International Regulatory Endeavor Towards Sound Development of Human Cell Therapy Products

February 18-19th, 2015
Hitotsubashi Hall, Tokyo, Japan

Organized by
International Alliance for Biological Standardization (IABS)

With the support from
Pharmaceuticals and Medical Devices Agency (PMDA)
Japan Science and Technology Agency (JST)
National Institute of Biomedical Innovation (NIBIO)

Under the auspices of
Ministry of Health, Labour and Welfare (MHLW)
Forum for Innovative Regenerative Medicine (FIRM)
Japan Pharmaceutical Manufacturers Association (JPMA)
The Japanese Society for Regenerative Medicine (JSRM)
This meeting will bring together an outstanding and diverse group of speakers from regulatory agencies, industry, and academia, all of whom are at the forefront of the cell therapy field. The major objective of the meeting is to highlight the important regulatory considerations that are unique to human cell therapy products, as well as to promote international dialogue and exchange of information and points of view in this evolving field. The scope of the cell therapy products that will be covered in this meeting are human cell derived and substantially manipulated cell therapy products (hCTPs). To develop novel hCTPs and to translate them more efficiently and effectively into products that contribute more to human health care, it is essential that they be based on a sound scientific rationale. Manufacturers and control authorities should take into account common scientific core elements, as well as the specifics of the cell source, manufacturing process, product administration procedures, and diseases in question. As a part of such an endeavor, it is critical to share a common recognition among interested parties with respect to the essential scientific and technological elements for CMC, pre-clinical and clinical studies of all types of substantially manipulated hCTPs. In other words, a challenge should be made so that we can develop a minimum consensus package that encompasses scientific principle/concepts, general considerations and technical requirements commonly applicable to all hCTPs. Also, as an important aspect of sound scientific regulatory considerations for hCTPs, it is very important to recognize the differences between “traditional” biological/biotechnological products and hCTPs regarding relevant scientific and technical elements. By taking such an approach, we intend to clarify specific points to consider for the evaluation and control of hCTPs that are different from those of traditional biological/biotechnological protein products with respect to quality, safety and efficacy. Throughout these discussions, it is also expected that the minimum requirements for each regulatory concern will be identified. For individual products, relevant technical and medical requirements should be added to the minimum consensus package taking into account the nature, specific characteristics, intended clinical use and ways of transplantation of the product in question. In addition, we also will identify special points/issues to consider for specific type of products, as well as very critical points/issues for various type of products, which have to be resolved, improved, and/or developed in terms of sound scientific regulation in order to facilitate the availability of products in a rational and timely manner, and which will be valuable globally to public health.
Organizing Committee
Takao Hayakawa 1), Kindai Univ., Japan
Takashi Aoi, Kobe Univ., Japan
Akifumi Matsuyama, NIBIO, Japan
Akihiro Umezawa, NICHD, Japan
John Petricciani, IABS President, USA

Yoji Sato, National Institute of Health Sciences, Japan
Yuzo Toda, FIRM Chairperson, Japan
Masayuki Yamato, Tokyo Women's Medical Univ., Japan
Daisaku Sato, PMDA, Japan

Program Committee
Takao Hayakawa 1), Kindai Univ., Japan
Takashi Aoi, Kobe Univ., Japan
Mira Choi, MFDS, Korea
Joyce Frey-Vasconcells, Formerly with FDA, USA
Karin Hoogendoorn, Novartis, Switzerland
Surapol Issaragrisil, Mahidol Univ., Thailand
Akifumi Matsuyama, NIBIO, Japan
Jimmy McBlane, MHRA, UK
John Petricciani, IABS President, Formerly with WHO & FDA, USA
Matthias Renner, PEI, Germany
Anthony Ridgway, Health Canada, Canada
1)Chair of Cell & Gene Therapy Committee, IABS

Yoji Sato, National Institute of Health Sciences, Japan
Glenn Smith, TGA, Australia
Glyn Stacey, UKSCB/NIBSC, UK
Yuzo Toda, FIRM Chairperson, Japan
Jean-Hugues Trouvin, Univ. Paris Descartes, France
Masayuki Yamato, Tokyo Women’s Medical Univ., Japan
Daisaku Sato, PMDA, Japan
Masayuki Shibasaki, FIRM Secretariat, Japan
Akihiro Umezawa, NICHD, Japan
Ivana Knezevic, WHO
Pierrette Zorzi-Morre, Formerly with AFSSAPS, France
AGENDA (as of 4 FEB. 2015)

Day 1 – Wednesday, FEBRUARY 18, 2015

8:45  Registration Open

9:25  Opening & Introduction by IABS President, John Petricciani (Formerly with WHO and US FDA)

9:35  Welcome Note by Chief Executive PMDA (Co-sponsor), Tatsuya Kondo

9:45  Welcome Note by JST (Co-sponsor), Shoichiro Tonomura

9:55  Session 1  Keynote Lecture
    Chairs: Kunihiko Suzuki (FIRM, Japan)

(9:55)  Current regenerative medicine field and the implications of changing regulations.
    Mahendra Rao (NYSCF, USA)

10:45  Break

11:00  Session 2  Introduction of the meeting including the concept of a minimum consensus package
    plus case by case approaches for evaluating human cell therapy products [hCTPs]
    Chairs: Matthias Renner (PEI, Germany) and Surapol Issaragrisil (Mahidol Univ., Thailand)

(11:00)  Challenges for developing a minimum consensus package plus case by case approaches for evaluating cell
    therapy products
    Takao Hayakawa (Kindai Univ., Japan)

11:45  Lunch

13:00  Session 3  Specific points to consider for the evaluation and control of hCTPs that are different
    from those of traditional biological/biotechnological protein products (1)
    Chairs:, Jean-Hugues Trouvin (Univ. Paris Descartes, France), Pierrette Zorzi-Morre (Formerly with
    AFSSAPs, France)

(13:00)  3.1  GXPs
    Daisaku Sato (PMDA, Japan)

13:30  3.2  CPC
    Tomohiro Morio (Tokyo medical and dental university, Japan)
14:00  3.3  Starting cells, other raw materials, manufacture-related substances and non-cellular component constituting the complex final products, if any  
Daisuke Maeda (PMDA, Japan)

14:30  3.4  Establishment of relevant cell line, cell bank and/or critical intermediate(s); processing of cells  
Glyn Stacey (NIBSC, UK)

15:00  3.5  Preparation of desired cell products, Formulation, Characterization of cells at critical stages  
Jean-Hugues Trouvin (Univ. Paris Descartes, France)

15:30  Break

15:50  3.6  Verification of manufacturing process and consistency of manufacture, process control, comparability  
Karin Hoogendoorn (Novartis, Switzerland)

16:20  3.7  Product stability, quality control of final products, storage and transport procedure at critical steps  
Pierrette Zorzi-Morre (Formerly with AFSSAPs, France)

16:50  3.8  Industry View  
Junichi Koga (JPMA, Japan)

17:20  Panel Discussion  
Moderators: Anthony Ridgway and Jean-Hugues Trouvin  
Speakers and Carl Burke (Janssen R&D, USA)

18:20  End of Day 1

18:30  Networking Reception
Day 2 – Thursday, FEBRUARY 19, 2015

8:45  Registration Open

9:00  **Session 4**  Specific points to consider for the evaluation and control of hCTPs that are different from those of traditional biological/biotechnological protein products (2)

*Chairs: Jimmy McBlane (MHRA, UK), Yoji Sato (NIHS, Japan)*

(9:00)  4.1 Pre-clinical safety evaluation
Jimmy McBlane (MHRA, UK)

9:30  4.2 Proof of Concept, mode of action, biodistribution
Akifumi Matsuyama (NIBIO, Japan)

10:00  4.3 Clinical Issues
Kazuo Yano, Masayuki Yamato (Tokyo Women's Medical Univ., Japan)

10:30  Break

10:45  4.4 Industry View
Kentaro Yoshimatsu (JPMA, Japan)

11:15  **Panel Discussion**
Moderators: Christopher Bravery and Yoji Sato
Speakers and Carl Burke (Janssen R&D, USA)

11:50  Lunch

13:00  **Session 5**  Identification of specific points/issues for specific types of products, as well as very critical points/issues for various types of products (1)

*Chairs: Glyn Stacey (NIBSC, UK), Takashi Aoi (Kobe Univ., Japan)*

(13:00)  5.1 Somatic cells, Somatic stem cells (Autologous, Allogeneic)
Matthias Renner (PEI, Germany)

13:30  5.2 iPS (iPS-like) Cells (Autologous, Allogeneic)
Takashi Aoi (Kobe Univ, Japan)

14:00  5.3 ES cells
Akihiro Umezawa (NICHD, Japan)
14:30  **Session 6**  Identification of specific points/issues for specific types of products, as well as very critical points/issues for various types of products (2)

*Chairs: Anthony Ridgway (Health Canada, Canada)*

(14:30)  6.1 Adventitious agents (Virus, sterility, and prion evaluation on cell sources, final products, culture media and ancillary products; use of human/animal derived raw materials other than target cells)

_Hiroyuki Yokote_ (The Chemo-Sero-Therapeutic Res. Inst, Japan)

15:00  **Break**

15:20  6.2 Specifications

_Takao Hayakawa_ (Kindai Univ., Japan), _Norihisa Sakamoto_ (PMDA, Japan)

15:50  6.3 Potency

_Anthony Ridgway_ (Health Canada, Canada)

16:20  6.4 Measurement reliability over the product lifecycle: The need for reference materials of hCTPs

_Christopher Bravery_ (Formerly with MHRA, UK)

16:50  6.5 Tumorigenicity

_Yoji Sato_ (NIHS, Japan)

17:20  6.6 WHO considerations

_Ivana Knezevic_ (WHO)  TBC

17:50  **Panel Discussion**

*Moderators: John Petricciani and Takao Hayakawa*

*Speakers and Daisaku Sato*

18:30  **Concluding Remarks**

_John Petricciani_  (IABS President, USA)

**CLOSE OF MEETING**
Aims of Sessions

Session 1  Keynote Lecture
Keynote lecture by an outstanding scientist in the stem cell biology or cell therapy field.

Session 2  Minimum consensus package plus case by case approaches for evaluating human cell therapy products (hCTPs)
The major objective of the meeting is to highlight the important regulatory considerations that are unique to human cell therapy products.
The scope of the cell therapy products that will be covered in this meeting are human cell derived and substantially manipulated cell therapy products (hCTPs).
To develop novel hCTPs and to translate them more efficiently and effectively into products that contribute more to human health care, it is essential that they be based on a sound scientific rationale. Manufacturers and control authorities should take into account common scientific core elements, as well as the specifics of the cell source, manufacturing process, product administration procedures, and diseases in question. As a part of such an endeavor, it is critical to share a common recognition among interested parties with respect to the essential scientific and technological elements for CMC, pre-clinical and clinical studies of all types of substantially manipulated hCTPs. In other words, a challenge should be made so that we can develop a minimum consensus package that encompasses scientific principle/concepts, general considerations and technical requirements commonly applicable to all hCTPs.
All interested parties including basic and clinical researchers, industry, as well as regulators can use such a “minimum consensus package” as a common platform for their activities. For an individual case, various ad-on packages may be set by taking into account the product specific profile, target disease, development stage, experiences of use, and so on.
Subsequent sessions (Sessions 3-6) will address in detail: 1) specific points to consider for the evaluation and control of hCTPs that are different from those of traditional biological/biotechnological protein products; and 2) identification of specific point/issues for a specific type of product, as well as very critical points/issues for various types of products. Preceding this, the concept and scientific elements of a minimum consensus package plus the case by case approach for hCTPs for product development, evaluation, and control will be overviewed.
The overall concept is that cell therapy can be promoted efficiently, effectively and reasonably through the use of such a “minimum consensus package” + add-on packages for individual cases.

Session 3-4  Specific points to consider for evaluation and control of hCTPs that are different from those of traditional biological/biotechnological protein products (1)-[2]
Scientific elements for hCTPs development, evaluation and control may include: 1) GXP, 2) Cell processing center (CPC), 3) Justification of source and selection of human cells that serve as raw materials, including autologous or allogeneic donor screening criteria and eligibility, 4) Suitability and quality control of raw materials and manufacture-related substances other than target cells, 5) Expected function and safety of non-cellular components constituting the final products together with cells, 6) Establishment of relevant cell line, cell bank and/or critical intermediate(s); processing of cells, 7) Preparation of desired cell products, 8) Formulation (Preparation of final product), 9) Characterization and grasp of specific profiles of cells at critical stages (e.g. starting, bank, intermediate, final), 10) Verification of the manufacturing process and consistency of manufacture as well as process control, 11) Comparability assessment upon changes in the manufacturing process, 12) Product stability, 13) Quality control of final products from product aspects (including setting specifications) and process aspects, 14) Setting storage and transport procedure of cells/products at critical steps, 15) Pre-clinical safety evaluation, 16) Proof of concept, mode of action, and biodistribution, and 17) Clinical trial.
Core scientific principles/concepts and many technical considerations on hCTPs may be basically similar to those already well-defined as the outcome of many discussions, a significant amount of experiences accumulated and consensus achieved for the traditional biological/biotechnology products. However, active ingredients of hCTPs are cells that possess a unique nature, which is different from those of proteins as active ingredients of the traditional biological/biotechnology products. Therefore, as an important aspect of sound scientific regulatory considerations for hCTPs, it is very significant to recognize the differences between “traditional” biological/biotechnological products and hCTPs with respect to various relevant scientific and technical elements. By taking such an approach, this meeting intends to clarify specific points to consider for the evaluation and control of hCTPs that are different from those of traditional biological/biotechnological protein products with respect to quality, safety and efficacy.

Some examples that may be concerned and addressed in these sessions are as follows:

For the eligibility of starting cells, raw materials, and manufacture-related substances of biological origin, what are reasonable acceptance criteria? What are differences between the vial safety evaluation for hCTPs (and other biological raw materials) and those for protein products described in the ICH-Q5A (Viral safety)? For cell banks, what are differences between cell banks for production of hCTPs and those in the ICH-Q5D (Cell substrate)? How should we evaluate and maintain the quality of cell banks for hCTPs? How is the ICH-Q5C (Product stability) applicable for hCTPs? How is ICH-Q6B (Product characterization, Product quality control, Specifications etc.) applicable for hCTPs?

For mode of action, can we really identify the primary mode of action of all (or any) hCTPs, which may lead to a potency assay?

For comparability, what are the differences between comparability for hCTPs and that for protein products described in ICH-Q5E? Discussion may include: When is it needed? What is its purpose? Are there general principles to apply in individual cases? In case of autologous hCTPs, are products from different donors regarded comparable? In case of allogenic hCTPs, are products from different cell banks/donors regarded comparable? What is required to show the biocomparability of allogeneic hCTPs?

For pre-clinical safety testing using animals, what are differences in general and specific considerations between hCTPs and protein products covered by the ICH-S6? What is the rationale for animal testing? Are there any relevant animal models? How useful are the results?

For clinical evaluations of hCTPs, possible design and interpretation of clinical trials for hCTPs will be addressed in comparison to those for typical protein products, as well as those for orphan drugs. Throughout these discussions, it is also expected to point out what is a minimum requirement for each regulatory concern.

Session 5-6 Identification of specific point/issues for specific types of products, as well as very critical points/issues for various types of products (1)-[2].

For individual products, relevant technical and medical requirements should be added to the minimum consensus package taking into account the nature, specific characteristics, intended clinical use and ways of transplantation of the product in question. Among elements addressed in Session 3 and 4, there are several elements that are very important for product development, evaluation and standardization, but that need further discussion in terms of relevant regulatory requirements and testing methods.

Session 5 intends to identify special points/issues to consider for specific types of products such as products derived from processing of human (autologous or allogeneic) somatic cells/somatic stem cells, human (autologous or allogeneic) iPS (iPS-like) Cells, and ES cells, respectively.

Session 6 intends to identify very critical points/issues for various types of products, which have to be resolved, improved, and/or developed in terms of sound scientific regulation in order to facilitate the availability of products in a rational and timely manner. These may include: Adventitious agents issues (virus, sterility, and prion evaluation for cell sources, final products, culture media and ancillary products; use of human/animal derived raw materials other than target cells), specifications, potency, and tumorigenicity.
For establishing specifications, issues to be discussed may include: How should we set the specification of hCTPs? What is the intended use(s)? Are there examples from the past? Are there general principles to apply in individual cases, while recognizing that there also may be specific requirement in an individual case?

For potency, though it depends on the individual intended clinical use and is desirable to relate to POC, discussion may include: Why is it needed? How has it been defined? How can we evaluate potency of hCTPs, without sufficient knowledge or relevant assay system in relation to specific mode of action of hCPTs in question? A quantitative acceptance criterion of potency assay should be acceptable, but is a qualitative criterion acceptable? Are there examples from the past? Are there general principles to apply in individual cases?

For tumorigenicity, presentation would mainly focus on pluripotent stem cell-derived products. It may also include: Background on why this is an issue; Is this an issue only for pluripotent stem cell-derived products? How should we, and can we, evaluate the tumorigenicity of hCTPs? Is there any possibility to establish general guidance available on test systems and how to interpret results?

These topics would be presented by experts who have significant experience with relevant general considerations and who may provide some informative technical data. A panel discussion at the end would be very beneficial to get different points of view expressed and maybe even get agreement on some items.