Specification and Process Control

Yoshiaki Maruyama, Ph.D.
Review Director,
Office of Cellular and Tissue-based Products
PMDA, Japan

Disclaimer:
The views and opinions expressed in this presentation are those of the presenter and should not necessarily represent the views and opinions of the PMDA.

Outline

- General Consideration
- Specific Points to Consider for hCTPs

Outline

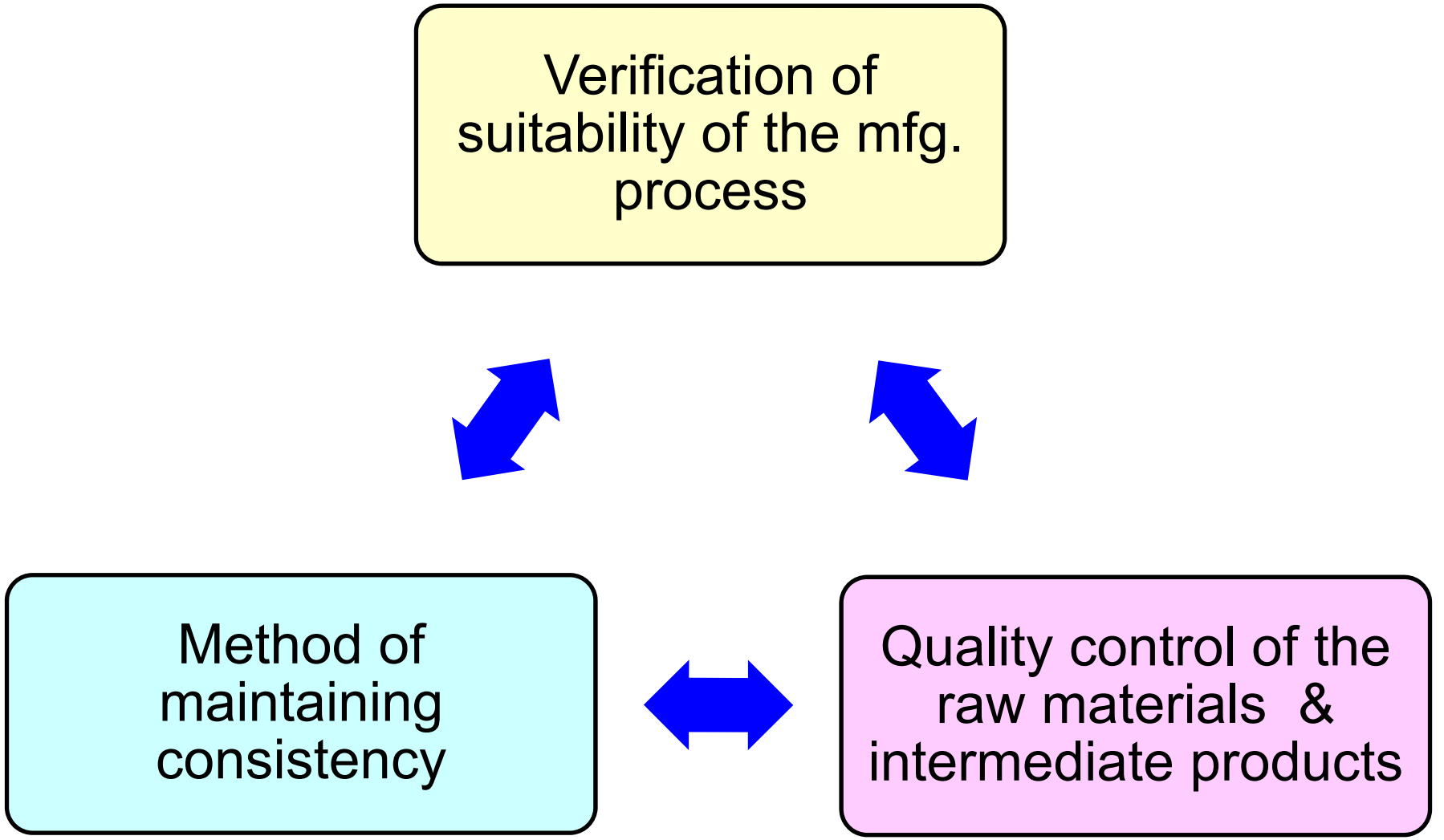
- General Consideration
- Specific Points to Consider for hCTPs

Specifications

Can be established and used for :

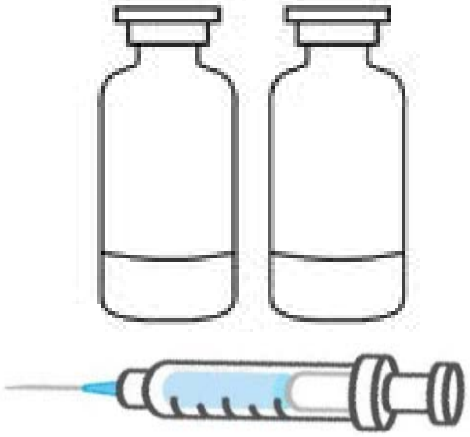
- Quality control of materials, drug substance and intermediate
- The release of the final products
- Verification of the validity of the manufacturing process
- Maintenance of consistency
- Stability testing

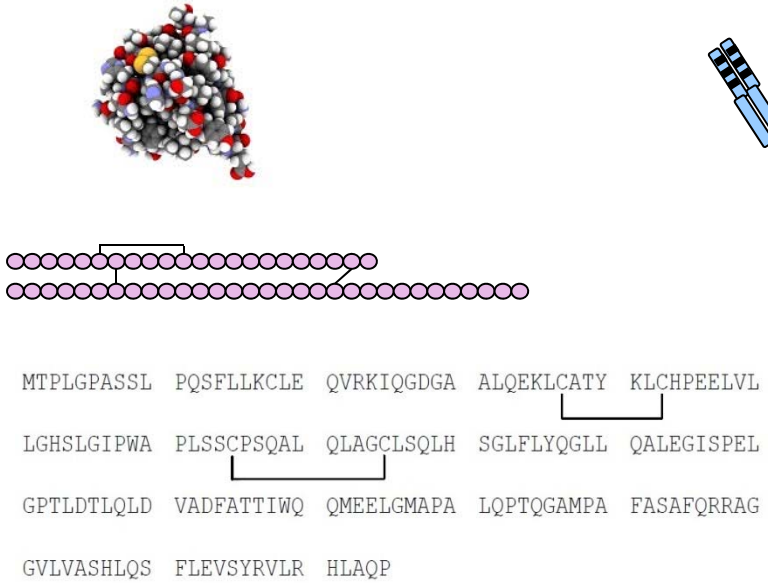
Specifications of the Final Product

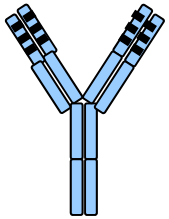


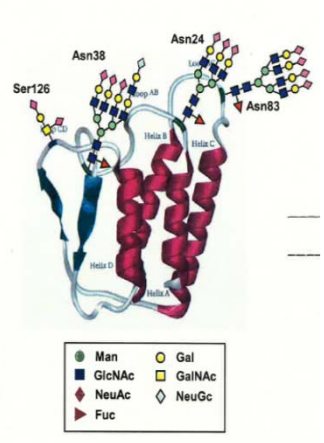
Justification of the Specification

The manufacturer should provide the rationale and justification for including and/or excluding testing for specific quality attributes.









Outline

- General Consideration
- Specific Points to Consider for hCTPs

Outline

- General Consideration
- Specific Points to Consider for hCTPs

Ref. Japan Tissue Engineering Co., Ltd. (J-TEC), HP

http://www.jcrpharm.co.jp/news/20151126_3991

http://www.mhlw.go.jp/stf/shingi2/0000104129.html

Guidelines on Quality for Biological Products

- Q5A; Viral safety evaluation of biotechnology products derived from cell lines on human or animal origin
- Q5B; Analysis of the expression construct in cells used for production of R-DNA derived protein products
- Q5C; Stability testing of biotechnological/biological products
- Q5D; Derivation and characterization of cell substrates used for production of biotechnological/biological products
- Q5E; Comparability of biotechnological/biological products subject to changes in their manufacturing process

- Q6B; Specifications: Test procedures and acceptance criteria for biotechnological/biological products

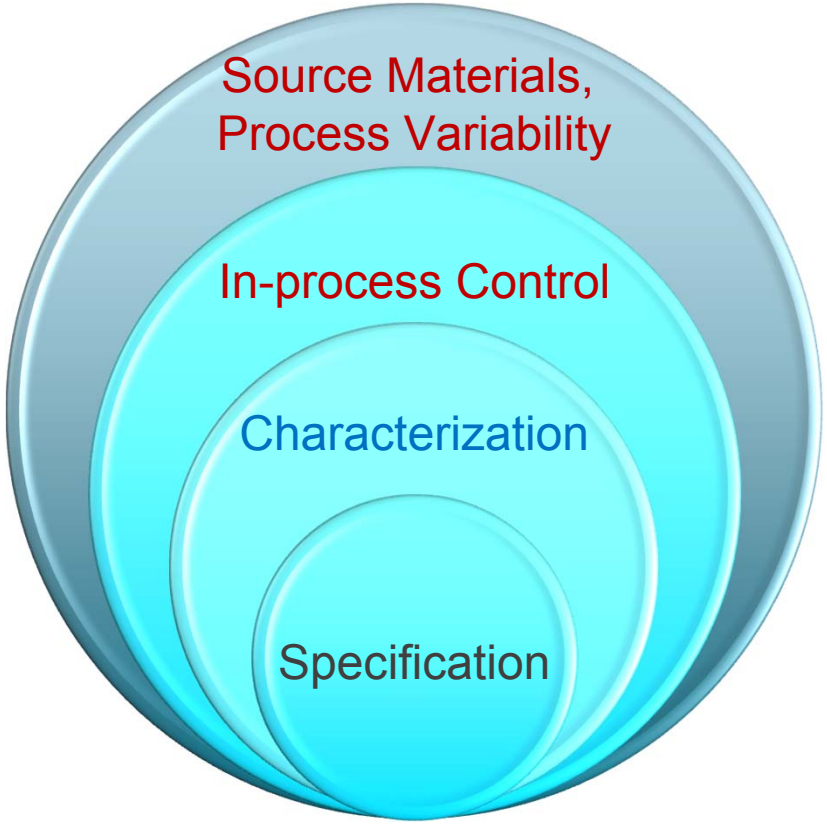
Differences between Cells and Proteins

- Live cells
- Heterogeneity, lot-to-lot quality consistency
- Variability of test methods
- Difficulty in identifying quality attributes to describe product efficacy and safety

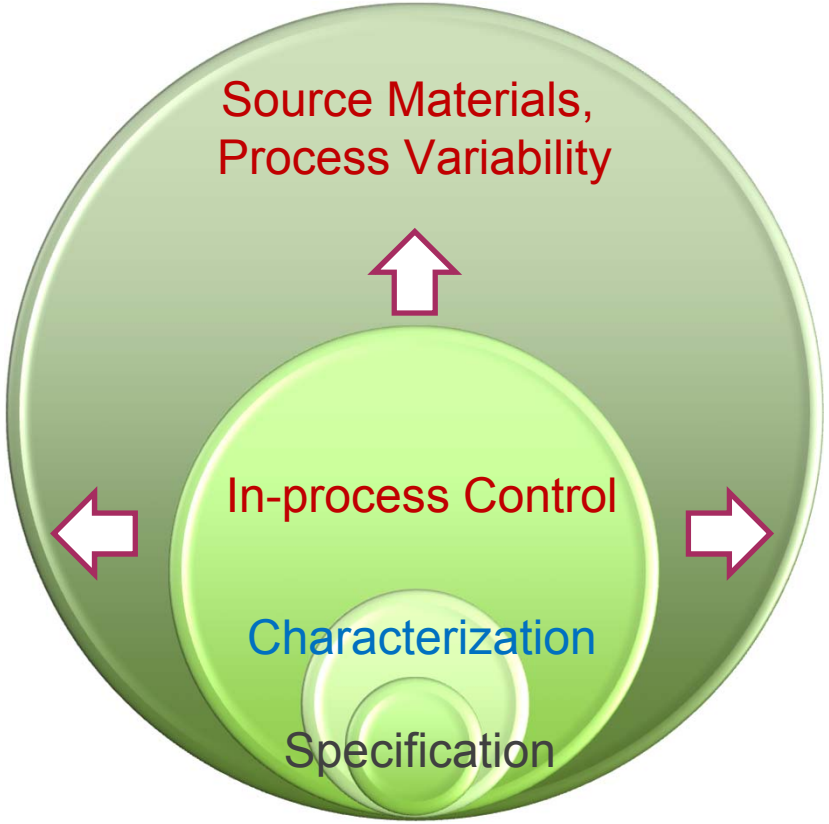
Setting specification for hCTPs would be different from those of traditional biotechnological/biological products.

Quality Concept of hCTPs

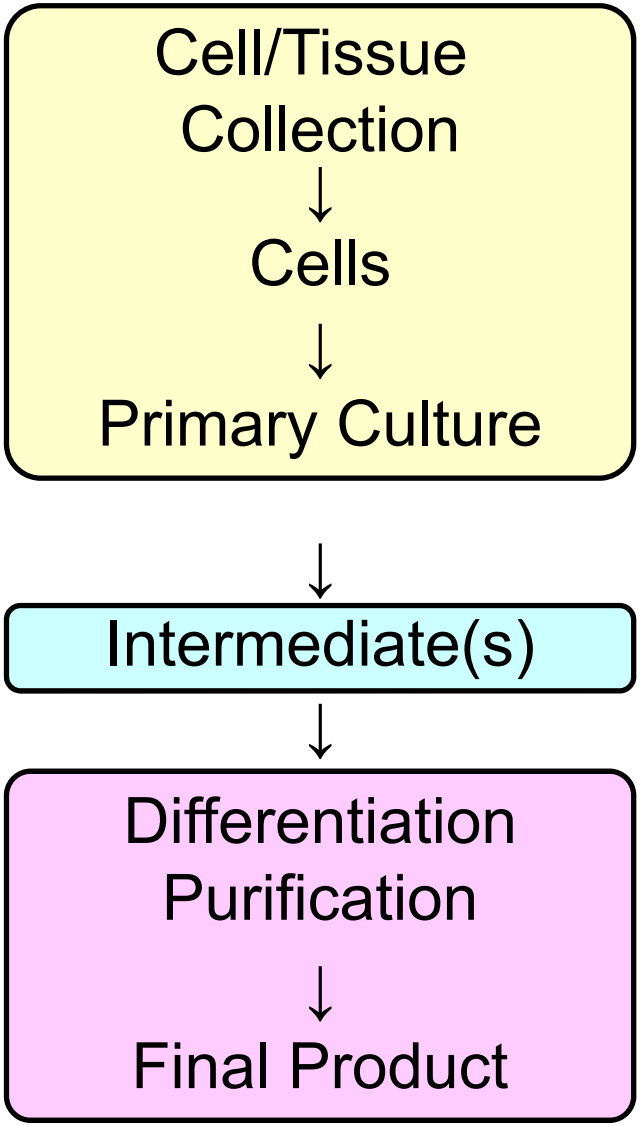
Biotechnological/biological products



hCTPs



Understanding of Process



The quality of the product is verified by meeting properties defined in the specifications by

(1) Controlling the variability of raw materials and manufacturing process, through in-process control and intermediate product testing.

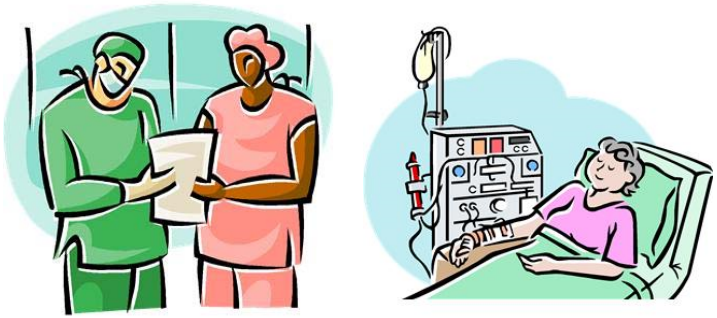
(2) Conducting characterization in advance to find the quality attributes and the variability of the product manufactured through the controlled manufacturing process.

Quality System in Manufacturing and Quality Control

- The validation can be insufficient to assure quality during the early stage of development.
- It is critical to ensure quality assurance by developing a flexible control strategy, which is scientific and based on the quality risk, for each stage of development.
- Verification and other methods should be appropriately utilized.

Specific Features of hCTPs Specifications

- Specifications for hCTPs are well linked to clinical procedures.
- Medical specialists engage at critical stages of cell therapy relying on institution and doctors.
- Medical translation can be taken into considerations when setting specification of the final product of hCTPs.



Specifications for the Final Products

Specifications	
Identification	Biochemical markers, immunological markers, characteristic products, and other appropriate genotypes or phenotypes of the intended target cells and tissues
Purity	Undifferentiated cells, cells exhibiting abnormal growth, transformed cells, contaminating cells
Tests for process-related impurities	Raw materials, non-cellular components, media ingredients (including feeder cells), chemical reagents, or any other process-related materials
Tests for cell-derived undesirable physiologically active substances	
Sterility tests, Tests for the presence of mycoplasma, Endotoxin tests, Virus tests	
Potency tests, Specific biological tests	Secretion of a specific physiologically-active substance from the cell, specific (quantitative or qualitative) biological testing that takes into account the cell type
Mechanical compatibility tests	
Assay	Cell number and cell viability

Specifications for the Final Products

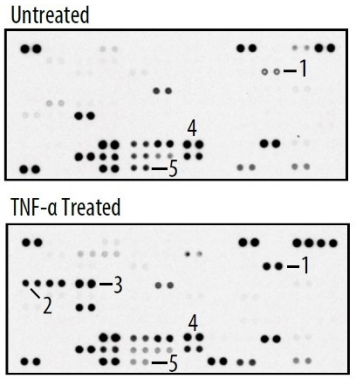
Specifications	
Identification	Biochemical markers, immunological markers, characteristic products, and other appropriate genotypes or phenotypes of the intended target cells and tissues
Purity	Undifferentiated cells, cells exhibiting abnormal growth, transformed cells, contaminating cells
Tests for process-related impurities	Raw materials, non-cellular components, media ingredients (including feeder cells), chemical reagents, or any other process-related materials
Tests for cell-derived undesirable physiologically active substances	
Sterility tests, Tests for the presence of mycoplasma, Endotoxin tests, Virus tests	
Potency tests, Specific biological tests	Secretion of a specific physiologically-active substance from the cell, specific (quantitative or qualitative) biological testing that takes into account the cell type
Mechanical compatibility tests	
Assay	Cell number and cell viability

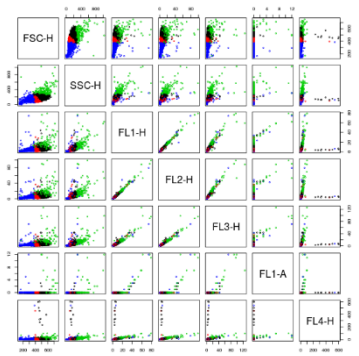
Potency Assay (1)

- Potency support prediction of efficacy of product.
- If the secretion of a specific physiologically active substance from the cells or tissues is responsible for the efficacy or the essential effect of a product during its intended use, establish test parameters and/or acceptance criteria related to this substance in order to demonstrate the intended effect.

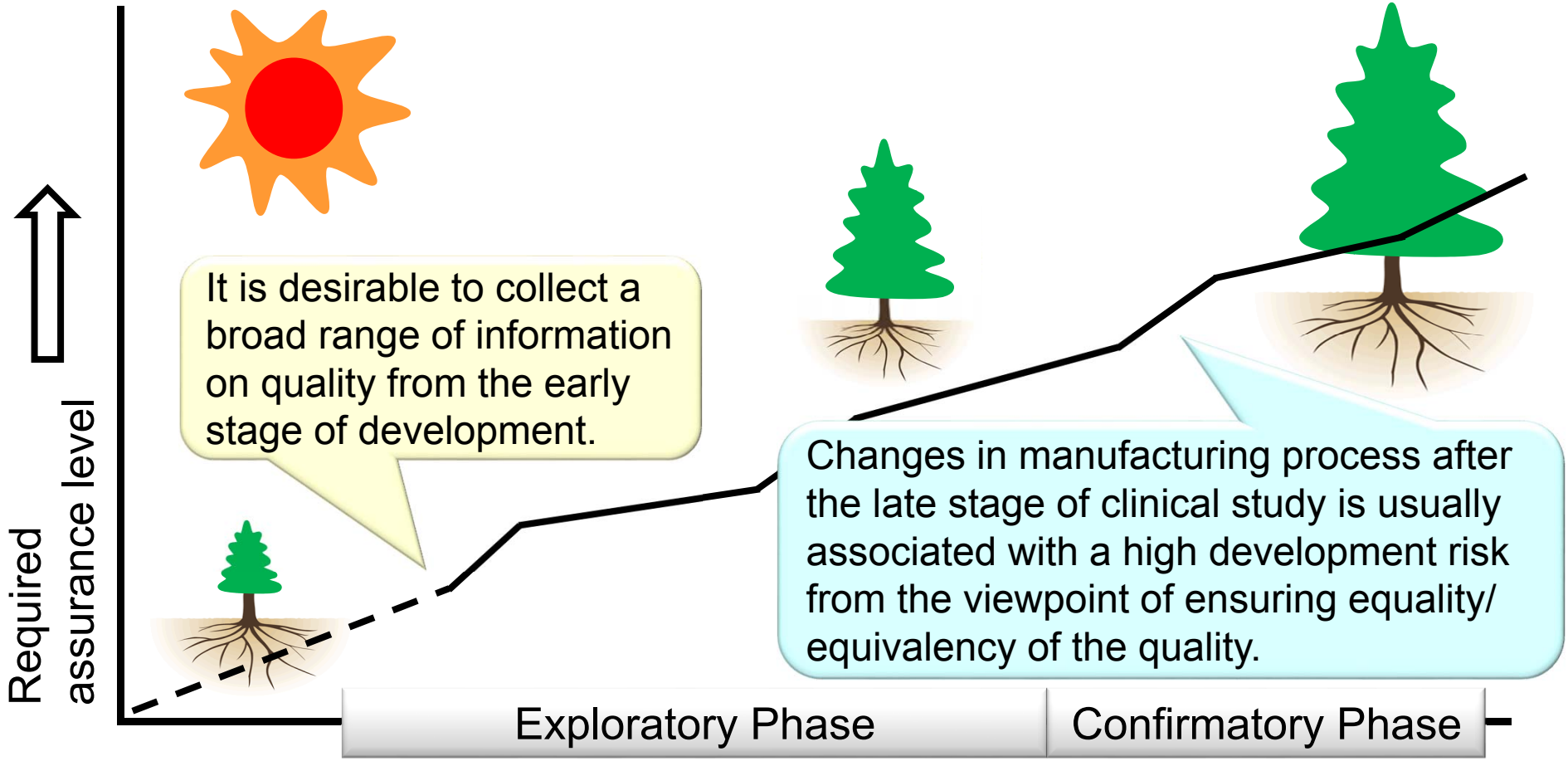
Potency Assay (2)

- Set acceptance criteria for potency or the amount of the active substance in question produced by the desired cells or for an expression product secreted from the cells should be consider.
- Potency assay may result in critical cell characteristics, as qualitative assay.
  - ✓ Biochemical markers
  - ✓ Immunological markers
  - ✓ Phenotype-specific markers





Control Strategy Considering Product Lifecycle



Collect a broad range of information on quality, especially potency and to be refined as CQA assay in later phase.

Thank you for your attention!

Please visit the PMDA website

http://www.pmda.go.jp

http://www.pmda.go.jp/english/index.html