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

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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).

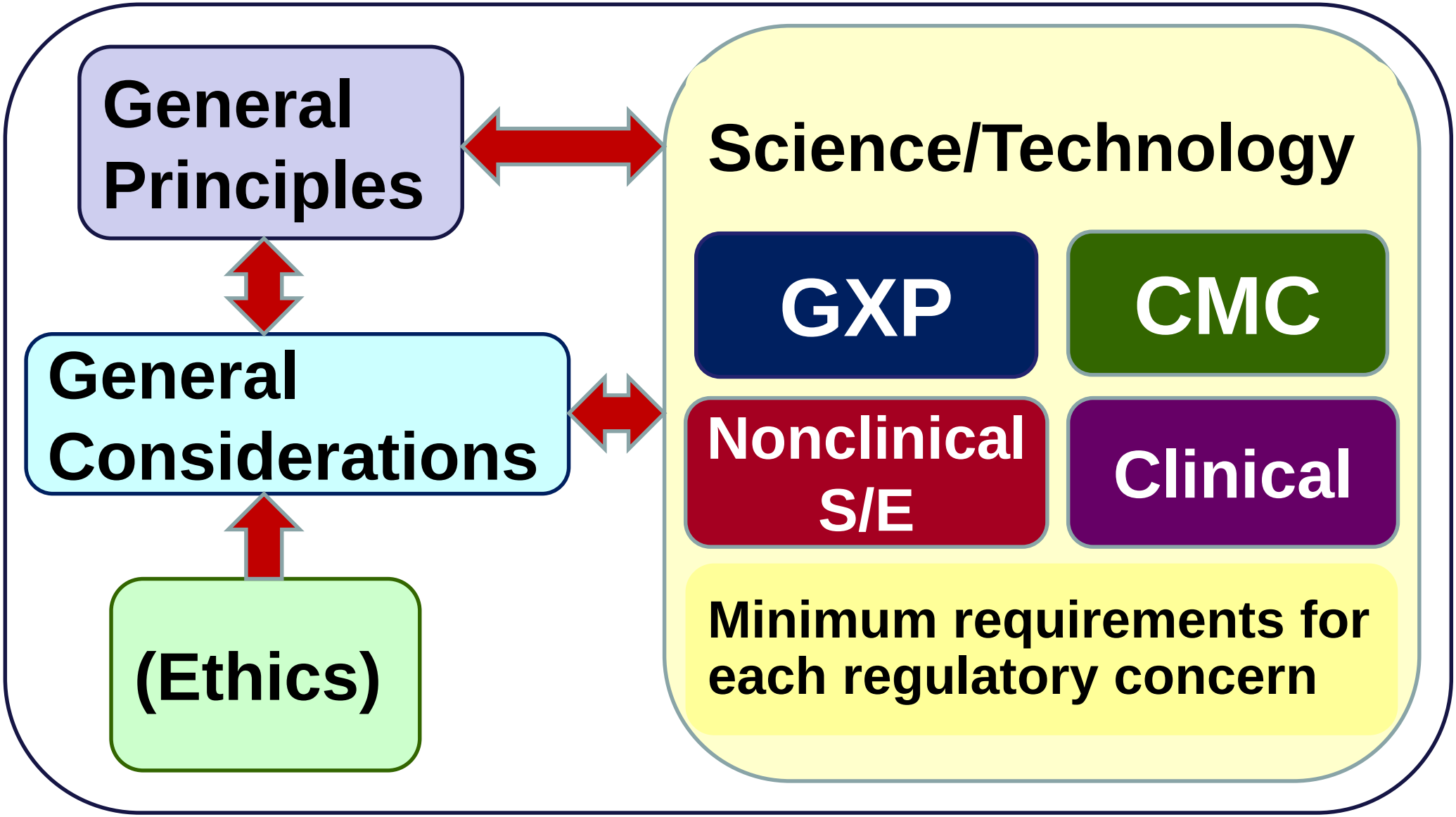
To develop novel hCTPs and to translate them more efficiently and effectively into products that contribute more to human health care, it is essential that they be based on a sound scientific rationale.

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.

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.

Elements of Minimum Consensus Package



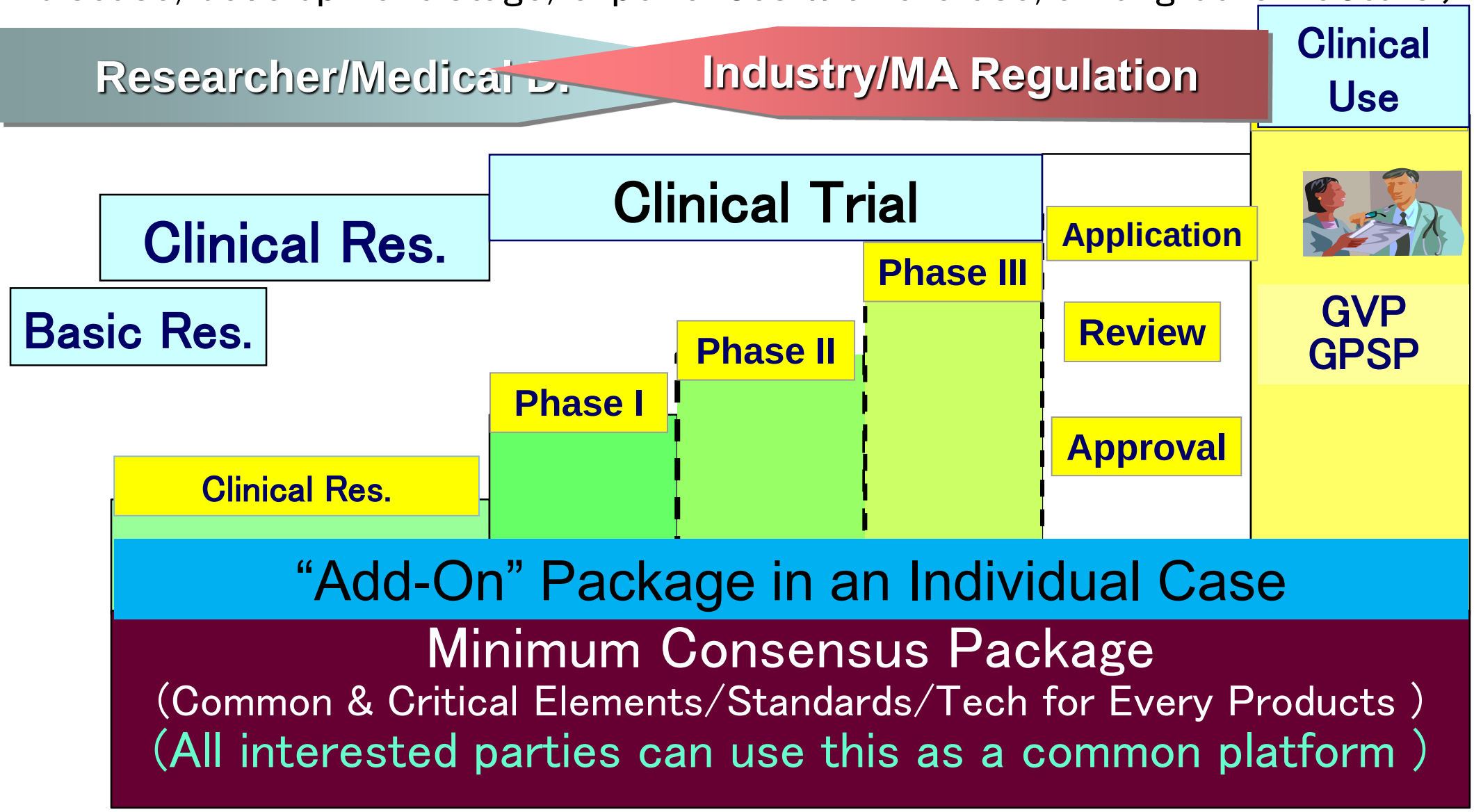
How to develop MCP

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

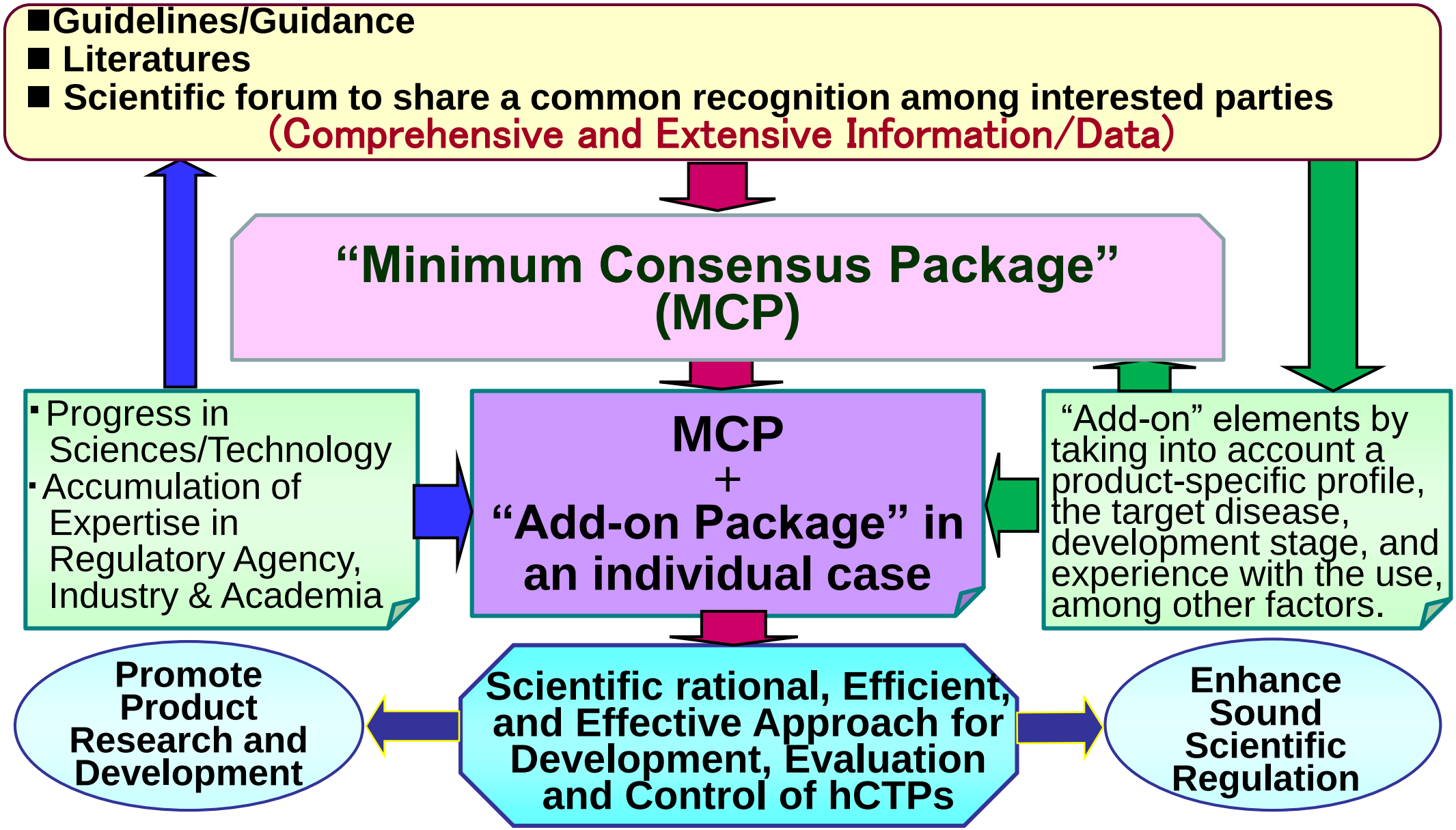
Identify common core scientific and technological elements for CMC, nonclinical and clinical studies **of all types of** substantially manipulated **hCTPs**.

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 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.)



How MCP contribute to Development, Evaluation and Control of hCTPs



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 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

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

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 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

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.

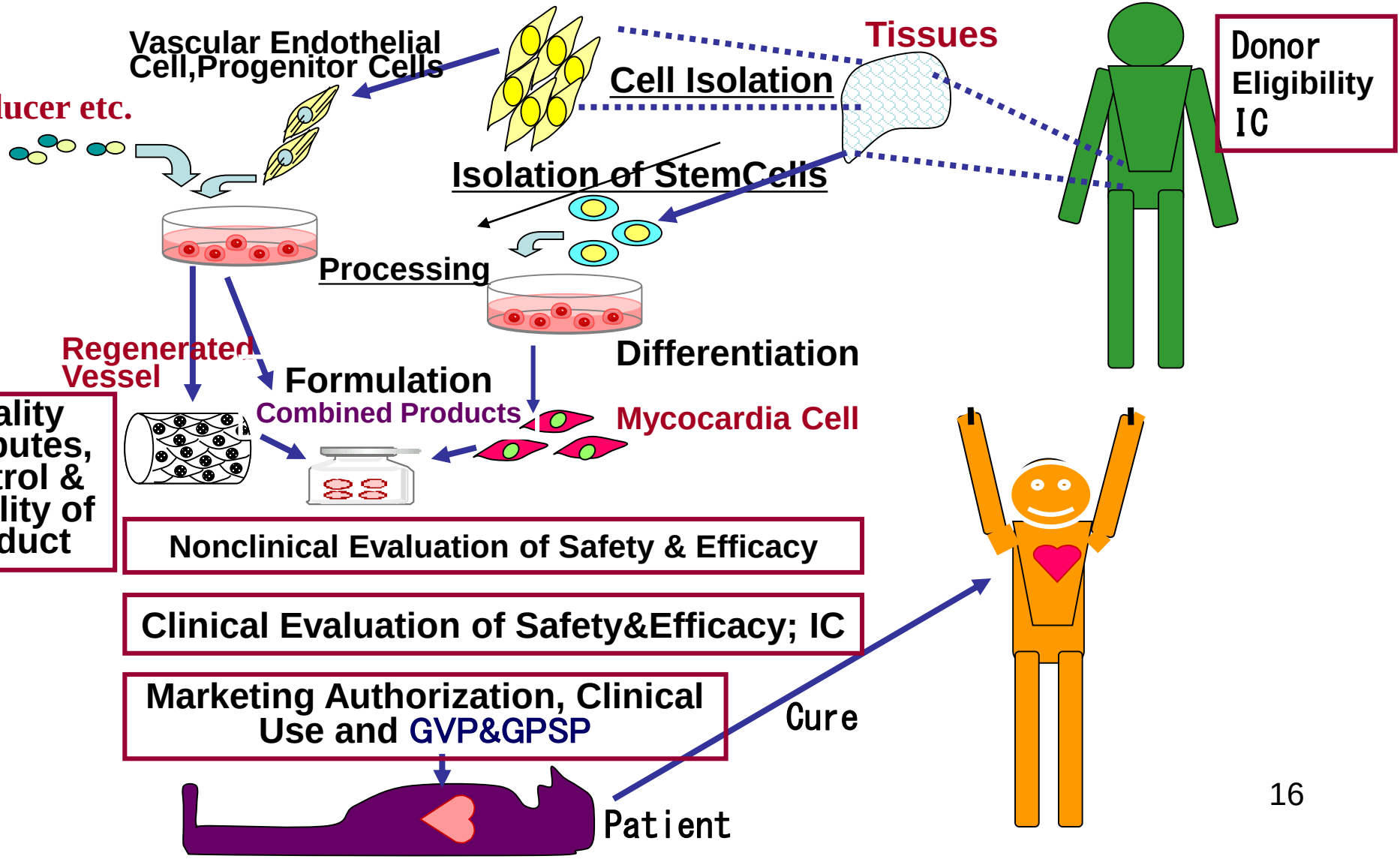
General Consideration on Sound Scientific Requirements for Product Development, Evaluation and Control (6)

- 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.

Development, Evaluation and Control of hCTPs

Characterization and Understanding of Specific Profiles of Cells at Critical Steps of Manufacture and Their Eligibility, Eligibility of Other Raw Materials and Manufacture-Related Substances and Their Quality Control

Verification of Mfg Process & Constancy of Manufacture



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.

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.)

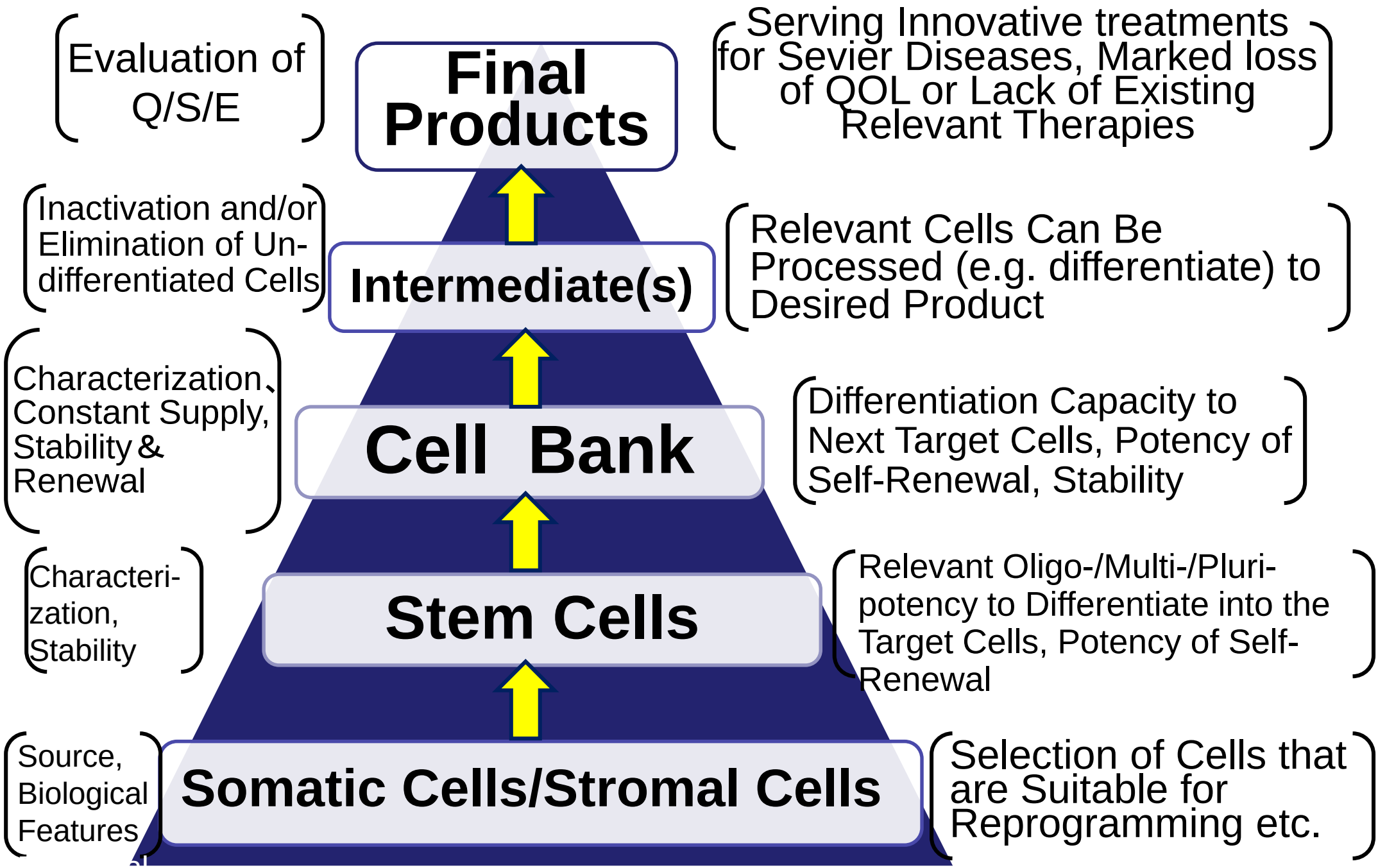
Suitability and Quality Control of Raw Materials and Manufacture-Related Substances other than Target Cells

- 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

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.


Evaluation of Q/S/E
Final Products
Serving Innovative treatments for Sevier Diseases, Marked loss of QOL or Lack of Existing Relevant Therapies
Inactivation and/or Elimination of Un-differentiated Cells
Intermediate(s)
Relevant Cells Can Be Processed (e.g. differentiate) to Desired Product
Characterization、Constant Supply, Stability & Renewal
Cell Bank
Differentiation Capacity to Next Target Cells, Potency of Self-Renewal, Stability
Characteri-zation, Stability
Stem Cells
Relevant Oligo-/Multi-/Pluri-potency to Differentiate into the Target Cells, Potency of Self-Renewal
Source, Biological Features
Somatic Cells/Stromal Cells
Selection of Cells that are Suitable for Reprogramming etc.

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.

Establishment of Relevant Cell Line (2)

- It is necessary to demonstrate the maximal number of passages within which the cells remain stable.
- In some cases, it may be important to discuss the possibility of tumorigenicity and malignant transformation of an established cell line and to investigate such a possibility using an appropriate animal model, where necessary.

Establishment of Cell Banks (1)

- When a cell bank is established at any stage during manufacture of hCTPs, describe
  1) The rationale for preparing the cell banks;
  2) The methods used to prepare the cell banks;
  3) The characteristics of the cell banks; and
  4) The storage, maintenance, control methods, and
  5) Renewal methods as well as any other processes and tests performed.
- Explain the appropriateness of each.

Establishment of Critical Intermediate Cell Lines(1)

- It should be noted that in some cases, the establishment of a cell line (intermediate cell line) as an intermediate product may be important for the stable manufacture of a safe final product and for scientific validity of the procedure. When such a measure is chosen, explain its advantages and appropriateness.
- If a cell line that exhibits a different phenotype is established in stages, describe the methods (e.g., methods for induction of differentiation, isolation, culturing, and cell line establishment of the target cells as well as the media, culture conditions, culture duration, and the yield at each stage) until establishment of each respective cell line, and explain their appropriateness to the extent possible.

Establishment of Critical Intermediate Cell Lines(2)

- To maintain stability and consistency of the quality of the intermediate cell lines, identify CQA of the cells and set acceptance criteria.

  (**CQA**: e.g., cell purity, morphological features, phenotype-specific markers, karyotype, cell growth properties, and multi/pluripotency)

- It is important to demonstrate the maximal number of passages or of cell divisions within which the cells can proliferate while maintaining their quality in terms of the criteria specified.

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 (described later) are not considered "processing."

Minimal Manipulations & Manufacture

- “Minimal manipulations” are defined as isolation of a tissue, homogenization of a tissue, separation of cells, isolation of a specific cell, treatment with antibiotics, washing, sterilization by gamma-irradiation or other methods, freezing, thawing, and other procedures that do not change the original properties of the cells or tissues.
- “Manufacture” : Actions undertaken up until the final product is released to market. This includes: Processing of Cells and Minimal Manipulations.

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 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:

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:

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 mfg. process and constancy of manufacture as well as process control(2)

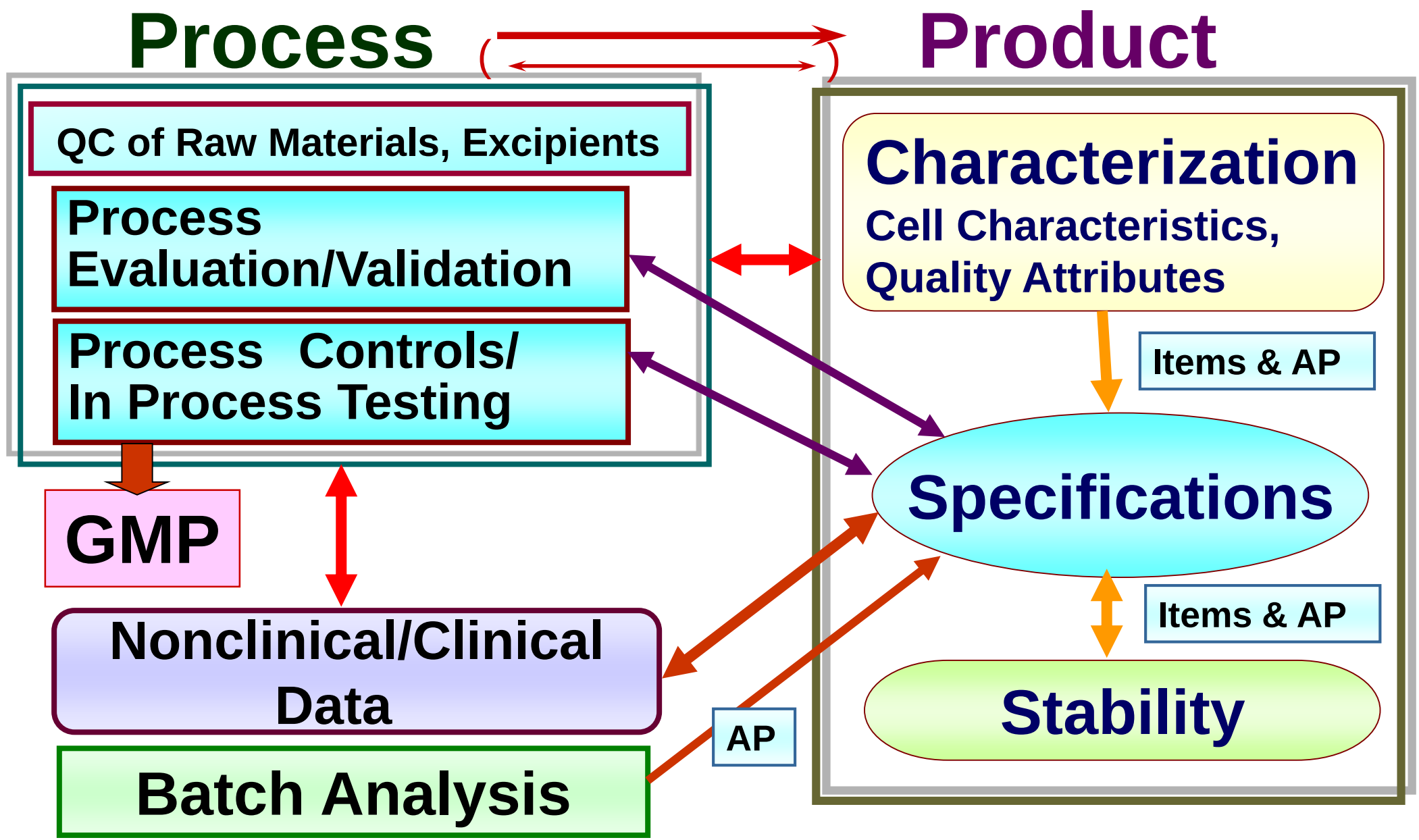
- Verify, to the extent possible, the validity of the mfg. method and the technology employed in order to maintain constancy of manufacture and thereby consistency of the quality of the product from the mfg perspective.
- Note that quality, safety, and consistency are ensured by mutual complementary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



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 (3)

- The purpose of the assessment at the initiation of clinical trials is to confirm that the product in question is unlikely to pose significant Q/S problems during investigational clinical trials.
- Therefore, it is possible to set provisional specifications with allowance for some variation on the basis of measurements performed on a few test specimens, as long as one can be certain of the relationship between the results of clinical tests and the quality attributes after the clinical trials.
- However, testing for sterility and the absence of mycoplasma is essential.
- It should be noted that the quality control strategy including specification should be enriched and developed along with the progress of clinical trials.

Specifications for the final product (4)

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, (potency) 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.

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.

Comparability assessment after changes in a mfg. process (2)

Subjects to Change:

- Cell substrates, other raw materials and manufacture-related substances (source, preparation methods and even type)
- Culture conditions
- Processing methods
- Formulation
- Storage and/or transportation methods

Criteria:

- Old Products *vs* New Products
- How to assess comparability in terms of Q/S/E

Comparability assessment after changes in a mfg. process (3)

- Because there are a number of variations in the content, extent, and type of a comparability test of an individual product and in a specific case, it is difficult to devise technical guidance that is applicable to all situations.
- The design of comparability studies and evaluation of the results should be focused on the comparison of new products with old products in terms of safety, efficacy, or/and quality on a case-by-case basis.

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.

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 animal testing.

Preclinical Safety Testing of hCTPs (2)

- In the case of puluripotent 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 are safety concerns.
  - To reduce the risk of contamination with such cells as much as possible via thorough analysis at the cell bank and/or at an intermediate-product stage or by developing and utilizing methods that effectively separate, remove, and/or inactivate these contaminating undifferentiated cells from the target cells during the mfg. process.
  - The administration route for the target cells may be selected to aid in the minimization of the safety risks.
  - It may be simple but useful to demonstrate that transformations other than those intended and abnormal proliferation of non-target cells have not occurred, for cells expanded beyond the limit set for routine cultivation.

Preclinical Safety Testing of hCTPs (3)

- Animal testing of products of human origin does not always yield meaningful results. Thus, there may be a scientific rationale for preparing product models of animal origin and testing on appropriate experimental animals if more useful information may be obtained. In such a case, consider conducting tests on suitable animal models for each target disease.
  - However, because the use of identical procedures in nonhuman animals will not necessarily yield cell groups that possess characteristics identical to those of cells that constitute a hCTP and because a product of animal cell origin that was manufactured using identical processing, including culture conditions, will not necessarily be comparable to a hCTP, careful feasibility studies are required beforehand when adopting, conducting, and evaluating such studies. When conducting animal experiments using an animal model product obtained from nonhuman animal species, explain the suitability of the extrapolation.

Preclinical Safety Testing of hCTPs (4)

- Depending on the case, consider test systems that employ cells and clearly explain the appropriateness of the test system when conducting tests using this kind of approach.
- 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 (5)

- 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.
- For transgenic cells, demonstrate expression efficiency, sustainability of expression, and biological activity of desired products of the (trans)gene and discuss the feasibility of the anticipated clinical efficacy (POC) of the hCTP in question.
- Where appropriate models of products derived from processing of animal cells and/or animal models of a disease are available, use them to study the potential therapeutic efficacy of the product.

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.

- These studies are expected to estimate the survival of cells/tissues administered to patients and the duration of their effects and to determine whether the intended efficacy is successfully achieved.

Pharmacokinetics/Biodistribution of hCTPs (2)

- Clarify, using animal studies, the rationale for the administration method for the hCTPs.
- It is assumed that local administration is preferable to systemic administration.
  - However, if the benefits to patients can be explained in a rational manner, it is acceptable to use systemic administration.
- An administration method that minimizes distribution of a hCTP to organs other than the target organ is preferred.
- When the cells or tissues are directly applied or alternatively targeted to a specified site where they can be expected to perform their actions, clarify the localization, and discuss the effect of the localization on the efficacy and safety of the product.

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 presumed risks and anticipated potential 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 the results of preclinical studies, experience with related products, knowledge of the disease process, and other scientific information.

- In this presentation, the concept and scientific elements of a minimum consensus package plus the case by case approach for hCTPs for product development, evaluation, and control have been overviewed.
- Subsequent sessions (Sessions 3-6) will address in detail: 1) specific points to consider for the evaluation and control of hCTPs that are different from those of traditional biological/biotechnological protein products; and 2) identification of specific point/issues for a specific type of product, as well as very critical points/issues for various types of products.

The overall concept is that cell therapy can be advanced efficiently, effectively and reasonably through the use of such a “Minimum Consensus Package” + “Add-on Package” in an individual case.