July 22, 2019
Tokyo, Japan

The 25th Annual Meeting of Japan Society of Gene and Cell Therapy

The Minimum Consensus Package for Securing the Quality and Safety of Human Cell-Based Therapeutic Products

細胞加工物の品質・安全性確保の技術要件に関するミニマム・コンセンサス・パッケージ

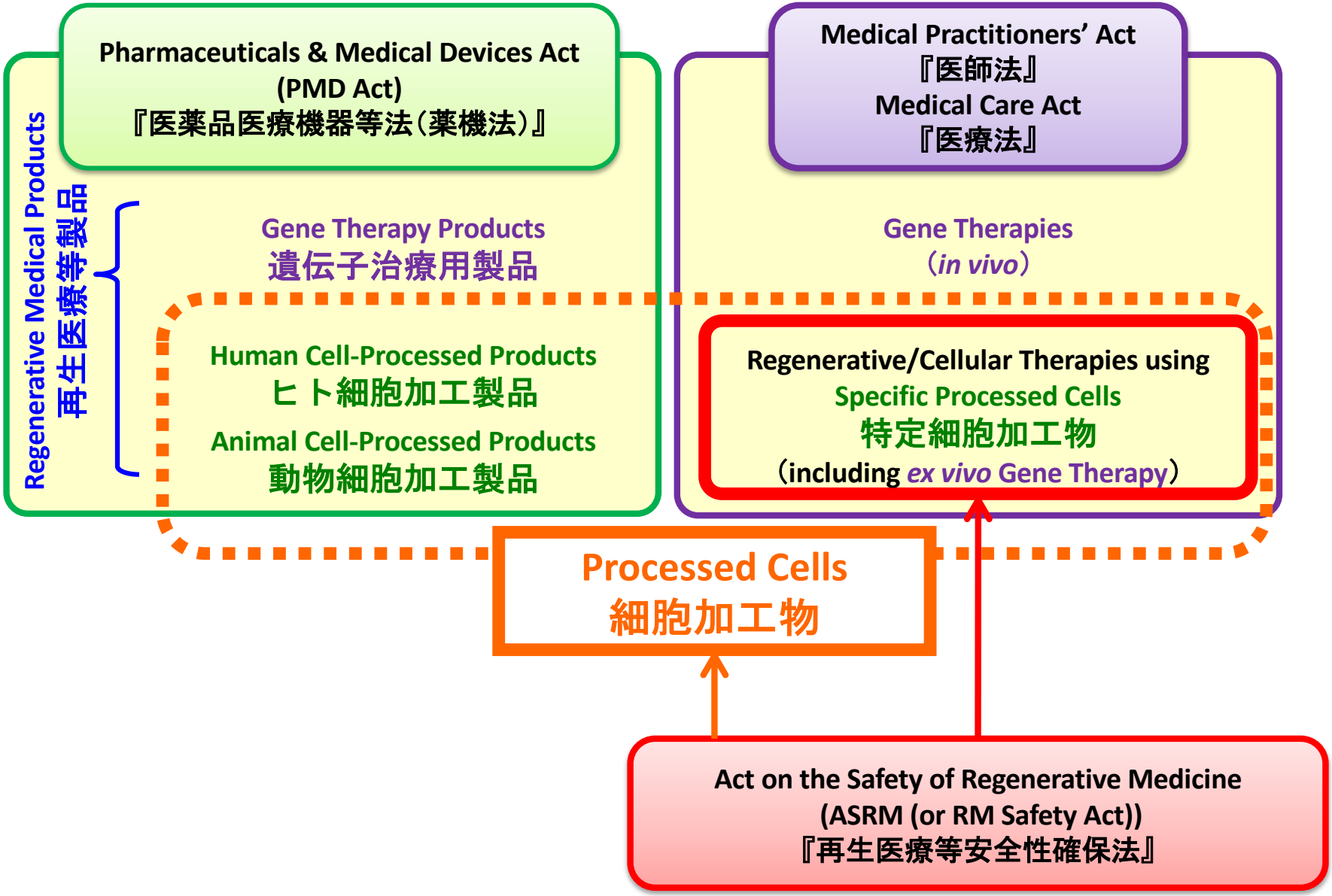
Yoji SATO, Ph.D.
Head, Division of Cell-Based Therapeutic Products,
National Institute of Health Sciences, Kanagawa, Japan
Director, The Japanese Society for Regenerative Medicine, Tokyo, Japan

Disclosure of COI

Author：Yoji SATO

I have no COI with regard to our presentation.

“Processed Cells”（細胞加工物）



The Major Guideline Documents for Quality and Safety of Human Cell-Processed Products regulated under the PMD Act（薬機法）

Good Tissue Practice (GTP) Guidelines

General Principles for the Handling and Use of Cell/Tissue-Based Products
PFSB/MHLW Notification 1314 (12/12/2000) Appendix 1
細胞・組織利用医薬品等の取扱い及び使用に関する基本的考え方
医薬発第1314号 別添1（2000年）

Standard for Biological Ingredients
MHLW Public Notice 210 (2003)/375 (2014)
生物由来原料基準
厚生労働省告示 210号（2003年）/375 号（2014年）

Good Gene, Cellular, and Tissue-based Products Manufacturing Practices (GCTP)

Ministerial Ordinance on Good Practices for Manufacturing Control and Quality Control of Regenerative Medical Products
MHLW Ord. 93 (2014)
再生医療等製品の製造管理及び品質管理の基準に関する省令
厚生労働省令第93号（2014年）

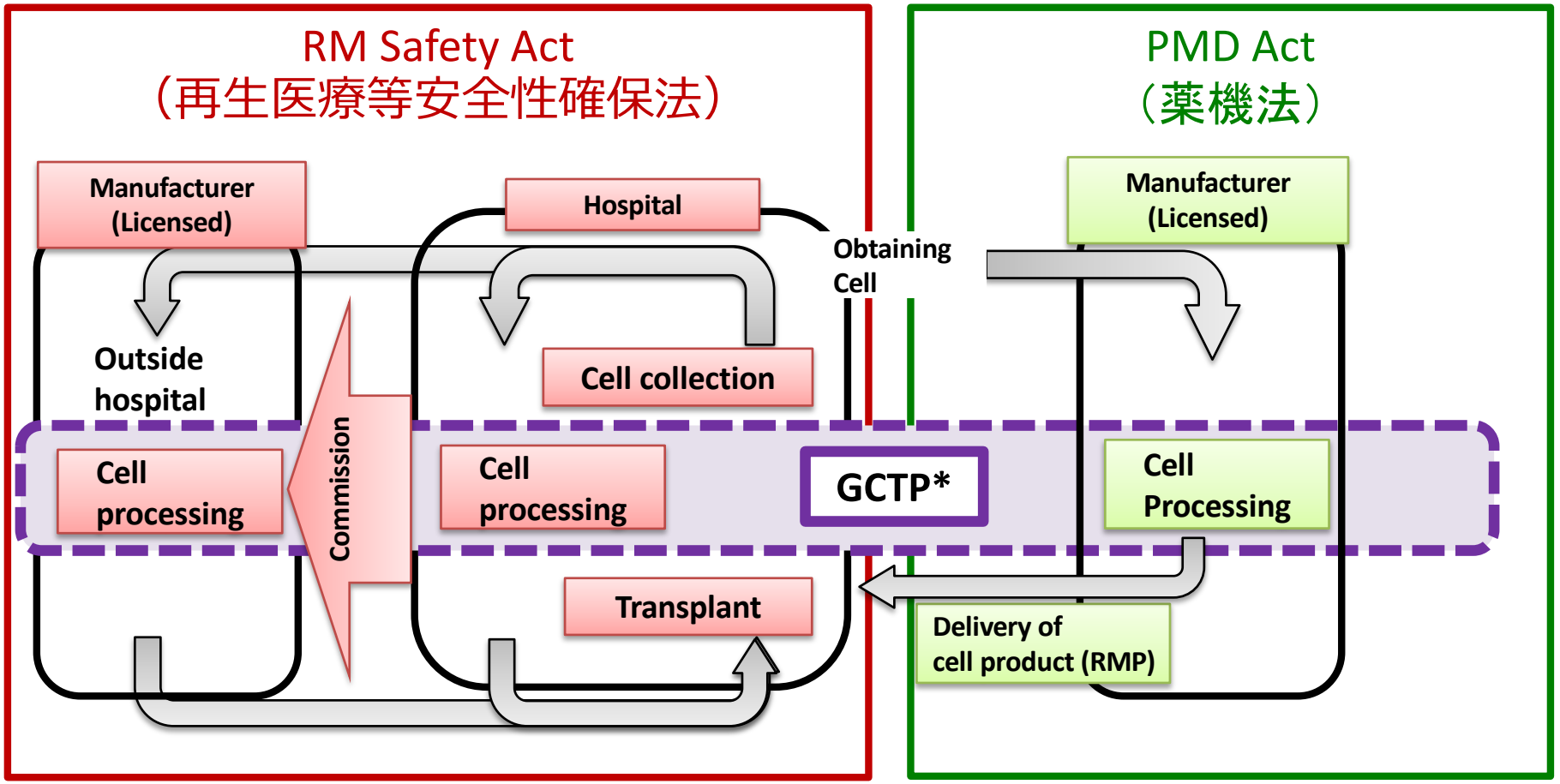
Manufacturing Facility Standard

Regulations for Buildings and Facilities of Pharmacies, etc.
MHW Ord. 2 (1961)/87 (2014)
薬局等構造設備規則
厚生省令第2号（1961年）/87（2014年）

Consistent Parts of the Two Acts

Medical technologies using processed cells
(except clinical trials under PMD Act.)

Regenerative Medical Products



*** GCTP (Good Gene, Cellular, and Tissue-based Products Manufacturing Practice)**

Guideline Documents on Technical Requirements for Quality and Safety of Human Cell-Processed Products regulated under the PMD Act（薬機法）

Technical Requirements for CTPs Derived from Specific Source Cell Types
（原料細胞種別の技術要件）

ヒト（自己）由来細胞・組織加工医薬品等の品質及び安全性の確保に関する指針
Guideline on ensuring quality and safety of products derived from processed autologous human cell/tissue
PFSB/MHLW Notifications No.0208003 (8/02/2008)

ヒト（同種）由来細胞・組織加工医薬品等の品質及び安全性の確保に関する指針
Guideline on ensuring quality and safety of products derived from processed allogeneic human cell/tissue
PFSB/MHLW Notifications No.0912006 (12/09/2008)

ヒト（自己）体性幹細胞加工医薬品等の品質及び安全性の確保に関する指針
Guidelines on ensuring the quality and safety of pharmaceuticals and medical devices derived from the processing of autologous human somatic stem cells
PFSB/MHLW Notification 0907-2 (2012)

ヒト（自己）iPS（様）細胞加工医薬品等の品質及び安全性の確保に関する指針
Guidelines on ensuring the quality and safety of pharmaceuticals and medical devices derived from the processing of human induced pluripotent stem(-like) cells
PFSB/MHLW Notification 0907-4 (2012)

ヒト（同種）体性幹細胞加工医薬品等の品質及び安全性の確保に関する指針
Guidelines on ensuring the quality and safety of pharmaceuticals and medical devices derived from the processing of allogeneic human somatic stem cells
PFSB/MHLW Notification 0907-3 (2012)

ヒト（同種） iPS（様）細胞加工医薬品等の品質及び安全性の確保に関する指針
Guidelines on ensuring the quality and safety of pharmaceuticals and medical devices derived from the processing of human induced pluripotent stem(-like) cells
PFSB/MHLW Notification 0907-4 (2012)

ヒトES細胞加工医薬品等の品質及び安全性の確保に関する指針
Guidelines on ensuring the quality and safety of pharmaceuticals and medical devices derived from the processing of human embryonic stem cells
PFSB/MHLW Notification 0907-5 (2012)

Guideline Documents on Technical Requirements for Quality and Safety of Human Cell-Processed Products regulated under the PMD Act（薬機法）

Technical Requirements for CTPs Derived from Specific Source Cell Types
（原料細胞種別の技術要件）

Problems

- **There is no document, which corresponds to these guidelines and should be officially referred to by Certified Special Committees for Regenerative Medicine under the RM Safety Act.**

再生医療等安全性確保法には、これらの技術要件指針に相当する文書（＝（特定）認定再生医療等委員会が正式に参照すべき文書）がない。

- **Regardless of the legislation (PMD Act or RM Safety Act), when there are several interpretations about the technical requirements, and if you do not know the purpose of the requirements or the principles behind them, a strict but unreasonable interpretation may be taken within the breadth, just because of "just in case",**

技術要件の解釈に幅がある場合、**技術要件の目的や背景にある原則を知らないと**、薬機法下であっても安全性確保法下であっても「念のため」という理由で不合理に、幅の中でも**厳しめの解釈が採られる可能性**がある。

⇒⇒⇒ **The levels of technical requirements usually become higher with time**

技術要件のハードルが高くなってしてしまうおそれ

⇒⇒⇒ **hindering efficient product development**

実用化の阻害

Necessary and Sufficient Items to Ensure Quality & Safety

- For research and development, as well as the review for approval of individual human cell based products, appropriate studies and the evaluation of data should be conducted on the basis of the risk of products by taking into consideration the type, characteristics, and method of clinical application of each product to accurately and reasonably secure the quality and safety of these products. Excessive studies or data should not be required.

個別製品の研究開発や承認審査にあたっては、その品質および安全性を的確にかつ合理的に確保するために、各製品の種類や特性、臨床適用法などをふまえた製品のリスクに基づく適切な試験の実施やデータの評価がなされるべきであり、過剰な試験やデータが求められるべきではない。

- However, to ensure the quality, safety, etc., of individual products, it is not easy for the developers themselves to select necessary and efficient matters and to evaluate the data among comprehensive matters indicated in the current guidelines. This issue has become a bottleneck for development.

しかし、現行の指針等で示されている網羅的事項の中から、個別製品の品質および安全性等を確保するために必要かつ十分な項目の選択およびデータの評価を開発者自身で判断することは容易ではなく、開発の隘路となっている。

Necessary and Sufficient Items to Ensure Quality & Safety

- an cell
  on the
  nd
  he quality

For more reasonable, efficient, and effective product development, it is useful to share technical elements and standards (minimum consensus package [MCP]), which will be common bases for anticipated major human cell based products, among the stakeholders.

必要かつ十分な項目の選択およびデータの評価のためには、
想定される大多数の製品に共通の基本となる技術要件や基準
（ミニマム・コンセンサス・パッケージ：MCP）を開発側と審査側で共有することが有用

的に確保
な試験の実

- the
  e data
  become a

bottlened nt.

しかし 行の指針等で示されている網羅的事項の中から、個別製品の品質および安全性等を確保するために必要かつ十分な項目の選択およびデータの評価を開発者自身で判断することは容易ではなく、開発の隘路となっている。

What is “Minimum Consensus Package [MCP]” for the Evaluation of the Quality, Safety, etc., of Processed Cells for Regenerative/Cellular Therapies

- Technical elements and standards, which will be common bases for anticipated major human cell based products

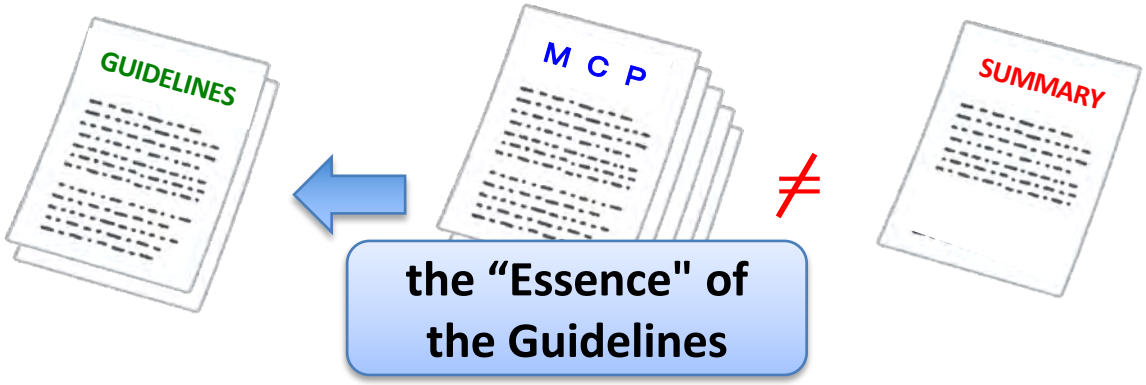
想定される大多数の製品（細胞加工物）に共通の基本となる技術要件や基準

- Clarifying and explaining the background and rationale for selections of tests and/or endpoints and technical elements
- Providing the points of attention for interpretation and application

技術要件GL（自己・同種指針、幹細胞5指針）に記載された試験・評価項目・技術要件の背景や根拠、解釈・運用面にあたっての留意事項も記載

＝This document aims to prevent unreasonable interpretations of the guidelines and excessive operations, by sharing the minimum necessary recognition (principle, background, purposes, etc.)

最低限必要な認識（原則・背景・目的など）を共有することによって、
GLの解釈・運用のブレ（不合理・過剰な要求）を防ぐことを目指す



The National Consortium for Regenerative Medicine

WG for Quality and Non-Clinical Safety Evaluation GLs（MCP-WG）

JSRM

Co-chairs

Takao Hayakawa	(Osaka Univ.)
Yoji Sato	(NIHS)

Members

Takashi Aoi	(Kobe Univ.)
Akihiro Umezawa	(NCCHD)
Kiyoshi Okada	(Osaka Univ.)
Keiya Ozawa	(Jichi Medical Univ.)
Kazuhiro Takekita	(Osaka Univ.)
Akifumi Matsuyama	(Fujita Health Univ.)
Satoshi Yasuda	(NIHS)
Masayuki Yamato	(Tokyo Women's Medical Univ.)

Observers

Division of Regenerative Medicine Research, AMED
Research and Policy Division, MHLW
Medical Device Evaluation Division, MHLW
Office of Cellular and Tissue-based Products, PMDA

AMED 国立研究開発法人 日本医療研究開発機構 Japan Agency for Medical Research and Development

厚生労働省

Pmda 独立行政法人 医薬品医療機器総合機構 Pharmaceuticals and Medical Devices Agency

Guidelines on Technical Requirements and Standards as Common Basis for the Evaluation of the Quality, Safety, etc., of Human Processed Cells (Draft)
ヒト細胞加工物の品質及び安全性等評価に共通の基本となる技術要件・基準指針（案）

Contents

Guidelines on Technical Requirements and Standards as Common Basis for the Evaluation of the Quality, Safety, etc., of Human Processed Cells (Draft)
ヒト細胞加工物の品質及び安全性等評価に共通の基本となる技術要件・基準指針（案）

Contents

Guidelines on Technical Requirements and Standards as Common Basis for the Evaluation of the Quality, Safety, etc., of Human Processed Cells (Draft)
ヒト細胞加工物の品質及び安全性等評価に共通の基本となる技術要件・基準指針（案）

Objective　目的

… this guideline (draft) has been prepared to promote a more reasonable, efficient, and effective product development and to contribute to the promotion of practical regenerative medicine applications by suggesting technical requirements and standards (minimum consensus package [MCP]), which will be common bases for anticipated major human processed cells, and by applying them with the current guidelines.

・・・本指針（案）は、想定される大多数の製品に共通の基本となる技術要件や基準（ミニマム・コンセンサス・パッケージ：MCP）を提言し、現行指針と合わせて活用することにより、より合理的、効率的、効果的な製品開発を促進し、再生医療実用化の推進に寄与することを目的として作成した。

Guidelines on Technical Requirements and Standards as Common Basis for the Evaluation of the Quality, Safety, etc., of Human Processed Cells (Draft)
ヒト細胞加工物の品質及び安全性等評価に共通の基本となる技術要件・基準指針（案）

Contents

Guidelines on Technical Requirements and Standards as Common Basis for the Evaluation of the Quality, Safety, etc., of Human Processed Cells (Draft)
ヒト細胞加工物の品質及び安全性等評価に共通の基本となる技術要件・基準指針（案）

General Points of Attention　一般的留意事項 (1)

…there are many types of manufacturing methods, types and characteristics of critical intermediate products or final products, and clinical application methods of human processed. Furthermore, the scientific progress in this field is incessant, and expertise and knowledge are constantly accumulating. Therefore, it is not always appropriate to consider the present guidelines as all-inclusive and definitive. Consequently, when testing and evaluating each product, it is necessary to adopt a flexible approach that is based on a rationale that reflects scientific and technological advances at that point in time while taking into consideration the objectives of this and related guidelines.

Risk-Based Approach

・・・ヒト細胞加工物の製造方法、重要中間製品や最終製品の種類及び特性、臨床上の適用法は多種多様であり、また、本分野における科学的進歩や経験の蓄積は日進月歩である。本指針を一律に適用したり、本指針の内容が必要事項すべてを包含しているとみなしたりすることが必ずしも適切でない場合もある。したがって、個々の製品についての試験の実施や評価に際しては本指針や関連指針の目的・趣旨を踏まえつつも、その時点の学問の進歩を反映した合理的根拠に基づき、ケース・バイ・ケースで柔軟に対応すること。

リスクベースアプローチ

Guidelines on Technical Requirements and Standards as Common Basis for the Evaluation of the Quality, Safety, etc., of Human Processed Cells (Draft)
ヒト細胞加工物の品質及び安全性等評価に共通の基本となる技術要件・基準指針（案）

General Points of Attention　一般的留意事項 (2)-1

The basic points of attention prior to the initiation of the investigational clinical trials (clinical researches) of human processed cells are to determine:

- whether there are any quality and safety problems that would obviously hinder the application of such cells to humans,
- whether certain quality characteristics of the product are understood sufficiently to establish a relationship between the clinical findings and the quality characteristics, and
- whether the constancy of the quality characteristics can be ensured within a definite range.

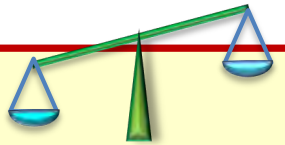
治験（臨床研究）を開始するにあたっての基本的留意点は，

- 当該製品にヒトへの適用により支障となる品質および安全性上の明らかな問題が存在するか否か，
- 臨床で得られた知見との関係性を照合できる程度に品質特性が把握され，
- その一定範囲の恒常性が確保されているか否か

を確認することにある。

Guidelines on Technical Requirements and Standards as Common Basis for the Evaluation of the Quality, Safety, etc., of Human Processed Cells (Draft)
ヒト細胞加工物の品質及び安全性等評価に共通の基本となる技術要件・基準指針（案）

General Points of Attention　一般的留意事項 (2)-2



In this case, it is important to perform evaluations by adopting the following viewpoints:

- Risks that were clearly anticipated for processed cells should be eliminated as much as possible by using the available technology at that time to clarify the scientific appropriateness of the results of such actions.
- Subsequently, the remaining “anticipated risks” should be weighed against the “potential risks associated with the loss of an opportunity to receive new treatment” for patients who suffer from diseases that are serious and life-threatening, involve significant functional impairment, or confer a significant decrease in quality of life (QOL) resulting from the loss of a certain degree of a physical function or form, or for which existing therapies have limitations and do not result in a cure.

Furthermore, by disclosing all of the abovementioned information to patients (e.g., information on risks versus expected benefits), the decision on whether to receive the new treatment has to be entrusted to such patients.

- その際，明らかに想定される細胞加工物のリスクをその時点の学問・技術を駆使して排除し，その科学的妥当性を明らかにした上で，なお残る「想定リスク」と，
- 重篤で生命を脅かす疾患，身体の機能を著しく損なう疾患，身体の機能や形態を一定程度損なうことによりQOL　を著しく損なう疾患などに罹患し，従来の治療法では限界があり，克服できない患者が「新たな治療機会を失うことにより被るかもしれないリスク」

とのリスクの大小を勘案し，かつ，これらすべての情報を開示した上で患者の自己決定権に委ねるという視点を持つこと，すなわち，リスク・期待されるベネフィットの情報を開示した上で治験（臨床研究）に入るかどうかの意思決定は患者が行うという視点を入れて評価することも重要である。

Guidelines on Technical Requirements and Standards as Common Basis for the Evaluation of the Quality, Safety, etc., of Human Processed Cells (Draft)
ヒト細胞加工物の品質及び安全性等評価に共通の基本となる技術要件・基準指針（案）

General Points of Attention　一般的留意事項 (2)-3

- For materials to be attached to the application when initiating a clinical trial/research, the requirements and contents indicated in this guideline and the related guidelines to be referred to for individual products are not necessarily fulfilled completely.
- Appropriate materials should be reasonably prepared and submitted at the time of celinical trial/research application, on the premise that materials ensuring the quality and safety of the processed cells at the time of marketing authorization application will be enriched and developed in line with this and the related guidelines during the process of clinical trials/researches.
- 治験（臨床研究）開始申請時の添付資料については、

  本指針や個々の製品において参照すべき関連指針に示された要件や内容をすべて充たすことを必ずしも求めているわけではない。
- 製造販売承認申請時における品質および安全性の確保のための資料は治験（臨床研究）の進行とともに本文書や関連指針に沿って充実整備されることを前提に，治験（臨床研究）開始時点でその趣旨に適う条件を充たし，合理的に作成された適切な資料を提出すること。

General Points of Attention　一般的留意事項 (3)

■ **The main target in manufacturing processed cells, and evaluations of their quality and safety/efficacy at nonclinical, clinical and post-marketing phases is**

the final product

■ **細胞加工物の製造や品質，非臨床安全性や非臨床有効性，臨床上の安全性，有効性，市販後の安全性評価における対象の核心は**

最終製品

である。

Guidelines on Technical Requirements and Standards as Common Basis for the Evaluation of the Quality, Safety, etc., of Human Processed Cells (Draft)
ヒト細胞加工物の品質及び安全性等評価に共通の基本となる技術要件・基準指針（案）

General Points of Attention　一般的留意事項 (4)

- **Similarly, the matters, test methodss, standards, and other technical requirements described in these guidelines are intended to be considered, selected, applied, and evaluated on the basis of the contents and degrees that meet each purpose.**
- **Interpretation and application at or within the highest or maximum level or range are not necessarily required.**
- **By taking into consideration this objective, the applicant should clarify that the considered background, selection, and application, as well as the evaluated contents and degrees, are suitable for each purpose and are deemed appropriate on the basis of scientific rationality.**

- 本指針に記述された事項，試験方法，基準その他の技術要件は，それぞれの目的に適う内容と程度をもとに考慮，選択，適用，および評価されるべきことを意図しており，
- **必ずしも最高・最大限の水準・範囲での解釈，運用を求めているわけではない。**
- この趣旨を踏まえ，申請者は，考慮した背景，選択，適用，および評価した内容と程度がそれぞれの目的に相応しく，
- **科学的合理性からみて妥当であること**を明らかにすること。

Guidelines on Technical Requirements and Standards as Common Basis for the Evaluation of the Quality, Safety, etc., of Human Processed Cells (Draft)
ヒト細胞加工物の品質及び安全性等評価に共通の基本となる技術要件・基準指針（案）

Contents

Guidelines on Technical Requirements and Standards as Common Basis for the Evaluation of the Quality, Safety, etc., of Human Processed Cells (Draft)
ヒト細胞加工物の品質及び安全性等評価に共通の基本となる技術要件・基準指針（案）

Applications and significance of these guidelines 本指針の活用方法・意義

MCP allows a reasonable approach for securing the quality of a product from a regulatory aspect, thus making itself a common platform to which technical elements can be added by taking into consideration the characteristics of each product and by referring to current comprehensive guidelines. MCP also shifts seamlessly the clinical studies under the Act on the Safety of Regenerative Medicine to developments under the Law on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (PMD Act) and smoothly facilitates the Regulatory Science Strategy Consultation and/or the review for approval to accelerate the promotion of practical regenerative medicine applications.

MCPは、これを共通のプラットホームとし、これに現行の網羅的指針等を参考に各製品の特性等を踏まえた技術的要件を選択して上乗せする、という合理的アプローチを可能にし、再生医療安全性確保法下での臨床研究等から医薬品医療機器等法下での開発への切れ目のない移行、行政での薬事戦略相談や承認審査などが円滑に進行し、再生医療実用化を加速するなど、規制面から国際的優位性を確保するための方策でもある。

The essence of the Essence of the Guidelines
The essence of MCP（MCPのこころ）

- **"Time" and "life" are irreplaceable.**
  かけがえのない「とき」と「いのち」。
- **Deliver what they need as quickly as possible.**
  一日も早く必要なものを必要なひとに届ける。
- **Do things that only humans can do.**
  人間にしかできないことをする。
- **Think for yourself, show your imagination and connect it to creation.**
  自ら考え、想像力を発揮し、創造につなげる。
- **Clarify the purpose of each.**
  それぞれの目的を明確にする。
- **Learn and understand the subject, respond to it efficiently and effectively based on scientific rationality and ethics, and show justification of the responses.**
  対象について学び、理解し、科学的合理性、倫理性に基づき、効率的、効果的に対応し、妥当性を示す。
- **Position individual elements in the whole and understand their significance.**
  個別要素は全体の中で位置づけ、意義づける。
- **Each person who is involved does his part, goes beyond his position and goes public.**
  関係者それぞれが本分を尽くし、立場を超え、公にいたる。

出典：早川堯夫　神奈川県立産業技術総合研究所平成30年度教育講座資料

Thank you for your attention!

ご清聴、ありがとうございました！

CONTACT INFORMATION:

Yoji Sato, PhD

Head, Division of Cell-Based Therapeutic Products

National Institute of Health Sciences

E-mail: yoji@nihs.go.jp

佐藤　陽治

国立医薬品食品衛生研究所　再生･細胞医療製品部