

**5th DIA Cell and Gene Therapy Products Symposium in Japan**  
**- Regenerative Medicine from Innovation to Industrialization -**  
**December 10-11, 2020**

# **Challenge to comparability evaluation and change control of Cell Therapy Product**

**Kazumi SAWAGUCHI, Ph.D**  
**SanBio Company Limited Regulatory Affairs**

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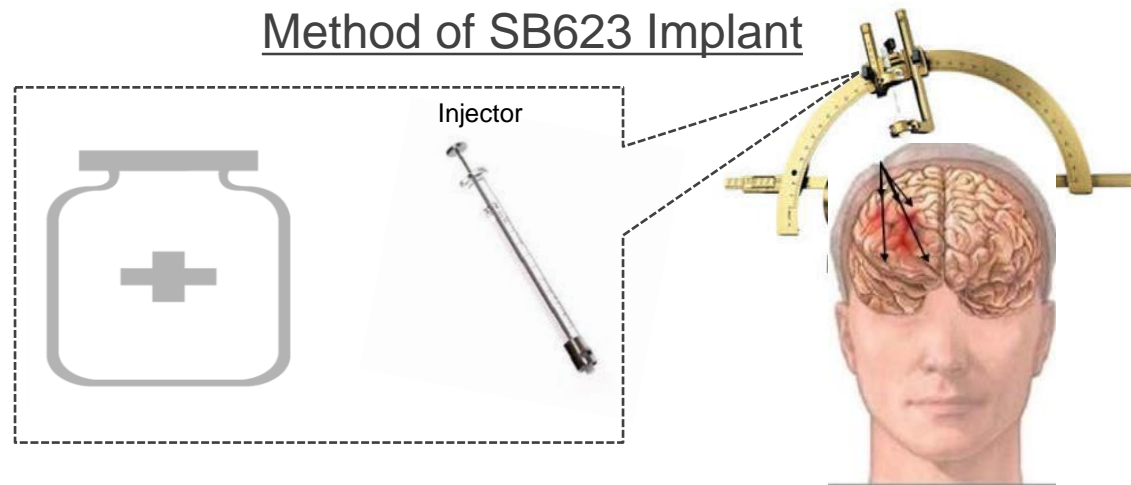
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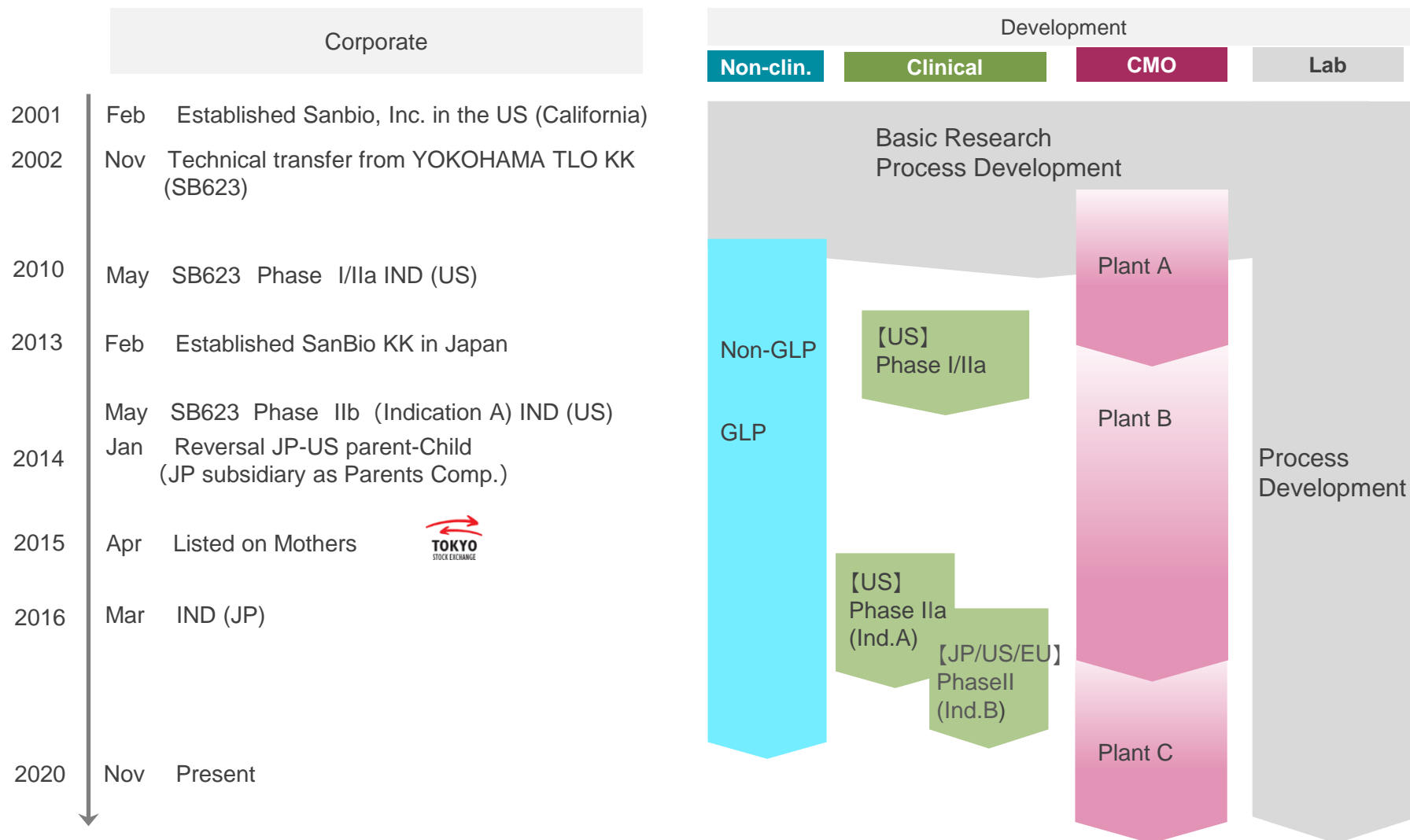
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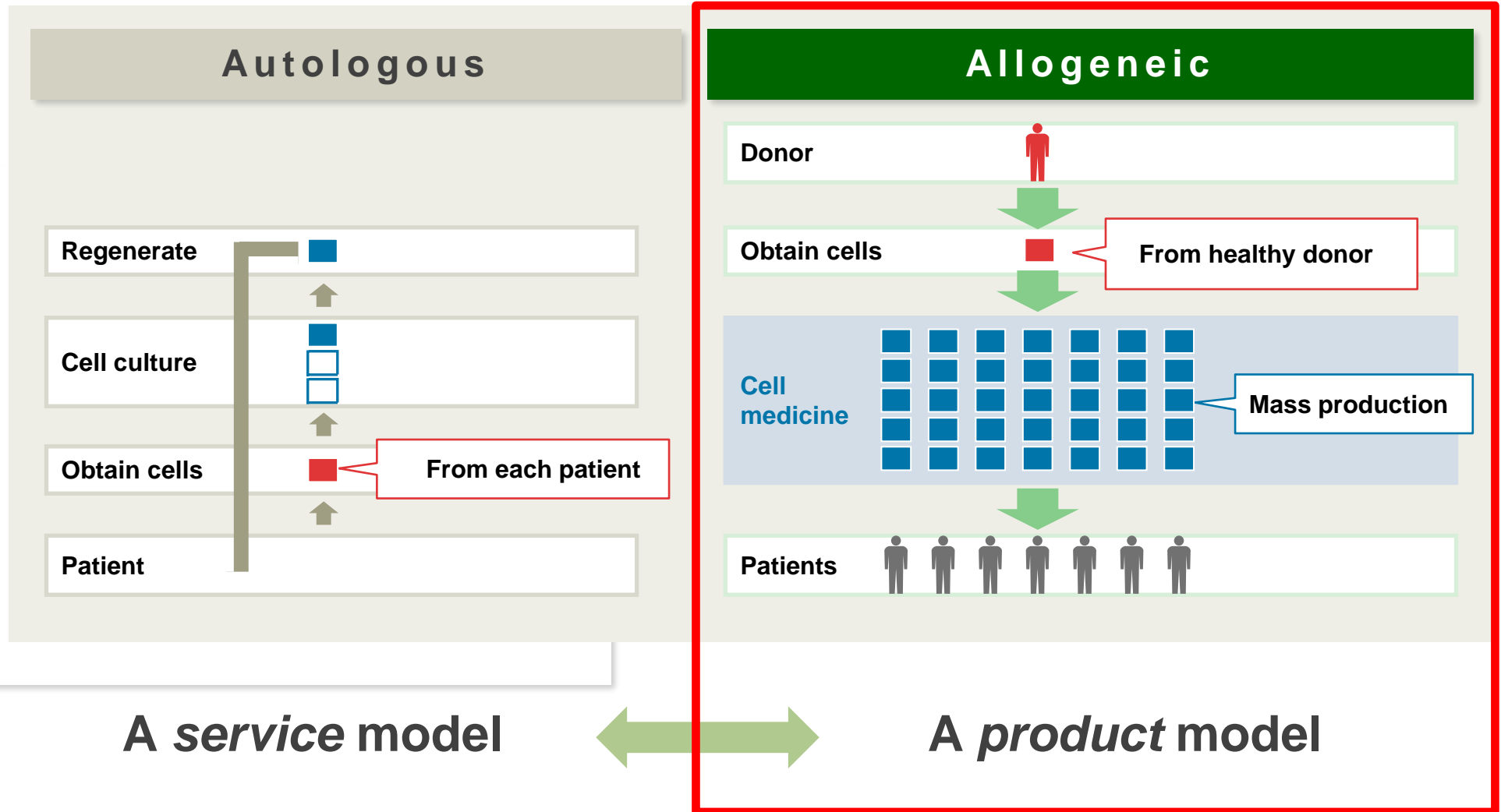
- ▶ SB623 are modified allogeneic mesenchymal stromal cells(MSC) transiently transfected with human Notch-1 intracellular domain
- ▶ Implantation of SB623 cells in the peri-infarct region



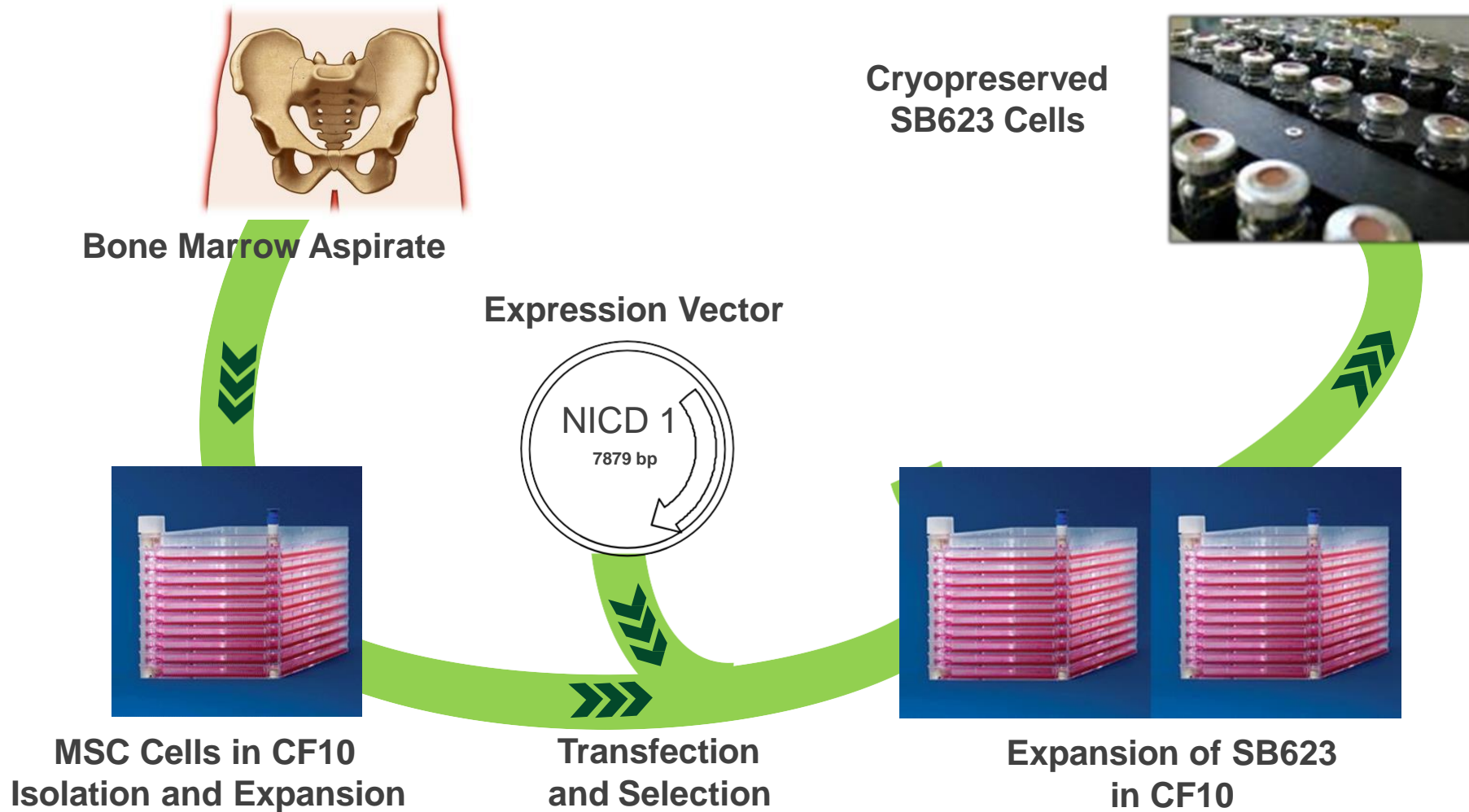


※POC: Proof of Concept

## Select Allogeneic Model in Order to Make RM Available to All Patients

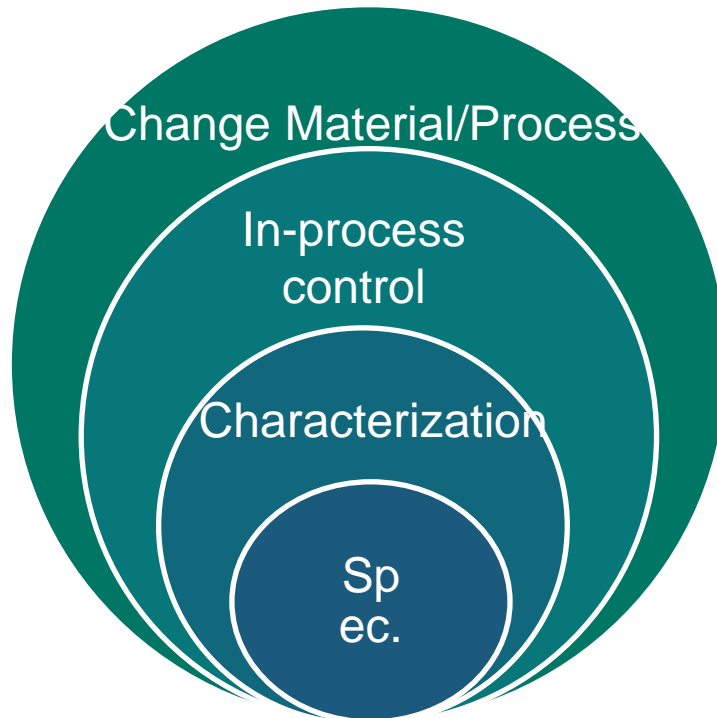


## Large Scale Production of Cells Derived From Bone Marrow

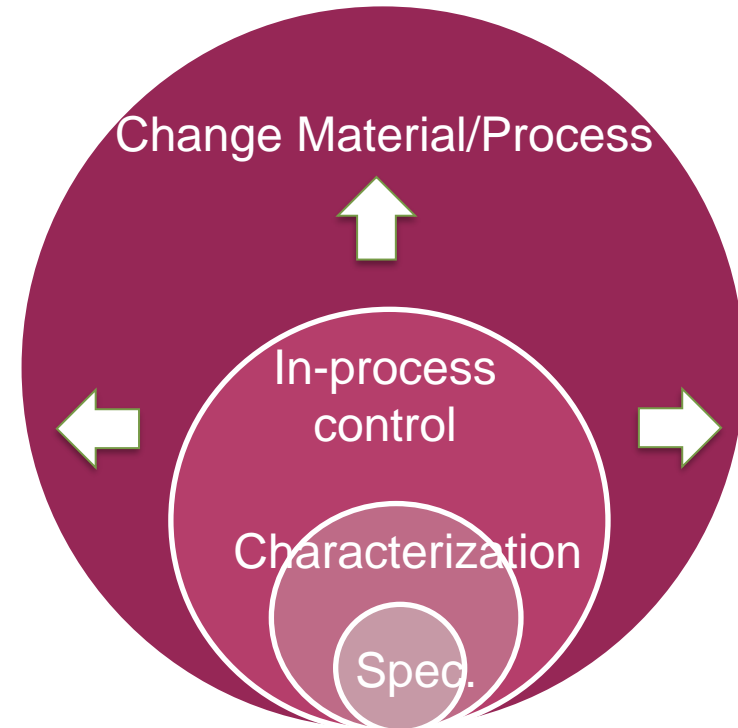


- It is difficult to grasp all the quality of cell therapy product by the Spec., as the information is limited.
- The idea of quality control by controlling raw materials and manufacturing processes is important.

## Image of current Bio product



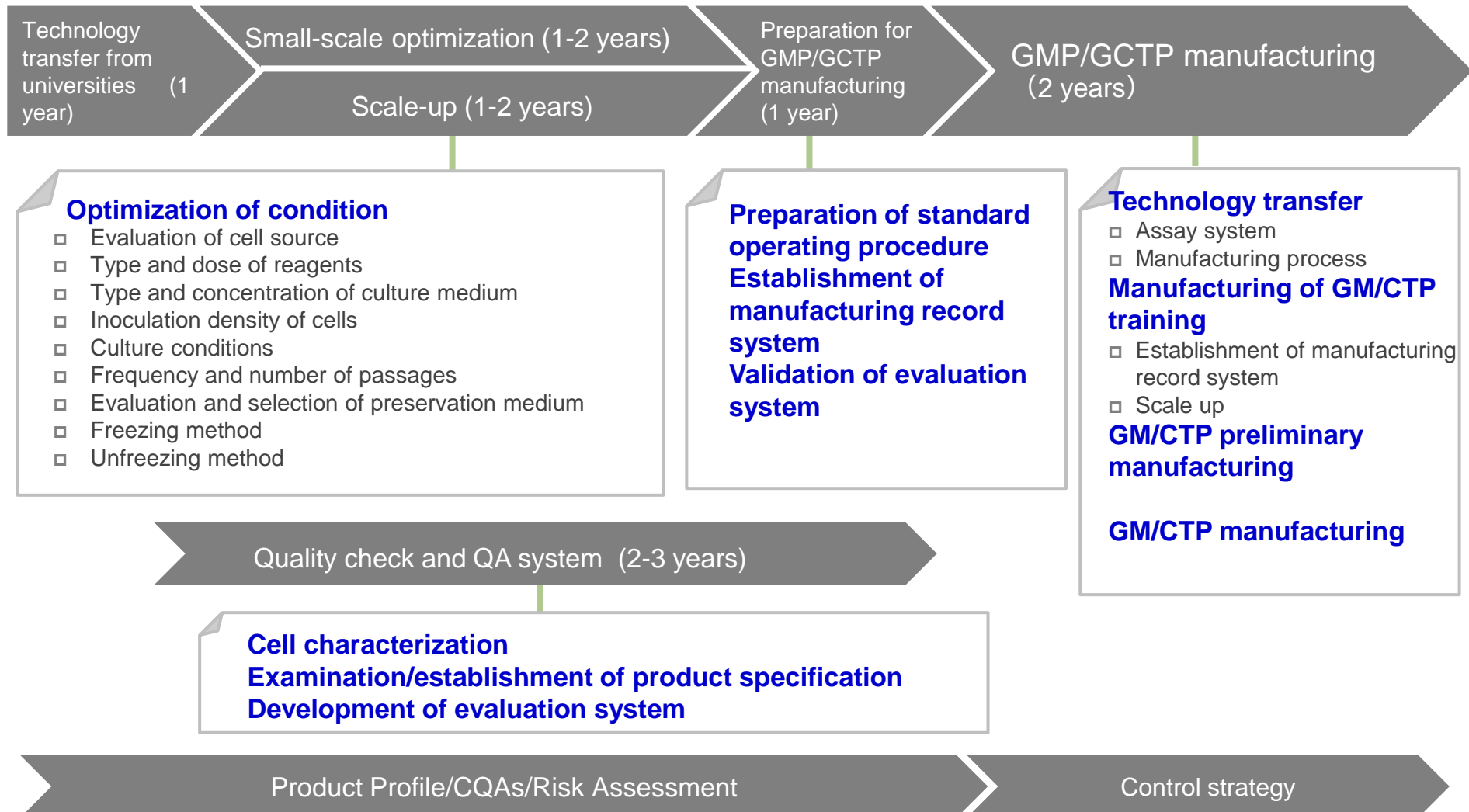
## Image of Cell therapy product



Ref. R.Maruyama et.al Perspectives and practical strategies for obtaining approval / reviewing products for regenerative medicine / gene therapy products, Science & Technology, 2020.9 P 186

# Strategy of Scale-up Manufacturing from Lab to CPC

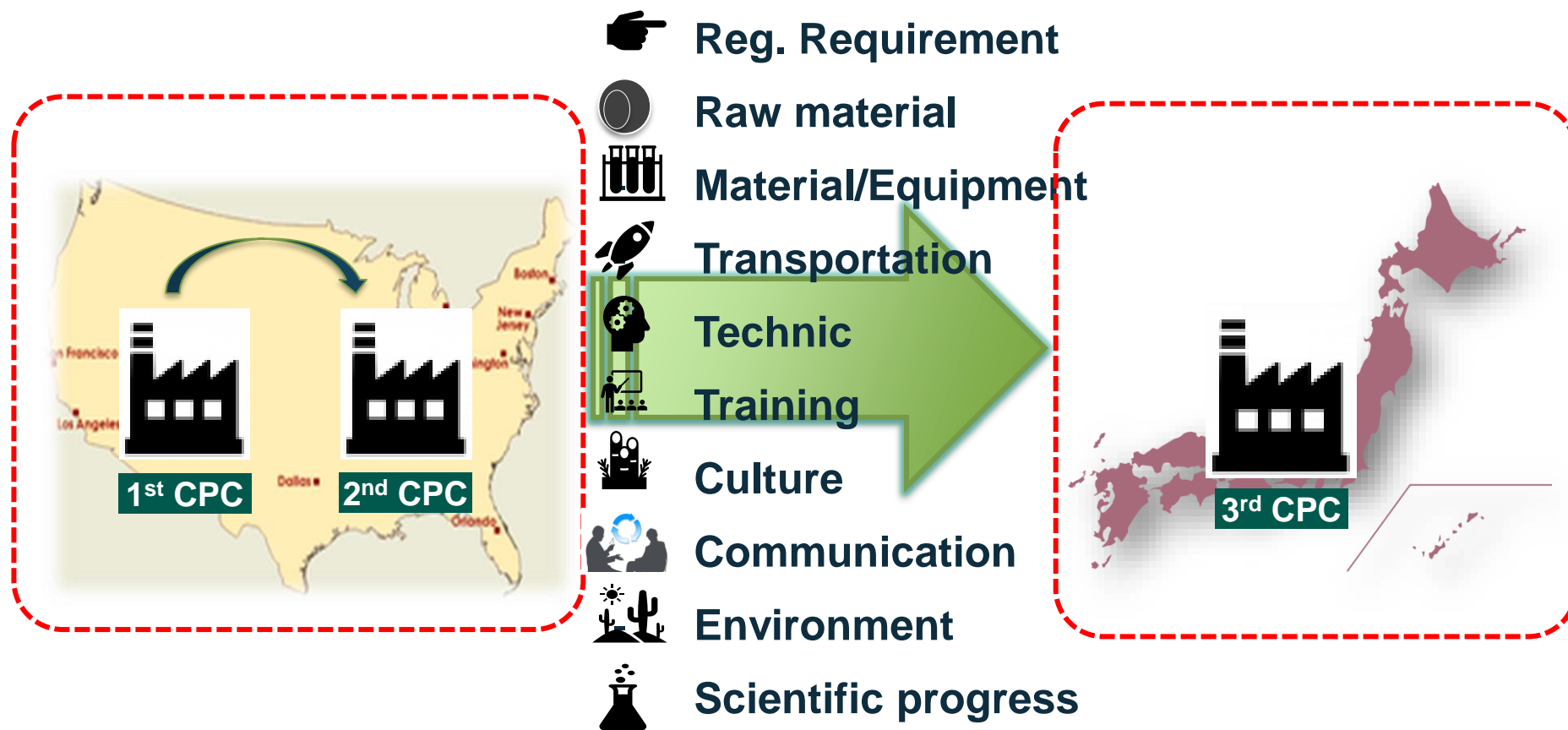
## It Takes Time to Develop Large Scale Production Technology



\* GCTP: Good Gene, Cellular, and Tissue-based Manufacturing Practice \* CPC: Cell Processing Center



- ▶ Raw Materials (Human-derived materials)
  - Risk of infection/Viral contamination
  - Material variability/Donor-to-donor variability
- ▶ Process Development
  - Knowledge management from academic field
  - Comparability for process changes (e.g. scale up)
  - Limited materials for process evaluation
  - Identification of CPP (Critical Process Parameter) and CQA (Critical Quality Attribute)
- ▶ Manufacturing control
  - GCTP
  - Aseptic process considerations
  - Viral safety considerations
  - Process performance consistency
- ▶ Analysis
  - Complex characteristics
  - Specification (potency assay etc.)



SanBio Lab/CMC/QC Team



\* CMC: Chemistry, Manufacturing and Control

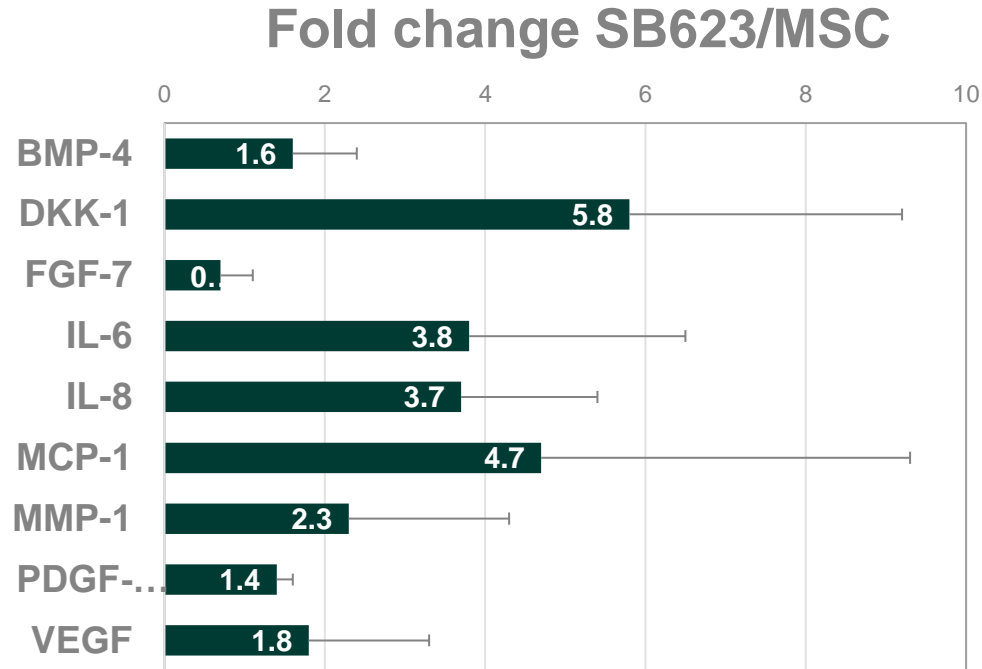
# Quality characteristics of cell therapy products

Ref. The 16<sup>th</sup> Congress of the Japanese Society for Regenerative Medicine  
PMDA Dr. Oyama 2017

Evaluation item	Example of test method (Case by Case depending on the position of the test)
Identity test	Description, Cell phenotype, Differentiation ability, Tumorigenesis etc.
Cell purity test	Cell phenotype, Proliferation abnormality etc.
Process-related Impurities	Manufacturing process-related substances (Serum-related Albumin, Antibiotics, etc.)
Unintended Product-related physiologically active impurities	Physiologically active substances, etc.
Safety	Chromosome abnormality, Soft agar colony forming ability, Virus, Mycoplasma, Endotoxin, Sterility, etc. (secured as in-process control)
Potency assay, efficacy test, Mechanical compatibility	Protein expression, Secretion ability, Differentiation ability, Cell phenotype, Cell proliferation ability, Cell survival, Cell/cell interaction etc.
Content	No of cell, Cell viability, etc.

\*Quality characteristics related to efficacy and safety can be important quality characteristics, but it is still necessary to organize and discuss what kind of quality characteristics correspond to each product containing cells.

\* We can debate about what quality characteristic items and standard values should be set in the titer test.

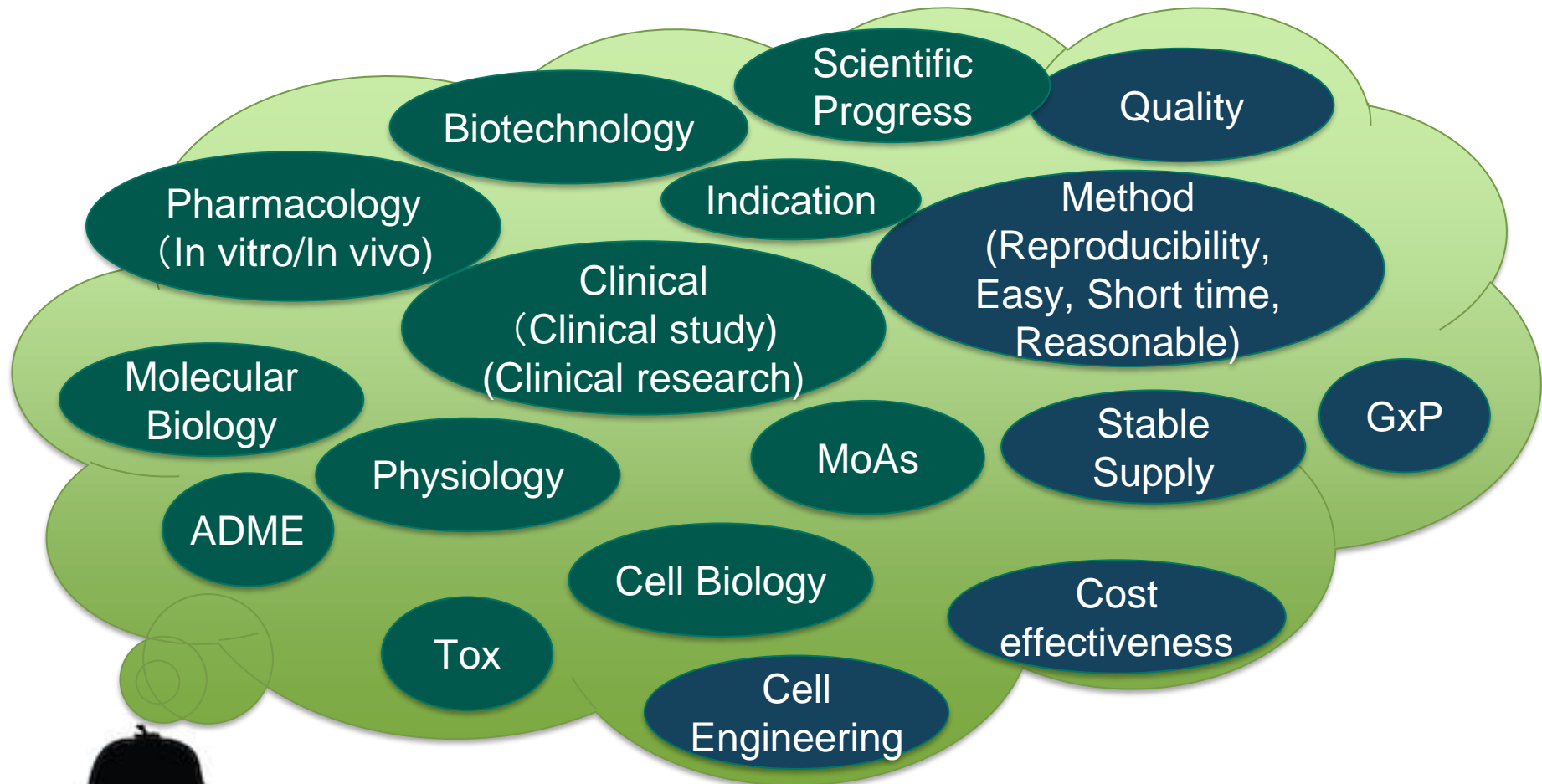


Quantify various biologically active substance in culture supernatant using antibody array kit.

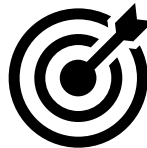
**Can these active substance be subject to “Potency assay”?**

Ref: Tate et al, : Cell Transplant 2010; 19(8): 973–984 revised

# Setting of Potency Assay



Set the Potency Assay



Change/add the Potency Assay





## ► For Cell therapy product

1. Cells are alive
2. Quality characteristics are complex, diverse and heterogeneous
3. There are technical restrictions on the implementation of specification tests and manufacturing control
4. The specification only confirms an important part of quality and can only be established on various assumptions.

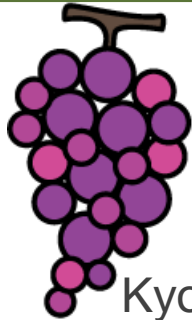
## ► Points to consider

1. Full understanding of quality characteristics (characteristic analysis)
2. Understanding process variations that lead to quality fluctuations (quality risk management)
3. Invisible quality parts should be managed as quality fluctuations from the upstream of the process (quality control strategy)

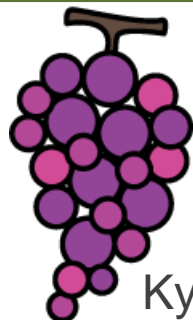
# Image of heterogenous, complex and divers



A



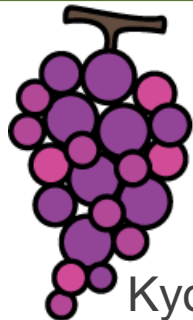
Kyoho



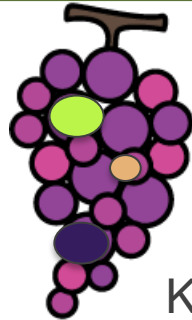
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- ☐ Same Spices
- ☐ Same Quality

B



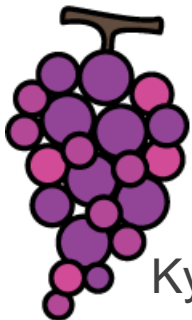
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Kyoho

- ☐ Same Spices
- ? Comparable ?  
Color/Maturity/Taste etc.

C



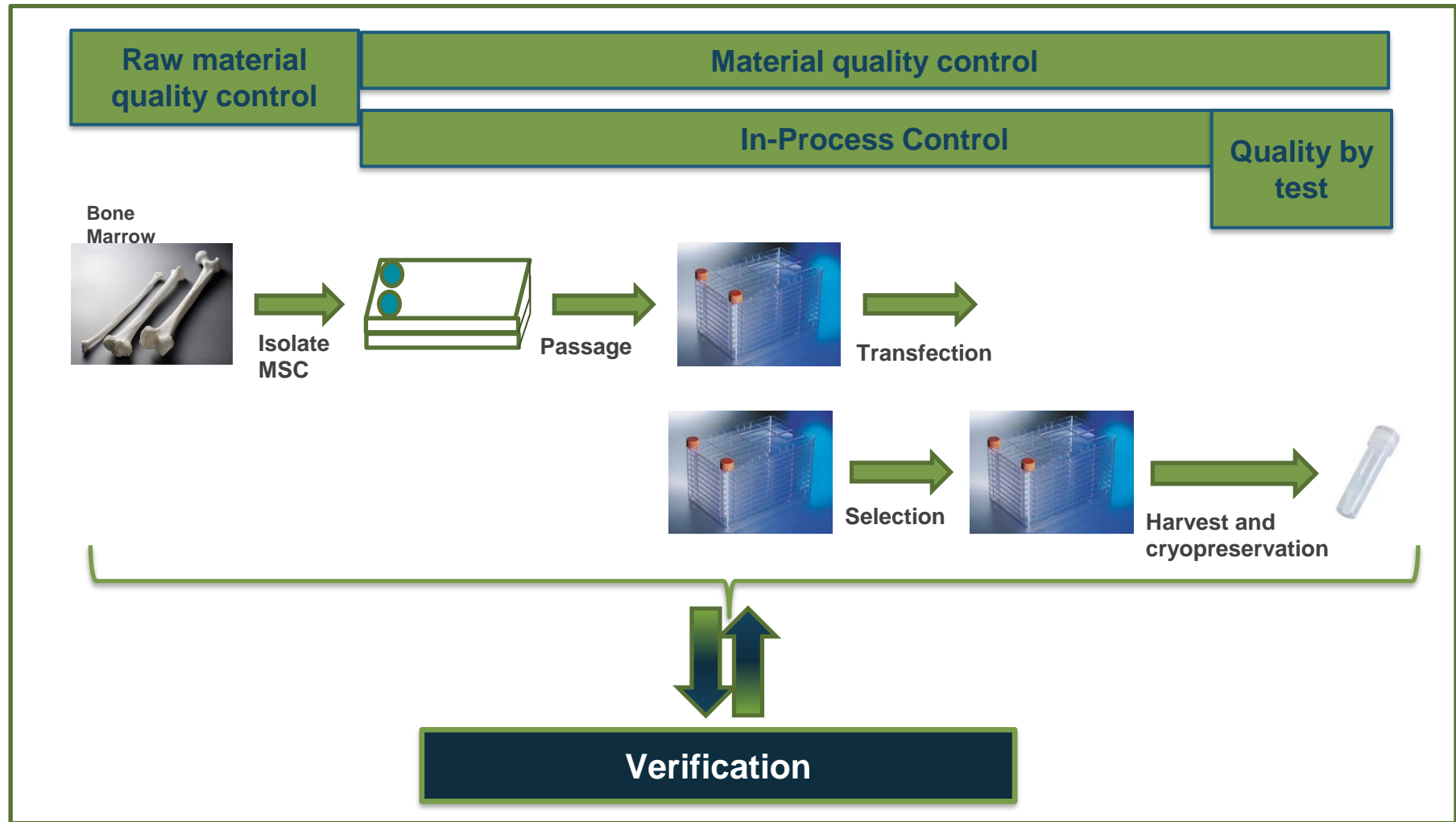
Kyoho



Muscat

- ☐ Same Spices
- X Different Quality  
Taste is different!

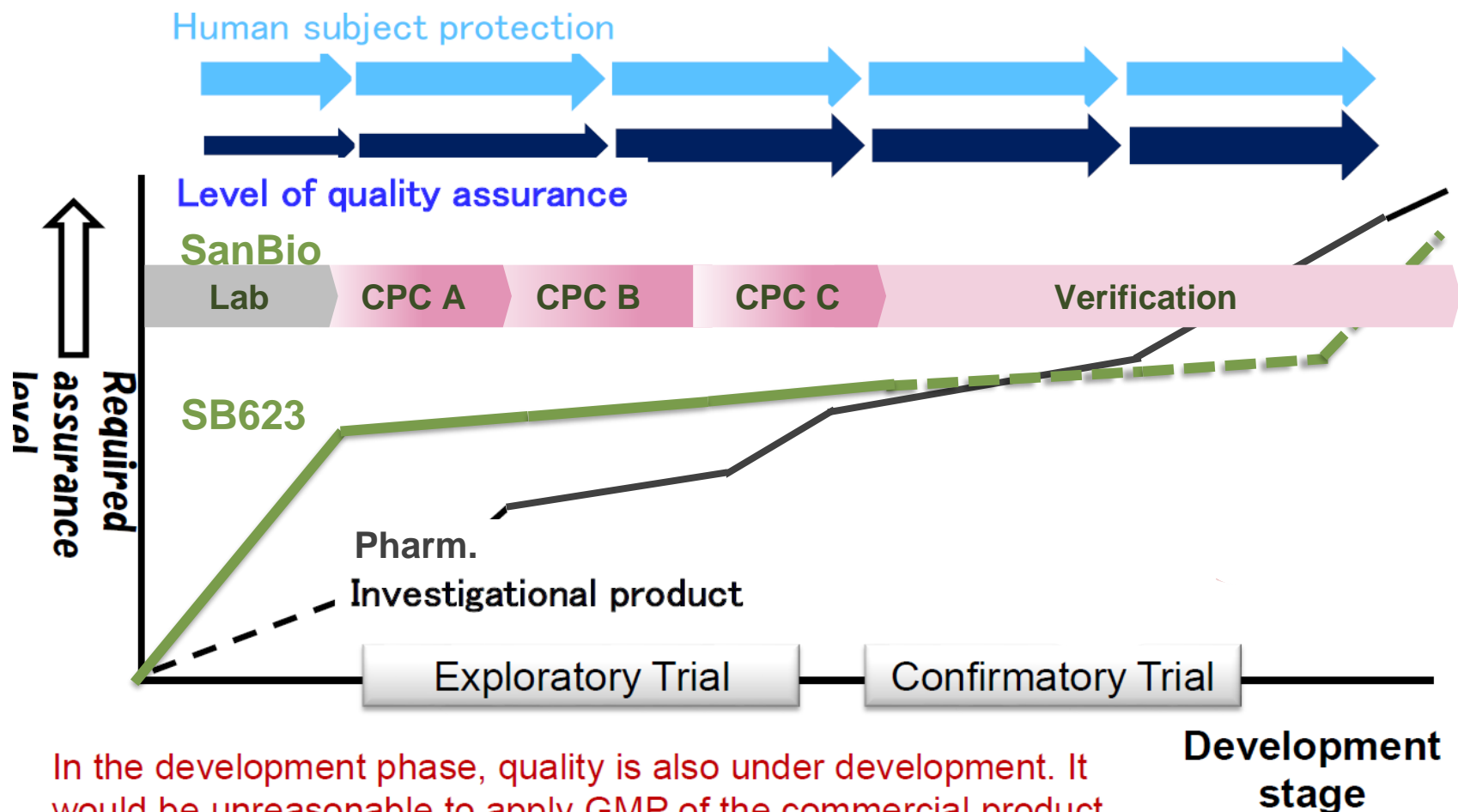
# Image of Quality control strategy for SB623





# Life cycle plan of SB623 from lab to CPC

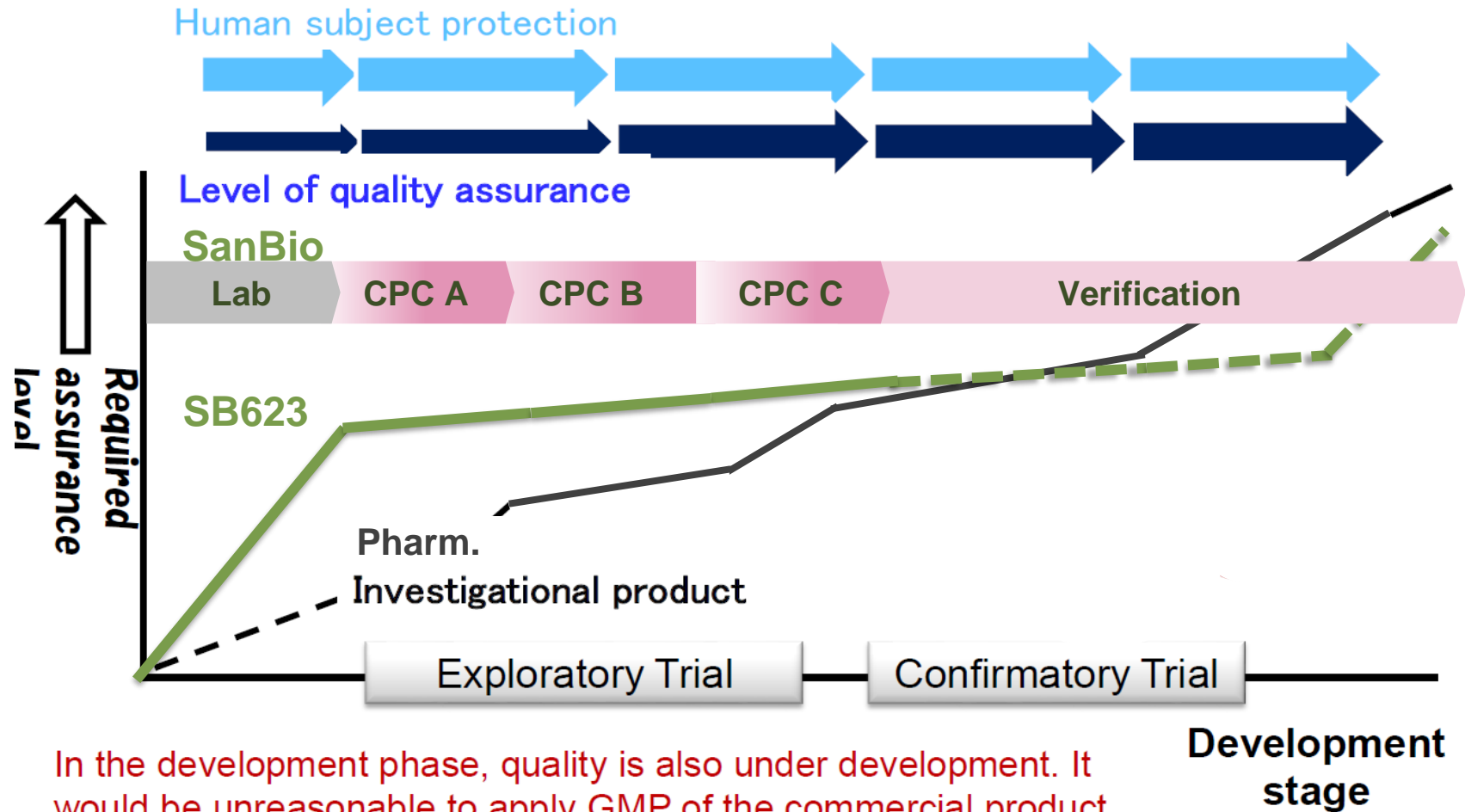
Ref. IABS, JST(NIBIO), PMDA and WHO joint Workshop Dr.Sato Feb 2015



In the development phase, quality is also under development. It would be unreasonable to apply GMP of the commercial product level. Flexible risk based approach would be more appropriate.

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