



Indian Canvas of Cell & Gene Therapy

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INDIAN COUNCIL OF MEDICAL RESEARCH

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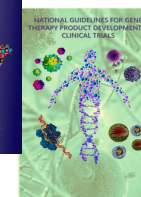
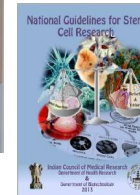
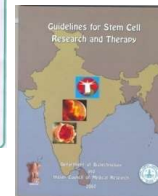
Ministry of Health & Family Welfare

Outline of the regulatory framework

- Drug & Cosmetics Act 1940 & Rules 1945
- **New Drugs & Clinical Trial Rules-2019** (NDCTR)
[https://cdsco.gov.in/opencms/export/sites/CDSCO WEB/Pdf-documents/NewDrugs_CTRules_2019.pdf](https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdf-documents/NewDrugs_CTRules_2019.pdf)
- Indian Medical Council Act 2002 (Professional Conduct, Etiquettes and Ethics)
- Drugs and Magical Remedies (The Objectionable Advertisements) Act-1954

ICMR Guidelines for Cell & Gene Therapy Journey so far....

- **Draft Guidelines for Stem Cell Research & Regulation 2002**
- **Guidelines for Stem Cell Research & Therapy 2007**
- **National Guidelines for Stem Cell Research 2013**
- **National Guidelines for Stem Cell Research 2017**
- **National Ethical Guidelines for Biomedical & Health research Involving Human Participants - 2017**
- **National Guidelines for Gene Therapy Product Development & Clinical Trials – 2019**
- **National Guidelines for HSCT – 2021**
- **Evidence based status of Stem Cell Therapy for Human Diseases**



Other Ethical & Scientific Considerations

Stem Cells

- Live cells/tumour formation
- Health, Safety of Donor
- Collection/Processing/Storage
- Manufacturing & Quality assurance
- Release Criteria
- Evidence based application
- Commercialisation of unapproved therapy

Gene Therapy Products

- Correction of gene defects/protein expression
- Appropriate selection of GT vector
- Ensuring clinically relevant expression/correction
- Preventing unwanted side effects
- Unnatural advantage

NGSCR 2017, NGHCT-2021, EBSSCT-2021

- To curb unethical practices of offering unapproved SCT
- Provide list of approved applications of SCT
- Definitions of level of manipulation and categorisation of SCR
- Harmonising existing regulations and its appropriate implementation
- Education and awareness of stakeholders
- Education regarding status of SCT
- Guidance to industry
- Status of cord blood and other stem cell banking
- Voiced for regulatory reforms

Challenges in SCR&T

- Minimal manipulation:
 - Processing neither alters the number nor the biological characteristics & function of the cells (or tissue)
 - Processing includes: isolation/separation, washing, centrifugation and suspension in culture media/reagents, cutting, grinding, shaping, overnight culturing without biological and chemical treatment, decellularization and cryopreservation (not >72 hrs)
 - Clinical application using such cells need regulatory approval if these are meant for **homologous use for unapproved indications**
 - If the minimal manipulated cells are to be used for **non-homologous purposes**, approval from CDSCO is mandatory before initiating any clinical application
 - If cells / tissue are removed and implanted into the individual during the same surgical procedure within a single operation, it should not undergo processing steps beyond centrifugation/rinsing/cleaning/sizing.

Need for Regulations

- Desperate vulnerable population falling prey
- Financial toxicity
- Internationally being criticised
- No systematic study to understand safety and efficacy
- false promise/hope to cure incurable disease conditions
- Several complaints from patients /NGOs/Patients advocacy groups

Keeping minimally manipulated stem cells out of the purview of definition of new drug means legitimising its use.

National Guidelines for Gene Therapy Product Development and Clinical Trials

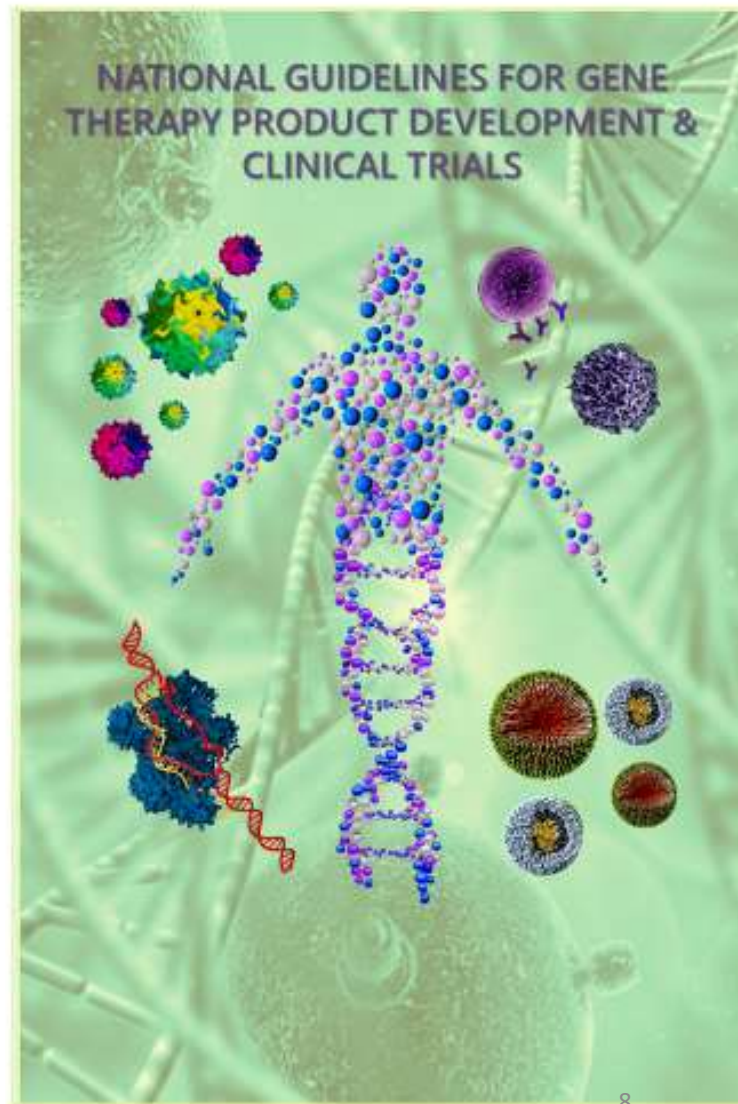


Indian Council of Medical Research
Department of Health Research

Central Drug Standards Control Organisation
Directorate General of Health Services

Ministry of Health & Family Welfare

&
Department of Biotechnology
Ministry of Science & Technology



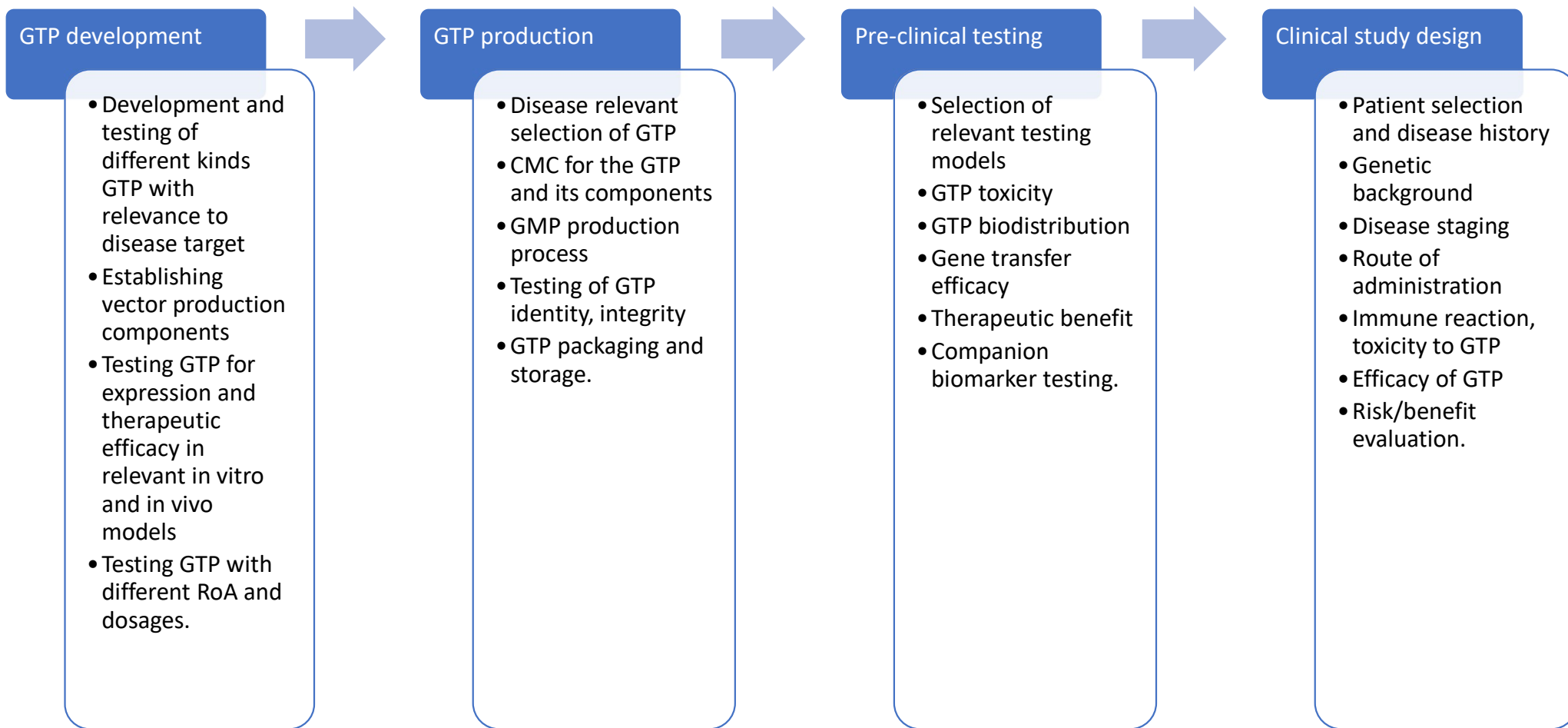
Purpose

- guide and enable the stakeholders to comprehend and comply with the regulatory requirements for research and development of GTPs in India.
- provides basic guidance for research involving human participants, including clinical trials, pertaining to the broad area of gene therapy
- covering all the technologies and processes for all mendelian, non-mendelian and other complex disorders.
- Disease-specific guidelines will subsequently be developed
- Process specific guidelines

Contents of the guidelines

- Preamble
- Aims & Scope
- General Principles
- Classification of Gene Therapy
- Ethical and Scientific Considerations
- Mechanism for Review & Oversight
- Responsibilities of investigators/institution/sponsors/IEC/committees
- Considerations for Chemistry, Manufacturing and Control, Quality Assurance, Product Attributes for Human Gene Therapy Products
- GMP Guidelines: Infrastructure, Personnel
- Requirements for Preclinical evaluation of investigational strategies/products for gene therapy
- Requirements for Clinical Trials
- International Collaboration and International procurement of GTPs
- Awareness and Education of Stakeholders
- Publicity and Advertisements in All Media including Electronic and Print
- Periodic Review of Guidelines

Designing a GTP trial application



Annexure: GTP approval process

**Trial
proposal**

- *The proposal should clearly define the GTP, its proposed application, production and testing processes and clinical trial design.*

IBSC

- *The IBSC will oversee and establish if proper procedures are planned for use in the GTP production and testing process.*

RCGM

- *All GTPs and recombinant nucleic acid materials to be used and procedures thereof must be approved by RCGM prior to production.*

IEC

- *The local ethics committee is the first step towards initiating the trial or human application. The clinical trial design must be approved by the IEC and monitored by them.*

GTAEC

- *The proposal is evaluated by the GTAEC for scientific, clinical and ethical content and recommend changes or refinements. The trial investigators may consult the GTAEC for specific advice or to refine their strategies.*

CDSCO

- *Upon approval of the RCGM and recommendations of the GTAEC, CDSCO will evaluate and approve each trial or marketing approval for each GTP application.*

IEC

- *Upon prior approval from CDSCO, the local IEC will now allow the initiation of the trial and ensure proper monitoring of all trial related procedures.*

Gene Therapy Advisory and Evaluation Committee (GTAEC)

Department of Health Research (DHR), Ministry of Health and Family Welfare, Government of India

Secretariat, ICMR Headquarters, Ansari Nagar, New Delhi-110029

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Welcome to **GTAEC**
Gene Therapy **Advisory and Evaluation Committee**

Gene Therapy Advisory & Evaluation Committee

Mandate

- Provide handholding, pre-IND consultations for investigators & industry
- Robust evaluation of GTPs and GT-clinical trials, providing technical and scientific inputs to CDSCO-SEC for expediting and facilitating regulatory process.
- Formulation and periodic updating the guidelines
- Education & Awareness of stakeholders

Mission

- Streamline regulatory framework in coordination with various government agencies
- Scientific & ethical conduct of research & development of GTPs
- Safety of human participants
- Facilitate Indigenous development of affordable GTPs

New Drugs & Clinical Trial Rules 2019

- 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)**'.
- **New Drugs & Clinical Trial Rules-2019** (NDCTR), for stem cells and other cell-based products including GTPs.
- Clinical trials are a must before these can be used for any indication.

Background

- Under the provisions of DCA,1940-regulatory control over the manufacture and sale of drugs is exercised by the State Licensing Authorities appointed by State Governments.
- As per NDCTR 2019, **“new drug” includes “ stem cell derived product”** intended to be used as a drug.
- Representations have been received over clarification of definition for streamlining regulation of stem cell derived products.

Definitions

- It is clarified that **stem cell derived product** means a drug which has been derived from processed stem cells and which has been processed by **means of substantial or more than minimal manipulation** with the objective of propagation and/or differentiation of a cell/tissue, cell activation, and production of a cell line, which includes 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.

Strengths of the regulatory framework

Regulations

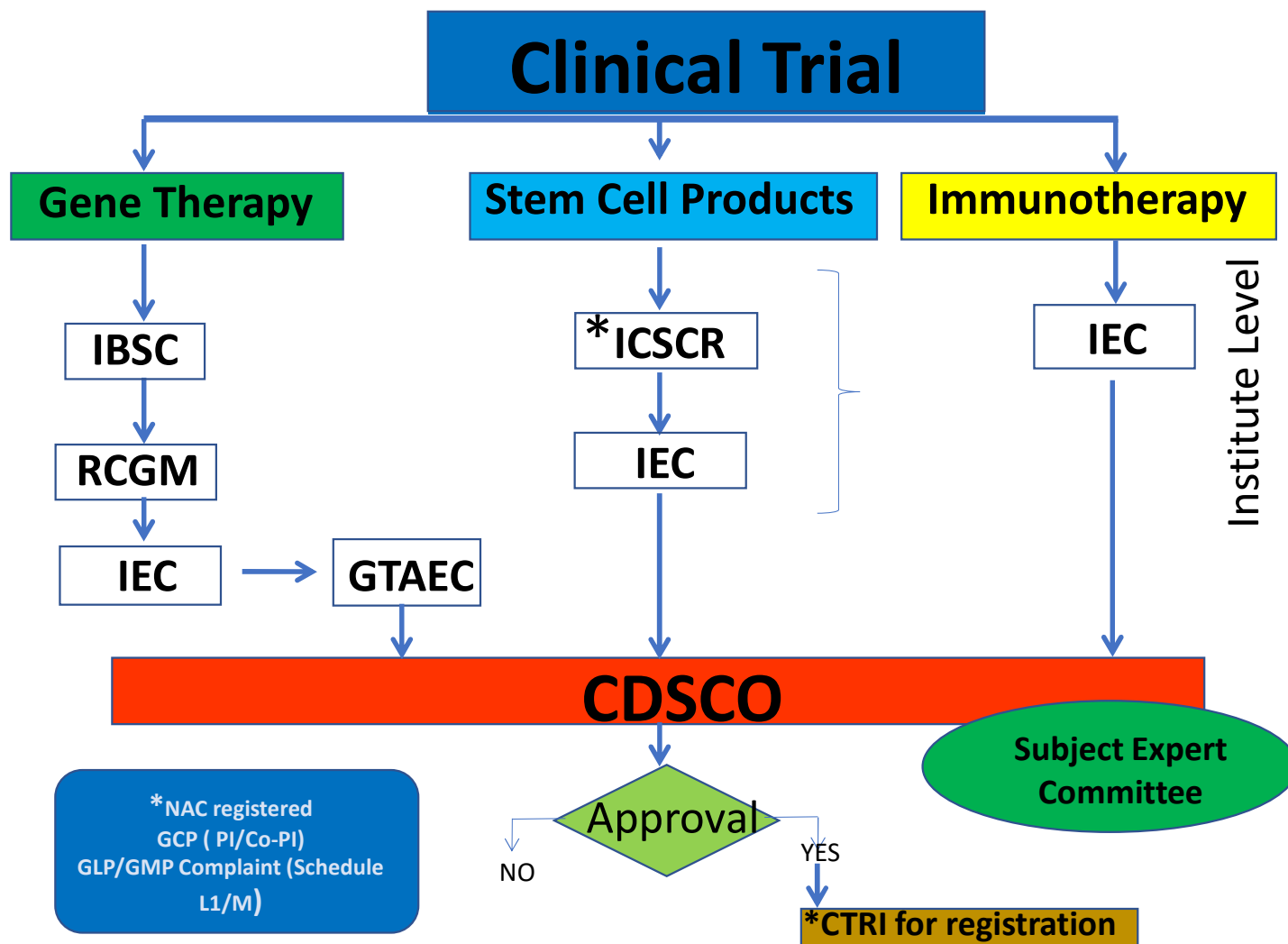
- Stem cell derived product, gene therapeutic product or xenografts, intended to be used as drug shall continue to be a **new drug forever**
 - defines conduct of pre-clinical and clinical trials
 - Timeline:
 - Drug discovered in India (30 days)
 - Drugs already approved somewhere (15 days)
- no permission is required for conduct of **Academic clinical trial** (drugs or drug formulation already licensed and approved and is tried for any new indication or new route of administration or new dosage) **Does not apply to New Drugs**

Guidelines

- Elaborately define stem cell and GTPs; provide clear guidance to researchers/scientists/industry on different requirements in term of donor selection/ preclinical and clinical trial conduct, personnel, GMP, CMC, release criteria etc.
- Clearly defines the levels of manipulation and approval required at each stage.
- Established Apex committees (NAC-SCRT and GTAEC) for hand holding, monitoring, guidance and policy making
- Provides a comprehensive overview of the path to initiate a stem cell and gene therapy trial, within an enabling framework, yet with stringent regulatory oversight

Specific Considerations

- A structured multilayer monitoring involving IBSC, RCGM, CDSCO and GTAEC
- For SC products ICSCR, IEC, CBBTDEC , NAC-SCRT (ESCs/iPSCs)
- Germline or in utero gene therapy is prohibited in India
- Somatic cell gene editing is permissible but need to assure no biodistribution to gonads
- Therapeutic use of stem cells for unapproved indications is not permissible, only to be done under the realm of clinical trials with necessary approvals
- Investigators involved in clinical trials with CGTP must have domain expertise and GCP training.
- Infrastructure has to be cGMP certified by CDSCO
- Major challenge is to curb unethical use of stem cell and cell-based products



Approved Cell Based Products

S. No	Name (MA holder)	Product description and indication(s)	ATMP
1.	CARTIGROW™ (Chondron ACI) (RMS Regrow)	Autologous cultured cartilage cells for treatment of articular cartilage defects	Cell Therapy product
2.	UREGROW™ (RMS Regrow)	Autologous adult live cultured buccal epithelial cells	Cell Therapy product
3.	OSSGROW™ (Ossron ABI) (RMS Regrow)	Autologous cultured osteoblasts for avascular necrosis of hip	Cell therapy product
4.	APCEDEN (APAC Biotech)	Autologous monocyte derived mature dendritic cells for treatment of prostate, ovarian, colorectal and non-small cell lung carcinoma	Cell therapy product
5.	Stempeucel (Stempeutics Research)	Ex vivo cultured adult allogeneic mesenchymal stromal cells for treatment of critical limb ischemia due to Thromboangiitis Obliterans (Buerger's disease)	Cell therapy product

Informed Consent Form

- Lack of understanding of gene therapy in the public
- Audio/visual recording of consent mostly missing in the ICF
- Lack of clarity to the participants regarding:
 - Voluntary participation
 - Reproductive considerations
 - Risks and benefits of participating in the trial
 - Alternatives available
 - Compensation in case of injury
 - Post trial access
 - Long term follow up

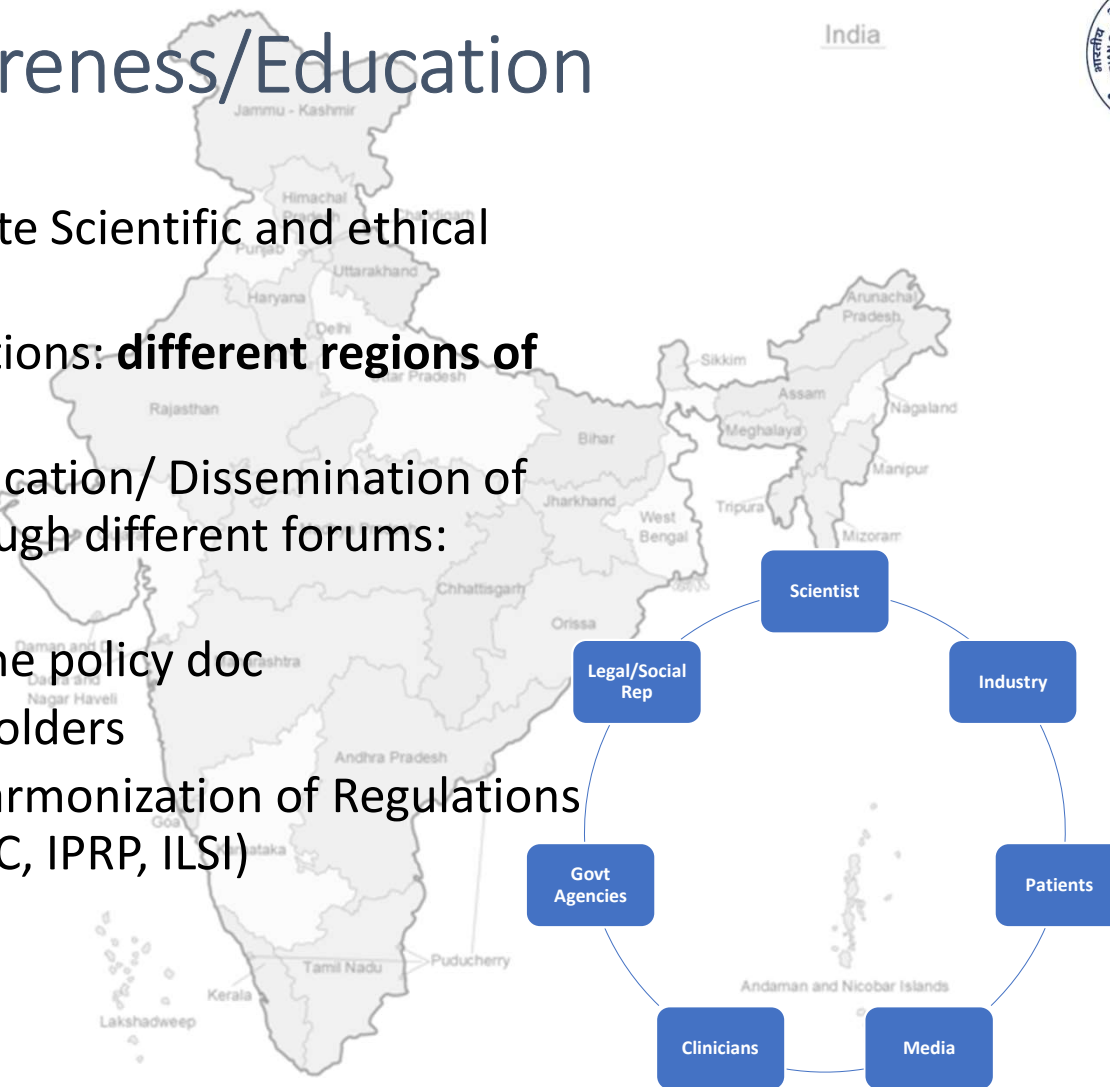
Solutions

- Foster regulatory convergence among countries
- Build on multi-stakeholder collaboration
- Utilize work-sharing, reliance, and recognition
- Consider developing regulatory mechanisms for accelerated pathways and early engagement
- Allow for innovative clinical trial design
- Use post-market confirmatory studies

PAN India Awareness/Education



- Endorse/promote Scientific and ethical practices
- Public Consultations: **different regions of India**
- Awareness/ Education/ Dissemination of knowledge through different forums: Masses
- Consensus on the policy doc
- FAQs for Stakeholders
- International Harmonization of Regulations (WHO, ISCT, APAC, IPRP, ILSI)



Initiatives taken by India

- GTAEC- Gene Therapy Advisory and Evaluation Committee- apex advisory body to GOI on gene therapy research and development
- National Apex Committee for Stem Cell Research & Therapy (NAC-SCRT)
- Dissemination of information and awareness to the public
- Formulation of process specific and disease specific guidelines for gene therapy product development
- Hand-holding of scientists and researchers at different stages of product development
- Reviewing the clinical trial applications considering scientific, ethical, social issues
- Constitution of advisory groups for guiding patients