SY-16 3月21日（木） 8:30～10:30 （第11会場 ホテル日航新潟 4F 朱鷺B）
シンポジウム16　標準　～アカデミアと産業界をつなぐためのツール～

Development of Cell Manufacturing Process Management System as JIS
JISとしての細胞製造マネジメントシステムの開発

Ryuji Kato
Graduate School of Pharmaceutical Sciences,
Nagoya University

筆頭演者は、過去１年間（1月～12月）において、
本演題の発表に関して開示すべきCOIはありません。

Actions toward the “Industrialization of Regenerative Medicine”

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

Guidance for Industry

Draft：2017.2.18.

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010 or email at ocod@fda.hhs.gov, or from the Internet at https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

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

ARM and NIIMBL Release Project A-Cell to Bring Quality by Design Principles to Cell-Based Therapy Manufacturing

Washington, DC – July 26, 2022

Effort to address challenges to the manufacturing scale-up of cell-based therapies follows release of Project A-Gene for gene therapy in 2021

The Alliance for Regenerative Medicine (ARM) and the National Institute for Innovation in Manufacturing BioPharmaceuticals (NIIMBL) today released Project A-Cell, a multistakeholder collaboration to incorporate Quality by Design (QbD) principles into a manufacturing case study of a Chimeric Antigen Receptor T-cell (CAR-T) therapy.

Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products

Draft Guidance for Industry

This guidance document is for comment purposes only.

2022.7.19

Submit one set of either electronic or written comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or email ocod@fda.hhs.gov, or from the Internet at https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances.

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
July 2023

We should use Quality by Design concept.
We should effectively use “standards”.

Definition of “Standard”

Standard： 標準＝拘束力はない。世界的な団体によって承認されている。

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： 規制＝各国で守ることが必須。

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

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

ICH guideline：「標準」的位置づけだが、規制当局の承認を必要とする。

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.

Common opinions

We are planning JIS in this field. How do you think?

✦It’s so tough already. Why do we need MORE regulations?

JIS / ISO is not a regulation.
Free to use. No punishment.

✦Is it really needed in abroad? Is it recommended by FDA?

ISO is the “World’s standard”.
FDA is now strongly acting for it!

✦What is written? We are familiar with ICH, but not ISO.

Introduced in this talk.

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

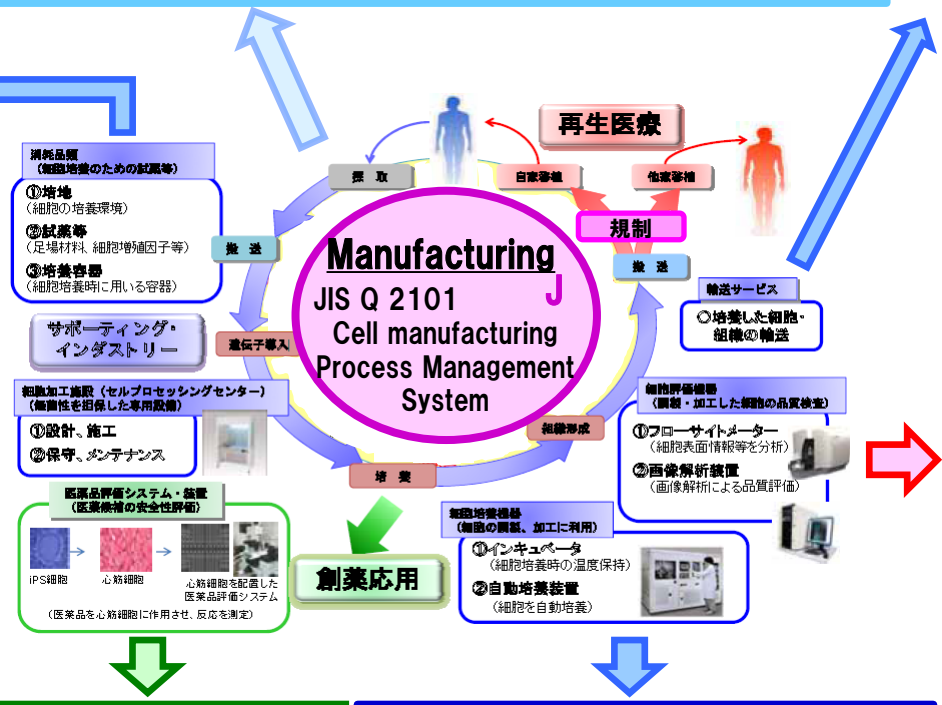
ISO/WD 16921-1:Gene Delivery Systems — Part 1: Vocabulary

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

Challenge for development of standard in cell manufacturing field

International Organization for Standardization

TC276 WG4 members

SY-20 3月22日（金）9:00～11:00
（第3会場 朱鷺メッセ 3F 中会議室301）
シンポジウム20
細胞製造の安定化に向けた最新技術

Aspects from Industry

FIRM Forum for Innovative Regenerative Medicine

Chair
Yoshitsugu Shitaka

Practical research

AMED

Establishment of QbD-based control strategy and Advanced Core Ecosystem in cell manufacturing
(**ACE** project)
Project Leader
Prof. M. Kino-oka (Osaka Univ.)

JIS

Development of JIS Q 2101

Challenge for development of standard in cell manufacturing field

Development of JIS Q 2101

2023.07: Draft making committee

↓

8 months of discussion (5 meetings)

↓

2024.02: Draft submission

↓

10 months “Deliberation” with “Public comments”

↓

2025.03 Hopefully…

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委員長	加藤　竜司	名古屋大学	中立者
委員	河内　幾生	富士フイルムホールディングス株式会社	生産者
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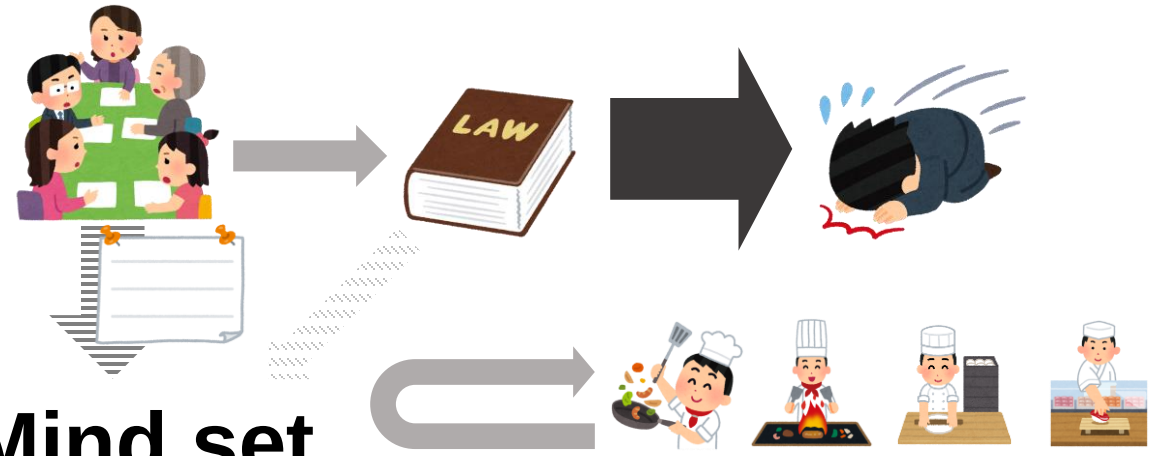
関係者	野田　慎一	独立行政法人 医薬品医療機器総合機構	使用者
関係者	櫻井　信豪	東京理科大学	使用者
関係者	松原　吉紀	Minaris Regenerative Medicine株式会社	生産者
事務局	佐土原哲也	一般社団法人再生医療イノベーションフォーラム	



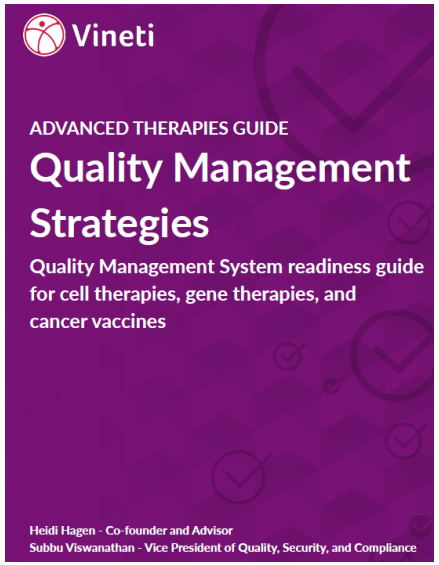
Mind set

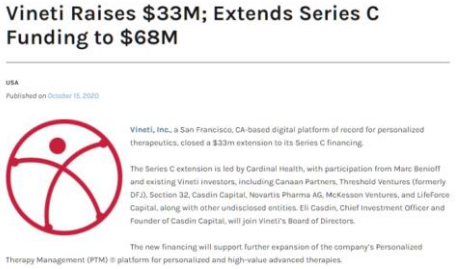
Development of standard is not making “detailed RULE BOOK”.

Making Mindset for Objective

What is the “Mindset” for quality control?

Quality Management System = Make quality management like SYSTEM




Vineti Raises $33M; Extends Series C Funding to $68M

USA

Published on October 15, 2020

Vineti, Inc., a San Francisco, CA-based digital platform of record for personalized therapeutics, closed a $33m extension to its Series C financing.

The Series C extension is led by Cardinal Health, with participation from Marc Benioff and existing Vineti investors, including Canaan Partners, Threshold Ventures (formerly DFJ), Section 32, Casdin Capital, Novartis Pharma AG, McKesson Ventures, and LifeForce Capital, along with other undisclosed entities. Eli Casdin, Chief Investment Officer and Founder of Casdin Capital, will join Vineti's Board of Directors.

The new financing will support further expansion of the company's Personalized Therapy Management (PTM) ® platform for personalized and high-value advanced therapies.

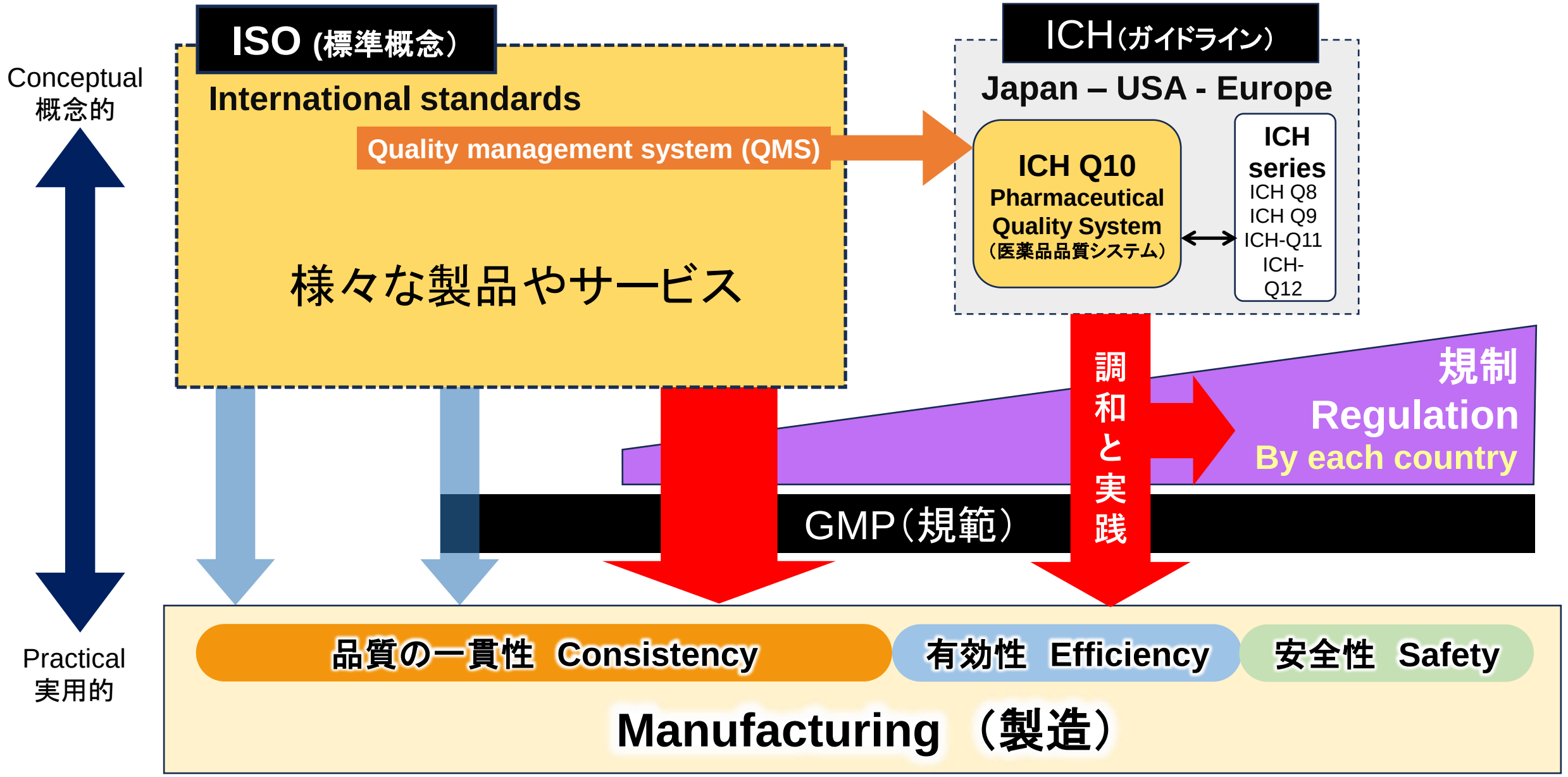
QUALITY MANAGEMENT SYSTEMS (QMS) - THE ESSENTIALS

True biopharmaceutical quality requires a robust “Quality Management System” (QMS). In order to carry out its mission to ensure patient safety, the FDA requires Quality oversight of all aspects of drug product production throughout the product lifecycle and recommends that biopharmaceutical companies operate a full QMS.[1,2,3,4,5] The EMA has similar requirements and directs companies to conform to ICH Q10.[6]

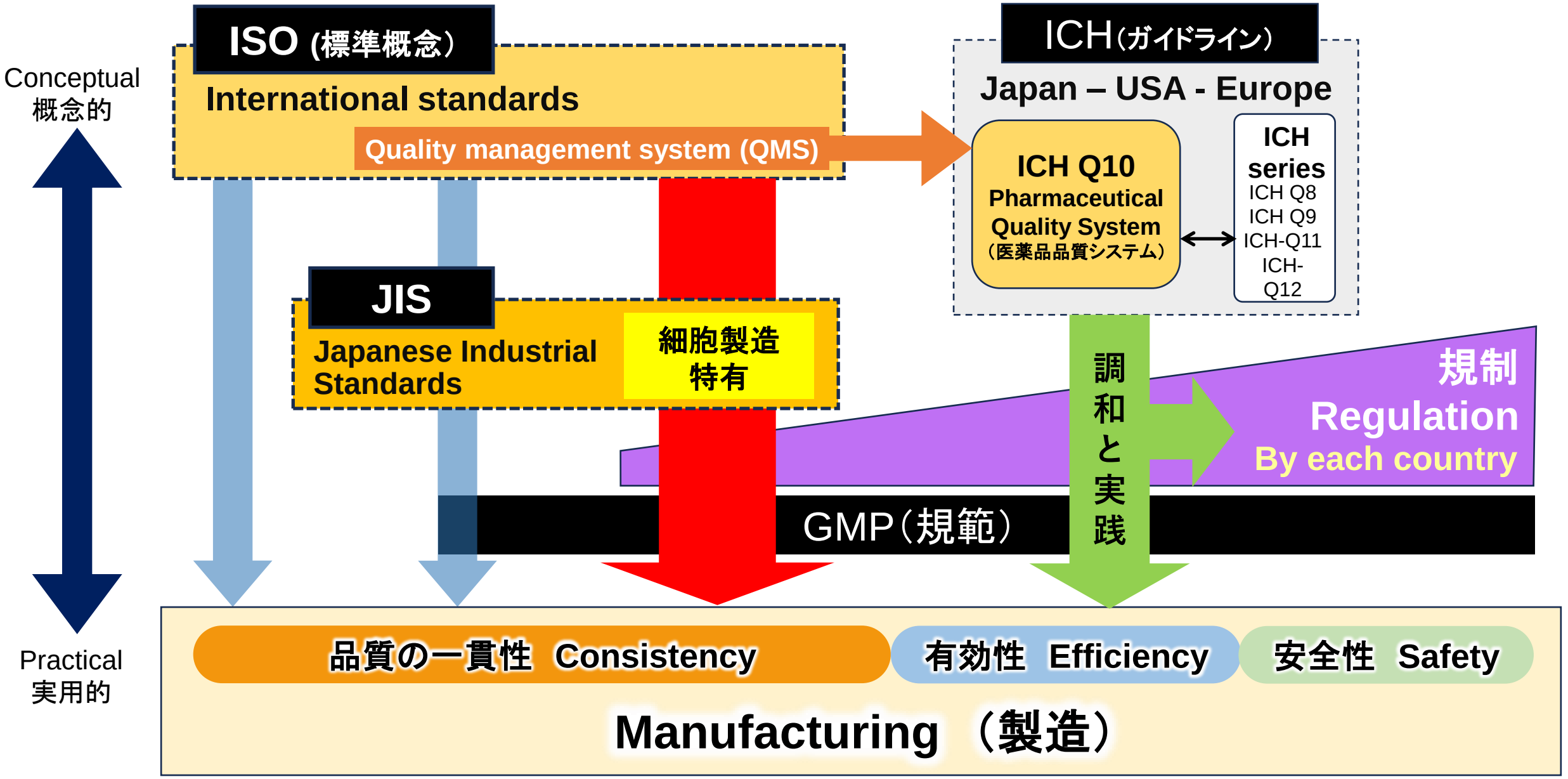
At the highest level, a QMS is defined by the FDA as a “Management system to direct and control a pharmaceutical company with regard to quality.”[2] Or put another way, a QMS is a basket of tools and systems used by an organization and its supply chain stakeholders to ensure that a quality drug product is produced and delivered every time. This includes elements such as quality control testing, training, vendor audits, standardized processes, lot genealogy, and in-process drug product labeling. Many of these QMS activities are collectively known as “current Good Manufacturing Practices” (cGMP), which are commonplace in the biopharma industry, but not in healthcare settings and other parts of the ecosystem for advanced therapies. This extension of cGMP into non-traditional settings is one of the key differences involved in implementing a robust QMS for advanced therapies.

Asking “Can you create YOUR OWN RULE for quality control?”

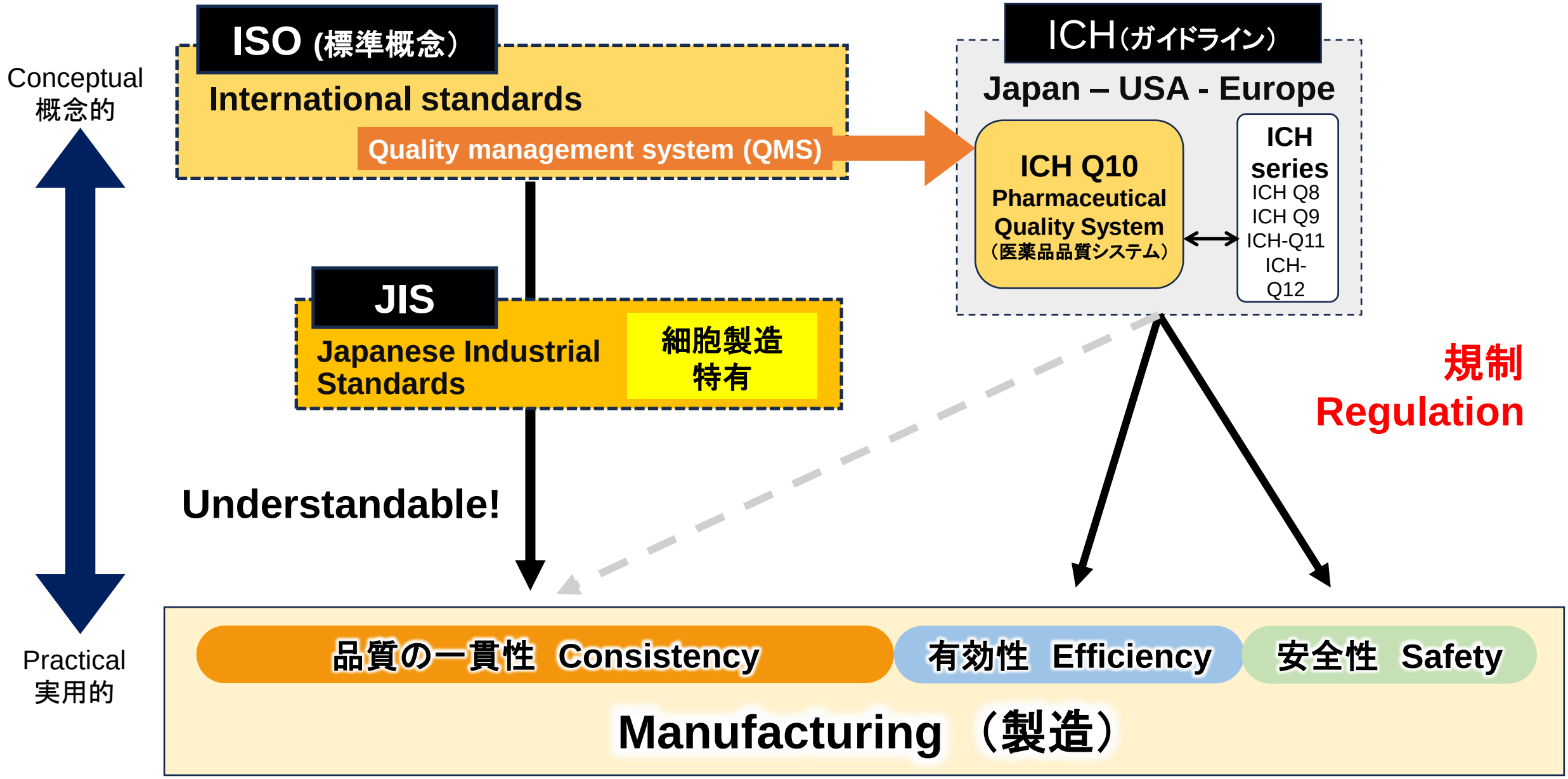
Standards & Regulations toward “cell manufacturing”



Standards & Regulations toward “cell manufacturing”



Standards & Regulations toward “cell manufacturing”



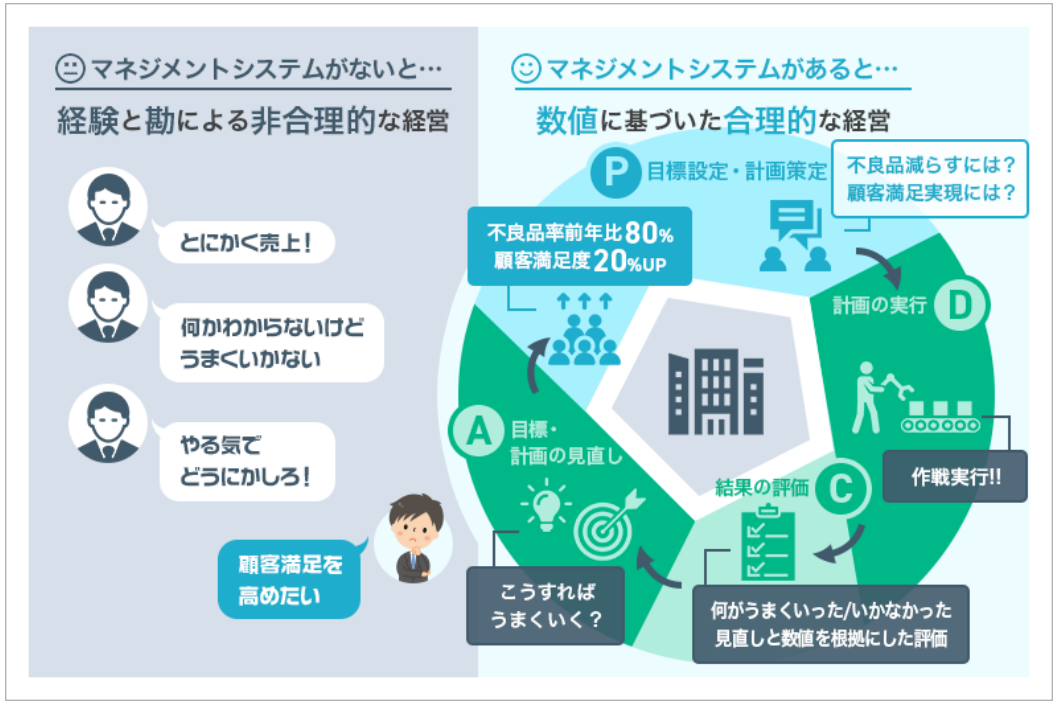
Concept of “Standard for Cell Manufacturing”

“Cell manufacturing Processing Management System (CPMS)”

Cell manufacturing version of “ISO 9001”

ISO 9001

Quality Management System （QMS）
「品質に関して組織を指揮し
管理するためのマネジメントシステム」



https://activation-service.jp/iso/column/2735

QMS ＝ Managing organization

~~Rule book~~

Framework for Making OWN rule

2 main concepts

Risk-based thinking ＋ PDCA Cycle ＝

・How to consider finding CQA/CPP
・Terms and definitions

Consistent quality management

Concept of developing standard : CPMS

“Cell manufacturing Processing Management System (CPMS)”

<Objectives >
Supporting the establishment of QMS (Quality Management System) to achieve consistent cell quality throughout the entire product lifecycle of therapeutic cells.

Introduction of QMS concept
↓
Standardizing the mindset, perspective, common sense, and concepts
↓
Acquiring the capability of "QMS-based operation" in various organizations
↓
Realizing stable cell manufacturing (from material acceptance to shipping)

QMS (Quality Management System) concept from ISO9001

ISO 9001の構成は次の通りです。

まえがき	
序文	0.1 一般 0.2 品質マネジメントの原則 0.3 プロセスアプローチ 0.4 他のマネジメントシステム規格との関係
1 適用範囲	
2 引用規格	
3 用語及び定義	
4 組織の状況	4.1 組織及びその状況の理解 4.2 利害関係者のニーズ及び期待の理解 4.3 品質マネジメントシステムの適用範囲の決定 4.4 品質マネジメントシステム及びそのプロセス
5 リーダーシップ	5.1 リーダーシップ及びコミットメント 5.2 方針 5.3 組織の役割、責任及び権限
6 計画	6.1 リスク及び機会への取組み 6.2 品質目標及びそれを達成するための計画策定 6.3 変更の計画
7 支援	7.1 資源 7.2 力量 7.3 認識 7.4 コミュニケーション 7.5 文書化した情報
8 運用	8.1 運用の計画及び管理 8.2 製品及びサービスに関する要求事項 8.3 製品及びサービスの設計・開発 8.4 外部から提供されるプロセス、製品及びサービスの管理 8.5 製造及びサービス提供 8.6 製品及びサービスのリリース 8.7 不適合なアウトプットの管理
9 パフォーマンス評価	9.1 監視、測定、分析及び評価 9.2 内部監査 9.3 マネジメントレビュー
10 改善	10.1 一般 10.2 不適合及び是正処置 10.3 継続的改善
付属書 A（参考） 付属書 B（参考）	新たな構造、用語及び概念の明確化 ISO/TC 176 によって作成された品質マネジメントシステム及び品質マネジメントシステムの他の規格類

https://www.jqa.jp/service_list/management/service/iso9001/

The concept of “Standard for Cell Manufacturing”

Aspect of Management System Standard (MSS) from ISO9001

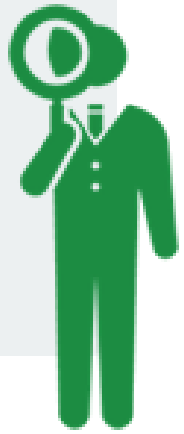
認証取得の効果

① 社会的信頼の獲得

② 第三者の視点による
問題の発見

③ 継続的な改善

認証証明書
（登録証）

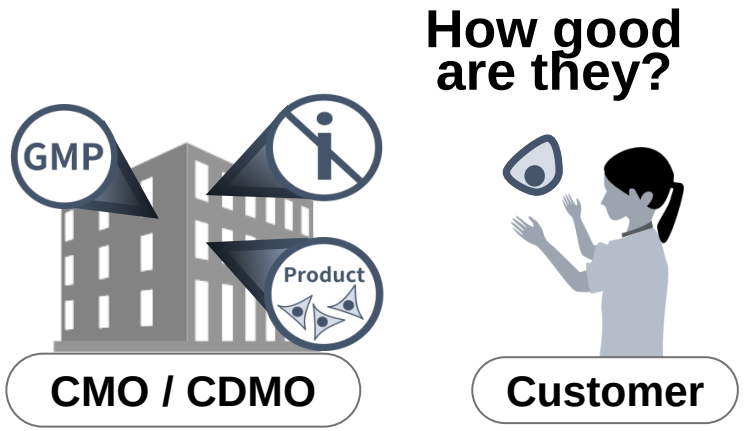


https://www.jqa.jp/service_list/management/management_system/

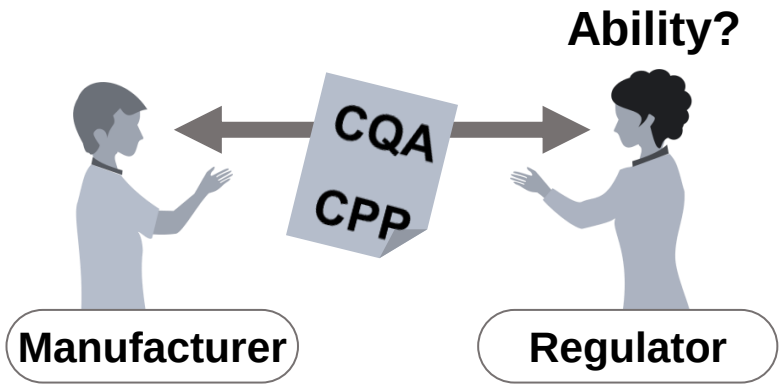
Vision of "cell manufacturing capability certification" can make an important brand for manufacturers, especially CMOs and CDMOs.

Concept of CPMS (Cell manufacturing Process Management System)

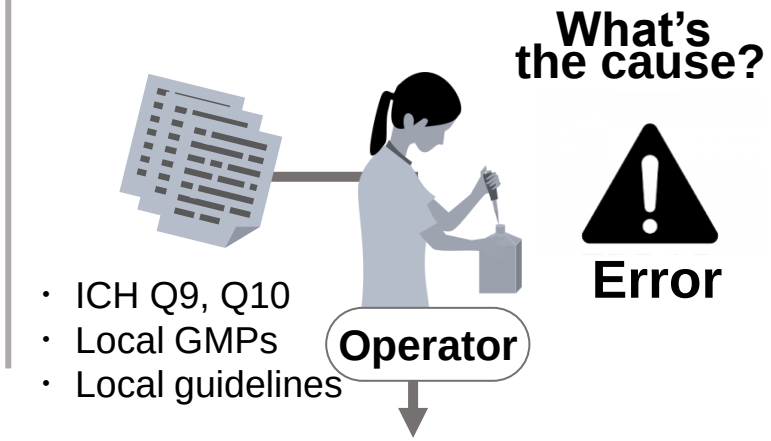
■Gap case1 : Customer understanding



■Gap case2 : Regulatory understanding

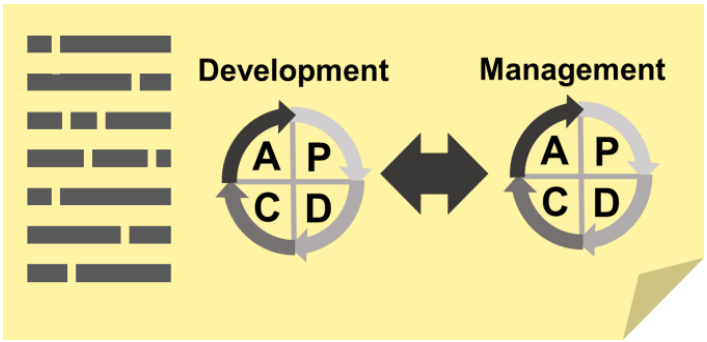


■Gap case3 : Reasonable PDCA



JIS

Framework document



Written in Japanese!

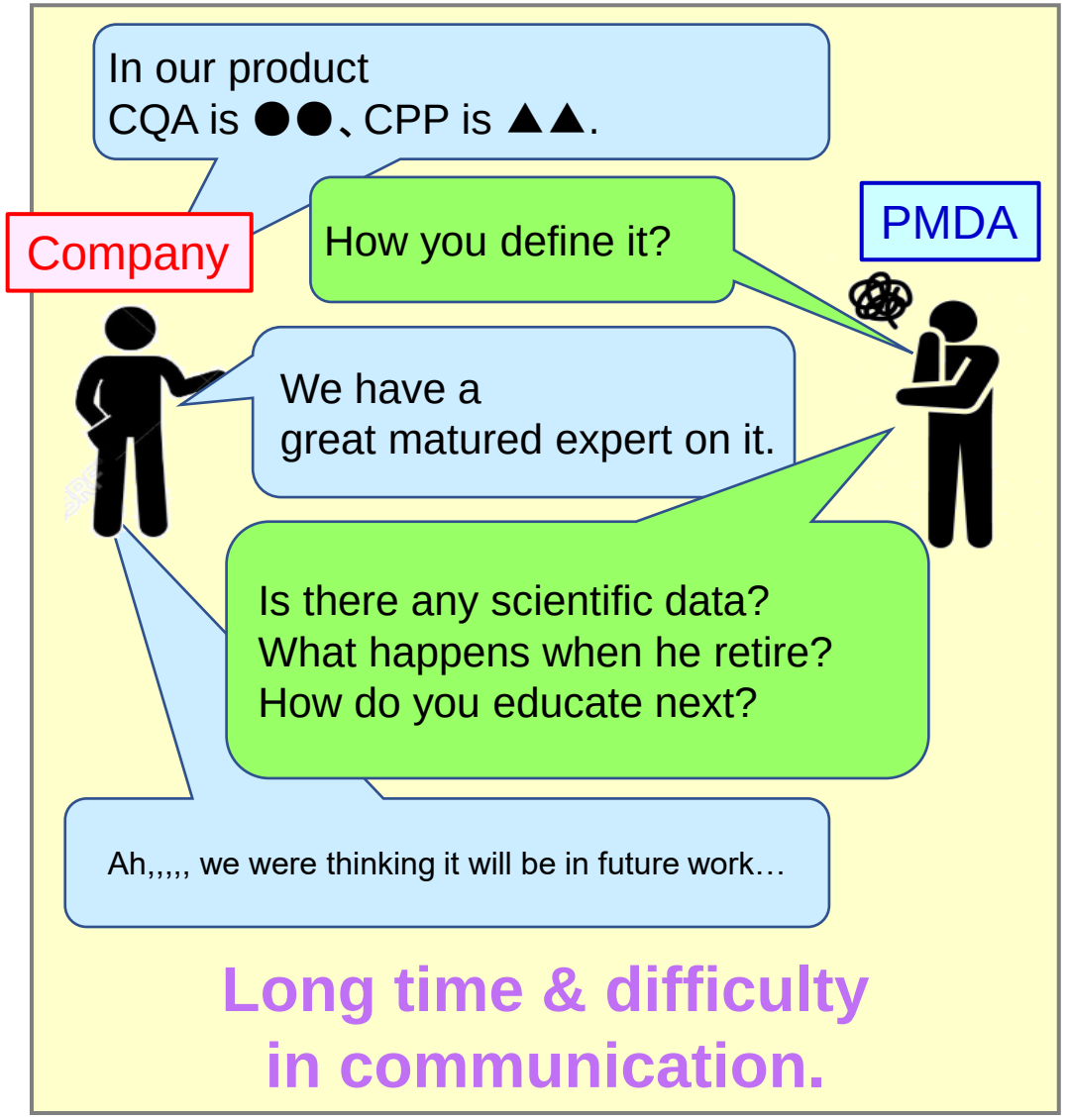
+

Instruction

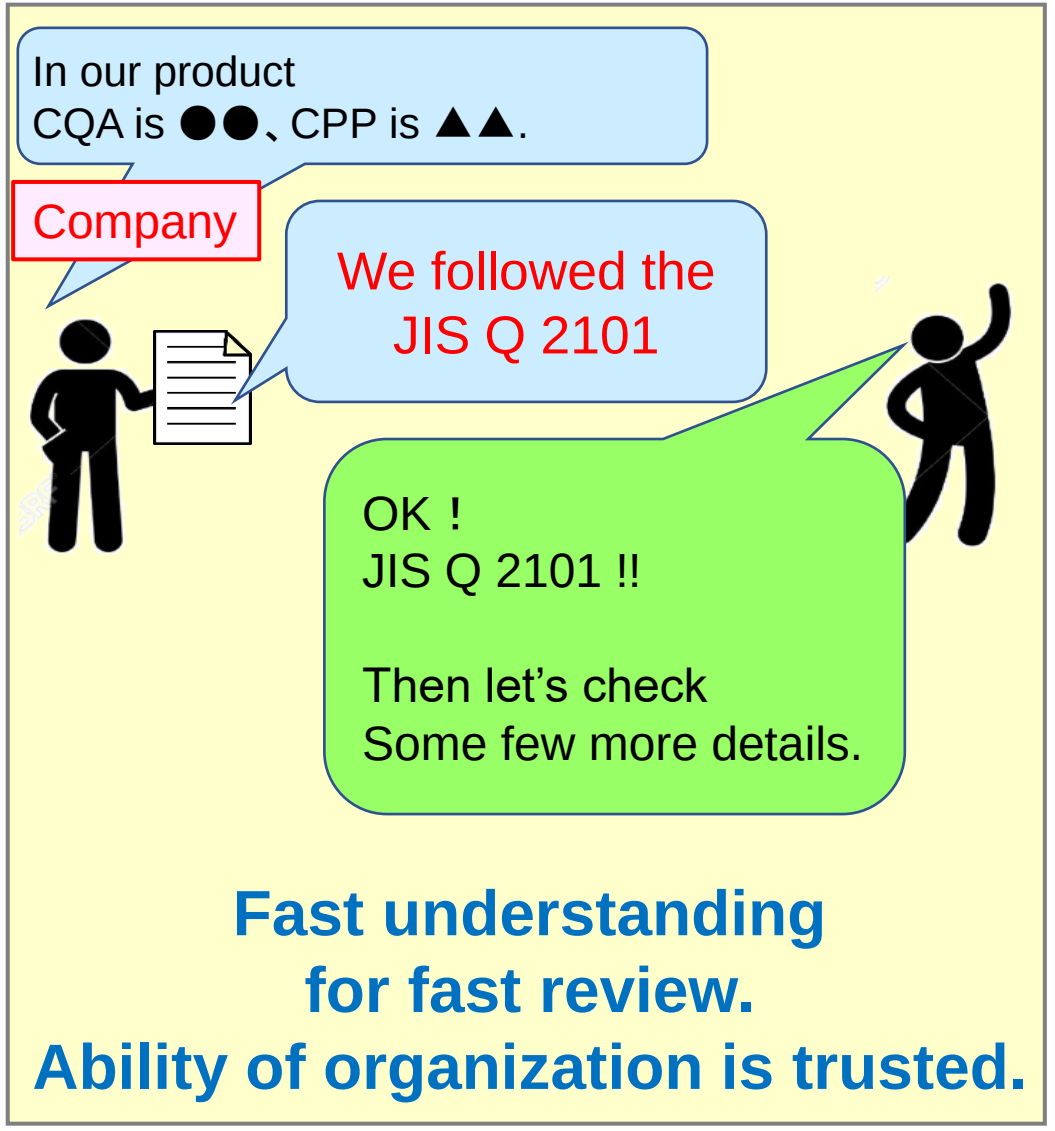
More episodes and details about the document.

Expected effect of JIS standard in cell manufacturing

Before
(without standard)



After
(with JIS Q 2101)



For whom CPMS is effective?

“Consistent quality control” is a difficult task in every stage.

NEVER too early!!!

CPMS target

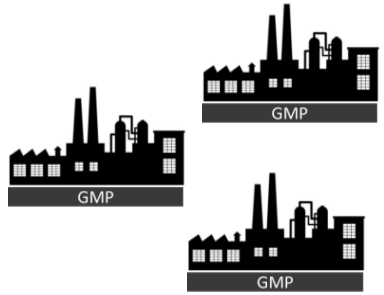
Researches
Not ready for
cell manufacturing.

Basic research

Academia/start-up
Who aim for cell
manufacturing.

Laboratory
(Process development)

Clinical trial-level
(Tech transfer)



Larger-scale
Scale-up / Scale out
(Commercial)

NOT familiar to GMP

Familiar to GMP

Concept of JIS 2101

✦**Not a rule book.**

But a “framework” to make your OWN rules.

✦**Not a manual describing “what to do”.**

But describing “how to do” and “how to think” for cell specific cases.

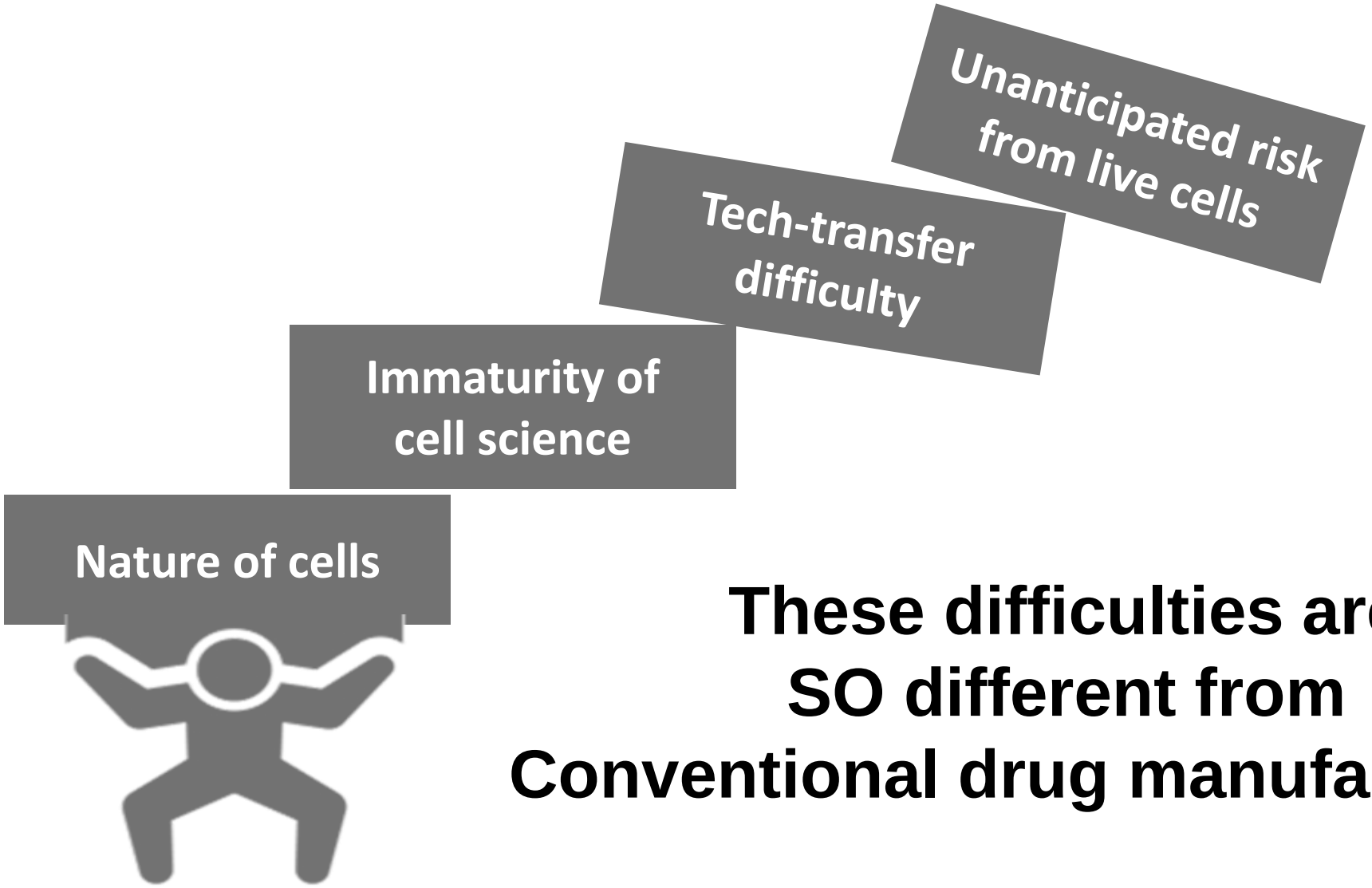
✦**Not a textbook nor technical note.**

But its “concept” and “the first step idea” is written.

✦**Not an obligation.**

But it’s worth reading through for better communication and plan.

Cell-specific difficulties



These difficulties are SO different from Conventional drug manufacturing!

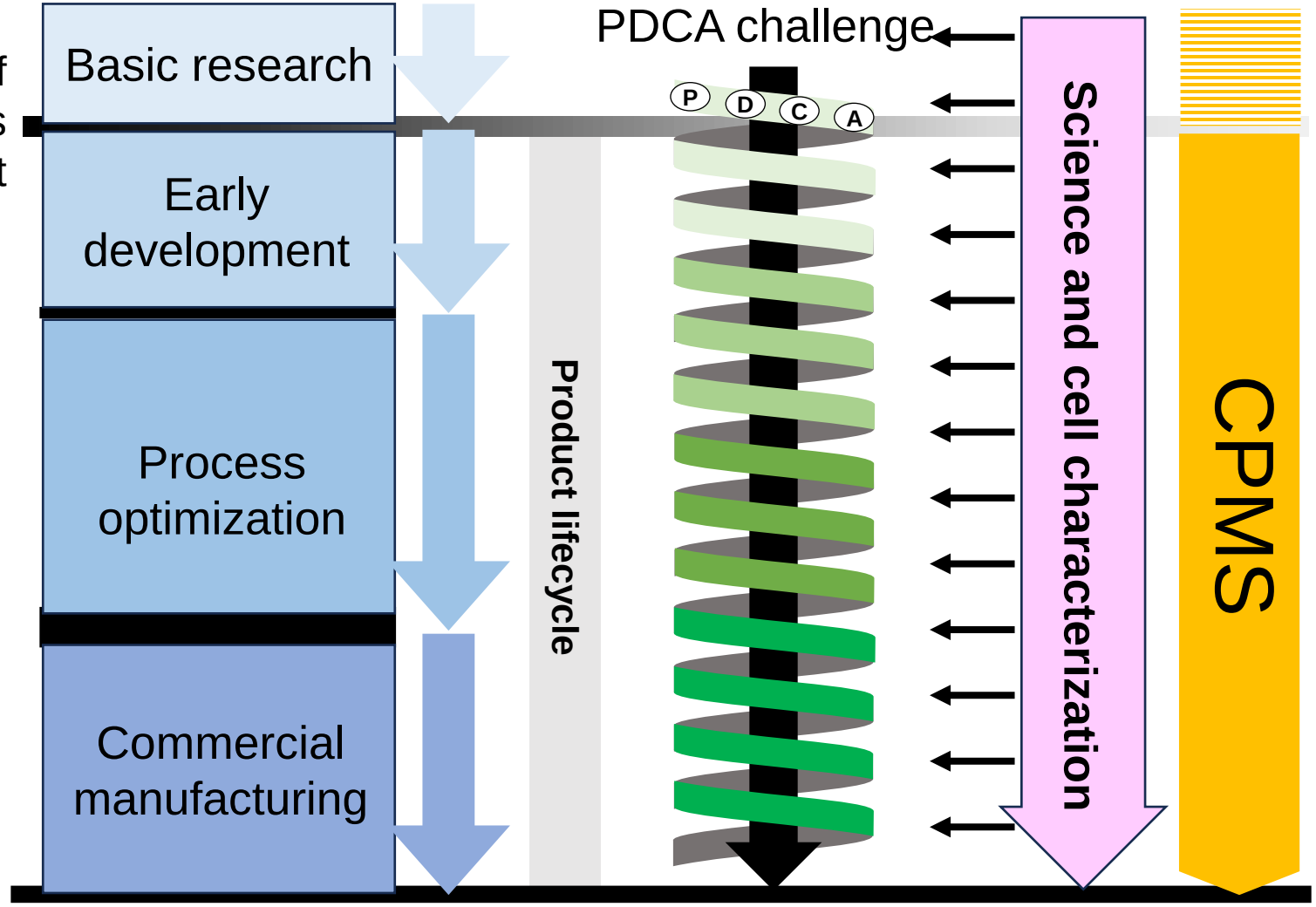
What is the specificity in Cell Manufacturing Process?

Cell-specific difficulties

- **Unanticipated risk from live cells**
- **Tech-transfer difficulty**
- **Immaturity of cell science**
- **Nature of cells**

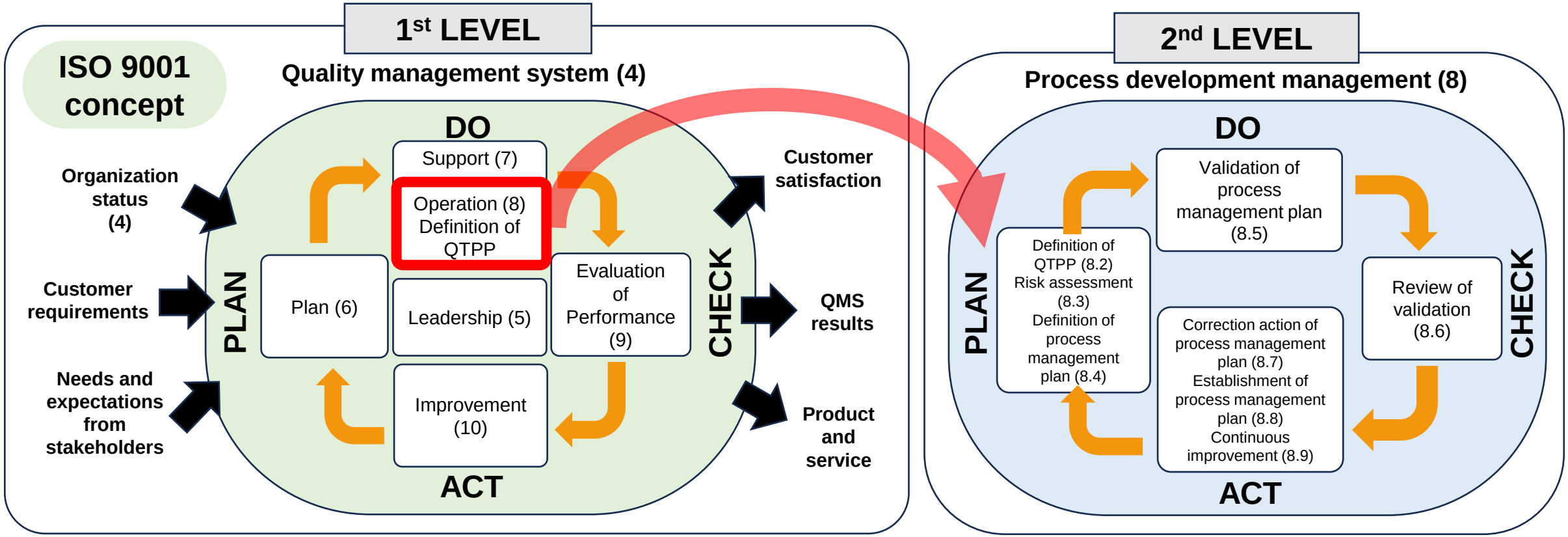
Typical flow of drug process development

Manufacturing with cell-specific difficulties



Continuous improvement is ESSENTIAL

“Cell manufacturing Processing Management System (CPMS)”



How to do “Organization management”

How to do “Process development”

CPMS is linked to QbD

Conventional quality management concept

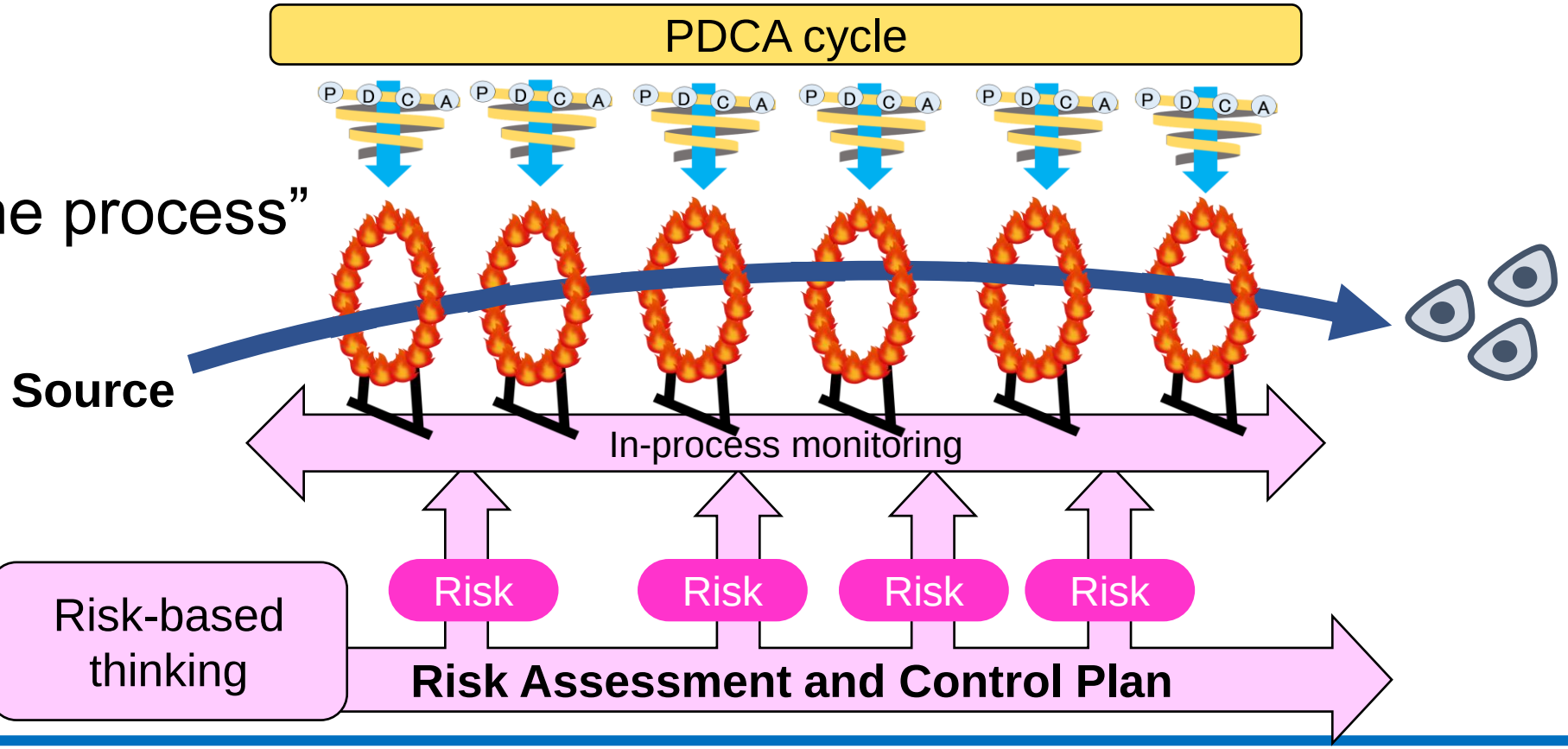
Manage to make “the same product”

QbT

(Quality by Testing)

Cell manufacturing = long, fragile, and complex

Manage to make “the same process”



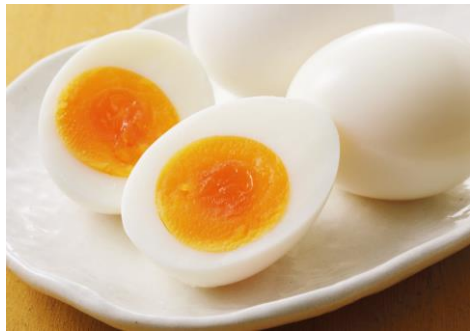
QbD Quality by Design

Approach-based	Process Validation
Just defining operation	prove that the process is good.
↓	↓
With out testing	Show that it is good.
↓	↓
Without tasting	**Make it delicious.**

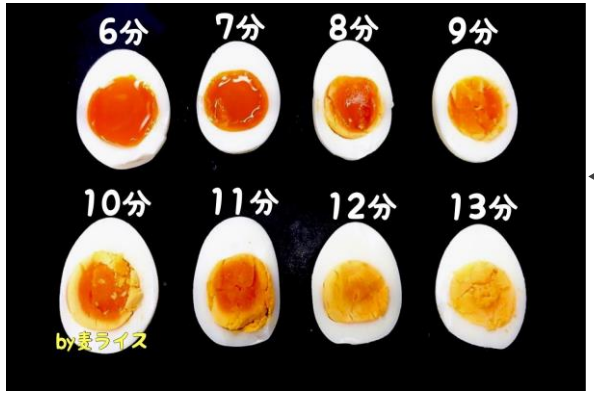
Without tasting **Make it delicious.**

①Define the quality!

美味さ＝半熟度＋表面ツルリ： QTPPの決定！ **Quality**



②Think about important point!



③Test and find-out the design space.

④Keep the time

Design

Quality by Design: Introduction episode

Without tasting **Make it delicious.**

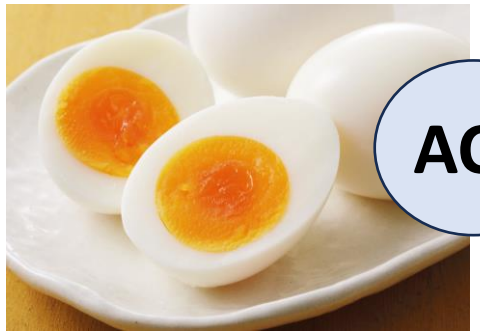
①Define the quality!

美味さ＝半熟度＋表面ツルリ： QTPPの決定！

Quality

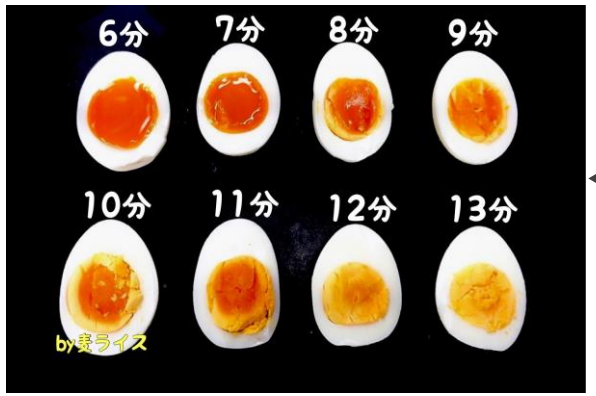
PLAN

CHECK



ACT

②Think about important point!



④Keep the time

Design

③Test and find-out the design space.

DO

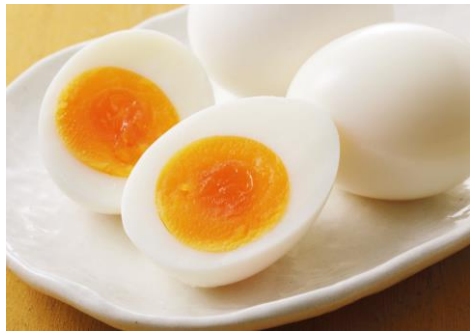
Without tasting　Make it delicious.

①Define the quality!

Process validation

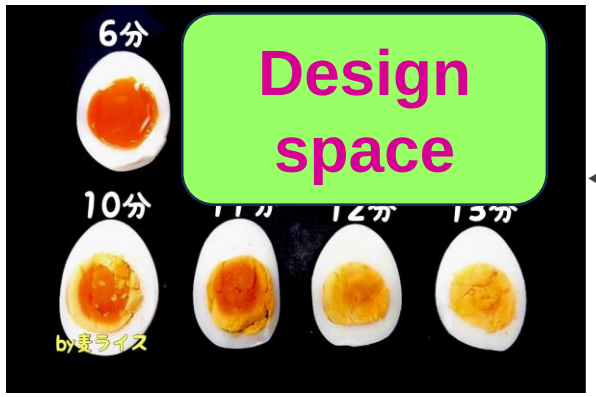
美味さ＝半熟度＋表面ツルリ： QTPPの決定！

「黄身の半熟度」
「ムケやすさ」:
CQA



②Think about important point!

Risk-based Approach



Design space

・水の量
・卵と水の比率
・鍋のサイズ
・温度
・時間

PPs

③Test and find-out the design space.

④Keep the time

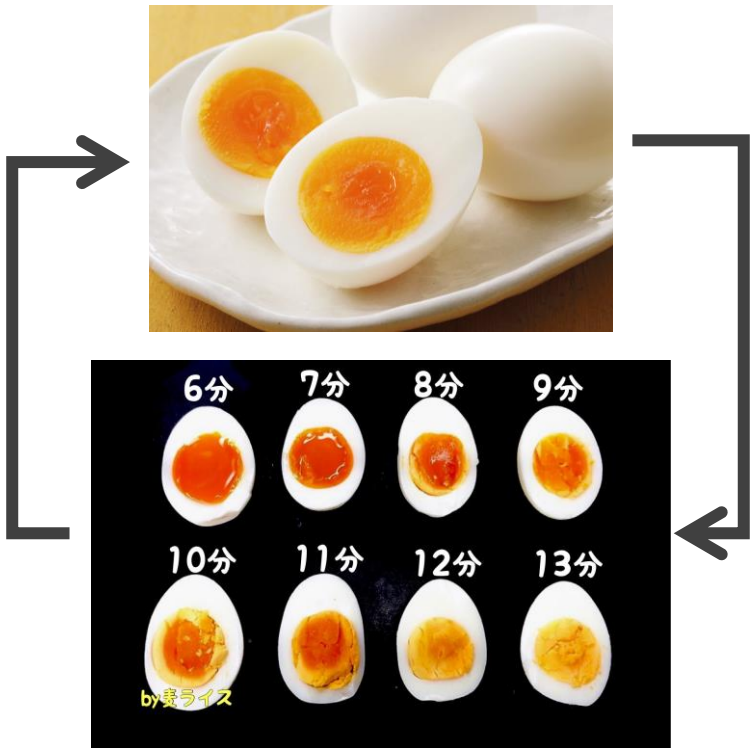
沸騰時間
CPP

PAT

Quality by Design is only achievable with “framework standard”

Without tasting

Make it delicious.



- ✦ Target taste can be different.
- ✦ Kitchen equipment can be different.
- ✦ Cooking volume can be different.

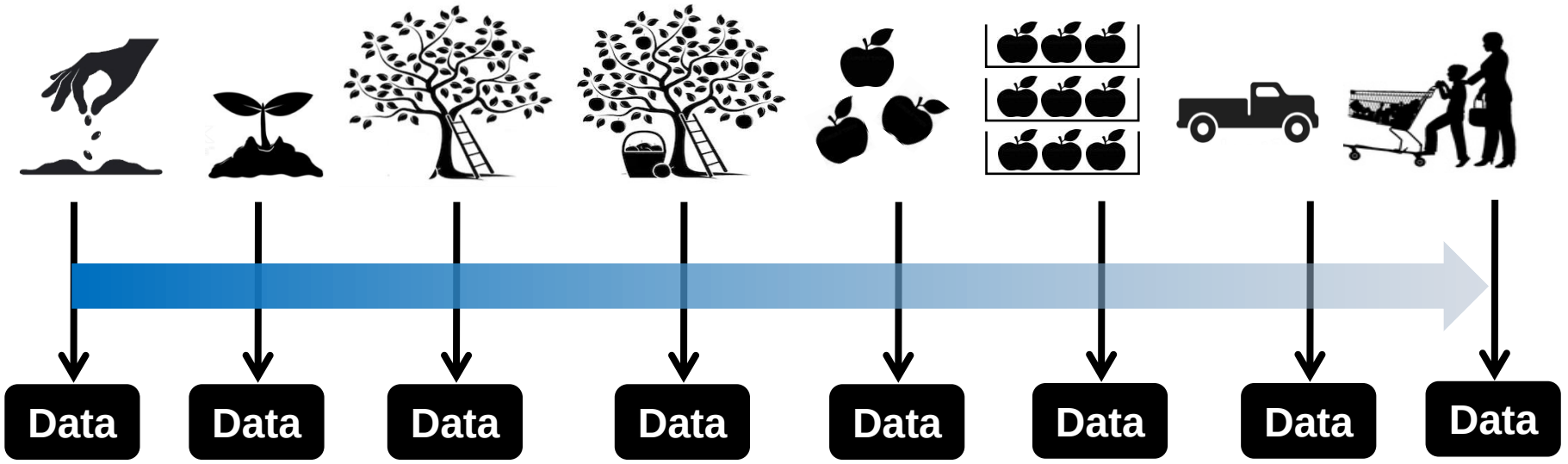
~~**Rule book**~~

Framework for Making OWN rule

CPMS = Quality Management System (QMS)

Risk-based thinking ✚ PDCA Cycle

Important points for “the future cell manufacturing”



Knowing the process by DATA Do you have quantitative data?

Ability to manage QbD Have you introduced QMS?

Organization ability to understand the process

JIS

Framework document + Instruction

JIS Q 2101

Expectations for JIS Q 2101 (CPMS)

Conceptual
概念的

Practical
実用的

ISO (標準概念)

International standards

Quality management system (QMS)

ICH (ガイドライン)

Japan – USA - Europe

ICH Q10
Pharmaceutical Quality System
(医薬品品質システム)

ICH series
ICH Q8
ICH Q9
ICH-Q11
ICH-Q12

JIS

Japanese Industrial Standards

細胞製造特有

JIS

Please contact us!
If you are interested in!

JIS Q 2101

品質の一貫性 Consistency

有効性 Efficiency

安全性 Safety

Manufacturing （製造）