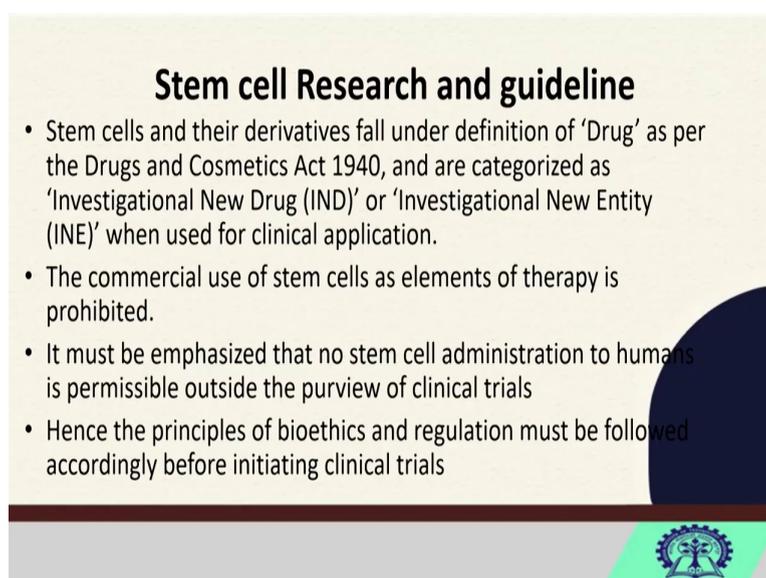


**Legal and Regulatory Issues in Biotechnology**  
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**Module - 01**  
**Regulation of Biotechnology Research**  
**Lecture - 06**  
**Stem Cell Research in India**

Hello again. So, in today's lecture, we are going to look into some basic's provisions related to Stem Cell Research in India.

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**Stem cell Research and guideline**

- Stem cells and their derivatives fall under definition of 'Drug' as per the Drugs and Cosmetics Act 1940, and are categorized as 'Investigational New Drug (IND)' or 'Investigational New Entity (INE)' when used for clinical application.
- The commercial use of stem cells as elements of therapy is prohibited.
- It must be emphasized that no stem cell administration to humans is permissible outside the purview of clinical trials
- Hence the principles of bioethics and regulation must be followed accordingly before initiating clinical trials



So, far we discussed what are the ethical consideration or challenges with respect to the embryonic stem cell research, a lot of ethical consideration whether you say when it is derived from the human embryo or when it is a induced pluripotent cell or even when it is a cloning procedure where the somatic nuclear has been transfused to a oocyte.

So, in India, the stem cells and the derivatives are categorized under the definition of the 'Drug' as per the Drugs and Cosmetic Act of 1940 and they are categorized as 'Investigational New Drug, IND' or 'Investigational New Entity or INE' when they are used for the clinical applications.

Because we have already discussed the stem cell has a lot of potential because of its ability to differentiate into specific types of the cells or the tissue. So, these are popularly used for this regenerative therapy.

But in India, so far the commercial use of the stem cells as the element of therapy is prohibited because it is more like a individual treatment depending on the persons need those cells are programmed and accordingly it develops and functions. So, it is emphasized that no stem cells administration to the human is permissible outside the purview of the clinical trial.

So, in India, it is more an ongoing area of development. So, it is so far like a sort of a clinical trial process, where it is studied and being developed so far. So, as we have seen in the code of ethics or for the clinical trial regulation, so there are also principles of the bioethics and the regulations applicable to this kind of the stem cell research, even before initiating the clinical trials.

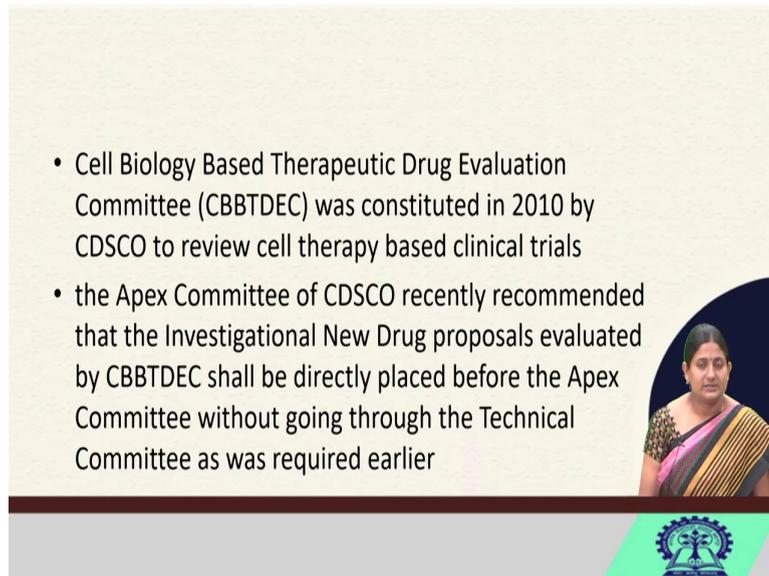
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So, if we see in India, the there are so like in 2007, we have the first guideline specific to the stem cell research and therapy. So, that is known as the guidelines for stem cell research and therapy and then, we have this national guideline for stem cell research of 2013, which is again for revised in the year 2017.

So, these guidelines are being developed by the department of biotechnology in collaboration with the Indian council of Medical Research. So, as an when we are progressing or developing with respect to the new standards of standards or process for the stem cell research and they are a there has been changes in the guidelines as well. So, these are the current guidelines available in our country for the research purposes of the stem cells.

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- Cell Biology Based Therapeutic Drug Evaluation Committee (CBBTDEC) was constituted in 2010 by CDSCO to review cell therapy based clinical trials
- the Apex Committee of CDSCO recently recommended that the Investigational New Drug proposals evaluated by CBBTDEC shall be directly placed before the Apex Committee without going through the Technical Committee as was required earlier

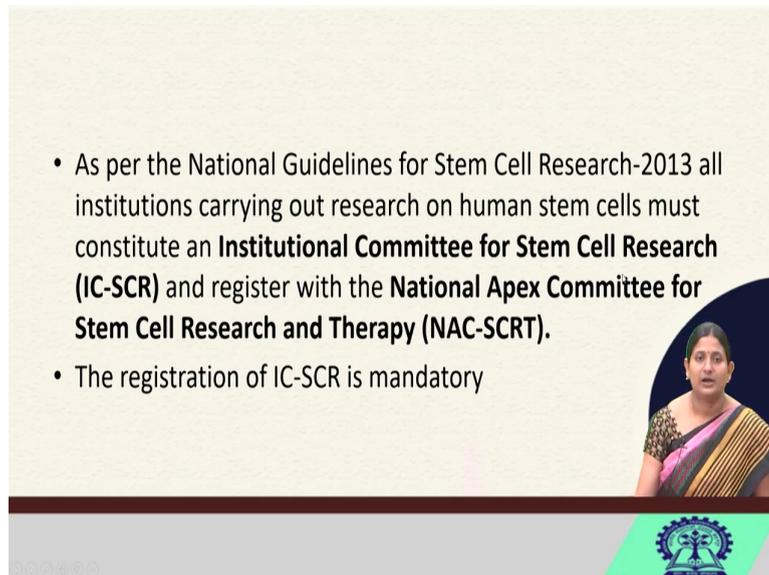
So, as I mentioned the it is the stem cell products are considered as a kind of a drug under the Central Drug Standard Control Organization of the India. So, when a drug is being used by certain human treatment is used by the for or by the humans, so it has to be properly evaluated.

So, these in the year 2010, there was a committee named as the Cell Biology Based Therapeutic Drug Evaluation Committee, CBBTDEC which is basically responsible to review the cell therapy based clinical trials. So, after that thing, it was again evaluated by some technical committee and finally, the approval was given by the DCGI.

But very recently the Apex Committee of the CDSCO has recommended that the Investigational New Drug proposals means the drugs under the drugs which are under investigation means under the clinical trials should be evaluated by this CB, this committee Cell Biology Based Therapeutic Drug Evaluation Committee.

And it need not took place to the technical committee before or the further approval. It may be directly placed before the Apex committee, once it is reviewed by the appropriate Cell Based Therapeutic Drug Evaluation Committee.

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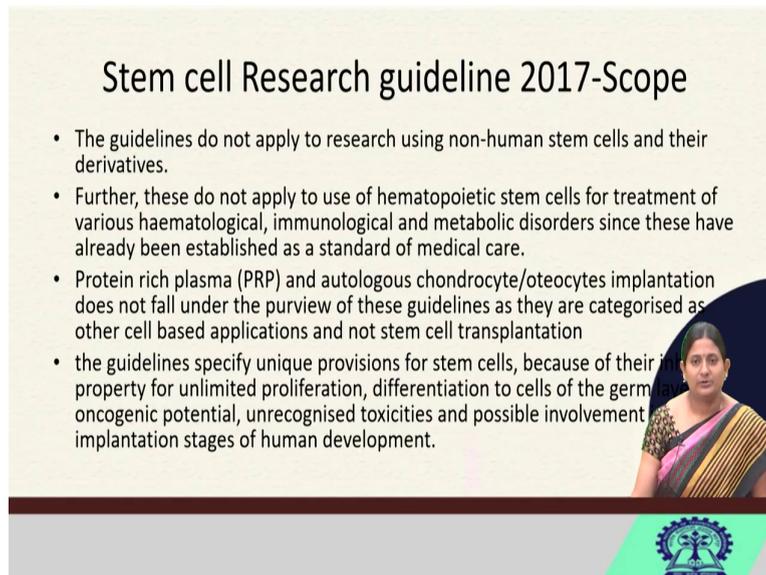


- As per the National Guidelines for Stem Cell Research-2013 all institutions carrying out research on human stem cells must constitute an **Institutional Committee for Stem Cell Research (IC-SCR)** and register with the **National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT)**.
- The registration of IC-SCR is mandatory

So, as per the national guidelines for the stem cell research of 2013, it for the first time mandated that all the institutions which are carrying out research on the area of the human stem cells must constitute an institutional committee for the stem cell research. Like we have this ethical committee for various animal research or the human research, so similarly, for the stem cell research also, there is a mandatory constitution of the committee which is known as the Institutional Committee for the Stem Cell Research.

And it has to be registered with the National Apex Committee for the Stem Cell Research and the Therapy and this kind of registration or the constitution and the registration is mandatory for all the institutes, who are involved in stem cells research.

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### Stem cell Research guideline 2017-Scope

- The guidelines do not apply to research using non-human stem cells and their derivatives.
- Further, these do not apply to use of hematopoietic stem cells for treatment of various haematological, immunological and metabolic disorders since these have already been established as a standard of medical care.
- Protein rich plasma (PRP) and autologous chondrocyte/osteocytes implantation does not fall under the purview of these guidelines as they are categorised as other cell based applications and not stem cell transplantation
- the guidelines specify unique provisions for stem cells, because of their property for unlimited proliferation, differentiation to cells of the germline, oncogenic potential, unrecognised toxicities and possible involvement in early implantation stages of human development.

So, now, as I said, we are in the process of developing or researching more and more in the area of the stem cells. So, here I would like you to present briefly the scope and the purpose of this guideline and what are the important points the guidelines specifies. So, basically if you see the stem cell research guideline of 2017, this guideline is particularly for the human stem cells.

So, this does not apply to the research using the non-human stem cells and their derivatives. It is particularly for the human stem cells. And further, this guideline also do not apply to the use of the hematopoietic stem cells, which are used generally for the treatment of the various hematological or immunological or metabolic disorders.

Because already these kind of hematopoietic stem cells are well established in the standard medical care practices across countries. There are some products which are kept outside the purview of this guideline are the protein rich plasma or the autologous chondrocytes or the osteocytes implantation. So, they are not covered under this guideline.

And this guideline is particularly designed in a way that it has kept in mind the unique provision for the stem cells because the stem cells ability to proliferate unlimitedly and differentiate into different cells of the germline or different cells which might have oncogenic

or the cancerous property or it may lead to the unrecognized toxicity or the safety issues and possibly, possible involvement with the implantation stages of the human development.

So, we do not know much about the consequences of such kind of the research. So, the guidelines have been formulated in such a way that whether whenever a research with the stem cells is being carried out, it should take care of all the points which may be a point of concern at the later stage.

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**Stem cell Research guideline 2017**

- The guideline therefore focuses on:
  - 1. Monitoring mechanism and regulatory pathway for basic, clinical research and product development based on categories of research and level of manipulation.
  - 2. Procurement of gametes, embryos and somatic cells for derivation and propagation of any stem cell lines, their banking and distribution.
  - 3. Other important areas like international collaboration, exchange of cell/lines and education for stakeholders and advertisement

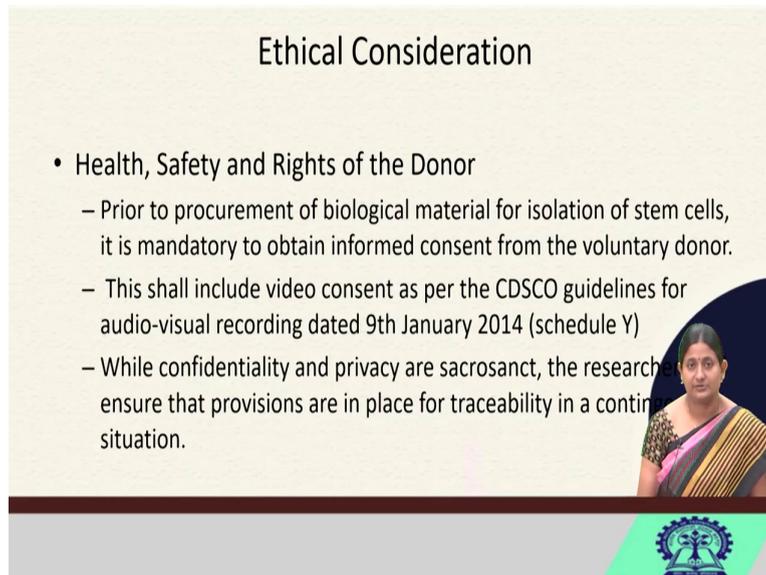
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So, basically the 2017 guideline focuses on the monitoring mechanism and the regulatory pathway for the basic clinical research and the product development based on the categories of the research and level of manipulation of the stem cells, which we will discuss little bit later in this class.

And then, it also tries to identify and solve the issue related to the procurements of the gametes, embryos or the somatic cells for the derivation and the propagation of the stem cell lines, their banking procedures and their distribution. Because we have seen how there might be an ethical issue, while when you are procuring or when you are deriving the stem cells. So, all those points are also being covered here.

The other important areas such as the international collaboration in the human stem cell research or the exchange of the cell lines or for the education or the advertisement purpose. So, all these issues are also being dealt with in this current guideline of the 2017.

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The slide is titled "Ethical Consideration" and contains the following text:

- Health, Safety and Rights of the Donor
  - Prior to procurement of biological material for isolation of stem cells, it is mandatory to obtain informed consent from the voluntary donor.
  - This shall include video consent as per the CDSCO guidelines for audio-visual recording dated 9th January 2014 (schedule Y)
  - While confidentiality and privacy are sacrosanct, the researchers ensure that provisions are in place for traceability in a continuing situation.

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One of the important parts of this stem cell research is the stem cell research guideline is the ethical consideration. So, we have seen starting from the Nuremberg code to other code of ethics for the human clinical trial, this needed a separate ethical consideration because the health or the safety of the rights of the donor, particularly in the stem cells is little bit different from the normal or other kind of the biomedical research.

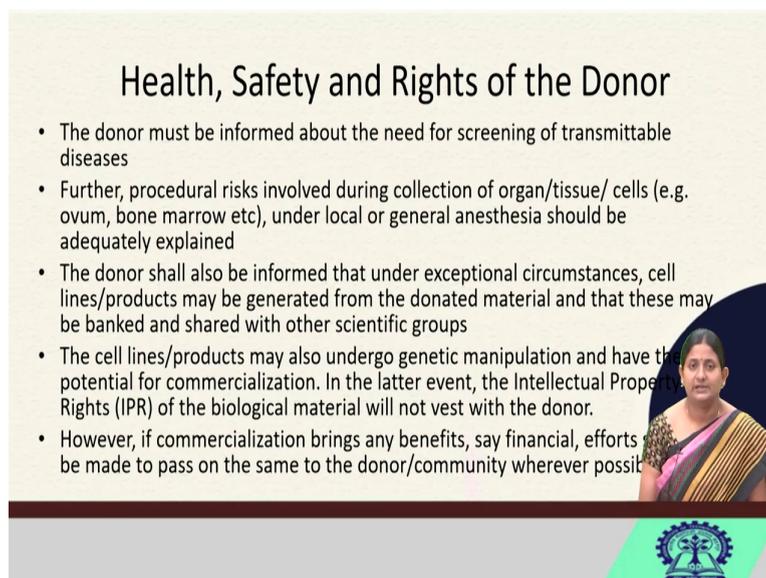
So, prior to the procurement of the biological material for the isolation of the stem cells, it is mandatory to obtain the informed consent from the voluntary donors. So, now informed consent means basically a process where the donor is made aware about the usage, the implications and other related aspect of the whole scientific research and whatever implication, it may have on his or her health.

So, everything has to be properly explained to the donor and now, as per the revised guideline of 2014, the informed consent has to be a video record. So, a video consent as per the guideline of the CDSCO should be recorded and it is not only the written consent; but it is a recorded consent, where it has to be properly conveyed to the donor that what are the issues

or what implication, it may have on his health, on his social well-being or other related aspects.

While the confidentiality and privacy are two important things related to any research, so the research ensures that the confidentiality and privacy of the donor as well as donor's identity has to be maintained all the way.

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**Health, Safety and Rights of the Donor**

- The donor must be informed about the need for screening of transmittable diseases
- Further, procedural risks involved during collection of organ/tissue/ cells (e.g. ovum, bone marrow etc), under local or general anesthesia should be adequately explained
- The donor shall also be informed that under exceptional circumstances, cell lines/products may be generated from the donated material and that these may be banked and shared with other scientific groups
- The cell lines/products may also undergo genetic manipulation and have the potential for commercialization. In the latter event, the Intellectual Property Rights (IPR) of the biological material will not vest with the donor.
- However, if commercialization brings any benefits, say financial, efforts should be made to pass on the same to the donor/community wherever possible

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And it also emphasizes the health and safety as well as the rights of the donor. So, like the donor must be made aware like what are the need of screening of the transmittable diseases and what kind of risk, he may be exposed to like during the collection process of the organs or the tissues or the cell, whether it is a ovum or a bone marrow etcetera.

And what may be the other health risk associated with the local or the general anesthesia should be explained to the voluntary donor and it should be voluntary in nature; you should you cannot compel anyone to donate this kind of stem cells. And the donor should be informed under the exceptional circumstances that the if required the donated material may be the cell lines or the products, they may be banked or shared with the other scientific groups for further studies and that consent must be taken prior.

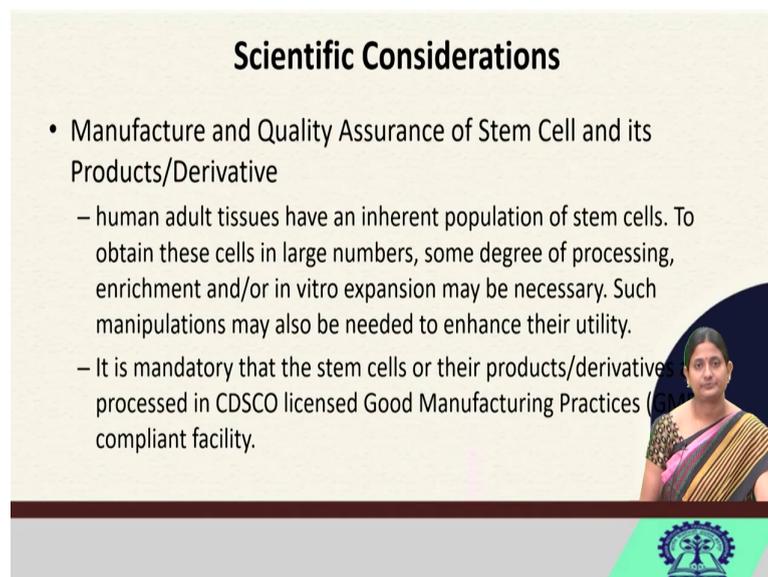
So, the cell lines and the products may also go genetic manipulation and like since they have the potential for the commercialization. So, the intellectual property right issues with respect

to the biological material must be clarified and the once, it is donated generally the IPR does not vest with the donor. So, that issue that points must be made clear before it is donated or during the informed consent procedure.

But again, if there are certain commercial benefit or a financial profit is achieved. So, again, the provision related to same whether or not the commercialization aspect or the profits profit should be shared with the community or the donor or possibility of that must also be discussed with the donor.

So, these are the because you know this even though this does not sound important at that at the point when it is collected, but it might have a greater implication at the later stage. We will discuss more about that issue in the upcoming classes how the IPR issues or the benefit sharing issues might be a problem. So, that has to be taken care of at the earliest.

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**Scientific Considerations**

- **Manufacture and Quality Assurance of Stem Cell and its Products/Derivative**
  - human adult tissues have an inherent population of stem cells. To obtain these cells in large numbers, some degree of processing, enrichment and/or in vitro expansion may be necessary. Such manipulations may also be needed to enhance their utility.
  - It is mandatory that the stem cells or their products/derivative processed in CDSCO licensed Good Manufacturing Practices (GMP) compliant facility.

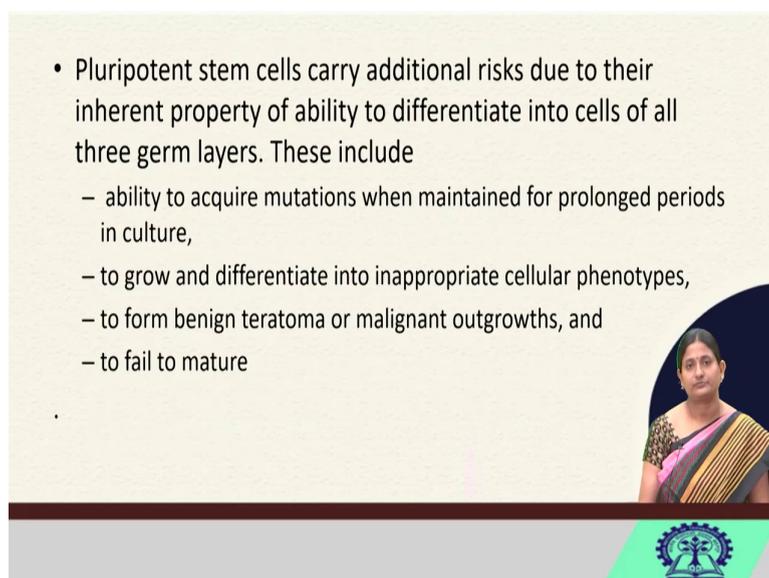
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So, the ethical consideration, rights of the donor that is one of the critical part of the regulation; other apart from that there are scientific consideration because you know the stem cells are very vulnerable to changes. They are the cells continuously dividing. So, when it is stored in an external condition or appropriate condition, sometimes there might be some changes. So, proper monitoring or identification of the proper cell line is also important.

And so, the how these cell cells are being processed, how the enrichment or other in vitro expansion process are needed that has to be properly tested and evaluated and it is mandatory that the stem cells and their product are processed in a facility that is GMP certified, good Manufacturing Practices like it has been prescribed in our Drugs Act.

Like what should be the GMP standard for in a premises, where the stem cell research can be carried out so and how where it is being stored, how it is where the experiments are being conducted. So, all the standards are already being provided in our Drugs Act. So, that has to be maintained properly.

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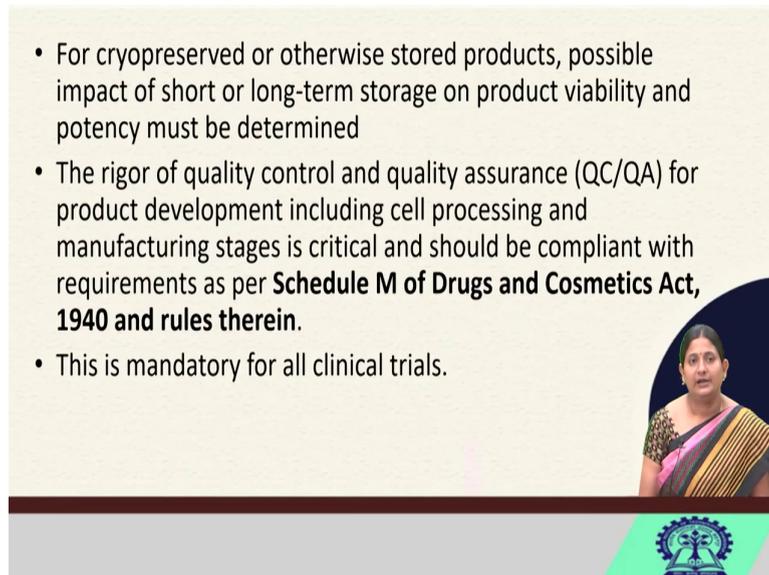
- Pluripotent stem cells carry additional risks due to their inherent property of ability to differentiate into cells of all three germ layers. These include
  - ability to acquire mutations when maintained for prolonged periods in culture,
  - to grow and differentiate into inappropriate cellular phenotypes,
  - to form benign teratoma or malignant outgrowths, and
  - to fail to mature

And when it comes to the pluripotent stem cell, it has further risk because again their inherent ability to differentiate into cells of all the three germs layer. So, they are more prone to the mutation if they are maintained for the prolonged period of the time and you know so, the human embryonic stem cell can grow into 200 different types of the cell. So, you can understand the processes, the biological processes which might take place.

So, the chances of mutation is very high there and it like it may grow and differentiate into inappropriate cellular phenotypes which is not required, if it is stored for a long period of the time and it may lead to maline or many malignant outgrowth or the cancerous outgrowth or it may sometimes fail to mature.

So, there may be lot of issues when the stem cells are stored or preserved for a long period of the time. So, care must be take into ensure that whatever the stem cells are being used, they are at the proper state so that later on their effectiveness can be properly evaluated.

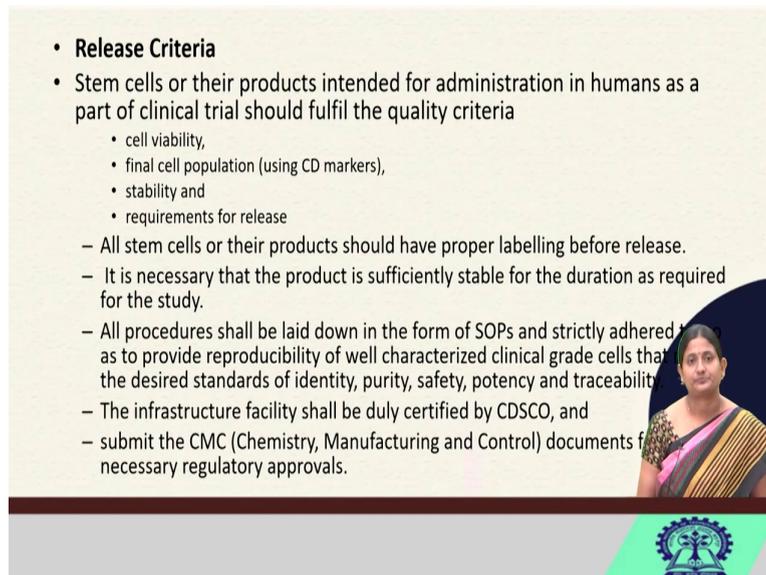
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- For cryopreserved or otherwise stored products, possible impact of short or long-term storage on product viability and potency must be determined
- The rigor of quality control and quality assurance (QC/QA) for product development including cell processing and manufacturing stages is critical and should be compliant with requirements as per **Schedule M of Drugs and Cosmetics Act, 1940 and rules therein.**
- This is mandatory for all clinical trials.

And for the cryopreserved or otherwise stored product, possible impact of the short- or long-term storage on the product viability and potency must be determined. And the quality control and quality assurance process for the stem cells are much more rigorous and again, the requirements of the Schedule M of the Drugs and Cosmetic Act must be maintained. And it is mandatory for all the clinical trials happening with respect to the stem cells.

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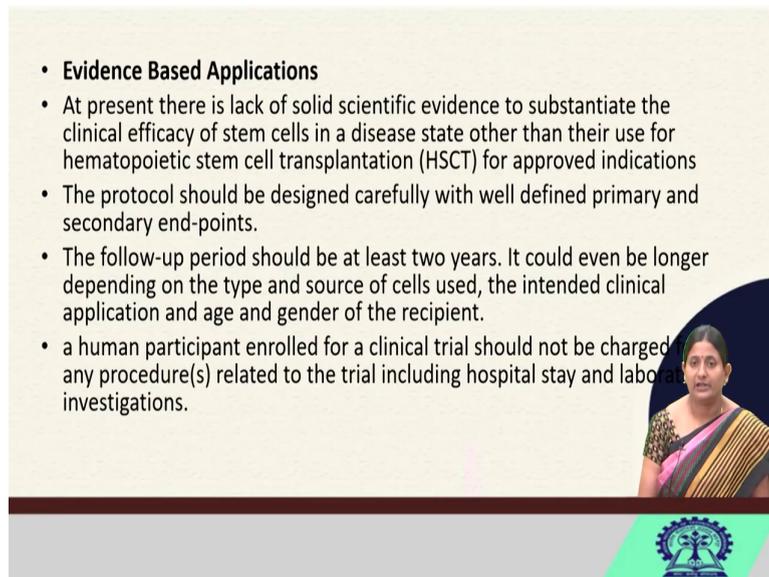


- **Release Criteria**
- Stem cells or their products intended for administration in humans as a part of clinical trial should fulfil the quality criteria
  - cell viability,
  - final cell population (using CD markers),
  - stability and
  - requirements for release
- All stem cells or their products should have proper labelling before release.
- It is necessary that the product is sufficiently stable for the duration as required for the study.
- All procedures shall be laid down in the form of SOPs and strictly adhered to as to provide reproducibility of well characterized clinical grade cells that meet the desired standards of identity, purity, safety, potency and traceability.
- The infrastructure facility shall be duly certified by CDSCO, and
- submit the CMC (Chemistry, Manufacturing and Control) documents for necessary regulatory approvals.

So, when the stem cells is received and then again, it is released? So it has to be tested with respect to certain criteria like the cell viability, what is the final cell population which can be determined by various marker process, stability and the other requirements. So, these are more of a scientific requirement which needs to be tested and properly documented before the stem cells are being used.

All the standard operating procedure must be properly maintained and desired standards of the identity, purity or the safety or traceability of the product must be maintained. So, that portion has also been emphasized in the guideline.

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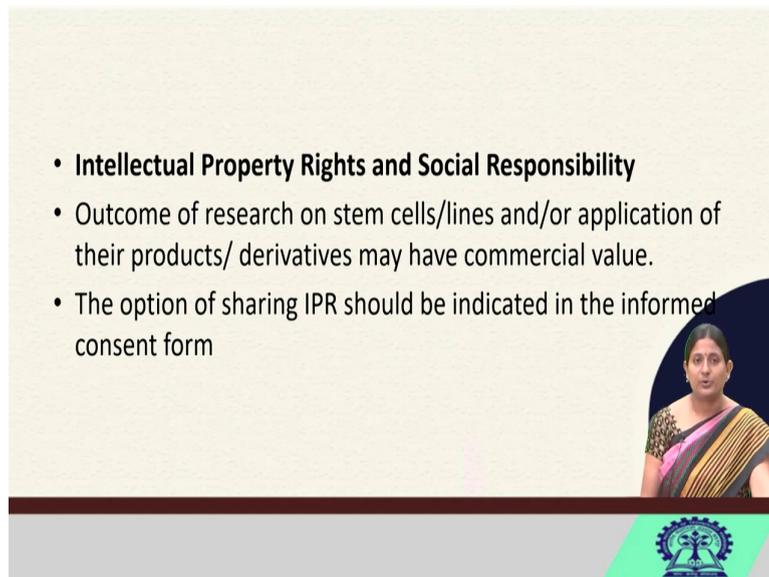
- **Evidence Based Applications**
- At present there is lack of solid scientific evidence to substantiate the clinical efficacy of stem cells in a disease state other than their use for hematopoietic stem cell transplantation (HSCT) for approved indications
- The protocol should be designed carefully with well defined primary and secondary end-points.
- The follow-up period should be at least two years. It could even be longer depending on the type and source of cells used, the intended clinical application and age and gender of the recipient.
- a human participant enrolled for a clinical trial should not be charged for any procedure(s) related to the trial including hospital stay and laboratory investigations.

And then, it also says something about the evidence-based application, where like what is the clinical efficacy of the stem cells in a particular disease state and their use of the in use in appropriate indications? So, though the hematopoietic stem cells has been already been proven, other for other it has been not it has not been proved at as yet.

So, for every trial, the protocol must be designed carefully and it mentions that the follow up period for this kind of clinical trials must should be at least for 2 years; even it can be longer depending on the type or the source of the cell used or age and gender of the recipient.

And it also says that the human participants enrolled for the clinical trial should not be charged and the procedure related to the trial including the hospital stay and other investigation process, laboratory investigation and the cost related to that should be borne by the investigator or the company who is carrying out that kind of research, but not the participant.

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- **Intellectual Property Rights and Social Responsibility**
- Outcome of research on stem cells/lines and/or application of their products/ derivatives may have commercial value.
- The option of sharing IPR should be indicated in the informed consent form

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Then, the intellectual property or the various IP whether you say patents or trademarks or other things, so the outcome of the research on the stem cells or stem cell lines or the application of the product and the derivatives might have commercial value and so, what would be the probable or best option for the sharing of such IPR should be indicated in the informed consent form.

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### Mechanism for Review and Oversight

- A separate mechanism for review and monitoring is essential both at institutional and national levels.
- **A National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT)** has been established. It monitors and oversees research activities at the national level and lays guidelines for basic and clinical research.
- **The Institutional Committee for Stem Cell Research (IC-SCR)** approves and monitors stem cell research (basic and clinical) at the institutional level.
- These oversight committees shall ensure that the review, approval and monitoring processes of all research projects in the field of stem cell research is conducted in compliance with the national guidelines.
- It is mandatory for all institutes and entities engaged in stem cell research to establish an IC-SCR and register the same with NAC-SCRT.

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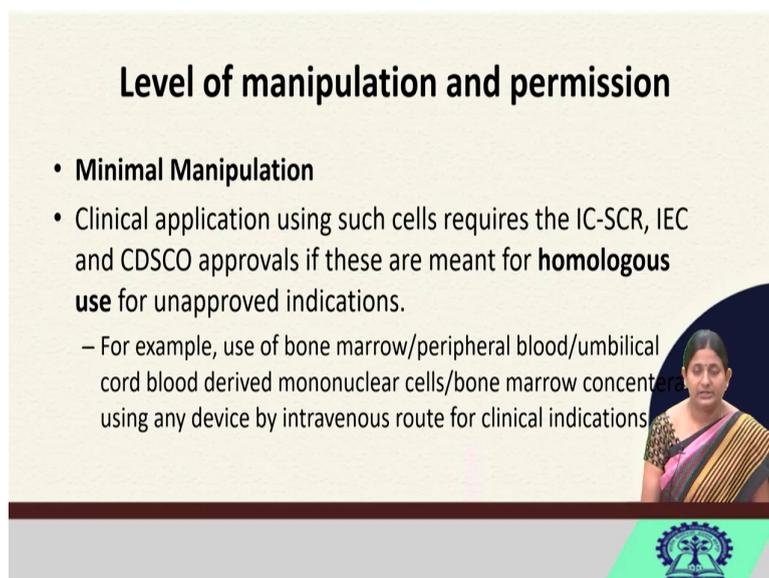
So, apart from the scientific, ethical and safety concerns which are described in the guideline, there they it also gives you a mechanism for the review and the oversight. So, we already I discussed in the initial slides that ok, there are two there is a compulsory constitution of a body with the National Apex Committee on the Stem Cell Research and Therapy.

So, that is the body by the CDSCO. So, this National Apex Committee on the Stem Cell Research and Therapy which is basically established as a body which will monitor and oversee the research activities at the national level and it lays down the basic guideline for the clinical and the basic research.

And at the institutional level, so we have the Institutional Committee for the Stem Cell Research which basically approves and monitors the stem cell research at the institutional level. So, these committees are basically ensure that the review, approval and the monitoring process for the research projects related to the stem cells should are being carried out with the compliance of the guide guidelines and the registration with the NAC-SCRT is mandatory for the institutional committees.

So, these are the two committees which basically review the whole process; then finally, we have the CDSCO or the Central Drug Standard Control Organization which gives the final approval for the clinical trial or related process for the stem cells.

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**Level of manipulation and permission**

- **Minimal Manipulation**
- Clinical application using such cells requires the IC-SCR, IEC and CDSCO approvals if these are meant for **homologous use** for unapproved indications.
  - For example, use of bone marrow/peripheral blood/umbilical cord blood derived mononuclear cells/bone marrow concentrate using any device by intravenous route for clinical indications

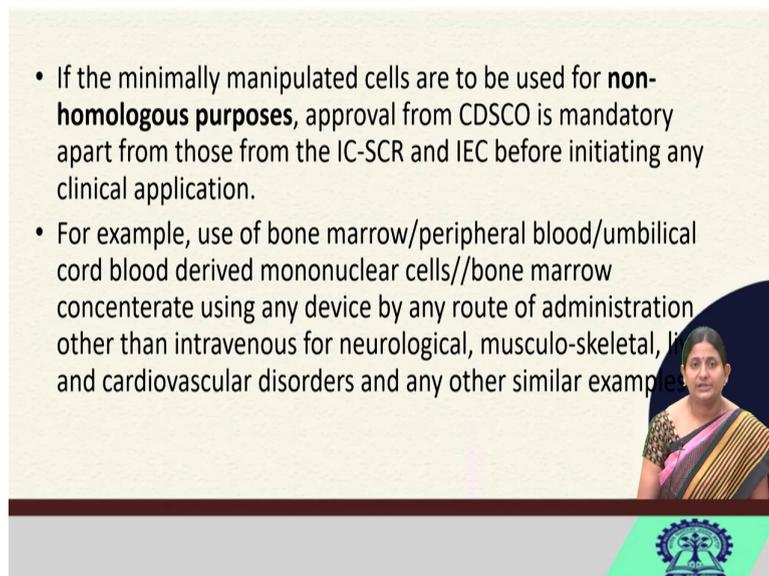


So, now, depending on the level of manipulation on the stem cells, the permissions or the approval process depends. So, there are different levels of manipulations. There may be minimal manipulation, there may be moderate manipulation or there may be severe manipulation.

So, if there is minimal manipulation, though the clinical application of such cell requires the permission from the IC-SCR, Institutional Ethics Committee and the CDSCO approval and it is if it is meant for homologous use for unapproved indication, means in the same individual or the body.

For example, the use of this bone marrow or the umbilical cord blood derived mononuclear cells or bone marrow concentration are using the device by the intravenous route for the clinical indication. So, it requires the permission from the Institutional Committee, Institutional Ethics Committee and the CDSCO.

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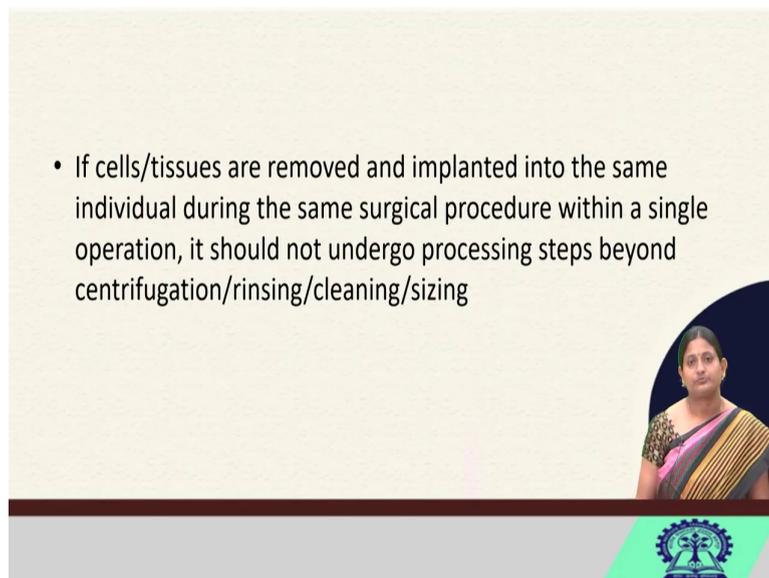
- If the minimally manipulated cells are to be used for **non-homologous purposes**, approval from CDSCO is mandatory apart from those from the IC-SCR and IEC before initiating any clinical application.
- For example, use of bone marrow/peripheral blood/umbilical cord blood derived mononuclear cells//bone marrow concentrate using any device by any route of administration other than intravenous for neurological, musculo-skeletal, and cardiovascular disorders and any other similar examples.

And if the minimally manipulated cells are used for the non-homologous purpose, approval from the CDSCO is mandatory apart from this institutional committee before even initiating the clinical application process ok. So, this is one example, where the use of the bone marrow or the peripheral blood or the umbilical cord blood derived mononuclear cells, if used by any

device by any route of administration other than the intravenous or the neurological, musculoskeletal or cardiovascular for the cardiovascular diseases.

So, if it is for homologous purpose, there is certain kind of permission requirement and if it is for the non homologous purposes, then also we need a different like more before the clinical application, we need the permission from the CDSCO.

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So, what may constitute a minimal manipulation, when the like cells are tissue cells or the tissues are removed and implanted into the same individual during the same surgical procedure within a single operation and you should not undergo the processing steps beyond centrifugation, rinsing, cleaning or the sizing. So, then it is considered as the minimal manipulation.

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## Substantial manipulation

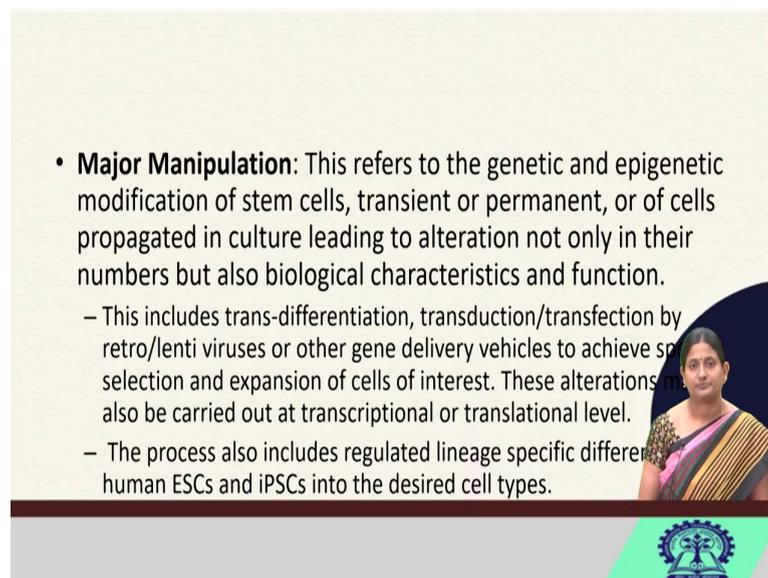
- Clinical trials using cells that have undergone more than minimal manipulation require approvals from CDSCO only after obtaining clearances from IC-SCR and IEC.
  - For example, adipose tissue may be more than minimally manipulated if the processing alters the original relevant characteristics of the tissue relating to its utility for reconstruction, repair, or replacement.
  - Adipose tissue is sometimes processed by various means (e.g. enzymatic digestion, mechanical disruption etc.) to isolate its non-adipocyte or non-structural components. In some instances, these non-adipocyte or non-structural components are cultured and expanded. Processing to isolate non-adipocyte or non-structural components e.g. Stromal Vascular Fraction (SVF) from adipose tissue (with or without subsequent cell culture or expansion) is considered more than minimal manipulation. Clinical trials using SVF will therefore require approval by IC-SCR, IEC and CDSCO.



And then, there is another process called the substantial manipulation, where the clinical trials using the cells that have gone more than minimal manipulation requires the approval from the CDSCO, only after obtaining the clearances from the Institutional Committee and the Ethics Committee.

In some cases, these cells are modified or these whatever they are minimally, they are more than minimally manipulated before the use of the same in the body. So, in that case, the nature of the permission or the sequence of the permission becomes little bit different.

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- **Major Manipulation:** This refers to the genetic and epigenetic modification of stem cells, transient or permanent, or of cells propagated in culture leading to alteration not only in their numbers but also biological characteristics and function.
  - This includes trans-differentiation, transduction/transfection by retro/lenti viruses or other gene delivery vehicles to achieve selection and expansion of cells of interest. These alterations can also be carried out at transcriptional or translational level.
  - The process also includes regulated lineage specific differentiation of human ESCs and iPSCs into the desired cell types.

And major manipulation is basically refers to the genetic and the epigenetic modification of the stem cells which may be a transient or the permanent manipulation and it leads to the alteration not only in their numbers, but also the biological character or the function ok.

So, here like the process of regulating the lineage specific to different human embryonic stem cells or induced pluripotent stem cells for the desired cell type are coming under the purview of this major manipulation, where the trans differentiation or the use of various retro or lentiviruses or other gene delivery vehicles to achieve the selection and expansion of the cell of the interest. So, this is more complicated process.

So, substantial manipulation, so there also the level of permission is again like in each step, you need to have the permission and final CDSCOs approval is needed before this kind of applications can be carried out in the human subjects.

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## Categorization of Research

- Permissible Areas of Research
- In vitro studies using stem cells isolated from tissues can be done with prior approval of IC-SCR and IEC.



So, if you see the total guideline, the guideline has divided the whole stem cell research into two criteria; first permissible area of the research and it has again in vitro studies using the stem cells isolated from the tissues, which can be done with the prior approval of the IC and the IC-SSR and the Institutional Ethics Committee.

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- Establishment of new human ESC lines from spare embryos or iPSC lines from fetal/adult somatic cells or SSCs from fetal or adult tissues, with prior approval of the IC-SCR and IEC,
  - provided appropriate informed consent is obtained from the donor
  - the same shall be registered with NAC-SCRT through IC-SCR with appropriate documentation including details regarding their derivation and characterization
  - cell lines may be deposited/registered in an accredited cell bank for potential use by other investigators.
  - Pluripotent stem cell lines intended for use in clinical research/trials need approval of CDSCO after obtaining clearances from IC-SCR and IEC.
  - The cell lines should have unique identification number for future reference.



So, in the permissible area of the research, like you have to provide the appropriate plan or the design of the experiment and then only, it is allowed and you can carry out with the respective permissions from the respective committees.

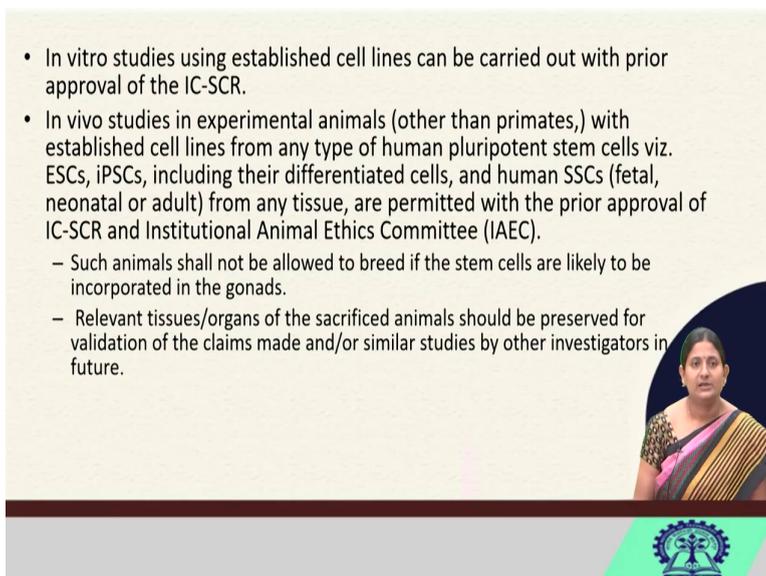
For example, the establishment of the new human embryonic stem cell lines from the spare embryos or the induced pluripotent cell embryo lines from the fetal or adult somatic cells or the somatic stem cells or from the fetal or adult tissues with prior approval of the Institutional Committee and can be done or provided appropriate informed consent is obtained from the donor and it should be registered in the NAC-SCRT committee through this Institutional Committee for the Stem Cell Research with appropriate documentation.

And including the details regarding their derivation and the characterization means how the new human stem cells lines are being developed, all the scientific documentation has to be provided and then, the cell lines should be deposited or registered in the accredited cell banks for the potential used by the other investigators.

Then, the pluripotent stem cells lines intended for the use in the clinical research need approval from the CDSCO after ensuring the clearance from the IC-SCR and the Institutional Ethic Ethics Committee. And then, the cell line should be provided with a particular reference unique identification number for the future reference. So, you have to maintain this process which is given in the guideline so that you can also carry out the establishment of the new human embryonic stem cell research.

So, this falls under the permissible area of the research provided you meet this criterion. So, you may refer to the national guideline of 2017 first for broader understanding. I am just giving you the basics of the or the basic points which are mentioned in the guidelines.

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- In vitro studies using established cell lines can be carried out with prior approval of the IC-SCR.
- In vivo studies in experimental animals (other than primates,) with established cell lines from any type of human pluripotent stem cells viz. ESCs, iPSCs, including their differentiated cells, and human SSCs (fetal, neonatal or adult) from any tissue, are permitted with the prior approval of IC-SCR and Institutional Animal Ethics Committee (IAEC).
  - Such animals shall not be allowed to breed if the stem cells are likely to be incorporated in the gonads.
  - Relevant tissues/organs of the sacrificed animals should be preserved for validation of the claims made and/or similar studies by other investigators in future.

Similarly, in vitro studies using the established cell lines can also be carried out with prior approval of this Institutional Committee. Then, but for the in vivo studies in experimental animals other than the primates, with established cell lines from any type of human pluripotent stem cells including their differential stems and human stem cells from any tissue are permitted with the prior approval of the Institutional Committee as well as the Institutional Animal Ethics Committee because it involves the usage of the experimental animals.

And there are also certain consideration that the animals where the in vivo studies are being carried out, these animals shall not be allowed to breed if the stem cells are likely to be incorporated in the gonads or the relevant tissues or the organs of the sacrificed animals should be preserved for the validation of the claims made by the investigator in the future.

So, these animals must not be allowed to reproduce as well as the relevant tissues must be properly placed so that if any issues arise, so it has to be properly validated. Yes, it has used in a proper manner so that evidence has to be preserved.

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### Restrictive Areas of Research

- Creation of human pre-implantation embryos by In vitro fertilization (IVF), Intracytoplasmic Sperm Injection (ICSI), Somatic Cell Nuclear Transfer (SCNT) or any other method with the specific aim of deriving ESC lines for any purpose.
- The investigator needs to provide reasoning taking into consideration the following:
  - The proposed research cannot be carried out with existing ESC lines, or those that can be derived from spare embryos.
  - Minimum number of embryos/blastocysts required for such research must be clearly defined.
  - Research teams involved should have appropriate expertise and require training in derivation, characterization and culture of ESCs.



There are restrictive areas of the research. So, under the restrictive areas of the research like creation of the human pre implantation embryos by in vitro fertilization, intracytoplasmic sperm injection, somatic cell nuclear transfer process or any other method with the specific aim of deriving the embryonic stem cell lines for any purpose is a restrictive area.

So, if you want to carry out any of this process as mentioned there, you need to provide the reasonable or reasoning for taking out such kind of the study. For example, you have to propose that the proposed research cannot be carried out without the exist with the existing embryonic cell lines.

So, it has it needs new embryonic stem lines for carrying out this research and you have to provide the reasoning that how much how minimally you are using this embryo or the blastocysts, you have to properly define in your research plan.

And also the research team should have appropriate expertise and training for the derivation, characterization and culture of the embryonic stem cells. So, this process has like if you want to carry out any of the restrictive areas of the research, proper validation of the research plan is one of the essential criteria.

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- Clinical trials sponsored by multinationals, employing cell products developed outside India, should have clearances from the regulatory authorities of the country of the origin and shall need prior approval from CDSCO following clearance from both IC-SCR and IEC of the trial site.
- All international collaborations require approvals from the respective funding agencies followed by approval from the Health Ministry's Screening Committee (HMSC) as per Government of India Guidelines
- Import of any type of stem cells and/or their products/derivatives requires license from CDSCO as per the established regulations. These should have prior clearances from the regulatory authorities of the country of the origin.

And then, regarding the international collaboration or sponsor research, so the clinical trials sponsored by the multinational companies or which are developed cell lines which are developed outside the India should get the clearance from the regulatory authorities from the respective country as well as it needs prior approval from the CDSCO following the clearance from both the Institutional Committee on the Stem Cells Research as well as the Institutional Ethics Committee of the trial site.

And the all the international collaboration requires approvals from the respective funding agencies, followed by the approval of the ministry screening committee as per the government of India's guideline.

And import of any type of the stem cells or their products or the derivatives of their things requires the license of the CDSCO as per the established regulation and only if they have a prior clearance from the regulatory authorities of the country of the origin, then only these processes are initiated.

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- Research involving introduction of human ESC/iPSC/SSCs into animals (including primates), at embryonic or fetal stages of development for studies designed to understand the patterns of differentiation and integration of human cells into non-human animal tissues shall conform to the following:
  - If the expected outcome of the study is suggestive of a possibility that human stem cells could contribute in a major way to the development of brain or gonads of the recipient animal, the scientific justification for such experiments must first be substantiated with data.
  - Animals derived from such experiments shall not be allowed to breed.
  - Such proposals would need approval of the NAC-SCRT for additional oversight and review after clearance has been granted by the IC-SC and IAEC (or CPCSEA).



And so, if there are research which involves the introduction of the human embryonic stem cells or induced pluripotent stem cells or somatic stem cells into the animals including the primates at the embryonic or fetal or the any other developmental state, then, it has to be again supplemented with certain information.

Because it is again a development of the chimera, where you are trying to incorporate the human stem cells into the animal may be to understand the pattern of differentiation and the integration. So, what exactly you want to study? The expected outcome of the study and possibility that the stem cells can contribute majorly for the development of the brain or any other germ line cells of the recipient animals and the scientific justification of the such experiment must be substantiated with the data.

And animals derived by such experiments should not be allowed to breed as well as it needs the approval for the from the NAC, the National Apex Committee on the Stem Cell Research and Therapy and also, it needs the in-house clearance by the Ethics Committee and the Internal Committee on the stem cell research.

So, the more complicated the research, you need more and more detailed plan and proof of evidence of a validated plan so that it ensures that the research are not carried out for any

purpose which is not good for the society or which will not give a result, where it is not that beneficial.

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- Studies on chimeras where stem cells from two or more species are mixed together at any stage of early development (embryonic or fetal), for understanding patterns of development and differentiation would also require prior approval of NAC-SCRT after clearance has been granted by the IEC and IC-SCR.



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- Genome modification including gene editing (for example by CRISPR-Cas9 technology) of stem cells, germ-line stem cells or gamete and human embryos is restricted only to in vitro studies.
- It will require thorough review by the IC-SCR, IEC and IBSC, and finally by Review Committee on Genetic Manipulation (RCGM).
- Research teams involved should have appropriate expertise, requisite training and infrastructure in gene editing/genome modification and characterization.
  - Only spare embryos, germ-line cells or gametes should be used.
  - The source of somatic cells and/or minimum number of embryos, germ-line cells or gametes required for this research should be clearly defined.
  - Genome modified human embryos should not be cultured beyond fertilization or formation of primitive streak, whichever is earlier.

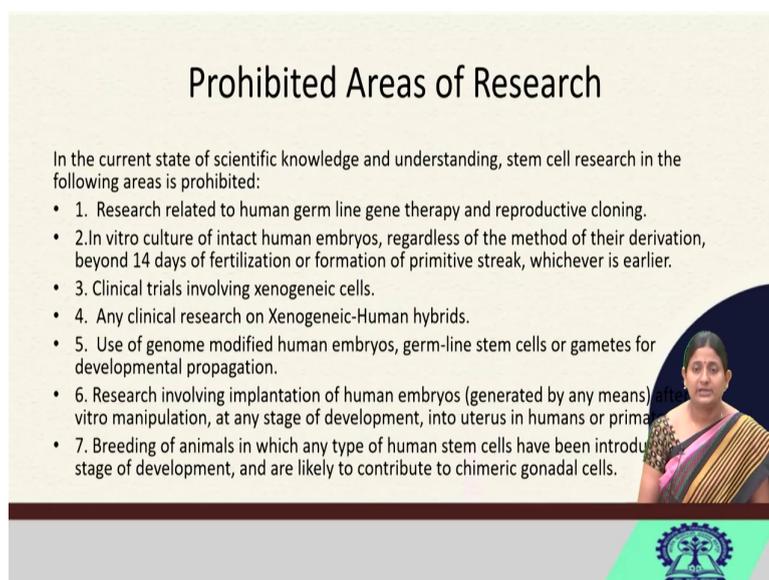


So, again, studies on the chimeras also need a special permission. So, these are the various aspects which are mentioned in the guideline. And also, if you are trying to carry out certain genome modification, maybe using the available gene editing technology, maybe the CRISPR technology or the other any other technology, it requires the review by all the

committees like Institutional Committee, Ethics Committee as well as the Institutional Bio Safety Committee and finally, it has to be reviewed by the Review Committee on the Genetic Manipulation.

These are the committee developed by the department of biotechnology. When we go to next module, we will read more about this committee, what are the functions of this committee. So, here these permissions are required and the expertise of the research team is also very utmost importance in carrying out such things.

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### Prohibited Areas of Research

In the current state of scientific knowledge and understanding, stem cell research in the following areas is prohibited:

- 1. Research related to human germ line gene therapy and reproductive cloning.
- 2. In vitro culture of intact human embryos, regardless of the method of their derivation, beyond 14 days of fertilization or formation of primitive streak, whichever is earlier.
- 3. Clinical trials involving xenogeneic cells.
- 4. Any clinical research on Xenogeneic-Human hybrids.
- 5. Use of genome modified human embryos, germ-line stem cells or gametes for developmental propagation.
- 6. Research involving implantation of human embryos (generated by any means) into uterus, after in vitro manipulation, at any stage of development, into uterus in humans or primates.
- 7. Breeding of animals in which any type of human stem cells have been introduced at any stage of development, and are likely to contribute to chimeric gonadal cells.

Also, the guideline interestingly mentions certainly certain prohibited areas of the research. So, the stem cell research are prohibited in some particular areas. First like the research related to the human germ line gene therapy and reproductive cloning is prohibited in India.

And in vitro culture of the intact human embryo regardless of the method of their derivation beyond 14 days of the fertilization or formation of the primitive streak, whichever is earlier is prohibited in India. Clinical trials involving the Xenogeneic cells are prohibited. Fourth, any clinical research on the Xenogeneic and human hybrids are also prohibited.

Use of the genome modified human embryos germ line, stem cells or gametes for the developmental propagation are also prohibited in India. The research involving the

implantation of the human embryos by in vitro manipulation at any stage of the development into the uterus of the human or the primates are also prohibited in India.

Breeding of the animals in which any type of the human stem cells has been introduced in any stage of the development and which may contribute to the chimeric gonadal cells are also prohibited in India. So, these are the few restrictive areas or the prohibited areas where research is totally prohibited.

So, any company or any organization interested in the stem cell research must adhere to this guideline and adhere to the standard standards prescribed in the guidelines before they carry out any stem cell research in India; while there are few clinical trial candidates in other countries in India, we have we are also progressing.

But again, it is yet to develop comparative standards or comparative like we are not that developed like the other countries like US or particularly in United States, where already some of the products are also in the market. Here it is only restricted to the clinical research.

So, this is briefly about the Indian regulation on the stem cell research. Going forward, we will discuss more about the regulatory aspects of the other biomedical products India and in other countries as well.

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**REFERENCES**

- Mittal S, Stem cell research: The India perspective, *Perspect Clin Res.* 2013 Jan-Mar; 4(1): 105-107.
- Sharma A, Stem cell research and policy in India: current scenario and future perspective, *J Stem Cells*, 2009;4(2):133-40.

The slide features a portrait of a woman in a saree in the bottom right corner. At the bottom, there are logos for the Indian Council of Medical Research (ICMR) and the National Health Authority (NHA).

So, these are the few references. Also, you may find the guidelines in the DBT websites for the stem cell research; you may go through it for a detailed understanding.

So, thank you very much for attending the session. Looking forward for the other sessions.

Thank you.