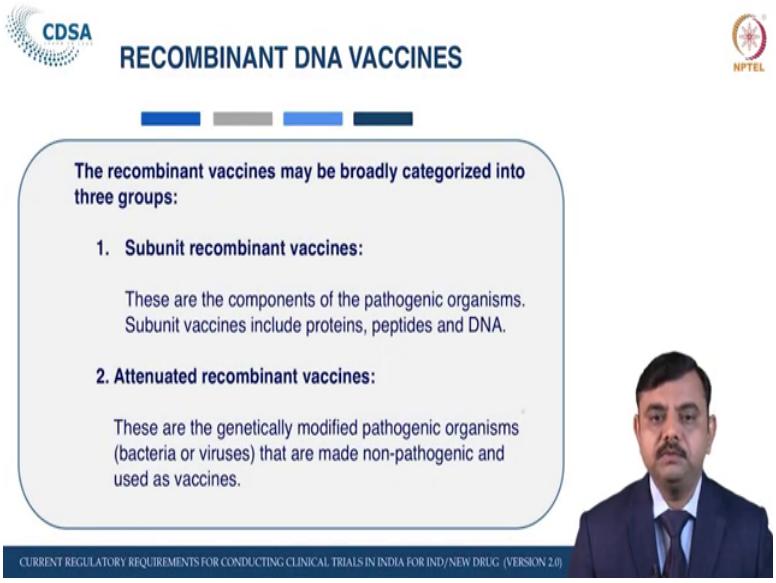
(Refer Slide Time: 05:47)



The basic principle involved in the this biosimilar product that a new biological product claiming to be a "similar" to a reference medicinal product. Standard generic approach, that is demonstration of bioequivalence is scientifically not appropriate. And the biosimilar product approach will have to be based on the comparability that is demonstration of the similarity between the existing product and the new product.

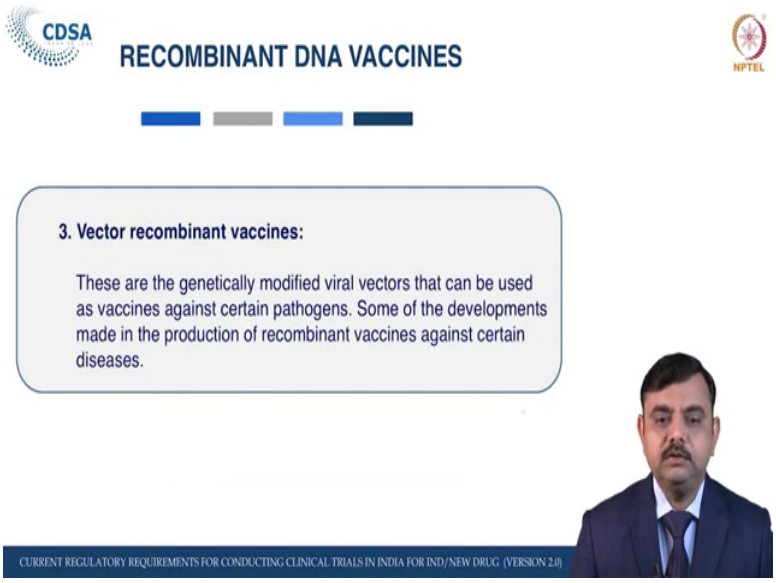
More likely to be applied to highly purified product, which can be thoroughly characterized. Products such as vaccines, blood or plasma derived product, gene or cell therapy product, these are not acceptable. Let us see what is Recombinant DNA vaccine.

(Refer Slide Time: 06:40)



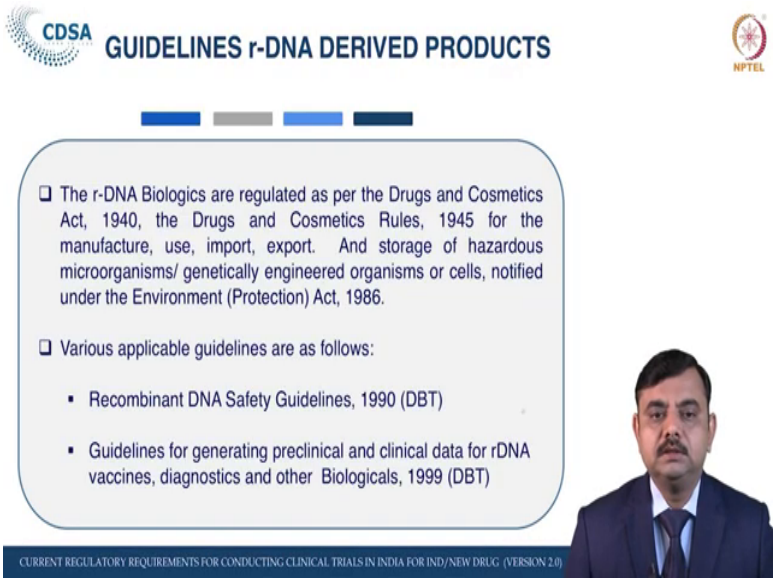
So, the recombinant vaccine maybe broadly categorized into three groups that is Subunit recombinant vaccine; Attenuated recombinant vaccine and Vector recombinant vaccine. The subunit recombinant vaccine, these are the components of the pathogenic organism. Subunit vaccines include like a protein, peptides and DNA. Attenuated recombinant vaccine are the genetically modified pathogenic organism. Pathogenic organism, we know that bacteria or viruses that are made non-pathogenic and used as a vaccine.

(Refer Slide Time: 07:22)



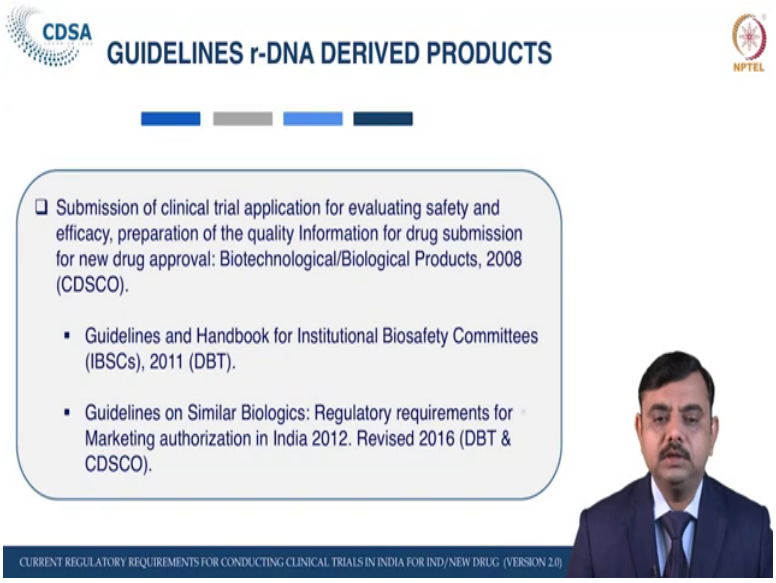
The vector recombinant vaccine, these are the genetically modified viral vectors that can be used as a vaccine against certain pathogens. Some of the development made in the production of recombinant vaccine against in certain diseases.

(Refer Slide Time: 07:47)



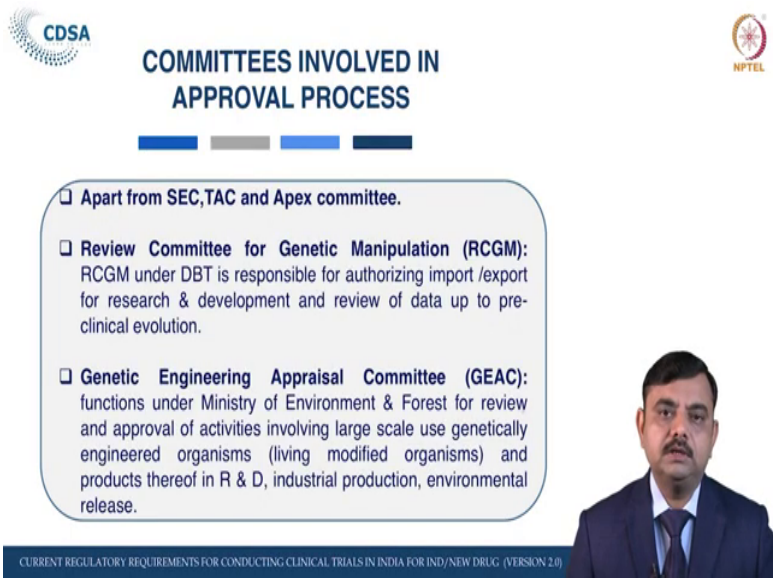
And the guideline to be followed further, r-DNA derived product are these. These are the guidelines what have been shown on the slides. So, I am not going to read it all. So, various applicable guidelines, I have been given like Recombinant DNA Safety Guideline from DBT; Guideline for generating preclinical and clinical data the guideline of 99, again it is from the DBT; then, CDSCO has also published this guidelines in 2008. There is a one handbook which was for the Institutional Biosafety Committee.

(Refer Slide Time: 08:26)



And again, there are revised guideline which are now in existence from the CDSCO. Let us see what is the difference in the giving the approval to this product.

(Refer Slide Time: 08:39)



So, we have seen in our chemical entity, that the committee involved are Subject Expert Committee, TAC committee and Apex committee; after the thorough deliberation with this committee, the product approval gets. Apart from these committees, the other special committees are there to review the applications pertains to this biological and the r-DNA. These committees are Review Committee for Genetic Manipulation, we call it as a RCGM. RCGM is under DBT and it is responsible for authorizing import export for R and D that is research and development purpose. And it is responsible to review the data up to preclinical evaluation.

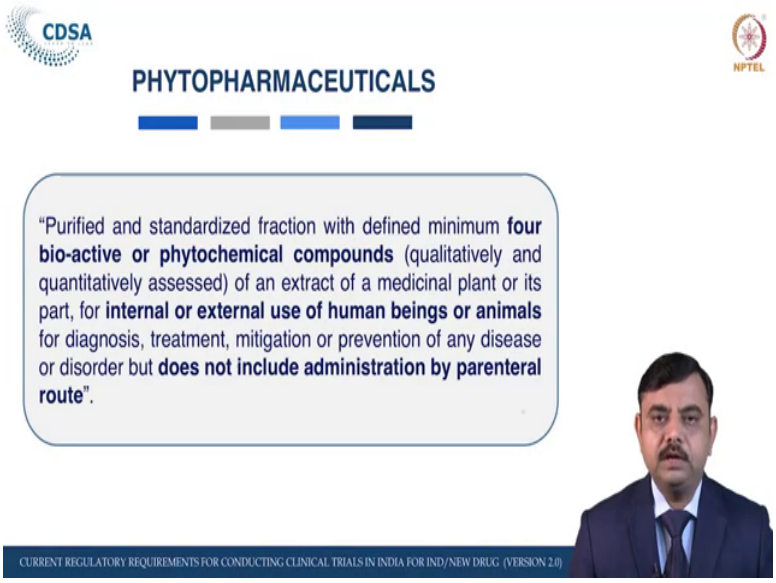
So, these committees responsible up to preclinical evaluation. Once the preclinical evaluation is been over, then they give the recommendation to the CDSCO and according to the for the clinical trial conduct the CDSCO reviews the application. The another committee involve is a Genetic Engineering Appraisal Committee that is a GEAC, it functions under the Ministry of

Environment and Forest for review and approval of activities, involving large scale use genetically engineered organism that is LMO. We call its Living Modified Organism and products thereof in R and D industrial production and environmental release.

(Refer Slide Time: 10:25)

CDSCO as we know it is a Central Drug Standard Control Organization and it is a national regulatory authority under the Ministry of Health and Family Welfare and it is responsible for grant of import export, the Clinical Trial Approval and permission for Manufacture and Market. The various State Licensing Authorities, they are there for the Grant of Manufacture and sale licenses.

(Refer Slide Time: 10:59)



Let us see the other part that is a Phytopharmaceutical. So, the phytopharmaceutical has been defined in the Rule 2 Sub Clause aa, we have seen in our earlier lecture. These are a "purified and standardized fraction with a defined minimum four bio-active or phytochemical compound. They are qualitatively and quantitatively assessed of an extract of medicinal plant or its part for internal or external use of human beings or animals for diagnosis treatment mitigation or prevention of any disease or disorder, but it does not include administration by parenteral route".

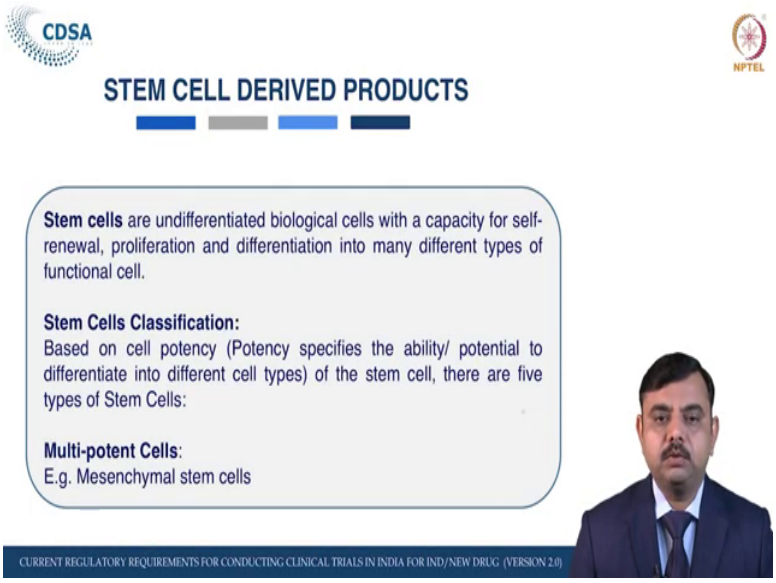
The data to be submitted along with the application to conduct clinical trial or manufacture of phytopharmaceutical drug in the country. It has been given in our New Drug and Clinical Trial Rule 2019, in Schedule II, Table IV, we have already covered in our previous lecture. Let us

have just look at this data. So, this has been divided into the two part; part A, part B. Part A is data to be submitted by an applicant and the human or clinical pharmacological information.

(Refer Slide Time: 12:10)

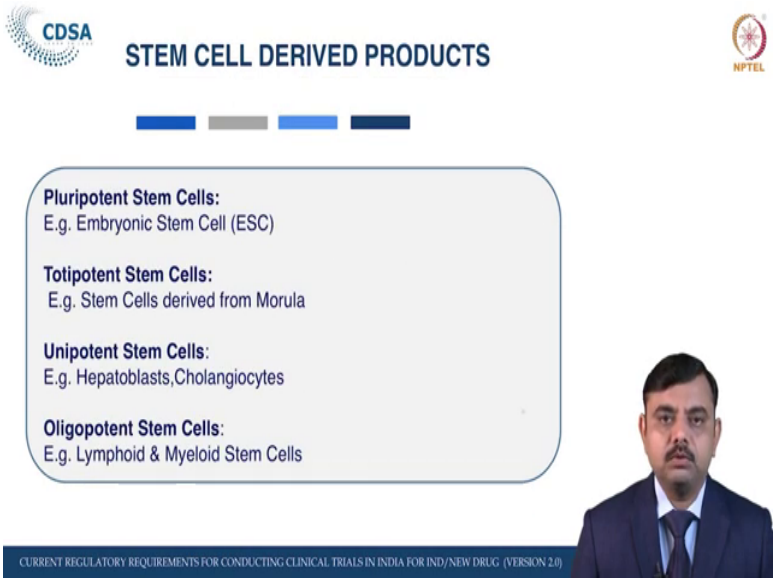
And part B is a data generated by the applicant like identification, authentication, source of plant used for extraction and fraction, the process of extraction and other data. Let us have a look at the stem cell derived product.

(Refer Slide Time: 12:26)



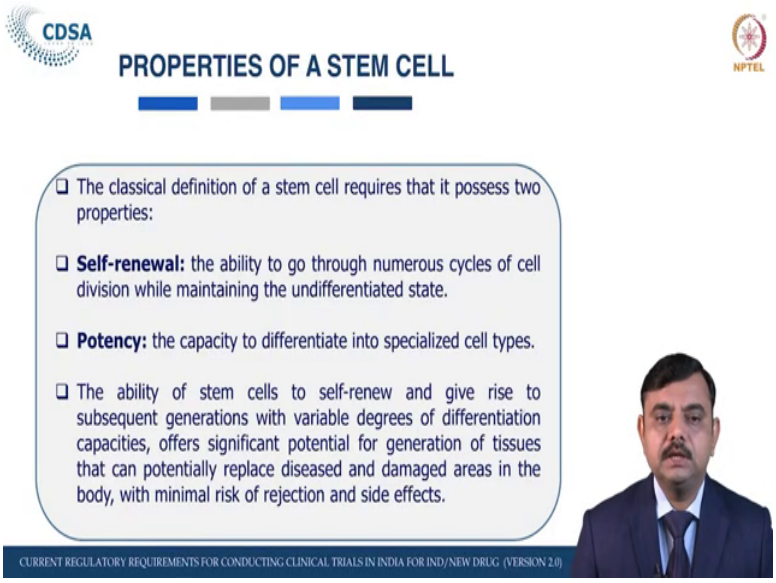
So, these stem cells are undifferentiated biological cells with the capacity for self renewal, proliferation and differentiation into many different types of functional cells. Based on the potency of the stem cell there are there are five types of cells these can be divided into the five types; the Multi-component Cells like a Mesenchymal cell. Then, Hematopoietic cells.

(Refer Slide Time: 13:05)



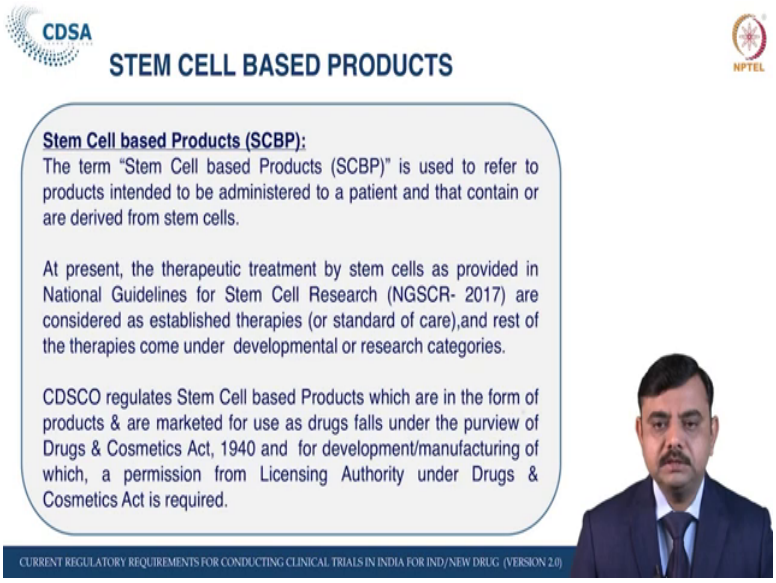
Then, Pluripotent Stem Cell for example, Embryonic Stem Cells or induce of pluripotent stem cells; these are pluripotent stem cell. Then, Totipotent Stem Cells like a Stem Cells derived from Morula. And Unipotent Stem Cell which are for example, Hepatoblasts or the Cholangiocytes, these are the unipotent stem cells and the last is the Oligopotent Stem Cells for example, Lymphoid or the Myeloid Stem Cells.

(Refer Slide Time: 13:31)



The classical definition of stem cell requires that it should posses two properties. The Self-renewal and the Potency. Self-renewal is the ability to go through numerous cycles of cell division while maintaining the undifferentiated state. And the potency, it is the capacity to differentiate into a specialized cell types. The ability of stem cell to self renew and give rise to subsequent generations with variable degree of differentiation, capacities, offers significant potential for generation of tissues, that can potentially replace diseased and damaged areas in the body, with minimal risk of rejection and side effects.

(Refer Slide Time: 14:19)



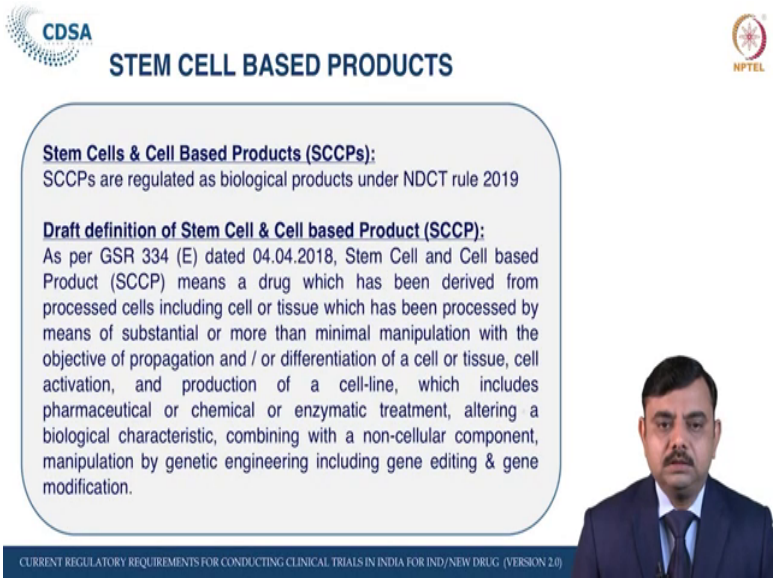
Stem cell and Stem Cell based product, we call SCCP's are regulated as a drug under Drug and Cosmetic Act, Section 3b. However, the research on the stem cells and stem cell products comes under the ICMR and researcher shall follow National Guideline for Stem Cell Research, 2017.

There is always confusion where to apply whether it comes under the purview of regulation or not. So, by this slide, we try to give the clarity. The terms stem cells based product is used to refer to product intended to be administered to patient and that content or are derived from stem cells.

At present, the therapeutic treatment by stem cells as provided in the NGSCR that is National Guideline for Stem Cell Research, 2017 are considered as established therapies and rest as I have mentioned come under the development of research category. CDSCO being a national

regulatory authority regulate stem cell based product which are in the form of a product and are marketed for use as a drug that falls under the purview of D and C Act, 1940 and for development, manufacturing this as it is coming under the purview of D and C Act. A permission from licensing authority is a required.

(Refer Slide Time: 15:47)



Stem cell and a Stem cell based product; as I have mentioned regulated as a biological product under New Drug and Clinical Trial Rule 2019 and as per the GSR 334 dated 04.04.2018, Stem cell and stem cell based product means a drug which has been derived from processed cells including cell or tissue which has been processed by means of substantial or more than minimal manipulation with the objective of propagation and or differentiation of a cell or tissue, cell activation, and production of a cell-line. Which include, pharmaceutical or chemical or enzymatic treatment, altering a biological characteristic, combining with a non-cellular

component, manipulation by genetic engineering including gene editing and gene modification.

The what is mean by minimal manipulation and other things that are also given in this a GSR. A separate task for some stem cell research and regenerative measure has been constituted to consider the proposal on their scientific merit by the department of biotechnology.

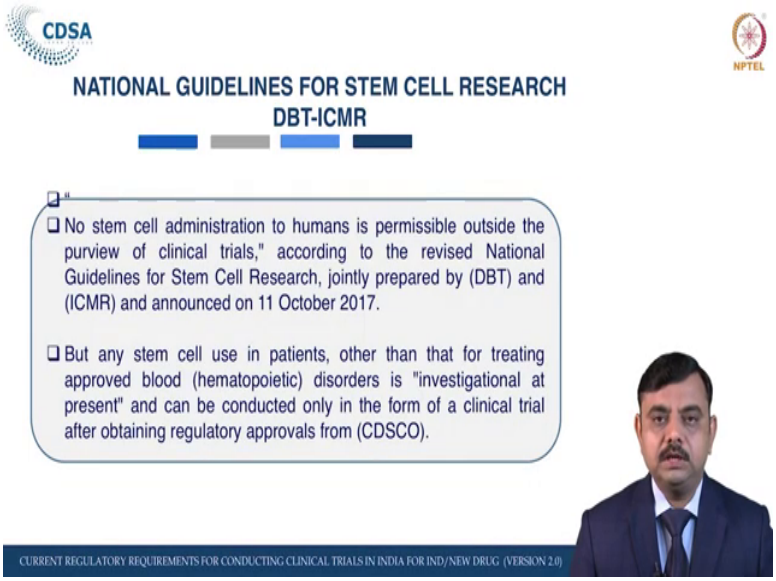
(Refer Slide Time: 17:26)

So, apart from the for the evaluation of it, apart from the Subject Expert Committee, then Technical Advisory Committee and Apex Committee at the CDSCO, one more committee that is CBBTDEC that is Cellular Biology Based Therapeutic Drug Evaluation Committee. It is constituted by the Government of India, Ministry of Health and Family Welfare under the Chairmanship of Secretary, Department of Health Research and DG, Director General, ICMR.

To advise the DCGI, in matter pertaining to the regulatory pathway leading to the approval of clinical trial and marketing authorization for the therapeutic product.

Ministry of Health and Family Welfare wide order number DCGI miscellaneous 2010 slash 2010 parts stem cells TFQC dated 1st September, 2010 has constituted a core IND panel of expert namely Cellular Biology Based Therapeutic Drug Evaluation Committee under the Chairman of the Secretary.

(Refer Slide Time: 18:23)

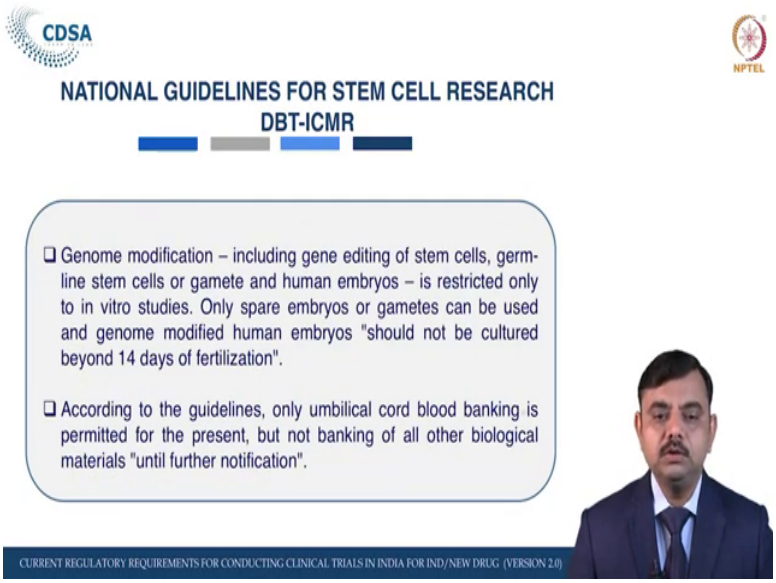


Let us move towards our next slide which is stem cell research. So, as I have mentioned stem cell research is as per the guideline developed by DBT and ICMR. So, as per these guidelines that is the National Guideline for Stem Cell Research, “No stem cell administration to human is permissible outside the purview of clinical trial,” according to the revised, National

Guideline for Stem Cell Research, jointly prepared by Department of Biotechnology and ICMR and this has been announced on 11th October, 2017.

But any stem cell use in patients, other than that for treating approved blood that is hematopotic like a disorder is “investigational at present” and can be conducted only in the form of clinical trial after obtaining regulatory approval. It means, it require a clinical trial permission from the CDSCO.

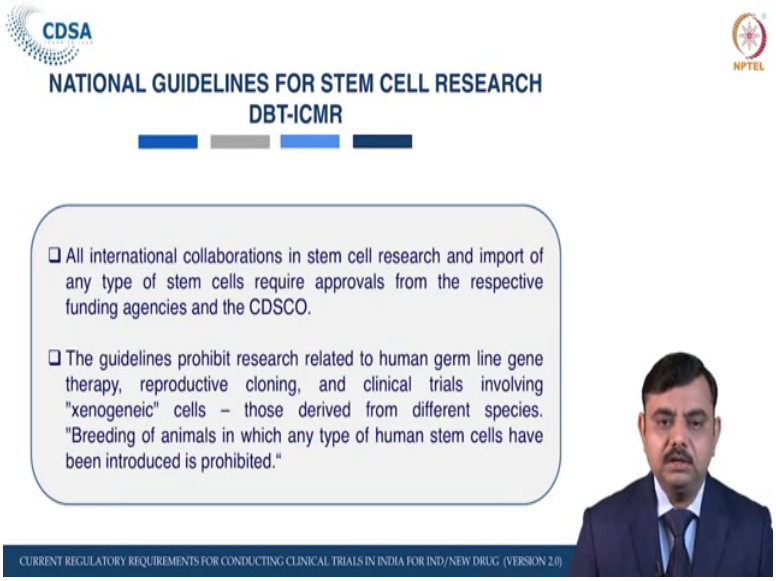
(Refer Slide Time: 19:19)



Genome modification including gene editing of stem cells, germline stem cells or gamut and human embryos - is restricted only to in vitro studies, not embryos. Only spare embryos or gametes can be used and genome modified human embryos “should not be cultured beyond 14 days of fertilization”. According to these guidelines, only umbilical cord blood bank is

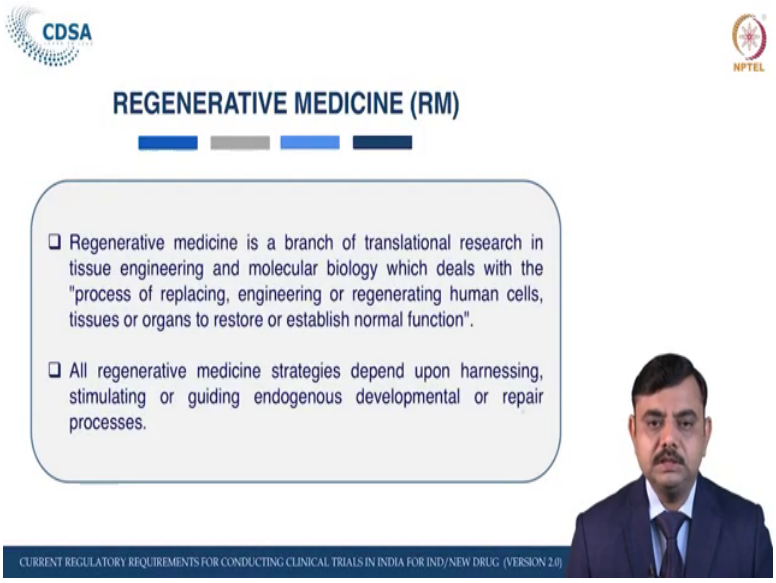
permitted for the present, but not banking of all other biological materials “until further notification”.

(Refer Slide Time: 19:54)



All international collaboration in stem cell research and import of any type of stem cell require approval from the respective funding agencies and regulatory approval from the Central Drug Standard Control Organization. The guidelines prohibit research related to human germ line gene therapy, reproductive cloning, and clinical trials involving “xenogeneic” cells - those derived from different species. “Breeding of animal in which any type of human stems have been introduced is prohibited”.

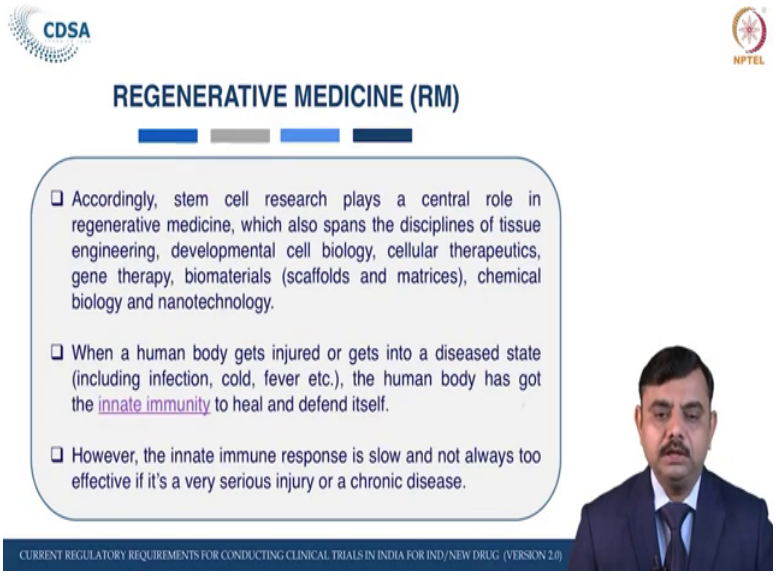
(Refer Slide Time: 20:36)



Let us see what is the regenerative medicines. This is also another area of concern. So, the regenerative medicine is a branch of translational research in tissue engineering and molecular biology which deals with the “process of replacing, engineering or regenerating human cells, tissues or organ to restore or establish normal function”.

All regenerative medicine strategies depend upon harnessing, stimulating or guiding endogenous developmental or repair process.

(Refer Slide Time: 21:12)



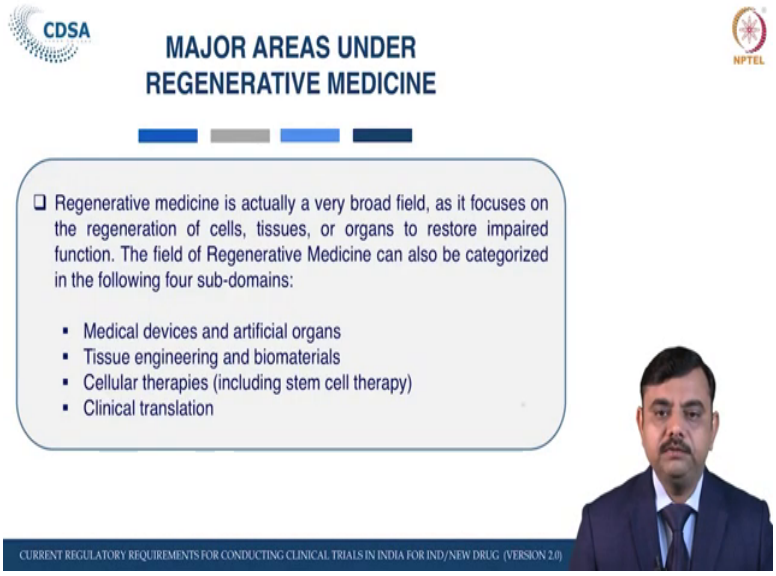
Accordingly, stem cell research plays a central role in regenerative medicines, which also spare the discipline of tissue engineering, developmental cell biology, cellular therapeutics, gene therapies, biomaterial including scaffold and matrices, chemical biology and nanotechnology.

When a human body gets injured or get into a diseased state including infection, cold or fewer, the human body has got the innate immunity to heal and defend itself. However, the innate immune response is slow and not always too effective if it is a very serious injury or chronic diseases.

(Refer Slide Time: 21:57)

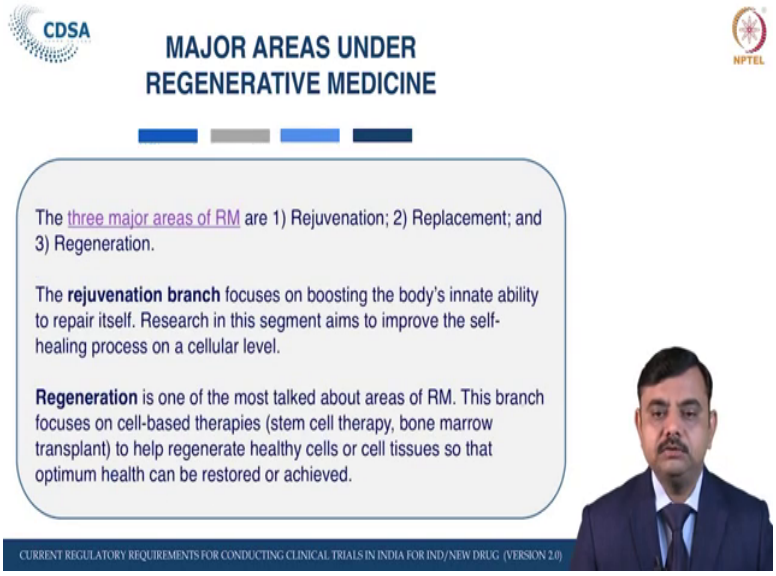
Here comes the Regenerative Medicine, it has got the potential to improve the healing process of the body on its own and or accelerate the healing process through clinical intervention. Regenerative medicines works towards repairing damaged tissue and organs and to find a way to cure previously untreatable injuries and diseases.

(Refer Slide Time: 22:29)



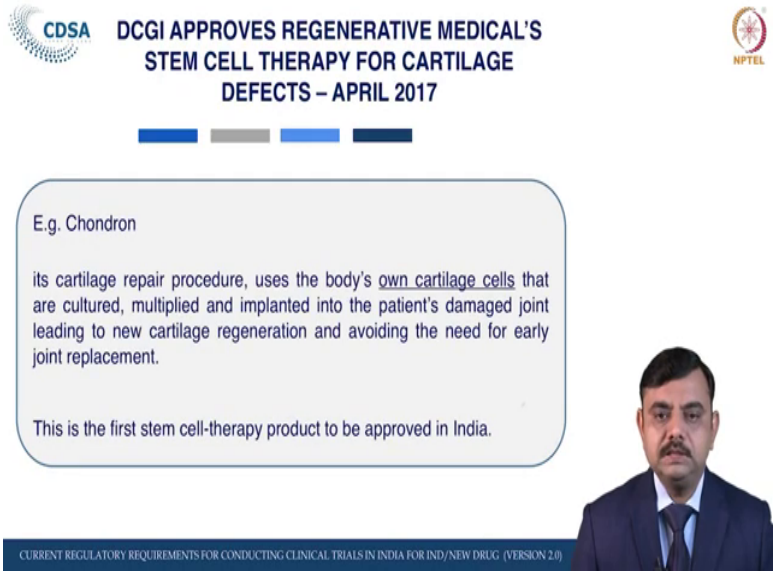
So, there are major areas under regenerative medicine is actually, a very it is a very broad field, as it focuses on the regeneration of cells, tissue or organs to restore impaired function. The field of regenerative medicines can also be categorized in the following four sub-domains that is Medical devices and artificial organs; Tissue engineering and biomaterials; Cellular therapies; Clinical translational.

(Refer Slide Time: 22:58)



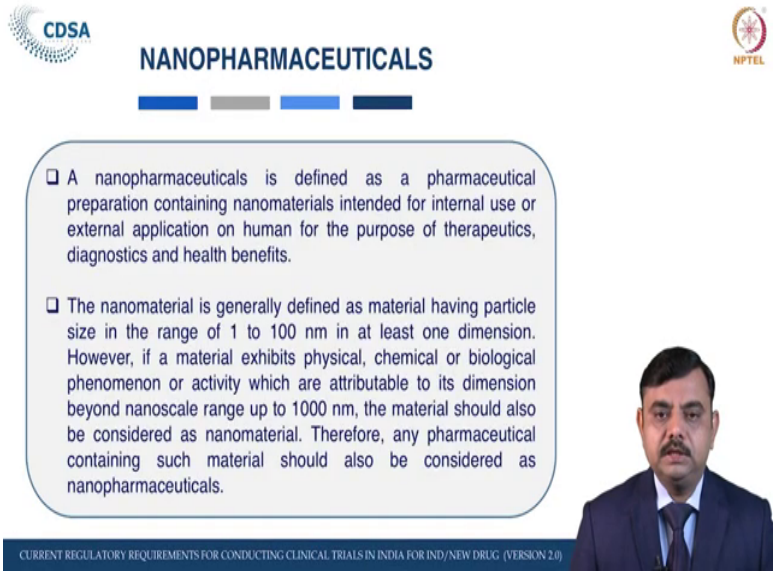
The three major areas are Rejuvenation, Replacement and the Regeneration; that is 3 R's. The regeneration branch focuses on boosting the body's innate ability to repair itself. Research in this segment aims to improve the self healing process on a cellular level. Regeneration is one of the most talked about areas of regenerative medicine. This branch focuses on cell-based therapies to help regenerate healthy cells or cell tissues so that optimum health can be archived.

(Refer Slide Time: 23:39)



DCGI in April 2017 has approved a one of the product that is called Chondron. Its a cartilage repair procedure and uses the body's own cartilage cell that are cultured, multiplied and implanted into the patients damaged joint leading to a new cartilage regeneration and avoiding the need for early joint replacement.

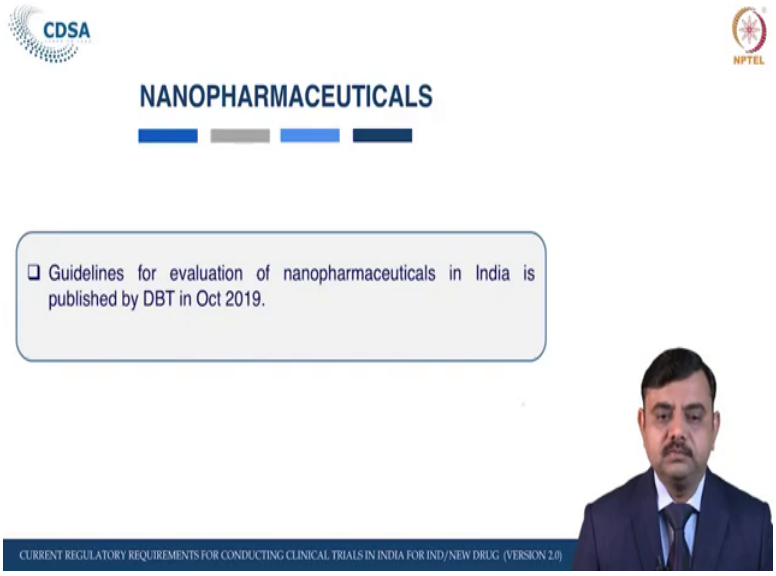
(Refer Slide Time: 24:10)



The another area of concern is nanopharmaceuticals, let us see what is the nano pharmaceuticals. It is defined as a pharmaceutical preparation containing nanomaterials intended for internal or external application on human for the purpose of therapeutics, diagnostics and health benefit.

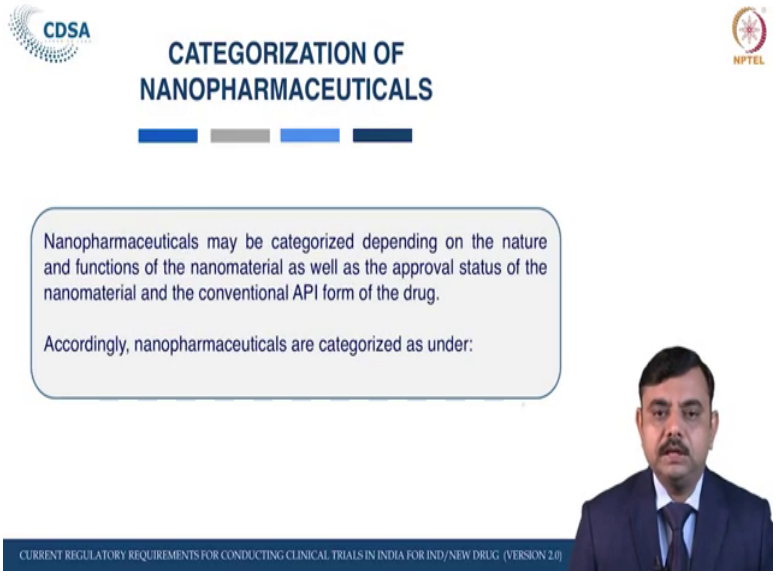
The nanomaterial is generally defined as material having particle size in the range of 1 to 100 nanometer in at least one dimension. However, if a material exhibits physical, chemical or biological phenomena or activity which are attributed to its dimension beyond nanoscale range up to 1000 nanometer, the material should also be considered as a nanomaterial. Therefore, any pharmaceutical containing such a material should also be considered as a nanopharmaceutical.

(Refer Slide Time: 25:04)



The Guidelines for evaluation of nano pharmaceutical in India has been published by DBT in October 2019.

(Refer Slide Time: 25:13)



The categorization of nanopharmaceuticals this nanopharmaceuticals can be categorized depending on the nature and functions of the nanomaterial as well as the approval status of the nanomaterial and the conventional API from the drug.

Accordingly, this is this has been classified into the based on the basis of a, here the table has been given.

(Refer Slide Time: 25:41)

The basis for categorization is degradability of nano particles, fabricating material and in these the categories are biodegradable, non-biodegradable. The examples are protein, lipid, biopolymers and for the non-biodegradable relatively less use in pharmaceutical product. They are like gold, silver, platinum. Based on nature of nanoparticles the organic nanoparticles, inorganic nanoparticles, multicomponent nanoparticle. These are have been divided.

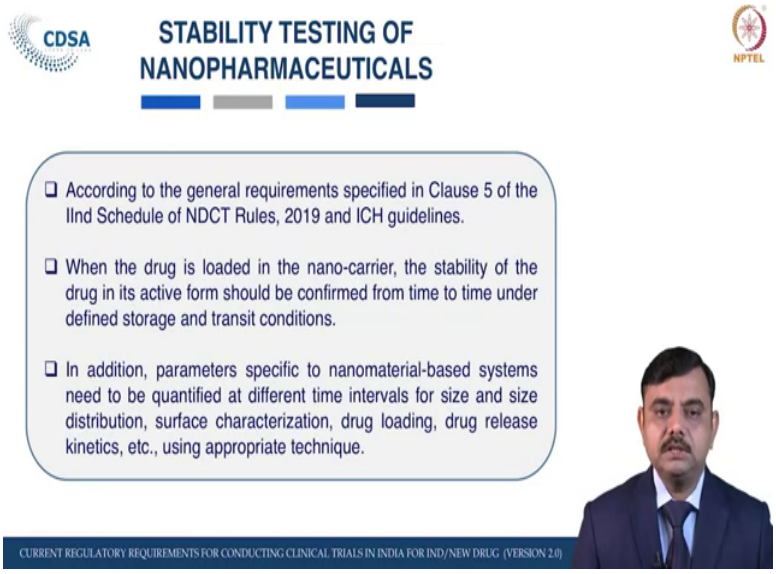
Then, based basis for the categorization one more basis per categorization is nano form of the ingredients. The nano carriers loaded with API example micelles, polymer, conjugate, polymeric nanoparticle, carbon-based material. Then, API converted to the nanoform drug may be converted into nanoparticle or nanocrystal. Thereby, an increasing their potential for improved dissolution and bioavailiabilty; example are nanocrystals of sirolimus, tacrolimus and the fenofibrate.

(Refer Slide Time: 26:56)

Specific consideration for evaluation of nano pharmaceutical, in the context of Second Schedule of the New Drug and Clinical Trial Rule, 2019. General requirement as specified in the Second Schedule of the New Drug and Clinical Trial Rule, 2019 will be applicable for all the Nanopharmaceuticals. However, due to the inherent complexity in nanotechnology- based product, a 'case by-case approach' should be adopted for evaluating their quality, safety and efficacy.

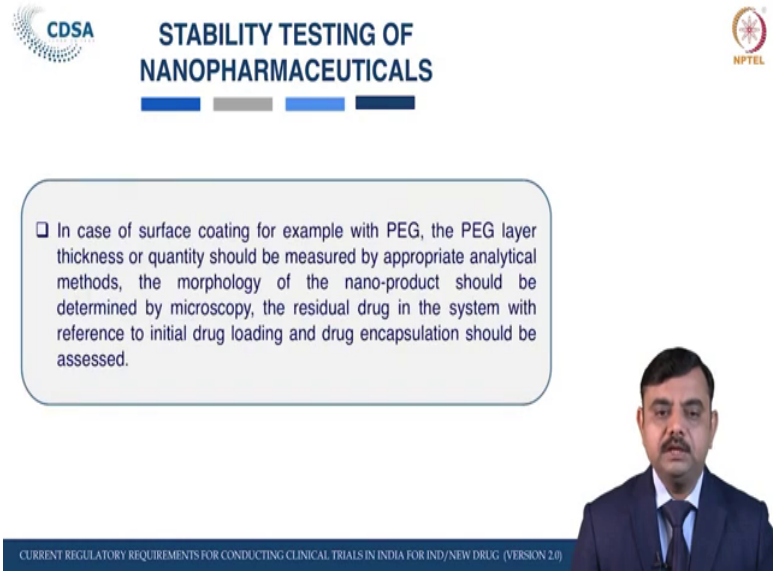
In case of liposomal formulations specific, US-FDA guideline for 'Liposomal Drug Product' of April 2018 maybe consulted. Let us see in brief about stability testing of nano pharmaceutical.

(Refer Slide Time: 27:43)



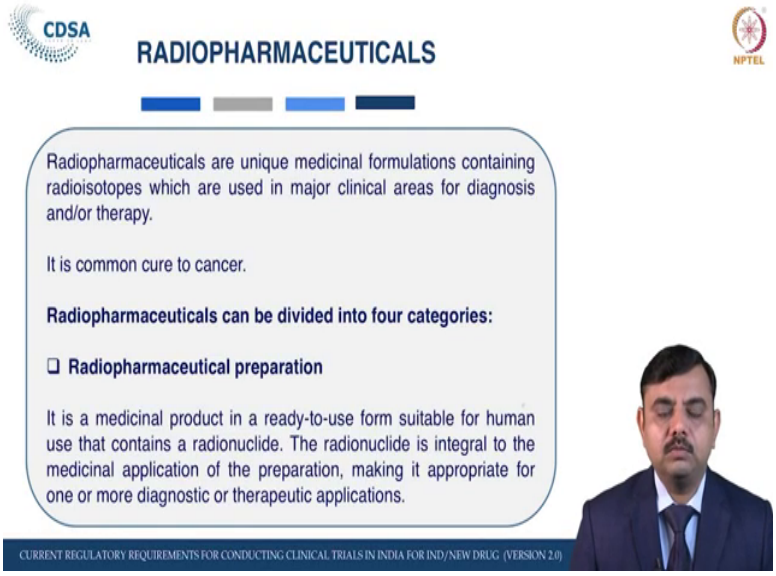
According to the general requirements specified in Clause 5 of the IInd Schedule of NDCT Rule, 2019 and also in the ICH guidelines. When the drug is loaded in the nano-carrier, the stability of the drug in its active form should be confirmed from time to time under defined storage and transit conditions. In addition, parameters specific to nanomaterial-based system need to be quantified at different time interval for size and size distribution, surface characterization, drug loading, drug release kinetics, and other using appropriate techniques.

(Refer Slide Time: 28:25)



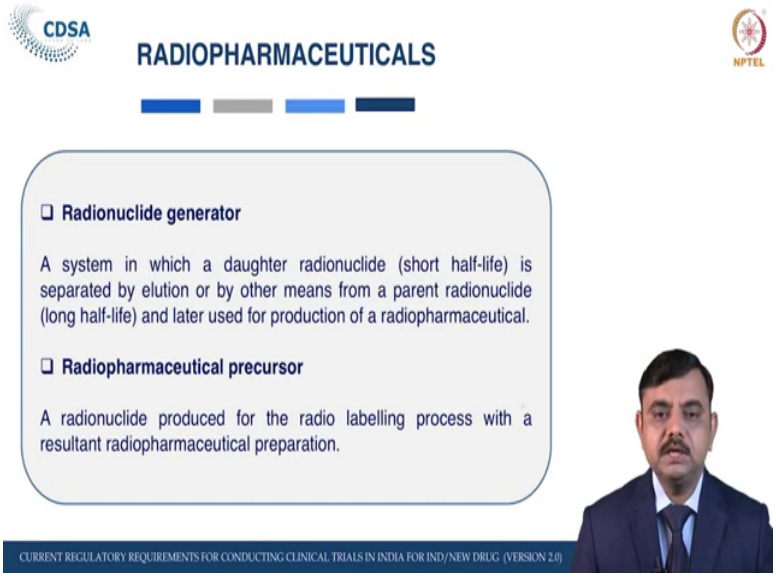
In case of surface coating for example with PEG, on the PEG layer thickness or quantity should be measured by appropriate analytical method. The morphology of the nano-product product should be determined by microscopy, the residual drug in the system with reference to initial drug loading and drug encapsulation that should be assessed.

(Refer Slide Time: 28:52).



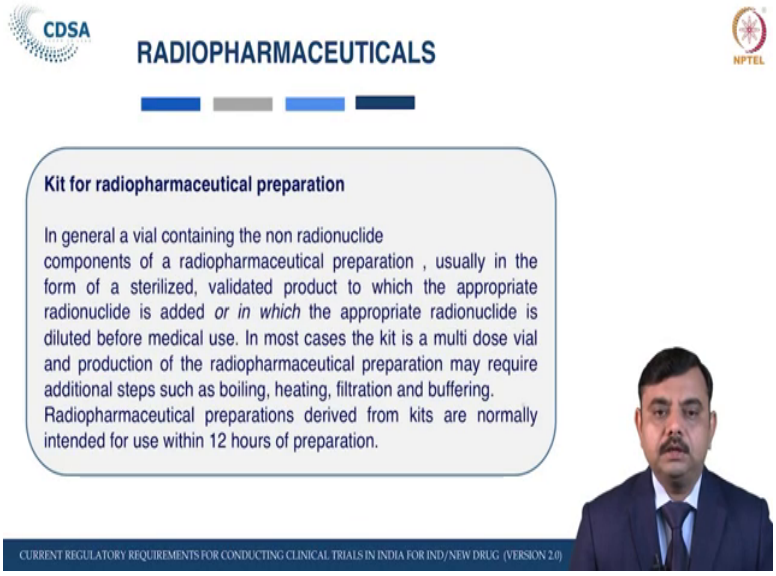
The next area of the concern is the Radiopharmaceutical. So, let us see what are these radiopharmaceuticals? Radiopharmaceuticals are unique medicinal formulation containing radio isotopes which are used in major clinical areas for diagnosis and for therapy, as we know that it is a common treatment for the cancer.

(Refer Slide Time: 29:14)



These radiopharmaceutical can be divided into the four categories; that is Radiopharmaceutical preparation; Radionuclide generator; the Radiopharmaceutical precursor and the, Kit for the radiopharmaceutical preparations.

(Refer Slide Time: 29:23)



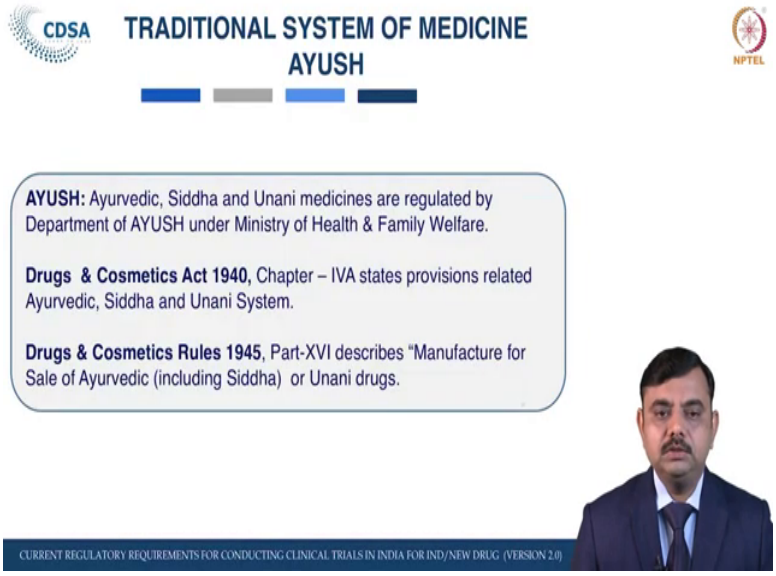
What are these? It has been given in this slide; you can see. It is radiopharmaceutical the last category that is kit when they are derived from the kits are normally intended for use within 12 hours of the preparation.

(Refer Slide Time: 29:45)

Let us see why these are special. The regulatory permission need to be taken. In case of the radiopharmaceutical also, the regulatory permission is required. As like we have seen the different committees are involved in the evaluation of the different kind of product and the biologicals. For the radiopharmaceutical, the no objection certificate is required from the Bhabha Atomic Research Center and as per the guideline the radiation exposure must be within permissible limit.

Pregnancy need to be ruled out, then radiation guideline must be followed if death occurs with radiation implant and appropriate training is necessary in handling this radioactive substances. Now, moving towards the next area of concern, that is a traditional system of medicines like AYUSH and other.

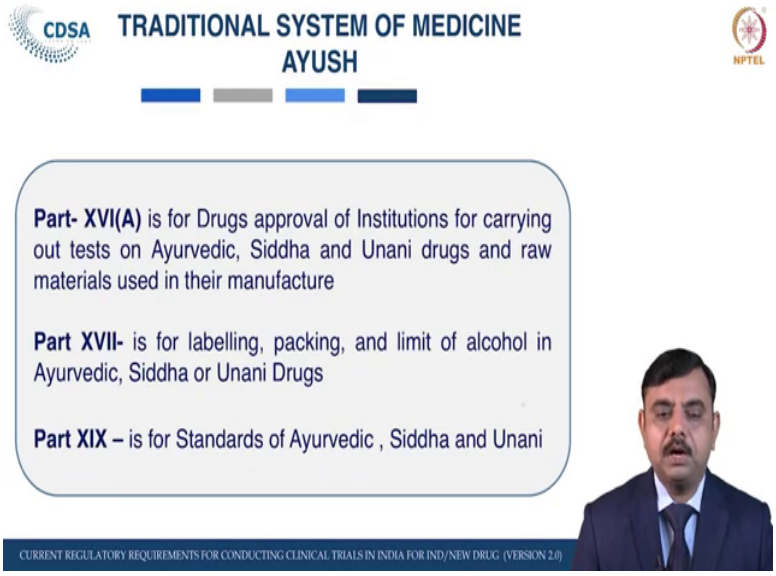
(Refer Slide Time: 30:44)



So, the AYUSH is the Ayurvedic, Siddha and Unani medicines which are regulated by Department of AYUSH under Ministry of Health and Family Welfare. This has been some part of this has also been regulated by the department like CDSCO and the other State Licensing Authorities also involved Drug and Cosmetic Act, 1940, Chapter IVA, it states the provisions related to the Ayurvedic, Siddha and Unani system. So, the License for manufacturing and the sales and the standards require that has been given into the Chapter IVA of Drug and Cosmetic Act.

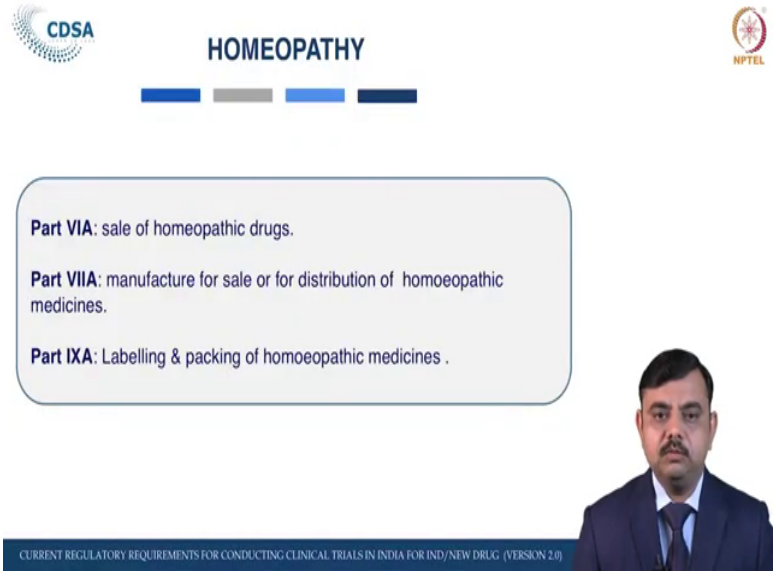
Drug and Cosmetic Rule 1945 in the Part-XVI describes the "Manufacturer for Sale of Ayurvedic including Siddha or Unani drugs.

(Refer Slide Time: 31:39)



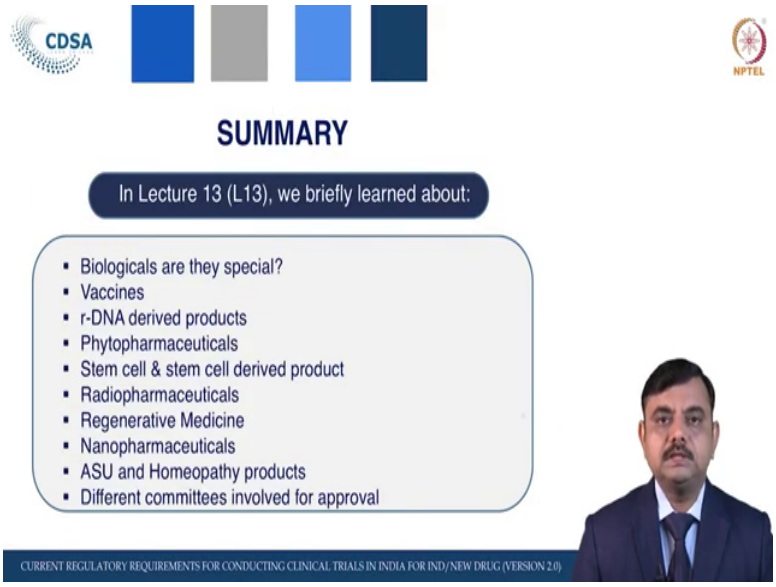
Then, Part-XVI A is for approval of Institution for carrying out test on Ayurvedic, Siddha and Unani drugs and raw material used in their manufacture. Part XVII- is for labeling, packing and limit of alcohol in Ayurvedic, Siddha and Unani system. Part XIX - is for Standards of Ayurvedic, Siddha and Unani drugs.

(Refer Slide Time: 32:12)



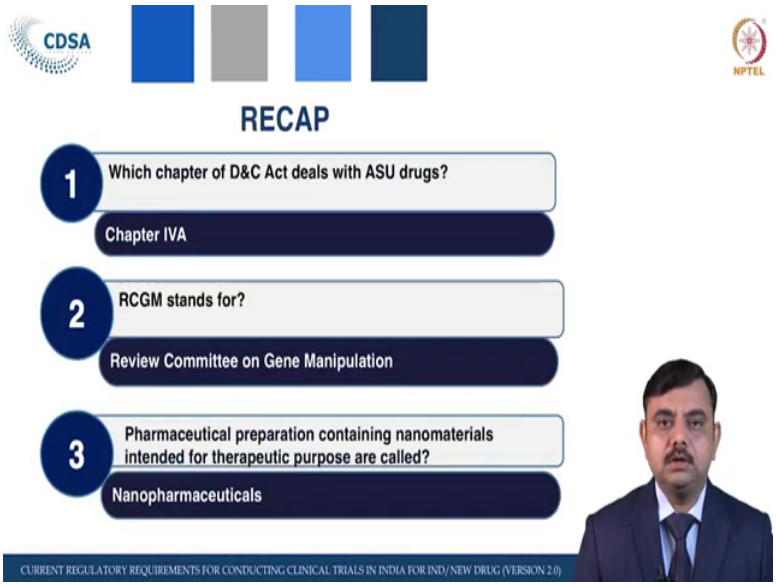
One more area of concern from these traditional medicine is a Homeopathy and the Part-VIA of drug and cosmetic rule is deals with the sale of homeopathic drug. Part VIIA is related to the manufacture for sale or for distribution of homeopathic medicines and Part IXA is related to the labeling and packing up homeopathic medicines.

(Refer Slide Time: 32:36)



So, these are the areas of concerns, let us see what we have seen in this lecture in brief. So, in this lecture we have seen what are the biologicals, which are the area of concern and why these biologicals are special in nature, what are the r-DNA derived product, what are the phytopharmaceuticals, then stem cells, stem cell derived product, radiopharmaceutical, regenerative medicine, nano pharmaceutical, then traditional system, homeopathic system and we have seen the different committees involve in that.

(Refer Slide Time: 33:17)



So, now this is a time for you to give the answer. The first question for you, which chapter of D and C Act deals with Ayurvedic, Siddha and Unani drugs? So, the chapter has been given in the Drug and Cosmetic Act, 1940. So, this is a Chapter IVA which deals with the Ayurvedic, Siddha and Unani system. Question number 2, RCGM stand for? You have to give the full form of the RCGM. So, it is a Review Committee on Gene Manipulation. The third question you have to fill in the blank. Pharmaceutical preparation containing nanomaterial intended for therapeutic purpose is called? What it is called? So, it is a Nanopharmaceutical. So, these are the areas of special concerns.

And always there is ambiguity about these areas whether to apply for the license or not; which ministry which department, it deals with. Hope now it is a very clear from this lecture and you

have enjoyed this lecture. We will see you again in our next lecture. Till then, you take care. Bye, bye and all the best.