Meeting report

Report of the international conference on regulatory endeavors towards the sound development of human cell therapy products*

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Abstract

The regulation of human cell therapy products is a key factor in their development and use to treat human diseases. In that regard, there is a recognized need for a global effort to develop a set of common principles that may serve to facilitate a convergence of regulatory approaches to ensure the smooth and efficient evaluation of products. This conference, with experts from regulatory agencies, industry, and academia, contributed to the process of developing such a document.

Elements that could form a minimum consensus package of requirements for evaluating human cell therapy products were the overall focus of the conference. The important regulatory considerations that are unique to human cell therapy products were highlighted.

Sessions addressed specific points that are different from those of traditional biological/biotechnological protein products. Panel discussions complemented the presentations.

The conference concluded that most of the current regulatory framework is appropriate for cell therapy, but there are some areas where the application of the requirements for traditional biologicals is inappropriate. In addition, it was agreed that there is a need for international consensus on core regulatory elements, and that one of the major international organizations should take the lead in formulating such a consensus document.

Keywords: stem cells, therapy, transplantation

Abbreviations

ADMPs adipose tissue-derived multi-lineage progenitor cells

ATMP advanced therapy medicinal products

BLA biologics license application

CBMPs cell-based medicinal products

CCl₄ carbon tetrachloride

CMC chemistry, manufacturing, and controls

CPFs cell processing facilities

CPPs critical process parameters

CQAs critical quality attributes

ECBS Expert Committee on Biological Standardization

ESC embryonic stem cells

EU European Union

FDA Food & Drug Administration

FIRM Forum for Innovative Regenerative Medicine

GLP good laboratory practice

GMP good manufacturing practice

GTP good tissue practice

hCTPs human cell therapy products

hPSC human pluripotent stem cell
IABS International Alliance for Biological Standardization
ICDRA International Conference of Drug Regulatory Authorities
ICH International Conference on Harmonization
IDE investigational device exemption
INN International Nonproprietary Name
iPSC induced pluripotent stem cells
ISCB International Stem Cell Banking Initiative
JPMA Japan Pharmaceutical Manufacturers Association
JSRM Japanese Society for Regenerative Medicine
JST Japan Science & Technology Agency
MHRA Medicines and Healthcare Products Regulatory Agency
MLHW Ministry of Health, Labour and Welfare
MMPs matrix metalloproteinases
MOA mode of action
MSCs mesenchymal stem cells
NIBIO National Institute of Biomedical Innovation
OTCD ornithine transcarbamylase deficiency
PMA premarket application
PMDA Pharmaceuticals and Medical Devices Agency
POC proof of concept
QRM quality risk management
SCLs stem cell lines
UK United Kingdom
UN United Nations
USA United States of America
WHO World Health Organization
WHO TRS WHO Technical Report Series

1. Introduction

Over the past decade, there have been a number of international workshops and meetings in which various issues related to the regulation of human cell therapy products (hCTPs) have been discussed. In addition, a variety of guidelines and regulations currently exist or are in development by both governmental and professional organizations in different regions of the world where cell therapy research and development activities are underway. As a result, there is a need for a global effort to develop a set of common principles that may serve to facilitate a convergence of regulatory approaches to ensure the smooth and efficient evaluation of products that may lead to approvals and use as new therapeutic agents.

To initiate the process of developing a document on this subject, a workshop jointly sponsored by the International Alliance for Biological Standardization (IABS) and the Japan Science & Technology Agency (JST) was held in Kyoto, Japan on 7-8 March 2014. Manuscripts of key presentations at that meeting are *in press*. Based on the information presented at the Kyoto meeting and the recommendations of the participants, this followup conference on regulatory endeavors towards the sound

development of hCTPs was held in Tokyo, Japan, on February 18-19, 2015. The major objective of the meeting was to highlight the important regulatory considerations that are unique to human cell therapy products. This meeting brought 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 scope of the hCTPs that were covered in this meeting included human cell-derived and substantially manipulated hCTPs.

The conference organizing committee included manufacturers, regulators, and academics from multiple international organizations. Over 170 scientists from 9 countries (Canada, China, France, Japan, Korea, Spain, Thailand, United Kingdom (UK), United States of America (USA)) attended the conference. Regulatory agencies, manufacturers, academia, and nongovernmental organizations were represented. The meeting provided a forum for review of the current regulatory environment and discussion of how new approaches might facilitate the more efficient development of approvable hCTPs. Finally, the conference addressed the path toward global acceptance and implementation of a scientifically sound regulatory framework for hCTPs.

The objectives of the workshop were to:

- Review the usefulness and limitations of current regulatory systems for traditional biological/biotechnological protein products
- Discuss the application of these systems to hCTPs
- Initiate a dialogue for international collaboration to achieve the adoption of a rational regulatory framework for hCTPs
- Lay the groundwork for regulatory acceptance of a harmonized approach to the regulation of hCTPs, taking into account that some differences from other biologicals exist

Dr. John Petricciani (IABS, Switzerland) opened the workshop by acknowledging support from the World Health Organization (WHO), the Pharmaceuticals and Medical Devices Agency (PMDA), the Japan Science and Technology Agency (JST), and the National Institute of Biomedical Innovation (NIBIO) of Japan, along with the Ministry of Health, Labour and Welfare (MLHW) of Japan, the Forum for Innovative Regenerative Medicine (FIRM), the Japan Pharmaceutical Manufacturers Association (JPMA), and the Japanese Society for Regenerative Medicine (JSRM). In addition, the organizing and scientific program committees were acknowledged for their help in developing the conference.

Dr. Petricciani reminded the participants that IABS had sponsored a cell therapy meeting in 2014 that was held in Kyoto, Japan. This conference builds on that experience. He also pointed out that the regulation of biologicals has more than a 100 year history, and that regulation evolved along with advances in science and medicine, particularly since the development of biotechnology in the 1980s.

The meeting objectives were described as: 1) Identify regulatory considerations that are unique to cell therapy; 2) noting the regulatory differences between “traditional”

biological products and hCTPs; and 3) Identify core scientific / technical elements for chemistry, manufacturing, and control(CMC), nonclinical, and clinical studies so that they could be used as the basis for a minimum consensus regulatory package.

He suggested that while background experience in the regulation of biological products should be considered, it is important to resist the temptation to try to fit hCTPs into each and every aspect of current regulatory frameworks (i.e., do not try to fit square pegs into round holes).

Dr. Tatsuya Kondo, PMDA, and **Dr. Shoichiro Tonomura**, JST, welcomed the participants, and expressed their support for the objectives of the conference which are consistent with the missions of their respective organizations.

Dr. Mahendra S. Rao (New York Stem Cell Foundation, USA) presented the keynote lecture on the current regenerative medicine field and the implications of changing regulations. He pointed out that the field of regenerative medicine is broad and covers multiple cell types that can be either used directly or processed further to develop a final cellular product. Cells also can be combined with other cells, bioengineered materials and/or modified by gene engineering techniques to generate products. The products are currently regulated in the USA under several pathways, and approval has been obtained by companies under each of these pathways.

The biggest change in the rules in the USA has been clarification on: 1) the final donor consent, 2) what will be regulated by the Food & Drug Administration(FDA) and what will be classified as the practice of medicine, and 3) the requirements for licensure of cord blood banks.

Although industry has in principle welcomed these clarifications and the proactive stance that FDA has taken, there are several concerns as related to the lack of coordination internationally between regulatory agencies, the absence of the availability of standards and calibration material and the concern that the special characteristics of cells that are immortal will make certain regulations difficult to implement if blindly or too rigorously applied.

Several countries have identified roadblocks that may make regenerative medicine products difficult to generate and have taken different approaches to resolve them. Japan has implemented a change in rules by legislation, the European Union (EU) has defined a separate class of advanced therapy medicinal products and the USA has developed a fast track and orphan disease processes, and a more liberal exemption policy.

Dr. Rao suggested that an important clarification that induced pluripotent stem cells (iPSCs) and embryonic stem cells (ESCs) are not the final product, but rather are intermediates used to manufacture the final product and that rules regulating the use of such intermediates should be applied to ESCs and iPSCs rather than identifying or conflating them with the product that is derived from them. This would obviate many of

the issues and roadblocks that hinder development of this subset of regenerative medicine based therapies.

In summary, Dr. Rao suggested that the following points related to hCTPs should be considered by regulatory authorities:

- 1) clarify consent and ownership and donor payment; 2) create an international database; 3) consider iPSCs as input material for manufacture and use a 510K-like approach for iPSC lines; 4) accept that iPSCs can be made under Good Laboratory Practice (GLP) conditions; 5) make calibration material available; 6) standardize what are reasonable requirements for residual pluripotent cells; 7) clarify what is a reporting requirement for a cell line used to make multiple products and what kind of data needs to be maintained; 8) clarify the kind of tests and numbers of lots that will need to be tested for an autologous therapy; 9) define follow up requirements in a clinical trial for cells that integrate; and 10) harmonize these rules internationally.

Dr. Takao Hayakawa (Pharmaceutical Research and Technology Institute, Kindai University, Japan) presented an overview of challenges for developing a minimum consensus package plus case by case approaches for evaluating human cell-derived and substantially manipulated hCTPs.

It was explained that a minimum consensus package should encompass scientific principle/concepts, general considerations, and essential core scientific and technological elements.

Further detailed explanations of the minimum consensus package were made regarding 1) general principles, 2) general consideration on sound scientific requirements for product development, evaluation and control, 3) CMC, 4) nonclinical safety, 5) nonclinical efficacy, and 6) clinical study including monitoring and follow-up after marketing authorization. CMC elements included: 1) justification of the source and selection of human cells that serve as raw materials, including autologous or allogeneic donor screening criteria and eligibility; 2) suitability and quality control of raw materials and manufacture-related substances other than the target cells; 3) the expected function and safety of non-cellular components constituting the final products together with the cells; 4) establishment of a relevant cell line, cell bank, and/or critical intermediate(s); 5) processing of the cells; 6) preparation of the desired cell products; 7) formulation (preparation of the final product); 8) characterization and understanding of specific profiles of cells at critical stages (e.g., starting, bank, intermediate, and final stage); 9) verification of a manufacturing process and constancy of the manufacture as well as process control; 10) comparability assessment after changes in a manufacturing process; 11) product stability; 12) quality control of final products on the basis of product aspects (including setting of specifications) and process aspects; and 13) setting storage and a transport procedure for the cells/products at critical steps.

It was emphasized that all interested parties including basic and clinical researchers, industry, as well as regulators could use such a “minimum consensus package” as a common platform for their activities concerning hCTPs for product development,

evaluation, and control. For an individual case, various add-on packages might be set by taking into account the product specific profile, target disease, development stage, experiences of use, among other factors. The overall concept was that cell therapy could be promoted efficiently, effectively and reasonably through the use of such a “minimum consensus package” plus add-on packages for individual cases.

2. Specific points to consider for the evaluation and control of hCTPs that are different from those of traditional biological/biotechnological protein products

Dr. Daisaku Sato (PMDA, Japan) addressed Good Tissue Practices (GTP) for hCTPs that are aimed at source material requirements and manufacturing practices of the target cells, which includes source material selection, donor eligibility, equipment and process control, and record keeping requirements for traceability. The main purpose of the GTP requirements is to prevent the introduction, transmission, and spread of communicable diseases by cell therapy products. The various layers of quality control of the cells in the course of the manufacturing process address that point. They may involve cells as starting materials, a cell bank system (including iPSCs / ESCs), intermediates, and final products. GTP is an operational part of quality assurance in a continuous and routine manufacturing operation.

For the manufacture of hCTPs, it is first necessary to select and justify the source and origin of the cells used as raw materials. Types of cells that could be considered include allogenic or autologous, and stem cell or non-stem cells. In principle, the source material selection criteria and tests to assess eligibility of a donor should reflect up-to-date knowledge of potential infectious agents and should deal with remaining uncertainty of the safety of advanced manufacturing technologies. The source material selection criteria and tests might depend on the risk of transmission of an infectious agent in the context of the proposed use of those materials.

Basically, relevant bacteria, fungal and viral infections have to be excluded through interview, screening and testing in light of the latest knowledge of infectious diseases and considering a donors' history of having received a transfusion or transplantation of an organ. As a part of GTP, cell collection operation and preservation should also be properly controlled, while protecting a donor's personal information and obtaining prior informed consent from the donor (including issues of the donor's property rights). Finally, in the storage of the cells collected, mix-up and cross-contamination of cells from different donors must be prevented. Records that allow traceability also may be necessary if a retrospective survey has to be carried out due to transmission of an infectious disease that is suspected to be associated with the hTCP. In addition to human cells, other source materials also are required to comply with safety criteria for preventing infectious disease transmission, including the risk of prion protein derived from bovine source materials from countries affected by bovine spongiform encephalopathy.

In the process from source material collection to product manufacturing, a quality management system should be in place in addition to quality and manufacturing control. The philosophy of quality risk management (QRM) can be derived from the International Conference on Harmonization (ICH) Q9 guidelines even in the field of cell processing.

Setting the control level to be achieved should be considered, from the perspectives of the equipment / facilities (hard) and the quality system (software). Once established, it should be managed and improved with particular attention to sterility and contamination in manufacturing control. However, in an aseptic operation, the unique challenges of hCTPs regarding the inability to sterilize the cell raw materials must be kept in mind. Finally, a flexible risk-based approach would be more appropriate, based on knowledge. For example, in the case where manufacturing experience is limited, implementation of validation may necessarily be difficult. As in the case of investigational medicinal products, an approach based on QRM could be taken. Risk-based scientific evaluation should be applied to achieve patient protection.

Dr. Tomohiro Morio (Tokyo Medical and Dental University, Japan) began by stating that common minimal requirements should be applied for all cell processing facilities (CPF), even though many different kinds of hCTPs may be handled in a given facility.

CPFs should have a suitable size, construction, and location and should have an easy-to-clean room where dust accumulation is minimized. Appropriate lighting, ventilation, plumbing and drainage systems should be considered. Zoning, flow design, and room pressure setting are important considerations for an open-cell processing system. The cleanliness level should be determined on a case-by-case basis.

The combination of suitable CPF hardware and an adequate management system is important when operating a CPF. It is critical to consider the prevention of: 1) the introduction of communicable diseases by environmental control, 2) cross-contamination by reasonable change-over operations, 3) spread of contamination by biological containment, and 4) mix-up by setting up an appropriate flow line and operating procedures.

The frequency and locations of environmental monitoring and procedures for change-over should be determined individually by risk-assessment. A scientific risk assessment approach and the development of innovative technology are needed to operate CPFs safely and confidently.

Dr. Daisuke Maeda (PMDA, Japan) addressed scientific points to consider on the quality and safety of materials used in manufacturing hCTPs.

Quality of final products (hCTPs) is affected by various factors. Quality of the materials is one of the critical factors and should be determined on a case-by-case basis approach depending on the characteristics of the product and its control strategy as a whole.

As for starting materials, the following points were highlighted: 1) donor eligibility criteria are key elements, especially regarding infectious agents, 2) reasons for selection of the cell/tissue should be provided with its desired/ targeted cell profile, 3) the cell characteristics and biological function should be shown, and 4) appropriate handling and processing are required.

Regarding other materials, the following items were stressed: 1) adequacy of using other raw materials and manufacturing-related substances should be shown, 2)

appropriate quality control with defined acceptance criteria must be in place, 3) non-cellular components constituting the final product should be justified in terms of the quality and the safety of hCTPs, and 4) appropriate/ sufficient information should be collected and provided.

Dr. Glyn Stacey (NIBSC, UK) addressed important issues in the establishment of relevant cell lines and seed stocks and their expansion and processing.

In the development of novel therapies the use of human pluripotent stem cell (hPSC) lines with fundamental scientific or ethical contraindications or lack of traceability may put both product and patients at risk. The key aspects of assessment of candidate cell lines are donor selection and overall quality assurance of the cell banking and manufacturing process, and this report focused on the suitability of the candidate cell line seed stocks.

Important elements of donor cell suitability including microbiological and genetic risk as well as appropriate donor consent and donor history, have recently been revisited in the UK, specifically for cells and tissues intended for use in cell therapy [1]. Microbiological risk assessment of donated cells is vital to evaluate any risk associated with the tissue of origin and the donor's history and lifestyle. Such assessments should include consideration of acute infections and organisms that may cause post-donation disease. Clearly the organisms of greatest concern will be those most likely contaminants that may persist or replicate in, or transform, human cells. Genetic risks due to donor genetic predisposition to disease states, are difficult to assess and the genetic lesion may not penetrate into an in vitro cellular phenotype. Thus, the screening of donors for mutations which might affect efficacy of cell therapies in general may not be helpful, although more focused genetic examination of cell lines may be of value when a specific product application is identified.

In establishing cell line seed stocks, traceability for starting materials (e.g. cell line, DNA constructs, scaffolds) and raw materials (those culture materials that are unlikely to persist in the final product) is crucial to help assure safety. In Europe the process of derivation of a seed stock is subjected to the European Tissues and Cells Directive. For clinical trials such seed stocks should be used to establish master and working cell banks under a good manufacturing practice (GMP) license that can provide a reliable and consistent source of cells for manufacture over many decades.

Some methods used for cell bank testing may be considered crucial for release of cell banks (e.g. sterility test, mycoplasma test, cell identity profile, viability, virology) and will require careful validation. Other tests may confirm useful characteristics which may not be readily quantifiable or are noncritical and may therefore be used as "informational" tests (e.g., cell markers, assays for pluripotency potential, karyotype, levels of differentiated cells). However, the exact regime of testing and status of each test ('release' or 'for information') will need to be directed by the nature of the cell lines involved, on a case by case basis.

The International Stem Cell Banking Initiative (ISCBi) [2] as established a global consensus drawing on broad ranging expertise, to provide guidance on the key issues for the development of seed stocks of pluripotent stem cell lines for clinical use [3]. It recommended the establishment of a dossier for the entire process of isolating, banking and testing the cell line, which can be used by regulatory authorities to establish compliance with regulation or by investors to carry out due diligence to assure the cell line was suitable for development of a clinical product.

The expansion and differentiation of hPSCs into therapeutic cells is a complex and potentially unstable process and careful in-process controls will be important to avoid wasted time and resource on cultures which may become unsuitable at an early stage to assure acceptable product. Monitoring of the differentiation process should evaluate the starting culture and consideration should also be given to the most critical phases of change in cellular composition (such as proliferation of 'blast' progenitor cells); particularly where they deviate from protocols based on natural developmental pathways. Key to such decisions on selecting the most appropriate in-process test methods is an in depth scientific understanding of the cell system used and what affects it (i.e., the first principle of Good Cell Culture Practice as published by Coecke et al. [4]).

Many countries are developing large scale 'haplobanks' of lines expressing homozygous HLA-types to provide a degree of immunological matching for patients and international coordination for this activity may be helpful. The European Commission funded database of hPSCshESCreg[5] is providing a growing source of information on ethically sourced hPSCs of all types and national origins and provides a useful starting point to evaluate hPSC lines for research and development. However, international consensus on the requirements to establish the quality of these seed stocks, will be vital to facilitate equitable access to safe and effective advanced therapies. In this regard the ISCBi consensus guidance on the development of seed stocks of stem cell lines [3] is a useful reference point for researchers, clinicians, commercial investors and regulators.

Dr. Jean-Hugues Trouvin (University Paris Descartes, France) covered the main issues relating to the production and formulation processes from which cell-based products are derived. Cell-based products are now regulated in many regions as "medicinal products" and more specifically as biological medicinal products. As such most of the technical requirements to be documented for biologicals apply to cell-based medicinal products (CBMP). His presentation was based on the European regulation 1394/2007 set up for advanced therapy medicinal products (ATMP). The wide diversity of products classified as CBMP and their complex molecular and biological features call for an adapted approach for qualification and validation of those products, while keeping in mind the main issues which are common to all biologicals. As a starting point, he pointed out that for biologicals, including CBMP, the dogma is still "the process makes the product", thus highlighting the need for establishing well-elaborated and validated processes (for manufacturing both the drug substance and drug product) before it can be envisaged to transfer them to a GMP-certified facility for routine production.

The specific issues addressed during his presentation include:

- i) the starting materials entering the manufacturing processes (cells, scaffolds, matrices, excipients, etc..) to give rise to the drug substance and drug product are key elements in the final quality of the desired product. As such, they should be carefully selected, described, and characterised. Their intrinsic variability (autologous or allogeneic origin from a single donation up to a well established cell line) should be considered in establishing the various steps of the process. The process has to be robust enough to accommodate the initial variability of the starting material.
- ii) The processes themselves are complex and encompass several steps, some of which are critical in terms of impact on the quality profile and quality attributes of the desired product. Identification of the critical process parameters is the main objective of a relevant pharmaceutical development.
- iii) Manufacture and formulation of CBMP make use of raw materials (as defined in the EU regulation). Although the raw materials do not enter the composition of the final product, their intrinsic quality and consistency is an important point to be considered as they do contribute to the overall quality profile of the final product. Any change in the quality or qualification of the raw materials may have a detrimental effect on the desired product.
- iv) Validation of the manufacturing process and formulation process are part of pharmaceutical development and should be considered in liaison with the quality control strategy before setting the specifications and release criteria (see P. Zorzi presentation). Among the numerous issues to be considered regarding the process and its development, changes introduced during the development and/or at the time of the transfer to the manufacturing site for marketing are particularly important. The question of “what to do if a change is introduced” is crucial and should be answered, case by case, using the comparability approach.
- v) On the specific aspect of complying with the GMP rules for manufacture, whereas it is acknowledged that GMP contributes to an acceptable process, in terms of environmental conditions, flow of materials and staff members, training, standard operating procedures, etc., GMP compliance does not assure the final quality of the desired product. The quality profile of a given product is primarily dependent upon the pharmaceutical development (formulation and manufacture), the validation of the process steps and identification of the critical process parameters to reach the target product profile. It is thus important to dedicate efforts towards the development of the process and its validation and not just contemplating whether or not GMP are fulfilled at the time of the routine manufacture.

To illustrate these issues, Dr. Trouvin presented some examples of CBMP recently approved via the European centralised ATMP procedure. The three products taken as examples (Chondrocelect®, MACI® and Provenge®) are all of autologous origin and consist of cell preparations ready to use with short shelf life. Based on a careful reading of their respective European public assessment reports, some important conclusions were drawn in the application of the quality issues. *Inter alia*, Dr. Trouvin stressed the importance of declaring, in the marketing authorisation dossier, a well-established and

validated manufacturing process. This process is an integral part of the authorisation and it may become an issue where a new manufacturing site is proposed. This question of a “declared and validated manufacturing site”, which is complementary to the GMP issue, has been a “major objection” during the marketing authorisation assessment of Provenge®, and is the reason for the current suspension of commercialisation of MACI® in Europe, in the absence of an approved and validated manufacturing site.

The last point of the presentation was to answer the initial question posed by Dr. Hayakawa in his introductory remarks, whether for CBMP it can be proposed a “minimum consensus package” for technical requirements commonly applicable to all CBMPs, and whether this package should be common or different from requirements applied to other more conventional biologicals and biotechnology derived products. In Dr. Trouvin’s opinion, it should be acknowledged that although CBMP are biologicals, their development deserve specific considerations illustrated above. Dr. Trouvin reminded the conference of the concept of a “risk-based approach” developed in the European regulation. This approach is a reasonable answer to the uncertainties and specificities of those products, still in their infancy, since it allows a more flexible development strategy.

Karin Hoogendoorn (Novartis, Switzerland) discussed manufacturing consistency and comparability strategies for autologous CBMPs, including genetically modified cells.

To manufacture an autologous CBMP consistently is a challenge, giving the inherent variability of the starting material (i.e., donor cells) and the read outs for relevant test methods, including product purity, impurities, and potency. Particularly in early development, critical quality attributes (CQAs) for both the starting material and the final cell product and critical process parameters (CPPs) for the cell manufacturing process, have not been defined. Hence, it is difficult to determine which variability is acceptable and does not impact the product quality, safety, and efficacy.

The second half of her presentation focused on a comparability exercise for an autologous genetically modified cell product in early development. Changes to the manufacturing process, manufacturing site, and starting material (i.e., vector) were discussed, using healthy donor cells as model to investigate the impact of the changes on the product quality. Product release and additional characterization data were discussed. It was once more stressed that defining the CQAs and CPPs as well as extensive additional product characterization, with a focus on methods able to pick up changes, are critical to assess if the post-change product has comparable quality and safety profile as the pre-change product.

Dr. PierretteZorzi (Pharma Biotech Consultant, France) addressed the overall quality control of CBMPs covering release specifications, stability, storage and transport, focusing on the similarities and differences with other biotech products, within the European legal framework.

Firstly she reminded the audience that the European Commission did not set up a new system for the sole purpose of ATMPs, but instead took a global and integrated approach, building upon existing legislation. Consequently ATMPs are addressed within

a single and coherent framework for all medicinal products, taking into account their regulatory and technical specificities.

ATMPs cover a large variety of products, the cellular part being from allogeneic or autologous origin (this conference was limited to human cells, therefore xenogeneic cells are not considered). hCTPs can be extensively or minimally manipulated, and combined with additional substances (e.g., scaffold, biomolecules).

Many peculiarities are attached to these products: difficulty to identify/quantify the active moiety, variability inherent to the cells, difficult if not impossible to perform complete characterization, and potency testing is often challenging. Other criteria to take into account during development and commercialization are the limited amount of starting materials, and short product shelf life.

But it should be emphasized that similar peculiarities are also common features of biotech products (e.g., a complete characterization is often difficult, heterogeneity of product profile, an animal model is not always available). The differences between CBMPs and biotechnology products lie more in the order of magnitude of these peculiarities. Thus it was considered that principles described in biotech guidelines provided good grounds for the development of CBMP and that they should be complemented by dedicated technical guidelines addressing specific issues: 1) a multidisciplinary guideline covering quality/safety/efficacy, 2) another on potency testing for cell based immunotherapy for the treatment of cancer, 3) another one for cultured chondrocytes, 4) and a guideline dedicated to stem cell-based medicinal products.

Based on these guidelines (biotech and CBMP), the quality control of CBMPs follow the same principles as biotechnology products mentioned in ICH Q6B, and the setting of specifications is the result of an overall control strategy, which includes:

- Control of raw materials and excipients, taking into account particularly their safety with regard to adventitious agents such as viruses, mycoplasma, bacteria, and fungi. (For which biotech guidelines are fully applicable)
- Characterization studies
- A well-controlled and validated process with appropriate in-process testing, which ensures a production of consistent batches.
- Adherence to GMPs,
- Stability testing
- Data of batches used in clinical studies batches, which are representative of the commercial production scale.

The rationale for establishing specifications being the same, the differences from biotechnology products only relate to the type of studies to be conducted due to the cellular nature of the product. The CBMP guidelines underline the following key elements:

- Cellular component(s) linked to the therapeutic indication should be characterized in terms of phenotypic/genotypic profiles;

- When the biological activity is linked to a complex mixture of cells, they should be characterized and controlled.
- Unwanted cells and the non-viable cells should be appropriately controlled
- Tumourigenic potential and genetic stability should be evaluated
- The potency assay is a critical point. In case there is no animal model available, the *in vitro* assay should be correlated with the intended biological activity. International reference preparations are not available, so in house reference materials should be characterized with regard to composition, purity and biological activity
- Demonstration of absence of bacteria for products having a short shelf life needs to be based on alternative testing methods according to the European Pharmacopoeia.

To date, four products have been authorized in the EU. Their evaluation was successfully conducted combining general biotech guidelines and specific ones for CBMPs. The questions raised in the course of the evaluation were mainly related to functionality of the cells, correlation of a potency assay with the clinical situation, microbial safety, process consistency, and comparability of clinical batches with commercial batches.

In conclusion, the EU regulatory framework and technical guidelines, (biotech and CBMPs) provide sufficient flexibility to ensure the quality of CBMP products and an evaluation consistent with other medicinal products.

Dr. Junichi Koga (JPMA, Japan) discussed some of the challenges faced by industry in the field of cell therapy and the need for the regulatory process to support industry to move ahead in this emerging field of science and medical practice. While there are some similarities with existing protein-based biological products, manufacturing and control of cell therapies is an especially difficult area because they are quite different for living cells.

It was emphasized that regulation should follow the science which is still evolving in the area of cell therapy. Dr. Koga pointed out that in the early days of ICH, all of the parties brought experience and ideas together and discussed the issues extensively, relying heavily on already accumulated science and experience as well as the needs of patients, as opposed to debating philosophy. At the present time, individual countries and regions either have been or are now taking steps to address the regulation of cell therapies, but expertise in this new field is quite limited and the guidance needs to cover a wide variety of anticipated hCTPs in terms of technical details.

Dr. Koga suggested that at this early point in the development of the field of cell therapy, serious consideration should be given to addressing international regulatory guidance, recognizing that the content of which should be commonly applicable to all types of hCTPs. In other words, the guidance should be at a “high level” (scientific principle/concepts and essential core scientific elements) rather than technical details. This could be accomplished through well recognized international organizations,

typically such as WHO. Ultimately the goal of such activities should be to accelerate clinical development of cell therapies for patient benefit.

Panel 1 Discussion

After the series of presentations (summarized above) mainly dedicated to the pharmaceutical/quality issues for hCTPs, the objectives of the panel discussion were to highlight and discuss points for which international consensus could help in the elaboration of core regulatory elements to be considered for hCTPs development, launching, and regulatory oversight.

The first issue was on the extent to which the good practice (and particularly GMP) rules should apply for hCTPs and where the frontier between development stages and routine production steps should be set. In particular, and echoing Dr. Rao's presentation (see previous session) to determine whether, for human ESCs or human iPSCs, the first steps for obtaining/collecting, selection, qualification and further amplification of relevant clones should be considered as belonging to the development process or be included as the first step(s) of the "routine manufacturing process" to be conducted under GMP conditions.

The comparison of stem cells with obtaining engineered cell lines, used as cell-substrates in the production of biotechnology-derived proteins, should be taken as a good example (see ICH guideline Q5D) where the establishment of the cell-bank system is part of the developmental approach.

As regards the elements of the manufacturing process, and considering the inherent complexity of both the process and the resulting product, process and product should be seen as an indivisible unit, with a need for an adequate validation of the manufacturing site, to ensure that, on a daily basis, all batches of hCTPs exhibit a similar quality and efficacy profile. This issue is not trivial. For example, when hCTPs with a very short shelf life must be administered within a short timeframe, multiple manufacturing sites have to be operational as close as possible to the bedside of the patient. The recent European examples with Provenge® and MACI® and authorised manufacturing sites (see Dr. Trouvin's presentation) call for a careful attention in the qualification and validation of the operational performances of multiple manufacturing centres.

The potency assay was the next issue to be raised for which the need for a flexible approach was stressed. It is well-acknowledged that this quality attribute is key in the characterization studies and quality control strategy, while keeping in mind how challenging it is to develop a relevant assay. Flexibility and a stepwise approach was again recommended, taking into account the stage of development of hCTPs. By extension, the wider issue on how to set specifications was opened, and the panel agreed that using the ICH Q6B guideline could be a valid option. However, some adaptation may need to be considered, particularly as regards specific Quality attributes, inherently variable due to the particulars of the starting materials for hCTPs (cells of autologous origin up to cells derived for a well-established cell bank). In the Q6B guideline, there may be some aspects not applicable in the same way as for recombinant proteins. Again the concept of "minimum requirements" was proposed, and

particularly not attempting to fit square pegs into round holes! Specification issues, including a potency assay, were to be discussed in the following session and presentations.

Tumorigenicity was the next issue addressed by the panel, acknowledging that the tumorigenic potential should be seen both as a quality-related and safety-related issue. For hCTPs, where the cells are the end-product administered to patients, it is of importance to dedicate efforts in the development and validation of analytical tests capable of detecting a low level of undifferentiated cells in the final product, and particularly for stem cell-derived hCTPs.

In a wider perspective, the panel addressed, as a last item, the option proposed by Dr. Hayakawa on a "minimum consensus package" to be set as reasonable requirements for hCTPs taking from the existing body of regulatory texts, what has proven to be relevant and efficient in ensuring quality and safety of biologicals and biotechnology products.

It was reiterated that hCTPs should not be directly compared to other biologicals, although they share common features, among them structural complexity and inherent variability. The question was instead how to introduce a reasonable level of flexibility, particularly at the early phase of clinical trials and proof of concept. For hCTPs and their promising clinical applications, there is a desire to address the needs of patients, by making some adaptations to allow smooth development of those products, while not lowering the quality requirements which have to be maintained for the safety of the recipients. This has to be addressed considering not only the quality issues, but also the nonclinical and clinical aspects (discussed in the next sessions) before final recommendations can be drawn.

Dr. James McBlane (MHRA, UK) addressed the preclinical safety evaluation of human cell therapy products. At a high level, objectives of preclinical testing are the same for a hCTP as for any other medicinal product: 1) provide evidence of proof of concept (i.e., will the product will have some therapeutic benefit?), 2) provide evidence for reasons to expect that subjects who are given the product, either in trials or in routine medical use, will not be harmed by the product, and 3) allow a decision on whether any human dosing is appropriate with the proposed product based on these two perspectives. Preclinical studies may be carried out to explore mechanisms of an effect and also to provide information on safety of the product that cannot be generated by studies in humans (e.g., risks to reproductive health and of cancer).

At a more detailed level of consideration of the individual product, hCTPs have features that require consideration that are not relevant for other types of product. These include whether cells are autologous or allogeneic, whether the cells have been subject to any genetic modification and whether there are risks associated with distribution of the cell product from its site of administration. Concerning persistence, a single administration of a cell therapy product could provide long-term exposure to the product which is generally not so with other products - this difference might have a major influence on timing of preclinical studies: if the expectation is of long term exposure from a single treatment, this might suggest that all preclinical data are required prior to any human

dosing, whereas this is not the case for other types of biological product, where staged preclinical testing, related to the degree of clinical exposure, is the norm. Given a finite number of human cell types that can be used as hCTPs, this suggests the possibility of cross-referencing preclinical studies done in support of other cell therapies and also that dose selection for a cell product may be based more on clinical experience with other, potentially similar, products than to preclinical testing. However, this approach depends on understanding that results from ahCTP used in one setting can be applicable to another product used in a different setting. This raises concerns about the degree to which it is necessary to show comparability of products used.

How these different considerations relevant to hCTPs should be accommodated within current regulatory structures and whether there is merit in considering a common understanding in different parts of the world regarding what types of data are expected for human cellular therapy products are topics that should be discussed further.

Dr. Akifumi Matsuyama (NIBIO, Japan) presented an overview of issues related to the mode of action (MOA) and proof of concept (POC) using a case study. Once the manufactured cells are assigned as a candidate for a cell-based medicinal product, non-clinical studies are conducted, and the study package should include in vitro and/or in vivo studies to demonstrate the MOA, POC, and the safety of the candidate. Dr. Matsuyama then described a case in which adipose tissue-derived multi-lineage progenitor cells (ADMPCs) could be developed as a cell-based medicinal product for liver cirrhosis.

To treat patients with liver cirrhosis, the pathogenesis and pathophysiology should be reflected in the MOA. Liver fibrosis is characterized by excessive accumulation of extracellular matrix with inflammatory status in situ. Therefore, in developing a cell-based medicinal product, anti-inflammatory cytokines and fibrinolytic enzyme secretion are anticipated as the MOA. After showing the appropriate MOA, the MOA and the POC should be bridged. The key issue is the selection of an appropriate animal model(s).

In developing a cell-based product, the MOA in this case is that the cells act as a vehicle for delivering anti-inflammatory cytokines and matrix metalloproteinases (MMPs). Chronic administration of carbon tetrachloride (CCl₄) induces radicals, followed by inflammation, and results in fibrosis of the parenchyma. To establish POC after bridging to MOA, the appropriate route of administration should be considered. In this case, systemic administration via the hepatic artery or portal vein would be appropriate for the clinical use of an experimental product. Mice could be used in the animal POC study with systemic administration via the tail vein since their hepatic artery is too small for use experimentally.

In this case study, the POC for cell-based products for improving liver fibrosis and function was achieved by systemic administration of ADMPCs. After POC has been established, the results can be discussed in terms of whether the animal model accurately reflects human clinical pathophysiology. The CCl₄-induced chronic liver fibrosis in mouse models in the case study does not reflect the status of non-alcoholic steatohepatitis, whose main trigger is insulin resistance. This is a limitation of the POC study.

In his conclusion, Dr. Matsuyama stated that the MOA should be based on the pathophysiology of the target disease, the POC study should be designed to bridge to the MOA, and the limitation(s) of the study should be acknowledged before use in clinical trials.

Dr. Kazuo Yano, Dr. Masayuki Yamato (Tokyo Women's Medical University, Japan) discussed clinical evaluation and associated issues. They pointed out that since hCTPs belong to a relatively new class of medical products, limited information is available on the classification and premarket evaluation of hCTPs in the USA, the EU, and Japan. They then summarized their studies which surveyed the definition, legislation, and approval system of a total of twenty one hCTPs that were approved as nine autologous hCTPs, and twelve allogeneic hCTPs, which included six somatic cell therapy products, as well as five unrelated allogeneic placental/umbilical cord blood products, and as a gene therapy medical product in Japan, the USA, and the EU between January 1996 and October 2013 (Fig.1) [6,7].

Autologous hCTPs were handled administratively as: 1) accelerated approval of a biological product, 2) humanitarian investigational device exemption (IDE) approval, 3) premarket application (PMA) approval, 4) biologics license application (BLA) approval, and 5) new drug application approval with specific targeting of post-approval registry or surveillance. Of nine autologous hCTPs, four products had been evaluated using clinical experiences or open clinical trials with a small number of subjects, although the other products had been evaluated using comparative clinical trials with control treatment. Autologous hCTPs would need postmarket-oriented evaluation rather than premarket-oriented evaluation [6].

In allogeneic hCTPs, six somatic cell therapy products were submitted for market authorization in the USA, four were as a PMA, one as an IDE, and one as a BLA. Five of them were conducted as pivotal clinical trials with investigational device or comparator such as control treatment to confirm safety and efficacy after conducting pilot or feasibility trials. These allogeneic hCTPs had an advantage in that it was possible to conduct controlled, randomized trials because the lot size for those products was large [7]. Five unrelated allogeneic placental/umbilical cord blood products submitted for market authorization in the USA were in BLAs. As for the clinical data, FDA indicated that the cord blood transplantation study, and some of the other clinical studies that were submitted, did not comply with Good Clinical Practice. These clinical data were evaluated for clinical effectiveness and safety with reference to historical controls. In addition, only one gene therapy product was approved as an ATMP in market authorization under exceptional circumstances in the EU. Regulation No1394/2007 regarding ATMPs was issued in 2007 by the European Commission. Three clinical trials which involved 27 subjects were conducted using no control treatment for ethical reasons [8].

These studies suggest that pivotal clinical trials should be conducted using various study designs according to the target disease, clinical indication, and cell source. Furthermore, premarket clinical evaluations of hCTPs should use not only clinical experience but also historical control data. In addition, the approval system or pathway should be flexible and adaptive to the specific situation.

Dr. Kentaro Yoshimatsu (JPMA, Japan) considered pre-clinical safety, biological evaluation and clinical evaluation of hCTPs based on the 7 different cell types/cell sources: tissue-derived, autoiPSCs, alloiPSCs/ESCs, auto somatic stem cells, allo somatic stem cells, auto gene-engineered cells, and encapsulated allo gene-engineered cells. Among hCTPs from those 7 cell types/cell sources, tumorigenicity for auto iPS cells and alloiPSCs and immunogenicity for alloiPSCs/ESCs and allo somatic stem cells were highlighted as important types where a pre-clinical safety risk assessment is especially needed. The level of difficulty for establishing a potency assay and batch release control for the hCTPs from auto gene-engineered and encapsulated allo gene-engineered cells seems not to be higher than that for traditional biologicals, because factors produced by those cells can be measured. For other products, the level of difficulty for auto hCTPs would be high, for allo hCTPs moderate, and especially high for auto somatic stem cell-derived hCTPs. The clinical evaluation for hCTPs should be discussed based on the target disease/indication.

In vitro pre-clinical safety evaluation may be necessary depending on the specifics of the hCTP. The timing of the completion of animal studies is an important issue for the development of hCTPs. The period of the study, species, and doses (no-observed-adverse-effect level, minimum anticipated biological effect level, dose-response) are items for regulatory consultation. In some cases, depending on the hCTP, there can be difficulties with the *in vitro* biological evaluation/potency assay, and the availability of animal models (small animal, nonhuman primate) is critical. The design of the clinical study depends on the target disease/ target indication. The supply of clinical trial materials affects the clinical development time-line and should be planned appropriately.

hCTPs are anticipated as innovative treatments for intractable diseases. The following points are emphasized toward the smooth development of hCTPs: 1) risk and benefit assessment is required depending on hCTPs and the clinical application/indication (life threatening and no alternative treatment), 2) information disclosure of discussions between sponsor and a regulatory authority (minimize duplicate effort, avoid wasting time and money for development), 3) establish a minimum consensus package, 4) flexibility of regulatory authority and sponsor (appropriate risk management during development and after launch), 5) business model change at pharmaceutical industry (from intensive marketing to medical professional), 6) economical evaluation of the product (sustainability and initial public investment), 7) public understanding (patients explicit/tacit knowledge).

Panel 2 Discussion

Most of the discussion centered around tumorigenicity testing as part of the non-clinical safety assessment of hCTPs. Such tests are used to determine the risk of tumor formation when the cells are administered to humans in a clinical trial. For example, the route/site of administration of hCTPs in a tumorigenicity test was discussed. Although the subcutaneous administration of hCTPs into immunocompromised animals may be easy and feasible, and may have sufficient capacity to accommodate the clinical dose of hCTPs, the panelists agreed that the actual clinical target tissue/organ would be a more

appropriate site to evaluate the potential for tumorigenicity in humans because the effects of the microenvironment on the hCTPs should be taken into consideration. Several factors that could make a difference in the biological response of the inoculated cells, based on the local micro-environment, were highlighted: 1) trophic effects of mesenchymal stem cells on cancer cells; 2) the potential contribution of the extracellular matrix to the proliferation of tumor cells; and 3) immunologically privileged sites. It also was pointed out that the number of pluripotent stem cells required for tumor formation may differ for various tissues/organs. It was suggested that in order to properly interpret any studies using subcutaneous inoculations, the results should be cross-referenced to the results of tests done at a site comparable to that used in the clinical setting. The overall data package should then be considered in a risk management plan. It was agreed that the number of cells administered in the non-clinical safety assessment is an important consideration in determining the acceptability of the proposed dose of ahCTP in clinical studies.

3. Identification of specific points/issues for specific types of products, as well as very critical points/issues for various types of products

Dr. Glyn Stacey (NIBSC, UK) presented an overview of somatic cells and somatic stem cells (Autologous, Allogeneic). He pointed out that an extremely broad range of somatic tissues have been utilized for cell-based treatments, including brain, heart, placenta, different epithelia and haematopoietic cells. Stem cell populations isolated from many of these sources, also have been proposed for clinical application as reported by Li et al. [9]. Adding to the complexity of these treatments are the various processing methods that may be adopted for bioprocessing including cell culture expansion, differentiation, purification and incorporation onto scaffolds.

Characterization of cell-based products to assure they will have the appropriate functionality in patients proscribes the development of functional assays to assess product potency. However, the establishment of such assays is extremely challenging, especially where the mode of action is not well-understood. Clearly, there is an urgent unmet-need here in the field of regenerative medicine, and this has led to the use of surrogate markers of biological function, which may be associated with but not necessarily implicated in product function. There is a risk of confusion between tests for identity for the product active ingredient (i.e., therapeutic cell type).

It is important that manufacturers of a cell-based medicine have sufficiently robust and informative scientific data associated with it to give confidence in its safety, reproducibility and potency. In addition, suitable informative characterization (rather than simple release criteria) on the product will enable ongoing iterative product improvement in terms of phenotypic tolerances, new biomarkers, interpretation and genetic changes). In addition to characterization of the therapeutic cell type, it also is important to understand the nature and potential impact of non-therapeutic cells occurring in the final product, sometimes referred to as "contaminants" as clearly, they may influence efficacy and safety.

A particularly popular group of treatments are based on the use of so-called "mesenchymal stem cells" (MSCs). Typically they are "fibroblast-like" cells which have been isolated from more than 20 different types of tissues, with different characteristics and multiple proposed therapeutic modes of action. This diverse group actually comprises a number of distinct cell types in vivo including pericytes, skeletal stem cells, mesangioblasts and "mesenchymal" stromal cells. In addition to this, processing and in particular cell culture expansion, can lead to significant changes in subpopulations of cells within MSC preparations which may impact their biological activity. In order to understand the value of these cell types for therapy it will be important to be able to clearly and accurately specify the tissue origin, isolated cell type, and processing methods (tissue preparation, culture, purification etc.) for each product. In addition, careful characterization will be necessary to assure appropriate assessment and control of the impact of the manufacturing process.

In the coming years it will be important to address a number of areas for scientific development. Unfortunately, numerous aspects of cell culture evaluation are based on parameters which demand high levels of user skill, but which also are challenging to quantify such as passage levels, confluency, and microscopic morphology. New approaches to quantify and interpret the wealth of information captured and processed by the eye and brain of experienced operators will be a significant step forward to facilitate a better understanding of cell therapies and enable their automation. Somatic cell therapy also commonly suffers from the constraints of short shelf lives which would benefit from the development of rapid microbiological testing methods. In the longer run, there is a crucial need for the development of preservation technologies that will increase the flexibility for time and place of use. The impact of preservation and recovery will need careful scientific evaluation to assure consistency of the final product. In addition, many somatic cell sources lack scalability for multiple patient, non-autologous uses, and a move towards the use of expandable tissue progenitors or pluripotent cell lines may be needed. Some somatic cell therapies also are dependent on the use of feeder cell culture systems which introduce additional sources of variability and microbiological risk. Qualified and safety tested feeder cell banks are needed for such applications (for example, the NIBSC 3T3 cell bank used for skin engraftment and limbal stem cell transplant) and ultimately these will need to be replaced with acellular matrices.

In conclusion, Dr. Stacey reminded the attendees that the use of somatic cells and somatic stem cells are developing a very diverse and complex group of advanced therapies for the future. This represents a significant challenge for implementation of good regulatory approaches. Manufacturers should develop a robust scientific understanding of the starting materials and the impact of bioprocessing including cell culture, purification, scaffold seeding and preservation. This will be vital to assure appropriate batch control for potency and safety and standardization through the development of control materials which, due to the diversity in these treatments, may need to be established on a case by case basis.

Dr. Takashi Aoi (Kobe University, Japan) discussed some of the issues associated with iPSCs that are generated from somatic cells by introducing small sets of reprogramming

factors. From a regulatory point of view, "donor individuals" and "quality control of the cells" should be specific points to consider.

In contrast to ESCs that are generated from early embryos, iPSCs are generated from living donor individuals. Therefore the donors' right to privacy must be protected, and decision-making about uses of the cells should include consideration of the donor. Infection and genetic factors are important in judging the eligibility of donors to ensure the safety of iPSC-based products. However, attention also should be given to the burden on the donor of multiple enquiries, repeated several times in some cases, about his/her health status. In addition, the scientific rationale for each eligibility criterion should be justified.

Regarding quality control of iPSCs and their derivatives, it is important to avoid confusing "Quality" and "Attributes". In contrast to chemical products and conventional biologicals, a virtually unlimited number of cell attributes could be assessed. Among them, sets of critical attributes should be specified for quality control of a specific cell-based product. Some attributes might be universal, but the majority are likely to be specific for a specific product. Based on this understanding, it is essential to carefully consider which attributes are selected for an iPS cell bank that is established without any, as yet, specified clinical application.

Another issue on the quality control of iPSCs is whether it is possible to standardize test methods for cell attributes. For some attributes, standardization might well be possible. For example, cell size could be measured and specified in a standardized manner because an international standard exists. Whereas other attributes, such as differentiation, potency, viability, etc., lack reference standards to measure the attributes reproducibly. However, even when mean cell size in vials are the same in a lot of a product, the individual cells in a vial certainly vary in their size.

Based on the recognition of differences between iPSC-based products and other biological products, appropriate quality control practices are required to ensure the safety and efficacy of any hCTPs that might be developed.

Dr. Akihiro Umezawa (NICHD, Japan) discussed human ES cell-processed products to treat patients with hyperammonemia, a metabolic disturbance characterized by an excess of ammonia in the blood, due to an ornithine transcarbamylase deficiency (OTCD) that leads to mental retardation. Living donor liver transplantation has been indicated for this neonatal disease, and outcomes are favorable. However, neurological impairment associated with OTCD often occurs before liver transplantation that is usually performed at an age of 5 months. For bridging to liver transplantation, hESC-based therapy is being considered. To this end, hepatocytes derived from ES cells as an investigational new drug were prepared. Sequencing analysis revealed that the ES cells used as a starting material have intact urea cycle-associated enzymes. The cell

products expressed enzymes and exhibited metabolic activity related to ammonia *in vitro*. To perform POC studies *in vivo*, OTCD mice were generated.

Manufacturing process of pharmaceuticals from *in vitro* fertilized embryos to ES cells requires documentation of necessary information [10]. These requirements are important to guarantee quality consistency as well as to ensure quality and safety of the final products. Consistency of the manufacturing process for the final products can be scientifically validated and guaranteed by thorough analysis and control of the ESC-derived product and critical intermediates. As for the ESC-based product, the presence of undifferentiated cells in the final product is a major concern (i.e., ectopic tissue formation and tumorigenesis). Accordingly, it is important to have a strategy and tactics to develop the final product by managing the manufacturing and validation processes, rather than discussing safety issues at the ES cell level. Efforts need to be employed to minimize potential risks by developing efficient methods to eliminate or inactivate undifferentiated cells. It also is noteworthy that further refinement of the evaluation of the purity of the cell population is needed using techniques such as morphological features, phenotype-specific markers, karyotype, cell growth properties, and pluripotency of the starting material (ESC), critical intermediates, and the final product.

Dr. Hiroyuki Yokote (The Chemo-Sero-Therapeutic Research Institute, Japan) discussed the general area of adventitious agents, including virus, sterility, and prion evaluation on cell sources, final products, culture media and ancillary products as well as the use of human/animal derived raw materials other than target cells. He pointed out that there were many discussions on adventitious agents for traditional biological/biotechnology products in the past. One of the outcomes of those discussions was ICH-Q5A (Viral safety). Many traditional biological/biotechnology products have been developed using that guideline. The core scientific principles/concepts and the technical considerations of ICH-Q5A also could be applied for hCTPs. However, such principles/concepts or considerations may need some revision or explanatory descriptions in order to address the special features and requirements of hCTPs.

With respect to quality control of raw materials, the elimination of adventitious agents in the manufacturing process and testing on the final product, the basic approach is the same for traditional biological/biotechnology products and hCTP products.

On the other hand, in view of hCTP characteristics, it is not possible to use techniques such as aseptic filtration or standard virus elimination treatments. Therefore, the method to control against adventitious agents differs between the two product categories.

Also, for hCTPs, it is important to consider that there are two types of risk that must be balanced: the “unknown risk of any adventitious agents that may remain” against the “risk that a patient may suffer by losing an opportunity to receive a new treatment.”

Donor selection criteria and eligibility characteristics are different for autologous hCTPs and allogeneic hCTPs. In the case of autologous cells, where the cell therapy is derived from the patient, the emphasis is on reducing the risk of transmitting infectious diseases to personnel involved in manufacturing the product and the healthcare workers who treat patients. Whereas, in the case of allogeneic cells, selection and eligibility criteria

for a donor, and cell/tissue derived from the donor, who is not the patient, place an emphasis on reducing the risk of transmitting infectious diseases to the patient in addition to the personnel involved in manufacturing the product and the healthcare workers who treat patients.

Dr. Takao Hayakawa (Kindai University, Japan) and **Dr. Norihisa Sakamoto** (PMDA, Japan) reviewed various aspects regarding specifications of hCTPs. General considerations on specifications applicable to hCTPs were described. To ensure product quality and consistency of hCTPs, a relevant combination of product and process elements is important. Specification is a typical product element which is set and justified from the standpoint of comprehensive quality control, taking into consideration the mutually complementary relationships among 1) verification of the suitability of the manufacturing process, 2) the method of maintaining consistency, and 3) quality control of the raw materials and intermediate products. Since specifications are chosen to confirm the quality rather than to fully characterize the product, the rationale and justification for including and/or excluding testing for specific quality attributes should be provided. It is desirable that specifications of the final products include CQAs that may impact the safety and efficacy of the product.

Specific points to consider for specifications of hCTPs were then described. Setting specifications for hCTPs as well as their role in medical treatment would be different from those of traditional biological/biotechnological protein products described in ICH-Q6B. It has been emphasized that the active ingredient of hCTPs is the cells that are an assembly of various cell subpopulations that are inherently variable and heterogeneous living systems, and have extremely complex biological and structural features in comparison with protein products whose CQAs can be shown at the chemical and molecular levels. Nevertheless, it was noted as specific features of hCTPs that cells could be characterized and controlled at critical stages from starting cells through final products. Specifications of the final product of hCTPs therefore could be set taking into consideration such a series of cell characterizations as a whole. Also, it is anticipated that a wide variety of hCTPs will be developed, and that have individually specific natures and functions, as well as formulations such as a cell sheet. Furthermore, they are the subject of transplantation when they are applied in patients in a surgeon-dependent manner. In some cases such as skin, cornea, and retinal pigment epithelium in the form of cell sheet, the medical specialists might be the best assessors of certain aspects of the quality of hCTPs in a special field (e.g., morphology, elasticity, resilience) rather than biochemical analysts. Such specific medical translation could be taken into consideration when setting specifications of the final product of such hCTPs.

Specifications will differ among final products, depending upon the type and properties of the desired cells, manufacturing methods, intended clinical use, the mode of administration of each product, stability, and available test methods. These parameters should be taken into consideration when setting the acceptance criteria and test procedures for a specific product. Among possible quality control parameters and tests that might be considered for setting specifications for an individual final product, it was pointed out that some of the test items (e.g., cell viability, identity, purity, sterility, mycoplasma, and endotoxin) should be applied in all cases.

In summary, they emphasized that: 1) the developer/manufacture must know the product in question in order to select CQAs and get the best combination of test items; 2) maintain a robust process; 3) maintain a balance with medical needs; 4) regard hCTPs as elements of medical translation; 5) rely on the institution and doctor for their expertise; 6) refine specifications during product development and at the post-approval stage; 7) accumulate expertise; 8) develop relevant analytical methodology; and 9) make decisions using scientific common sense.

Dr. Anthony Ridgway (Health Canada) began his discussion with issues and challenges associated with hCTPs that include reliance on aseptic processing and the inability to filter-sterilize product, which places greater emphasis on the importance of qualification programs for all manufacturing components. Maintaining cellular viability can be a challenge, compounded by the stresses of freezing and thawing; and if not cryogenically frozen, there are challenges associated with short shelf lives affecting product distribution and the conduct of testing for microbiological safety. The manufacturing of hCTPs typically involves separation and maturation steps and these steps may feature an approach to measuring potency; and it may be a goal to have the potency assay help indicate the relative lack of non-intended cell types that are considered impurities and may cause unwanted effects. The intended cell type may also undergo further maturation *in vivo* acquiring multiple mechanisms of action and migrating to distal sites, and so the desired *in vivo* effects may depend on uncontrolled events well removed from the timing of conduct of the potency assay.

Although hCTPs fall outside the scope of ICH Q6B, the principles expressed in this guideline regarding the establishment of potency assays are relevant, and adaptation and adherence can help satisfy regulatory expectations. Potency (expressed in units) is a quantitative measure of biological activity based on a relevant product attribute. The activity doesn't always need to mimic the clinical situation but a correlation should be established in pharmacodynamics or clinical studies such that results can be demonstrated to contribute to the prediction of clinical efficacy. Potency measurements are especially important for the quality control of complex products, where even combinations of physicochemical measurements may not provide the correlation necessary. Potency measurements also help assure identity, purity and stability, and are crucial to assessment of comparability. More than one bioassay may be necessary. Nevertheless, technical limitations may prevent development of a suitable bioassay. In such cases, assays based on immunochemical, molecular or biochemical characteristics of the product can also be used to demonstrate potency, provided they directly reflect or, more likely, can be correlated with a biological activity. Biomarkers can be useful, but should not change under conditions that affect cell function. Those that correlate with cell survival and *in vitro* differentiation are useful and can often be detected through genomic and/or proteomic techniques. Also, a typical dose response curve approach may not work for hCTPs – a bioassay more indicative of potency may be a collection of biomarkers turned on and off in a specific pattern. Such a qualitative approach could perhaps be linked with a quantitative analytical method. Although a true potency assay may not be a regulatory requirement early in product development and can evolve with the product during development, it is very important, and useful, to

demonstrate early on the capability of the assay for use in rejecting sub-potent material. Validation may come late in development with wide variability allowed.

In the final segment of the presentation, Dr. Ridgway provided background to the development and selection of the potency assays for two hCTPs that have obtained marketing approval in some major jurisdictions; and discussed potency for dendritic cells, a class of hCTPs for which numerous products are under development.

Provenge® comprises autologous CD54+ antigen-presenting cells primed with tumour antigen, and is clinically indicated for advanced prostate cancer that is unresponsive to hormonal therapy. The product potency is based on a measure of both the number of CD54+ cells and the level of up-regulation of CD54 on the cell surface. Prochymal® comprises allogeneic, phenotypically selected, adult, mesenchymal, stem cells and is clinically indicated for the treatment of acute graft versus host disease. Prochymal® potency is based on two Enzyme Linked ImmunoSorbant Assays: one that measures TNF R1 receptor expression, and another that measures the inhibition of IL-2R-alpha expression. For dendritic cells, there are several assays useful for their functional evaluation and that could be candidate potency assays; but there are several good reasons why the production level of IL-12 is favored for this purpose.

In conclusion, Dr. Ridgway suggested that using a matrix of assays together capturing viable cell number along with relevant characteristics and/or activities of the hCTP had potential value for some cell types.

Dr. Christopher Bravery (Consulting on Advanced Biologicals Ltd, UK) discussed the problem of ensuring the measurements we make today can be reproduced in a year or decade or longer time. Measurement reliability is normally assured by selection, optimization and validation of analytical methods and the use of appropriate reference materials to ensure the methods used are reliable over time (method drift). Reliable methods are a prerequisite to monitoring process consistency, and together with product reference materials help identify process drift over the product lifecycle (likely decades).

Determining the quality of hCTPs requires novel and complex analytical methods (e.g., for potency [11]) and while it is normally clear which substance (analyte) is being measured (e.g., quantification of cytokine or increase in cell number (proliferation)), the quantity to be measured (measurand [12]) is often uncertain and may in effect be defined by the assay [13]. All measurements need to relate to a reference, and that reference needs to either be reproducible (constant of nature, reference method) or physical (reference material). Reference materials need both to be stable (years or longer) and sufficiently similar to the sample to be measured [14] to ensure the analytical method measures the same analyte and measurand.

Using an apparently simple example of measuring the protein content of human plasma, depending on the analytical method employed, different results can be obtained, most of which can be explained by the chemistry of the methods. Importantly, some methods, such as Lowry, will give a different result if bovine serum albumin is used as the calibrator (protein reference material) compared to using human serum albumin as the calibrator. This example helps to emphasize two key points, firstly the reference

material needs to be sufficiently similar to the substance being measured, something that poses obvious issues when measuring biological activity of living cells. Secondly, it demonstrates the importance of using orthogonal methods employing different measurement principles as part of characterization.

Dr. Bravery concluded that preparing reference materials that are suitable for assays that measure the complex biological activities of living cells pose particular problems, yet the need is greater because exactly what is being measured cannot always be easily understood. Living cells do not make ideal reference materials because by their very nature they are dynamic and constantly changing. It may be that more novel approaches are required.

Dr. Yoji Sato (NIHS, Tokyo) reviewed tumorigenicity tests for the quality and safety of cell-based therapeutic products. Tumorigenicity is one of the major concerns for hCTPs, particularly for ES/iPS cell-derived products. However, there are no international guidelines for tumorigenicity testing that is specific for hCTPs. The WHO Technical Report Series 878 (WHO TRS 878) is the only international guideline currently available for tumorigenicity testing, but it excludes viable cells when they are used directly for therapy by transplantation into patients or when they are developed into cell lines for the purpose of using them as therapeutic agents by transplantation.

There can be three purposes of tumorigenicity testing for hCTPs: 1) quality control of raw materials, 2) quality control of intermediate/final products, and 3) nonclinical safety assessment of final products. For the quality control of raw materials (e.g. ESCs/iPSCs and allogeneic somatic cell banks), tumorigenicity can be one of several critical quality attributes of homogeneous cell substrates, to which the same approaches as in WHO TRS 878 may be applicable. However, for other purposes, standardization of tumorigenicity testing remains to be achieved. By understanding the abilities and limitations of each test, appropriate tests should be selected to meet the criteria needed to evaluate each hCTP.

In the case of tumorigenicity testing for quality control of intermediate/final products, the amount of tumorigenic cellular impurities is a relevant attribute. Cell growth analysis [15], soft-agar colony formation assay [16], or highly-sensitive *in vivo* assays using severe immunodeficient animals [16] may be used to detect potential transformed/tumorigenic cellular impurities. No matter which method is employed, the lower limit of detection needs to be determined in advance. In the case of ESC/iPSC-derived products, the amount of residual pluripotent cells also needs to be determined by methods such as real time quantitative reverse transcription polymerase chain reaction [17], flow cytometry [17] and direct cell expansion under *in vitro* conditions favorable to ESCs/iPSCs [18]. For the nonclinical safety assessment of final products, a highly-sensitive *in vivo* assay may need to be performed, considering the characteristics of the animal model, test protocol, biodistribution of the cells, as well as the product characteristics and the target patient population. In the test protocol, the site/route of administration is an important issue, because tumorigenic potential at the microenvironment comparable to that in the clinical setting needs to be examined. The selection of positive control cells is another important issue in the evaluation of the tumorigenic potential of hCTPs.

Dr. Ivana Knezevic (WHO, Switzerland) was unable to attend the conference, but was represented by Dr. John Petricciani who delivered her talk on WHO norms and standards with some consideration for the field of hCTPs. Dr. Knezevic informed the conference that WHO norms and standards for biologicals form the backbone of their activities to meet the needs of 194 WHO member states in improving public health activities and that written standards for vaccines is an example in a well regulated area. As part of its mandate to assure the quality of biological products used for treatment of a broad range of diseases, WHO is taking a number of initiatives to assist national regulatory authorities and manufacturers of biological products to achieve this goal.

One of these initiatives is focused on the development of WHO international standards for quality, safety and efficacy parameters for regulatory evaluation of biological medicinal products. These standards are defined for biologicals in general, but also for individual vaccines or classes of biologicals by the Expert Committee on Biological Standardization (ECBS). They are published in the WHO TRS in the form of recommendations and guidelines for production, quality control and evaluation of vaccines and other biologicals, and serve as international regulatory standards for WHO member states that are using these documents as a basis for establishing national regulatory requirements. WHO standards are available to the users, free of charge, and can be found at WHO biologicals web site [19].

Such standards are meant to define safe and efficacious vaccines, and are intended to be scientific and advisory in nature. In addition, they serve as a benchmark for global acceptability of these products and are a starting point for setting national requirements as well as a basis for prequalification of vaccines for United Nations (UN) supply (i.e., assessment before purchase decision by UN agencies). Moreover, it is important to understand that written standards are living documents that can be revised in response to scientific advances. There was then further discussion on implementation workshops and regulatory convergence of national regulatory requirements.

In addition, WHO International Standards and Reference Preparations define the International Unit of biological activity and provide a basis for calibration of assays. Detailed information about WHO International Standards and Reference Preparations is available [20]. They are used as primary standards for the establishment of secondary (working) standards and are essential for quality assurance of biologicals. WHO Collaborating Centers for biological standardization play a pivotal role in the development of international reference preparations. In particular, the UK NIBSC is the lead center for the development and distribution of international reference preparations.

Dr. Knezevic then went on to describe WHO cell banks and the WHO Study Group on cell substrates. WHO written standards of particular relevance to cell therapies are WHO recommendations for the evaluation of animal cell cultures as substrates for the

manufacture of biologicals [21] and the Revised Recommendations on cell substrates that were adopted by the ECBS in 2010 [22]. Notably, it was stated that stem cells for therapy are beyond the scope of that document. At that time, it was recognized that two types of pluripotent stem cell lines (SCLs), namely human ESC and iPSC lines, had been isolated and were considered as potential substrates for manufacturing biologicals in the future. Some scientific considerations for the regulatory evaluation of SCLs, including advantages and disadvantages, were addressed in that document.

With regard to WHO & cell therapy, WHO's current position is that it is monitoring scientific advances in the development of cell therapies and will attempt to address needs of WHO member states as resources permit. On the other hand, the ECBS recognized the importance, and a need, for standardization of cell therapies on several occasions (2007, 2010, 2011). However, WHO's limited resources has not allowed their inclusion in the work plan up to now.

Dr. Knezevic noted that the INN (International Nonproprietary Name) Expert Group is developing an INN nomenclature scheme for cell therapy products. An INN Working Group on cell therapy was established (November 2014) and efforts are being made to harmonize INN and the United States Adopted Names schemes. Details of the discussion are summarized on the INN web site [23]. The Working Group will report to the INN Expert Group during the 60th INN Consultation (13-15 April 2015).

The Network of WHO Collaborating Centers for Standardization and Evaluation of Vaccines is an important component of WHO's activities in the biologicals field, and the network may play a role in addressing needs for cell therapy in the future. Detailed information on the network is provided on WHO web site [24] and is also published [25]. The terms of reference of the network were described and the members were listed [26].

Dr. Knezevic then informed the conference that the 16th International Conference of Drug Regulatory Authorities (ICDRA), was held in Rio de Janeiro, 24-29 August 2014, and that a workshop was devoted to the current status and future vision of regulating advanced therapies. ICDRA encouraged member states to develop regulatory expertise for cell therapy medicinal products appropriate for the specific nature of these products. In addition, ICDRA recommended that WHO should consider providing guidance on manufacture, non-clinical and clinical development of cell therapy medicinal products, taking into account existing guidelines, points to consider and recommendations, with the collaboration of leading regulatory authorities. In parallel with those recommendations, the 2014 World Health Assembly adopted a resolution on regulatory system strengthening that requests WHO to "...increase support and guidance for strengthening the capacity to regulate increasingly complex biological products and, where appropriate, ... somatic-cell therapy...".

In conclusion, development of measurement standards, standardization of the assays and regulatory convergence in the evaluation of cell therapies are the areas where WHO needs to guide its member states. Dr. Knezevic suggested that a way forward could include the following activities:

- IABS should continue to provide opportunities such as this conference to explore issues in cell therapy, and to develop and publish meeting reports and recommendations for consideration by WHO at a later date when resources are available
- WHO might organize consultations with regulators, manufacturers, and academia to review current approaches for evaluation of most advanced cell therapy products and attempt to reach international consensus on quality, safety and efficacy for cell therapies should be carefully planned
- Reach agreement on: a) type of guidance document and scope that would be useful to the field; b) outline the document; and c) determine how best to integrate the relevant parts of the 2010 WHO cell substrate guidance document
- Identify what measurement standards are needed, and initiate development of standards that are priorities as a joint effort of WHO collaborating centers
- Provide a progress report to the ECBS in 2015

Panel 3 Discussion

Throughout sessions 5 and 6, a recurrent theme was whether cell therapy could be accommodated within the current regulatory framework. While it was recognized that many, if not most, of the current requirements for biologicals might be applied to cell therapy, there are special considerations that need to be kept in mind, and there are particular regulatory elements that are difficult to address. For example, establishing a potency test based on cellular functionality, and constructing/interpreting a relevant tumorigenicity test were highlighted.

The issue of definitions, such as those for starting materials, and the applicability of Good Manufacturing Practices to cell therapy were mentioned as problem areas where clarity is needed. In that regard, a “road map” could be helpful to show the progression of a cell therapy from the initial derivation of the cell line through to subclone(s), qualification for use as starting materials for cell banks, and eventual use in clinical studies. Recognizing that there are numerous routes to new cell therapy products, a flow diagram incorporating the different kinds of bioprocesses and analytical techniques could provide a clear view on how to set criteria for managing cell therapies and how best to utilize biotechnology experience and procedures. It also was suggested that the standards used for gene therapy packaging cell lines could be useful to consider.

Additional discussion of the definition and interpretation of terms took place. Purity, potency, identity, “contaminants”, active ingredient intermediates, and others were identified as particularly important. It was suggested that the field should work towards a standard lexicon for cell therapy as a useful step towards standardization.

Active discussion took place on study design for tumorigenicity tests, including issues related to the appropriate control materials and when they should be used. When a positive control is required, it should be well-characterized and generally available as a reference preparation. In that regard, the well-recognized problem of generating variable results using different sources of the same control cell line was emphasized. The role of new *in vitro* assays, and variety of responses from regulators on what is an acceptable study for tumorigenicity were identified as problems that need to be addressed. The site of inoculation, cell test sample preparation/formulation, most appropriate animal model(s), and the validity of *in vitro* models were cited as examples where further discussion and consensus would be very helpful to the field. Animal models and whole body imaging also were suggested as topics for future discussion.

4. Conclusions

Dr. John Petricciani (IABS, Switzerland) concluded with a summary of the major points that had emerged from the conference. Most of the current regulatory framework is appropriate for cell therapy, but there are some areas where the application of the requirements for traditional biologicals is inappropriate, and those need to be identified, discussed, and rationalized. The current system is flexible and can accommodate cell therapies even though the field is complex due to the variety of cell types and resulting products, patient populations, clinical indications, and manufacturing systems.

A major difficulty in the field of hCTPs is trying to balance: 1) potential patient benefit and risk; 2) societal and political expectations; and 3) regulatory risk of being too conservative or too permissive.

There is a need for international consensus on: 1) core regulatory elements; 2) "add-on" elements; 3) case-by-case evaluation & decision; and 4) reference reagents for specific tests.

Discussions on how to achieve consensus led to a general agreement that WHO could play a major role if resources were made available. And potentially several professional organizations, including IABS, could contribute. However, the key to making progress is the identification of a "lead" organization, preferably WHO, that is willing and able to assume responsibility for taking the next step(s) by building upon the results of this conference.

Based on conference discussions, two followup activities could contribute to regulatory progress in the cell therapy field: 1) a matrix could be developed contrasting current requirements of the EU, FDA, Japan, China, and Korea to identify points of agreement and divergence as a basis for further discussion; 2) based on experience with bone marrow transplantation, identify points that could facilitate or inhibit cell therapy product development.

This conference represents progress by identifying issues and a regulatory approach

that can be considered by a broader audience in due course. Further consideration of a way forward towards an international consensus is essential, and action should be taken by one of the major agencies to achieve this.

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References

1. <https://www.gov.uk/government/publications/donation-of-starting-material-for-advanced-cell-based-therapies>
2. <http://www.stem-cell-forum.net/>
3. Andrews PW, et al., on behalf of the International Stem Cell banking Initiative, Points to consider in the development of seed stocks of pluripotent stem cells for clinical applications. *Regenerative Medicine* 2015; 10:(02s) (doi: 10.2217/RME.14.93)
4. Coecke S, Balls M, Bowe G, Davis J, Gstraunthaler G, Hartung T, Hay R, Merten O-W, Price A, Shechtman L, Stacey GN and Stokes W, Guidance on Good Cell Culture Practice. A report of the second ECVAM Task Force on Good Cell Culture Practice, *ATLA* 2005;33: 1-27.
5. www.hesreg.eu/
6. Yano K, Tsuyuki K, Watanabe N, Kasanuki H, Yamato M: The regulation of allogeneic human cells and tissue products as biomaterials. *Biomaterials* 2013; 34(13):3165-3173.
7. Yano K, Watanabe N, Tsuyuki K, Ikawa T, Kasanuki H, Yamato M: Regulatory Approval for Autologous Human Cells and Tissue Products in the United States, the European Union, and Japan. *Regenerative Therapy* 2014; 1:45-56. doi:10.1016/j.reth.2014.10.001

8. Watanabe N, Yano K, Tsuyuki K, Okano T, Yamato M: Re-examination of regulatory opinions in Europe: possible contribution for the approval of the first gene therapy product Glybera. *Molecular Therapy - Methods & Clinical Development* 2015, 2 Article number:14066, doi:10.1038/mtm.2014.66
9. Li MD, Harold Atkins H, Bubela T. The global landscape of stem cell clinical trials. *Regenerative Medicine* 2014; 9(1):27-39 (doi:10.2217/rme.13.80).
10. Hayakawa T, Aoi T, Umezawa A, Ozawa K, Sato Y, Sawa Y, Matsuyama A, Yamanaka S, Yamato M. A Study on Ensuring the Safety and Quality of Pharmaceuticals and Medical Devices Derived from the Processing of Human Embryonic Stem Cells. *Regenerative Therapy* 2015; in press.
11. Bravery CA, J Carmen, T Fong, W Oprea, KH Hoogendoorn, J Woda, SR Burger, JA Rowley, ML Bonyhadi and W Van't Hof. Potency assay development for cellular therapy products: an ISCT review of the requirements and experiences in the industry. *Cytotherapy* 2013; 15:9-19.
12. Barwick VJ and E Prichard, eds. Eurachem - Terminology in Analytical Measurement - Introduction to VIM 3. (2011). www.eurachem.org.
13. Bravery CA and A French. Reference materials for cellular therapeutics. *Cytotherapy* 2014; 16:1187-96.
14. Bristow AF. Assignment of quantities to biological medicines: an old problem re-discovered. *Philos Trans A Math PhysEngSci* 2011;369:4004-13.
15. Kono K, Takada N, Yasuda S, Sawada R, Niimi S, Matsuyama A, Sato Y. Characterization of the cell growth analysis for detection of immortal cellular impurities in human mesenchymal stem cells. *Biologicals* 2015;43:146-9.
16. Kusakawa S, Machida K, Yasuda S, Takada N, Kuroda T, Sawada R, Okura H, Tsutsumi H, Kawamata S, Sato Y. Characterization of *in vivo* tumorigenicity tests using severe immunodeficient NOD/Shi-scid IL2R^{gnull} mice for detection of tumorigenic cellular impurities in human cell-processed therapeutic products. *Regenerative Therapy* 2015;1:30-7.
17. Kuroda T, Yasuda S, Kusakawa S, Hirata N, Kanda Y, Suzuki K, Takahashi M, Nishikawa S, Kawamata S, Sato Y. Highly sensitive *in vitro* methods for detection of residual undifferentiated cells in retinal pigment epithelial cells derived from human iPS cells. *PLoS One* 2012;7(5):e37342.
18. Tano K, Yasuda S, Kuroda T, Saito H, Umezawa A, Sato Y. A novel *in vitro* method for detecting undifferentiated human pluripotent stem cells as impurities in cell therapy products using a highly efficient culture system. *PLoS One* 2014 Oct 27;9(10):e110496.
19. <http://www.who.int/biologicals/publications/trs/areas/vaccines/en/index.html>
20. http://www.who.int/biologicals/reference_preparations/en
21. Recommendations for the evaluation of animal cell cultures as substrates for the manufacture of biological medicinal products and for the characterization of cell

banks. Replacement of TRS 878, Annex 1. Annex 3 in WHO Expert Committee on Biological Standardization. Sixty-first report. Geneva, World Health Organization, 2013; (WHO Technical Report Series, No. 978.

22. http://www.who.int/biologicals/vaccines/TRS_978_Annex_3.pdf
23. http://www.who.int/medicines/services/inn/inn_bio_ct/en/index.html
24. http://www.who.int/biologicals/collaborating_centers/en/
25. Knezevic I, Griffiths E, Petricciani J, Bramley D. The WHO network of collaborating centres on standardization and regulatory evaluation of vaccines. *Biologicals* 2012; 40 (6):499-506.
26. WHO collaborating centers for standardization and evaluation of vaccines: National Institute for Biological Standards and Control, (NIBSC) UK; Department of Bacterial Pathogenesis and Infection Control, National Institute of Infectious Diseases (NIID), Japan; Immunobiology and Biochemistry Group, Office of Laboratories & Scientific Services, Therapeutic Goods Administration (TGA), Australia; Center for Biologics Evaluation and Research (CBER) FDA, USA; National Institute of Food and Drug Safety Evaluation (NIFDS), Ministry of Food and Drug Safety, Republic of Korea; Biologics and Genetic Therapies Directorate, Health Canada, Canada; Institute for Biological Product Control (IBPC) of the National Institutes for Food and Drug Control (NIFDC), China; Division of Virology, Paul-Ehrlich-Institute (PEI), Germany.

Figure 1. Approved human cell and tissue products in Japan, USA, and EU as of 31 August 2013

Figure 1