



Review

Recent policies that support clinical application of induced pluripotent stem cell-based regenerative therapies[☆]Kentaro Azuma^{a,*}, Shinya Yamanaka^{a,b}^a Center for iPS Cell Research and Application, Kyoto University, Kyoto 606-8507, Japan^b Gladstone Institute of Cardiovascular Disease, San Francisco, California 94158, USA

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ABSTRACT

In Japan, a research center network consisting of Kyoto University to provide clinical-grade induced Pluripotent Stem Cells (iPSC) and several major research centers to develop iPSC-based regenerative therapies was formed for the clinical application of iPSCs. This network is under the supervision of a newly formed funding agency, the Japan Agency for Medical Research and Development. In parallel, regulatory authorities of Japan, including the Ministry of Health, Labour and Welfare, and Pharmaceuticals and Medical Devices Agency, are trying to accelerate the development process of regenerative medicine products (RMPs) by several initiatives: 1) introduction of a conditional and time-limited approval scheme only applicable to RMPs under the revised Pharmaceuticals and Medical Devices Act, 2) expansion of a consultation program at the early stage of development, 3) establishment of guidelines to support efficient development and review and 4) enhancement of post-market safety measures such as introduction of patient registries and setting user requirements with cooperation from relevant academic societies and experts. Ultimately, the establishment of a global network among iPSC banks that derives clinical-grade iPSCs from human leukocyte antigens homozygous donors has been proposed. In order to share clinical-grade iPSCs globally and to facilitate global development of iPSC-based RMPs, it will be necessary to promote regulatory harmonization and to establish common standards related to iPSCs and differentiated cells based on scientific evidence.

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1. Introduction

Induced pluripotent stem cells (iPSCs) were firstly made from mice in 2006 [1] and from humans in 2007 [2,3]. iPSCs share many characteristics with embryonic stem cells (ESCs), including the

ability to self-renew and differentiate into all cell types of the adult body. However, because iPSCs are made not from a fertilized egg but from somatic cells, their creation avoids the destruction of fertilized eggs and allows them to be acquired from donors whose genetic characteristics and other health records are already well

Abbreviations: iPSC, induced pluripotent stem cell; ESC, embryonic stem cell; HLA, human leukocyte antigen; RMP, regenerative medicine product; R&D, research and development; AMED, Japan Agency for Medical Research and Development; MEXT, Ministry of Education, Culture, Sports, Science and Technology; MHLW, Ministry of Health, Labour and Welfare; METI, Ministry of Economy, Trade and Industry; JST, Japan Science and Technology Agency; NIBIO, National Institute of Biomedical Innovation; NEDO, New Energy and Industrial Technology Development Organization; FY, fiscal year; CIRA, Center for iPS Cell Research and Application; IRB, Institutional Review Board; RM Act, the Act on the Safety of Regenerative Medicine; Riken CDB, Riken Center for Developmental Biology; IBRI, Institution of Biomedical Research and Innovation; PMDA, Pharmaceuticals and Medical Devices Agency; NIHS, National Institute of Health Science; PAL, Pharmaceutical Affairs Law; PMD Act, Pharmaceuticals and Medical Devices Act; GMP, good manufacturing practice; GCTP, Good Gene, Cell, Cellular and Tissue-based Products Manufacturing Practice; DMF, Drug Master File; LVAD, left ventricular assist device; J-MACS, Japanese Registry for Mechanically Assisted Circulatory Support; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; U.S., United States; GAIT, Global Alliance for iPS Cell Therapies; WHO, World Health Organization; CFR, Code of Federal Regulations; FDA, Food and Drug Administration; BLA, Biological License Approval; IND, Investigational New Drug; ICH, The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; PIC/S, The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme.

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documented. Like ESCs, iPSC-based products are used as research tools for drug toxicity testing, such as drug-induced QT prolongation [4–6]. A unique application of iPSCs is that they can be derived from diseased patients, which gives them a distinct advantage over ESCs for disease modeling and drug discovery [7–21].

Regarding cell therapy applications, it is expected that iPSC-based products from healthy donors can be used for allogeneic therapies. By carefully selecting donors that have homozygous human leukocyte antigens (HLA), it will be possible to reduce immune rejection and thus also the dose of immunosuppressive agents [22–35]. In addition, iPSCs have the potential for autologous therapies, further reducing the risk of immune rejection [36,37].

In Japan, the discovery of iPSCs has stimulated strong government support for the development and commercialization of iPSC-based technology, including generous research funding. This support was amplified after the Nobel Prize in Physiology or Medicine was awarded in 2012. In addition, regulatory authorities have reevaluated policy in order to facilitate effective and efficient regulatory clearance for marketing approval of this technology [38–45]. In this manuscript, we will review relevant policies and collaborative efforts among academia, industry and government agencies. We also discuss potential regulatory and ethical challenges related to future international cooperation for HLA homozygous iPSC banks, which are being used as sources for iPSC-based regenerative medicine products (RMPs).

2. Role of public funding to facilitate R&D on iPSC-based regenerative therapies

2.1. Establishment of Japan Agency for Medical Research and Development

In order to promote medical research and development (R&D), including regenerative medicine, the Japan Agency for Medical Research and Development (AMED) was established as a new National Research and Development Agency on April 2015 [40,43,46]. AMED is organized to consolidate national medical R&D funding, which was previously operated directly by the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Ministry of Health, Labour and Welfare (MHLW) and Ministry of Economy, Trade and Industry (METI) or through the Japan Science and Technology Agency (JST), National Institute of Biomedical Innovation (NIBIO) and New Energy and Industrial Technology Development Organization (NEDO) [47]. AMED also consolidates the operation of the research center network for realization of regenerative medicine (fiscal year (FY) 2015 budget: 8.99 billion yen) from MEXT, regenerative medicine clinical application program (FY2015 budget: 2.78 billion yen) from MHLW and regenerative medicine industrial technology development support program (FY2015 budget: 2.5 billion yen) from METI (Fig. 1) [48,49].

2.2. Collaboration for regenerative medicine related to the iPSC stock project

For R&D toward iPSC-based regenerative therapies, close collaboration between research centers that generate and provide (or distribute) iPSCs and those that differentiate iPSCs into final products are important. Therefore, MEXT and JST initiated a new program, “Research center network for realization of regenerative medicine” in FY 2013 (Fig. 2) [50]. Under this program, the Center for iPSC Cell Research and Application (CiRA), Kyoto University, was selected as a core center for iPSC research to conduct “iPSC stock development projects for regenerative medicine”. Four research centers (Keio University, CiRA, Riken and Osaka University) were selected as “Centers for Clinical Application Research on Specific

Disease/Organ (Type A Centers/Institutions)”, which aim at the clinical application of iPSC-based regenerative therapies by FY 2017, making them national leaders in iPSC-based regenerative therapy R&D. Overall, the program consists of many other iPSC-based regenerative therapy R&D projects. Table 1 shows examples of disease/organ research projects related to iPSC-based regenerative therapy being done by at least one of the four institutions under this program. Many of these projects involve collaborations using the iPSC stocks provided by CiRA.

One of the primary roles of CiRA is to provide seed stocks of iPSCs for the development of therapeutic products [51–53]. The stock generated from HLA-homozygous donors is expected to reduce the risk of immune rejection upon the transplantation of differentiated cells to recipients having the same HLA haplotype [22–35]. Therefore, CiRA is developing a series of clinical grade iPSCs from HLA-homozygous donors in collaboration with the Japan Red Cross, the Japan Marrow Donor Program and cord blood banks.

In general, user research centers will expand and establish their own cell banks of iPSCs or of downstream stem/progenitor cells for pre-clinical and clinical studies. In the case that the research center derives iPSCs from a source other than the CiRA iPSC stock for therapeutic purposes, CiRA will provide technical assistance when necessary. For example, the two institutes will characterize and analyze the iPSC-based differentiated cells together. For the development of iPSC-based regenerative therapy, in addition to general pre-clinical toxicity testing, additional consideration of tumorigenicity related to residual undifferentiated cells, contaminant cells, cells genetically transformed to malignancy during culture, or residual vectors is essential [54–63]. The relationship between genomic abnormalities of iPSCs or final products and tumorigenicity is not yet elucidated. To appropriately analyze genomic abnormalities of the final products, it is necessary to compare genome information from the original donor cells, iPSCs and differentiated cells. CiRA will be responsible for the genome analysis, and user research centers will be responsible for tumorigenicity studies. The results of these works will be used to optimize quality standards for both iPSCs as raw material and differentiated cells as final products.

2.3. Expansion of clinical research infrastructure

To facilitate academia-based clinical research of iPSC-based regenerative therapies, collaboration with hospitals that have experts who can prepare clinical research protocols and manage clinical research, is important. Therefore, MHLW and MEXT started several grants for clinical research infrastructure [40]. These grants facilitate early-phase and exploratory clinical trials using iPSC-based regenerative therapies. Osaka University and Keio University Hospitals have been awarded the early/exploratory clinical trial center grant since 2011 [64], and Kyoto University Hospital the clinical research core center grant since 2012 [65]. MHLW certified Institutional Review Boards (IRBs) at these three institutions in April 2015 based on a new certification program [66]. Osaka, Keio and Kyoto Universities also established specially certified regenerative medicine committees to review clinical research protocols for iPSC-based therapies under the new Act on the Safety of Regenerative Medicine (RM Act) enacted in November 2014 [39,43,67,68]. Although the Center for Developmental Biology (CDB), Riken, does not have its own hospital, it has already begun iPSC-based retinal pigment epithelium (RPE) clinical research by coordinating with Institution of Biomedical Research and Innovation (IBRI) Hospital, which has been awarded the Japan initiated global trial center grant since 2012 [69]. These grants were transferred from MHLW to

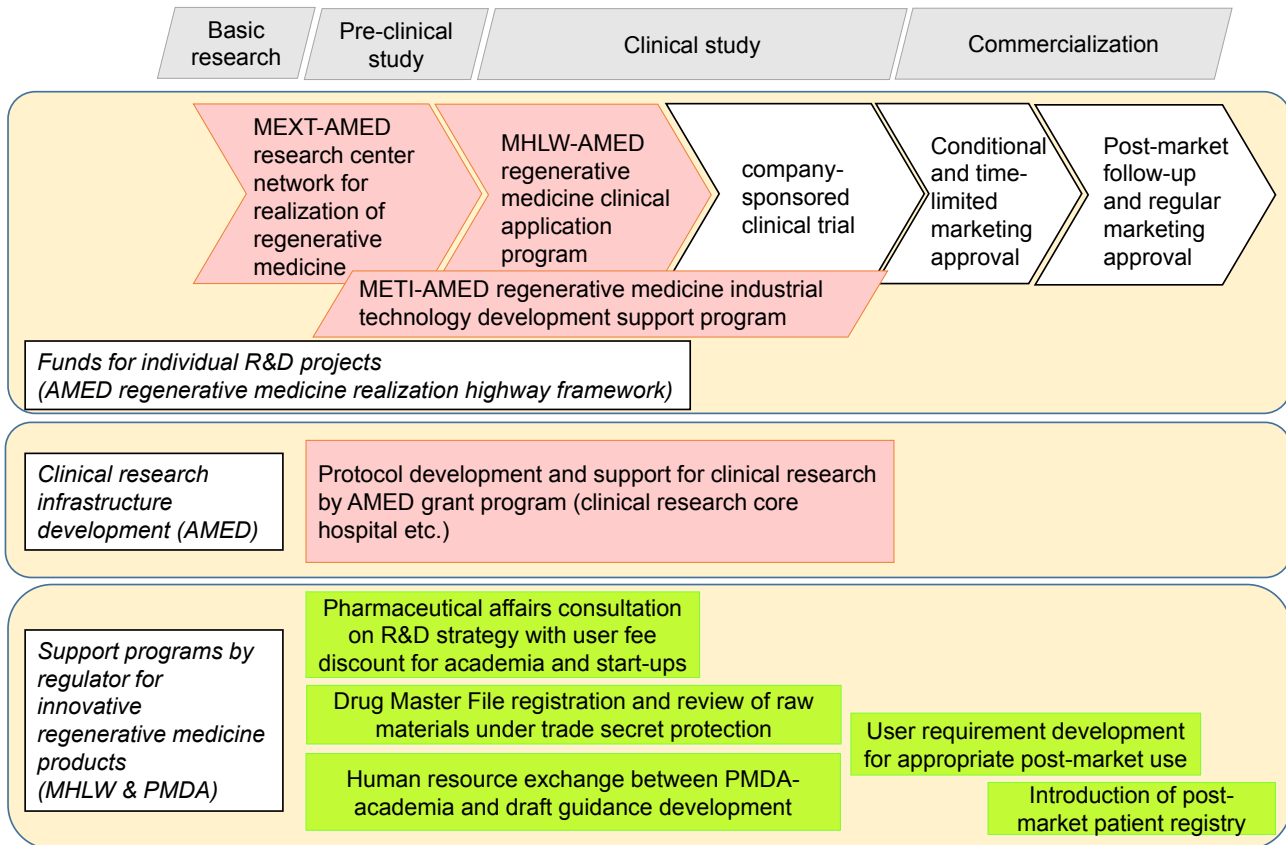


Fig. 1. Overview of support programs for the R&D of regenerative medicine products. AMED, Japan Agency for Medical Research and Development; MEXT, Ministry of Education, Culture, Sports, Science and Technology; MHLW, Ministry of Health, Labour and Welfare; METI, Ministry of Economy, Trade and Industry.

AMED as part of the “AMED innovative medical technology generation center program” [48,49].

2.4. Collaboration between PMDA and research institutions to develop guidelines for iPSC-based regenerative medicine products

A unique scheme that encourages close interactions between regulatory authorities and research institutions was introduced recently in Japan. For innovative products under development by academia, such as iPSC-based RMPs, regulatory requirements have sometimes been unclear. However, effective regulatory guidelines cannot be made by the regulatory authorities without input from active scientists. Therefore, MHLW initiated a new grant program, “Initiative for Accelerating Regulatory Science in Innovative Drugs, Medical Devices and Regenerative Medicine”, in 2012 [70,71]. R&D programs related to iPSC-based RMPs at CiRA, Osaka University and Riken CDB have been awarded these grants. In this program, reviewers at the Pharmaceuticals and Medical Devices Agency (PMDA) or scientific experts at National Institute of Health Science (NIHS) visit research institutions periodically to give scientific advice and remain updated with on-going development of innovative technologies. In exchange, researchers visit PMDA as part-time or full-time employees and provide technical advice to support PMDA’s review and consultation. The intent of these bi-directional exchanges is to have all parties better understand their partners’ motivations and goals. An expected outcome of this five-year program (FY2012–FY2016) is to have researchers and PMDA’s or NIHS’s visiting scientists together develop a draft of guidelines. After appropriate public consultation, MHLW will finalize and publish these documents as official guidelines that

clarify regulatory requirements to facilitate the commercialization of innovative iPSC derived RMPs.

In addition to this scheme, there are other mechanisms for developing such guidelines. One is MHLW’s regulatory science research grants, which have led to general guidelines for iPSC-based RMPs that were published in 2012 [72–75]. Another is a specific program that began in 2006 and drafts evaluation guidance for innovative products. Under this program, MHLW, NIHS, and PMDA work together with academic experts and have published guidelines for iPSC-based RPE cells in 2013 (autologous) and 2014 (allogeneic) [76,77]. Currently, new guidelines for iPSC-based cartilage products are under preparation [78].

3. Revised regulatory policy to promote R&D of RMPs

Along with the actions described above, there are several regulator-led initiatives that are designed to promote the R&D of RMPs (Fig. 1). In this section, we review current regulatory policy related to RMPs relevant to future iPSC-based RMPs.

3.1. Introduction of conditional, time-limited approval for RMPs

The Pharmaceutical Affairs Law (PAL) was revised and renamed to the Pharmaceuticals and Medical Devices (PMD) Act, which became effective in November 2014 [38–45,79,80]. In this revision, a new product category, RMPs, which is separate from drugs and medical devices, was introduced, and its specific regulation was established. Because RMPs are extremely difficult to evaluate for effectiveness due to the heterogeneity of cells, a new approval system in which MHLW can give conditional and time-limited

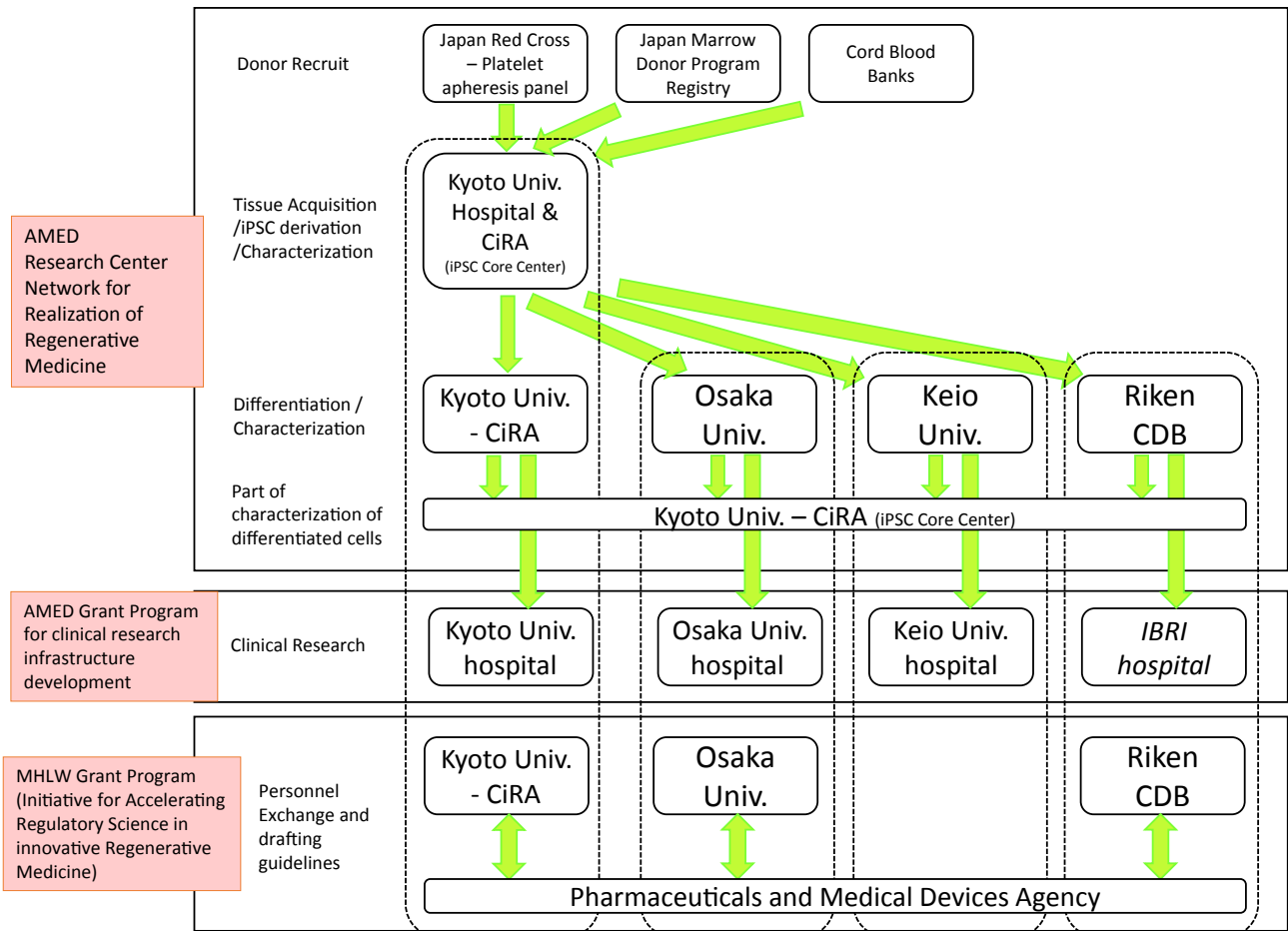


Fig. 2. iPSC stock related R&D collaboration involving major research centers and regulatory agencies. AMED, Japan Agency for Medical Research and Development; MHLW, Ministry of Health, Labour and Welfare.

Table 1
iPSC-based regenerative therapy R&D projects under the AMED regenerative medicine network program.

Kyoto University	Riken	Osaka University	Keio University
Dopamine-producing neurons	Retinal pigment epithelium cells	Corneal epithelium cells	Neural progenitor cells
Platelet	Photoreceptor cells	Corneal endothelium cells	Corneal endothelium cells
Cartilage	Natural killer T cells	Cardiomyocytes	Cardiomyocytes
Cardiomyocytes	Teeth	Hepatocytes	
Kidney	Hair		
Pancreas	Secretory glands		
Skeletal muscle			

Note: Other institutions participating but not shown include Osaka National Hospital (neural progenitor cells), Yokohama City University (liver), the University of Tokyo (liver and pancreas), Kumamoto University (liver), Chiba University (liver) and National Center of Neurology and Psychiatry (skeletal muscle).
Reference: summarized from the JST regenerative medicine network program website (<http://www.jst.go.jp/saisei-nw/>).

approval after confirmation of probable benefit and safety was introduced. Upon this probationary approval, approval holders must apply for regular approval within a specified period (normally maximum 7 years) or the approval will expire. In addition, Good Manufacturing Practice (GMP) that considers the unique characteristics of RMPs was introduced as Good Gene, Cell, Cellular and Tissue-based products Manufacturing Practice (GCTP) [81].

Under the new PMD Act, two products were approved as new RMPs on September 18 2015. One product, Temcell® HS Inj. by JCR Pharmaceuticals Co., Ltd for Acute Graft-versus-Host Disease following hematopoietic stem cell transplant, was awarded regular approval [82,83]. Another product, HeartSheet® Autologous Skeletal Myoblast Sheets by Terumo Corporation for severe heart failure

caused by chronic ischemic heart disease, was awarded conditional and time-limited approval for 5 years [84,85].

3.2. Introduction of new consultation program for early stage development and simplification of clinical trial plan review

Under the PMD Act, article 80-2, intensive review by PMDA and MHLW is required for the first clinical trial protocol of any new drug, medical device or RMP within 30 days of application submission. However, this time period is demanding when considering the quality and safety of RMPs. Therefore, pre-clinical review by the Pharmaceutical and Medical Device Evaluation Center of NIHS (consolidated to the PMDA in 2004) and the MHLW Pharmaceutical

and Food Sanitation Council before submission of the first clinical trial protocol had been required since 1999 [86–88].

Prior to the recent revision of the PMD Act, MHLW held “the committee of regenerative medicine regulatory framework”, which consisted of regenerative medicine experts, from 2009 to 2011. This committee discussed improvements to the PMD Act. Accordingly, in July 2011, MHLW and PMDA introduced an early stage consultation program that mainly targets academia and start-up companies and replace the official additional pre-clinical review of quality and safety of RMPs [89,90]. In this new consultation program, named pharmaceutical affairs strategy consultation, PMDA gives advice related to R&D strategy [91]. The review of quality and safety data under the pharmaceutical affairs strategy consultation is required before submission of the first clinical trial protocol for any RMP. Pharmaceutical affairs strategy consultation usually requires fees for each official meeting, but for the mandatory consultation related to quality and safety, a one-time consultation fee can be paid. In addition, by subsidy from MHLW, discounts of up to 90% can be procured for academia and start-up companies. This consultation has considerably simplified pre-clinical reviews and reduced uncertainty of what quality and safety data are required in the pre-clinical phases because of constant communication between the sponsors and PMDA. CiRA has used this pharmaceutical affairs strategy consultation to confirm the quality and safety of its iPSC stocks and other iPSC-based RMPs [92].

More recently, MHLW announced the introduction of fast-track consultation and review program designed specifically for drugs, medical devices and RMPs that act against diseases in urgent need of innovative therapy and are initially developed in Japan or will include Japan in a multi-national clinical trial [93,94].

3.3. Expansion of Drug Master File registration systems for raw materials of RMPs

A Drug Master File (DMF) registration system for the raw materials of drugs or medical devices, such as active pharmaceutical ingredients, was introduced in 2005 [95]. This system allows PMDA to review information directly submitted by raw material manufacturers who are not applying for clinical trials or seeking regulatory approval, thus allowing these manufacturers to protect trade secrets. In December 2012, subjects of DMF registration were expanded to include raw materials related to RMPs, such as cells (iPSCs and ESCs), media, medium additives (sera, growth factors and cytokines) and other materials [96,97]. Raw material manufacturers can directly register manufacturing and quality control information, specifications related to human or animal derived materials, information related to the donors of the cells, specifications of the cells and non-clinical test data [98,99]. These data can be reviewed directly by PMDA not only during the approval review, but also before clinical trials, including during the pharmaceutical affairs strategy consultation, to confirm the quality and safety of the raw materials and final products.

3.4. Introduction of post-market patient registry for RMPs

Unlike most drugs, which disappear within a few days by metabolism or elimination after the end of administration, many RMPs stay in the patient body long after transplantation. Therefore, long-term patient follow-up is essential for reliable evaluation. From this perspective, RMPs share similar characteristics with implantable medical devices, such as left ventricular assist devices or hip replacement implants, which are often included in a patient registry for recognition of post-market safety issues [100,101]. PMDA has experience in developing and operating J-MACS (Japanese registry for Mechanically Assisted Circulatory Support), which

is a patient registry for mechanical circulatory support implantation devices and built on a similar data structure as North America's INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) [102–106]. Leveraging this experience and in response to the introduction of the new conditional, time-limited approval system, a new patient cohort registry that records post-market safety and efficacy data of RMPs is currently under development by MHLW and PMDA [41,44].

A MHLW-sponsored committee to discuss the design of a patient registry system for RMPs was formed in January 2013. Based on their conclusions, PMDA commenced the development of a registry, aiming for launch by the end of FY2015 [107,108]. It is expected that this new patient cohort registry of RMPs will generate useful post-market safety and efficacy data, which can be used for regular approval review after conditional and time-limited approval.

3.5. User requirements for appropriate use of RMPs

Another safety measure to consider for conditional, time-limited approval is the requirements of users, such as medical institutions and medical doctors, for RMPs that require novel or complex surgical techniques. In 2011, in response to increasing complexity, MHLW introduced a new program to facilitate the development of post-market user requirements for facilities and physicians [109]. In this program, MHLW, PMDA and related academic societies worked together to set post-market user requirements during the approval review of innovative medical devices and RMPs. These requirements have been adopted as conditions for National Health Insurance reimbursement coverage. These standards are already being applied to an autologous cultured cartilage product, JACC[®], that is manufactured by Japan Tissue Engineering Co., Ltd. and was approved in July 2012 [110–114]. The Japanese Orthopaedic Association proposed the user requirements of JACC[®], including the necessary facilities, human resources, experience, training, expertise, etc. [115]. These standards are also used to determine the conditions for reimbursement [116,117]. Currently, user requirements for autologous skeletal muscle derived cell sheets for heart failure are under preparation [118]. It is expected that future iPSC-based RMPs will also fall under this scheme and appropriate human and facility standards in order to secure the product efficacy and safety set by MHLW, PMDA and relevant professional societies.

3.6. Alternative scheme to provide regenerative therapies under early stage, small-scale human clinical research

Apart from clinical trials under the PMD Act, which aims for the commercialization of RMPs, there is an alternative scheme to use iPSC-based regenerative therapies under physician discretion. This scheme is recognized as “clinical research” and is not intended for commercialization [40,43,86,87]. It is unique to Japan, but shares some common characteristics with the “Hospital Exemption” scheme in EU member states [119].

Until recently, clinical research using human stem cells was regulated under the independent, non-legally binding guideline, “Guidelines for Clinical Research Using Human Stem Cells” [120]. The RM Act [41,43,68], enacted since November 2014, replaced this guideline. The RM Act stipulates stricter standards to provide regenerative medicine for medical institutions, and manufacturing and quality control standards for cell processing centers. However, the RM Act also removed a ban on the outsourcing of cell processing to companies outside medical institutions. Previously, such outsourcing was considered an infringement of the PMD Act, which

prohibits the provision of unapproved products except for those used in clinical trials.

There are several differences in procedures and requirements between clinical research under the RM Act and clinical trial under the PMD Act. Fig. 3 summarizes the differences. As described in the Section 3.2, PMDA consultations are required before the initiation of clinical trial under the PMD Act. This process is not trivial, but provides clarity for regulatory clearance when submitting a clinical trial plan and new RMP approval application later. On the other hand, there is no official consultation mechanism before submitting a clinical research plan to the MHLW under the RM Act. Therefore, the review period of the clinical research plan is longer in the RM Act (90 days) than is the clinical trial plan in the PMD Act (30 days). Furthermore, additional data might be requested after submitting a clinical research plan. The technical requirement of IRBs (named “specially certified regenerative medicine committees” under the RM Act for high risk regenerative therapies such as iPSC-based therapies) is also stricter in the RM Act than in the PMD Act.

Clinical research under the RM Act is not subject to Good Clinical Practice (GCP), which means clinical research data are not accepted in the new RMP approval application under the PMD Act. However, in Japan, without first-in-human clinical research experience, companies tend to hesitate to invest money and effort on clinical trials. Therefore, it is generally considered that clinical research is more suitable for small-scale clinical study, such as first-in-human study by academia using limited government research funding, since the costs of clinical research is cheaper than that of clinical trial. Upon confirmation of feasibility, the technology is transferred to a company. For example, regarding recently approved “Heart-Sheet[®]”, after initial clinical research conducted by a university, a company conducted additional clinical trials for regulatory submission according to the PMD Act [84,85].

However, it is also argued that considering the commercialization of regenerative medicine products in the future, it might be better to switch from early stage clinical research to clinical trial as soon as possible or even begin at clinical trial [87]. Since regulatory requirements for iPSC-based regenerative therapy under the RM Act are strict, whether the clinical research scheme will be used the same way as previous guidelines is unclear.

There is another argument that because the RM Act regulates “clinical practice” outside of “clinical research”, it might be possible to proceed from clinical research to clinical practices under the RM Act without commercialization as RMPs. However, this alternative route may not be suitable for iPSC-based regenerative therapies, because (1) it is unclear when the iPSC-based regenerative therapies are considered not “clinical research” but rather “clinical practice”, (2) the RM Act requires a burdensome procedure such as IRB and MHLW review even for “clinical practice”, and (3) National Health Insurance coverage scheme for “clinical practice” under the RM Act is unclear.

4. Challenges for international collaboration using clinical grade iPSCs

In addition to the iPSC stock project at CiRA [51,52], several other projects, such as those at Cellular Dynamics International Inc. in the United States (U.S.) and Cell Therapy Catapult in the United Kingdom, are generating iPSCs prepared from HLA homozygous donors [121–123]. Other countries are in planning phases for the same [33]. Assuming these nations meet minimal standards, it is expected that they can provide iPSCs of a specific HLA haplotype to other countries where the same HLA haplotype is relatively rare in donors [28–34]. Thus, a global cooperation network among these

iPSC banks (haplobanks), or the Global Alliance of iPSC Therapies (GAiT), has been proposed.

In relation to the commercialization of iPSC therapies, each country or region has its own regulations and ethical standards. Although some international guidelines or voluntary standards for other products can be applied (Fig. 4), because RMPs such as iPSCs are relatively new, most R&D processes are not in global agreement. Therefore, to share clinical-grade iPSCs internationally, there are several potential regulatory challenges that must be overcome. Discussion about these regulatory challenges has been initiated by several international expert groups such as International Stem Cell Banking Initiative (ISCBI), International Alliance for Biological Standardization (IABS) and GAIT [33,124–126].

4.1. Cell sourcing and donor eligibility before iPSC derivation

4.1.1. Informed consent and donor protection

When cells or tissues are sourced from HLA homozygous donors, it is necessary to meet regulation and ethical standards, such as informed consent, protection of donor privacy, and (non-) remuneration [127–132]. As recommended for blood donations by the World Health Organization (WHO) [133], voluntary and non-remunerated donations of source cells for RMPs are required in several countries including Japan [130]. As a result, iPSCs derived from remunerated donors may not be suitable for international exchange when used as RMPs.

Considering the protection of privacy, how to access potential donors from cooperating blood centers, cord blood banks or bone marrow registries are under discussion [29,30,32,126,127,129]. Donor privacy related to genome analysis, including issues around incidental findings, are regulated under diverse ethical standards among countries and also under wider discussion within medical and ethical communities [9,30,33,127,134–142].

4.1.2. Donor screening and testing for infectious agents

The diversity of donor screening regulations might hinder the acceptance of iPSCs from foreign haplobanks [127,130,131, 143–146]. For example, the Code of Federal Regulations (CFR) of the U.S. Food and Drug Administration (FDA) requires the use of “appropriate FDA-licensed, approved, or cleared donor screening tests” (21 CFR1271.80(c)) and also requires testing be “performed by a laboratory that either is certified to perform such testing on human specimens under the Clinical Laboratory Improvement Amendments of 1988 (42 U.S.C. 263a) and 42 CFR part 493 or has met equivalent requirements, as determined by the Centers for Medicare and Medicaid Services” (21 CFR1271.80(c)) [144]. The exchange of iPSCs from foreign haplobanks might be hampered by difficulties in conforming specific requirements across borders, such as specifically approved kits and certified laboratory. A flexible policy regarding donor screening results under appropriate foreign regulations is desirable.

The acceptance of iPSCs derived from previously collected cord blood in foreign countries is also not clear, as cord blood regulations are not internationally harmonized. For example, in the U.S., cord blood is subject to biological license approval (BLA) or investigational new drug (IND) requirements under the Federal Food, Drug, and Cosmetic Act [123,147], but in Japan cord blood is subject to different regulations under the Act for Appropriate Provision of Hematopoietic Stem Cells to be Used in Transplantations [131,148,149]. Like above, flexible policy for iPSCs derived from cord blood is desirable.

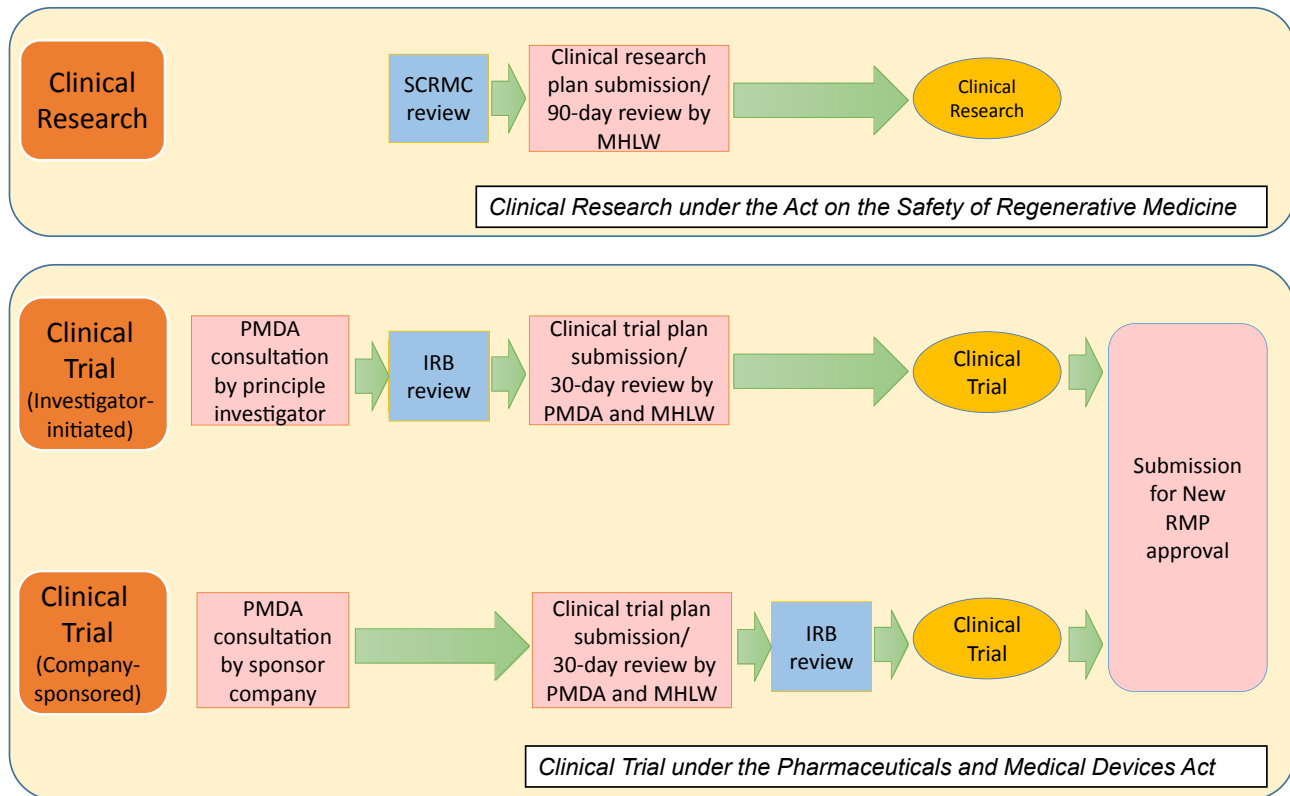


Fig. 3. Procedures to initiate Clinical Research under the Act on the Safety of Regenerative Medicine (RM Act) and Clinical Trial under the Pharmaceuticals and Medical Devices Act (PMD Act) for iPSC-based regenerative therapies. SCRCM, Specially Certified Regenerative Medicine Committee; IRB, Institutional Review Board.

4.2. Manufacturing and quality control of iPSC and differentiated cells

4.2.1. Manufacturing methods and raw material information

There are a variety of methods for generating clinical grade iPSCs using non-integrated vectors such as episomal plasmid, Sendai virus and mRNA [150–159]. It is expected that several manufacturing methods will be acceptable from a regulatory perspective [33]. The use of xeno-free, feeder-free raw materials for manufacturing clinical grade RMPs is generally desirable and rapidly increasing [154]. It should be carefully checked, however, whether animal-derived materials are used as or in the manufacturing process of raw materials and whether the safety of these materials, such as traceability and virus clearance, if applicable, meet standards. In order to use RMPs based on iPSCs provided from foreign haplobanks for clinical trials, it is also important to gain the cooperation of the raw material supplier who provides necessary information to the manufacturer of the RMPs or to the foreign regulatory authorities through DMF registration, as described in the Section 3.3, or similar mechanisms.

4.2.2. Quality standards

Quality standards for iPSCs of research-grade and clinical-grade have been already discussed in several academic societies or consortiums, such as the International Stem Cell Banking Initiative [33,124,155,157,160,161]. Other existing guidelines for biotechnology products, such as those of the International Conference on Harmonisation¹ of Technical Requirements for Registration of

¹ Renamed to the International Council for Harmonisation on October 2015 (<http://www.ich.org/about/organisational-changes.html>).

Pharmaceuticals for Human Use (ICH) might be applicable for the generation of a master cell bank [162,163]. Clear regulatory guidelines for the evaluation of iPSCs and RMPs may be helpful to promote efficient R&D. However, to further refine the standards necessary for iPSCs, it might be necessary to gather more data of both iPSCs and iPSC-based RMPs under a collaborative mechanism between haplobanks and user research centers developing RMPs, as exemplified in the Section 2.2. For the time being, it is expected that so long final products are safe and effective, they will receive approval by regulatory authorities that consider appropriate specification of iPSCs as a raw material and final product, even without international consensus on standards or regulatory guidelines.

Because different clones of iPSCs from the same donor may have different propensities of differentiation [164], it is probably best to defer to user research centers for the selection of clones until better predictive methods for differentiation propensity are established [165]. In addition, because iPSC-based RMPs vary in characteristics and number of cells, quality standards for one product may not be universal. For example, there is less need to concern platelets derived from iPSCs [166] with tumorigenicity resulting from genomic abnormalities compared with other RMPs, because of the absence of a genome in platelets. Therefore, universal standards risk inefficiencies. Another issue relates to the donor background. Depending on the disease targeted by the RMP, additional requirements of the donor's health and genetic background or specific virus screening might be necessary [167]. For example, allogeneic clinical trials of retinal pigment epithelium cells need screenings for retinal diseases [77,168]. Considering the above issues, it will be desirable to have regulator-led international forums, such as ICH, include academic experts in order to develop flexible but sufficient criteria for multi-purpose iPSC haplobanks that leverage empirical evidence generated from scientific studies.

Development stage	Issues to be considered	Reference documents/scheme
Tissue Sourcing	<ul style="list-style-type: none"> Informed consent Donor screening Protection of donor privacy 	JP: Standards for biological ingredients, Ethical Guideline for human genome/gene analysis research US: 21 CFR 1271, CLIA EU: EUTCD, EUBD ISO 15189, WMA Declaration of Helsinki, UNESCO Universal declaration on bioethics & human rights
iPSC Generation	<ul style="list-style-type: none"> Manufacturing and QC methods GMP requirements and inspection Transportation and storage 	ICH Q series, Pharmacopeia(JP, USP, Ph.Eur.) ISO (TC150/SC7, TC194/SC1, TC198, TC210, TC212, TC276 etc.) OECD Guidelines for BRCs, ISCBI PIC/S GMP Guide, ISO 13485, GHTF SG3&4, MDSAP
Manufacturing Differentiated Cells		
Non-Clinical Testing	<ul style="list-style-type: none"> In vitro and in vivo test design GLP requirements and inspection Acceptability of foreign data 	ICH S6, ICH M3, ISO 10993, WHO TRS878 OECD-GLP-MAD
Clinical Trial	<ul style="list-style-type: none"> Clinical trial design Adverse event reporting GCP requirements and inspection Acceptability of foreign data 	ICH E8-E10, GHTF SG5/N3 ICH E2A, ICH E2F, GHTF SG5/N5 ICH E6 (ICH-GCP), ISO 14155 (ISO-GCP) ICH E5
Review and Approval	<ul style="list-style-type: none"> Submission dossier Approval requirements Conditional approval option 	ICH M4(CTD), M8(eCTD) GHTF STED, IMDRF RPS-ToC JP: Conditional and time-limited approval US: Breakthrough therapy designation, Accelerated Approval, HDE EU: Conditional MA, Adaptive licensing
Post-Market	<ul style="list-style-type: none"> User facility/physician requirements Adverse event reporting Post-market patient follow-up 	ICH E2B-E, GHTF SG2/N54 IMDRF Registry WG, GHTF SG5/N4

Fig. 4. Overview of development stage, issues and major reference documents/schemes related to iPSC-based regenerative medicine products. CLIA, Clinical Laboratory Improvement Amendments; EUTCD, European Union Tissues and Cells Directives (2004/23); EUBD, European Union Blood Directive (2002/98); WMA, World Medical Association; UNESCO, United Nations Educational, Scientific and Cultural Organization; ICH, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; JP, Japanese Pharmacopoeia; USP, United States Pharmacopoeia; Ph.Eur, European Pharmacopoeia; ISO, International Organisation for Standardization; TC, Technical Committee; SC, Subcommittee OECD, Organisation for Economic Co-operation and Development; GL, Guideline; BRC, Biological Resource Centres; ISCBI, International Stem Cell Banking Initiative; PIC/S, Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme; GMP, Good Manufacturing Practices; GHTF, Global Harmonization Task Force; SG, Study Group; MDSAP, Medical Device Single Audit Program; WHO, World Health Organization; TRS, Technical Report Series; GLP, Good Laboratory Practice; MAD, Mutual Acceptance of Data; GCP, Good Clinical Practice; STED, Summary Technical Documentation; IMDRF, International Medical Device Regulators Forum; RPS-ToC, Regulated Product Submission- Table of Contents; HDE, Humanitarian Device Exemption; MA, Marketing Authorization.

4.2.3. GMP standard and inspection

GMP for RMPs or GCTP in many countries is generally consistent with the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly referred to as PIC/S) GMP Guide, which was drafted in consultation with pharmaceutical inspection authorities from 46 countries [169–171]. However, it is not yet clear to what extent GMP controls are required for the generation of iPSCs, which are at a relatively early stage of the manufacturing process and well before the stage of a master cell bank for specific RMPs [32,143,172]. In addition global cooperation for haplobanks may require each haplobank receives inspection from several national regulatory authorities. A higher level of regulatory cooperation in order to mutually rely on the GMP inspection reports from other regulatory authorities is desirable [173].

4.2.4. Addition of iPSCs to existing RMPs

Another unresolved issue unique to iPSC-based RMPs, especially regarding haplobanks, is the extent of additional tests for the inclusion of new iPSC lines [33,143]. The same product from different cell lines may not have universal properties. Therefore, a number of causes for the variability must be considered, including

- (1) changes from clones of the same donor,
- (2) different donors from the same manufacturing site and manufacturing method,
- (3) changes in manufacturing methods (including changes in media or reagents) from the same manufacturing site,
- (4) different manufacturing sites from the same manufacturing method, and
- (5) different manufacturing methods that meet the same specifications and criteria.

Changes in cell lines and master cell banks are allowed in previously approved allogeneic RMPs, such as Apligraf[®], or Gintuit[™], both from Organogenesis Inc, in the U.S. based on extensive characterization and through premarket approval supplement for manufacture process change [172,174]. A similar approach for new iPSC lines would allow approval holders of RMPs derived from HLA-homozygous iPSCs to add new HLA-type iPSC lines to existing RMPs. However, there is neither agreement for required comparability data nor scientific evidence to justify that changes in the cell bank do not affect product safety or efficacy. If the new iPSC line requires excessive testing, cost may prohibit the inclusion of this line for RMP development, potentially resulting in the RMP only

serving patients with frequent HLA phenotypes, thus creating an ethical conflict. Regulatory judgment that considers maximization of public health in accordance with the concept of regulatory science should be applied [175].

5. Conclusion

In this article, we reviewed recent developments of collaborative R&D schemes between clinical grade iPSC manufacturers and user research centers, as well as government policies to facilitate the establishment of R&D and regulatory infrastructures in Japan. In addition, we reviewed potential challenges for further collaboration with research center overseas. We expect some of these challenges will be resolved with growing scientific knowledge gained from pre-clinical studies and the clinical development of RMPs. The resolution of other issues for the wide deployment of iPSC therapies should come from further collaboration between regulators and researchers.

Conflict of interest

Shinya Yamanaka is a scientific advisor of iPS Academia Japan without salary.

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