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厚生労働科学研究費補助金
再生医療等研究事業

再生医療の研究振興のシステム構築および実施普及に向けた社会受容の在り方に関する研究

平成19年度　総括研究報告書

主任研究者　　川上　浩司

平成20（2008）年　3月

目　次

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研究要旨

本邦における再生医療の普及に向けて、国内外の医薬品審査行政機関における安全性ガイドラインを調査・検討し、また研究者や民間からのヒアリングにより実施上のボトルネックを抽出することで、細胞等を用いた再生医療の安全性確保に必要な評価・検証方法を提案する。さらに、社会・国民に受け入れられるよう、オープン議論、広報と啓発も兼ねて国民シンポジウムを企画・参集し、再生医療の実施を支援する体制を整えていく。

A．研究目的

わが国において細胞・組織・臓器を使用した再生医療を実現化する場合には、ドナーの理解、基礎研究を行っていく際の細胞供給バンクシステムの整備などに加えて、臨床研究を遂行する場合には薬事法の適応範囲内および適応外においても認可行政側の対応を整備し、またその対応のためにも安全性の評価基準を設置しなければならない。再生医療を受ける患者の立場としては、国家としての行政対応、患者保護（臨床試験の段階においては被験者保護）、場合によっては細胞・組織の流通由来の明示、製造における安全性の担保が懸念事項となる。再生医療の研究振興のみならず将来の普及のためは、現在から厚生労働行政の一環として社会受容に関連する上記の事象を整理、解決していく必要がある。

現状では、細胞再生医療にはautologous（自己由来）およびallogenic（同種由来）の2つのクラスが存在する。自己由来の場合その開発は医療施設の医師・研究者主導の臨床研究あるいは治験、同種由来の場合は通常は薬事法の規定内にはいるために治験として行われている。また、臓器・組織を利用した再生医療においては、xenotransplantation（異種由来）あるいは同種由来の場合があり、これらは医療機器の範疇で取り扱われることが多い。しかしながら、米国においては、所轄官庁である食品医薬品庁（Food and Drug Administration; FDA）によりこれらは殆どbiologics（生物製剤）の範疇内で審査・医療（臨床試験）が行われてい

る。さらに、先端医療に関しては、研究者主導の研究成果応用・医師主導臨床研究・企業主導によらず、すべての未承認製剤の臨床試験はFDAにより審査・認可をうけて実施する必要がある。このため、大学等アカデミアにおける再生医療研究と産業化に向けた治験が同時に被験者の安全性を担保される努力がされつつ実施されていることになる。

以上のような現状と事実を踏まえて、我が国において再生医療の普及に向けて研究を進めていく。本研究の成果は厚生労働省、文部科学省を中心にバックアップしている再生医療が現実化した際に国民に受け入れられる素地を形成し、それによって先端医科学という学問の更なる発展、先端医療の普及と国民の健康の増進、さらに国策としての新興産業としても再生医療を国際社会に発信し得るインフラ構築を形成するという効果があると信じる。

B．研究方法

平成18年度には、米国における新規医療製品の承認と臨床試験に対する行政対応のシステム、さらに細胞製剤、組織製品に関する各種ガイドラインを検討した。

今年度は、欧州における当該分野の規制の動向およびガイドラインを調査した。また、平成18年度に引き続き、日本国内で再生医療に関係する研究者、企業、臨床試験や医療を行う医療施設・医師、審査当局（医薬品医療機器総合機構）からヒアリング結果から、再生医療を推進するにあたっての科学的懸念事項、医療現場での懸念事項、倫理的・社会的懸念事項、および行政側としての諸問題についてまとめ、さらに、産学連携の諸問題や産業化の障壁についても研究した。

（倫理面への配慮）

本研究は、レギュラトリーサイエンスに資する安全性評価のガイドラインのあり方について公表された通知やヒアリングから検討するものであり、個人情報やヒト生体資料を扱うことなく、特定の個人を観察や介入の対象とするものでもない。したがって、倫理面の特段の配慮には該当しない。

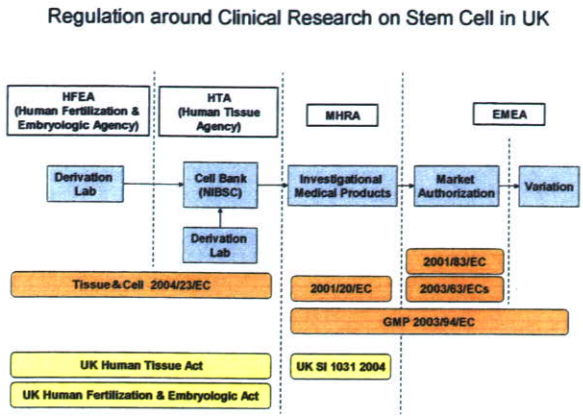
C．研究結果

C-1．欧州における再生医療製品開発における規制の枠組み

欧州においては、再生医療製品は通常の医薬品の規制となるDir. 2001/83/ECとDir. 93/42/EECとのギャップに入るという判断のもと、2004年以降はAdvanced Therapies Medicinal Products (ATMP)規制が導入された。その後、2007年に人細胞を利用した医薬品に関するドラフトガイドライン“draft guideline on human cell-based medicinal products”(EMEA/CHMP/410869/2006)が発表されている。

なお、欧州内でも、英国についてとはくに細胞再生治療の規制について整理した。

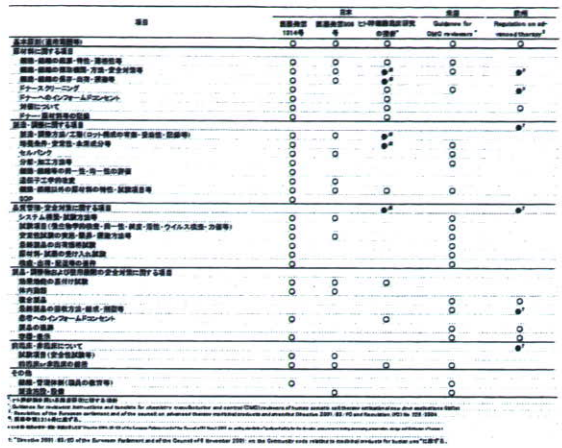
（図：英国における再生医療臨床試験の規制について）



C-2. 国際各局における再生医療製品開発における規制の枠組み

国際各局における再生医療製品開発における規制調査により、日本(医薬発 906 号通知、1314 号通知)、米国(Guidance for Reviewers: Instructions and Template for Chemistry, Manufacturing, and Control (CMC) Reviewers of Human Somatic Cell Therapy INDs. Draft Guidance, FDA-CBER, August 2003)、欧州各局の関連ガイドラインにおいてはそれぞれの守備範囲自体はほぼ同様であるが、運用などに違いがあることが示唆された。

(図:日米欧における再生医療製品に関する規制の比較について)



C-3. 日本国内で再生医療に関係する研究者、企業、臨床試験や医療を行う医療施設・医師、審査当局(医薬品医療機器総合機構)からのヒアリング結果:規制・制度、社会、倫理

日本国内で大学発の技術などを用いて再生医療の開発を行っている企業 10 社の経営・開発の責任者および医薬品医療機器総合機構の審査担当の方から、意見を聴取した。まず、日本における開発段階での問題点としては、以下のような項目が挙げられた。

表 ヒアリング調査結果:日本における開発段階での問題点・改善が望まれる点

		問題点・改善が望まれる点	企業数			
			細胞		遺伝子	その他
			自家	他家		
製造・技術関連	規格・基準関連	・品質確保(受け入れ、出荷、製造工程等)の基準・規格の決定・管理が困難	4	2		
		・品質・安全性・有効性等の評価システムの確立や基準の標準化が必要	3	1		
		・細胞培養の評価システムの確立と標準化が必要	1			
		・不純物の適正値が不明	2	1		
		・CPCに関して統一基準がない	1			
	GMP関連	・GMP準拠施設を設計・建設する際の構造基準が不明確	1			
		・治験薬GMPが何かはっきりしていない	1	1		
	その他	・製品が均一でなく、品質管理にも企業ごとにバラつきがある	5			
		・成分の抽出・精製・滅菌ができない	1			
		・組織ソースの入手が困難	1	1		
		・遺伝子治療薬のデータベースが当局にない			1	
前臨床関連		・安全性の基準が不明(腫瘍原性、免疫原性等)	3	2		
		・有効性の確認がどこまで必要か不明	1	1		
		・安定性の目安・ルールがない(保存性能・細胞活性	1			
		・日米でデータを共有できないことがある				1
臨床試験		・対象者を集めにくい	3	1	1	
		・事業用細胞、組織の入手が困難	1	1		

開発上の主な問題点としては、規格・基準、品質管理に関連する意見が多く認められた。

また、日本における法規制や社会的側面での問題点や改善点が望まれる点としては、以下のような項目が挙げられた。

表　ヒアリング調査結果：日本の法規制・社会的側面での問題点・改善が望まれる点

		問題点・改善が望まれる点	企業数			
			細胞		遺伝子	その他
			自家	他家		
法規制面	法規制関連	・医師法と薬事法の改存が問題	2			1
		・バイオロジクスのカテゴリーが必要	3			1
		・自家と他家の区別化が必要	1	1		
		・combination productが多数あるので複数のフレームアウトが必要	1			
		・ガイドラインの整備が必要	3			
		・細かく分かれた臨床試験の簡略化が必要	1	1		
	審査関連	・審査に時間がかかる、対応が遅い	2			
		・preINDのハードルが高い	3	2		
		・効果等を通常の医薬品と比較する傾向にある	1			
		・グループ審査で意見が統一されていない	1			
		・事前相談を充実させてほしい		1		
社会的側面		・資金支援制度が貧弱	4	1	1	
		・社会的インフラ整備(医療特許、医療機関の体制等)の必要性	2			
		・再生医療に対する過剰や一般社会の理解不足	1	1		
		・マスコミ報道の正しいあり方が必要		1		
その他		・人材不足(細胞培養、基礎研究、製品開発等)	2	1		
		・細胞の所有権に関する検討の必要性	1			
		・NDA後の薬価算出の事例がない	2		1	

行政の立場からの意見も総合すると、法規制関連ではバイオロジクス(生物製剤)のカテゴリーの設置の要望が多く、審査について確認申請のハードルが高いという問題点などが浮き彫りとなった。

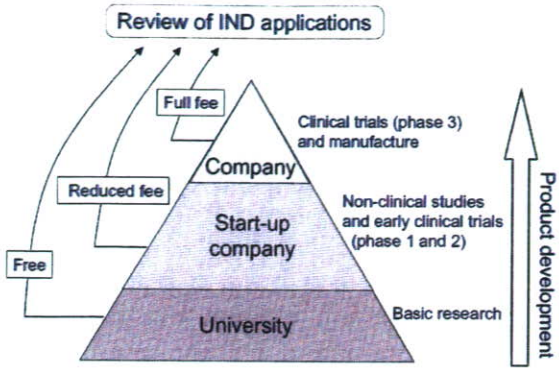
C-4.　日本国内で再生医療に関係する研究者、企業、臨床試験や医療を行う医療施設・医師、審査当局（医薬品医療機器総合機構）からのヒアリング結果：産学連携、産業化

産学連携に関する問題点として、最も多くの回答者が、両者の認識のずれ、特に多くの大学関係者にビジネスの概念、すなわち、事業性(知的財産など)、迅速性の重要さ、再生医療製品に関する大量生産による製造の考えなどがないことがわかった。allogenic より auttologous のほうが安全でよいという考えが再生医療の研究者で主流であり、流通や産業化の観点からより普遍的である allogenic の研究は一歩遅れているかもしれない、基礎研究と製品の研究開発の違いを認識していないことを指摘していた。こういった大学関係者の誤った認識を改めていくとともに産業・企業について知識のある大学関係者を育てていくことが重要であろう。

一方、産学連携をうまく進めている大学関係者もおり、彼らは大学関係者間にも産学連携に対する温度差があることを指摘していた。それにも関わらず大学内の規定が一律で、産学連携の知識や経験の乏しい関係者と同じように活動を制限されることに不便さを感じていた。活躍のできる大学関係者を活躍できる環境におくこと、すなわち人事評価において、論文のインパクトファクターによらない評価すなわち臨床研究の支援や基礎のみならず applied bioscience に対する理解が、今後産学連携を効果的に進めていくためには有効であろう。

産業化に関して、行政審査費用に関する指摘もあった。米国では審査費用において企業規模が考慮されており、ベンチャー企業は審査費用が少なくてよい、大学は費用がかからないという方法がとられている。しかし科学的審査は一様に行われている。一方、日本では企業規模に関わらず費用は一律であり、また薬事法外であることから大学からは医師主導治験以外の臨床研究は科学的審査とアドバイスのための申請をすることができない。日本の再生医療分野では大学から技術移転されベンチャー企業で製品開発されることが多いことから、産学連携やその後の製品開発を順調に進めていくためにも、欧米のような手法を導入し、ベンチャー企業のような規模の小さい企業が申請しやすい環境を整えることが重要である。

（図：医薬品規制行政と社会との連携）



D. 考察

再生医療を含むバイオテクノロジー利用製品の安全性評価の科学的側面については、日米欧の考え方はほぼ同様であるが、ガイドラインの扱われ方や基準の柔軟な運用には本邦と異なることが明らかになった。

また、欧米においては再生医療などの先端医療の振興策が医薬品規制行政との連携によって推進されており、日本においても新しいレギュラトリーサイエンスの考え方の導入は必須であると示唆された。

E. 結論

本邦における再生医療の発展と社会への受容の実現のための、科学的懸念事項、医療現場での懸念事項、倫理的・社会的懸念事項、および行政側としての諸問題についてまとめ、さらに、産学連携の諸問題や産業化の障壁についても研究した。

F. 健康危険情報

該当なし

G. 研究発表

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名古屋.

H．知的財産権の出願・登録状況
　該当なし

研究成果の刊行に関する一覧表レイアウト

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
川上浩司	細胞移植のための周辺環境：細胞医薬の日米の考え方の違い	田畑泰彦	遺伝子医学MOOK別冊 進みつづける細胞移植治療の実際.	メディカルドゥ社	日本	2008	

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
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Koji Kawakami	Keynote presentation. Special report from the 3rd DIA multitrack workshop in Japan: Scientific review and clinical development of advanced therapeutics and biologics	*Global Outsourcing Review*	9	10-15	2007
Koji Kawakami and Hiroko Yamane	Clinical research in Japan: ways to alleviate unnecessary regulatory burdens.	*RCEIIS-Electronic Journal in Communication, Information and Innovation in Health*	1	57-61	2007

HEAP 21601–11 ARTICLE IN PRESS

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Health Policy xxx (2008) xxx–xxx

HEALTH POLICY

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Overview of the clinical application of regenerative medicine products in Japan

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Abstract

Objective: To identify barriers to the clinical application of regenerative medicine products (RMPs) in Japan.

Methods: Current Japanese regulatory systems and guidelines were compared with those of the United States (US) and the European Union (EU). A questionnaire was administered to representatives from 23 Japanese companies and 10 research institutes, and an in-person semi-structured interview was conducted with representatives from 10 companies that develop RMP.

Results: We found that Japan, the US and the EU have similar pre-clinical safety guideline frameworks relating to RMP. However, differences exist between these countries with respect to their review and approval systems and the implementation of guidelines, and these represent major barriers to the clinical application of RMP in Japan. Most companies studied are facing regulatory hurdles such as stringent review processes and regulatory guidelines that do not provide detailed practical examples of the pre-clinical quality and safety data required.

Conclusions: These results suggest that effective regulatory infrastructure including regulatory systems, guidelines, and communication channels between product developers and regulatory bodies are essential for the prompt clinical application of RMP in Japan.

Keywords: Regenerative medicine; Biologics; Regulatory guideline; Interview survey

1. Introduction

Regenerative medicine technology, which involves the collection and processing of biomaterials from human bodies then transplantation or injection of these into patients, has been developed with the aim of partially or completely curing damaged or dysfunctional organs or tissues in the human body. Ten years ago, the field of regenerative medicine was expected to develop rapidly to offer new opportunities for the treatment of disease and to grow to become a major business area. However, the application of regenerative medicine products (RMPs) has been very

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0168-8510/$ – see front matter © 2008 Published by Elsevier Ireland Ltd.
doi:10.1016/j.healthpol.2008.02.011

much delayed in Japan relative to other developed countries.

In the United States (US) and the European Union (EU), RMP are already on the market, for example Carticel® (cultured autologous chondrocytes produced by Genzyme Biosurgery; Cambridge, MA) and Myskin™ (cultured autologous keratinocytes produced by CellTran; Sheffield, United Kingdom). In these countries and others, a large number of clinical trials have been initiated to assess the safety and efficacy of RMP [1–3]. In contrast, in Japan, RMP are not yet available in the market, and only a small number of clinical trials of RMP have been initiated.

In 2002, the Japan Patent Office (JPO) estimated that the market for RMP in Japan would reach US $3 billion by 2010 and US $19 billion by 2020 [4]. However, Japanese companies and investigators developing RMP have arrived at market size estimates that are far less than those of the JPO.

In Japan, barriers to the clinical application of RMP can be classified into technological problems and others. University researchers, medical doctors, and companies (mainly start-ups) have gone to a great deal of effort to overcome the technical obstacles. For example, these players have worked to improve the quality of the biomaterials and cellular products available for possible clinical use. However, researchers and companies in the field are greatly concerned that these "other" problems (i.e. other than technological problems) still represent a major obstacle for the clinical application of regenerative medicines. Although it has become critical to identify barriers to the development of RMP, these "other" problems in Japan in this context have never been investigated systematically.

In this study, we compared current Japanese regulatory systems and guidelines with those in the US and the EU to identify barriers to the clinical application of RMP in Japan. We also conducted structured interviews with representatives of Japanese companies that develop RMP to clarify the nature of these barriers.

2. Methods

2.1. Survey of regulatory processes and guidelines

We compared the regulatory approval systems for pharmaceuticals and biologics in Japan, the US, and the EU. Additionally, we surveyed the regulatory guidelines in place for cellular and tissue-based products and analyzed the regulatory topics covered in the guidelines. The major guidelines relating to the chemistry, manufacturing, and control (CMC) of cellular and tissue-based products in Japan are the "Notice for the quality and safety of cellular and tissue-based pharmaceuticals and medical devices" (notification no. 906) [5] and the "Notice for the quality and safety of pharmaceuticals utilizing human- or animal-derived materials" (notification no. 1314), both issued by the Drug and Food Bureau of the Ministry of Health, Labour and Welfare (MHLW) [6] under the Pharmaceutical Affairs Law (PAL), and the "Guidelines for clinical research utilizing human somatic stem cells", issued by the Health Service Bureau of the MHLW [7] under the Medical Affairs Law (MAL). In the US, the Food and Drug Administration (FDA) guidelines entitled "Guidance for reviewers: instructions and template for CMC reviewers of human somatic cell therapy investigational new drug applications (INDs)" represent the major guidelines relating to RMP [8]. In the EU, the European Commission issued guidelines entitled "Regulation of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No. 726/2004" [9], which are the major guidelines relating to RMP.

2.2. Surveys of companies developing RMP

We first conducted an initial survey to investigate issues in the successful development of RMP, which we administered to representatives of 39 Japanese companies and 21 research institutes that are actively involved in research into and/or development of RMP. Subsequently, we conducted interviews with representatives of 10 companies that responded to the questionnaire, which also had RMP under clinical development. Semi-structured in-person interviews were conducted in November and December 2006. Company presidents or persons responsible for the development of the company's products were interviewed. The interviews took approximately 1.5 h and were recorded using an IC recorder. Each interview was transcribed verbatim and the responses were analyzed. The interview included queries with regard to candidate RMP (e.g. material, source, place of manufacture, and clinical phase) and

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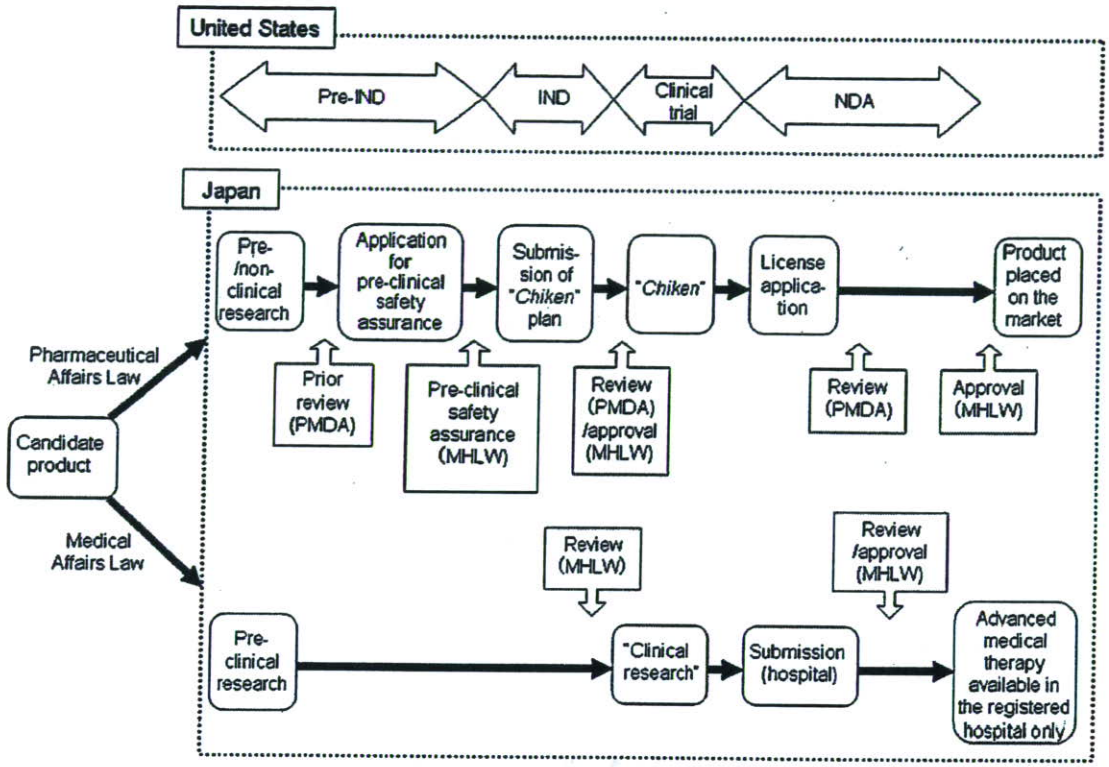

Fig. 1. Procedures for product development and obtaining regulatory approval for biologics in the US and Japan. IND, Investigational new drug; NDA, new drug application; PMDA, Pharmaceuticals and Medical Devices Agency; MHLW, Ministry of Health, Labour and Welfare.

questions regarding the problems the company faces in developing the product (e.g. regulation, the public, technology, pre-/non-clinical studies, and clinical trials). Participants were given a list of questions 1 week prior to the interview (see Appendix A for interview questions). At the end of each interview, the interviewer reviewed the questions and answers with the interviewee in an attempt to ensure that all questions were fully answered. Responses were analyzed by categorizing segments of the transcripts into topic areas, then classifying them using material categories [10]. This categorization process was independently performed by the first and last authors, and both categorizations were adjusted by consensus.

3. Results

3.1. Regulatory paths in Japan, the US, and the EU

Fig. 1 shows the procedure for product development and the process for obtaining regulatory approval for biologics, including cellular and tissue-based products, in Japan and the US. In Japan, clinical trials belong to one of two categories: "*Chiken*", which is regulated under the PAL, and "clinical research" for unapproved therapeutics, which is regulated under the MAL. In the case of "clinical research", the scientific and ethical aspects of new technology or therapeutics to be applied to patients and application forms are assessed only by the institute's review board, not by a regulatory agency. In the case of "*Chiken*", each applicant must submit a clinical trial application to the Pharmaceuticals and Medical Devices Agency (PMDA), a regulatory agency supervised by the Japanese MHLW. Moreover, for cellular and tissue-based products, before submitting a clinical trial application to the PMDA, each applicant must first submit a review package to the PMDA for specific review by the PMDA of the quality and safety of the product. In contrast, in the US, all applicants, including companies and university researchers, are required to submit an investigational new drug (IND) application to the FDA as the IND sponsor. Thus, all protocols and applications are subject to FDA con-

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trol with no exceptions. In the EU, pharmaceutical approval for marketing in the member states for a method involving an industrial process is administered by the European Medical Agency (EMEA). This process is applied to products that are prepared industrially or manufactured. Products that are prepared in full and used in a single hospital, in accordance with a medical prescription for an individual patient, are excluded from EMEA control.

3.2. Regulatory guidelines for RMP

The regulatory topics described in the major guidelines relating to the CMC of cellular and tissue-based products in Japan, the US and the EU are listed in **Table 1**. In the US, guidelines entitled "Guidance for reviewers: instructions and template for CMC reviewers of human somatic cell therapy investigational new drug applications (INDs)" provide detailed instructions regarding the pre-clinical specifications and safety of RMP. Non-clinical safety studies are regulated under guideline S6 of the international conference on harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH S6) [11]. In Japan, notification nos. 906 and 1314 of the Drug and Food Bureau of the MHLW regulate the pre-clinical specifications and safety of candidate products, and notification no. 1314 outlines some points relating to non-clinical safety studies that apply in addition to those listed in ICH S6. In the EU, regulations relating to advanced therapy products are mainly to be found in "Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use" [12] and ICH S6. Although the types of guidelines varied, the safety issues covered in these guidelines were largely similar.

3.3. Questionnaire administered to Japanese companies and researchers

Before conducting interviews with company representatives, we administered an initial questionnaire to representatives from Japanese companies and researchers in institutes that are involved in conducting research into and development of RMP. The aim of this questionnaire was to obtain a preliminary understanding of issues surrounding the application of RMP in Japan. To determine which was considered the most important issue for the prompt utilization of RMP in Japan, we sent out a questionnaire listing possible issues including regulatory guidelines, the review system, detailed guidelines about bioethics, rules for the collection/distribution of human cells and tissue, organization/management of cell bank systems, research grant systems, and others. Twenty-three out of 39 companies and 10 out of 21 research institutes responded. Out of the 33 responses, the most critical issue for the early realization of RMP was thought by 16 (48%) to be review of the regulatory guidelines and by 5 (15%) to be revision to the review system. Research grant and bioethics issues were also noted as being important.

3.4. Interviews of company representatives

Because we found that there are multiple barriers (e.g. regulatory and review system issues) to the prompt clinical application of RMP in Japan, we decided to further investigate these issues. We conducted semi-structured interviews with representatives from companies that are actively engaged in developing RMP for future clinical application. The companies involved are listed in **Table 2**.

3.4.1. Product development and manufacturing

Regarding issues relating to the development and manufacture of RMP, respondents from companies developing gene or peptide-related products stated that they did not face any manufacturing problems because they were easily able to meet the ICH guidelines in developing their products (**Table 3**). On the other hand, respondents from 6 of the 10 companies developing cellular-based products noted that they had difficulty in characterizing their cellular products prior to clinical trials. In addition, respondents from 4 of 10 companies noted that the regulatory safety-evaluation guidelines and examples of quality, safety, efficacy, and lot-to-lot consistency for cellular products in the current regulatory guidelines dose not describe specific issues and examples. Respondents from five companies developing autologous cellular products noted that maintaining the lot-to-lot consistency of products is difficult, and respondents also commented that the quality control methods used varied among companies. Regarding non-clinical studies, respondents from 5 of the 10 com-

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Table 1
Comparison of topics covered in regulatory guidelines concerning the CMC of cellular and tissue-based products in Japan, the US, and the EU

Topic	Japan			US	EU
	Notification no. 1314	Notification no. 906	Guidelines for clinical research[a]	Guidance for CMC reviewers[b]	Regulation on advanced therapy[c]
Scope	○	○	○	○	○
Material and cell collection					
Description of cells and/or tissues (source, characterization, and suitability)	○	○	○	○	
Cell and/or tissue collection (institute, method, safety)	○	○	○[d]	○	○[e]
Storage, release, and shipping of cells and/or tissues	○	○	○[d]		○[e]
Donor screening	○		○	○	
Informed consent for donors	○		○		
Donation	○		○		○
Documents linking donors and materials	○		○		
Product manufacturing and preparation					○[f]
Process used for manufacturing and preparation (manufacture of lots, validity, documentation)	○	○	○[d]		
Cell culture (culture conditions, stability, serum components)	○		○[d]	○	
Cell bank system	○	○		○	
Processing procedure	○			○	
Evaluation of identity and consistency	○				
Modifications by genetic engineering	○	○			
Description of regents used in manufacturing (characterization, type of testing)	○	○	○	○	
Standard operating procedure	○				
Safety and quality control of product			○[d]		○[f]
Procedure for safety and quality control	○	○	○	○	
Type of testing (microbiological testing, identity, purity, viability, viral testing, potency)	○			○	
Product stability (testing, shipping method)	○	○	○	○	
Final product release criteria testing	○			○	
Acceptance criteria (materials and regents)	○			○	
Requirements for testing, release, and shipping of products	○			○	
Testing and application of final products					
Efficacy testing	○	○	○		
Pharmacokinetics	○	○			
Combination products				○	○

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Table 1
(*Contined*)

Topic	Japan			US	EU
	Notification no. 1314	Notification no. 906	Guidelines for clinical research[a]	Guidance for CMC reviewers[b]	Regulation on advanced therapy[c]
Collection method, components, type of final product				○	○[d]
Informed consent for patients	○		○		
Product tracking				○	○
Labeling and packaging	○			○	○
Pre-/non-clinical trials					○[f]
Type of safety testing	○	○			
Summary of pre-/non-clinical trials	○	○	○	○	
Other					
Structure and management system of institute	○			○	
Manufacturing institute and facilities		○		○	

[a] Guidelines for clinical research utilizing human somatic stem cells (Health Service Bureau of the MHLW).
[b] Guidance for reviewers: instructions and template for chemistry, manufacturing, and control (CMC) reviewers of human somatic cell therapy investigational new drug applications (INDs).
[c] Regulation of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No. 726/2004.
[d] Notification no. 1314 applies.
[e] For donation, procurement and testing of human tissues and cells, "Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells" applies.
[f] "Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use" applies.

Table 2
Key characteristics of the 10 companies that provided a representative for interview and their candidate products

Year founded	Nature of candidate product	Relevant law	Development stage
1999	Autologous cells (epidermal) Autologous cells (cartilage) Autologous cells (corneal epithelium)	PAL	License application Application for pre-clinical safety assurance
1994	Autologous cells (epidermal cells and fibroblasts)	PAL	Application for pre-clinical safety assurance
1921	Autologous cells (skeletal myoblasts)	PAL	Application for pre-clinical safety assurance approved
1999	Autologous cells (bone marrow stem cells)	MAL	"Clinical research"
2001	Autologous cells (dendritic)	MAL	Pre-clinical research
2001	Autologous cells (corneal epithelium)	MAL	"Clinical research"
2000	Allogenic cells (corneal epithelium) Autologous cells (oral mucosa)	PAL	Completion of pre-clinical research Pre-/non-clinical research
2002	Allogenic cells (somatic and embryonic stem cells)	PAL	Pre-/non-clinical research
1999	HGF gene	PAL	Phase 3 in "*Chiken*"
2004	Peptide	PAL	Pre-/non-clinical research

PAL, Pharmaceutical Affairs Law; MAL, Medical Affairs Law.

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Table 3
Major issues relating to the clinical application of regenerative medicine products in Japan

Issue	Number of companies[a] (autologous cells, allogenic cells, genes, other)
Manufacturing and technology issues	
Standards	
Decisions about criteria relating to the quality of the products are difficult	4/6, 2/2, 0/1, 0/1
Regulatory safety-evaluation guidelines and examples of quality, safety, and efficacy of the products are necessary	3/6, 1/2, 0/1, 0/1
GMP	
The definition of GMP is not clear	1/6, 1/2, 0/1, 0/1
Others	
Ensuring lot-to-lot consistency of the products is difficult	5/6, 0/2, 0/1, 0/1
Quality control methods vary among companies	5/6, 0/2, 0/1, 0/1
Pre-/non-clinical issues	
Regulatory guidelines for safety, stability, and efficacy of the products are not clear	3/6, 2/2, 0/1, 0/1
CMC and animal data obtained by US companies cannot be utilized in the regulatory review package in Japan	0/6, 0/2, 0/1, 1/1
Clinical trial issues	
Recruiting study subjects is difficult	3/6, 1/2, 1/1, 0/1
Preparing allogenic cells for study is difficult	1/6, 1/2, 0/1, 0/1
Regulation issues	
Regulation	
There are two separate paths for clinical trials	2/6, 0/2, 0/1, 1/1
There is no approval category for "biologics"	3/6, 0/2, 0/1, 1/1
The regulatory guidelines were still imperfectly articulated, and that detailed examples should be provided	3/6, 0/2, 0/1, 0/1
Autografts and allografts should be distinguished in the regulatory guidelines	1/6, 1/2, 0/1, 0/1
The review path for combination products needs to be clarified in the guidelines	1/6, 0/2, 0/1, 0/1
Review	
The review period is too long	2/6, 0/2, 0/1, 0/1
Opinions differ among reviewers	1/6, 0/2, 0/1, 0/1
The pre-clinical review to ensure the quality and safety of the products is too stringent	3/6, 2/2, 0/1, 0/1
Reviewers tend to compare the efficacy of regenerative medicine products with that of traditional products	1/6, 0/2, 0/1, 0/1
Social issues	
The governmental research grant is limited	4/6, 1/2, 1/1, 0/1
Understanding of and knowledge about regenerative medicine among the general public and patients is at a low level	1/6, 1/2, 0/1, 0/1

GMP, good manufacturing practice.
[a] Number of companies that mentioned each major issue identified in the interview.

panies stated that regulatory guidelines for the safety, stability, and efficacy of the products should be more clearly outlined by regulatory agencies. One respondent pointed out that pre-clinical safety and animal data obtained by US companies or contract research organizations cannot be utilized as part of the regulatory review package in Japan. A number of respondents noted that it is difficult to recruit study subjects and prepare allogenic cells for study at the clinical trial stage.

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3.4.2. Regulatory systems and society

As noted previously, there are two regulatory paths for clinical trials in Japan: "*Chiken*" under the PAL and "clinical research" under the MAL. Respondents from 3 of the 10 companies were concerned with the existence of two separate clinical trial paths (Table 3). It was pointed out that once the clinical trial was initiated as the "clinical research" pathway and later the company chooses to proceed with development of the product candidate, they need to initiate the Phase 1 clinical trial again to go through the "*Chiken*" process. Furthermore, as pointed out by respondents from four companies, there are only two categories for regulatory approval under the Japanese PAL: pharmaceuticals and medical devices as medicinal products; there are currently no approval categories specific to biologics. Respondents from these companies suggested that a new "biologics" category be established, which would include RMP for regulatory approval under the PAL, because the characteristics of RMP are markedly different from those of traditional medicinal products, which generally comprise small molecules.

With respect to regulatory guidelines, respondents felt that the framework of the relevant Japanese guidelines was adequate. However, respondents from 3 of the 10 companies suggested that the content of these regulatory guidelines were still imperfectly articulated, and that detailed examples should be provided. They suggested the following were changes that should be made to the regulatory guidelines (by one respondent each): a distinction should be made between autologous cellular products and allogenic cellular products, and the review path for products utilizing biologics and tissue engineering should be clarified.

Regarding the regulatory review of clinical trials under the PAL ("*Chiken*"), two respondents believed that the regulatory review period is time consuming, and one respondent noted that the existence of differing opinions among reviewers often causes confusion among sponsors. Five of the 10 respondents believed that the pre-clinical review to assure the quality and safety of the product prior to initiating clinical trials was too stringent, since the regulatory reviewers tend to require candidate products to be shown to be completely safe. One respondent noted that although regenerative medicine is a new field, regulatory reviewers tend to compare the efficacy of RMP with that of medicinally approved products.

Regarding social issues, 6 of the 10 respondents believed that the Japanese governmental research grant is limited for supporting research into regenerative medicine. Two respondents also believed that understanding of and knowledge about regenerative medicine among the general public and patients is still at a low level.

4. Discussion

Because the field of regenerative medicine in Japan is currently not actively progressing toward clinical application, we investigated the current regulatory systems and guidelines for cellular and tissue-based products in Japan, the US, and the EU. Although the frameworks for pre-clinical safety guidelines relating to RMP are quite similar in Japan, the US, and the EU, differences do exist with respect to the review and approval systems and implementation of the guidelines, and these were found to be major causes of the delayed clinical application of RMP in Japan.

Following an initial questionnaire, we conducted interviews with representatives of 10 Japanese companies that are actively developing RMP for clinical application. Respondents felt that a major barrier is the existence of two separate categories of clinical trials: "*Chiken*" and "clinical research". In Japan, research and development of high-risk biotechnology therapeutics such as RMP generally tends to be carried out by researchers who have obtained governmental research grants or funds from venture capitals, not by established pharmaceutical companies. Thereafter, once clinical development of the candidate drugs has proceeded to some extent, the drugs are likely to be bought by pharmaceutical companies. However, clinical data obtained during "clinical research" under the MAL cannot be utilized for the regulatory review of clinical trial "*Chiken*" under the PAL, because in the relevant law it is considered that the "clinical research" has not been performed using "good clinical practice". This system of separate pathways not only complicates the development of RMP, but also problematic in that data acquired from the "*Chiken*" and "clinical research" pathways cannot be combined for consideration. Moreover, these problems cause difficulties for management of the intellectual property in RMP because the development period is extended, thus reducing incentives for phar-

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maceutical companies to industrialize the RMP. In the US, following the Kefauver–Harris Amendments to the Federal Food, Drug, and Cosmetic Act in 1962, which aimed to protect patient rights and safety, the FDA released a document entitled "Notice of claimed investigational exemption for a new drug" in 1966. This document permitted uniform control of clinical data, and since then the quality of INDs has improved markedly. Moreover, the provision of IND for clinical researchers has been promised in the US. The EU Clinical Trials Directive, which was introduced in May 2004, enforces a central regulatory review for both non-commercial clinical research and commercial clinical trials that aim to support the approval of drugs and biologics. In the interests of achieving a situation where research and clinical development can be carried out efficiently and quickly, we recommend that the separate pathways that currently exist in Japan be combined into a single organized clinical trial pathway, similar to the IND system in the US. This system provides different stakeholders (i.e. researchers, medical doctors, and pharmaceutical companies) with flexibility in drug development.

We found that the Japanese guidelines relating to RMP cover pre-clinical safety issues, including fundamental characterization of the product. However, our interviews revealed that a number of companies developing human cellular-based products urgently require clear examples relating to pre-clinical studies and characterization of cellular and tissue-based medical products. Representatives from a number of companies also stated that their companies are urgently in need of quality, safety, and efficacy guidelines for regenerative medicine candidate products. Therefore, we recommend that the contents of notification nos. 906 and 1314 issued by the Drug and Food Bureau of the MHLW be revised to allow prompt clinical application of RMP in Japan. We also recommend that autologous and allogenic cellular products be distinguished in the guidelines because these cells differ in some important respects.

Regarding the review system, reviews that were too stringent and time consuming were considered barriers for the prompt clinical trial and application of RMP. Japanese regulatory agency tends to require the candidate products to be completely safe. This overly cautious approach has developed against a background of several safety issues with respect to medicinal products. For example, unheated blood products were used for the treatment of hemophilia patients in Japan until 1985, although a warning regarding the use of these products had been issued by the US Centers for Disease Control and Prevention in 1983. The ongoing use of such blood products thus caused HIV infections in Japan, and lawsuits were filed against the regulatory reviewers of the MHLW. This incident showed that there was the potential for regulatory reviewers to be subject to legal action and, hence, the regulatory review process became overly stringent. Therefore, we believe that limited liability for the regulatory reviewers should be introduced, as long as the review is carried out with consideration given to current scientific evidence.

Frequent communication between product developers and the regulatory body is also essential, especially during the early stage of development. Advice from the regulatory reviewer prior to clinical trials can help companies to develop manufacturing schemes and perform appropriate pre-clinical good laboratory practice studies. There is also the potential for the regulatory body to advise on planning the clinical trial from a regulatory point of view. It is also important that the number of regulatory reviewers be increased. Although respondents in this study considered that the performance of reviewers had improved in recent times, there are only approximately 30 reviewers in the Office of Biologics of the PMDA, whereas there are more than 800 reviewers and administrators in the FDA's Center for Biologics Evaluation and Research. Currently, the PMDA is attempting to increase the number of regulatory reviewers **[13]**. However, some company representatives pointed out that the quality and general understanding of the regulatory reviewers, for example having expert knowledge about regenerative medicine and experience working with researchers and companies, is more critical. To this end, we recommend that expert reviewers be sourced from pharmaceutical companies or academia, and that transparency is ensured by mandating that any conflict of interest be declared.

5. Conclusions

In this study, we found that the frameworks for pre-clinical safety guidelines relating to RMP were very similar in Japan, the US and the EU. However, the review system and implementation of the guidelines in Japan are different from those in US and the EU. Our

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interviews revealed that the major barriers to the clinical application of RMP in Japan are (i) the existence of two separate categories of clinical trials, (ii) the stringent review for pre-clinical assurance of quality and safety, and (iii) regulatory guidelines without practical examples showing how the pre-clinical data required for quality and safety assurance should be prepared. For the prompt development of RMP, we believe that the two separate regulatory pathways should be combined into a single organized clinical trial pathway, in line with the IND system. Furthermore, frequent communication between product developers and regulatory reviewers (including meetings) and development of some practical guidelines are necessary. This is the first study in which barriers to the clinical application of regenerative medicine in Japan have been identified. We hope that a revision of the regulatory systems and guidelines will be forthcoming, which will facilitate the clinical application of RMP.

Acknowledgements

We would like to thank the company representatives who participated in this study for their time, and the staff of the MHLW and the PMDA, who gave us valuable suggestions. We also thank Ms. Madoka Sasaki for her critical review of the manuscript. This study was supported by a Grant-in-Aid for Scientific Research from the Ministry of Health, Labour and Welfare, Japan and the Pfizer Health Research Organization to Koji Kawakami.

Appendix A

Interview questions:

1. Relating to the candidate product itself and manufacturing of the product
   - 1-1. Material (autologous cells, allogenic cells, genes, or others)
   - 1-2. Place of manufacture
   - 1-3. Targeted disease
   - 1-4. Barriers relating to manufacturing
   - 1-5. Barriers relating to current good manufacturing practice
2. Relating to research and development
   - 2-1. Pre-/non-clinical studies
     - 2-1-1. Outline of pre-/non-clinical studies
     - 2-1-2. Analytical methods
     - 2-1-3. Development stage
     - 2-1-4. Barriers relating to pre-/non-clinical studies
   - 2-2. Clinical trial
     - 2-2-1. Clinical phase
     - 2-2-2. "*Chiken*" or "clinical research"?
     - 2-2-3. Outline of the clinical trials
     - 2-2-4. Barriers relating to the clinical trials
3. Barriers in developing RMP
   - 3-1. Technological issues
   - 3-2. Regulatory issues
   - 3-3. Social issues
   - 3-4. Other issues

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