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H．知的財産権の出願・登録状況

H-1. 特許取得

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【名称】公益財団法人　ヒューマンサイエンス振興財団

特許出願番号　特願 2014-176861

発明の名称　悪性形質転換細胞の検出方法

特許出願日　　平成 26 年 9 月 1 日

H-2. 実用新案登録　なし

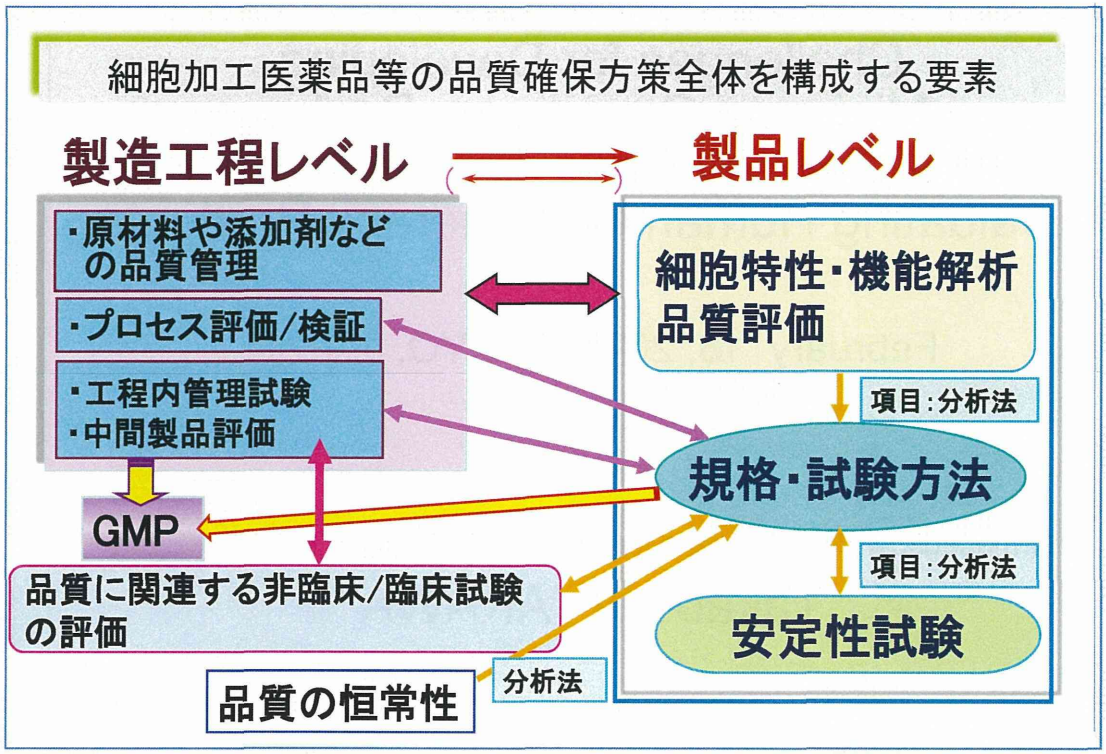
H-3.その他

【政策への提言】

1）「再生医療等の安全性の確保等に関する法律」、「再生医療等の安全性の確保等に関する法律施行令」及び「再生医療等の安全性の確保等に関する法律施行規則」の取扱いについて（平成 26 年 10 月 31 日医政研発 1031 第 1 号厚生労働省医政局研究開発振興課長通知）

2）生物由来原料基準の一部を改正する件」（平成 26 年厚生労働省告示第 375 号）；

〈Fig. 1〉



〈Table 1〉

最終製品の規格及び試験方法例：MCP項目（青字）

(1)細胞数並びに生存率＊暫定規格値
(2)確認試験：重要細胞特性指標を選択
(3)細胞の純度試験＊暫定規格値
(4)細胞由来の目的外生理活性物質に関する試験＊暫定規格値：
安全性上の重大な影響を及ぼす可能性が明らかに想定される場合
(5)製造工程由来不純物試験＊暫定規格値：　存在する可能性があるもので、かつ、品質及び安全性の面からみて望ましくない物質
(6)無菌試験及びマイコプラズマ否定試験
(7)エンドトキシン試験
(8)ウイルス試験
(9)効能試験＊暫定規格値
(10)力価試験＊暫定規格値：特定の生理活性物質が効能又は効果の本質
(11)力学的適合性試験＊暫定規格値：一定の力学的強度を必要とする製品

<Slide 1>

Challenges for Developing a Minimum Consensus Package plus Case by Case Approaches for Evaluating Human Cell Therapy Products

February 18, 2015, TOKYO, JAPAN

Pharmaceutical Research and Technology Institute, Kindai University

Takao HAYAKAWA

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Major Objective of the Meeting

The major objective of the meeting is to highlight the important regulatory considerations that are unique to human cell derived and substantially manipulated cell therapy products (hCTPs).

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To develop novel hCTPs and to translate them more efficiently and effectively into products that contribute more to human health care, it is essential that they be based on a sound scientific rationale.

Manufacturers and control authorities should take into account common scientific core elements, as well as the specifics of the cell source, mfg. process, product administration procedures, and diseases in question.

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As a part of such an endeavor, it is critical to share a common recognition among interested parties with respect to the essential scientific and technological elements for CMC, nonclinical and clinical studies of all types of substantially manipulated hCTPs.

In other words, a challenge should be made so that we can develop a minimum consensus package that encompasses scientific principle/concepts, general considerations and technical requirements commonly applicable to all hCTPs.

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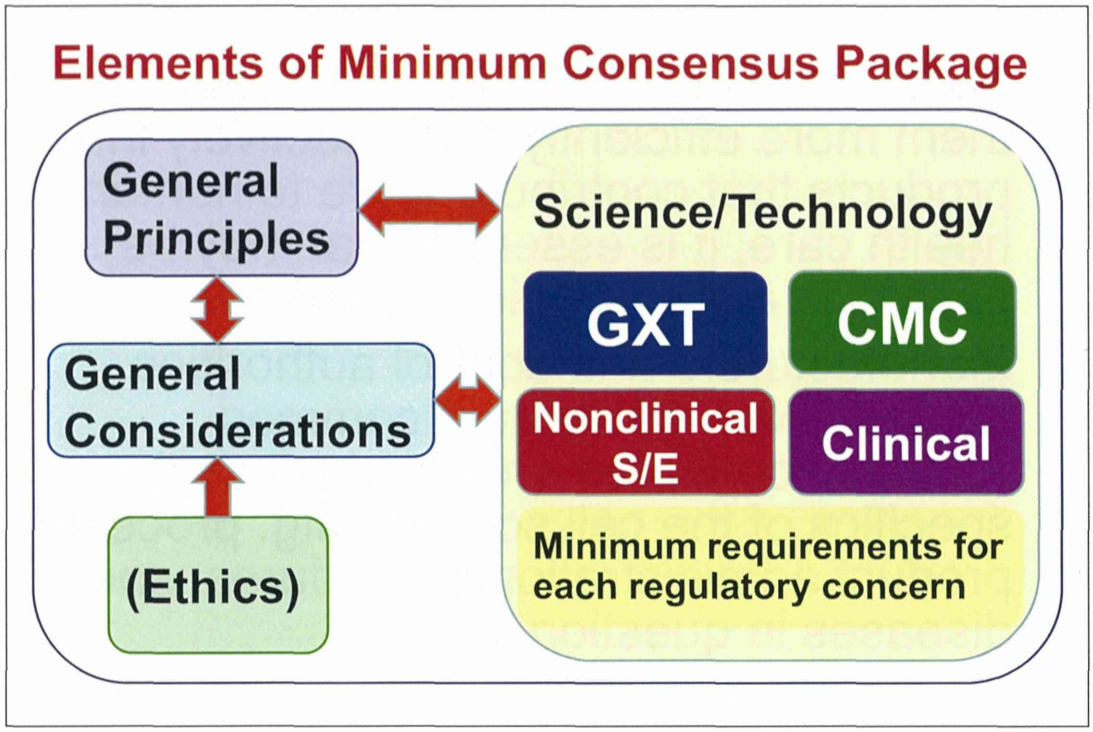

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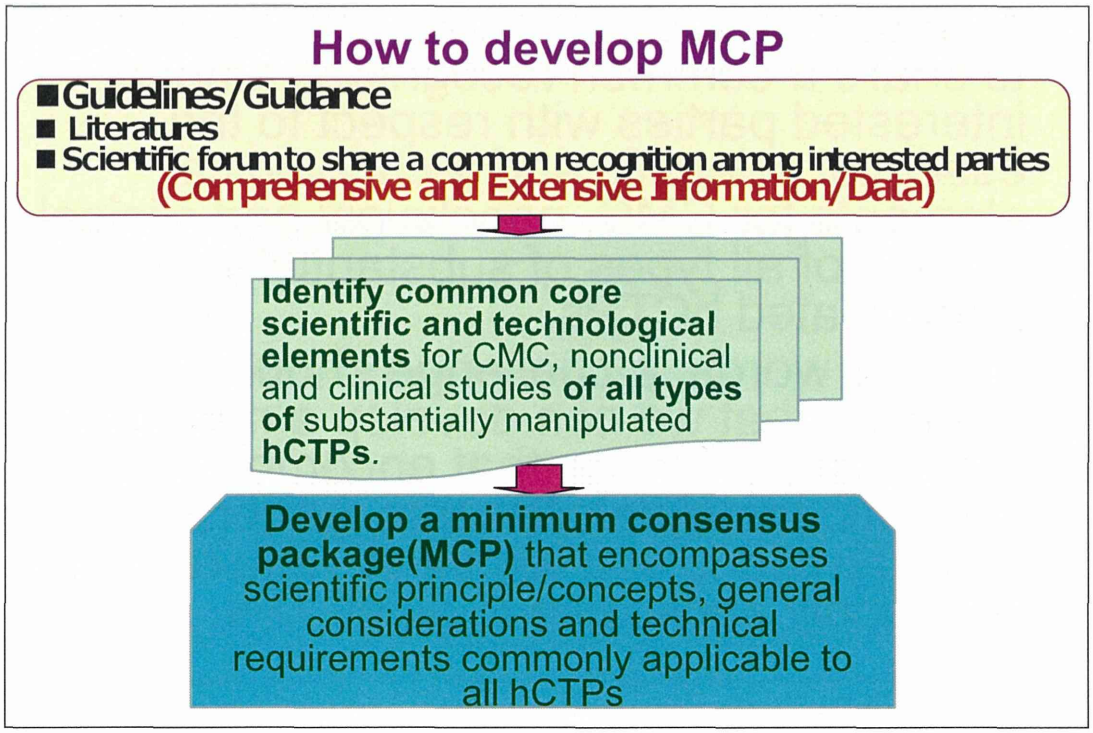

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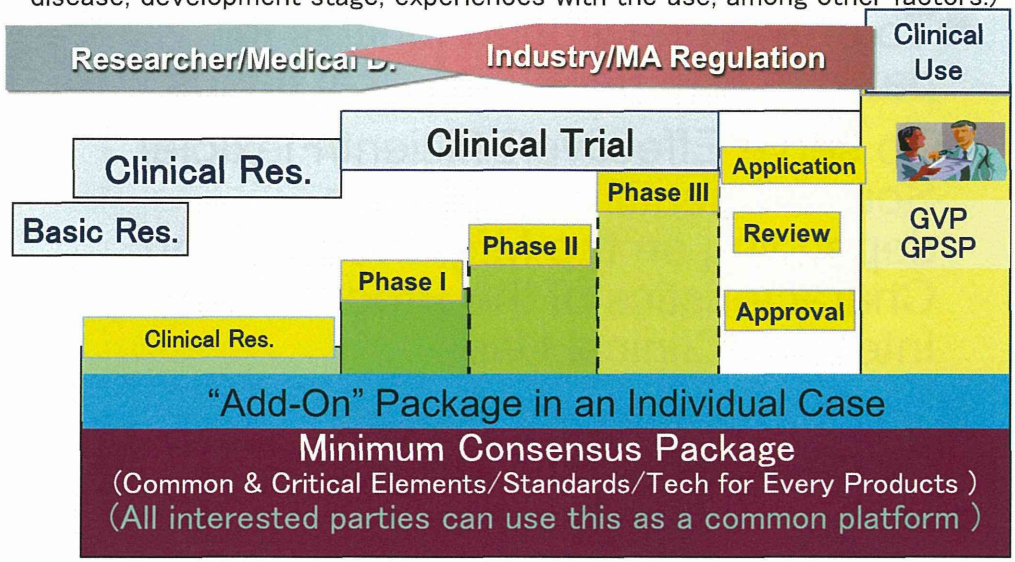
Cell therapy can be advanced efficiently, effectively and reasonably through the use of the Minimum Consensus Package + "Add-On Package" in an Individual Case (taken into account a product specific profile, the target disease, development stage, experiences with the use, among other factors.)



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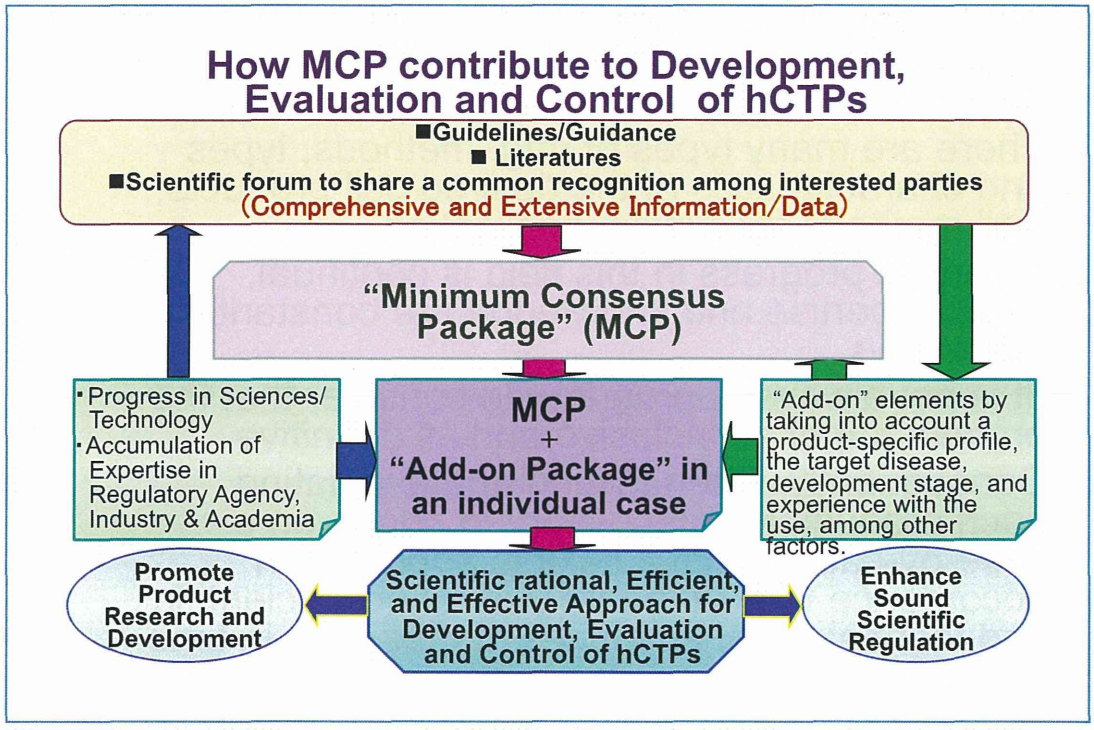

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General Principles

- To provide new opportunities to patients with unmet medical needs
- To serve Effective/Efficient/Flexible/ Sound Scientific Regulation depending on the Mfg. Process and Characteristics of the Product, and Intended Clinical Use
- To Promote Novel Product Development and Application

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General Consideration on Sound Scientific Requirements for Product Development, Evaluation and Control (1)

- There are many types of mfg. methods, types and characteristics of the desired cell products, and methods for clinical application
- Scientific progress in this field is continual, while expertise and knowledge are constantly advancing
- It is not always appropriate to consider that the present paper all inclusive and all definitive
- Consequently, when testing and evaluating each product, it is necessary to adopt, on a case-by-case basis, a flexible approach in accordance with rationale that reflects scientific and technological advances at that point in time

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General Consideration on Sound Scientific Requirements for Product Development, Evaluation and Control (2)

- The main purpose of evaluation of quality and safety of the desired cell products before conducting investigational clinical trials is to determine whether there are any quality and/or safety problems that would obviously hinder initiation of human clinical trials of the products in question
- Whether certain quality attributes (QA) of the product are understood sufficiently to establish a relationship between clinical findings and the QA
- Whether consistency of the QA can be ensured within a definite range

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General Consideration on Sound Scientific Requirements for Product Development, Evaluation and Control (3)

- Simultaneously, it is important to eliminate as much as possible any known risk factors associated with product quality and safety using up-to-date science and technology, and to describe the scientific appropriateness of the results of such an action.
- The remaining presumed risk factors should be weighed against the risks associated with not performing the trials on patients who suffer from diseases that are serious and life-threatening or that involve marked functional impairment , or a marked decrease in QOL resulting from the loss of a certain degree of a physical function or form, or for which existing therapies have limitations and do not result in a cure.

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General Consideration on Sound Scientific Requirements for Product Development, Evaluation and Control (4)

- Furthermore, it is important to entrust the patient with the right to make a decision after receiving all of the available information
- When applying for approval of investigational clinical trials, applicants can submit a reasonably prepared provisional nonclinical data package, which is prepared rationally by taking into account product aspects and patient aspects including a balance between the risk of the product *vs.* the risk facing the patient with/without treatment in question, in order to decide to initiate investigational clinical trials, on the premise that the data package submitted at the time of marketing authorization application/registration to ensure quality and safety will be enriched and developed in line with the existing guidance as the clinical trial progresses

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General Consideration on Sound Scientific Requirements for Product Development, Evaluation and Control (5)

- Applicants are encouraged to discuss with the related national/regional regulatory agency (NRAs) the type and amount of data that may be needed to initiate a particular clinical trial.
  - Because of differences in product origin, target disease, target patients, application sites, application methods, and processing methods, there may be numerous variations among individual data packages; these differences cannot be definitively clarified in the existing guidance.

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General Consideration on Sound Scientific Requirements for Product Development, Evaluation and Control (6)

- The items, test methods, criteria, and any other technical requirements described in the guidance are intended to be considered, selected, applied, and evaluated to serve each intended purpose.
  - They do not necessarily require the most stringent level of interpretation and practice. Applicants are encouraged to explain and provide justification for any consideration regarding the background, selection, application, and the content as well as the extent of the evaluation that are appropriate for their own purpose and are scientifically valid.

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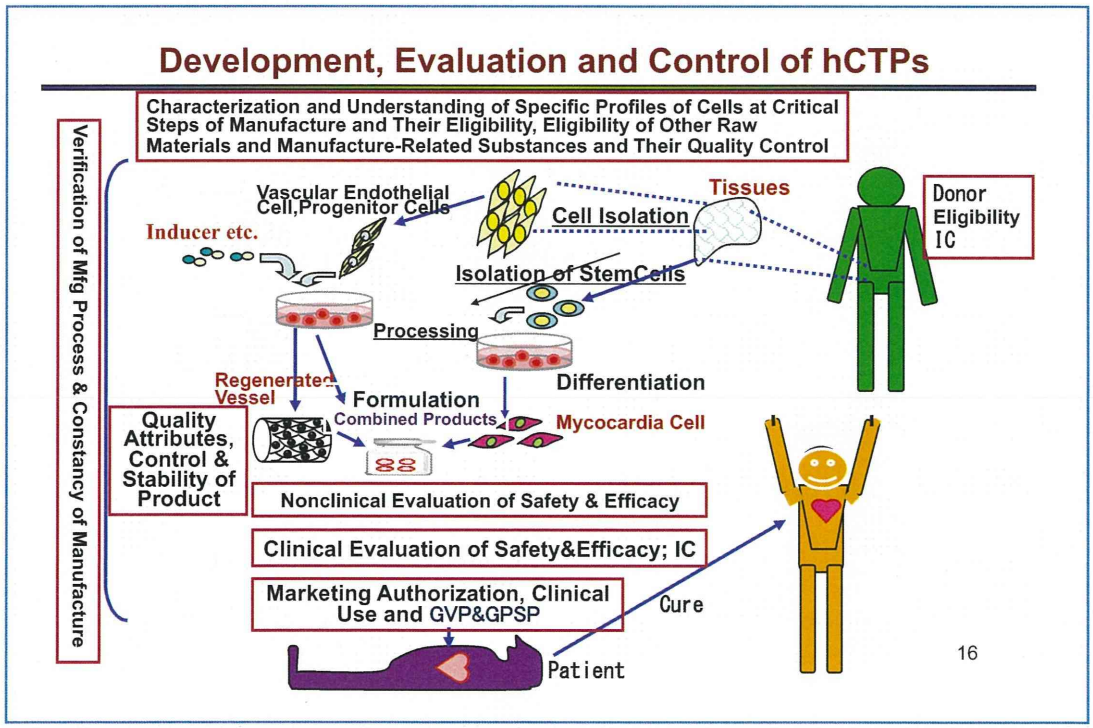

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Scientific and Technological Elements of MCP

- Process Element
- Product Element
- Nonclinical Safety
- Nonclinical Efficacy
- Clinical Study

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Justification of the Source and Selection of Human Cells that serve as Raw Materials(1)

- Select the source and origin of the cells used as raw materials, and explain the reasons for selecting these cells.
  - ☐ Autologous or allogeneic somatic cells
  - ☐ Autologous or allogeneic stem cells
  - ☐ Autologous or allogeneic iPS(-like) cells
  - ☐ ES cells
  - ☐ (Any other human cells)

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Justification of Source and Selection of Human Cells that serve as Raw Materials(2)

Donor selection criteria and eligibility:

- Indicate that the donor was selected in an appropriate and ethical manner and that the proper procedure was followed.
- Establish selection criteria and eligibility criteria that take into consideration age, sex, ethnic characteristics, genetic characteristics, a clinical history, the health condition, test parameters related to any type of infection that may be transmitted via cell and/or tissue samples, and immunological compatibility, and to explain their appropriateness.

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Proposed MCP for Autologous or Allogeneic Cells

Autologous Human Cells

- **Infectious Status of the Donor**, including infections of HBV, HCV, HIV, and HTLV.
- **Risk of Proliferation or Re-activation of the Virus during the Mfg. Processes**
- **Robust Process Control to Minimize Unevenness of "Custom-made" Products**
- **A limited Amount of Samples for Quality Evaluation of Products**

Allogeneic Human Cells

- **History, Source,** and **Derivation**
- **Donor Screening/Testing and Donor Eligibility** (Compatibility with donor qualification criteria, including ethical and medical aspects;Freedom from the presence of HBV, HCV, HIV, HTLV and pulvovirus B19 by screening and testing; Exclusion of potential infection of CMV, EBV and WNV by testing; Clinical history; Experience of blood transfusion or implanting; genetic etc.)
- **Medical Records of the Donor**
- **Cell Banking**
- **Potential Presence of Viruses in Products**
- **Immunological Problems** (e.g., rejection, GVHD etc.)

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Suitability and Quality Control of Raw Materials and Manufacture-Related Substances other than Target Cells

- Culture media (all components: e.g., serum, GF, antibiotics, media products such as DMEM, RPMI)
- Feeder cells
- Materials used for processing of cells (e.g., all chemical reagents, proteins, genes, vectors)
- Materials used for formulation

- Indicate their appropriateness for their intended use, and if necessary establish their specifications.
- Perform proper quality control for these materials.
- Prevent contamination with bacteria, fungi, viruses, and prions from biological materials

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Establishment of Relevant Cell Lines, a Cell Bank and/or Critical Intermediate(s)

- The ideal base camp(s) in the sustainable manufacture of desired cell-based products are cell lines, cell bank and/or intermediate cell products/lines that have been well characterized; they should be stable per se but can propagate under relevant conditions; can be renewed; are ready to constant supply upon request; and can differentiate properly into target cells.
  - For certain final products, it may be more feasible for the consistent, safe manufacture of the desired products to establish sustainable intermediate cell products/lines at an intermediate stage of the mfg. process than to emphasize characterization, evaluation, or control of cells at the raw-material stage, which may be difficult to perform.

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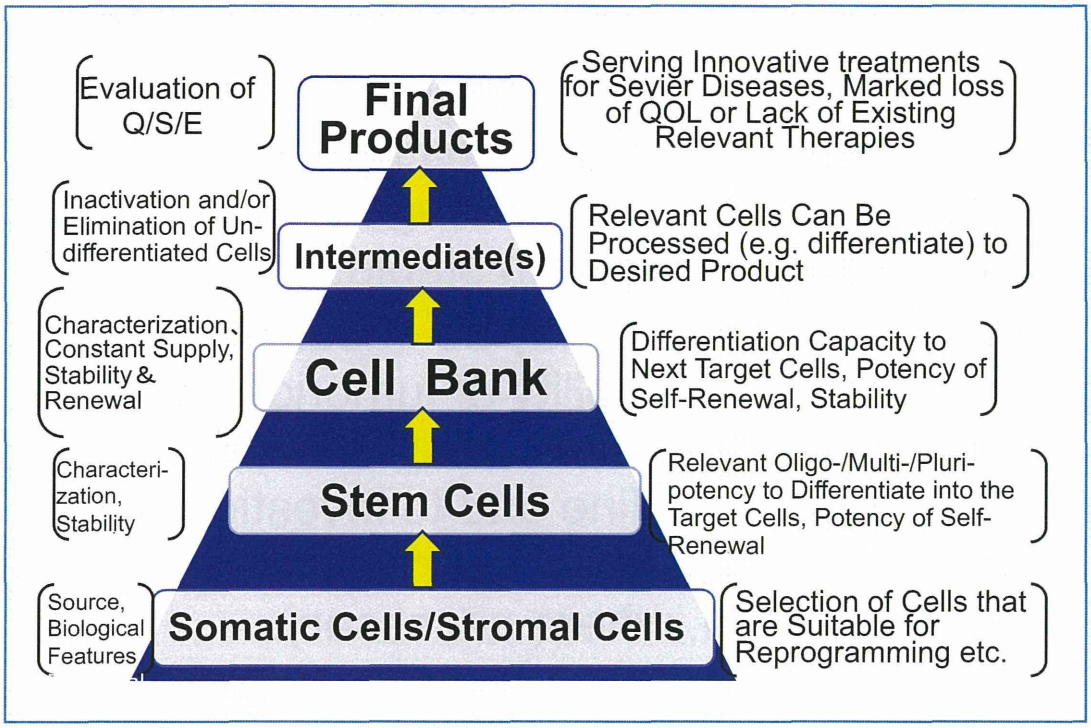

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Establishment of Relevant Cell Line (1)

- In general, for human cells of allogeneic origin, establish cell lines after having determined to the extent possible the genetic background of the donor and describe the method of establishment and its appropriateness to the extent possible.
- To ensure that the quality of the established cell line remains stable and consistent, identify the critical quality attributes (CQA) of the cells (e.g., cell purity, morphological features, phenotypic markers, karyotype, cell growth properties, and multi/pluripotency) and set acceptance criteria for them.