The 23rd Congress of the Japanese Society for Regenerative Medicine

Symposium 16 “Standards -A tool to connect academia and industry-”

International Standards in the field of Regenerative Medicine

2024-03-21

FUJIFILM Holdings Corporation

(Forum for Innovative Regenerative Medicine)

Ikuo Kawauchi

The content of this presentation is the personal opinion of the presenter and does not represent the opinion of the presenter's organization or any industry or regulatory official in any country.

International Standards in the field of Regenerative Medicine

FUJIFILM Holdings Corporation
(Forum for Innovative Regenerative Medicine)

Ikuo Kawauchi

The lead presenter has no COI to disclose regarding the presentation of this topic in the past year (Jan. to Dec.).

Agenda

1）About standard

2）Standards development

3）Standards in RM field

- Necessity
- Overview

Agenda

1）About standard

2）Standards development

3）Standards in RM field

- Necessity
- Overview

Definition of “standard”

standard

document, established by consensus and approved by a recognized body, that provides, for common and repeated use, rules, guidelines or characteristics for activities or their results, aimed at the achievement of the optimum degree of order in a given context

[SOURCE : ISO/IEC Guide 2:2004, 3.2]

regulation

document providing binding legislative rules, that is adopted by an authority

[SOURCE : ISO/IEC Guide 2:2004, 3.6]

ICH guideline

Guidelines considered scientifically and ethically appropriate for each topic in the areas of quality, efficacy, and safety of pharmaceutical products, discussed by experts representing each member in working groups and approved by regulatory authority representatives

[SOURCE : PMDA homepage; modified]

- Standards are not "binding rules." Its utilization make activities more efficient.
- Definition of ICH is same as standard except for inclusion of regulatory approval.

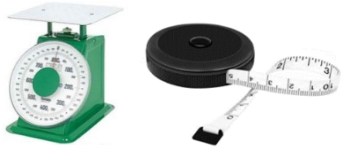
Examples of Standards

1) Compatibility

Battery 

Screw 

2) Performance evaluation procedure on manufactured goods

Measurement tools 

Test procedure
(Vehicle's fuel cost etc.) 

3) Qualification, Safety and Labels by criteria

Stove burner 

iphone's certification required 

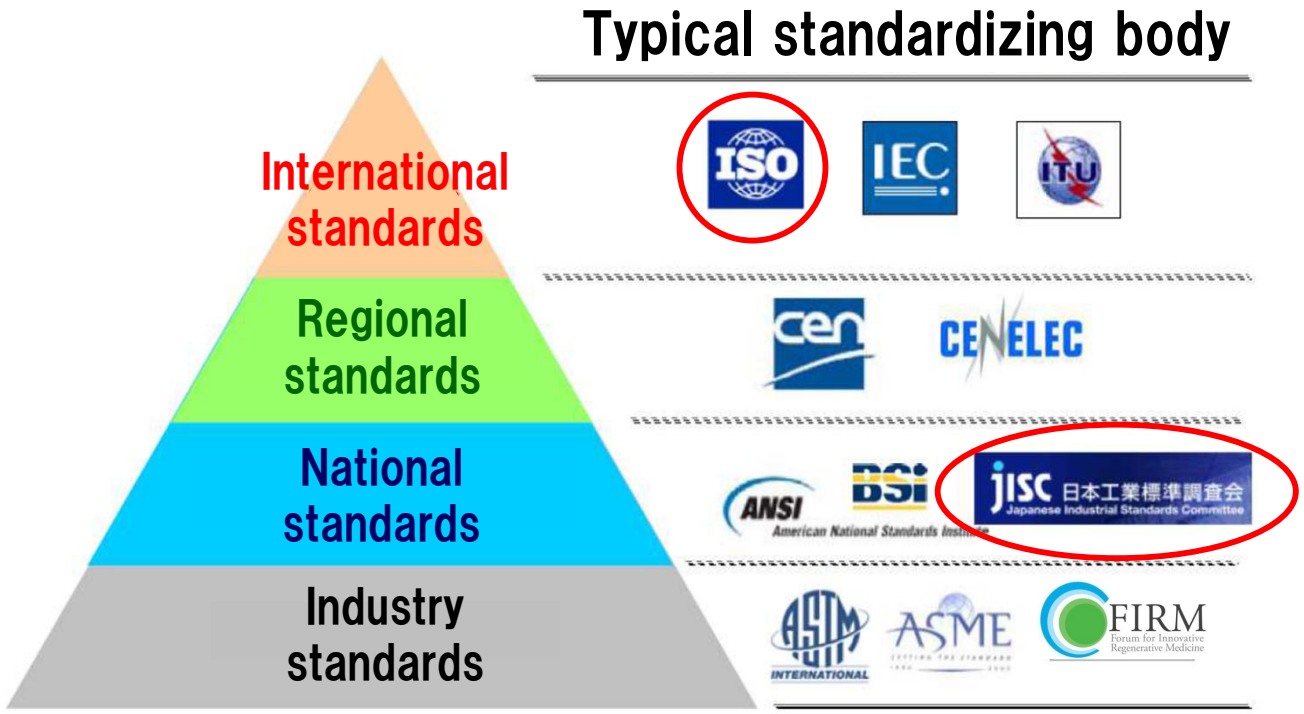
4) Management System Standard (MSS)

Quality Management System

Environment Management System 

➢ Standards specify not only "uniformity" but also "requirements to be achieved" and "way of thinking".

Types of Standards



- International standards form the widest consensus.
- ISO covers all industries except for electricity and telecommunications.

Agenda

1）About standard

2）Standards development

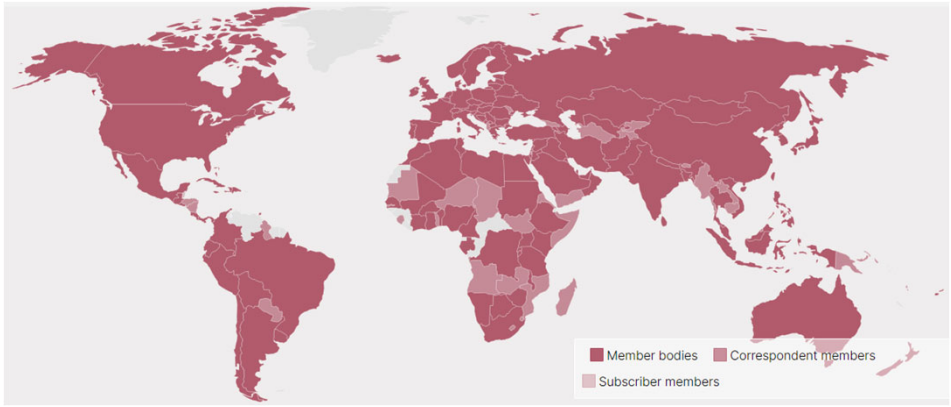
3）Standards in RM field

- Necessity
- Overview

ISO as a standard development organization

International Organization for Standardization

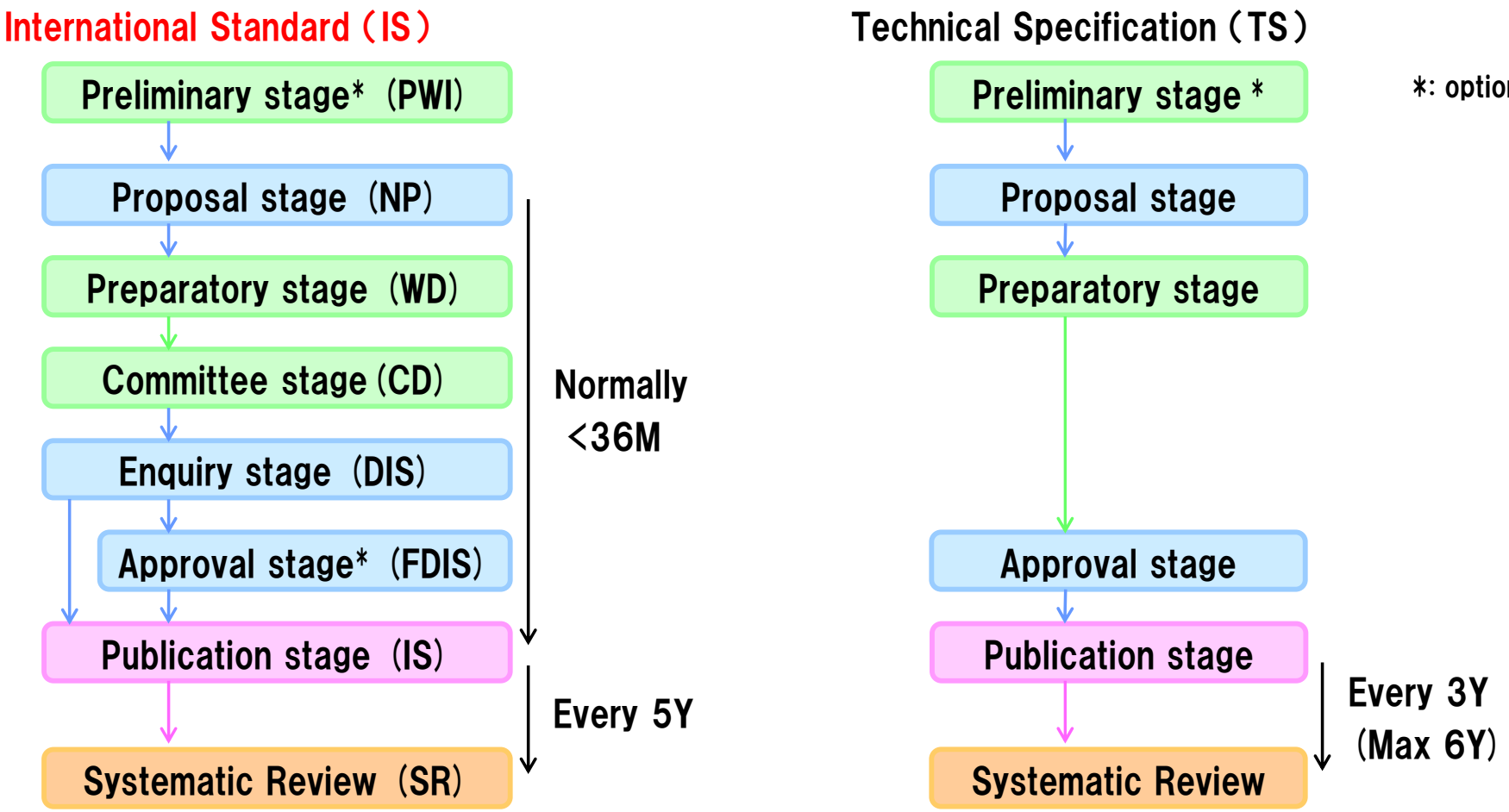
- Non-governmental organization established on 1947-02-23
- Developing international standards outside the electrical and telecommunications fields
- 268 Technical Committees by sector



All members : 170 Countries

Technical Committee	Title
ISO/TC 106	Dentistry
ISO/TC 150/SC 7	Tissue-engineered medical products
ISO/TC 194	Biological and clinical evaluation of medical devices
ISO/TC 198	Sterilization of health care products
ISO/TC 212	Clinical laboratory testing and in vitro diagnostic test systems
ISO/TC 229	Nanotechnologies
ISO/TC 276	Biotechnology

Development process of Standards



➢ Standard development proceeds based on voting and commenting.

Example of commenting sheet

Project

Template for comments and secretariat observations

Date:2024-01-25	Document: ISO/TC 276/WG 4 N 911	Project: General requirements for purification of extracellular vesicles

MB/ NC[1]	Line number	Clause/ Subclause	Paragraph/ Figure/Table	Type of comment[2]	Comments	Proposed change	Observations
JP-001				ge	EV is expected to be one of the pharmaceutical new modalities. While much academic knowledge has been accumulated in this area, the systematization of knowledge has not yet progressed.	It is useful to standardize the quality items that should be clarified when characterizing EVs, which are a part of cells, and the concept of their measurement methods.	Noted. I agree that systematization of knowledge is important in emerging area. However, characterization and measurement methods seem to be another theme.
IT-002		1		ge	The scope of the proposal is to standardize production of EVs for therapeutic use. However EV are not yet well characterize in research area , therefore it is premature to develop a standard on their therapeutic use.		Partially accepted. Research and development of EVs is premature. However, it is not appropriate reason not to develop standard. The purpose of standardize is clearly described in the definition of "standard" by ISO/IEC guide 2 to aim the achievement of the optimum degree of order in a given context. Regardless mature or premature, this document will be help for appropriate selection of purification methods.
-003		1		ge	The scope of the document is to standardize production of EVs for therapeutic purposes. The	Change the scope into a scope for research and/or diagnostic applications.	The purpose of this standardization is not to

By commenter

By project leader

Agenda

1）About standard

2）Standards development

3）Standards in RM field

- **Necessity**
- Overview

The Need for Standards in the Field of RM

Low molecular weight pharmaceutical

Quality, Safety and Efficacy are supported by several guidelines.

→ Standards by ISO are not necessary.

Regenerative Medicine

Industrial Structure of RM

The value chain of RM involves a wide range of stakeholders.

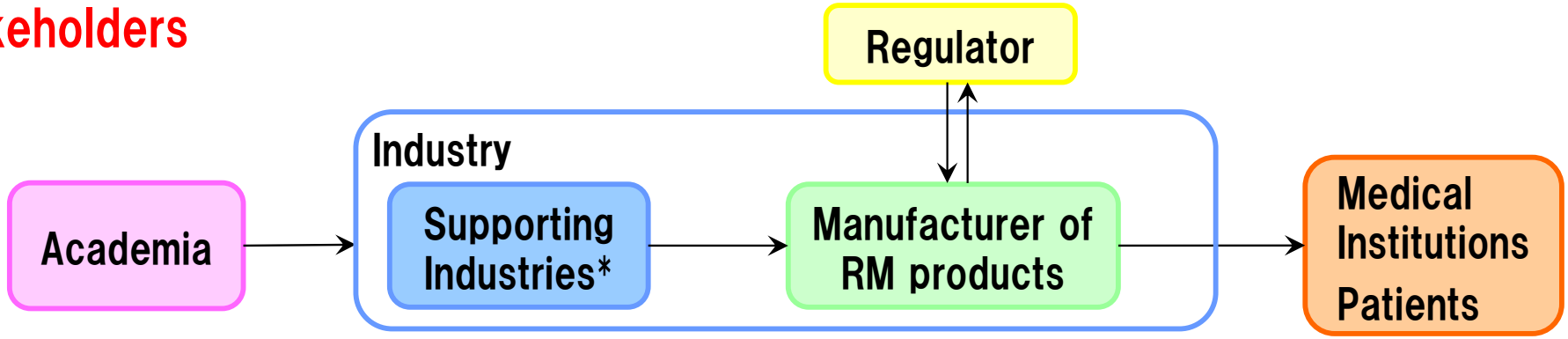
→ Standards are effective as provisions for order optimization.

Features of Cells

Complicated shapes → Existing guidelines are not applicable.

Industrial Structure of RM

Stakeholders



* Reagents, Media, Manufacturing equipment, Consumables, Inspection equipment, logistics, etc.

Necessity of standards

Stakeholders	Communication	Perspectives on standard utilization
Academia/Industry	Technology transfer	Common language for explanation of technology
Supporting Industries/ Manufacturer of RM	Transaction	Role of both parties
Manufacturer of RM/ Regulator	Approval review	Explanation to regulatory requirements

➢ Standards facilitate not only own activities but also communication among stakeholders.

Information required to apply for approval

Items need to be explained when applying for marketing authorization

添付資料の項目及び資料概要との関係

左欄		右欄	
1	起原又は発見の経緯及び外国における使用状況等に関する資料	ア	起原又は発見の経緯　に関する資料
		イ	外国における使用状況　〃
		ウ	類似する他の治療法との比較検討等　〃
2	製造方法並びに規格及び試験方法等に関する資料	ア	製品の構造、構成細胞、導入遺伝子　〃
		イ	使用する原料、材料又はそれらの原材料　〃
		ウ	製造方法　〃
		エ	規格及び試験方法　〃
3	安定性に関する資料		輸送、保存条件、有効期間の根拠　〃
4	効能、効果又は性能に関する資料		効力又は性能を裏付ける試験　〃

薬食発0812第30号（抜粋）

2 Documents related to manufacturing method, specification, test method etc.

raw materials to be used

manufacturing method

specification and test method

3 Documents related to stability

basis for validity period

4 Documents related to efficacy, effectiveness or performance

➢ Appropriate explanations are required not only about efficacy and effects, but also about manufacturing methods, materials and specifications

Features of Cells

Classification	Chemical products	Biologics	Cells
Chemical structure	Clear	Almost clear	Unclear
Size	1-5 nm	10-20 nm	10 um
Heterogeneity	None	Low	High
Measurement method	Established (NMR, MS, HPLC etc.)	Established (NMR, GPC, UV, Peptide map etc.)	Insufficient (Under development)

- Characteristics of biologics are similar to those of chemical products.
- Characteristics of cells are more complicated comparing to those of chemical products and biologics.

  →Some of current guidelines cannot be applied on cells.

Guidelines that exclude cells from the scope

ICH	Title	Scope
Q2	Validation of Analytical Procedures: Methodology: Text and Methodology	Due to their complex nature, analytical procedures for biological and biotechnological products in some cases may be approached differently than in this document.
Q6A	Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products	It is not sufficient to adequately describe specifications of biotechnological/biological products.
Q6B	Test Procedures and Acceptance Criteria for Biotechnological/Biological Products	This document does not cover cells.

➢ICH Q2, Q6 are not applicable to cells.

Recommendation of standards usage by FDA

21st Century Cures Act　2016-12-13

（An Act To accelerate the discovery, development, and delivery of 21st century cures, and for other purposes.）

provisions related to regenerative medicine are described in Section 3033-3036.

Sec. 3033. **Accelerated approval for regenerative advanced therapies.**

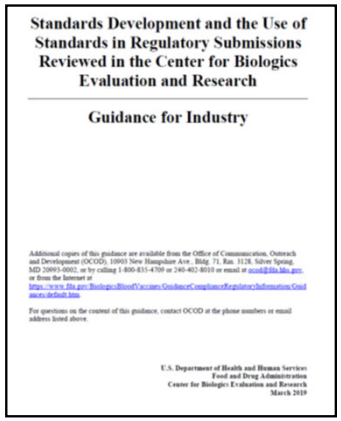
Sec. 3034. Guidance regarding devices used in the recovery, isolation, or delivery of regenerative advanced therapies.

Sec. 3035. Report on regenerative advanced therapies.

Sec. 3036. **Standards for regenerative medicine and regenerative advanced therapies.**

→ This section requires the establishment of standards and consensus definitions to support the development and review of regenerative medicine therapies, including with respect to the manufacturing processes and controls of such products.

FDA Guidance "Standards in Regulatory Submissions"　2019-03-26 (Draft: 2017-12-18)


Standards Development and the Use of Standards in Regulatory Submissions Reviewed in the Center for Biologics Evaluation and Research

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
March 2019

- ✓CBER staff participate in the development of standards.
- ✓CBER participates to help ensure that standards developed are not in conflict with FDA regulations or policies and to increases the likelihood that the standards under development will be suitable for products regulated.
- ✓The use of standards can facilitate product design, contribute to a more efficient evaluation of regulatory submissions and improving time to market.
- ✓FDA intends to preferentially use internationally harmonized standards.

→ list of standards recommended for use

Agenda

1）About standard

2）Standards development

3）Standards in RM field

- Necessity
- **Overview**

ISO/TC 276

ISO/TC 276：Biotechnology Chair：Germany

~~WG 3~~→SC 1：Analytical methods Chair：United States

- WG 1: Gene delivery
- WG 2: Cell characterization
- WG 3: Nucleic acid characterization

WG 2: Biobanks and bioresources
Convenor：Austria

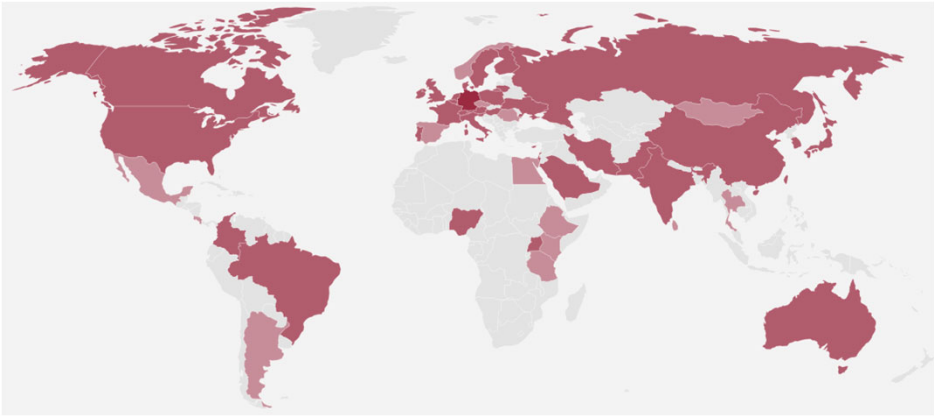
WG 4: Bioprocessing
Convenor：Japan

WG 5: Data processing and integration
Convenor：Germany

WG 6: Nucleic acid- and protein-based devices
Convenor：China

National mirror committee

- Forum for Innovative Regenerative Medicine (FIRM)
- About 86 participants from industry, government, and academia



Participating member : 37 countries

Australia, Austria, Belgium, Brazil, Canada, China, Colombia, Cyprus, Denmark, Finland, France, Germany, Hungary, India, Islamic Republic of Iran, Ireland, Israel, Italy, Japan, Republic of Korea, Lithuania, Luxembourg, Netherlands, Nigeria, Pakistan, Poland, Portugal, Russian Federation, Saudi Arabia, Singapore, Slovenia, Sweden, Switzerland, Uganda, Ukraine, United Kingdom, United States

Observing member : 16 countries

Argentina, Costa Rica, Czech Republic, Egypt, Ethiopia, Hong Kong, Kenya, Malta, Mexico, Mongolia, Norway, Romania, Spain, Sri Lanka, Thailand, United Republic of Tanzania

➢ Standards in the field of regenerative medicine are developed by SC 1 and WG 4.

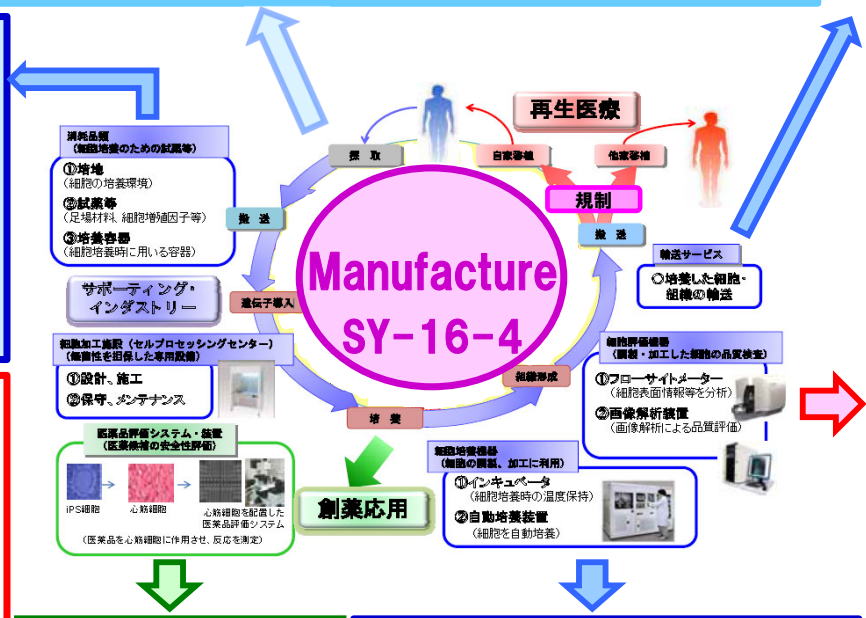
Overview of standards in regenerative medicine

Cellular starting materials

Supporting industries

Supporting industries

SY-16-5



Analytical methods

SY-16-2
SY-16-3

Related field
(Gene delivery System)

Related field
SY-16-2

Supporting industries

Red:Published、Blue:To be published by FY2024, J:Developed by Japan as PL

Overview of standards in regenerative medicine

Material cell

General requirements for Biobanking

ISO 20387:2018; General requirements for **biobanking**

Supply facility of Cellular starting materials

(under consideration)

Supporting Industry

Ancillary material J

ISO 20399:2022

Ancillary materials present during the production of cellular therapeutic products and gene therapy products

Packaging J

ISO 20404:2023

General requirements for the **design of packaging** to contain cells for therapeutic use

Gene Delivery Systems

Vocabulary

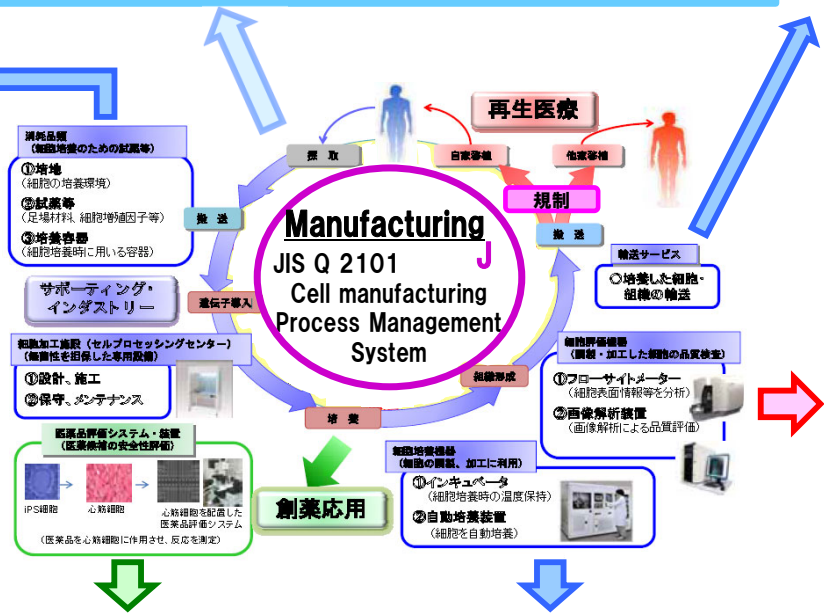
ISO/WD 16921-1:Gene Delivery Systems — Part 1: Vocabulary

Viral Vector

ISO/WD 16921-2:Gene Delivery Systems — Part 2: Guide for Methods for the Qualification of Viral Vectors

mRNA-Lipid Nanoparticles

ISO/PWI 16921-3:Gene Delivery Systems — Part 3: Guide for Methods for the Measurements of mRNA-Lipid Nanoparticles



Related field

Drug discovery J

Extracellular vesicle

(started development) J

Manufacturing equipment

Equipment system

ISO/TS 23565:2021

General requirements and considerations for **equipment systems** used in the manufacturing of cells for therapeutic use

Supporting Industry

transportation J

ISO 21973:2020:General requirements for **transportation** of cells for therapeutic use

Analytical method

testing and characterization J

ISO 23033:2021:General requirements and considerations for the **testing and characterization** of cellular therapeutic products

Cell counting - General guidance

ISO 20391-1:2018:**Cell counting** -- Part 1: **General guidance** on cell counting methods

Cell counting - Experimental design

ISO 20391-2:2019:**Experimental design and statistical analysis** to quantify counting method performance

Rapid microbial detection

ISO 24190:2023:Risk based approach for method selection and validation of methods for **rapid microbial detection** in bioprocesses

Cell viability

ISO/CD 8934:General considerations and requirements for **cell viability** analytical methods — Part 1: Mammalian cells

Cellular morphology J

ISO/DIS 24479:Minimum requirements for cellular morphological analysis

Red:Published、**Blue**:To be published by FY2024, J:Developed by Japan as PL

Diversification of modalities, related fields

Gene delivery systems (led by US, UK)

Reference	Title
ISO/WD 16921-1	Gene delivery systems — Part 1: Vocabulary
ISO/AWI 16921-2	Gene delivery systems — Part 2: Guide for methods for the qualification of viral vectors
ISO/PWI 16921-3	Gene delivery systems — Part 3: Lipid nanoparticles

Extracellular vesicles (EV) (JP)

- ✓ Vesicles secreted by cells, contain functional molecules such as proteins and nucleic acids.
- ✓ Manufacturing, purification and characterization are the main issues for standardization.

Organoid (KR)

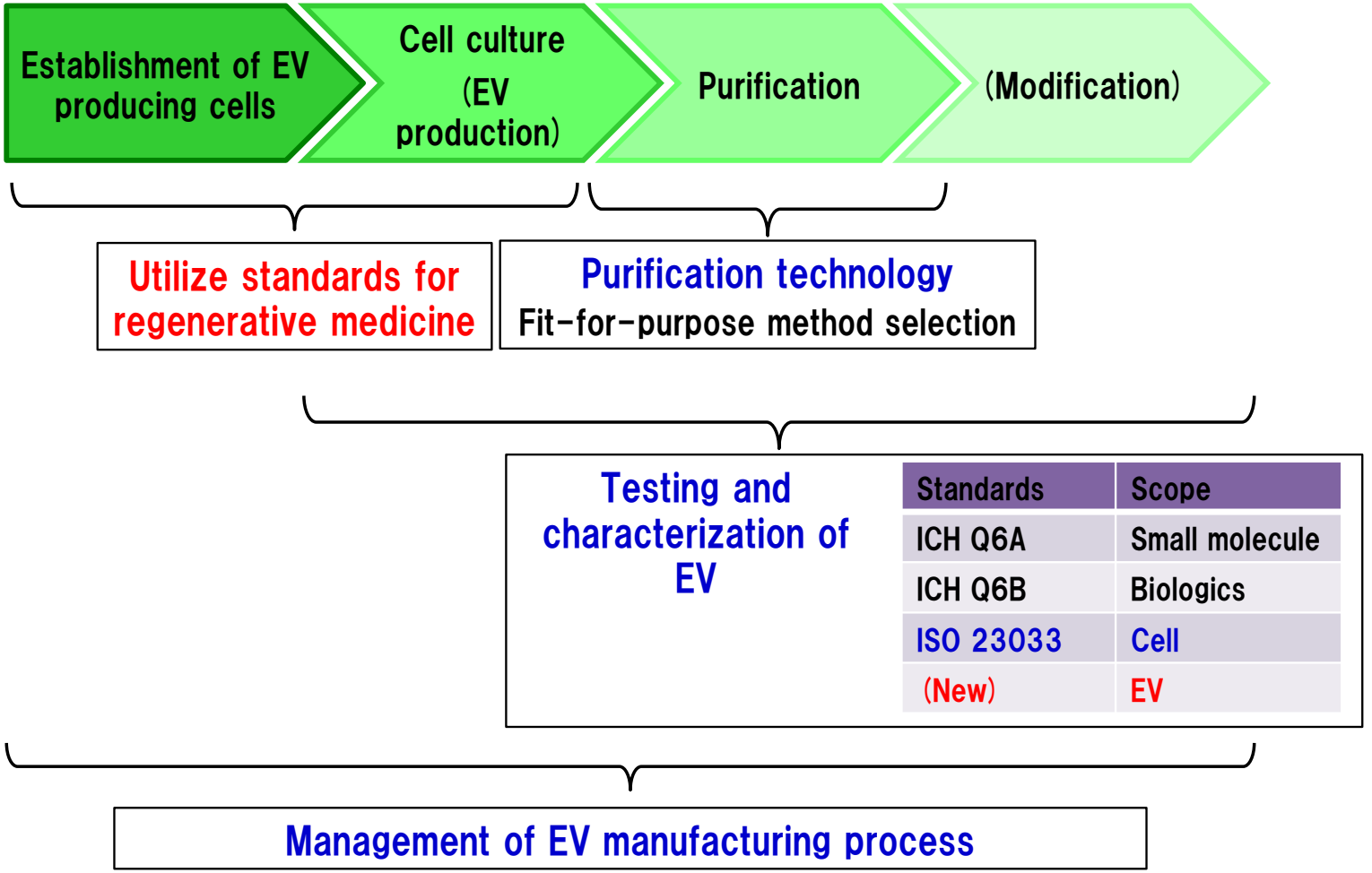
- ✓ Proposal notice about "Guidelines for manufacturing of organoid" came up from Korea.

MPS (Microphysiological system) (JP)

- ✓ ISO/TC 276 plans to develop standard that specifies the roles of users and suppliers.
- ✓ Device technology is discussed in ISO/TC 48/WG 3 (Laboratory equipment - Microfluidic Devices).

➢ Proceeding while considering priority fields.

Application of standards to exosome



Summary

- The usage of standards is optional, but they make activities, such as technology transfer and approval review, efficient.
- The feature of industrial structure of regenerative medicine and the difficulty of applying existing guidelines necessitate standards for regenerative medicine.
- Standards for regenerative medicine are classified as “analytical methods”, “manufacturing” and “products and services of supporting industries”.
- Standardization is also proceeding for diversified modalities and related fields.


FIRM
Forum for Innovative
Regenerative Medicine