7th India Japan Symposium

Regenerative Medicines Session

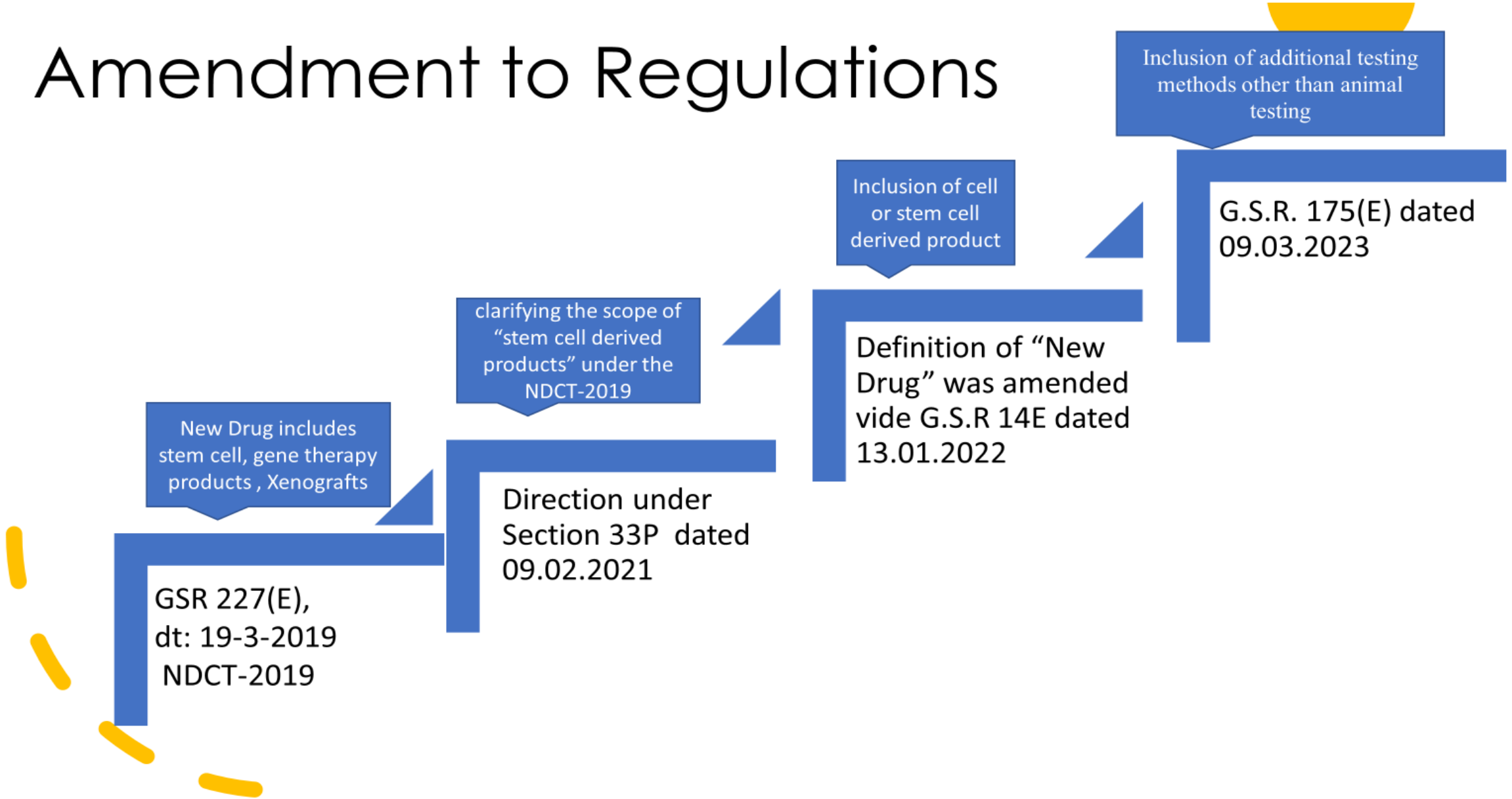
Regenerative Medicine Products &

Updates of recent approvals in India (CAR-T cell products)

10.07.2024 & 11.07.2024

CDSCO, New Delhi, Govt. of India.

Amendment to Regulations



Regulations: NDCT Rules 2019

- **Drugs &Cosmetics Act, NDCT Rules 2019**
- **Rule 2 (w)**
- **New Drug includes Cell, stem cell, gene therapy products, Xenografts, recombinant products, vaccines, Monoclonal antibodies**

- **Clarification provided under Section 33P directive:**
- **Cell & stem cell derived product** means a drug which has been derived from processed cells/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 or 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 & gene modification**.

- **The gene therapeutic product** is as a biologic that contains genetic material which are introduced into the human body for the purpose of treatment of disease etc. this may also include **nucleic acid, genetically modified organisms such as viruses, bacteria, fungi, engineered site specific nucleases** used for human genome editing and ex-vivo genetically modified human cells.

Section 33 P Directive

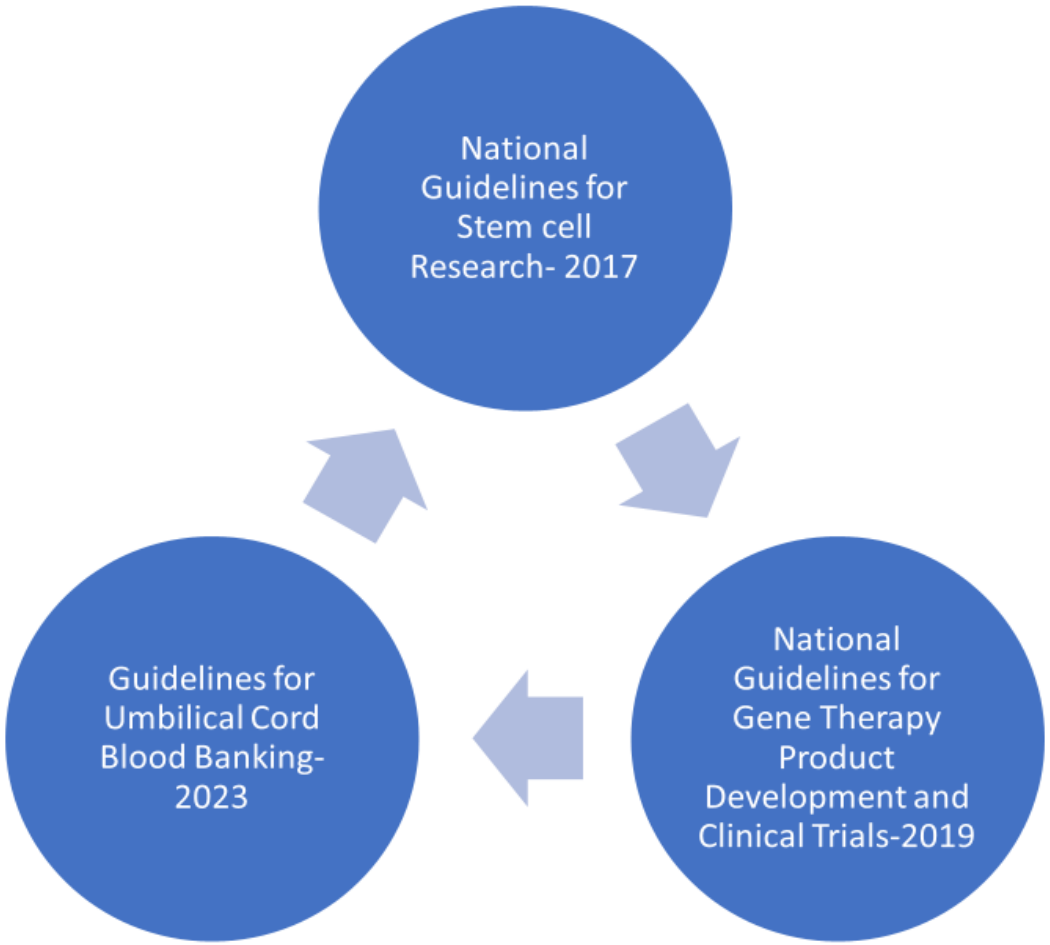
(i) Substantial or more than minimal manipulation means **ex-vivo alteration** in the cell population (T-Cell depletion, cancer cell depletion), **expansion**, which is expected to result in **alteration of function**.

(ii) The isolation of tissue, washing, centrifugation, suspension in acceptable medium, cutting, grinding, shaping, disintegration of tissue, separation of cells, isolation of a specific cell, treatment with antibiotics, sterilization by washing or gamma irradiation, freezing, thawing and such similar procedures, regarded as **minimal manipulations** and are **not considered as processing by means of substantial or more than minimal manipulation.**

(iii) Stem cells removed from an individual for implantation of such cells only into the same individual for use during the same surgical procedure should not undergo processing steps beyond rinsing, cleaning or sizing and these steps shall not be considered as processing.

Further, the **cell based products** and **tissue based products** which have been processed by means of **substantial or more than minimal manipulation** as per criteria mentioned above **covered under the New Drugs and Clinical Trials Rules, 2019.**

National Guidelines



Requirements and Guidelines for Permission to Import/Mfg of Cell & Stem cell derived product & Gene therapeutic Product

- Animal toxicology (Non-Clinical Toxicity studies):
- **Cell & Stem cell derived products:** suitable animal models that can demonstrate toxicological, pharmacological and Physiological responses, Local and systemic toxicity, tumor/ectopic tissue formation, survival/persistence, phenotype, Biodistribution, proliferation of cells
- **Gene therapy Products:** Immune responses to the ex-vivo modified cells, Vector and or expressed transgene, Viral vector reactivation, toxic effects of non- therapeutic vector proteins, level of viral replication in non target cells/tissues, insertional mutagenesis, oncogenicity, Vector biodistribution and transgene expression levels, developmental and reproductive toxicity
- Clinical trials, to prove their efficacy and safety- Phase 1, Phase 2 and Phase 3 before it is approved
- Phase 1/2 often combined to accelerate the time of development or help decrease costs. They are also combined in case the disease being studied is rare and the number of patients living with it very small.
- Phase 3 clinical trial usually done as RCT to compare the efficacy and safety of new therapy with the current treatments (if available), tends to be the longest and is usually the basis for marketing authorizations
- Conducting clinical trials for CGTs are more difficult than traditional pharmaceutical trials because the nature of risks associated are much higher- disease are either rare or severe, the number of patients might be limited, side-effects could be long-term, severe and unexpected, and the investment is much higher.
- There is a requirement to carefully engage with experts earlier on when translation is being planned

Regulatory Pathway for Biologics in general [Vaccine, r-DNA, CGTP]

IBSC and RCGM approval for import of cell bank

IBSC recommendations for R&D initiation to RCGM

RCGM approvals to initiate R&D activities

Application in Form CT-10 for approval in Form CT-11 to mfg batches for testing purpose

Application in Form 30 for Test license Form **29 (SLA)** to mfg experimental in batches

Joint inspection by CDSCO, SLA & subject expert

NOC to conduct PCT studies & (3 batch CMC data) Recommendation from RCGM to approach for clinical trials

Application in Form CT-04 for CT 06, CT-18 for import & MA and CT-21 for indigenous manufacturer for MA

SEC meetings

Permission in CT-06 to conduct CT (Phase I, II & III) / CT report Submission and CTRI registration before subject enrolment

90 Days each phase study and 30 Days for CT of IND discovered in India

Import/Manufacturing & Marketing Permission in CT-19 (DS), CT-20 (DP)/ CT-22 (DS), CT-23 (DP)

Application in 27D/27DA for grant of mfg. license in Form 28D/28DA to SLA

Grant of Form-28D/28DA from SLA counter sign. to CDSCO, Delhi.

DCG(I) counter sign & send it back to SLA in case of Form 28D /28DA.

3 months

Issue of mfg. license in Form 28/28D/28DA by SLA for CGTP based on CT 22&23

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Applicable NDCT 2019 Rules in Brief

- Broadly the New Drugs &Clinical trial Rules 2019 apply to NDs, INDs for human use, CT, BA,BE and regulation of ethics committee relating to CT, BA/BE study and biomedical health research
- Further the Definition of new drugs has been modified to incorporate novel drug delivery system (NDDS), living modified organism, monoclonal antibody, Cell and stem cell derived product, gene therapeutic products and xenografts
- **Application for NOC for Test license: CT-10**
- **Purpose:**
- 1) Manufacture of Trial batches of the IMP, for POC, Pre-clinical studies under GLP conditions and for conduct of Clinical trial with the IMP.
- 2)The IMP shall be manufactured under GMP conditions under CT-11 and manufacturing permission issued by the SLA in Form-29.
- 3) The Pre-clinical studies must be conducted with the approval of the IBSC for the Pre-clinical study protocol to study the safety and to identify the safe dose for First in human studies i.e. Phase I
- Upon receipt of the application, CDSCO zonal office along with the Officers of State Licensing Authority along with an Expert, inspect the facility and the processes for the manufacture of the IMP for the grant of CT-11 followed by issuance of Form 29 approval in Form 30 by the SLA

Animal Toxicology Requirements

- Flexibility given to adopt between General Guidance under Rules or ICH
- Studies may be planned, designed and conducted as per the ICH
- To promote safe, ethical development of new drugs in accordance with **3R (Reduce / Refine / Replace) principles.**

G.S.R. 175(E).— 9th March, 2023

2. In the New Drugs and Clinical Trials Rules, 2019, in the First Schedule, in paragraph 3, in sub paragraph (1), for clause (b), the following shall be **substituted**, relating to development methodology namely: —

"(b) (I) The general requirements of non-clinical studies have been specified in the Second Schedule.

(II) The non-clinical testing methods to assess the safety and efficacy of a new drug or investigational new drug include the following, namely: -

(i) Cell-based assay;

(ii) Organ chips and micro physiological systems;

(iii) Sophisticated computer modeling;

(iv) Other human biology-based test methods;

(v) Animal Studies.".

Application for Conduct of clinical trial: CT-04

- The product development data, non-clinical study data along with the Clinical Trial Protocol for the Phase I study shall be submitted to CDSCO in the CT-04 application, in accordance with the requirements under the II Schedule to the NDCT 2019 for review in consultation with the EXPERT COMMITTEE constituted under Rule 100.
- Approval by DCGI: CT-06 (Phase I, Phase II and where applicable Phase III)

DATA TO BE SUBMITTED ALONG WITH THE APPLICATION TO CONDUCT CLINICAL TRIALS OR IMPORT OR MANUFACTURE OF CELL OR STEMCELL DERIVED DRUG PRODUCT/ GENE THERAPEUTIC PRODUCT FOR SALE IN THE COUNTRY

1) Introduction:

2) General Requirements:

a) Chemical and pharmaceutical information

b) Cell Collection: Donor screening, Tests and other requirements for allogenic and autologous, Tissue typing {histocompatibility antigens, tissue typing process, acceptance criteria}, collection process

c) Banking procedures and Methods of cell / Vector/ Target gene sequences: origin, source, history of cells/Vector/target gene sequences, Procedure for cell culture, Passage control, IPQC, Characterization

Master cell/vector construct/host cell banking control, Phenotypic/genotypic characterization etc

3) Manufacturing Process and its Control:

a) Data on specification and validated test method for materials used during manufacturing

b) Manufacturing Process

c) Data on Formulation

d) Specification and quality control

4) Characterization:

a. Cell/ GTP Identity

b. Cell/ GTP purity

c. Vector Details

DATA TO BE SUBMITTED ALONG WITH THE APPLICATION TO CONDUCT CLINICAL TRIALS OR IMPORT OR MANUFACTURE OF CELL OR STEMCELL DERIVED DRUG PRODUCT/ GENE THERAPEUTIC PRODUCT FOR SALE IN THE COUNTRY

5. **Potency:**
6. **In vivo tumourogenicity**
7. **Quality Control and Release of Cell/ SCDP/ GTP:**
8. **Stability testing:**
9. **Container and closure system**
10) **Labelling:** Product information, Leaflet including Prescribing Information, storage conditions and expiry details including patient specific details if any.
11) **Quality Assurance:**
12) **Validation:**
13) **Product Tracking:** Tracking ID and marking system as per product nature, if any.
14) **Non-clinical Studies:**
15) **Clinical Studies:**
    a) **Human I Clinical pharmacology (Phase I)**
    b) **Therapeutic exploratory trials (Phase II)**
    c) **Therapeutic confirmatory trials (Phase III)**
    d) **Special studies: Bio-availability / Bio-equivalence if applicable**

DATA TO BE SUBMITTED ALONG WITH THE APPLICATION TO CONDUCT CLINICAL TRIALS OR IMPORT OR MANUFACTURE OF CELL OR STEMCELL DERIVED DRUG PRODUCT/ GENE THERAPEUTIC PRODUCT FOR SALE IN THE COUNTRY

16. PMS Study (Phase IV):

17. Pharmacovigilance and Risk Management Plan:

18. Regulatory status in other countries:

19. Prescribing Information, Summary of Product Characteristics

Note: The above requirements may not be applicable for all such type of product. The sponsor shall submit the data as appropriate depending upon the nature of the product.

Rules Applicable for Orphan Drug development affecting less than 5 lakh population in India as defined under the NDCT-2019 Rules

- A drug intended to treat a condition which affects <five lakh persons in India
- No fee for conduct of clinical trial
- Provision for accelerated/expedited approval process

Timelines for application of CT for IND

A. In case of CT, as part of discovery, research and manufacture and marketing in India

- Permission /Rejection/Query in 30 working days
- Deemed approval, if no reply in 30 working days. (However, the applicant has to intimate CLA about initiation of the trial)

B. For other applications for CT

- Permission /Rejection/Query in 90 working days
- Deemed approval, if no reply in 90 working days. (However, the applicant has to intimate CLA about initiation)

Accelerated approval of New Drug in special situations

- Provisions under ND & CT Rules, 2019 for relaxation, abbreviation, omission or deferment of data including local clinical trial data for approval of a new drug.
- **Accelerated Approval**
- **Accelerated approval process may be allowed to a new drug for-**
- Serious / life-threatening diseases
- Rare diseases
- Diseases of special relevance to Indian health scenario,
- For disease for which there is unmet medical need
- Disaster or special defence use
- **Accelerated approval may be allowed for a new drug for a disease taking into account -**
- severity, rarity or prevalence of the disease
- availability or lack of alternative treatments,
- there is a prima facie case of the product being of meaningful therapeutic benefit over the existing treatment

Accelerated approval process

- Surrogate endpoints may be considered rather than standard outcome measures such as survival or disease progression, which are reasonably likely to predict clinical benefit.
- In case of remarkable efficacy, marketing approval may be based on Phase II clinical trial data.
- Accelerated Approval may also be granted to a new drug intended for serious/ life threatening disease, disease of special relevance to India and Unmet medical need.

Phase IV CT may be required to validate the anticipated clinical benefit

Expeditious review process

- Applicable for a situation where the evidence for clinical safety and efficacy have been established even if the drug has not completed the all or normal clinical trial phases
- **In such case following conditions need to be satisfied**
- a. serious or life threatening or rare disease or condition;
- b. if approved, the drug would provide a significant advantage in terms of safety or efficacy
- c. there is substantial reduction of a treatment-limiting adverse reaction and enhancement of patient compliance that is expected to lead to an improvement in serious outcomes
- d. It is also applicable for new drug developed for disaster or defence use where new intervention has been developed and where real life clinical trial may not be possible.

It is also applicable for approval of an orphan drug

Approved New drugs –pathway for additional new claims

- The requirements of data depend on nature and regulatory status of the drug for the new claim.
- Usually, the requirement of animal pharmacological and toxicological data and clinical data are determined on case by case basis
- Consideration is given to the type of new claim as well as mechanism of action, pathophysiology of the disease and clinical data already generated in the approved claim.
- **The requirements may be abbreviated or relaxed or omitted under following conditions:**
- a. the drug is already approved and marketed in other country for the proposed new claim;
- b. clinical data supporting the benefit-risk ratio in favour of the drug in the proposed new claim is available;
- c. the clinical trial doesn't involve a route of administration, dose, patient population that significantly increases the risk associated with the use of the drug.

Pre and Post- submission meeting

- The applicant can ask for Pre and Post- submission meeting with payment of fees.

Schedules to the NDCT-2019 Rules

- General principles and practices for clinical trial
- Requirements and guidelines for permission to import or manufacture of new drug for sale or to undertake clinical trial with special provisions for expedite review, accelerated approval process like in case of unmet medical need, etc.
- Schedule II for non-clinical studies
- Conduct of clinical trial ,
- Formulae to determine the quantum of compensation in case of clinical trial related injury/permanent disability or death.
- Requirements and guidelines for conduct of BA/BE study of new drugs or IND.
- **Post marketing assessment of new drugs:** Phase IV studies, PMS protocols and studies, PSURs

Marketing Authorisation

- CT-23 : Permission to manufacture Pharmaceutical Formulation of NEW DRUG for sale or for distribution is issued by the CLAA based on the applicants CT-21 application

To promote research by MSME & academic research

- Fee for MSME 50% of the specified fee
- For Govt./ Autonomous institution, no fee for application to conduct CT

Cell & Gene Therapeutic Product approvals in India

	ImmunoACT HCAR19	Immuneel IMN 003A/ ARI-0001 (Spain)
Product	Actalycabtagene autoleucel (Autologous HCAR19 (2nd generation Anti-CD19-41BBCD3ζ chimeric antigen receptor T-cell therapy)). Brand Name: NexCAR19	Varnimcabtagene autoleucel (IMN-003A cells/anti-CD 19 CAR-T cells). Transduced with lentiviral vector to express a chimeric antigen receptor with anti-CD19 specificity (chimeric receptor: anti-CD19 scFv:CD8TM:4-1BB:CD3z) Brand Name: Qartemi
Vector/Antigen Module	3rd generation Lenti virus. humanized scFv is designed from FMC63 scFv (murine anti-human CD19 antibody)	3rd generation Lenti virus, a non-FMC63 murine scFv. a CD19 Lentiviral vector (3rd generation) is used to transduce T cells for the generation of CD19 CAR T cells
Dosage form	Cryopreserved viable CAR-T cells in infusion bag for single dose intravenous infusion (autologus) in 100 ml	Intravenous suspension, Autologous
Composition	Each 100 ml of cryopreserved cell suspension contains: 1×10^8 - 2×10^9 anti-CD 19 CAR-T cells, Excipients: Qs	0.1×10^6 to 5×10^6 anti-CD19 CAR-positive T cells / Kg in approximately 30 mL suspension, Excipients: Qs. The total dose is fractionated into 3 infusion bags (10%, 30%, and 60%).
Indication	Relapsed or Refractory B Cell Lymphomas Relapsed or Refractory B-Acute Lymphoblastic leukaemia	Relapsed /Refractory B-NHL in patients aged greater than 18 years of age
CT06 Phase 1	patients in India.	Spain patients
CT06 Phase 2	patients in India.	Indian patients
CT 23	CT 23 issued	CT 23 issued
Storage	The shelf life ot the cryopreserved cell suspension of Actalycabtagene autoleucel shall be 3 months from the time of manufacturing, when the infusion bag containing the product overwrapped in a sterile bag, placed in an aluminium cassette and stored at temperature ≤ -80°C as per stability data	12 months from the time of manufacturing, when the cryobag containing the product placed in an aluminum cassette and stored at temperature ≤ -150°C as per stability data
Conditions	to conduct a well-structured Post Marketing Study for Active Surveillance	to conduct a well-structured Post Marketing Study for Active Surveillance

Bone Marrow derived Mesenchymal Stromal Cells

S.No.	Name of the firm	Name of the Drug	Indication	Dosage Form
1	Stempeutics Research Pvt. Ltd. Bangalore	Stempeucell® (Adult Human Bone Marrow derived, cultured, pooled Allogenic Mesenchymal Stromal Cells)	Buerger's disease patients with established Critical Limb Ischemia in Rutherford III-5 or III-6, not eligible for or have failed traditional revascularization treatment, with rest pain and / or ulcers in the affected limb.	Injectable suspension for Intra-muscular use.
2	Stempeutics Research Pvt. Ltd. Bangalore	Stempeucel (Adult human Bone Marrow Derived, Cultured Pooled, allogeneic Mesenchymal Stromal cells)	Clinical Limb Ischemia due to Atherosclerotic Peripheral arterial disease in Rutherford 111-5 or 111-6, not eligible for or have failed traditional revascularization treatment, with rest pain and / or ulcers in the affected limb.	Injectable suspension for Intra-muscular use
3	Stempeutics Research Pvt. Ltd. Bangalore	Stempeucel (adult human bone marrow derived cultured pooled allogeneic mesenchymal stromal cells)	Grade II and Grade III osteoarthritis of knee based on kellgren and lawrence radiographic criteria in non-obese patients with BMI <30kg/m^2	Intra-articular injection.

Chondrocyte derived products

S.No.	Name of the firm	Name of the Drug	Indication	Dosage Form
1	Regenerative Medical Services Pvt. Ltd., Mumbai	Autologous Adult Live Cultured Chondrocytes in DMEM suspension for implantation (CHONDRON)	Additional Indication: Treatment for Articular Cartilage Defects (Autologous nature).	Autologous Cultured Chondrocytes suspended in sterile DMEM culture media filled in Type I borosilicate glass vial with Bromobutyl rubber capping and Aluminium Flap cover.

Osteoblasts derived products

S.No.	Name of the firm	Name of the Drug	Indication	Dosage Form
1	Regenerative Medical Services Pvt. Ltd., Mumbai	Autologous Adult Live Cultured osteoblasts in DMEM suspension for implantation (OSSRON)	Treatment for Avascular Necrosis of the Hip Joint.	Autologous adult live cultured osteoblasts in sterile DMEM culture media filled in Type I borosilicate glass vial with Bromobutyl rubber capping and Aluminium flap Cover.

Buccal Epithelial Cells derived products

S.No.	Name of the firm	Name of the Drug	Indication	Dosage Form
1	Regrow Biosciences Pvt Ltd	Autologous Adult live cultured Buccal Epithelial Cells (Uregrow)	For the treatment of bulbar urethral structure of atleast 1-2 cm in length in males for age group 18-56 years.	Autologous Adult Live Cultured Buccal Epithelial Cells in sterile DMEM culture media filled in Type I borosilicate glass vial with Bromobutyl rubber capping and Aluminium Flap cover.

Limbal Epithelial Cells derived products

S.No.	Name of the firm	Name of the Drug	Indication	Dosage Form
1	Reliance life sciences	an autologous bio-engineered composite limbal epithelial graft	indicated in unilateral partial or total limbal cell deficiencies like chemical/ thermal/ mechanical and ionizing radiation injuries., multiple surgical procedure or cryotherapies affecting the limbal region and contact lens-induced keratopathy.	Cultured autologous Limbal Cell Graft

Dendritic Cells based products

S.No.	Name of the firm	Name of the Drug	Indication	Dosage Form
1	APAC Biotech Pvt. Ltd., Gurgaon, Haryana	Dendritic cell immunotherapy product (APCEDEN ®)	For the treatment of Malignant solid Tumors (viz. Prostate, Ovarian, Colorectal and Lung Cancer in refractory cases).	Dispersion for intravenous infusion

Decellularized Dermis based products

S.No.	Name of the firm	Name of the Drug	Indication	Dosage Form
1	Pharma Leaf, Bangalore	Decellularized Dermis (Derma ACELL AWM)	Indicated for Homologous use for the replacement of damaged skin due to Diabetic foot ulcer, Venous leg ulcer, Dehisced surgical wounds and Traumatic burns.	Sterile Decellularized Human Dermis applied as a skin graft to wound bed with staples.

Other Products

Early Stage Development:

- Anti-CD19.CD20 CAR T cells Indication: CD19 and CD20 positive malignancies
- Anti CD20 CAR T-cells Indication: B cell malignancies
- Anti-Claudin 18.2 CAR-T cells Indication: Claudin 18.2+ solid tumors

Under Clinical Trial:

- **Anti-BCMA CAR-T cells Indication:** BCMA+B-cell diseases
- **HiPSC derived products :** Human induced pluripotent stem cells (hiPSC) derived retinal pigment epithelial cells for the treatment of Geographic Atrophy (GA) Secondary to Dry Age-related Macular Degeneration (d-AMD)
- **Chondrocyte derived products**: Autologus Cultured Disc chondrocytes embedded in PRF (Intervertebral disc degeneration ,disc herniation)

Gene Therapy products in Pipeline

- **Early Phase of Development:**
- **Govt.of India introduced the National Sickle Cell Mission**
- CSIR, Govt of India sickle cell Anaemia HCP Mission outputs: POC studies rapidly progressing for clinical translation of SCD gene editing therapy

- Zolgensma (Onasemnogene abeparvovec) for Spinal Muscular Atrophy (SMA) – Novartis, Global Clinical Trial (MRCT-India) for Import and Marketing Authorization

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Thank You
for Your Attention