Regulatory framework for Stem Cell and Products review in India

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Outline of Presentation

- Legal Provisions
- MCI Code of Ethics regulation
- Clinical trial requirements
- Screening committees
- Licensing Procedure
- Applications review system
- Guidance for Industry
- Draft Definition

Legal provisions

- **Stem Cells & Cell Based products (SCCPs) are regulated as Drugs.**

- **Guidelines for Stem Cell Research has been published by ICMR as National Guideline for Stem Cell Research 2017, which elaborates about restricted, prohibited and permitted research alongwith the minimal, substantial and major manipulation. Further the indications which does not require prior approval are given in Annexure III of the guideline. i.e. stem cell transplantation in certain blood disorders.**

- **Conducts Rules under Medical Council of India (MCI) for doctors governs treatment using Stem Cell.**

MCI code of ethics regulation

- The code of ethics regulation laid down by MCI shall be followed by the Physician which amongst others are as following:-

  Clause 2.3 Prognosis: The physician should **neither exaggerate nor minimize** the gravity of a patient's condition. He should ensure himself that the patient, his relatives or his responsible friends have such knowledge of the patient's condition as will serve the best interests of the patient and the family.

  Clause 3.2 Consultation for Patient's Benefit: In every consultation, the benefit to the patient is of foremost importance. All physicians engaged in the case **should be frank with the patient** and his attendants.

  Clause 3.7.1 : A physician shall **clearly display his fees** and other charges on the board of his chamber and/or the hospitals he is visiting. Prescription should also make clear if the Physician himself dispensed any medicine

  Clause 6.1: **A physician shall not** make use of him / her (or his / her name) as subject of any form or manner of **advertising** or publicity through any mode either alone or in conjunction with others which is of such a character as to invite attention to him or to his professional position, skill, qualification, achievements, attainments, specialities, appointments, associations, affiliations or honours and/or of such character as would ordinarily result in his self aggrandizement.

- All the Stem Cell treatments performed by the physicians which are exempted as standard practices etc. are covered under MCI regulations.

Definition of New Drug:

- **New Drug is defined as "A drug, including bulk drug substance which has not been used in the country to any significant extent under the conditions prescribed, recommended or suggested in the labeling thereof and has not been recognized as effective and safe by the licensing authority mentioned under Rule 21 for the proposed claims."**

- Rules 122A, 122B, 122DA and Schedule Y specify the requirements and guidelines for obtaining permission to manufacture/import of New Drugs or to undertake clinical trials.
- CMC data, pre-clinical, clinical trail data on safety & efficacy data has to be submitted for approval of stem cell & cell based product.
- Data is evaluated by the expert committee (CBBTDEC).

Various Screening Committees involved in Approval of SCCP in India

For Import / Marketing Authorization of the Stemcell Products in India:

1. **CBBTDEC Committee**
2. **Technical Committee**
3. **Apex Committee**

To Conduct Research in India:

1. ICMR.
2. National Apex Committee for Stem Cell Research and Therapy (NAC/ SCRT) – To oversee the activities in the field of stem cell research in India.
3. As per National Guidelines for Stem Cell Research 2017, approved indications for Hematopoietic stem cell transplantation (HCT) are mentioned under Annexure3 of the guidelines for adult as well as pediatric which does not require any prior approval.

Licensing Procedure

- **Indigenously manufacturers:** The applicant is required to obtain market authorization from DCG (I) in Form 46 before obtaining manufacturing license in Form 28 from State Licensing Authority.

- **Importers:** The applicant is required to obtain market authorization from DCG (I) in Form 45 before obtaining Registration Certificate in Form 41 and import license in Form 10.

Pathway for indigenous manufacturers

Application for Manufacturing of Experimental test batches for test and Analysis (Form 30) to the SLA

Joint inspection by Expert/SLA/

CDSCO Official

Permission for Manufacturing of Experimental batches of SCCPs for Test and Analysis (Form-29)

Pre -clinical studies as per Schedule Y

Application and protocol submission for conducting Phase I/II/III clinical study with the Experimental batches (Form 44)

(Pre - clinical data, Protocol for Clinical trial, CMC data as well as General Information as per CDSCO Guidance for Industry

CBBTDEC-Review of Application in consultation with subject Experts

Licensing procedure Contd….

Submission of Clinical Study Report of Phase I/II/III of SCCPs

Consultation with Subject Experts of (CBBDTEC)

Market Authorization Application in line with CTD format from manufacturer along with phase clinical trial report

Permission issued in Form 46 followed by license in Form 28

CTD Module:

(Module-1: Administrative information)
(Module-2: Overall Quality Summary)
(Module-3: Chemistry Manufacture, Control (CMC))
(Module-4: Non – clinical data)
(Module-5: Clinical Data)

Pathway for Importers

Application to Import of finished formulation of SCCPs for Test and Analysis in small quality (Form 12)

Application and protocol for conducting Phase III clinical study (Form 44)

(Pre - clinical data, Protocol for Clinical trial, CMC data as well as General Information as per CDSCO Guidance for Industry)

CBBTDEC-Review of Application in consultation with Subject Experts.

Submission of Clinical Study Report of Phase III with Imported manufactured product

Consultation with Subject Expert of CBBTDEC

Market Authorization Application as per CTD format from manufacturer along with clinical trial report

Permission issued in Form 45 followed by Registration Certificate in Form 41 & Import license in Form 10

CTD Module:

(Module-1: Administrative information)

(Module-2: Overall Quality Summary)

(Module-3: Chemistry Manufacture, Control)

(Module-4: Non – clinical data)

(Module-5: Clinical Data)

Clinical Trial requirement prior approval

- For New Drug products including biologicals discovered in India, clinical trial is required to be conducted right from Phase I.

- For New Drugs including biologicals approved outside India, Phase III studies need to be carried out to generate evidence of efficacy and safety of the drug in Indian patients when used as recommended in the prescribing information.

- Approval of new drugs is also considered based on clinical trial conducted in adequate number of Indian patients as a part of global clinical trial and the drug is also approved in other countries.

Clinical Trial requirement relaxation

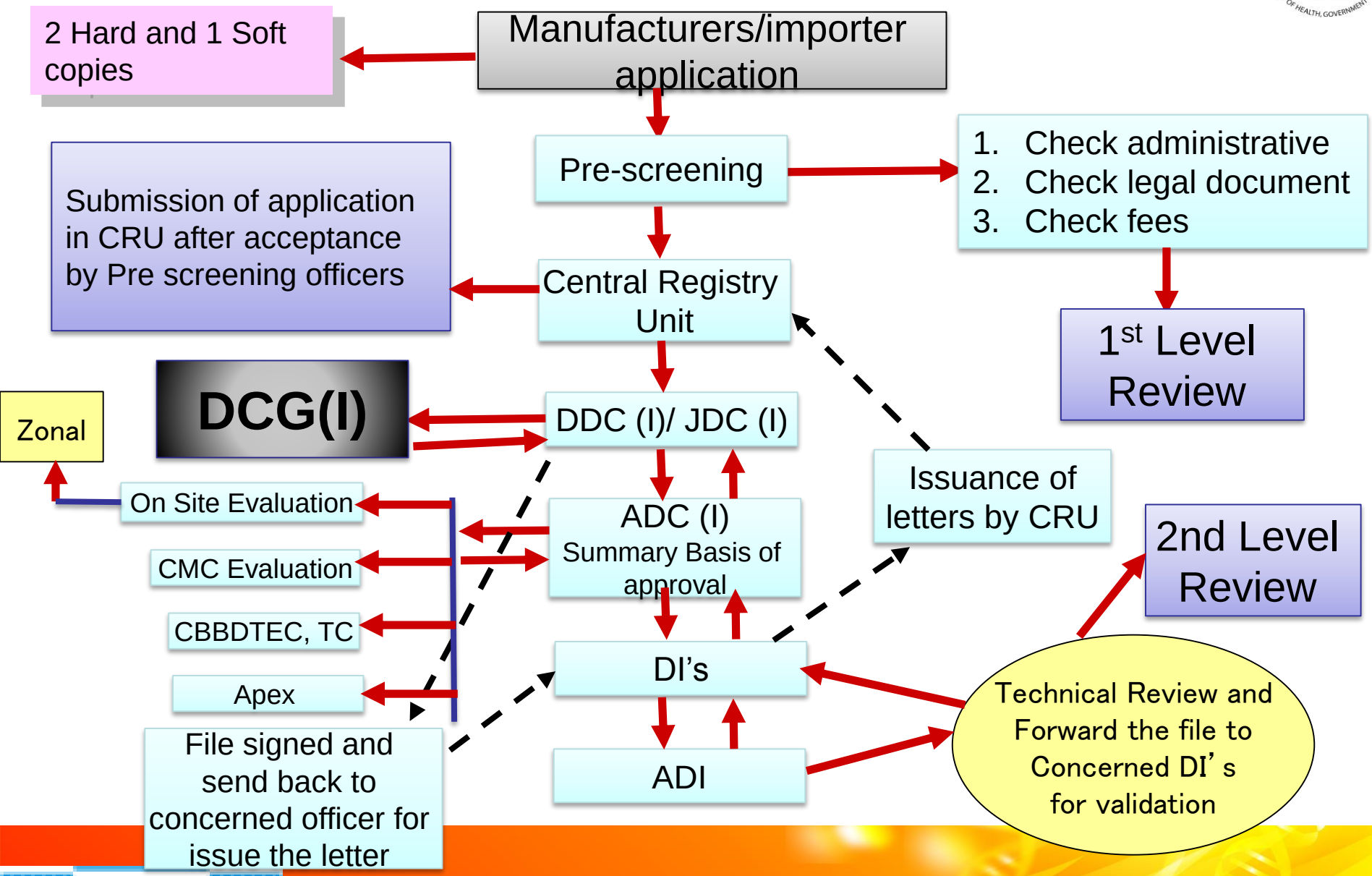
- As per Schedule Y of Drugs and Cosmetics Rules 1945, For drugs indicated in life threatening / serious diseases or diseases of special relevance to the Indian health scenario, the toxicological and clinical data requirements may be abbreviated, deferred or omitted, as deemed appropriate by the Licensing Authority .
- The requirement of submitting the results of local clinical trials may not be necessary if the drug is of such a nature that the Licensing Authority may, in public interest, decide to grant such permission on the basis of data available from other countries:
- The submission of requirements relating to Animal Toxicology, Reproduction studies, Teratogenic studies, Perinatal studies, Mutagenicity and Carcinogenicity may be modified or relaxed in case of new drugs approved and marketed for several years in other countries, if the Licensing Authority is satisfied that there is adequate published evidence regarding the safety of the drug, subject to the other provisions of these rules.

Conditional approval

Depending on the nature of the product, Market Authorizations are sometimes issued with specific conditions based on CT outcome like:

- The marketing approval shall be limited to manufacture for PMS Study.
- After completion of well structured PMS study, the results will be evaluated.
- The continued marketing will be permitted only if results are found satisfactory.
- It is also required to submit PSUR reports.

Review of applications:



Draft Rule for Stem Cell and Cell Based Products in India.

GSR No. 334 dated 04-04-2018

- Stem Cell and Cell based Product means
  - ✓ a drug which has been derived from processed cells including cell or tissue which has been processed by means of substantial or more than minimal manipulation
  - ✓ with the objective of propagation and / or differentiation of a cell or tissue,' cell activation, and production of a cell-line,
  - ✓ which 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.

Draft Rule for Stem Cell and Cell Based Products in India.

- Explanation - For the purpose of this clause–
  - ✓ (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, overnight culturing without biological and chemical treatment, 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) Human cells or tissues removed from an individual for implantation of such cells or tissues 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.

Guidance for Industry

- Submission of clinical trial application for Evaluating Safety and Efficacy.
- Requirements for permission of New Drugs Approval
- Post Approval Change in biological products:
- Quality safety and Efficacy Documents
- Preparation of the Quality Information for Drugs submission for New Drugs Approval.

Thank you