

Endeavour to
a Minimum Consensus Package
plus Case by Case Approaches for
Evaluating Human Cell Therapy Products

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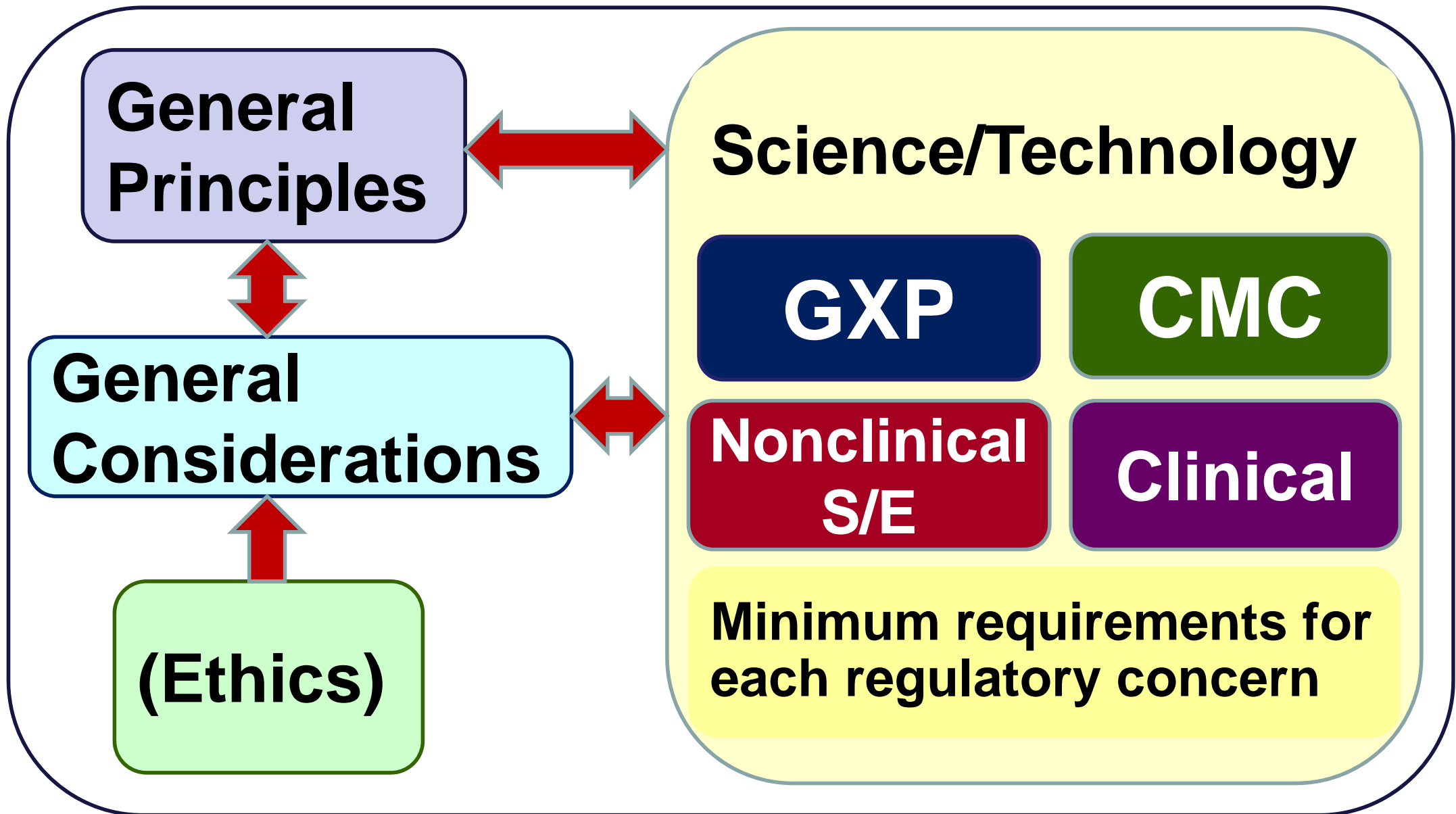
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To develop novel human cell therapy products (hCTPs) and translate them into appropriate therapies that contribute more to human health care, it is essential that all interested parties including basic and clinical researchers, industry, as well as regulators be on the same page based on scientific rationale by taking into account common scientific core elements, as well as the specifics of the therapy in question.

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, pre-clinical and clinical studies of all types of substantially manipulated hCTPs.

In other words, efforts should be made in order to develop a “minimum consensus package” that encompasses scientific principle/concepts, general considerations and technical requirements generally applicable to most hCTPs and that serves as a common platform for interested parties to work on.

Elements of Minimum Consensus Package



How to develop MCP

- Guidelines/Guidance
- Literatures
- Scientific forum to share a common recognition among interested parties
(Comprehensive and Extensive Information/Data)

Identify common core scientific and technological elements for CMC, nonclinical and clinical studies of all types of substantially manipulated hCTPs.

Develop a minimum consensus package(MCP) that encompasses scientific principle/concepts, general considerations and technical requirements commonly applicable to all hCTPs

Cell therapy can be promoted efficiently, effectively and reasonably, through the use of the Minimum Consensus Package + “Add-On Packages” for Individual Cases (by taking into account a product specific profile, the target disease, development stage, experiences with the use, among other factors.)

Researcher/Medical D.

Industry/MA Regulation

Clinical Use

Clinical Res.

Clinical Trial

Application



Basic Res.

Phase III

Review

GVP
GPSP

Phase II

Approval

Phase I

Clinical Res.

“Add-On” Package for Individual Cases

Minimum Consensus Package

(Common & Critical Elements/Standards/Tech for Every Products)

(All interested parties can use this as a common platform)

How MCP contribute to Development, Evaluation and Control of hCTPs

- Guidelines/Guidance
- Literatures
- Scientific forum to share a common recognition among interested parties
(Comprehensive and Extensive Information/Data)

“Minimum Consensus Package”
(MCP)

▪ Progress in Sciences/Technology
▪ Accumulation of Expertise in Regulatory Agency, Industry & Academia

MCP
+
“Add-on Package” in an individual case

“Add-on” elements by taking into account a product-specific profile, the target disease, development stage, and experience with the use, among other factors.

Promote Product Research and Development

Scientific rational, Efficient, and Effective Approach for Development, Evaluation and Control of hCTPs

Enhance Sound Scientific Regulation

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

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 the present paper all-inclusive and definitive
- Consequently, when testing and evaluating each product, it is necessary to adopt a flexible approach on a case-by-case basis, according to the rationale that reflects the scientific and technological advances at that point in time

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

- The main purpose of evaluating 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 the clinical findings and the QA
- Whether consistency of the QA can be ensured within a definite range

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.

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 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 application/registration to ensure quality and safety will be enriched and developed in line with the guidelines as the clinical trial progresses

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 an individual 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 guidelines.

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 evaluation that are appropriate for their own purpose and are scientifically valid.

Scientific and Technological Elements of MCP

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

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)

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

Donor selection criteria and eligibility:

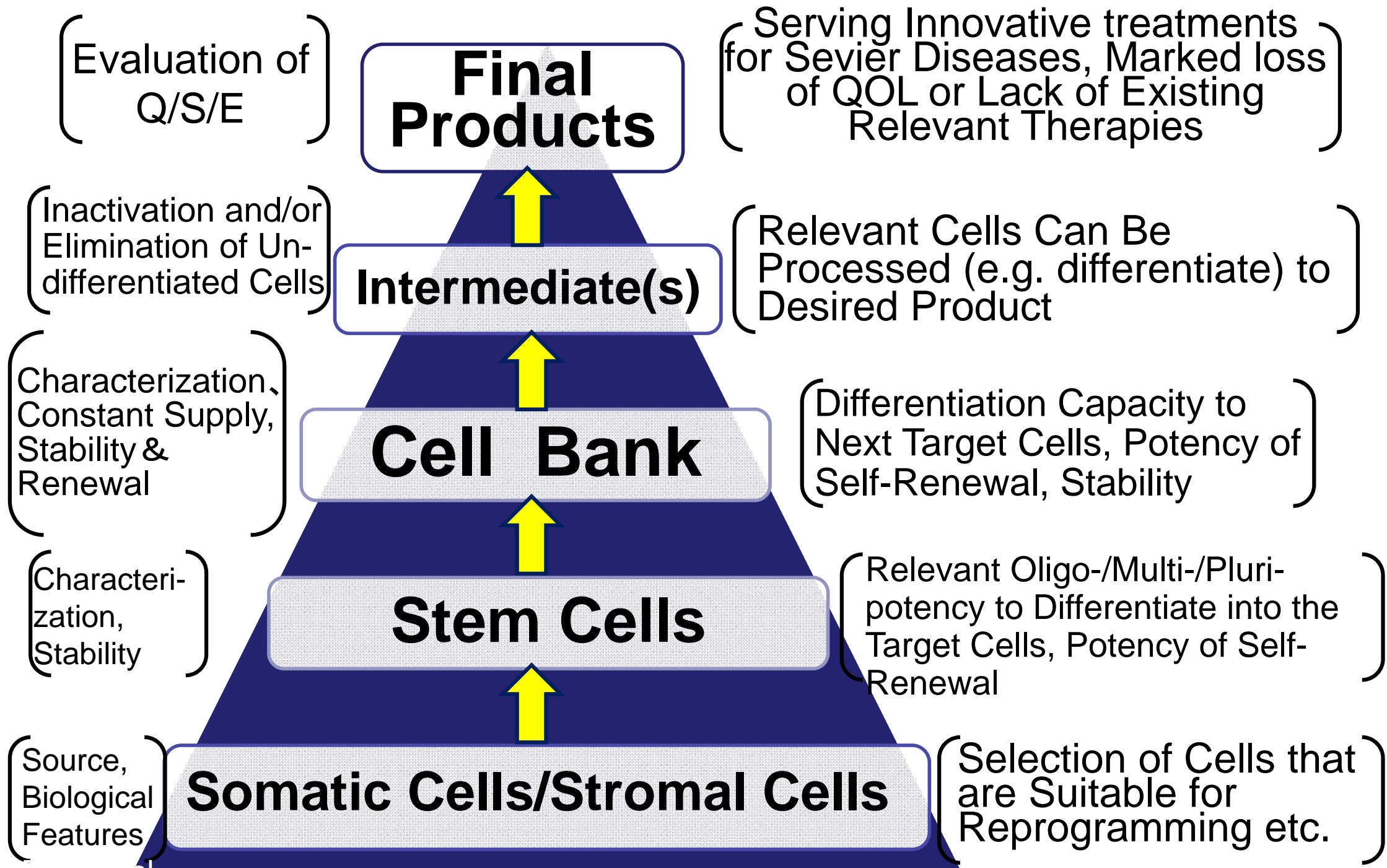
- Indicate that the donor was selected in an appropriate and ethical manner and that the proper procedure was followed.
- Establish selection criteria and eligibility criteria that take into consideration age, sex, ethnic characteristics, genetic characteristics, a clinical history, the health condition, 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.

Suitability and Quality Control of Raw Materials and Manufacture-Related Substances such as

- ❑ **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 the 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

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(s) and/or intermediate cell products/lines that have been well characterized; **They**
- should be stable per se but can propagate under appropriate conditions;
- can be renewed;
- are ready to constant supply upon request; and
- can differentiate into target cells.



Processing of Cells (1)

■ Processing of cells includes any processing of cells, such as 1) - 7) by means of 1) - 4) with the aim of preparing desired cell products to treat a patient or to repair or regenerate a tissue.

➤ 1) Propagation, 2) Reprogramming, 3) Direct reprogramming, and/or 4) Induction of differentiation of cells, 5) Production of a cell line, 6) Cell activation, or altering a biological characteristic as well as 7) Combination with an NCC

➤ 1) Cultivation, 2) Chemical, physical, and/or biochemical treatment(s), 3) Genetic engineering and/or 4) their combination, with the aim of preparing desired cell products to treat a patient or to repair or regenerate a tissue.

Processing of Cells (2)

- It is necessary to describe all important and relevant information concerning the cell processing employed. Provide individual technical details and explain the reason for using the said processing to obtain the target product from the mfg. perspective.
- So-called minimal manipulations are not considered “processing.”

Preparation of Desired Cell Products

- For preparation of desired cell products, describe the methods *via* which cells that serve as an active ingredient in the final product were prepared directly from a starting cell line or *via* an intermediate cell line derived from the starting cells.
- The methods to be described include any processing, isolation, and culture of the desired cells, and the media, culture conditions, culture period, and yields of the desired cells at each step.
- Describe to the extent possible the appropriateness of each method.

Formulation: Preparation of the Final Product

The form and packaging of the final product shall ensure the quality of the final product.

Characterization and Understanding of Specific Profiles of Cells at Critical Stages (1)

- Characterization and understanding of specific profiles of cells at critical stages (e.g., starting, bank, intermediate, and final stage) are essential.
- The content and extent of characterization of cells in question depend on each intended purpose, stage, quantitative limit on the sample, and reasonably available and applicable testing methods, and do not necessarily require the most stringent and extensive procedures.
- It is necessary to explain the appropriateness of the approach used.

Characterization and Understanding of Specific Profiles of Cells at Critical Stages (2)

Examples of Cell Characteristics may include:

- 1) Morphological characteristics,
- 2) Growth characteristics,
- 3) Biochemical markers,
- 4) Immunological markers,
- 5) Specific substances produced,
- 6) HLA typing (*allogenic*),
- 7) Other suitably chosen and appropriate Genotypic or Phenotypic indicators/markers,
- 8) Clinically useful stemness (*stem cells*),
- 9) Karyotype,
- 10) DNA fingerprinting,
- 11) Pluripotency (*iPS cells, ES cells*),
- 12) Differentiation potency,
- 13) Specific biological function;

Examples of Quality Attributes may include:

- 1) Contamination by non-target cells (Cell purity),
- 2) Cell viability,
- 3) Absence of unintended changes in cells cultured for duration beyond the proposed culture period,
- 4) Stability

Verification of a Mfg. Process and Constancy of Manufacture as well as Process Control(1)

- Describe in detail the mfg. method for minimal manipulation of cells/tissues and preparation of a characterized cell substrate that served as a raw material through the establishment of cell lines, cell banks, and/or critical intermediate cell products (if any), differentiated cells, and the final product.
- Describe the technical details of the process and necessary process control and product quality control.

Verification of a Mfg. Process and Constancy of Manufacture as well as Process Control(2)

- Verify, to the extent possible, the validity of the mfg. method and the technology employed in order to maintain constancy of manufacture and thereby consistency of the quality of the product from the mfg perspective.
- Note that quality, safety, and consistency are ensured by mutual complementary measures throughout the mfg.
- Note that the measures be rational and that they serve the intended purpose.

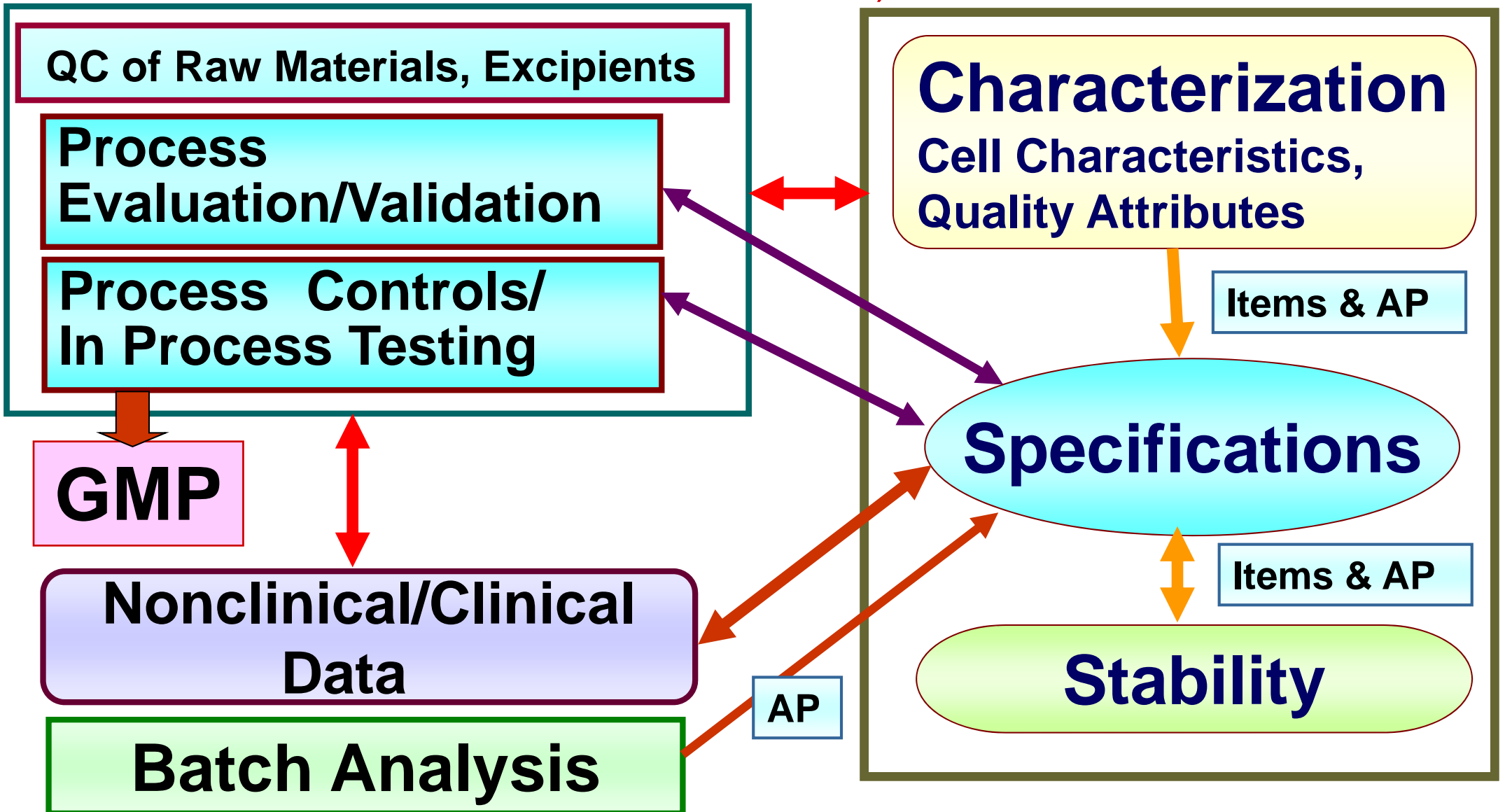
Quality Control of Final Products according to Product Aspects and Process Aspects

The overall quality control strategy of cell-based products includes:

- 1) Specifications (*a set of acceptance criteria and analytical procedures*) for the final products
- 2) Quality control of raw materials
- 3) Verification of the validity of the mfg. process
- 4) Maintenance of consistency, and
- 5) Proper quality control of intermediate products if any

Elements for Ensuring Product Quality and Consistency

Process (↔) **Product**



Specifications for the Final Product (1)

Specifications will differ among final products, depending upon the type and properties of the desired cells and tissues, mfg methods, intended clinical use, the mode of administration of each product, stability, and test methods available.

These differences shall be taken into consideration when setting the acceptance criteria and test procedures.

Specifications for the Final Product (2)

When setting specifications for an individual final product, it may be necessary to refer to the quality control parameters and tests shown below. It should be noted that they are just examples, and it is necessary to provide the rationale for these specifications.

- The Cell number and cell viability
- Tests of Identity
- Tests of Purity
- Tests for cell-derived undesirable physiologically active substances
- Tests for process-related impurities
- Sterility tests and tests for mycoplasma
- Endotoxin tests
- Virus tests
- Specific biological activity tests
- Potency tests
- Mechanical compatibility tests

Product Stability

- Taking into consideration the storage and distribution periods and the storage form, test the cell viability, and other characteristics of hCTPs, and/or critical intermediate products to establish storage methods and an expiration date. Explain their appropriateness.
- When product storage and use involves freezing and thawing, confirm that the freezing and thawing processes do not affect the stability or acceptance criteria of the product.
- Where necessary and possible, it is recommended to conduct stability studies on the products whose mfg. period or storage period exceeds normal periods in order to confirm to the extent possible the limits of stability. This does not apply if a product will be used immediately after its production.

Establishing the Storage and Transport Procedure for Cells/Products at Critical Steps

If cells, an intermediate product, or a final product needs to be stored and transported, the storage procedure and duration, the containers for the transport, and the transportation procedure (e.g., temperature control) shall be set and their appropriateness explained.

Comparability Assessment after Changes in a Mfg. Process (1)

If the mfg. process is altered at some point during development, and if test results that were obtained using products manufactured before the change in mfg. method are to be used in the application for clinical-trial or regulatory approval, it is necessary to demonstrate that the products manufactured before and after the change in the mfg. process are comparable.

Preclinical Safety Testing of hCTPs (1)

- Relevant animal tests and/or in vitro tests may be performed to elucidate concerns about the safety of a hCTP when it is scientifically reasonable and technically possible.
- For non-cellular constituents and process-related impurities, safety concerns should be addressed as much as possible by physicochemical analyses not by animal testing.

Preclinical Safety Testing of hCTPs (2)

- Conduct necessary and appropriate tests, taking into account the characteristics of the product and intended clinical use and evaluate and discuss the results in a comprehensive manner.

Preclinical Safety Testing of hCTPs (3)

- Transformations other than those intended and abnormal proliferation of non-target cells, which may have occurred during the manufacturing process may be safety concerns.
- For pluripotent stem cell derived products, the presence of undifferentiated cells in the final product and their potential to cause ectopic tissue formation, tumorigenicity, or malignant transformation may be safety concerns.

Preclinical Safety Testing of hCTPs (4)

- Compliance with GLP requirements may not be possible or feasible for some toxicology assessments. However, toxicology nonclinical studies should be in substantial compliance with GLP and deviations should be described and justified.
- The principles of Reduction, Refinement, and Replacement of Animal Use (the “3Rs”) should be considered during the development of a nonclinical program for a hCTP.

Nonclinical Studies Supporting the Potency or Efficacy of hCTPs

- A well-designed study using experimental animals and/or cells should be performed in order to demonstrate the functional expression, sustainability of an effect, and/or anticipated clinical efficacy (POC) of a hCTP to the scientifically reasonable and technically possible extent.

Pharmacokinetics/Biodistribution of hCTPs (1)

Pharmacokinetic studies of the internal behavior of cells/tissues that constitute the final products or expression products of transgenes (these studies may include absorption and distribution in experimental animals), should be performed to the technically possible and scientifically reasonable extent.

Clinical Trials (1)

- An investigational clinical trials can initiate after determination that there has been no quality or safety problems exist that might pose an obstacle to initiation of human clinical trials, taking into consideration the product's usefulness with reference to the study design.
- It is also important to entrust the patient with the right to make a decision after receiving all of the available information, including all information on identified/ presumed risks and anticipated benefits.

Clinical Trials (2)

- Clinical trials should have an appropriate study design and specified endpoints. They should be designed based on the desired cells/tissues, target disease, and method of application.
 - Target disease
 - Target subjects and patients who should be excluded as participants
 - Details of the therapy to be performed on the subjects, including the application of hCTPs and drugs used concomitantly, if any.
 - Appropriateness of conducting the clinical trials in light of existing therapeutic methods
 - Plan for explaining the clinical trial to the patients, including the currently known risks and benefits of the product

Clinical Trials (3)

- For early-phase clinical trials, especially first-in-human trials, the primary objective should be an evaluation of safety.
- The trial objectives may focus on characterizing the safety profile of the feasible dose or doses, rather than finding the maximum tolerated dose (MTD).
- A common secondary objective is to obtain preliminary assessments of product activity, using either short-term responses or longer-term outcomes that could suggest a potential for efficacy.
- Choice of the subjects to include in the trial depends on the expected risks and potential benefits, recognizing that there will be considerable uncertainty about those expectations in an early-phase trial.

Clinical use after marketing authorization

At the stage of clinical use after marketing authorization, major points to consider may include:

- 1) Quality control and maintaining consistency of the products intended for clinical use by means of specifications and good mfg. practices, and
- 2) Postmarketing surveillance

Monitoring and Follow-up (1)

- In addition to general tests and monitoring to look for unanticipated safety issues, evaluations might include:
 - Acute or delayed infusion reactions
 - Immune response to the product; Autoimmunity; Graft failure; GVHD
 - New malignancies,
 - Transmission of infectious agents from a donor, and viral reactivation.
- Attempts should be made to determine the duration of persistence of the product and its activity.
- The potential for migration from the target site, ectopic tissue formation, or other abnormal cell activity should be addressed.

Monitoring and Follow-up (2)

- In general, the duration of monitoring for adverse events should be designed to cover the time during which the product might reasonably be thought to present safety concerns.
- The appropriate duration of follow-up depends on:
 - Results of preclinical studies
 - Experience with related products
 - Knowledge of the disease process, and
 - Other scientific information.

The overall concept is that cell therapy can be promoted efficiently, effectively and reasonably through the use of such a “Minimum Consensus Package” + “Add-on Packages” for individual cases.