厚生労働省科学研究費補助金

医薬品・医療機器等レギュラトリーサイエンス総合研究事業

再生医療実用化加速に資するヒト幹細胞由来製品及び関連要素の品質及び安全性確保に関する総合的研究

平成 25 年度　総括・分担研究報告書

研究代表者　早　川　堯　夫

平成 26(2014)年 3 月

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目次

Ⅰ．　総合研究報告

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早　川　堯　夫

厚生労働科学研究費補助金　（厚生労働科学特別研究事業）

平成25年度総括研究報告書
再生医療実用化加速に資するヒト幹細胞由来製品及び関連要素の品質及び安全性確保に関する総合的研究

主任研究者　早川　堯夫　近畿大学薬学総合研究所所長

細胞・組織加工医薬品等による再生医療の実用化を望む声がますます強くなっている。基礎から臨床への効率的、効果的、合理的な実用化の為に必要な技術的要件や方策を出口である行政側が開発早期から示すことは、研究者、開発企業、規制側いずれにも有用であり、再生医療を国民のために円滑かつ迅速に提供するための必須要件である。

本研究は、わが国の再生医療実用化を推進するための適正な規制環境を世界に先駆けて整備し、国民の保健・医療の向上に資するとともに、当該分野の国際的優位性の確保を目差す行政施策活動の一環として位置づけられる。

本研究班は、平成20年に発出した「ヒト由来（自己及び同種）細胞・組織加工医薬品等の品質及び安全性の確保に関する指針」と題する２つの基本的行政通知をベースにヒト幹細胞に特化した留意事項を明示するべく着手していた「ヒト自己及び同種体性幹細胞、ヒト自己及び同種iPS細胞、並びにES細胞加工医薬品等の品質及び安全性の確保」に関する５つの指針案の充実、完成、施行及び解釈・運用の円滑化並びに国際社会への情報発信を目的に、平成23-25年度の間、研究を実施した。

まず、23年度には、ヒト幹細胞由来製品の品質・安全性確保指針通知のための最終原案を作成するために、学問・技術の進捗、海外の動向、幹細胞由来製品の実用化に関する国内での議論などをもとに調査・研究し、その成果を公表した。①ヒト幹細胞加工医薬品等の品質・安全性確保に関する指針整備と主なポイント（再生医療10巻(2011) 86-90頁）、② ヒト（自己）体性幹細胞加工医薬品等における総則、原材料及び製造関連物質、製造工程に関する留意事項（同誌、91-98頁）、③ ヒト（同種）体性幹細胞（同誌、99-106頁）、④ ヒト（自己）iPS（様）細胞（同誌、107-117頁）、⑤ヒト（同種）iPS（様）細胞（同誌、118-128頁）、⑥ヒトES細胞（同誌、129-140頁）、⑦最終製品の品質管理（同誌、141-146頁）、⑧非臨床試験及び臨床試験（同誌、147-152頁）。

平成24年度は、上記成果を行政通知化し、またパブコメ対応やQ&A事案を同定することによる施行及び解釈・運用の円滑化を図るため、行政当局との意見交換をはじめ、必要な科学的検討を行った。その結果、平成24年9月7日付けで、ヒト自己及び同種体性幹細胞、ヒト自己及び同種iPS（様）細胞、ES細胞加工医薬品等の品質及び安全性の確保に関する５つの指針通知（薬食発0907第2号,薬食発0907第3号、薬食発0907第4号、薬食発0907第5号、薬食発0907第6号）が発出された。

24年度から25年度にかけては、国際社会への情報発信について注力し、第11回日本再生医療学会国際規制WS(2012年6月)、第3回国際組織再生工学・再生医療会議（2012年9月）、世界幹細胞サミット2012（2012年12月）、第11回国際幹細胞学会（2013年6月)、第1回国際生物製剤標準化連盟（IABS）・JST国際シンポジウム（2014年3月）において、５指針の概要を発表するとともに、米国FDA、EU、カナダ、韓国、タイその他の規制担当者、各国の研究者、企業関係者等と意見交換を行った。また、研究の経過や背景及び５指針全文の英文版を作成し、国際社会に発表すべく日本再生医療学会の英文誌Regenerative Therapyに投稿した。さらに、5指針の普及に加えて製品の開発や評価をケース・バイ・ケースの原則に従い効率

的、効果的、合理的に促進させるために必要な、製品の由来、種類、対象疾患、開発段階等を踏まえた適切なアプローチをしていくベースとなる共通基本要件、基準に関する考え方の必要性や、わが国が独自のシーズの実用化を世界に先駆けて促進するため、新規の細胞基材や製造関連資材、製造方法等に対して活用できる規制環境とその整備についても検討、考察した。

なお、平成25年11月にいわゆる改正薬事法（医薬品医療機器法）と再生医療安全性確保法（再生医療新法）が国会で成立し、その施行に向け、関連政省令等の整備が進められている。今後、ヒト幹細胞加工製品をとりまく規制的取り扱いは、それに伴って変わってくるところもあると考えられる。しかし、法律や関連政省令等の正式施行はこれからであり、また、技術的要件等の本質は基本的に変わることはないと考えられるので、本報告書は過渡的状況であることをふまえつつも従来の枠組みの中での記述とする。

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A. 研究目的

細胞・組織加工医薬品等による再生医療は、ヒトの臓器や組織の確保が難しいわが国の医療状況下において強く期待されており、研究の進歩に伴う技術的な実現可能性の高まりとともに、医療としての実用化を望む声がますます強くなっている。基礎から臨床への効率的、効果的、合理的な実用化の為に必要な技術的要件や方策を出口である行政側が開発早期から示すことは、研究者、開発企業、規制側いずれにも有用であり、再生医療を国民のために円滑かつ迅速に提供するための必須要件である。

このような背景や総合科学技術会議等からの要請を受け、平成18・19年度の厚生労働科学研究事業でわが国の再生医療を適正な規制のもと推進するため、急速に発展する学問・技術、倫理上の観点、国際的動向等を反映した安全性評価基準の作成など規制のあり方について検討し、平成20年に「ヒト由来（自己及び同種）細胞・組織加工医薬品等の品質及び安全性の確保に関する指針」と題する２つの基本的行政通知の発出に至った。平成20-22年度の厚生労働科学研究事業では、特にヒト幹細胞に着目し、先述の基本的２通知をもとに、「ヒト自己及び同種体性幹細胞、ヒト自己及び同種iPS細胞、並びにES細胞加工医薬品等の品質及び安全性の確保」に関する５つの指針案の作成に着手、中間報告案を学術誌に公表した。（再生医療，9, 116-180, 2010）。

平成23-25年度の研究では、まず上記５指針案を行政的に通知し、その円滑な施行に資すること及び情報の国際発信をすることを目差し、そのために必要不可欠な学術面からみたさらなる充実、適正な解釈・運用のための検討及びパブコメ対応、Q/A事案の同定、英文版作成等を行うことを目的とする。また、上記の基本的な指針に加えて、製品の開発や評価をケース・バイ・ケースの原則に従い、効率的、効果的、合理的に促進させるために必要な、製品の由来や種類、対象疾患、開発段階等を踏まえた適切なアプローチをしていくベースとなる共通基本要件、評価基準に関する考え方の必要性に関する研究を目的とする。さらに、わが国が独自のシーズの実用化を世界に先駆けて促進するための必須要件である、新規細胞基材、新規製造関連資材、新規製造方法、新規適用法に対して活用できる規制環境と整備に関する研究を目的とする。

なお、平成25年11月にいわゆる改正薬事法（医薬品医療機器法）と再生医療安全性確保法（再生医療新法）が国会で成立し、その施行に向け、関連政省令等の整備が進められている。今後、ヒト幹細胞加工製品をとりまく規制的取り扱いは、それに伴って変わってくるところもあると考えられる。しかし、法律や関連政省令等の正式施行はこれからであり、また、技術的要件等の本質は基本的に変わることはないと考えられるので、本研究では過渡的状況であることをふまえつつも従来の枠組みの中での規制環境や情報をもとにした検討を目的とした。

B. 研究方法

わが国の再生医療を適正な規制のもと推進していくために平成18・19年度の厚生労働科学研究事業で急速に発展する学問・技術、倫理上の観点、国際的動向等を反映した安全性評価基準の作成など規制のあり方について検討し、通知の改定案を作成した。この案を基に、平成20年２月に「ヒト（自己）由来細胞・組織加工医薬品等の品質及び安全性の確保に関する指針（薬食発第0208003号）」及び平成20年９月に「ヒト（同種）由来細胞・組織加工医薬品等の品質及び安全性の確保に関する指針（薬食発第0912006 号）」がそれぞれ通知された。これらの改定案は治療に使用される細胞・組織加工医薬品等全般に関するものである。ヒト間葉系幹細胞、ヒト iPS細胞等のヒト幹細胞をより早期に実用

化するためには、これらに特化した留意事項についてさらに深く検討する必要がある。そのため、平成20年度の研究結果から、ヒト間葉系幹細胞等を中心とする体性幹細胞、iPS細胞、ES細胞などに由来する製品の薬事法下での臨床応用に向けて、研究・開発、確認申請、評価等を効率的、効果的、合理的に行う上で、必要と思われる技術、製造方法、特性解析方法、品質管理方法及び安定性評価に関する具体的留意事項、並びに安全性及び有効性に関する各種データとしてどのようなものがあるかに関しては、これらの３種類の原料細胞それぞれに特化した形でまとめる方向性が打ち出された。

この方向性と科学的原則の一貫性という観点から、平成21年度および22年度は、平成20年に通知されたヒト自己由来細胞・組織加工医薬品等全般に関する指針「ヒト（自己）由来細胞・組織加工医薬品等の品質及び安全性の確保に関する指針（薬食発第0208003号）」をベースとして、さらに、学問/技術の進歩、欧米の規制担当者や国内外の研究者への聞き取りなども含めて深く掘り下げて調査・研究し、①ヒト（自己）体性幹細胞及び②ヒト（自己）iPS細胞加工医薬品等の品質及び安全性の確保に関するそれぞれの指針案（中間報告）を作成した。また、平成20年9月に通知されたヒト同種由来細胞・組織加工医薬品等全般に関する指針「ヒト（同種）由来細胞・組織加工医薬品等の品質及び安全性の確保に関する指針（薬食発第0912006号）」をベースとして、③ヒト（同種）体性幹細胞、④ヒトES細胞、⑤ヒト（同種）iPS細胞に関するそれぞれの指針案（中間報告）を作成した。これらは学術誌に公表（再生医療，9,116-180，2010）した。本研究における23年度では、まず上記５指針案の完成に向けて、その後の当該分野の進捗、国内外での情報収集と議論をもとに、検討を重ね、以下の論文を公表し広く世にコメントを求めた。①ヒト幹細胞加工医薬品等の品質・安全性確保に関する指針整備と主なポイント（再生医療10巻(2011) 86-90頁）、②ヒト（自己）体性幹細胞加工医薬品等における総則、原材料及び製造関連物質、製造工程に関する留意事項（同誌、91-98頁）、③ ヒト（同種）体性幹細胞（同誌、99-106頁）、④ ヒト（自己）iPS（様）細胞（同誌、107-117頁）、⑤ヒト（同種）iPS（様）細胞（同誌、118-128頁）、⑥ヒトES細胞（同誌、129-140頁）、⑦最終製品の品質管理（同誌、141-146頁）、⑧非臨床試験及び臨床試験（同誌、147-152頁）。平成24年度は、上記成果を行政通知化し、またパブコメ対応やQ&A事案を同定することによる施行及び解釈・運用の円滑化を図るため、行政当局との意見交換をはじめ、必要な科学的検討を行った。その結果、平成24年9月7日付けで、ヒト自己及び同種体性幹細胞、ヒト自己及び同種iPS(様)細胞、ES細胞加工医薬品等の品質及び安全性の確保に関する５つの指針通知（薬食発0907第2号，薬食発0907第3号、薬食発0907第4号、薬食発0907第5号、薬食発0907第6号）が発出された。

24年度から25年度にかけては、５指針の円滑な施行に資すこと及び情報を国際発信することを目差し、それに必要不可欠な学術面からみた適正な解釈・運用のための検討及びパブコメ対応、Q/A事案の同定、国際学会での発表、英文版作成等を進める。また、5指針の普及に加えて製品の開発や評価をケース・バイ・ケースの原則に従い効率的、効果的、合理的に促進させるために必要な、製品の由来、種類、対象疾患、開発段階等を踏まえた適切なアプローチをしていくベースとなる共通基本要件、基準に関する考え方の必要性や、わが国が独自のシーズの実用化を世界に先駆けて促進するため、新規の細胞基材や製造関連資材、製造方法等に対して活用できる規制環境とその整備についても検討、考察する。

なお、平成25年11月にいわゆる改正

薬事法（医薬品医療機器法）と再生医療安全性確保法（再生医療新法）が国会で成立し、その施行に向け、関連政省令等の整備が進められている。今後、ヒト幹細胞加工製品をとりまく規制的取り扱いは、それに伴って変わってくるところもあると考えられる。しかし、法律や関連政省令等の正式施行はこれからであり、また、技術的要件等の本質は基本的に変わることはないと考えられるので、本研究では過渡的状況であることをふまえつつも一般には従来の枠組みの中での規制環境や情報をもとにした検討方法によっている。

C. 研究結果

C.1 国際社会への情報発信

国際社会への情報発信については、わが国が行おうとしている施策や考え方について、日本語を読解できない国際社会に情報発信しようとしている趣旨をふまえて、日本語を逐語訳するのではなく、内容やその背景としているコンセプトなどが最も理解しやすいような表現形式をとることとした。すなわち、日本語ですら解釈が分かれる事項や表記にかかわるパブコメ回答やQ/Aの対象となった箇所には、日本版を少し離れてもより正確な理解に繋がるような英語表記や解説を心がけた。正式文書はあくまで日本語での通知であることを前提とした上でかつ、英文版は正式通知の翻訳版では必ずしもなくとも、通知の概念、内容、趣旨を可能な限り正確に英語で伝えることを目的に、それ自体独立したものとして完成度を高めた。その結果を関連する国際学会や英文誌で公表した。

C.12.1 国際学会等での発表

24年度では第11回日本再生医療学会国際規制WS(2012年6月)、第3回国際組織再生工学・再生医療会議（2012年9月）及び世界幹細胞サミット2012（2012年12月）において５指針案の概要を発表したが、25年度では、第11回国際幹細胞学会（2013年6月）、第1回国際生物製剤標準化連盟（IABS）・JST国際シンポジウム（2014年3月）において、５指針の概要を発表するとともに、米国FDA、EU、カナダ、韓国、タイその他の規制担当者、各国の研究者、企業関係者等と意見交換を行った。

C.1.2 英文版作成

５指針の発出を受けて、５指針に至る研究の経緯と視点及び５指針全文の英文版を作成し、国際社会に発表すべく日本再生医療学会の英文誌Regenerative Therapyに投稿した。５指針を通して、共通の記述内容の部分はなるべく表記を統一するよう心がけたが、特に定義の部分については、英語的に同一である必要があり、統一した

以下に、投稿原稿を示す。

C.1.3 ヒト（自己）体性幹細胞加工医薬品等の品質及び安全性の確保についての研究の経緯と視点及びガイドライン英文版

Study on Ensuring the Quality and Safety of Pharmaceuticals and Medical Devices Derived from the Processing of Autologous Human Somatic Stem Cells

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Background (Chronology and Focus of the Study)

Development of regenerative medicine using cell-based products derived from the processing of human cells and tissues is keenly anticipated in Japan because of difficulties in securing human organs and tissues in our country. With technology breakthroughs and research advances, people are increasingly hopeful that medical technology using novel cell-based products will develop into therapies.

In a meeting of the Council for Science and Technology Policy held in November 2007, opinions were exchanged regarding induced pluripotent stem (iPS) cells, which were garnering considerable attention. The need to encourage and accelerate research on regenerative medicine was voiced. Subsequently, there was rapid movement towards the realization of new cellular therapies. Thus, action to ensure the smooth and efficient evaluation of products expected in the near future has become necessary.

The utilization of human stem cells, particularly human embryonic stem (ES) cells, in regenerative medicine had been regarded as difficult and has been limited by ethical considerations. However, in the United States, concrete efforts have recently been made to evaluate human stem cells in clinical trials. Research into the use of mesenchymal stem cells and induced pluripotent stem (iPS) cells is now conducted around the world. Identifying at an early stage of development the technical, medical, and ethical conditions necessary for the utilization of various types of stem cells is vital for their rapid application in patients.

In Japan, there have been two main approaches to the research, development, and clinical application of cell-based regenerative medicine. The first one is aimed at the marketing authorization of cell- and tissue-based products under the Japanese Pharmaceutical Affairs Law. In other words, this first approach involves research and development initiated by a company and follows a stepwise process toward evaluation and approval of the product by the relevant regulatory authorities. These steps include: regulatory consultation with respect to the quality and safety of the products to ensure that there are no obstacles to its application to humans in clinical trials; "clinical trials"; "product marketing authorization (manufacturing and import approval)"; and finally "clinical use". When adopting this kind of approach, researchers are encouraged to refer to certain official guidelines, such as Pharmaceutical Notification No. 1314 entitled "Ensuring the Quality and Safety of Pharmaceuticals and Medical Devices Manufactured Using Ingredients Derived from Humans and/or Animals," dated December 26, 2000. The second approach is "human stem cell clinical research" conducted, for the time being, according to the Medical Act. This is carried out in accordance with the Ministry of Health, Labor, and Welfare (MHLW) Notification No. 0703003, dated July 3, 2006 and entitled "Guideline Concerning Clinical Research Using Human Stem Cells," though the scientific contents are, on the whole, based on the aforementioned Pharmaceutical Notification No. 1314. Revised versions of MHLW Notification No. 0703003 were published in November 2010 and

October 2013, although the Chemistry, Manufacturing and Control (CMC) parts therein are based on MHLW Notification No. 0208003 and MHLW Notification No. 0912006, described later. Whether "human stem cell clinical research" can proceed will depend on deliberations at the MHLW Scientific Committee Meeting (most reviews are conducted by competent expert committees) and a decision from the Minister of Health, Labor, and Welfare. As human stem cell clinical research proceeds, research will be eligible to receive public funding as a "high level/advanced therapy" if it is determined, from the standpoint of efficacy and safety, to be medical treatment within the public healthcare funding system. It is anticipated that human stem cell clinical research will lead to the smooth development of products by industry.

The 2006/2007 scientific research group (group leader, Dr. Takao Hayakawa) of the MHLW inquired into preparing a revised version of "Guideline on Ensuring the Quality and Safety of Pharmaceuticals and Medical Devices Derived from the Processing of Human Cells and Tissues," which is Appendix 2 in Pharmaceutical Notification No. 1314, mentioned above, in response to requests that Japan should push forward with appropriate regulations for cell-based regenerative medicine by updating standards to reflect rapidly developing science and technology, ethical viewpoints, and international trends. The revised version was originally drafted as a single guideline. However, it was later split into two different guidelines in order to clarify the specific technical requirements for products derived from autologous cells and allogenic cells. The autologous cell guideline, entitled "Guideline on Ensuring the Quality and Safety of Products Derived from the Processing of Autologous Human Cells/Tissue" (MHLW Notification No. 0208003), was published in February 2008, and the allogenic cell guideline, entitled "Guideline on Ensuring the Quality and Safety of Products Derived from the Processing of Allogenic Human Cells/Tissue" (MHLW Notification No. 0912006), was published in September 2008. However, the guidelines dealt with autologous and allogenic cell and tissue products, respectively, in a general manner. Further study of critical issues related to the prompt development of products derived from human stem cells, such as human somatic stem cells, human ES cells, and human iPS cells, became necessary.

In fiscal year 2008, the Japanese MHLW convened a panel of experts entitled "Study Group on Ensuring the Quality and Safety of Pharmaceuticals and Medical Devices Derived from the Processing of Human Stem Cells." The panel, chaired by Dr. Takao Hayakawa, was established as an MHLW scientific research project.

The objective of the study group is to promote the sound development of products derived from human stem cells by investigating scientific and technological advances, ethics, regulatory rationales, and international trends regarding human stem cell-derived products and to establish and implement appropriate safety evaluation criteria.

The early activities of the study group (2008–2010) are summarized as follows:

(i) From a scientific and technological perspective, the group assessed the current state of and future outlook on the manufacture and clinical application of cell and tissue-based products derived from the processing of human somatic stem cells, human ES cells, and/or human iPS cells, with reference to the most

up-to-date research and information. In particular, the group presented the results of the study with respect to sources of human mesenchymal stem cells; the clinical application (including cellular therapy and gene therapy) for many different types of diseases; perspectives for the establishment and differentiation of iPS cells and clinical application of iPS cell-based products; and the current state of and views on therapeutic tissue engineering and its practical use in regenerative medicine.

(ii) The contents and significance of the existing "Guideline for Clinical Research Using Human Stem Cells" were analyzed, and the appropriateness of MHLW's review system for human stem cell clinical research was evaluated. This could lead to proposals of views that should be adopted and future directions that should be taken.

(iii) Guidelines and meeting reports were also analyzed, including two guidelines published by the Japanese government entitled "Guideline on Ensuring the Quality and Safety of Products Derived from the Processing of Autologous Human Cells/Tissues" (Pharmaceutical and Food Safety Bureau, No. 0208003, issued February 2008) and "Guideline on Ensuring the Quality and Safety of Products Derived from the Processing of Allogenic Human Cells/Tissues" (Pharmaceutical and Food Safety Bureau No. 0912006, issued September 2008); one guideline on clinical research involving stem cells published at the end of 2008 by the International Society for Stem Cell Research (ISSCR); and several reports on quality characteristics, preclinical trials, and monitoring of patients treated with products manufactured using cells derived from ES cells, which were presented in April 2008 at the 45th Cell Therapy-Gene Therapy Consultative Meeting held at the U.S. Food and Drug Administration (USFDA). This led to the identification of important parameters and factors for ensuring the quality and safety of products derived from human somatic stem cells, ES cells, and/or iPS cells.

(iv) Information on the organization and operation of the Committee for Advanced Therapy (CAT), established in 2009 by the European Medicines Agency (EMA), were collected and analyzed in order to assess the appropriateness of the Japanese system and regulations.

(v) As a result of the analyses and discussions described in (i)–(iv), in accordance with the Pharmaceutical Affairs Law, and with the clinical application of products derived from human somatic stem cells, iPS cells, ES cells, and other cells as the goal, the study group concluded that relevant guidelines should be tailored to specific cell sources and phenotypes (human autologous *vs.* human allogenic cells; somatic stem cells *vs.* iPS cells *vs.* ES cells *vs.* other cells) to facilitate efficient, effective, and rational research and development(R&D). Points to be considered include but are not limited to: technical details, the manufacturing process, characterization, quality control, stability evaluation, and the data necessary to guarantee the safety and efficacy of the products.
With this perspective in mind and with a desire for consistency in scientific principles and concepts, two interim reports on draft guidelines for products derived from the processing of autologous human somatic stem cells and autologous human iPS cells were prepared in 2009, on the basis of MHLW Notification No. 0208003. Three other interim reports on draft guidelines for products derived from the processing of allogenic human somatic stem cells, allogenic human iPS cells, and human ES cells,

respectively, were also prepared, on the basis of MHLW Notification No. 0912006. These five sets of draft guidelines were thoroughly discussed from a variety of viewpoints. They were then widely circulated among interested parties as articles in a relevant scientific journal to allow readers to comment (Hayakawa T., et al.: Journal of the Japanese Society for Regenerative Medicine), 9, 116–180 (2010)). Thereafter, these articles were updated and published as eight articles (Hayakawa T., et al.: Journal of the Japanese Society for Regenerative Medicine, 10, 86–152 (2011)) that served as the basis for the final draft guidelines. After extensive discussions with the study group and public consultation, the Pharmaceutical and Food Safety Bureau of MHLW issued five notifications on September 17, 2012 entitled "Guideline on Ensuring the Quality and Safety of Pharmaceuticals and Medical Devices Derived from the Processing of Autologous Human Somatic Stem Cells," "Guideline on Ensuring the Quality and Safety of Pharmaceuticals and Medical Devices Derived from the Processing of Allogenic Human Somatic Stem Cells," "Guidelines on Ensuring the Quality and Safety of Pharmaceuticals and Medical Devices Derived from the Processing of Autologous Human Induced Pluripotent Stem(-Like) Cells," "Guidelines on Ensuring the Quality and Safety of Pharmaceuticals and Medical Devices Derived from the Processing of Allogenic Human Induced Pluripotent Stem(-Like) Cells," and "Guidelines on Ensuring the Quality and Safety of Pharmaceuticals and Medical Devices Derived from the Processing of Human Embryonic Stem Cells."

Because these official notifications were written in Japanese, we translated them into English in order to introduce them to relevant international societies. The English versions were produced by free translation so that the concepts in the original Japanese versions could be interpreted as properly as possible.

In this paper, we introduce guidelines that describe the basic technological requirements for ensuring the quality and safety of pharmaceuticals and medical devices derived from the processing of autologous human somatic stem cells. There may be cases where certain final products derived from the processing of somatic stem cells that are multipotent and retain the ability to self-replicate may be used in a non-homologous manner, even if they are autologously derived. In other words, as a result of cell processing, the product could exhibit cell characteristics different from those of the starting cells, and the product might be applied and function at a site (cell environment) different from where the original cells localized. Concerns related to these points have been added to Notification No. 0208003, which serves as a basis for this guideline.

Before interpreting and implementing the present guideline, the following should be taken into consideration. The ultimate goal is to provide patients with new therapies that utilize regenerative medicine. The role of the guideline is to present the scientific principles, concepts, ideas, and technical elements that will achieve the specified goal in the most efficient and effective manner possible. Because a wide variety of products are anticipated, encompassing a variety of situations and circumstances, the guideline describe comprehensive points of concern. Therefore, it is critical to identify the relevant testing parameters and evaluation methods by taking into consideration the characteristics of the cells in question, the specific clinical objective, the

method of application, etc. Those that are applicable should be justified and implemented in an appropriate and flexible manner.

Several points should be kept in mind with regard to the development of medicinal products for regenerative medicine and the employment of this guideline. The desired products are expected to show a potential as a novel therapeutic method thorough relevant proof of concept (POC), and relevant data and/or information, indicating no critical concerns for product safety that might impede the use the product in humans for the first time. Thorough observance of the Declaration of Helsinki, including proper informed consent and right of self-determination on the part of the patient, is indispensable.

It should be emphasized again that the primary goal of our endeavor is to offer suitable medical opportunities as fast as possible to patients suffering from severe diseases that are difficult to treat with conventional medicine. The present guideline should be useful for this purpose. Therefore, it is important to interpret and employ the guideline in a flexible and meaningful way. Stringent observance of the guideline without taking into account the patients and their specific situations, which is like putting the cart before the horse, should be avoided.

It is evident that progress in the application of regenerative medicine is desirable for maintaining and improving peoples' health. The development of innovative and revolutionary medicinal products and therapeutic techniques should benefit our country as well as the international community. Regenerative medicine is a great way to make a peaceful international contribution that will be a legacy to mankind. In this context, the role of the government here is to promote clinical research and industrialization; regulations and guidelines are adopted such that we advance towards this common goal in a scientific, rational, efficient, and effective manner. All those involved, like players in the same arena with a common goal in mind, accumulating scientific data and concentrating wisdom, should continue to make great efforts to deliver these revolutionary cell-based products and therapeutic techniques to patients as rapidly as possible.

Guidelines on Ensuring the Quality and Safety of Pharmaceuticals and Medical Devices Derived from the Processing of Autologous Human Somatic Stem Cells (September 7, 2012)

Introduction

1. The present guidelines outline basic technical elements for ensuring the quality and safety of pharmaceuticals and medical devices derived from the processing of autologous human somatic stem cells. These products are hereafter referred to as autologous human somatic stem cell-based products or merely as the "desired cell products."

There are many different types of cell products and methods of clinical application. In addition, the scientific progress in this field is constantly advancing and experience and knowledge are constantly accumulating. Therefore, it is not always appropriate to consider the present guidelines all inclusive and definitive. Consequently, when testing and evaluating each individual

product, it is necessary to take, on a case-by-case basis, a flexible approach based on rationale that reflects the scientific and technological advances at that point in time.

2. The main purpose of evaluating the quality and safety of the desired cell products before conducting investigational clinical trials (e.g., at the time of "clinical trial consultation") is to determine whether there are any quality and/or safety problems that would obviously hinder initiating human clinical trials of the autologous human somatic stem cell-based products in question, whether certain quality attributes (QA) of the product are understood sufficiently to establish a relationship between the clinical findings and the QA, and whether consistency of the QA can be ensured within a definite range. Simultaneously, it is important to eliminate as much as possible any presumed known risk factors associated with product quality and safety using up-to-date science and technology and to describe the scientific appropriateness of the results of such action. The remaining unidentified risk factors should be weighed against the risks associated with not performing the trials in patients who suffer from diseases that are serious and life-threatening, that involve marked functional impairment or a marked decrease in quality of life (QOL) resulting from the loss of a certain degree of physical function or form, or for which existing therapies have limitations and do not provide cures. Furthermore, it is important to entrust to the patient the right to make a decision after providing all of the information available. When applying for investigational clinical trials, applicants can submit a provisional non-clinical data package, which is prepared reasonably by taking into account product aspects and patient aspects including a balance between risk of product *vs* risk of patient with/without treatment in question, ~~,~~ for determining to initiate investigational clinical trials, on the premise that the data package submitted at the time of marketing authorization application/registration to ensure quality and safety will be enriched and developed in line with the guidelines as the clinical trial progresses.
Finally, applicants are encouraged to discuss with the Pharmaceuticals and Medical Devices Agency (PMDA) the type and amount of data that may be needed to initiate an individual clinical trial. Because of differences in product origin, target disease, target patients, application sites, application methods, and processing methods, there may be numerous variations between individual data packages that cannot be definitively clarified in the present guidelines.

3. The items, test methods, criteria, and any other technical requirements described in the present guidelines are intended to be considered, selected, applied, and evaluated to serve each intended purpose; they do not necessarily require the most stringent level of interpretation and practice. In accordance with the purpose of the present guidelines, applicants are encouraged to explain and justify how the background, selection, application, and the content and extent of

evaluation are appropriate and scientifically rational.

Chapter I General Principles

I. Objective

The present guidelines outline basic technical elements for ensuring the quality and safety of pharmaceuticals and medical devices derived from the processing of autologous human somatic stem cells (excluding allogenic somatic stem cells). These products are hereafter referred to as autologous human somatic stem cell-based products or merely as the "desired cell products."

II. Definitions

The definitions of the technical terms used in this guideline are as follows:

1. "Human somatic stem cells": Cells that are collected from humans or cells that are obtained from such cells through cell division and that possess multipotency and maintain the ability to self-renew or a similar ability. In other words, tissue stem cells (e.g., hematopoietic stem cells, neural stem cells, mesenchymal stem cells [including bone marrow stromal stem cells and adipose tissue-derived stem cells], corneal stem cells, skin stem cells, hair follicle stem cells, intestinal stem cells, hepatic stem cells, and skeletal muscle stem cells) or cell groups that have abundant populations of these cells (e.g., whole bone marrow cells that include hematopoietic stem cells), including vascular precursor cells, umbilical cord blood, and bone marrow stromal cells. "Human somatic stem cells" also include cells obtained by culturing these cells in vitro. Human embryonic stem (ES) cells, human induced pluripotent stem (iPS) cells, human induced pluripotent stem-like (iPS-like) cells, human embryonic germ (EG) cells, human multipotent germline stem (mGS) cells, human parthenogenesis stem cells, human nuclear transplant stem cells, human cancer cells, human cancer stem cells, and cells derived from these cells are not included. (Note: The definitions for human ES cells, human iPS cells, and human iPS-like cells are provided in other guidelines, specifically in "Guidelines on Ensuring the Quality and Safety of Pharmaceuticals and Medical Devices Derived from the Processing of Human ES Cells" and "Guidelines on Ensuring the Quality and Safety of Pharmaceuticals and Medical Devices Derived from the Processing of Allogenic/Autologous Human iPS(-Like) Cells," respectively.)

2. "Processing of cells and tissues": Any processing of a cell or tissue, such as propagation and/or differentiation, production of a cell line, activation of a cell by pharmaceutical or chemical treatment, alteration of a biological characteristic, combination with a noncellular component, and manipulation by genetic engineering, with the aim of preparing desired cell products to treat a patient or repair or regenerate tissue.

Isolation of tissue, disintegration of tissue, separation of cells, isolation of a specific cell, treatment with antibiotics, washing, sterilization by gamma irradiation or other methods,

freezing, thawing, and other such procedures regarded as minimal manipulations are not considered processing.

3. "Manufacture": Actions undertaken before the final product (an autologous human somatic stem cell-based product) is released to market. This includes, in addition to the processing of cells and tissues, minimal manipulations such as separation of tissue, disintegration of tissue, separation of cells, isolation of a specific cell, treatment with antibiotics, washing, sterilization by gamma irradiation or other methods, freezing, thawing, and other procedures that do not change the original properties of the cells or tissues.

4. "Phenotype": A morphological or physiological characteristic that is expressed by certain genes under defined environmental conditions.

5. "Donor": Persons who donate their own cells or tissue, which serve as the raw material for an autologous human somatic stem cell-based product. For an autologous human somatic stem cell-based product, a patient is definitely a donor. (Note: A patient is identified as a donor for actual treatment. It is also presumed that cells/tissues obtained from a donor other than the patient are used for the purpose of test production during research and development stages.)

6. "Transgenic construct": A construct that contains a vector for introducing a target gene (a specific gene encoding a desired protein or RNA) into a target cell, the target gene itself, and the coding sequences of the elements essential for the expression of the target gene.

Chapter II Manufacturing Methods

Describe all important and relevant information concerning the manufacturing method, taking into account the items listed below. This information will help ensure the quality, safety, and efficacy of the final products, and it is important for guaranteeing consistency in quality from a manufacturing perspective. It should be noted that quality, safety, and consistency are assured by mutual complementary measures throughout the manufacturing process. It is most important that the measures are rational and that they serve the intended purpose. It may be acceptable to omit a portion of the items listed below, if the quality, safety, and constancy of the final products can be established by suitably chosen quality tests, control of the final or intermediate products, or control of the manufacturing process.

I. Raw Materials and Materials Used in Manufacturing

1. Human cells and tissues used as raw materials

(1) Features of biological structure and function, selection criteria

Explain and justify the reasons for selecting the cells and tissues used as raw materials, with reference to the characteristics of their biological structure and function, such as morphological characteristics, growth

characteristics, biochemical indicators, immunological indicators, specific substances produced, and other suitably chosen and appropriate genotype or phenotype indicators (or markers). In particular, demonstrate that the somatic stem cells used as a raw material possess clinically useful stemness. Stemness in this case does not necessarily indicate the potential for multilineage differentiation, but refers to the ability to differentiate into cells that have an expected function in vivo. In addition, although demonstrating the differentiation in vitro is desirable, it may suffice to show differentiation in vivo if a rational explanation is provided. For example, when using myocardial stem cells, which are somatic stem cells, as a raw material, it is acceptable to show that myocardial stem cells can differentiate into cardiomyocytes. This should lead to the identification of the main cell characteristics that will be employed when applying cells to the patient.

It is acceptable to perform tests using test specimens obtained from a donor other than the patient at the research and development stages before the beginning of the clinical trial. In any case, it is recognized that quantitative limits and technological limits to sample analysis will affect the extent to which such studies can be performed.

(2) Considerations with respect to the donor

To ensure the safety of the patient, the personnel involved in manufacturing the product, and the health care workers who treat a patient, establish test parameters by which to assess possible infection of the cells and/or tissues and justify the appropriateness of the parameters. Particular consideration shall be given to hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and human T-lymphotropic virus (HTLV).

Establish eligibility criteria that take into consideration the genetic characteristics, history, and health of the patient and others and justify the appropriateness of the patients as donors. Donor genome or gene analysis shall be performed in accordance with "Ethics Guidelines for Human Genome and Gene Analysis Research" issued jointly on December 28, 2004 by the Japanese Ministry of Education, Culture, Sports, Science, and Technology, Ministry of Health, Labor, and Welfare, and the Ministry of Economy, Trade, and Industry.

(3) Records related to the donor
Complete records related to the donor should be retained in order that any information necessary to ensure the safety of cells and tissues used as raw materials can be verified. Concrete measures shall be described. For patients and donors of test samples, it is sufficient to prepare and retain only specific information that relates to the intended use of the cells.

(4) Collection, storage, and transport of cells and tissues

(i) Eligibility of personnel and medical institutions collecting samples

Describe the technical requirements for personnel and medical institutions that collect the cells and tissues.

(ii) Suitability of the sampling site and sampling method

Describe the rationale for selecting the cell and tissue sampling sites and the sampling method. State how the selected sites are scientifically and ethically appropriate. For cell and tissue sampling methods, indicate the suitability of the equipment and drugs used and the measures adopted to prevent microbial contamination, erroneous sampling (mix-ups), and cross contamination.

(iii) Informed consent from donors

Describe the details of the informed consent from donors of the cells and/or tissues.

(iv) Protection of donor privacy

Indicate the measures adopted to ensure the protection of the donor's privacy.

(v) Tests to ensure donor safety

If tests such as those to confirm the state of the sampling site need to be performed in order to ensure the safety of the donor at the time of cell or tissue sampling, describe the details of the tests, as well as any interventions taken when test results indicated a problem existed.

(vi) Storage method and measures to prevent erroneous sampling (mix-ups)

If the cells and/or tissues need to be stored for a definite period of time, set the storage conditions and storage period and justify their appropriateness. Describe in detail the measures and procedures to be taken to prevent erroneous sampling (mix-ups).

(vii) Transportation methods

If cells and/or tissues need to be transported, set the containers used for transport and the transportation procedure (including temperature control, etc.) and justify their appropriateness.

(viii) Preparation of records and record-keeping procedures

Prepare written records for (i) through (vii) and describe the record-keeping procedures in detail.

2. Raw materials other than the target cells and tissues, materials used in manufacturing

Describe raw materials other than target cells and/or tissues, as well as materials used in the manufacturing process; indicate their appropriateness for the intended use; and, if necessary, establish their specifications (set of acceptance criteria and analytical procedures). Proper quality control for these materials should be implemented.

When so called "Biological Products" or "Specific Biological Products" (refer to Article 2.9 and 2.10 of the Pharmaceutical Affairs Law) are used as raw materials, use the minimum amount required and strictly obey the