Current Topics in Japan with respect to Evaluation and Control of Biotechnology Products

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PMDA
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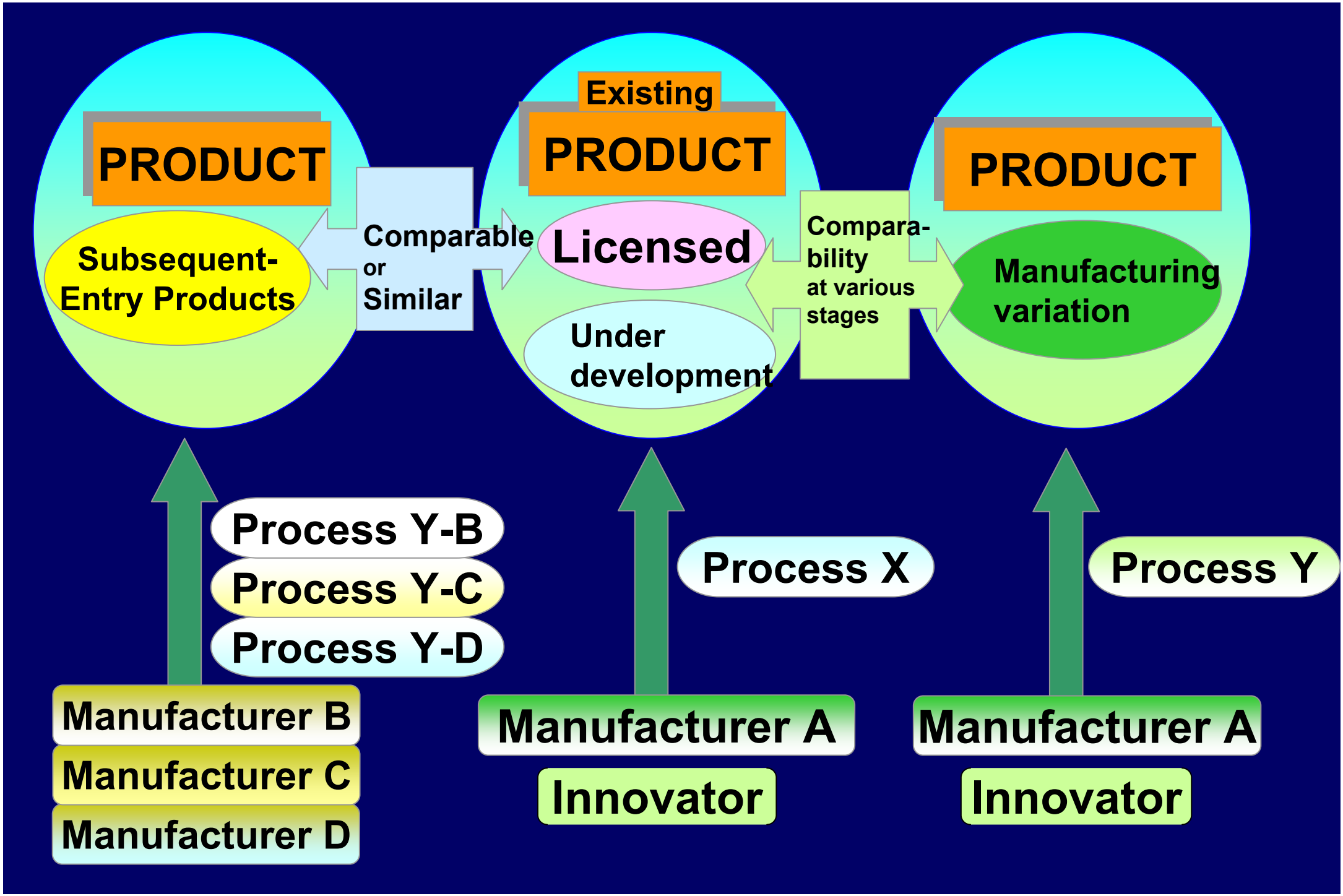
- Subsequent-Entry Protein Products
- Cells/Tissue-based Products

Current Situation in Japan regarding Subsequent-Entry Protein Products

- There are increasing interests in the development of subsequent-entry protein products in Japan
- There is no official guideline or guidance on subsequent-entry protein products in Japan
- There is a plan to develop relevant guidelines or guidance in Japan


PRODUCT
Subsequent-Entry Products
Comparable or Similar
Existing
PRODUCT
Licensed
Under development
Compara-bility at various stages
PRODUCT
Manufacturing variation
Process Y-B
Process Y-C
Process Y-D
Process X
Process Y
Manufacturer B
Manufacturer C
Manufacturer D
Manufacturer A
Innovator
Manufacturer A
Innovator

Provisional Terminology

- For convenience, when the term "subsequent-entry protein product" is used, it is intended to refer to any protein product that is produced using a new manufacturing process by a subsequent-entry manufacturer and claimed to be comparable or similar to an already existing protein product developed by an innovator. However, it does not necessary mean the product is comparable or similar to the innovator's product.
- For convenience, when the term "subsequent-entry comparable or similar product" is used, it is intended to refer to the subsequent-entry product that is proved to be comparable or similar to the innovator's product.

Subsequent-Entry Comparable Product
(e.g., Insulin and hGH)

For Drug Substance (DS), it is a SE product that is proven to be highly similar/comparable to the corresponding innovator's product. To reach such a conclusion, extensive CMC studies are needed. The chemical structure and properties of the "desired product" of DS should be the same as the targeted one by referring to well-known established data (literature). For drug product, it should be evaluated to be comparable to the innovator's product by relevant "comparability assessments" including quality considerations.

If there are certain concerns about possible adverse impact on S/E, relevant non-clinical/clinical studies should be performed, using the innovator's drug product, whenever possible. Its mechanism of action and clinical indication should be the same as the innovator's drug product.

Subsequent-Entry Similar Product (e.g., EPO)

For Drug Substance (DS), it is a SE product that is proved to be similar to corresponding innovator's product. To reach such a conclusion, extensive CMC studies are needed. The protein structure of the "desired product" of DS should be the same as or highly similar to the targeted one by referring to well-known established data (literature). For drug product, it should be evaluated to be comparable/similar to the innovator's product by relevant "comparability/conventional assessments" including quality considerations. Also possible adverse impact on S/E should be assessed by relevant non-clinical/clinical studies, using the innovator's drug product, whenever possible. Its mechanism of action and clinical indication should be the same as the innovator's drug product.

Concept regarding Subsequent-Entry Protein Products:

Whatever the Product is, ensuring its Quality, Safety and Efficacy is a crucial element for a product intended for therapeutic use.

A View regarding Subsequent-Entry Protein Products (1)

- Theoretically, "Subsequent-Entry Comparable Products" can be developed by using comparability approach for any kind of products, but, in practice, the success of such a development approach will depend on the product characteristics, availability of relevant analytical methods and reference product, intended clinical use and so on.

A View regarding Subsequent-Entry Protein Products (2)

- In some cases, "Comparability Concepts and Approaches" can lead to a reduced burden of testing for data submission for approval, and result in more rational, effective or economical drug development.

A View regarding Subsequent-Entry Protein Products (3)

- However, comparability study alone may not always suffice for ensuring Quality, Safety and Efficacy of certain "Subsequent-Entry Protein Products".
- In such a case, the combination of "Comparability Assessments" and "Conventional Assessments" may be appropriate to ensure Q/S/E of the "Subsequent-Entry Protein Products".

A View regarding Subsequent-Entry Protein Products (4)

- Also, there may be the case where “Conventional Approaches and Evaluation” is rather appropriate to ensure quality, safety and efficacy of “Subsequent-Entry Protein Products” in question.

A View regarding Subsequent-Entry Protein Products (5)

- There is no "Subsequent-Entry Comparable or Similar Product" that can be defined *a priori*.
- Certain subsequent-entry products may only be recognized as "Subsequent-Entry Comparable or Similar Products" as a result of relevant and sufficient tests and evaluation.

General Considerations : Product Aspects (1)

- The better one knows the product characteristics and intended clinical use, the more rational approaches can be taken.
- Therefore, first of all, extensive identification and characterization studies should be performed using state of the art analytical methods to reveal the molecular and quality attributes of the "Subsequent-Entry Protein Products".

Collectively, the quality attributes define the adventitious agent safety, purity, potency, identity, and stability of the product. Specifications measure a selected subset of the quality attributes.

General Considerations : Product Aspects (2)

- DRUG SUBSTANCE: in practice, "Subsequent-Entry Comparable Drug Substance" may be developed for nonconjugated protein products mentioned below, but not for many conjugated proteins like glycoproteins in terms of quality attributes.
- *Examples of nonconjugated proteins are Insulin, Somatoropin (hGH), Filgrastim (non-glycosylated met-G-CSF), Teceleukin (met-IL-2), Celmoleukin(IL-2), Interferon alfa 2a, Interferon alfa 2b and so on*

General Considerations : Product Aspects (3)

- DRUG PRODUCT: "Subsequent-Entry Comparable Drug Product" may be developed using a relevant "Comparability Exercise" when the "Subsequent-Entry Comparable DS" is available and both the proposed dosage form and clinical indication of subsequent-entry product correspond to those of innovator's drug product.

General Considerations : Product Aspects (4)

- DRUG PRODUCT: In the case where the innovator's drug product has more than one indication, the efficacy and safety of the subsequent-entry product claimed to be comparable have to be justified or, if appropriate, demonstrated separately for each of the claimed indications.
- Any new dosage forms and/or new clinical indications of a subsequent-entry product should be the subject of extensive "Conventional Assessment".

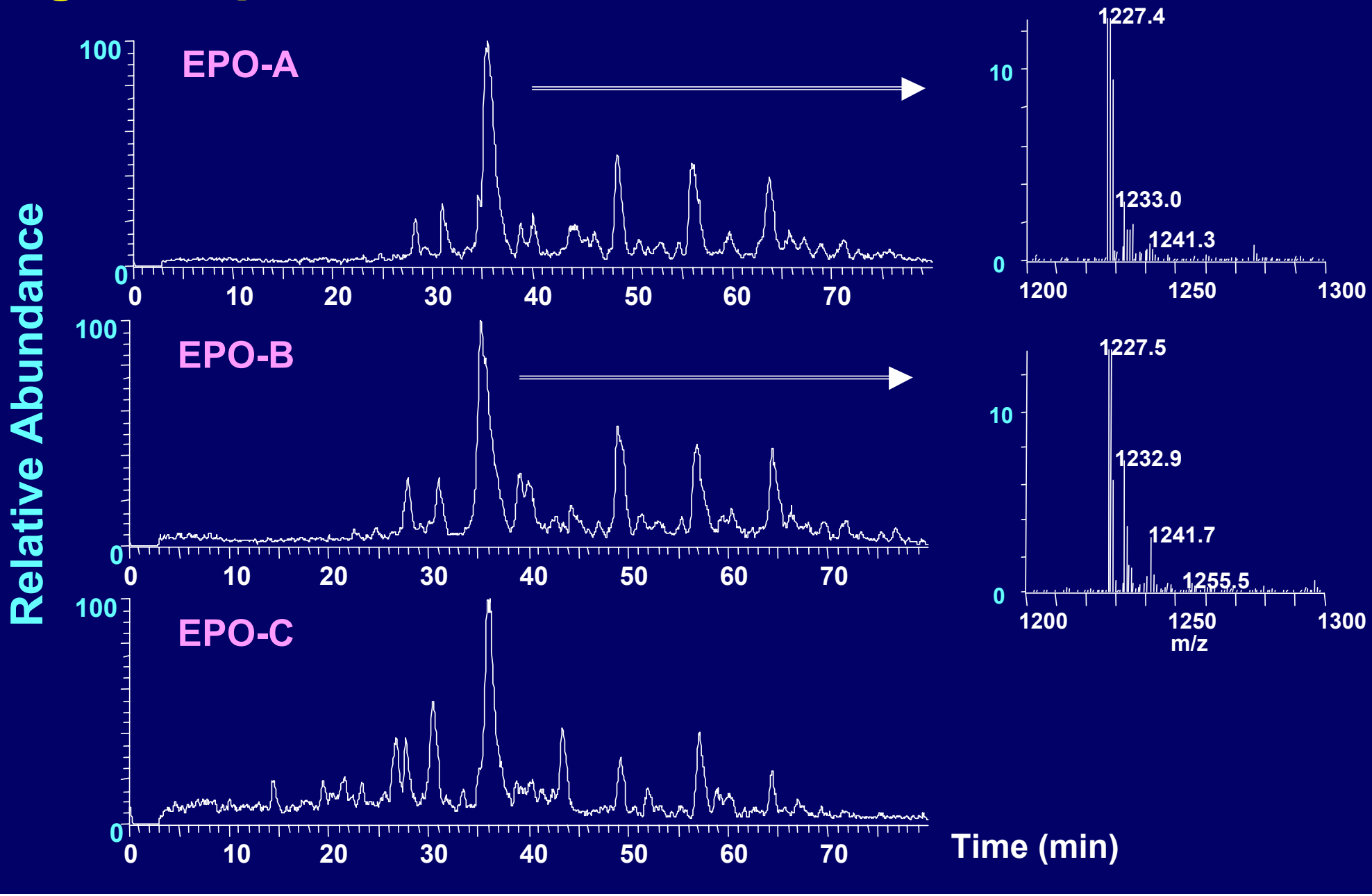
General Considerations : Product Aspects (5)

- Usually, it is difficult to develop "Subsequent-Entry Comparable Drug Substance" in the case of conjugated protein products like glycoproteins in terms of quality attributes, as described earlier. This is because of the complexity and uniqueness of molecular and product characteristics, as well as the lack of relevant reference products.
- Extensive studies much more than "comparability exercise" will be needed using state of the art analytical methods to reveal their specific molecular and quality attributes.

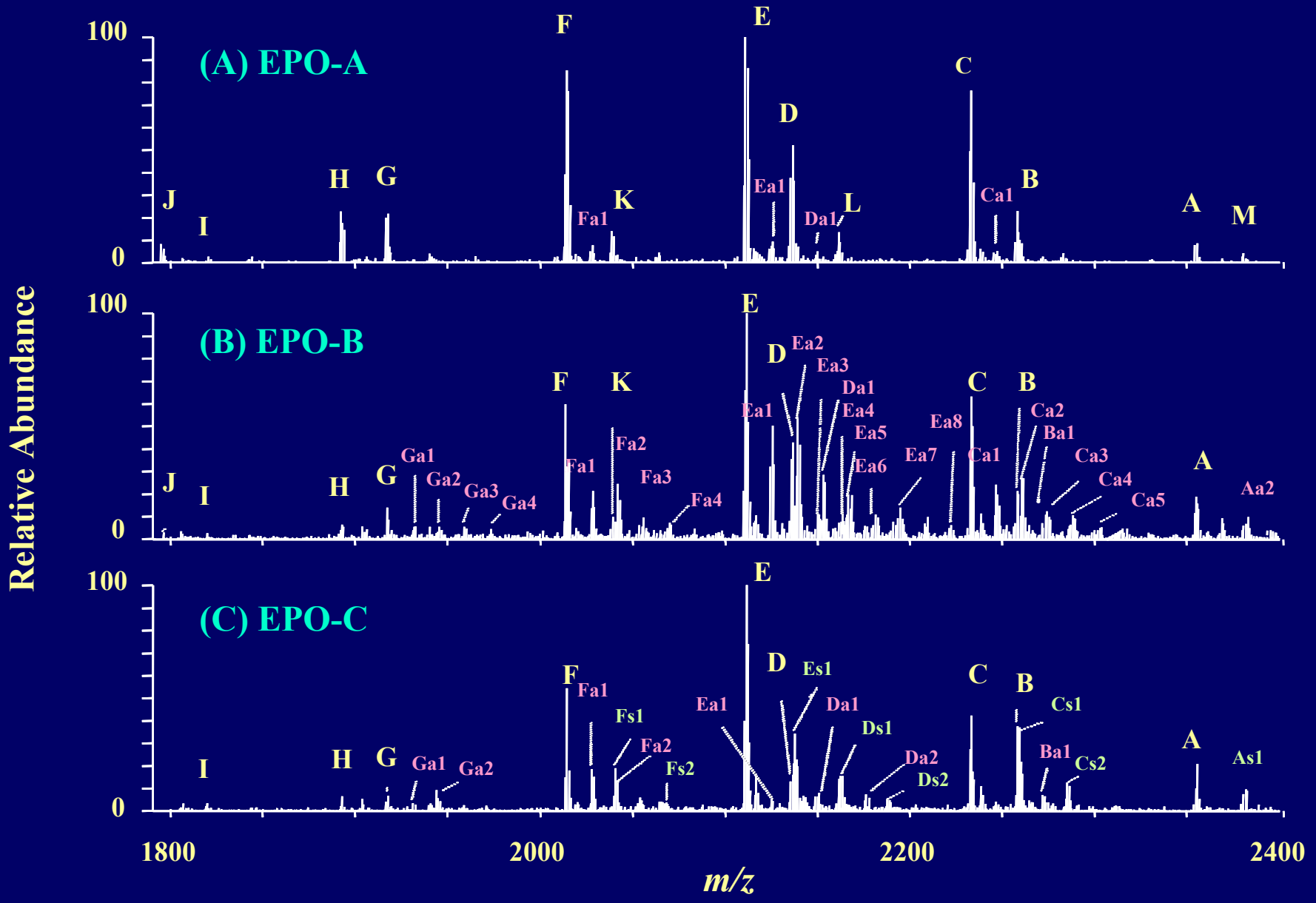
The nature of glycosylation of glycoproteins produced by certain biological systems is influenced by a number of factors, such as:

- Species-, cell- and tissue-specific glycosylation
- Method of establishment of the cell substrate
- Cell culture conditions
- Structural features of the expressed protein product

Sugar Maps of EPOs from Different Cell Substrates

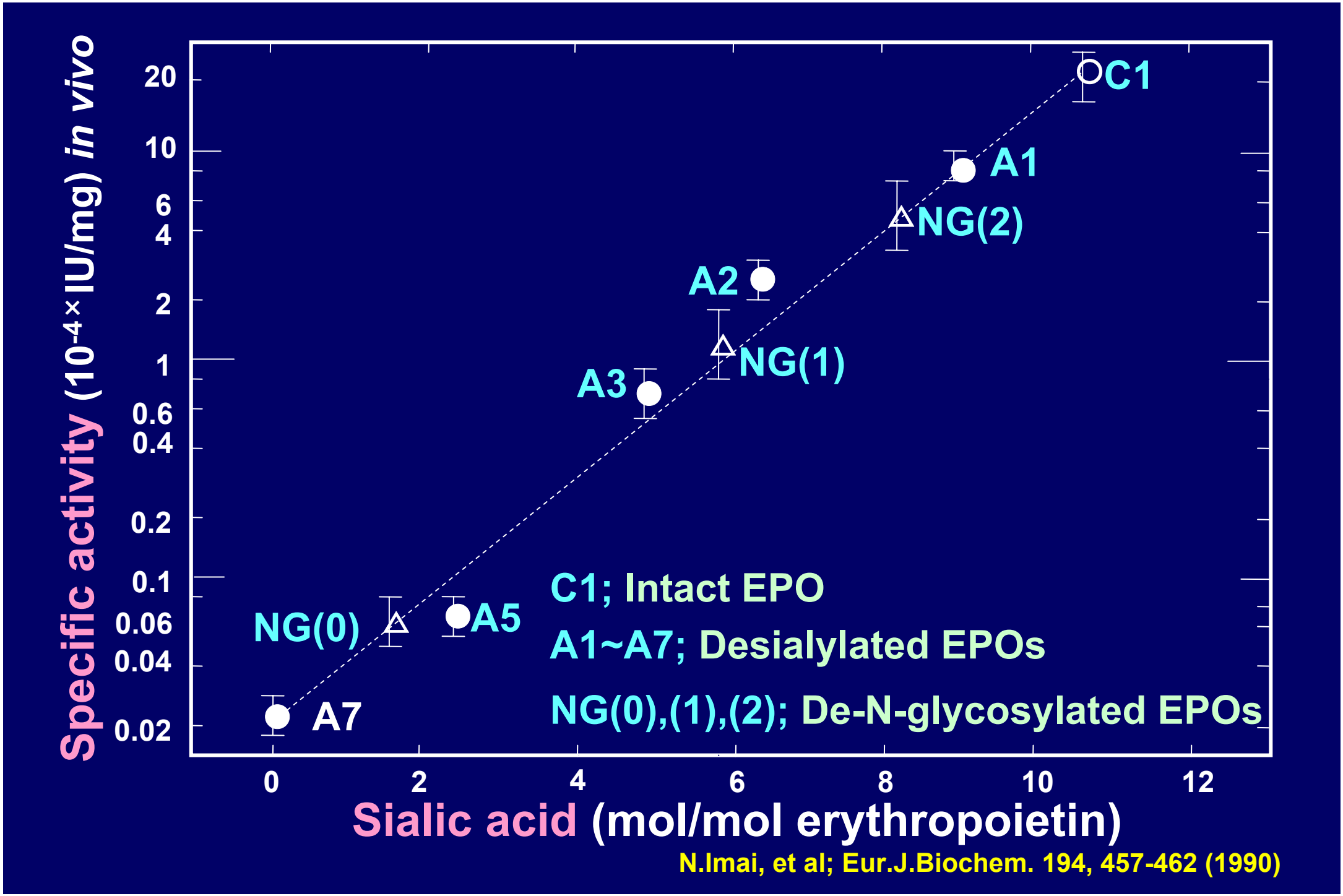


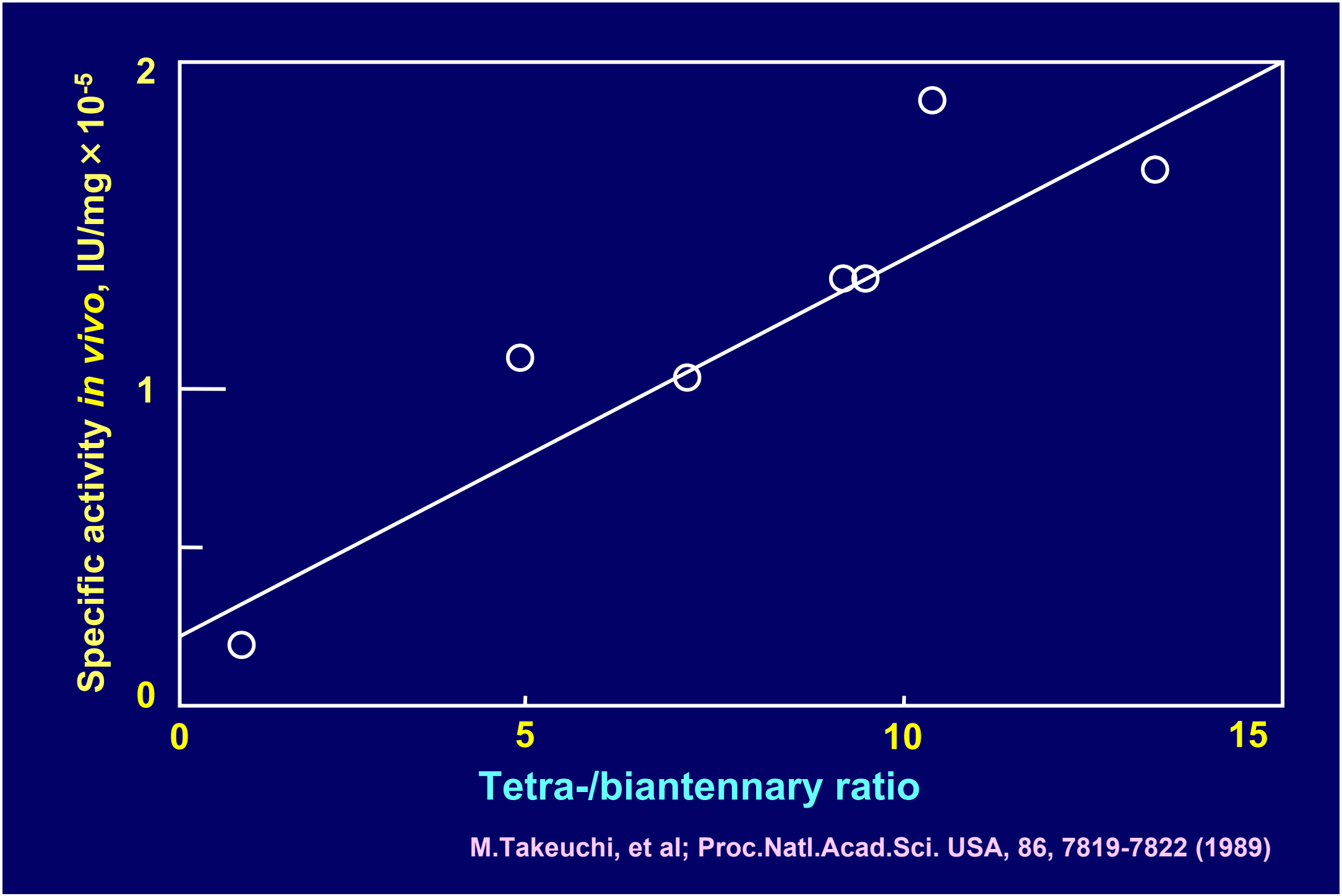
Mass spectra of N83 glycopeptides from EPO-A, -B, and -C



The nature of glycosylation (e.g., type of major oligosaccharide chains, occupancy of glycosylation sequence, glycoforms at each glycosylation site) **may affect** :

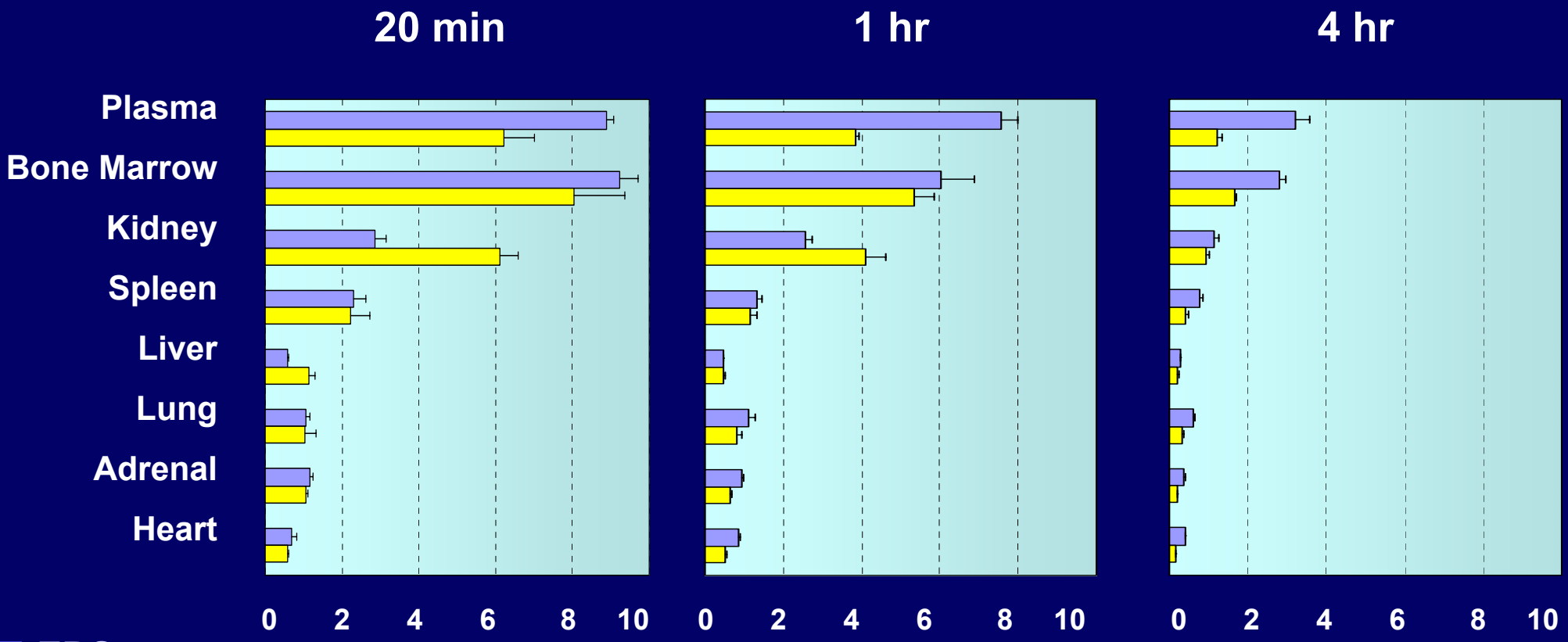
- **Specific biological activities**
- **Metabolic fate**
- **Stability**
- **Solubility**


Specific activity (10-4× IU/mg) in vivo
20
10
6
4
2
1
0.6
0.4
0.2
0.1
0.06
0.04
0.02
0
2
4
6
8
10
12
Sialic acid (mol/mol erythropoietin)
C1
A1
NG(2)
A2
NG(1)
A3
A5
NG(0)
A7
C1; Intact EPO
A1~A7; Desialylated EPOs
NG(0),(1),(2); De-N-glycosylated EPOs
N.Imai, et al; Eur.J.Biochem. 194, 457-462 (1990)



M.Takeuchi, et al; Proc.Natl.Acad.Sci. USA, 86, 7819-7822 (1989)

Tissue Distribution of Radioactivity After a Single Intravenous Administration of Radioiodinated Control EPO-tetra or EPO-bi in Male Rats



Blood、*86*（1995）

Immunogenicity of Glycoconjugates

- It has been reported that glycoconjugates containing N-glycolylneuraminic acid (one type of sialic acid detected in most mammals except in normal human tissues) are immunogenic in humans.

General Considerations : Product Aspects (6)

- While, in principle, “Conventional Assessment” will be needed to ensure Q/S/E of subsequent-entry conjugated protein products, a partial comparability study using relevant innovator’s drug products may provide certain information on specific biological characteristics of the products, which are useful for evaluation with respect to their Q/S/E.

General Considerations : Product Aspects (7)

- When certain “Subsequent-Entry Conjugated Protein Products” are evaluated to be useful for their intended clinical use, they can be approved for MAA and recognized as “Subsequent-Entry Similar Products.” The nonproprietary names should be different from the ones of the innovator’s products.

General Considerations : Product Aspects (8)

- Improvement of product Quality, Safety and/or Efficacy is always desirable and encouraged. If the results of the relevant studies on "Subsequent-Entry Protein Products" indicate an improved Q/S/E, and even though there is no comparability, the product would be acceptable.

General Considerations: Process Aspects

- Whatever the product is, establishment of a well-defined manufacturing process with its associated process controls is one of the critical elements for assurance of consistent drug production

Special Concerns on Product Safety(1)

- "Subsequent-entry protein products" may exhibit their own safety profile in terms of nature, seriousness, or incidence of adverse reactions including immunogenicity.
- Data from pre-approval non-clinical and clinical studies may be insufficient to identify all safety profiles.

Special Concerns on Product Safety(2)

Therefore, clinical safety of "Subsequent-Entry comparable or similar Products" should be monitored closely on an ongoing basis during the post-approval phase including continued benefit-risk assessment.

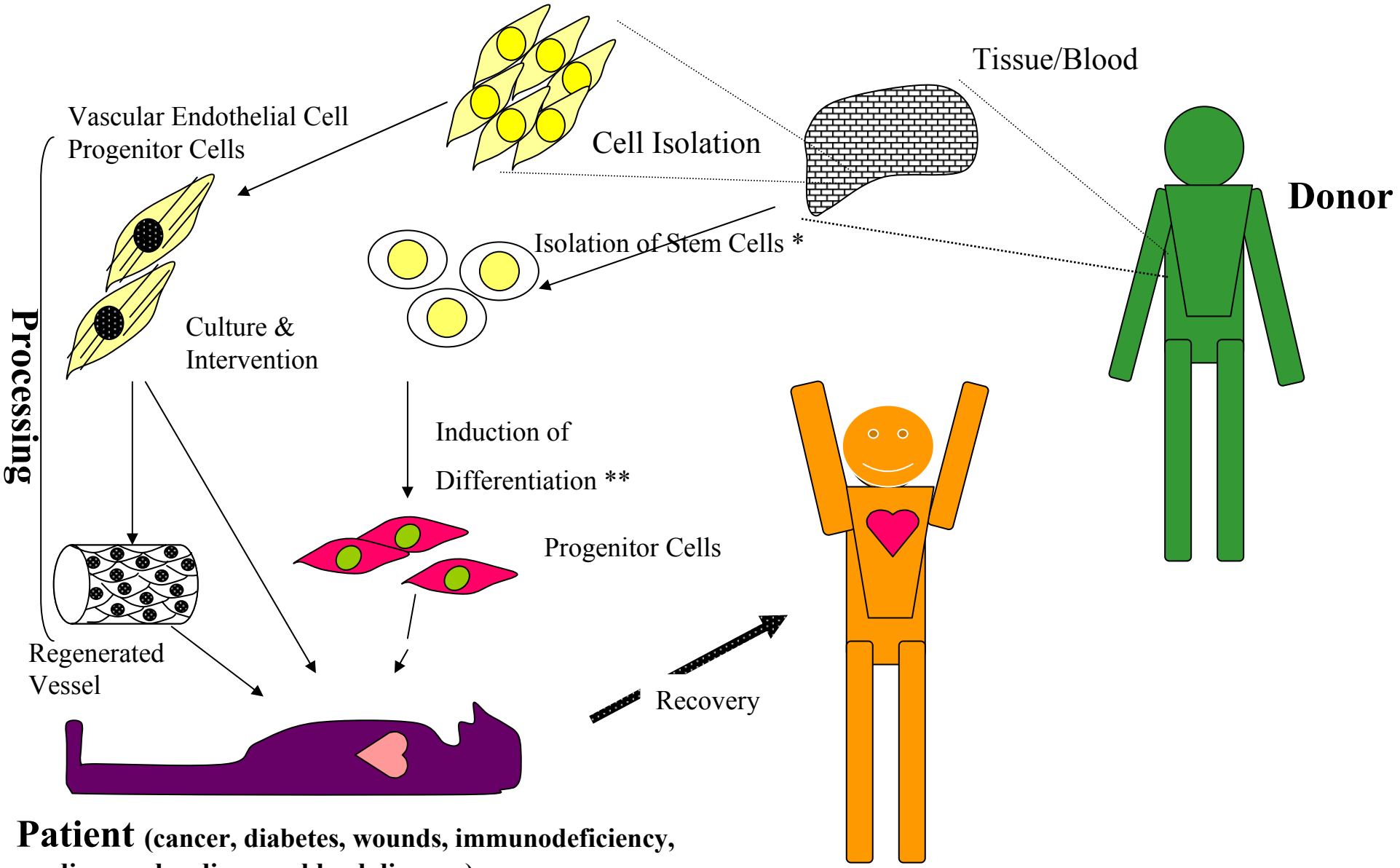
Special Concerns on Product Safety(3)

- The applicant should present a pharmacovigilance plan to address immunogenicity and potential rare serious adverse events.
- A specific risk management plan is required in situations when there is a safety signal in pre-approval non-clinical or clinical studies or when safety problems have been encountered with other products of the same class.

A View regarding Subsequent-Entry Protein Products Summary

- In principle, any "Subsequent-Entry Protein Products" can be accepted for marketing authorization application.
- Whatever the Product is, ensuring its Quality, Safety and Efficacy is a crucial element for a product intended for therapeutic use.
- Whatever the product is, establishment of a well-defined manufacturing process with its associated process controls is one of the critical elements for assurance of consistent drug production.

Cells and Tissue-based Products



Patient **(cancer, diabetes, wounds, immunodeficiency, cardiovascular diseases, blood diseases)**

To make novel biologicals contribute more significantly to human health care, it is essential that suitable measures based on sound scientific principles and approaches at the time be taken by the manufacturers and control authorities to assure the quality, safety, and efficacy of these products.

General Principles for the Handling and Use of Cells/Tissue-Based Products

– MHLW Notification No.266 (28 March 2001)

Guideline on Ensuring Quality and Safety of Products Derived from Processed Human Cells/Tissue

– MHLW Notification No.1314 (26 November 2000)

MHLW homepage
http://www.mhlw.go.jp/english/index.html

General Principles for the Handling and Use of Cells/Tissue-Based Products

- General Provisions
- Suitability for Cells and Tissue Collection
- Handling of Collected Cells and Tissue during Production
- Staff and Organization Management
- Use and Post-Marketing Safety Management
- Protection of Privacy
- Revision

Background and Purpose of "General Principles GL."

- For cells/tissue-based products, there are concerns on the introduction, transmission and spread of infectious diseases. Thus, it is essential to use raw materials free of infectious agents and to prevent microbial contamination during manufacturing process.
- It is necessary to prevent undesirable consequences caused by inappropriate manufacturing, handling and use of products.
- There is a need to establish consistent measures delineating material collection, manufacturing and use of the products.

Background and Purpose of "General Principles GL."

- The purpose of this guidance is to address general requirements to handle cells and tissues in order to assure the quality and safety of cells/tissue-based products in conjunction with the manufacturing process as well as to secure the scientific and ethical rationale of the handling operations.

General Provisions

General principle

The use of cells/tissue-based products should be confined to medical treatments where a clinical advantage over other products/treatments is expected, because the potential risk of the transmission of infectious agents or of other unknown factors derived from them can not be completely ruled out.

Major Elements addressed in "General Principles GL."

Suitability for Cells and Tissue Collection

- Requirements to be met by medical institutions at the cells/tissue collection stage
- Review by the IRB
- Explanation to and informed consent by the donor
- Matters related to selection criteria and eligibility of the donor
- Ensuring the appropriateness of the cells/tissue collection process
- Preparation of the cells/tissue collection record and the record of storage (at least 10years)
- Storage of appropriate samples including part of the collected cells/tissues for an appropriate period

Major Elements addressed in "General Principles GL."

Handling of Collected Materials during Production

- Establish and maintain consistent QC system appropriate for C/T or product characteristics
- Have segregated equipments/facilities/areas for each operation of product manufacturing: receipt of source materials, manipulation, storage of products
- Avoid handling or storing more than one C/T at the same time and in the same room (space) to prevent mistakes in handling and contamination
- Document and implement relevant SOPs
- Establish acceptance criteria of C/T as source material
- Establish acceptance criteria of reagents
- Test for suitability of final products/intermediates

Major Elements addressed in "General Principles GL."

Handling of Collected Materials during Production

- Eliminate risk of contamination due to infectious agents by the combination of various measures
- Take relevant approaches to quarantine products and measures of shipment and delivery
- Prepare and preserve the record of product manufacturing (at least 10years)
- Review and reflect up-to-date scientific knowledge and technology for establishing manufacturing processes and testing methods, where necessary and appropriate

Major Elements addressed in "General Principles GL."

Staff and Organization Management

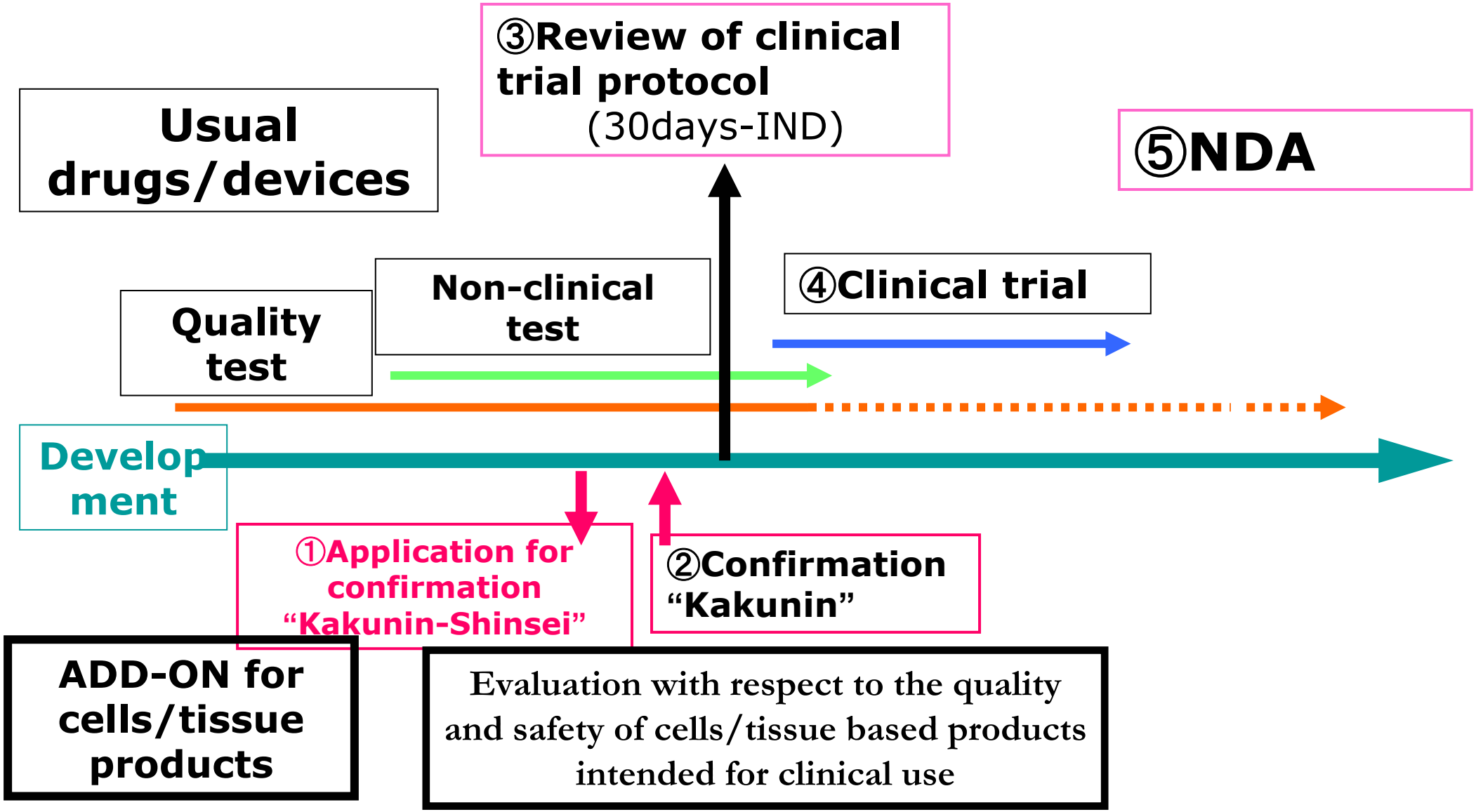
- Perform each operation and testing in the manufacturing process under the authority and the responsibility of the personnel qualified for each task.
- Appoint relevant personnel for managing patient's record and safety information
- Keep persons, who have the potential of giving undesirable effects including microbial contamination of the products, out of the facility
- Conduct periodic training
- Healthcare of staff

Major Elements addressed in "General Principles GL."

Safety Management at the Time of Use and Post Post-Marketing, Privacy

- Provision of appropriate information on the products at the time of their use
- Explanation to and consent from the patient as to product application
- Storage of final products as well as patients' sample such as blood
- Grasping information regarding hazardous events caused by products and in patients
- Protection of personal data

Flow of development and application of cells/tissue derived products



Revision of Guidelines on Ensuring Quality and Safety of Products Derived from Processed Human Cells/Tissues

Points to Consider in the Revision of Guidelines on Ensuring Quality and Safety of Products Derived from Processed Human Cells/Tissue

- Development of individual guidelines on autologous cells/tissue-based products and allogeneic ones, respectively, in order to clarify basic elements for ensuring the quality and safety of different class of products.
- Clarification of data requirements and evaluation for MAA submission and for the submission for evaluation of Q/S concerns on the product ("Kakunin-shinsei") before conducting investigational clinical trial(s). The latter is intended to evaluate if there is any quality and safety problem that might pose an obstacle to starting a clinical trial.
- Matters related to description instructions for "Kakunin-shinsei" are described in a separate document.
- The description of the guidelines should be easy to understand. Provide necessary background information by Q&A.

Guidelines on Ensuring Quality and Safety of Products Derived from Processed Autologous Human Cells/Tissue (Draft)

Chapter 1 General Rules

1. Purpose
2. Definitions

Chapter 2 Method of Manufacture

1. Raw Materials and Manufacture-Related Substances
   1. Desired cells/tissue
      (1) Characteristics of biological structures/functions and reasons for selection
      (2) Points to consider regarding infectious status of donors
      (3) Collection/preservation/transportation of C/T
   2. Raw materials and manufacture-related substances other than desired cells/tissue
      (1) In the case of cell culture
      (2) In the case of combination with noncellular/tissue components
      (3) In the case of modification of cells by genetic engineering

Guidelines on Ensuring Quality and Safety of Products Derived from Processed Autologous Human Cells/Tissue (Draft)

Chapter 2 Method of Manufacture(cont'd)

2. Manufacturing Process

1. (Non) formation of lot and provisions concerning lots
2. Method of manufacture
3. Characterization of processed cells
4. Form and packaging of final products
5. Constancy of the manufacture
6. Changes in the method of manufacture

3. Quality Control of Final Products

1. General statement
2. Method of controlling the quality of final products

Chapter 3 Stability of Products

Chapter 4 Non-Clinical Safety Study of Products

Chapter 5 Studies to Support the Effect/Performance of Products

Chapter 6 Internal Behavior of Products

Chapter 7 Clinical Study

Guidelines on Ensuring Quality and Safety of Products Derived from Processed Autologous Human Cells/Tissue (Draft)

1. The Guidelines stipulate the basic requirements that are necessary to ensure the safety and quality of pharmaceuticals and medical devices derived from processing of autologous human cells/tissues (hereinafter referred to as “Products derived from processed autologous Human Cells/Tissue” or merely as “Products”).
   However, “Products” vary in terms of types, characteristics and methods of clinical medication. In addition, scientific progress and accumulation of experience in this field are constantly advancing. Therefore, it is not always appropriate to apply the Guidelines without exception or to consider that the Guidelines include all necessary matters.
   Consequently, when conducting or evaluating tests on individual product it is necessary to take flexible approaches on a case-by-case basis in line with the purpose of the Guidelines and on the basis of reasonable grounds that reflect the advances in learning at the time.

Guidelines on Ensuring Quality and Safety of Products Derived from Processed Autologous Human Cells/Tissue (Draft)

2. The purpose of evaluation of Q/S concerns on the product prior to conducting investigational clinical trial(s), so-called "Kakunin-shinsei" , is to confirm whether or not there are quality or safety problems that will become obstacles when starting clinical trials of relevant products derived from processed autologous human cells/tissue.

Therefore, it is not required that data/information to be attached in applying for "Kakunin-shinsei" fulfill all requirements and include all contents which are indicated in the Guidelines. In applying for "Kakunin-shinsei" , applicants shall submit reasonably-prepared appropriate data/information, which fulfill conditions to meet the purpose as of that time, on the premise that data/information for ensuring quality and safety at the time of approval for MAA are enriched and developed along with the progress of clinical trials in line with the Guidelines.

Guidelines on Ensuring Quality and Safety of Products Derived from Processed Autologous Human Cells/Tissue (Draft)

In addition, the scope and degree of data/information required for "Kakunin-shinsei" differ depending on the origin of the product, subject disease, subject patients, site of administration, method of medication, method of processing and so on. A lot of matters are not always specifically described in the Guidelines.

Therefore, case-by-case consultation with the Pharmaceuticals and Medical Devices Agency is encouraged.

Chapter 1 General Rules

2. Definitions

The definitions of terms used in the Guidelines shall be as follows.

1. “Processing of cells/tissue” shall mean applying chemical treatment, alteration of biological properties, combination with noncellular/tissue components or modification by genetic engineering to artificially proliferate or activate cells/tissuefor the purpose of curing diseases or repairing or regenerating tissues.

The following shall not be deemed to be processing: separation of tissues, disintegration of tissues, separation of cells, isolation of a specific cell, treatment by antibiotics, washing, gamma ray, sterilization, freezing, thawing, etc.

Chapter 2 Method of Manufacture

1. Raw Materials and Manufacture-Related Substances

1. Desired cells/tissue
2. Raw materials and manufacture-related substances other than desired cells/tissue

2. Manufacturing Process

1. (Non)formation of lot and provisions concerning lots
2. Method of manufacture
3. Characterization of processed cells
4. Form and packaging of final products
5. Constancy of manufacture
6. Changes in the method of manufacture

3. Quality Control of Final Products

1. General statement
2. Method of controlling the quality of final products

Chapter 2 Method of Manufacture

1. Raw Materials and Manufacture-Related Substances

1. Desired cells/tissue

(1) Characteristics of biological structures/functions and reasons for selection

(2) Points to consider regarding infectious status of donors

(3) Collection/preservation/transportation of cells/tissue

1. Desired cells/tissues

(2) Points to consider regarding infectious status of donors

From the viewpoint of ensuring safety of patients, manufacturing workers and healthcare professionals, test items relating to infectious diseases shall be set in consideration of various infectious diseases that can infect through collected cells/tissue, and the propriety of the test items shall be demonstrated. In particular, attention shall be paid to hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV) and adult T-cell leukemia virus (HTLV).

1. Desired cells/tissue

(3) Collection/preservation/transportation of cells/tissue

①Eligibility of collectors and collecting medical institutions, etc.

② Propriety of the site and method of collection

③ Explanation to and written IC from donors.

④ Protection of donors' personal information.

⑤Tests and examinations to ensure donor's safety.

⑥ Method of preservation and measures to prevent mix-up.

⑦ Method of transportation.

⑧ Preparation of a record and method of storage.

2. Raw materials and manufacture-related substances other than desired cells/tissue

- Eligibility of all components used for processing and setting standards as appropriate
- Avoidance of use of serum, serum components, antibiotics in cell culture to the extent possible
- Attention to feeder cells derived from different animal species
- No adverse impact of noncellular/tissue components on desired C/T or products

Chapter 2 Method of Manufacture

2. Manufacturing Process

1. (Non) formation of lot and provisions concerning lots
2. Method of manufacture
3. Characterization of processed cells
4. Form and packaging of final products
5. Constancy of manufacture
6. Changes in the method of manufacture

Chapter 2 Method of Manufacture (cont'd)

3. Quality Control of Final Products

1. General considerations

The overall quality control strategy of "Products Derived from Processed Autologous Human Cells/Tissue", may consist of quality control of raw materials and intermediates, if any, verification of the propriety of the manufacturing process and maintenance of consistency thereof, specifications of final products and so on.

Specifications (a set of acceptance criteria and test methods) for final products shall be set by taking into account the type and character of subject cells/tissue, the method of manufacture, intended clinical use and the way of use of each product, stability and available test methods and so on.

Chapter 2 Method of Manufacture (cont'd)

3. Quality Control of Final Products

1. General considerations(cont'd)

In addition, specifications shall be set and justified from the perspective of achieving quality control purposes as a whole by taking into account the mutually complementary relationships between the verification of the propriety of the manufacturing process and the method of maintaining consistency/quality control of raw materials and intermediates.

Chapter 2 Method of Manufacture (cont'd)

3. Quality Control of Final Products

1. General considerations(cont'd)

The purpose of "Kakunin-shinsei" is to confirm that products can be deemed to have no quality/safety problems for conducting clinical trials. Therefore, it may be possible to set provisional specifications with allowances for some variation on the basis of the values measured on a few test specimens, as long as one can argue the relation between the results of clinical tests and such quality attributes after clinical trials. However, testing for sterility and presence of mycoplasma is essential.

Quality control strategies including specifications shall be enriched and developed along with the progress of clinical trials.

2. Quality control of final products

①Number of cells and survival rate
②Identification test
③Cell purity test
④Tests on cell-derived physiologically active substances other than desired ones
⑤Tests on process-related impurities
⑥Testing for sterility and presence of mycoplasma
⑦Endotoxin test
⑧Virus test
⑨Biological activity test
⑩Potency test
⑪Mechanical compatibility test

2. Quality control of final products (cont'd)

(8) Virus test

For cells that can proliferate HBV, HCV, HIV or HTLV, it is necessary to confirm that administration of products will not put patients at a disadvantage by conducting tests on the amounts of virus in intermediates, final products, etc. In addition, where components of biological origin are used in the manufacturing process, it may be necessary in some cases to consider conducting tests on final products to prove no contamination of virus derived from the said components. However, it is desirable that erratic parasitism is denied through tests on original components or process evaluation, wherever possible.

Chapter 3 Stability of Processed Human C/T

- For final products and/or critical intermediate stability tests using relevant parameters shall be conducted to set storage conditions and an expiration date.
- In the case of frozen storage and thawing, whether or not freezing and thawing processes have effects on the stability and specifications of products shall be confirmed.
- In the case of transporting final products, the transporting vessel and procedure of transportation (including thermal management) shall be set, and the propriety thereof shall be demonstrated.

Chapter 4 Non-Clinical Safety Test of Processed Human Cells/Tissue

- Appropriate animal tests or in vitro tests should be performed to a scientifically reasonable extent, if necessary and technically possible.
- Noncellular/tissue components and impurities shall be evaluated not by animal tests but by physical and chemical analyses, wherever possible.
- Test specimens of human origin are valuable. In addition, it is not always true that meaningful results can be obtained by testing products of human origin with experimental animals. Therefore, where more useful knowledge is expected to be obtained by preparing product models of animal origin and implementing tests under a test system applicable to appropriate experimental animals, it may rather be scientifically reasonable to use such test system.

Chapter 4 Non-Clinical Safety Test (Examples 1)

Points to consider on performing non-clinical safety studies are indicated below. These are just examples. It is not required to implement unreasonable tests, and appropriate tests shall be examined in consideration of the characteristics, etc. of relevant products.

1. It shall be demonstrated that genetic transformation other than the intended one has not occurred in cells cultured beyond the period of culture
2. The quantity of physiologically active substances produced by cells/tissue, such as various cytokines and growth factors, shall be determined as appropriate, and their effects in the case of being applied to the living body shall be considered.

Chapter 4 Non-Clinical Safety Test (Examples 2)

3. The possibility that application of products would affect normal cells or tissues of patients shall be examined and discussed.
4. The possibility that products, or expression products of transgenes would cause undesirable immune reactions shall be examined and discussed.
5. Where a manufacturing process involves foreign gene transfer, safety of transgenes and transgene products shall be demonstrated through examination of their properties. For cells, potential proliferative changes, tumorigenesis and canceration shall be discussed
6. In the case of using virus vectors, the abundance of proliferating viruses shall be examined.
7. Where it is easy to obtain products, including model products of animal origin, and there is a possibility that useful safety information relating to clinical applications will be obtained, implementation of a reasonably-designed general toxicity test shall be taken into consideration.

Chapter 5 Tests to Support the Effect or Performance of Processed Human Cells/Tissue (1)

1. For products, their functional expressions, persistence of their action and their effects expected as pharmaceuticals/medical devices shall be examined through appropriately-designed tests using test animals and cells to a technically possible and scientifically reasonable extent.
2. For transgenic cells, the expression efficacy of desired products from transgenes and persistence of expression as well as bioactivity of expression products and their effects expected as therapeutics shall be examined.

Chapter 5 Tests to Support the Effect or Performance of Processed Human Cells/Tissue (2)

3. Where appropriate models of products made from animal-derived cells/tissue or disease-model animals are available, therapeutic effects shall be examined using them.
4. At the stage of applying for “Kakunin-shinsei”, detailed experimental examination is not necessarily required if it is reasonably clarified by literatures or knowledge in and outside Japan that treatment based on the effect or performance of the relevant product is far more promising than other treatment methods.

Chapter 6 Internal Behavior of Processed Human Cells/Tissue

1. Studies relating to disposition of cells/tissue that constitute products or expression products of transgenes, including absorption and distribution in test animals should be performed to a technically possible and scientifically reasonable extent . Thereby, it is expected to presume the survival duration and duration of effect of cells/tissue in products that have been applied to patients and clarify the intended effect is achieved to a sufficient extent.
2. Where cells/tissue exert their actions after targeting to a specific site (tissue, etc.), localization shall be demonstrated.

Chapter 7 Clinical Study Plan

Safety evaluation at the time of applying for "Kakunin-shinsei" will be taken into account with expected clinical effectiveness. Therefore, scheduled domestic clinical trial plans for the products in question shall be evaluated in light of the following items.

1. Target disease
2. Trial subjects and patients who should be excluded from trial subjects
3. Details of treatment provided to trial subjects, including application of the products in question

Chapter 7 Clinical Study Plan (Cont'd)

4. Propriety of implementation of clinical studies in light of comparison with existing treatment methods
5. Ideas of matters to be explained to trial subjects, including risks and benefits that are assumed from information currently available

Incidentally, it is necessary to implement clinical studies by setting an appropriate study design and end point. Therefore, clinical studies shall be appropriately planned in light of the origin of desired cells/tissue, target disease and method of medication, etc.

Toward the Future

- Effective/Efficient/Flexible/Scientific Regulation depending on the Characteristics of the Product and Intended Clinical Use
- Up-dating and/or New Development of GLs
- Promotion of Novel Product Development and Application through Frequent Dialog among Regulatory Agency, Industry and Academia
- Acceleration of Review