

Nonclinical data required for clinical application of induced pluripotent stem cells (iPSCs)-based products

— Critique of Japanese Notifications compared with the policies of FDA and EMA — *

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Abstract

Clinical development of regenerative medicine using somatic stem cells is making steady progress toward practical application all over the world. Needless to say, clinical trials of cellular-based products are regarded as being in the experimental stage in the world and mostly have been conducted under the Pharmaceutical Affairs Law (PAL). Therefore, their efficacy and safety are rigorously evaluated by regulatory authorities based on quality-assured preclinical and clinical data, aiming at the goal of marketing authorization.

Currently in Japan, several investigator-initiated regenerative medicine clinical trials under the PAL have steadily achieved planned progress. On the other hand, “clinical research of iPSCs (induced pluripotent stem cells)” outside the control of PAL has been rapidly accelerated toward clinical application.

Considering this situation, we reviewed Japanese regulations related to preclinical assessment of cellular-based products, comparing with the regulatory policies of the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA). We found that Japanese regulations of regenerative medicine using cellular-based products mainly focus on quality control and manufacturing of cell preparations, while both the FDA and EMA intensively discuss about preclinical studies of cell preparations and risk factor examination, apart from the issue of manufacturing.

We conclude that in Japan all the clinical trials of cellular-based products should be conducted under the control of PAL and that regulatory science concerning preclinical and clinical assessment of such products should be discussed in greater depth based on the examination of FDA/EMA policies.

Key words

regulatory science, induced pluripotent stem cells (iPSCs), cellular-based products, risk based approach, research ethics

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1. Introduction

Development of regenerative medicine using somatic stem cells is making steady progress toward practical application all over the world. As of September 2013, 358 stem cell clinical trials have been registered with ClinicalTrials.gov. In accordance with the accumulation of clinical trial data, our knowledge of human stem cell physiology and pathology has deepened dramatically. It goes without saying that in order to use stem cellular-based products in medical practice, the efficacy and safety should be assessed and confirmed by strict non-clinical experimentation and clinical trials under the Pharmaceutical Affairs Law (PAL), and the products should be strictly reviewed and approved by the regulatory authorities. As is well known, legitimate clinical trials for regenerative medicine under the PAL are now proceeding smoothly in Japanese academia. With the support of the Coordination, Support and Training Program for Translational Research and the Network Program for Accelerating Translational Research by the Ministry of Education, Culture, Sports, Science and Technology, four somatic stem cell clinical trials are going on under the PAL (Table 1), and

future innovative technologies are also expected to be subjected to clinical trials as they are developed¹⁾.

On the other hand, against the background of a strong desire for the practical use of regenerative medicine using induced pluripotent stem cells (iPSCs), aggressive movements pushing “Clinical studies” exempt from the PAL and aimed at clinical application have become prominent in Japan with the enthusiastic support of the media. However, there are some unresolved safety issues with iPSCs, including the possibility of *in vivo* tumorigenicity and the expression of a totally unexpected phenotype by undifferentiated cells. Therefore, many researchers both inside and outside Japan are expressing concern over the situation in which the research institute and government in Japan jointly continue to push for clinical application without sufficient assessment and verification of preclinical studies by the regulatory authorities.

Coincidentally, *Nature Medicine* published a review on the tumorigenicity of iPSCs in the August issue (Vol. 19)²⁾ in 2013. The authors cited a large number of papers, reviewed the risk of tumorigenicity in human pluripotent stem cell (PSC) therapy, and discussed how the research should be. In that article, the authors referred to human embryonic stem

Table 1 Regenerative medicine clinical trials using somatic stem cells in Japanese academia

As of August 2013

	Product	Classification	Clinical trial	Target disease	Status
1.	Autologous bone marrow stem cells (CD34 ⁺)	Pharmaceuticals	Investigator sponsored	Severe leg ischemia	PI/II completed
2.	Autologous articular cartilage cells	Medical devices	Investigator sponsored	Knee cartilage	Underway
3.	Autologous myoblast sheet	Medical devices	Company	Severe heart failure (adult)	Underway
4.	Bone marrow derived autologous cultured stem cells (MSC)	Pharmaceuticals	Investigator sponsored	Cerebral infarction	Underway

cells (ES) clinical trials by Geron and Advanced Cell Technology and the iPSCs clinical trial in preparation by the RIKEN Center for Developmental Biology, and described the following conclusion:

“Our duty as PSC biologists and clinicians should be to thoroughly understand these cells of our own creation before we move PSC-based therapies to the patient bedside.”

In this article, we will discuss the data required before clinical application of iPSCs can be carried out in accordance with the scientist’s conscience, responsibility, and honor, with reference to the draft guidance proposed by the Food and Drug Administration (FDA), the United States Department of Health and Human Services in November 2012 (Draft Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products) (hereafter referred to as “FDA Draft Guidance”)³⁾ and the draft guideline proposed by the European Medicines Agency (EMA) on January 19, 2012 (Draft guideline on the risk-based approach according to Annex I, part IV of Directive 2001/83/EC applied to Advanced Therapy Medicinal Products) (hereafter referred to as “EMA Draft Guideline”)⁴⁾.

2. History of notifications issued in Japan and FDA guidance

The FDA notifications on cellular-based products began with the “Application of current statutory authorities to human somatic cell therapy products and gene therapy products” on October 14, 1993, and the FDA has continually revised and appended the recommendations “to reflect our current knowledge gained through advancements in the field and through experience gained through OCTGT’s (Office of Cellular, Tissue, and Gene Therapies) review of CGT (cell and gene therapy) products” (FDA Draft Guidance, Chapter I). Then,

in November 2012, the Center for Biologics Evaluation and Research (CBER)/OCTGT at FDA proposed the “FDA Draft Guidance”, which deals with the range of materials and preclinical information that serve as the basis for conducting clinical trials aimed at application for approval of cell and gene therapies (Table 2). This draft guidance clarified what the FDA expects from the applicant upon Investigational New Drug Application (IND) and Biologic License Application³⁾.

On the other hand, the notifications on cellular-based products in Japan began with “Quality and safety assurance of pharmaceuticals manufactured using human or animal-derived components as raw materials” (Notification of Pharmaceutical and Medical Safety Bureau (PMSB), the Ministry of Health and Welfare (MHLW); No.1314)⁵⁾ on December 26, 2000, followed by: the notification “Guideline for quality and safety assurance of pharmaceuticals and medical devices based on human autologous/allogeneic cells or tissue” (hereafter referred to as “Human (autologous) cells”)⁶⁾ and “Human (allogeneic) cells”)⁷⁾ in 2008; “How to complete the application form for ensuring the quality and safety of pharmaceuticals and medical devices based on processed cells or tissue”⁸⁾ in 2010 (the system of application for verification of pharmaceuticals from processed cells or tissues and pharmaceuticals for gene therapy has been abolished in association with the transfer to the Pharmaceutical Affairs Consultation on R&D Strategies); the notifications on “Guideline on ensuring the quality and safety of human autologous/allogeneic somatic stem cells-derived medical devices or pharmaceuticals” (hereafter referred to as “Human (autologous) somatic stem cells”⁹⁾ and “Human (allogeneic) somatic stem cells”¹⁰⁾ (revised from notifications of “Human (autologous) cells”⁶⁾ and “Human (allogeneic) cells”⁷⁾, respectively), “Guideline on ensuring the quality and safety of

Table 2 Guidance and notifications concerning cell preparations in the United States related to this paper

October 1993	Application of current statutory authorities to human somatic cell therapy products and gene therapy products
May 1996	Guidance on applications for products comprised of living autologous cells manipulated ex vivo and intended for structural repair or reconstruction
January 1997	Guidance for the submission of chemistry, manufacturing, and controls information and establishment description for autologous somatic cell therapy products
March 1998	Guidance for Industry: Guidance for human somatic cell therapy and gene therapy
August 2007	Guidance for Industry: Eligibility determination for donors of human cells, tissues, and cellular and tissue-based products
February 2008	Draft Guidance for Industry: Validation of growth-based rapid microbiological methods for sterility testing of cellular and gene therapy products
April 2008	Guidance for FDA Reviewers and Sponsors: Content and review of Chemistry, Manufacturing, and Control (CMC) information for human somatic cells therapy Investigational New Drug Applications (INDs)
January 2011	Guidance for Industry: Potency tests for cellular and gene therapy products
November 2012	Draft Guidance for Industry: Preclinical assessment of investigational cellular and gene therapy products
July 2013	Draft Guidance for Industry: Considerations for the design of early-phase clinical trials of cellular and gene therapy products

human autologous/allogeneic induced pluripotent stem (-like) cells-derived medical devices or pharmaceuticals (hereafter referred to as “Human (autologous) iPSCs”¹¹⁾ and “Human (allogeneic) iPSCs”¹²⁾, and “Guideline on ensuring the quality and safety of human embryonic stem cells-derived

medical devices or pharmaceuticals (hereafter referred to as “Human ES cells”¹³⁾ on September 7, 2012 (Table 3). Although these notifications do contain chapters describing nonclinical safety tests, most of the chapters are on the manufacture and quality control of cellular-based products. As noti-

Table 3 Laws and notifications concerning regenerative medicine in Japan related to this paper

December 26, 2000	Quality and safety assurance of pharmaceuticals manufactured using human or animal-derived components as raw materials (1314 notification)
February 8 and September 12, 2008	Guidelines for quality and safety assurance of pharmaceuticals and medical devices based on human autologous/allogeneic cells or tissues
April 20, 2010	How to complete the application form for ensuring the quality and safety of pharmaceuticals and medical devices based on cells or tissue (abolished on July 1, 2011 because of shift to the Pharmaceutical Affairs Consultation on R&D Strategies)
September 7, 2012	Guidelines on ensuring the quality and safety of human autologous/allogeneic somatic stem cells-derived medical devices or pharmaceuticals Also guidelines on human autologous/allogeneic iPS (-like) cells, and human ES cells
May 10, 2013	Act on the general promotion of measures to enable people to receive regenerative medicine rapidly and safely
May 24, 2013	Bill on safety assurance of regenerative medicine (under Diet deliberation)

fications leading to the conduct of regulatory science, however, in Japan the description of the preclinical studies that should be conducted before clinical trials and the application for marketing approval is poor in terms of the type of risk factors listed and the details explained, and the notifications are nowhere near the content of “FDA Draft Guidance”.

The regulatory authorities should ask for a strict evaluation based on the highest level of science available at that time. This is the reason why the FDA has prepared “FDA Draft Guidance” and is asking for public comments. It is the national policy of Japan to be a science and technology-oriented nation and medical innovations are the basis on which to enhance this national strength. It is the breadth and depth of basic science that drives the creation of innovations. Innovation cannot be promoted by relaxing regulations. Rather, regulations have been tightened in the U.S./E.U. because they are aiming for the highest level of science. In contrast, against the background of the recent rise in expectations for regenerative medicine using iPSCs, clinical application is being promoted without sufficient risk assessment in Japan. This is clearly inconsistent with worldwide trends in state-of-the-art science.

In this article, we will compare, and discuss the details of the regulations on cellular-based products by FDA, EMA, and Japan based on the FDA Draft Guidance and the EMA Draft Guideline. We demand the abolition of the five notifications including “Human (autologous) iPSCs” and the release of notifications on the preclinical evaluation of cellular-based products in reference to “FDA Draft Guidance.”

3. Summary of “FDA Draft Guidance” on the potential risk of stem cellular-based products

“FDA Draft Guidance” states that “Stem cell-derived products are characterized by a variable capacity for self-renewing replication through cycles of cell division and the capacity for differentiation into a variety of cell types with specialized properties/functions. Such differentiation and replication are primarily controlled by the physiologic milieu of the host in which the cells reside following *in vivo* administration. Similarly, contamination of a differentiated CT (cell therapy) product with undifferentiated stem cells or incompletely differentiated progenitor/precursor cells poses potential safety concerns,” (FDA Draft Guidance, Chapter IV.A.1) and points out that “Conditions found within the local microenvironment into which the cells are placed are likely to have an impact on the safety and/or bioactivity of the CT product. Given the biological attributes of some CT products, the potential for ectopic expression in target and non-target tissues also exists. Depending on their differentiation status and the extent of manipulation the cells undergo prior to *in vivo* administration, parameters such as cell morphology, phenotype, and level of differentiation following *in vivo* administration should be assessed in the animal studies” (FDA Draft Guidance, Chapter IV.E.3). In addition, “FDA Draft Guidance” states that functionally differentiated tissue-derived CT products “may retain some cellular characteristics of their tissue of origin. Additionally, their characteristics may change after *in vivo* administration, based on numerous specific extracellular cues.” (FDA Draft Guidance, Chapter IV.A.2) Based on these perspectives, “FDA Draft Guidance” refers to the risk factors of cellular-based products: 1. Administration

site reactions, 2. Potential inflammatory response in target and/or non-target tissues, 3. Host immune response to the cells, 4. Migration from the site of administration, 5. Potential to differentiate into an unintended/inappropriate cell type (ectopic tissue formation), 6. Unregulated/dysregulated proliferation of the cells within the host, and 7. Potential tumorigenicity. Furthermore, in the case of using *ex vivo* transduced cells or vectors, as it should be addressed before beginning clinical trial, aberrant localization to non-target cells/tissues, inappropriate immune activation or suppression, Phenotype/activation state of target cell(s), and potential for germline transmission (FDA Draft Guidance, Chapter IV.D, V.D.1).

In conclusion, “FDA Draft Guidance” states “the adequacy of any specific preclinical study or program will depend on the specific study design, subsequent implementation, and on the resulting data. Accordingly, it is important to submit a comprehensive preclinical assessment in the IND.” (FDA Draft Guidance, Chapter VII)

4. “EMA Draft Guideline” advancing “Risk-based approach”

In the “EMA Draft Guideline”⁴⁾, “Risk-based approach” is defined as a strategy aiming to determine the extent of quality, nonclinical and clinical data to be included in the Marketing Authorisation Application, in accordance with the scientific guidelines relating to the quality, safety and efficacy of medicinal products and to justify any deviation from the technical requirements as defined in Annex I, part IV of Directive 2001/83/EC¹⁴⁾. In addition, “EMA draft guideline” said that “It is important to appreciate that the risk-based approach profiles each risk inherent to the product and not the risk of a product as whole.”

The methodology of risk profiling is follows

(EMA Draft Guideline, Section4.3).

1st step: To identify risks associated with the clinical use of the Advanced Therapy Medicinal Product (ATMP)

2nd step: To identify product specific risk factors contributing to each identified risk

3rd step: To map the relevant data for each identified risk factors against each of the identified risks

4th step: To conclude on the risk factor – risk relationships (EMA Draft Guideline, Chapter 4.3)

The guideline addresses risk-based approaches to ATMPs from a broad perspective and meticulously illustrating by examples for matrices associated between risk factors and risks of ATMPs such as tumor formation, unwanted immunogenicity, treatment failure, disease transmission, unwanted tissue formation, unintended alteration of therapeutic gene expression, unintended alteration of cell homeostasis, unwanted targeting of cells/organs, and toxicity (EMA Draft Guideline, Chapter 4.2, Annex 1-3).

5. Avoidance of responsibility in the iPSCs notifications in Japan

The chapter entitled “Nonclinical safety tests” in both of the “Human (autologous) iPSCs” and “Human (allogeneic) iPSCs” notifications in Japan states that “Regarding the safety-related matters whose evaluation is considered necessary because of the product characteristics and application method, tests should be conducted within scientific rationality if technically possible” and encourages the assessment of the potential risk of iPSCs-based products. It also states that “If there is a possibility of tumorigenesis and carcinogenesis, the validity and rationality of the use should be explained taking the relevance to the expected efficacy into

consideration” (Chapter 4-6) and “Regarding the patients’ risk due to the tumorigenicity of the end product, evaluation should be conducted in a reasonable manner taking into consideration the balance with the benefits for the patient of treating the target diseases” (Chapter 4-6). In addition, it is described in “Introduction 2” that “It is important to evaluate the product taking into consideration the degree of risks of the ‘unknown risks’ that still remain after the product’s anticipated risks have been excluded using all current scientific and technological means and the scientific validity has been made clear, and the ‘Risks that may be posed by losing the chance of a new treatment’ in a patient who has a serious and life-threatening disease, a disease that significantly impairs bodily function, or a disease that significantly impairs QOL by compromising bodily function and morphology to a certain degree, but who cannot overcome the disease because of the limitations of existing therapies, and having the perspective of leaving the decision to the patient’s right of self-determination after all this information has been disclosed; i.e. it is important to evaluate the product after disclosure of the information on the risks and expected benefits and from the perspective that patients should decide whether or not to participate in a clinical trial.”

Notifications of “Human (autologous) iPSCs” and “Human (allogeneic) iPSCs” in 2012 state that the risks of using cell products could be relativized to the benefits and, after this has been explained, the decision is left to the patient’s right of self-determination. That is to say that the strict scientific assessment required for the minimization of risks was abandoned and the responsibility of risk assessment seems to be shifted to physicians and patients.

It is obvious that physicians have responsibilities to assess and predict the adverse events affecting

physical and mental status of patients caused by medical intervention. Obtaining informed consent cannot be exempted of this responsibility. It is the consensus of medical jurisprudence that informed consent of the patient should not be regarded as the waiver of liability from the possibly-illegal experimental intervention of which efficacy and safety have not been established. These notifications are, so to speak, a shift of responsibility from regulatory authorities to physician-patient relationship. On the other hand, the FDA plays a social responsibility by practicing faithfully conducts of regulatory science.

6. Logical and ethical problems in the notifications of Japan

iPSCs are typically derived by reprogramming of somatic cells and are these new type of stem cells are different from natural stem cells. Extreme care including an assessment of safety is required for their clinical application. We regard it critically dangerous that Japanese researchers are going to initiate clinical research without preparing sufficient nonclinical data for risk assessment to justify their administration of iPSCs-based products to human. The researchers seem to watch the balance between the risks of these products which “possibly causes tumorigenesis and carcinogenesis to the patients” and the “risks of patients who may lose the chance of access to a new treatment” and seem to leave the decision to the patient’s right of self-determination after explanation of the risk of the products. This kind of thought contravenes the spirit of the Declaration of Helsinki, which requires the “special protection of vulnerable groups” in the 2013 revision draft¹⁵⁾. Such a thought also contradicts the Medical Care Law requesting delivery of “qualified and appropriate” medicine. The researchers say about the chance of

patients to access a “new” treatment, however, the “new” treatment itself may pose an unexpected risk to the patients. It could not be achieved until evaluation by clinical trials has been completed that the chance of “new” treatment becomes the chance of “useful” treatment: the chance of a “new” treatment cannot be replaced with the chance of a “useful” treatment. If a patient does not receive a “new treatment” with an unknown risk, the patient will just follow the natural course. We must say that it goes against logic to balance the natural course against risks such as “possible tumorigenesis and carcinogenesis.”

“Therapeutic misconception” (physicians’ misconception that treatment will always be adequate) is a well-known concept in bioethical discussion but, in Japan, it is the regulatory authorities that are promoting this misconception. The 2013 draft revision of the Declaration of Helsinki¹⁵⁾ included a new provision stating that risk minimization and monitoring are the ethical duty of medical researchers. Moreover, the previous declaration had approved the use of unproven therapy for rescuing severe patients provided that a research plan was subsequently prepared, but in the present draft revision the request to prepare a research plan following use in one patient is stressed. Although the declaration is the ethical norm for individual physicians, approval by the government of the repeated conduct of an unapproved method would clearly contradict international ethical standards.

7. The physical risks of systemic administration

The chapter entitled “*In vivo* kinetics” in the “Human (autologous) iPSCs” and “Human (allogeneic) iPSCs” notifications states that “local administration is preferred to systemic administration” (Chapter 6-2) and “systemic administration can be

included as a usage if it can be reasonably explained that systemic administration is beneficial to treated patients in terms of efficacy. For example, taking measures to minimization of the distribution to places other than the organ to which engraftment is expected is assumed to be a reasonable method. Furthermore, even if ectopic engraftment occurs, the usage may be acceptable provided that no disadvantage (adverse effect on vital functions) to treated patients emerges. Bone formation of the relevant cells after ectopic engraftment in the heart and initiation of arrhythmia are assumed to be examples of the disadvantages of ectopic differentiation” (Chapter 6-2).

This chapter indicates that a usage in which ectopic engraftment occurs by systemic administration may be acceptable if disadvantages such as arrhythmia to treated patients do not emerge. However, this is an issue that cannot be discussed without presentation of the evidence supporting the usage even though systemic administration clearly results in ectopic engraftment at unexpected site. Even though it is not easy to determine whether or not an ectopic engraftment is disadvantageous to treated patients, their benefit/risk balance is determined by physicians, who perform the medical procedures, leading to the possibility that they will make self-righteous decisions. How in the world can physicians and patients determine the unknown risks? At present, there is no official guideline for the evaluation of tumorigenesis related to CT products and their derived cells. Under these circumstances, the first priority should be the patient’s safety and ectopic engraftment should not be permitted. This is the duty of those who take medical practices.

8. Defects of approach in the notification about the iPSCs in Japan

The FDA Draft Guidance and EMA Draft Guideline starts with the characteristics of cellular-based products and shows the points of attention for the evaluation of pre-clinical studies taking into account the risks inherent in such products. In contrast, the “Human (autologous) iPSCs” and “Human (allogeneic) iPSCs” notifications in Japan focus exclusively on efficacy regarding the evaluation of the data of nonclinical studies and toxicity is evaluated only from the viewpoint of efficacy.

On the other hand, the FDA Draft Guidance and EMA Draft Guideline have detected and identified as many risk factors as possible and have had thorough discussion based on strict evaluation. Application of novel or unknown treatments in humans requires careful investigation using a risk-based approach. Data required for the marketing approval should not be thoughtlessly collected, but necessary data concerning the inherent risks of each cellular-based product should be collected. This is a thoroughly risk-based approach, which is essentially different from the method of benefit/risk assessment. One needs to be cautious when using the latter method because one may lose the essence of the issue.

By the way, the approach to thinking about toxicity relative to efficacy in the “nonclinical safety test” (Chapter 4-6) and the approach to ectopic engraftment in “*in vivo* kinetics” (Chapter 6-2) in the “Human (autologous) iPSCs” and “Human (allogeneic) iPSCs” notifications were absent in the “1314 notification” in 2000, “Human (autologous) cells” and “Human (allogeneic) cells” notifications in 2008. Those were described for the first time in the five notifications in 2012, such as the “Human

(autologous) iPSCs” notification.

In these five notifications, it is described in the same content in common to chapters of “Nonclinical safety tests” and “*In vivo* kinetics”. The first place, is not to be described in the same content, the notifications of “Human (autologous) cells” and “Human (autologous) iPSCs”, but should be discussed in difference position.

It is evident that these notifications are not written from the perspective of a risk-based approach that asks for strict evaluation of each cellular-based product.

Cellular-based products are totally novel and much about them is still unknown, but the current science is immature. Therefore, in terms of methodology, a risk-based approach should be adopted, making full use of all current scientific knowledge, and the guidelines/notifications for cellular-based products should recommend/make obligatory careful evaluation based on the risks inherent in using cells.

9. The future of regulatory science in Japan

Considering that cell phenotype can change just as a result of passage culture whether temporarily or persistently a gene is transfected to the cell, the guidelines for iPSCs in Japan clearly lack the multifaceted approach of practical risk evaluation like that in the FDA Draft Guidance and EMA Draft Guideline because of an overexpectation of the efficacy of iPSCs. We cannot help having legitimate questions and profound concerns on this issue. With respect to the methodology for the regulatory science of cellular-based products, the only alternative should be detecting/identifying risk factors inherent in the relevant cellular-based products and solving the issues one by one from the standpoint of a risk-based approach as performed by

FDA Draft Guidance and EMA Draft Guideline.

Regarding the issue of tumorigenicity, because “There is currently no scientific consensus regarding the selection of the most relevant animal models to evaluate tumorigenic potential or the ability of current animal models to predict clinical outcome” (FDA Draft Guidance, Chapter IV.E.4), the evaluation should be conducted even more carefully. “FDA Draft Guidance” points out that, especially when associated with gene transfer, “Prolonged expression of transgenes such as growth factors, growth factor receptors, or immunomodulatory agents, may be associated with long-term risks due to unregulated cell growth, malignant transformation, autoimmune reactions to self-antigens, altered expression of the host’s genes, or other unanticipated adverse effects. The conduct of long-term preclinical studies should be considered to evaluate these concerns” (FDA Draft Guidance, Chapter V.D.3).

10. Tumorigenicity and long-term toxicity tests

The “FDA Draft Guidance” states that there is currently no scientific consensus regarding the most relevant animal models to evaluate the tumorigenic potential of CT products (FDA Draft Guidance, Chapter IV.E.4). However, it also states that prolonged expression of transgenes may be associated with long-term risks, and thus the conduct of long-term preclinical studies should be considered to evaluate these concerns (FDA Draft Guidance, Chapter V.D.3).

On the other hand, the “Human (autologous) iPSCs” and “Human (allogeneic) iPSCs” notifications state that the possibility of tumorigenesis and carcinogenesis should be assessed and discussed using appropriate animal models and that “If it is possible for tumorigenesis and carcinogenesis to

occur, the validity and rationality of the use should be explained taking the relevance to the expected efficacy into consideration” (Chapter 4-6). Here also, the discussion on toxicity is replaced with that on efficacy, and the faithful pursuit of regulatory science is abandoned. If tumorigenesis or carcinogenesis is a possibility, clinical trials using such products should be abandoned and it is improper to discuss a benefit/risk relationship with reference to efficacy. If a possibility of tumorigenesis or carcinogenesis arises in a nonclinical study, the regulatory authorities should at least ask for submission of data that can disprove carcinogenesis, with a valid test system and a highly reliable method such as GLP (Good Laboratory Practice), and evaluate the data; we believe that this is proper conduct of regulatory science and the duty of regulatory authorities.

With respect to this concern, the February 28, 2013 issue (Vol. 494) of *Nature*¹⁶⁾ cited a comment by the chief scientific officer at Advanced Cell Technology, “I cannot imagine any regulatory agency permitting such a trial without years of extensive pre-clinical testing,” regarding the start of a clinical trial on Takahashi’s iPS.

11. Serious problems of the Bill on safety assurance of regenerative medicine in Japan

As is evident from the difference in the regulations for cellular-based products in the U.S./E.U. and Japan, we are bound to say that the safety-related items in the notifications on the development of cellular-based products in Japan are extremely sloppy compared with those in the U.S./E.U.. Furthermore, the “Act on the general promotion of measures to enable people to receive regenerative medicine rapidly and safely” was promulgated on May 10, 2013 in Japan and the “Bill on

ensuring the safety of regenerative medicine” was submitted to the Diet on May 24, aiming to ease regulations in order to create innovations in the field of regenerative medicine. We have addressed many serious concerns about these subjects¹⁷⁾.

We must venture to question the abnormality in Japan that the first-in-human study is approved to be conducted as a “clinical study” exempt from the PAL. “In Focus” in the February 28, 2013 issue (Vol. 494) of *Nature* also mentioned that the clinical trial of Takahashi’s iPSCs is a clinical trial that, in “Japan’s somewhat confusing system,” cannot be used for the application for approval¹⁶⁾. If attention be paid to human ethics, the results of non-clinical safety tests should be finalized based on a risk-based approach under the PAL and a clinical trial based on GCP (Good Clinical Practice) should be conducted. The problem lies with the fact that a “clinical trial” exempt from the PAL is possible.

12. Origin and development of regulatory science

When human beings utilize science as technology, it often happens that a technological defect brings about an adverse effect. To minimize this risk, the advantages and disadvantages of the relevant technology need to be fully evaluated in advance. Regulatory science has the duty to control by laws and regulations the use and spread of such technology.

The origin of regulatory science goes back to the Kefauver-Harris Drug Amendments in the U.S. in 1962. These amendments stated explicitly the legal framework of modern regulatory science, such as safety assurance/premarket proof of efficacy of pharmaceuticals, report of GMP (Good Manufacturing Practice) and adverse reactions, and informed consent. At that time, the movement to protect consumer rights had become strong in the

U.S., leading to the proposal of consumer rights (the right to safety, the right to be informed, the right to be heard, and the right to choose) by President John F. Kennedy. Human society started down the path toward patient-based medicine by adopting these rights for patients who receive medical treatment. A year later, the GMP regulation, IND regulation, and regulations on monitoring pharmaceuticals came into effect, and this can be interpreted as the completion of the organization of the implementation system for regulatory science that we now use in the modern world. In Japan, the Ministry of Health & Welfare enforced the former GCP in 1990, and the new GCP ordinance based on the ICH-GCP, the global standard, was enforced completely eight years later in 1998, 36 years behind the U.S. Finally, medical administration based on scientific evidence had gone into action.

Moreover, in response to the Creutzfeldt-Jakob disease and HIV- contaminated blood scandals in the 1990’s, the laws and regulations on the engraftment and formulation of human-derived cells and tissues were enacted rapidly in the U.S./E.U. and so on in the early 21st century. In Japan, the “1314 notification,”⁵⁾ in which consent requirements were included with a focus on manufacturing control exclusively for cases with the purpose of application for marketing approval, was released and the subsequent regulations were introduced based on this notification. The direction on human tissues and cells in the E.U.¹⁸⁾ and the regulations on the human cellular and tissue-based products in the U.S.^{19,20)} have comprehensively organized a system for registration and inspection of the bank and manufacturing sites of human tissues and cells, whether or not they are intended for application for approval, from the perspective firstly of the response to the ethical issues of using the human body commercially as a resource and secondly of safety assurance in clinical application. By these

regulations, the system for securing traceability was established while ensuring protection for donors of human materials. The guidance for cellular-based products by the FDA and EMA, which was organized under the comprehensive regulatory system that segments and integrates issues specific to each cellular and tissue-based product and highly processed product, is a result of in-depth assessments of not only manufacturing control but also preclinical safety tests specific to cellular-based products. In particular, the FDA guidance^{3, 21)} is based on the concept of collecting additive preclinical data while monitoring clinical reactions and searching thoroughly for information both on safety and the characteristics of products, and shapes the basis of the life cycle management after marketing approval. In Japan, corporate toxicologists have trained themselves to comply with ICH-M3²²⁾ and S6²³⁾ purely from the viewpoint of what safety data are required in each step toward the marketing approval of chemically-synthesized products, but the clinical trials on human stem cells and gene therapy have been placed outside the regulation of pharmaceutical affairs and have been regulated by administrative guidelines. Accordingly, we have failed to create an environment in which knowledge of the biochemistry, pharmacology, toxicology, pharmacokinetics, pharmaceuticals, and analytical science of human cellular-based products is accumulated and integrated at regulatory agencies and academia. The bill on safety assurance of regenerative medicine and iPSCs notifications make very apparent the situation in Japan whereby researchers have been getting ahead of themselves by going with the clinical application of iPSCs without filling in these gaps between itself and the U.S./E.U.

Regulatory science has the characteristic of having a direct stake in business activity. Therefore, regulatory science is a type of science that calls for the highest level of strictness guided by one's

conscience and humanity possible at any given time and the strictness must be controlled and assured by laws. Despite this, the leading of regulations in the easy direction, with the aim of promoting innovations in health and safety in people's lives and the environment may lead to a collapse of science. Regulatory science can be properly implemented only by means of laws and regulations. This is because current science is intrinsically immature, and thus the highest level of quality demanded by modern society needs to be pursued thoroughly and continuously for technical development. Delivering patients a product for which the quality control and the reliability of the efficacy and safety data cannot be assured can by no means be regarded as medicine. Such behavior is inhuman and non-scientific. Patients of course do not want to be provided with "medicine" that does not assure efficacy and safety, and we strongly make an accusation that medical ethics is totally ignored in such "medicine."

13. Conclusion

To be a science and technology-oriented nation is the national policy of Japan and medical innovations are the basis for enhancing this national strength. As a measure to create innovations in the regenerative medicine field, a bill on safety assurance of regenerative medicine was submitted to the Diet in May 2013. We can appreciate the points that all regenerative medicines including medical treatment at one's own expense must be notified and that the violation of regulations and directions is subject to penalties such as imprisonment and punishment depending on the details. However, the fact is that the bill not only permits the conduct of regenerative medicine exempt from the PAL but also enables marketing of unapproved regenerative products after neatly shifting the responsibility to

physicians by legally defining the delivery of regenerative medicine as a part of medical practice¹⁹⁾. It is naive to think that innovations will be promoted by easing regulations. The basis of the creation of innovation is the power of science, and the U.S./E.U. has recently strengthened the regulations for regenerative medicine just because they are seeking for stronger and more precise science.

The principle of science in the modern world is to “conduct science by statute and revise statute by the progress of science.” It is stated in the preface of the PAL that “the aim is to improve health and hygiene by implementing necessary regulations to assure the quality, efficacy and safety of pharmaceuticals, quasi-drugs products, cosmetics, and medical devices and by taking measures for the regulation of designated drugs as well as by taking necessary measures to promote the research and development of pharmaceuticals and medical devices that are in particular clinical need. In disregard of this law, the efficacy and safety of pharmaceuticals and medical devices cannot be evaluated, and much less can reliability of them be assured. Development of pharmaceuticals exempt from the PAL, which is harmonized internationally, can hardly be accepted by the world. Therefore, the “Human (autologous) iPSCs” and “Human (allogeneic) iPSCs” notifications and the bill on regenerative medicine under Diet deliberation only inhibit the creation of innovation, in contrast to the initial purpose.

With reference to the start of a clinical trial using Takahashi’s iPSC, the February 28, 2013 issue (Vol. 494) of *Nature*¹⁶⁾ cited a comment on the insufficient regulations in Japan by the chief scientific officer of Advanced Cell Technology, “I cannot imagine any regulatory agency permitting such a trial without years of extensive pre-clinical testing”. To be singled out like this by *Nature* is nothing but a disgrace for the commonwealth of science in Japan. The review committee for clinical researcher

using human stem cells in Japan, which gave the green light for iPSCs clinical trials, bears grave responsibility. To begin with, considering that such a “clinical trial” is exempt from the PAL and is based on the “Guidelines for clinical researches using human stem cells,”²⁴⁾ which has little legal basis, the problem lies in the fact that the review committee is referred to as a regulatory authority.

Now that we should be aware that we already have been severely criticized from international community of science, we are obligated to accept the fact that as a matter-of-course we should develop not only iPSCs but also all stem cellular-based products, under the framework of PAL, with rigorous quality assurance and strict assessment of safety and efficacy.

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