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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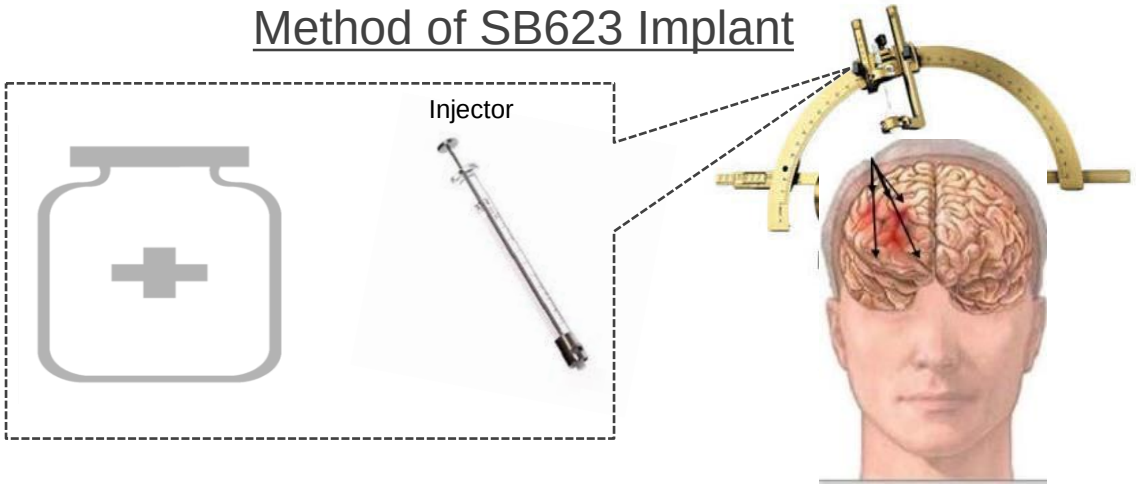
What is SB623

- 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

Method of SB623 Implant



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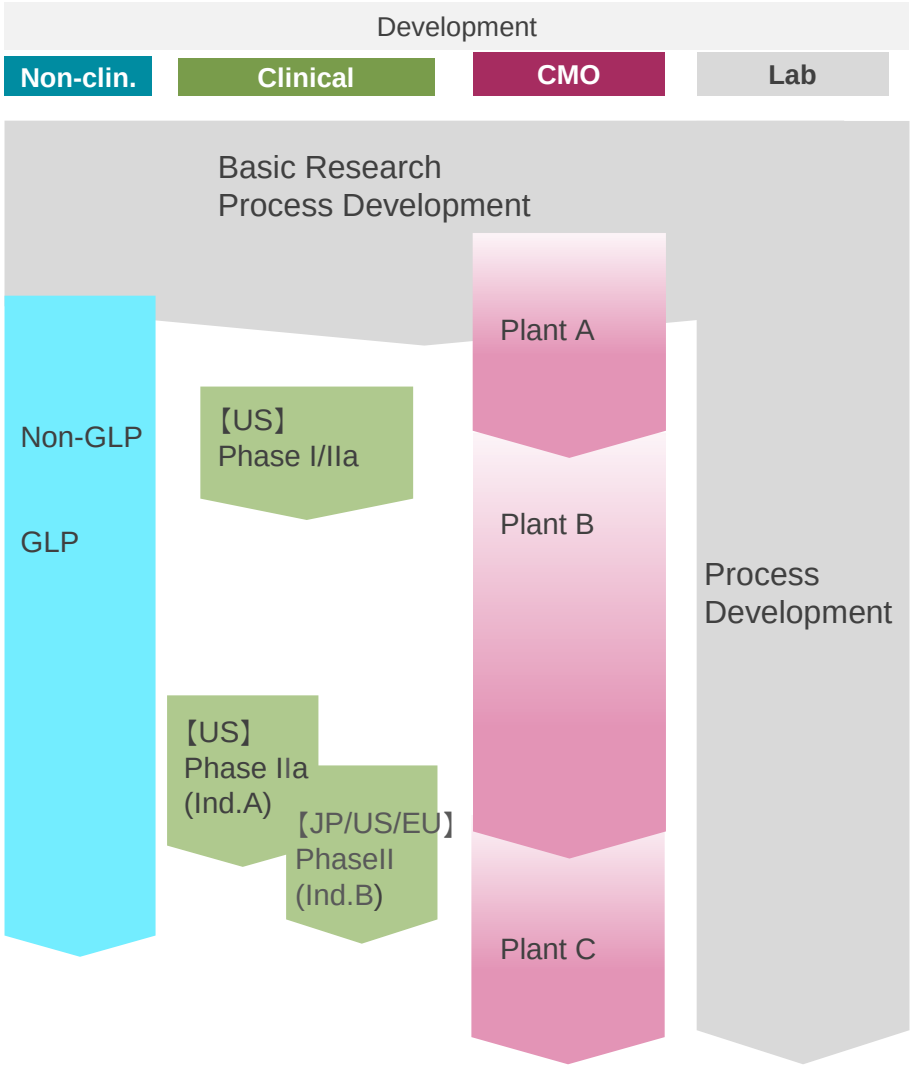
SanBio: History

	Corporate
2001	Feb Established Sanbio, Inc. in the US (California)
2002	Nov Technical transfer from YOKOHAMA TLO KK (SB623)
2010	May SB623 Phase I/IIa IND (US)
2013	Feb Established SanBio KK in Japan
2014	May SB623 Phase IIb (Indication A) IND (US) Jan Reversal JP-US parent-Child (JP subsidiary as Parents Comp.)
2015	Apr Listed on Mothers
2016	Mar IND (JP)
2020	Nov Present

※POC: Proof of Concept



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Allogeneic Approach

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

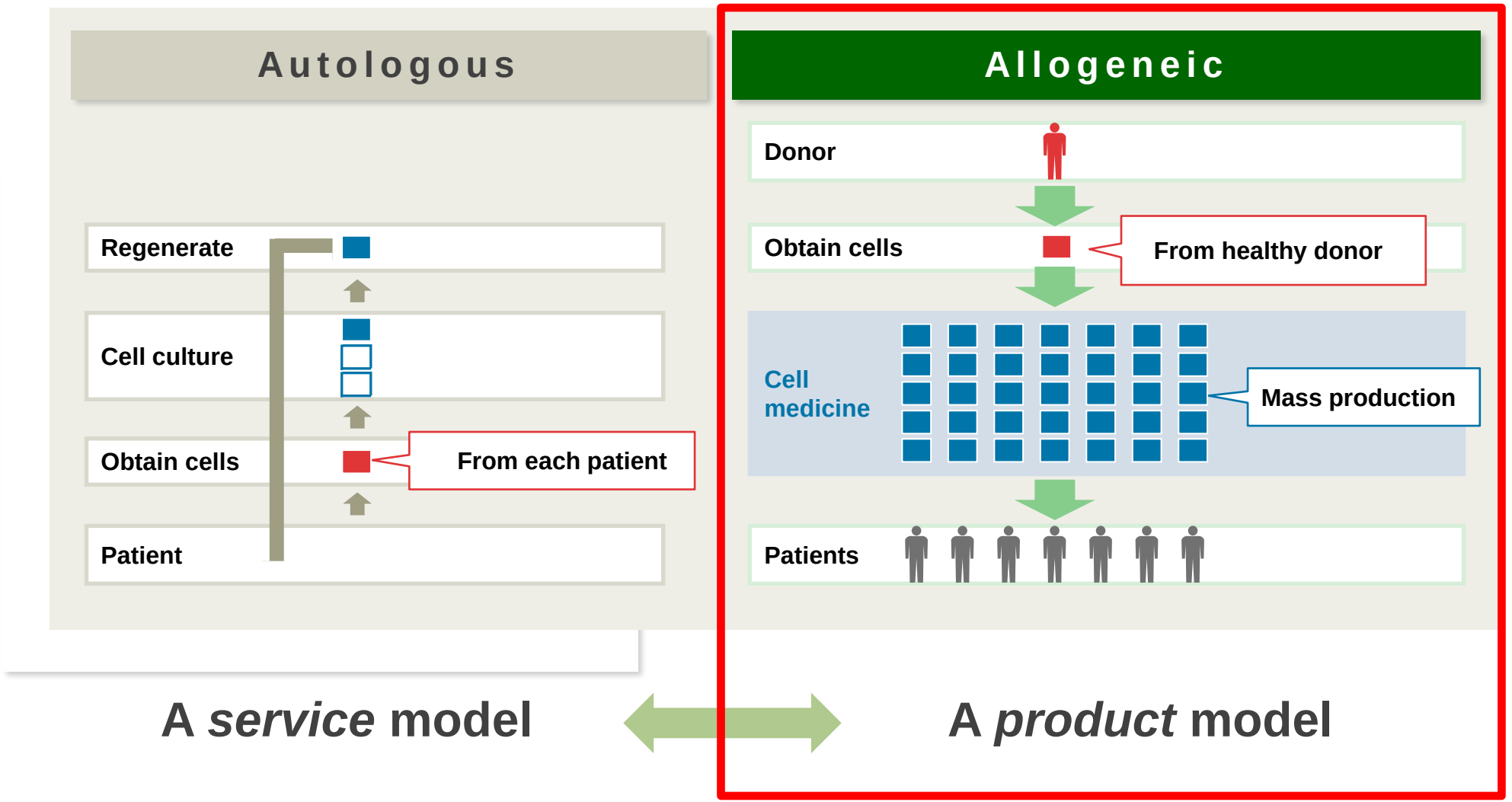

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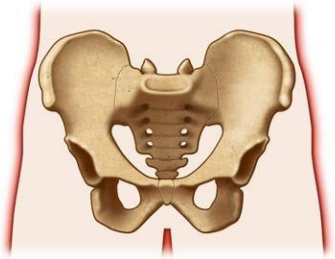
Image of Manufacturing Process of SB623

Large Scale Production of Cells Derived From Bone Marrow



Bone Marrow Aspirate

Cryopreserved
SB623 Cells

Expression Vector

MSC Cells in CF10
Isolation and Expansion

Transfection
and Selection

Expansion of SB623
in CF10

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Image of Product development and Quality control strategy setting

- 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

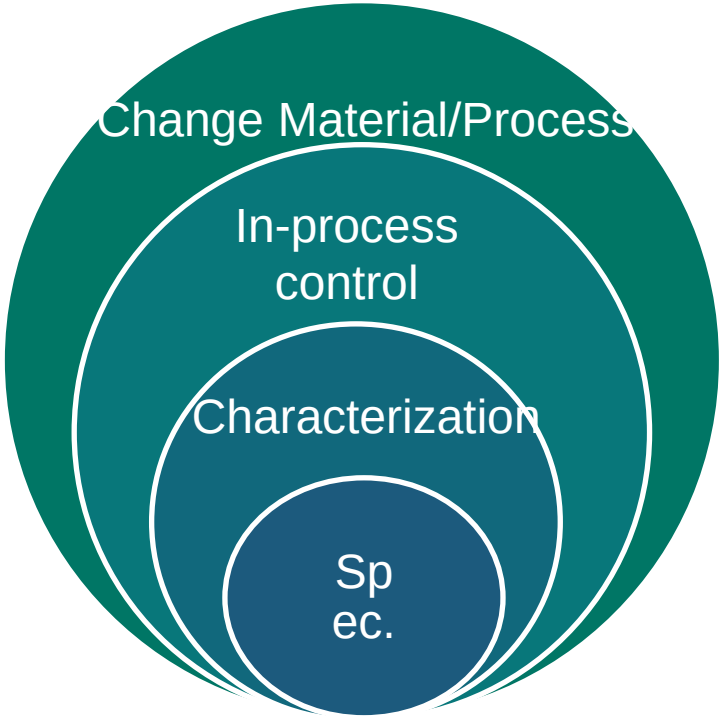
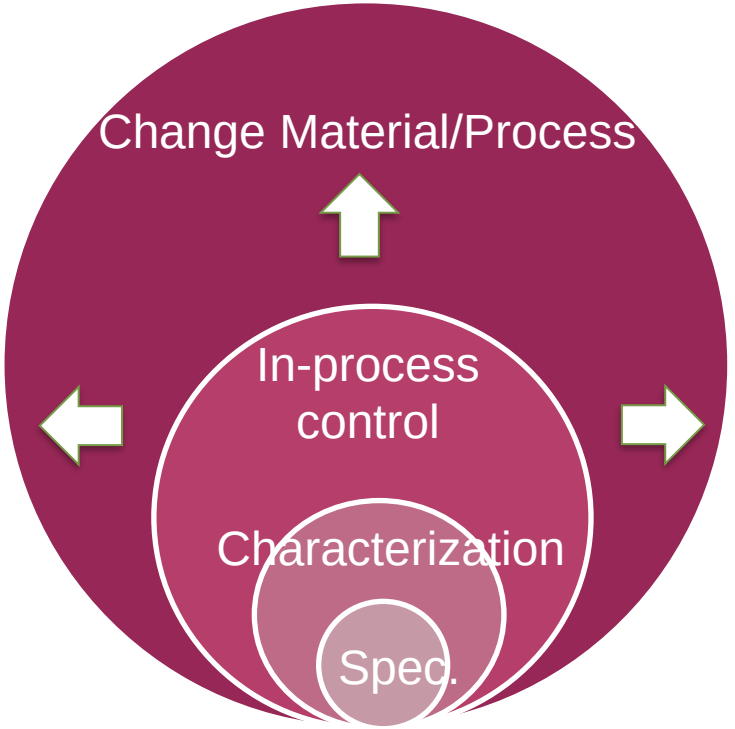


Image of Cell therapy product



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

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Strategy of Scale-up Manufacturing from Lab to CPC

It Takes Time to Develop Large Scale Production Technology

Technology transfer from universities (1 year)

Small-scale optimization (1-2 years)

Scale-up (1-2 years)

Preparation for GMP/GCTP manufacturing (1 year)

GMP/GCTP manufacturing (2 years)

Optimization of condition
- Evaluation of cell source
- Type and dose of reagents
- Type and concentration of culture medium
- Inoculation density of cells
- Culture conditions
- Frequency and number of passages
- Evaluation and selection of preservation medium
- Freezing method
- Unfreezing method

Preparation of standard operating procedure
Establishment of manufacturing record system
Validation of evaluation system

Technology transfer
- Assay system
- Manufacturing process

Manufacturing of GM/CTP training
- Establishment of manufacturing record system
- Scale up

GM/CTP preliminary manufacturing

GM/CTP manufacturing

Quality check and QA system (2-3 years)

Cell characterization
Examination/establishment of product specification
Development of evaluation system

Product Profile/CQAs/Risk Assessment

Control strategy

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

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Various challenges in the quality of SB623

- 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.)

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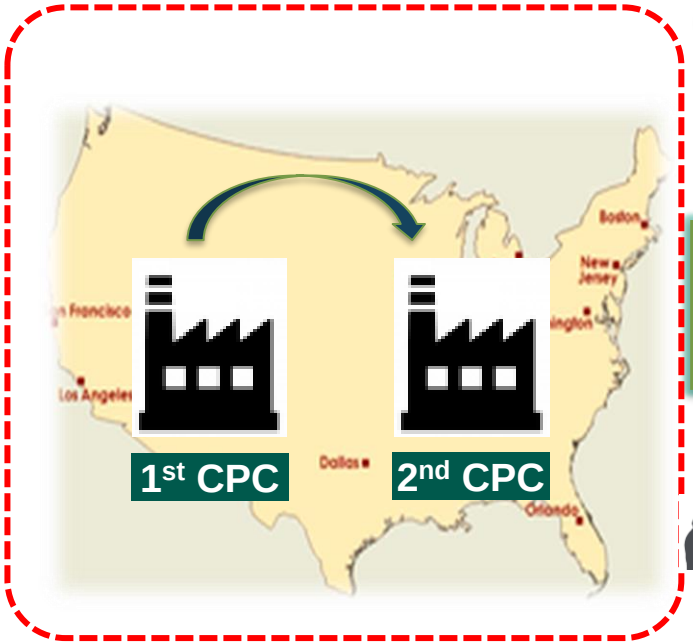
Points to consider when transferring or adding CPC to other countries



- Reg. Requirement
- Raw material
- Material/Equipment
- Transportation
- Technic
- Training
- Culture
- Communication
- Environment
- Scientific progress

SanBio Lab/CMC/QC Team

* CMC: Chemistry, Manufacturing and Control

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Quality characteristics of cell therapy products

Ref. The 16th 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.

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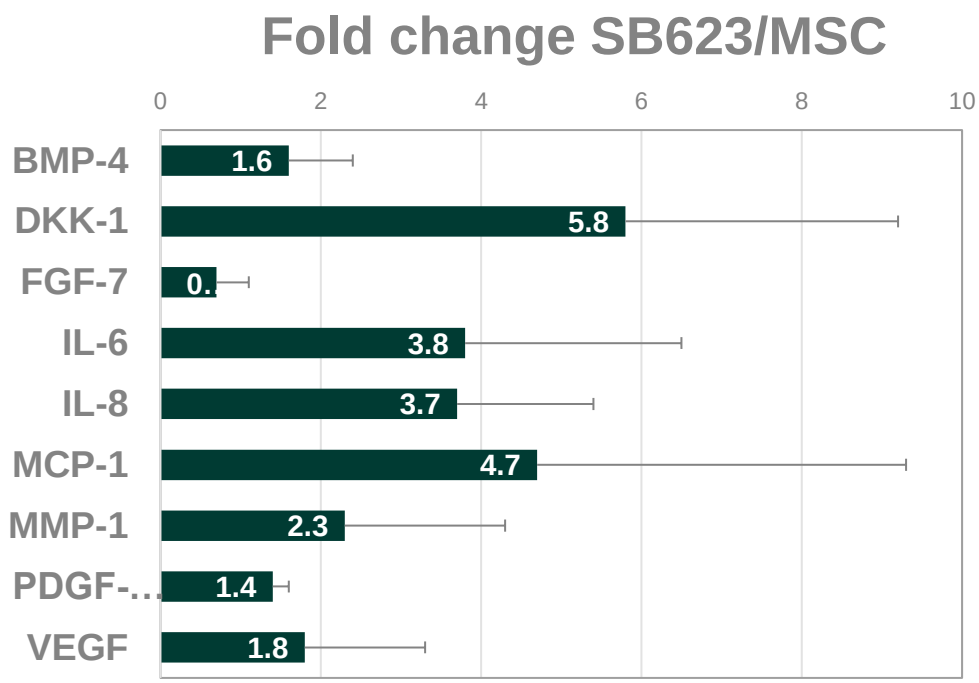
Production ratio of various biologically active substance of MSC and SB623



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

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Setting of Potency Assay

Scientific Progress
Quality
Biotechnology
Pharmacology (In vitro/In vivo)
Indication
Method (Reproducibility, Easy, Short time, Reasonable)
Clinical (Clinical study) (Clinical research)
Molecular Biology
GxP
Stable Supply
MoAs
Physiology
ADME
Cell Biology
Cost effectiveness
Tox
Cell Engineering

Set the Potency Assay

Change/add the Potency Assay

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Consider to set the specification for Cell therapy product

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

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)

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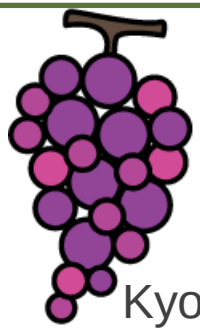
Image of heterogenous, complex and divers

A

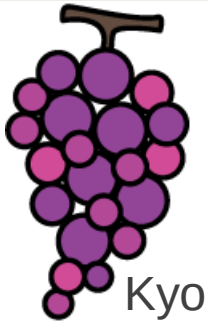


Kyoho

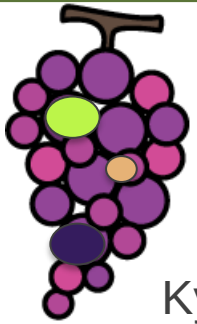
Kyoho

○ Same Spices
○ Same Quality

B



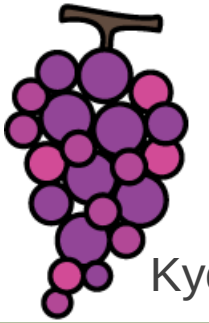
Kyoho



Kyoho

○ Same Spices
? Comparable ?
Color/Maturity/Taste etc.

C



Kyoho

Muscat

○ Same Spices
X Different Quality
Taste is different!

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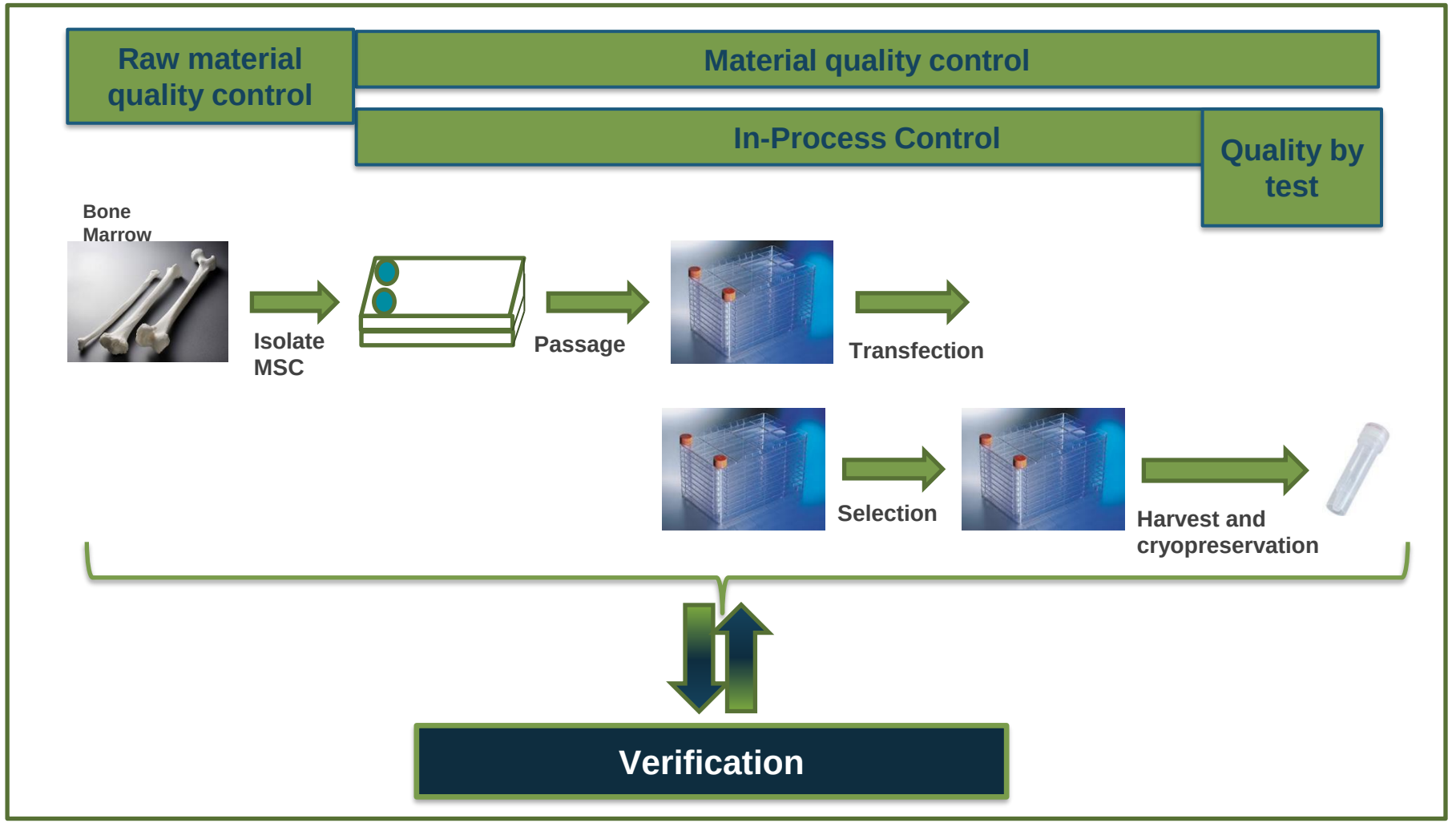
Image of Quality control strategy for SB623



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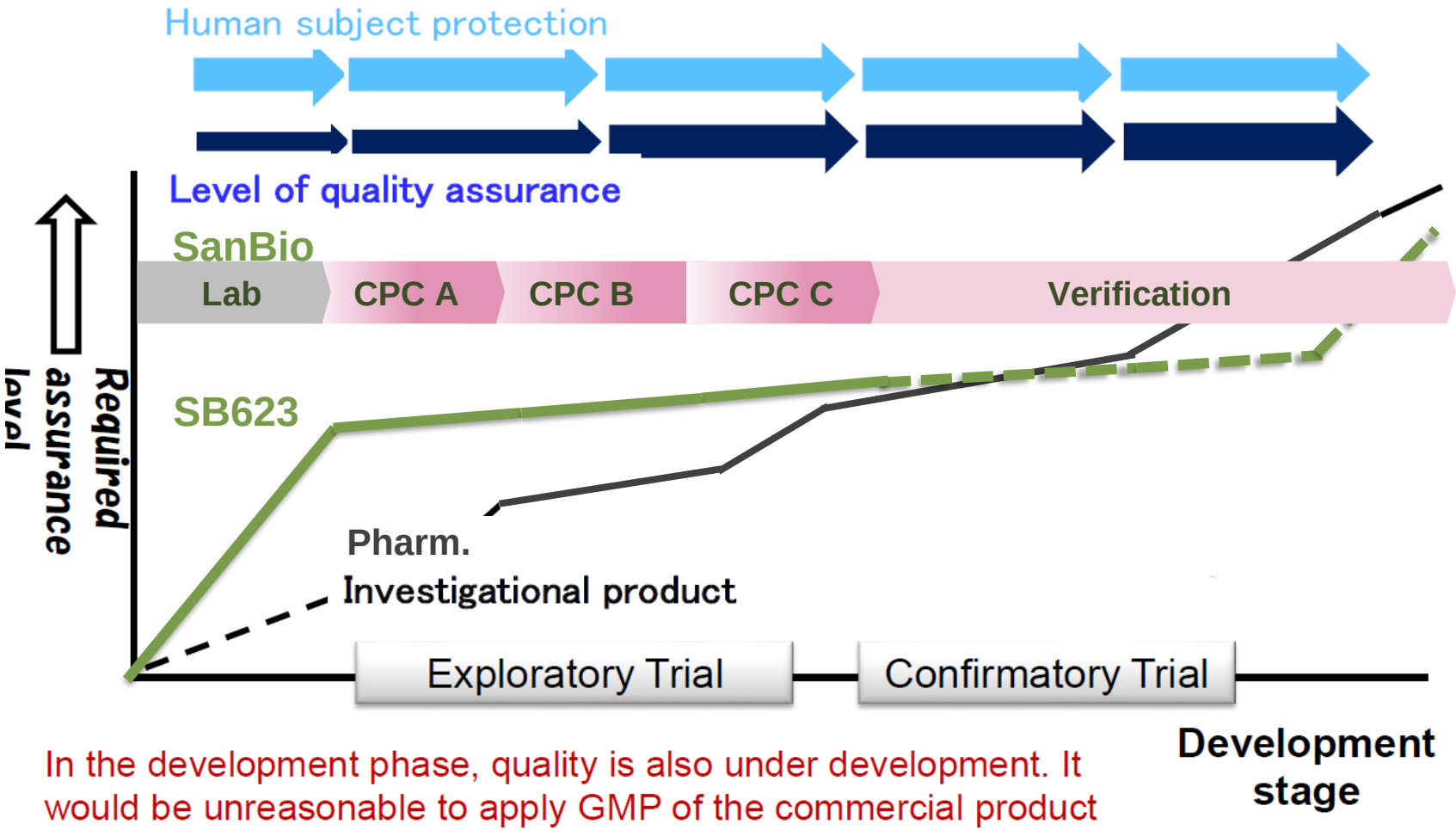
Life cycle plan of SB623 from lab to CPC

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.

Pharmaceuticals and Medical Devices Agency

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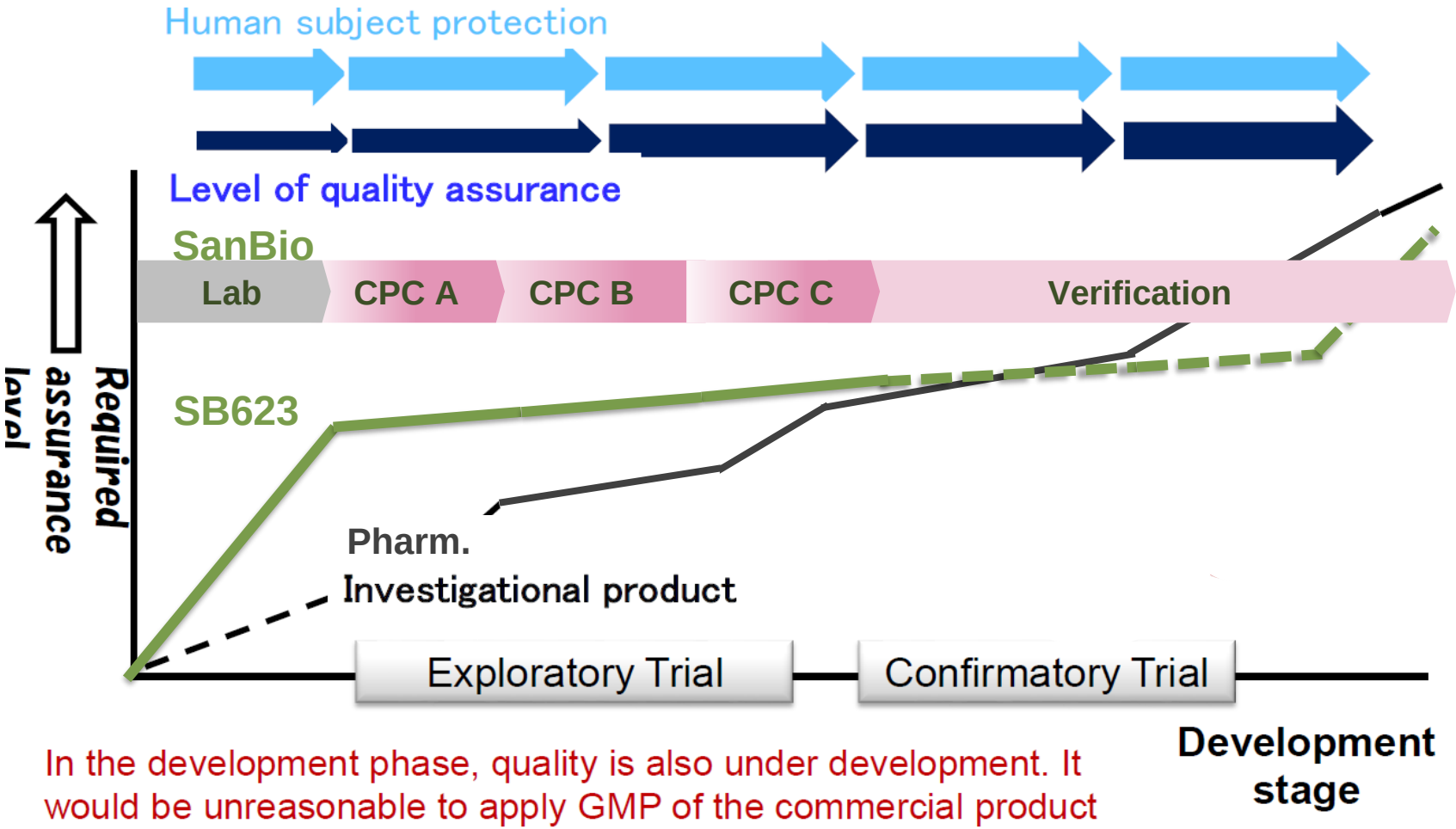

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