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-

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]		
Donor screening	○		○	○	○[e]
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				○	○

Table 1 (*Continued*)

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				○	○[f]
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.

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.

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 is 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 pharmaceutical 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 Center 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

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.

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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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Review

Safety assessment of biopharmaceuticals: Japanese perspective on ICH S6 guideline maintenance

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ABSTRACT — Safety assessment of biopharmaceuticals in preclinical studies is guided by the ICH S6 guideline issued in 1997. Along with enormous experiences and knowledge on safety assessment of some classes of biopharmaceuticals over the last decade, the necessity and feasibility of updating the guideline has been discussed. According to a recommendation by safety experts at the ICH meeting in Chicago in 2006, regional discussions of ICH S6 were held in the USA, EU and Japan. The meeting to clarify the values, challenges and recommendations for ICH S6 from Japanese perspective was held as a part of the first Drug Evaluation Forum in Tokyo on August 10, 2007. Of utmost importance, the "case-by-case" approach must be preserved as the basic principle of the ICH S6 guideline. It is our opinion that oligonucleotides, siRNA, aptamers and related molecules should be excluded from ICH S6 and may be more appropriate for separate guidance. However, based on experiences and accumulated knowledge, there are a number of issues that can be updated including new types of biopharmaceuticals such as bioconjugates, use of homologous proteins and transgenic animals, reproductive/developmental toxicity studies in non-human primates, *in vitro* cardiac ion channel assay and alternative approaches for carcinogenicity assessment. Preliminary recommendations for some of these topics were outlined at the meeting. The overall Japanese recommendation is that the ICH S6 guideline should be updated to address these topics.

Key words: ICH S6 guideline, Biopharmaceutical, Safety assessment, Preclinical

INTRODUCTION

Biotechnology-derived pharmaceuticals (biopharmaceuticals) appeared for the first time in the 1980s, and the numbers of biopharmaceuticals in the market and in development have increased dramatically over the last two decades. A number of concerns/questions were raised in the early 1990s about the scientific justifications for the safety assessment of biopharmaceuticals in preclinical studies, since preclinical safety guidelines for small molecular new chemical entities (NCEs) are usually not appropriate for biopharmaceuticals. To answer some of those questions, the ICH S6 guideline was issued in 1997. The ICH S6 guideline stresses the principle that preclin-

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ical safety evaluation of biopharmaceuticals should be addressed on a "case-by-case" basis. The "case-by-case" approach means that the design and evaluation of safety studies is justified based on an appropriately understanding: (1) of the pharmacology across species, (2) that differences between biopharmaceuticals and NCEs require different endpoints and studies, and (3) that the class of biopharmaceutical influences the endpoints and studies. These principles are still valid and must continue to be preserved. However, enormous experience and knowledge on safety assessment of some classes of biopharmaceuticals has been accumulated while novel types of biopharmaceuticals continue to be developed. Furthermore, to help clarify the regional interpretations of ICH S6, local documents on the safety assessment of biopharmaceuticals have been written in the USA (FDA, 1997; FDA, 2000; Hastings, 2007), EU (CPMP/372/01, 2001; CPMP/SWP/2600/01, 2002; EMEA/CHMP/SWP/294648, 2007) and Japan (Pharmaceutical Non-clinical Investigation Group, 2002; Nakazawa *et al.*, 2004). It was agreed at the ICH Chicago meeting in 2006 that regional meetings in the EU, USA and Japan would be convened to address the potential need for updating the ICH S6 guideline. Future discussions were to be guided by the following key questions: 1) What can be learned from case studies and experience? 2) What is the predictive value of preclinical studies?; and 3) Where does the ICH S6 guideline "work" and/or "not work"? In addressing these questions, topics considered to be important were: new types of biopharmaceutiocals, such as bioconjugates and oligonucleotide medicines, initial dose for first in human study (FIH) selected from preclinical data, non-human primate developmental toxicity studies, *in vitro* cardiac testing, genotoxicity tests, carcinogenicity studies and the use of transgenic models and homologous products. The Japanese regional meeting was held at the first Drug Evaluation Forum in Tokyo on August 10, 2007. Experts from industry, regulatory bodies and academia participated in the meeting. This paper summarizes the Japanese perspective on values, challenges and recommendations for ICH S6 guidelines that emerged from the meeting.

VALUES, CHALLENGES AND RECOMMENDATIONS FOR ICH S6 GUIDELINE

General principle

1. Scope

The ICH S6 guideline was developed for pharmaceuticals derived from biotechnology, i.e. medical products of proteins/peptides and their analogues. It can also be applied to chemically synthesized peptides, most of which have properties similar to biopharmaceuticals as well as to bioconjugates (a protein combined with chemical molecule or a part or full molecule of other protein), although some special considerations are needed, as discussed in the sections of genotoxicity testing, human *ether-a-go-go* related gene (hERG) assay and carcinogenicity studies. In the event that there is a safety concern about a chemical fragment derived from a bioconjugate through degradation and/or metabolism, the concern should be addressed as a NCE. Such considerations for bioconjugates would be shared for protein/peptide analogs with non-natural amino acids. On the other hand, oligonucleotide medicines including antisense, RNAi and aptamers have very different physicochemical and biological properties from biopharmaceuticals, and therefore may need a new guideline for preclinical safety assessment.

2. Basic principle

The most important concept established by the ICH S6 guideline is the "case-by-case" approach. The underlying principle is that an appropriate safety test should be used for each biopharmaceutical considering the available information and the unique nature of each entity. Thus, it allows flexibility in designing the best safety assessment possible and discourages uniformed application of a standard list of studies designed for NCEs. The overwhelming consensus of the meeting was that the "case-by-case" concept must be preserved.

3. Species selection

It is very important to select relevant species for the safety assessment of a biopharmaceutical based on its pharmacological and/or biological activities. However, no relevant animal species are available in some cases. No clear advice is written in the ICH S6 guideline on when and how to use transgenic animals or homologous proteins, although the guideline recommends that these alternatives may assist in the safety assessment of biopharmaceuticals.

The use of homologous proteins to address species difference is more common than transgenic animals. However, it is important to consider that it takes months to years to make and characterize a homologue, and thus the sponsor needs to make a decision as early as possible whether or not a homologue is needed for safety assessment. As described in the ICH S6 guideline, the production process, range of impurities/contaminants, pharmacokinetics, and exact pharmacological mechanism(s) may differ between the homologous form and the product intended for clinical use. The comparability of the homologue with

the clinical candidate is critical for the interpretation of the toxicity results obtained with the homologue. Therefore, the sponsor should pay particular attentions to characterizing the pharmacology and pharmacokinetics of the homologue. For monoclonal antibodies, literature information, *in vitro* binding, function assays, tissue cross-reactivity and Fc activity are useful for the characterization.

Another important consideration when interpreting results using a homologue is the margin of safety. Even if negative findings are obtained with a homologue, the sponsor should still be cautious in the risk assessment of the clinical candidate. Conversely, if a homologue produces more severe toxicity in a rodent study compared to data using the clinical candidate in a monkey toxicity study, it is not a foregone conclusion that the results from rodent homologue studies take precedence over those with the clinical candidate. Additional factors need to be considered including that the homologue may have different pharmacokinetics and/or pharmacodynamics from the clinical candidate. Furthermore, the physiology of the target organ in a rodent can differ significantly from human. Finally, physiological similarity between the monkey and human may make the interpretation of the nonhuman primate studies more relevant to risk assessment of man. Thus, a sponsor should interpret the results from studies using a homologue using case-by-case considerations of all available scientific information, including comparability data between a homologue and clinical candidate, physiology across species and literature data with similar products. If a relevant animal species is available for the clinical candidate, a rodent study with a homologue usually is not needed.

4. Dose selection

The ICH S6 guideline recommends the dose selection for toxicity studies should take pharmacokinetics, pharmacodynamics and the expected clinical dose into consideration. The need for observable toxicity at the highest dose remains controversial for biopharmaceuticals. In some cases, only exaggerated pharmacological effects may be observed in toxicological studies of biopharmaceuticals. It is advised in the Japanese "Points to consider" document (Pharmaceutical Non-clinical Investigation Group, 2002; Nakazawa *et al.*, 2004) that the highest dose may be justified based on the observed plateau for the pharmacodynamic response without respect to toxicological changes (i.e., the maximum pharmacological dose). Other justifications for the highest dose include the emergence of a toxicological change, a multiple of anticipated clinical dose, or a maximum feasible dose. Because multiple different approaches are currently being used, additional scientific discussion may be necessary to establish the best method for setting the highest dose in a preclinical safety assessment study.

The use of select animal data to determine a starting dose for FIH has had little predictive value in some cases (Expert Scientific Group, 2006). For example, no toxicological changes were observed at the highest dose of TGN1412 in monkeys, which was determined to be the maximum feasible dose (Investigator's Brochure, 2005). Many reasons including species differences, insufficient preclinical data and lack of consideration for pharmacology information may have been involved in the failure to predict a safe starting dose TGN1412. The minimum anticipated biological effect level (MABEL) approach, recently proposed in a EMEA guideline (EMEA/CHMP/SWP/294648/2007, 2007), has been proposed as a better method to predict a safe starting dose for FIH from preclinical information. However, Ozaki *et al.* (2006) have argued that for FIH studies in Japan, such a conservative approach would slow down the development of biopharmaceuticals and that the conventional no observed adverse effect level (NOAEL) approach is more appropriate. Therefore, a balance between regulatory control and innovation is needed to deliver safe and effective new medicines to patients. Learning from implementation of the MABEL approach in the EMEA guideline and its effect on the safety and/or duration of clinical development should be considered during future ICH S6 discussions.

INDIVIDUAL STUDIES

1. Repeat dose toxicity studies

There seems to be disharmony among three regions regarding the regulatory requirement on the duration of non-rodent repeat dose toxicity studies (i.e., 6 months vs. 9 months vs. 12 months). Six-month studies are acceptable in Japan and the EU unless there is a specific concern for the investigational biopharmaceutical. Available data from approvals supports the position (Clarke *et al.*, 2007). Further scientific discussion is needed.

It is recommended in the ICH S6 guideline that immunogenicity should be measured and characterized in a repeat dose toxicity study. This information is helpful for the interpretation of toxicity study results, but it has little predictive value for immunogenicity in humans, as discussed in the ICH S6 guideline. Although the recommendation for immunogenicity testing is still useful, there does not appear to be a clear need for immunogenicity in all studies. It may be more efficient and informative

for some biopharmaceuticals when the clinical treatment duration, patient population and biological activities of biopharmaceuticals (e.g., growth factors and immunosuppressants) are considered. Nevertheless, the necessity of carcinogenicity assessment for growth factors and immunosuppressants has not yet been fully scientifically justified. For instance, it was recently reported that negative results with mouse and rat growth hormones were obtained in 2-year bioassays (Farris *et al.*, 2007). The rodent findings are consistent with existing clinical data suggesting no risk for tumors following human growth hormone treatment in patients (Allen *et al.*, 1997). Thus, the animal findings provide little additional value for the carcinogenicity risk assessment of biopharmaceuticals if there is enough human data with similar molecules. Besides human growth hormone, carcinogenicity assessments were conducted for insulin and its analogues, basic fibroblast growth factor, FSH and PTH (Advisory Committee Briefing Document, 2001; Hodsman, 2005; Barbehenn *et al.*, 2001; FDA Draft Guidance, 2000). The relevance of these studies to human risk has not been determined.

The concern associated with these growth factors or hormones is mitogenicity but not mutagenicity. Furthermore, in many cases, rodents are generally inappropriate for assessing biopharmaceuticals due to a lack of pharmacological response or neutralizing antibody production. Thus, a 2-year rodent bioassay should not be a regulatory expectation. Proliferative lesions noted by histopathological examination in a chronic toxicity study using a relevant animal could be an early indicator of potential carcinogenicity. For histopathological evaluation, techniques such as proliferative cell nucleic antigen (PCNA) or replicative DNA synthesis (RDS) is recommended in the chronic toxicity study. However, proliferative changes are clearly not sufficient to fully characterize the human risk, which can only be determined by clinical data. Two-step carcinogenicity testing may be an option if rodents are relevant species, while rodent studies using homologous proteins or surrogate antibodies, or the use of humanized mice (Bugelskil *et al.*, 2000), may be other choices. Besides those *in vivo* data, results of *in vitro* proliferation assay using a target cells may be useful for the risk assessment carcinogenicity. It is important to consider all options and to select an approach on a case-by-case basis using scientific justification for the selected evaluation.

CONCLUSION

Japanese experts from industry, regulatory bodies and academia recommend updating the ICH S6 guideline to reflect experience and knowledge accumulated over the last decade, although the "case-by-case" approach must be preserved as a basic principle. The major areas for the update are as follows: 1) Transgenic animals and homologous proteins could be an alternative in the case of no available relevant animal species; however, there are limitations with regard to the safety margin, validation, historical data, and physicochemical and pharmacological differences from the clinical candidate. Therefore, if a relevant animal species is available for the clinical candidate, a rodent study with a homologue usually is not needed. 2) Monkey reproductive/development toxicity studies are feasible and meet regulatory requirement, although there are some technical difficulties. 3) Most biopharmaceuticals cannot block potassium channels because they cannot penetrate inside the cell to block the channel. However, if QTc prolongation is observed in an *in vivo* study, an *in vitro* study including hERG should be considered. 4) Alternative approaches for the risk assessment of carcinogenicity (e.g. a chronic toxicity study with proliferative markers in a relevant animal) are useful and justified in many cases, since the concern for biopharmaceuticals is mitogenicity rather than mutagenicity. 5) Bioconjugates are a new category of ICH S6 and need specific considerations, while oligonucleotides should be out of scope.

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to conduct immunogenicity testing only when changes in biopharmaceutical plasma levels or toxicity potentially related to immunogenicity are important to the overall risk assessment.

2. Reproductive/developmental toxicity studies

Because the ICH S6 guideline allows flexibility in designing toxicity studies, a sponsor may consider conducting a modified reproductive/developmental toxicity study in rodents or rabbits even with mild immunogenicity. However, these conventional animal species may not be applicable if severe neutralizing antibody production occurs or if there is a lack of pharmacological response. In these cases, non-human primates (NHP) studies with the human product, studies in rodents with a homologue or studies in transgenic animals may be useful alternatives (JPMA and PMDA collaboration group, 2003; Nishimura, 2004; Evaluation Report). Among these alternate choices, NHP should be the first choice due to difficulties in interpreting data from homologues or transgenic animal as noted above. However, there are difficulties in using NHP for reproductive/developmental toxicity studies including low fertility, single fetus, relatively high abortion rate, long life cycle and seasonal reproduction with Rhesus monkeys. Furthermore, practical and ethical concerns impact the use of large number of NHPs per group (i.e., more than 12 females per group for Embryo Fetal Development Study). Therefore, historical data on NHP results from the testing facility is critical for the interpretation of results from these studies.

3. Safety Pharmacology

The ICH S7A guideline (2000) applies to both biopharmaceuticals and NCEs, but it is unclear from the scope in the ICH S7B guideline (2005) whether or not an *in vitro* cardiac channel assay, such as hERG and action potential duration (APD) assays, is required for biopharmaceuticals. Therefore, there seems to be some confusion among countries on the regulatory requirement. The Japanese "Points to consider" document (Pharmaceutical Non-clinical Investigation Group, 2002; Nakazawa *et al.*, 2004) suggests that such an *in vitro* study should not be applied for biopharmaceuticals because in contrast to NCEs, biopharmaceuticals are unlikely to interact with this cellular channel (Tristani-Firouzi *et al.*, 2001; Recanatini *et al.*, 2005).

Some new findings reported after the publication of Japanese "Points to consider" document suggest that the ion current through the hERG channel can be modified by agents that do not block the channel. It has been reported that some toxins have high affinity for and block the hERG channel (Zhang *et al.* 2003; Zhang *et al.*, 2007). The toxin binding site is located external to the channel and consists of a specific amino acid sequence. Although most biopharmaceuticals are unlikely to bind to such a specific toxin-binding site or produce a secondary blockade of hERG channel, this possibility cannot be ruled out. However, it is likely that these effects would be detected by *in vivo* electrocardiogram (ECG) evaluations. Therefore, it is recommended that if there is a signal indicating QTc effects in an *in vivo* study, the mechanism should be discussed in context with relevant scientific information and/or *in vitro* study data including the hERG assay. Furthermore, bioconjugates with an organic linker may have properties of both biopharmaceutical and NCE. If small fragments derived from a bioconjugate are a concern, they may have to be dealt with like a NCE. However, it may be difficult to identify, synthesize and examine all possible chemical fragments of a bioconjugate using *in vitro* studies. Therefore, the decision to conduct or not conduct an *in vitro* study should be made based on the results of an *in vivo* study in which both a parent bioconjugate and all fragments are tested as a whole for the potential of QTc prolongation. If a scientific explanation from existing information is possible for QTc prolongation observed in an *in vivo* study, additional *in vitro* study may not always be needed.

It has also been reported that tumor necrosis factor-α (TNF-α) consistently and reversibly decreased hERG current probably by stimulating superoxide anion (Wang *et al*, 2004). This is a secondary effect but not direct blockade of the hERG channel. Testing for these potential secondary effects of biopharmaceuticals is not expected.

4. Genotoxicity studies

Genotoxicity studies routinely conducted for NCEs are not needed for most biopharmaceuticals because of the failure of transmembrane penetration of biopharmaceuticals, due to their high molecular weight. As described in the previous section, genotoxicity studies with some bioconjugates may provide scientific value for the assessment of their genotoxicity risk (Gocke *et al.*, 1999). The decision to conduct genotoxicity studies and the experimental design should be scientifically justified. For example, if no degradation of a bioconjugate occurs or if there is a precedent for using a particular linker, genotoxicity studies may not be needed.

5. Carcinogenicity studies

According to ICH S6 guideline, a standard carcinogenicity assessment is not needed for most biopharmaceuticals. However, there may be a cause for concern

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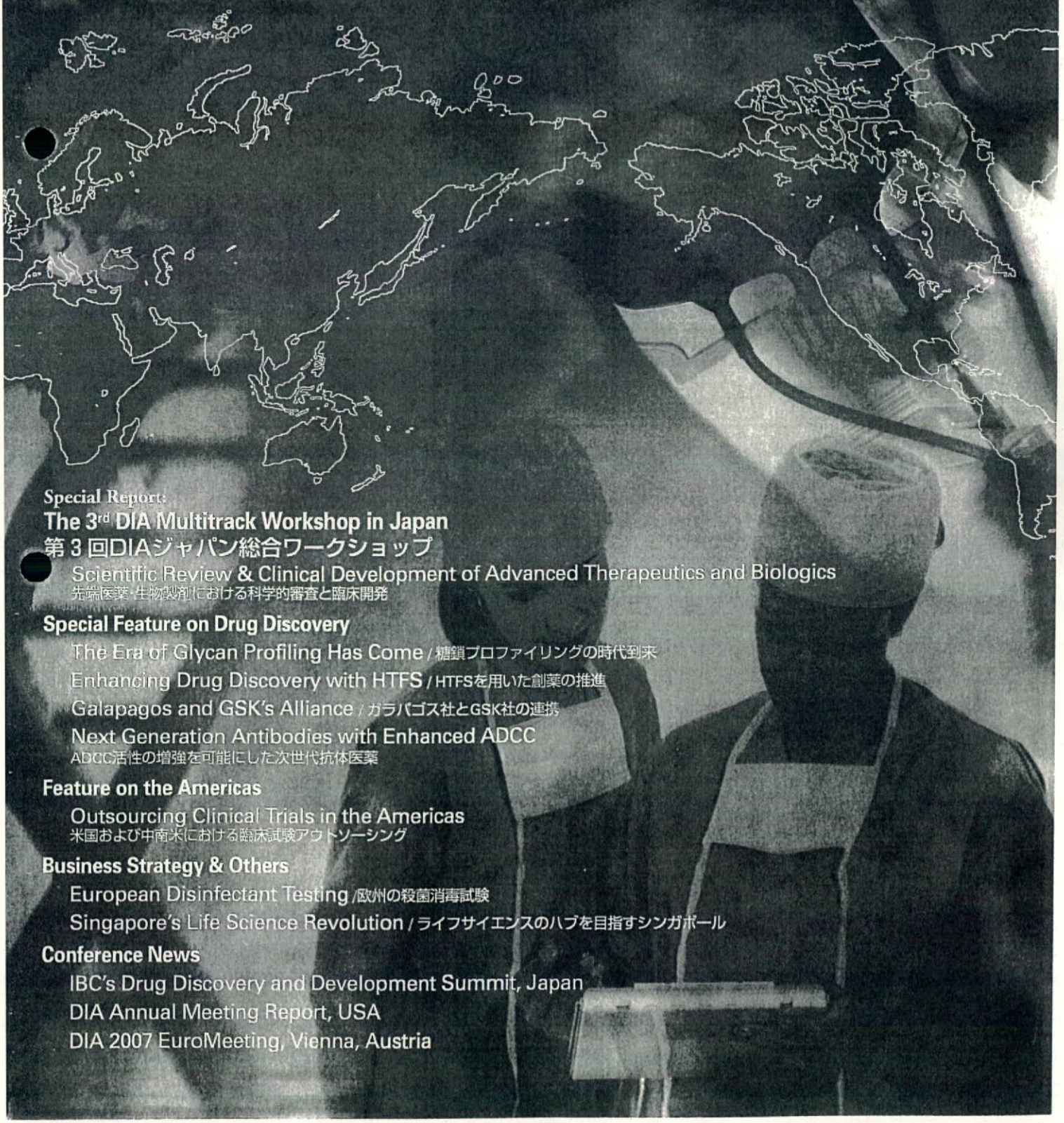

Special Report:

The 3rd DIA Multitrack Workshop in Japan
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Special Report from The 3rd Multitrack Workshop in Japan
スペシャルレポート：第3回DIAジャパン総合ワークショップ

本レポートは，2006年10月に東京にて開催された第3回DIAジャパン総合ワークショップの中から，川上浩司氏（京都大学大学院医学研究科 薬剤疫学分野教授）の基調講演"Scientific Review and Clinical Development of Advanced Therapeutics and Biologics"の概要をまとめたものである。

ポストゲノム時代に突入した現在，疾患の原因遺伝子をターゲットとする分子標的医薬などのいわゆる「バイオ医薬」の研究開発が世界的な潮流となっている。このような細胞や遺伝子をターゲットとする医薬品の研究開発では，従来の製薬企業における研究開発よりも，大学などのアカデミアにおける基礎研究から探索されたシーズを開発へつなぐほうがより効果的である。

しかしながら，日本においてはこのような医師・研究者による臨床研究の実施方法や費用に関する問題，規制当局側の審査・認可業務に関する問題など多くの課題を抱えている。

川上氏はこれらの問題点について生物製剤にフォーカスして日米の比較を示しつつ，産官学連携の必要性を唱えるとともに，今後日本が取り組むべき改革について提言した。

This report summarizes Keynote Presentation on "Scientific Review and Clinical Development of Advanced Therapeutics and Biologics", delivered by Prof. Koji Kawakami* (Professor, Dept of Pharmacoepidemiology, Kyoto University, Japan) during the 3rd Multitrack Workshop in Japan held in October 2006 in Tokyo.

In the post-genome era, so-called "bio-pharmaceuticals", such as molecular-targeted drugs against the causal gene of diseases, are increasingly becoming the main stream of drug research and development. Such R&D, using cells/tissues or genes, is more effectively performed in the academic environment as translational research (universities, research institutes/hospitals) rather than pharmaceutical company laboratories.

In Japan, however, there are accumulated issues including complicated methodology and funding for clinical research to be conducted by physicians/researchers, review and approval system related problems, including lack of experience of the officers at the regulatory agency.

Focusing on "Biologics", Prof. Kawakami discussed differences between FDA and PMDA (regulatory agency in Japan under the Ministry of Health, Labour and Welfare), showed future perspectives that Japan has to seriously and urgently tackle, and made proposals towards collaboration of industry, regulatory agency and academia.

先端医薬・生物製剤における科学的審査と臨床開発について
Scientific Review and Clinical Development of Advanced Therapeutics and Biologics

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生物製剤とは何か

米国における生物製剤の認可行政機関であるFDAのCBER（Center for Biologics Evaluation and Research; 生物製剤評価研究センター）の定義によれば，生物製剤とはヒトや動物，その他の生物など，いわゆる"living source"に由来する細胞，組織，遺伝子などに修飾を加えてヒトの治療法として用いるものの総称である。多くの生物製剤は規格化（characterization）が困難な複合物であり，他に治療法のない疾患や症状に対する先端医療として用いられ，バイオテクノロジーを駆使して製造されている。

現在，FDAのCBERにおいて審査・認可を受ける品目リストを**Table 1**に，また，実際に日・米にて開発中の生物製剤例を**Table 2**に示す。

What are Biologics?

The word "Biologics" is a terminology for materials derived from "living sources", such as cells/tissues and genes from humans, animals and/or microorganisms. Most biologics are complex mixtures that are not easily identified or characterized, and most biologics are manufactured using biotechnology including gene manipulation. Biological products often represent the cutting-edge of biomedical research and, in time, may offer the most effective means to treat a variety of medical illnesses and conditions that presently have no other treatments available (definition by CBER at FDA).

Current list of Biologics at CBER is shown in **Table 1**, and some examples of biologics under development in Japan and the US are shown in **Table 2**.

表1　FDA (CBER)において審査・認可を受けている生物製剤の品目リスト
Table 1. List of Biologics (CBER, FDA)

・細胞治療＆遺伝子治療	– Cellular & Gene Therapy
・ワクチン(癌ワクチン，感染症に対する予防的ワクチンなど)	– Vaccines（tumor, prophylactic)
・アレルゲン(アレルゲンパッチテスト，診断用テスト)	– Allegenics (Allergen patch tests, diagnostic tests)
・医療用デバイス(HIV診断キット，他)	– Devices (HIV test kits, etc)
・移植用組織(骨，皮膚，角膜，他)	– Tissue (bone, skin, corneas, etc)
・血液(血液成分，関連製剤)	– Blood (blood components and related products)
・異種間移植	– Xenotransplantation

表2　開発中の生物製剤の例（主として日・米，一部UK)（{P} はPhase)
Table 2. Some examples of Biologics under development: Japan and US (*UK) {Phase}

Biologics	Japan	USA (*UK)
Gene Therapy 遺伝子治療	**Anges MG**（大阪大発） HGF vascular disease (angiogenesis/血管再生治療) {P2 in US, P3 in Japan}	遺伝子治療として承認されたものはまだないが，P３に入っているものがある。 **Introgen** Adenovirus-p53 (head & neck cancer) {P3}
	Oncolys BioPharma（岡山大発） Telomelysin®(hTERTp-Ad5, for various solid tumors) {P1 in US}	
Cancer Vaccines 癌ワクチン	**GreenPeptide, Co.**（久留米大発） Peptide vaccine—"tailormade" {P1 in Japan}	**Vical, Inc** Malignant melanoma DNA vaccine (HLA-B7) {P2}
		Cell Genesys GM-CSF (GVAX) for prostate cancer (前立腺癌) {P3}
Cell & Tissue Therapy 再生治療	**BCS, Inc**（東海大と共同開発） Autologous skin regeneration (自家皮フを用いた再生) {preclinical}	***Intercytex (UK)** Topical woundcare product for persistent chronic wounds　褥創，静脈性潰瘍 {P3}
Blood Substitutes 血液代替物	**Oxygenix, Co., Ltd.**（早稲田大発＆慶應義塾大学発） Artificial Red Blood Cells (OXY-0301) 人工酵素運搬体) {preclinical}	
RNAi RNA干渉，siRNA薬		**Alnylam Pharmaceuticals** Direct RNAi™, ALN-RSV01 (respiratory syncytial virus) {P1}
		Sirna Therapeutics, Inc.** Sirna-027 (siRNA for AMD) {P2} (**acquired by Merck in Oct. 2006)

米国FDAにおける生物製剤の審査プロセス

米国でclinical trialを実施したい企業や大学の研究者，大学発ベンチャーなど(すべてsponsorと呼ばれる)は，例外なくIND (Investigational New Drug Application)を準備してFDAの該当機関に提出し，承認されれば臨床試験を開始できる。すなわち，未承認薬のclinical trialsはスポンサーが製薬企業であれ，アカデミアであれ，すべてIND制度による一元管理になっている。

なお，IND申請に先立ち，スポンサーはpre-INDと呼ばれる予備審査を受けることができる。これはIND申請内容を簡略化して記載し，かつ，FDAに質問したい事項を含んだプレゼンテーションパッケージのようなもので，IND本申請におけるポイントや質問事項，問題点などを事前に無料相談できる制度である。

Pre-INDに引き続き，IND申請となるが，たとえば，遺伝子治療を例にとると，CBER内のOffice of Cellular, Tissue, and Gene Therapies (OCTGT)が審査・認可業務を担当しており，その中の3部門の審査官による審査の流れは**Fig. 1**のとおりである。

Review Process of Biologics at CBER (FDA)

In the US, companies and academia, bioventure companies from universities are called "sponsors", and all sponsors are requested to submit IND (Investigational New Drug application) to FDA. If approval is given, they can start the clinical trial. As such, regardless of companies and academia, clinical trials for non-approved drugs (and/or indications) are centrally controlled by FDA.

Sponsors may request preliminary advice from FDA as a form of pre-IND. Pre-IND is a kind of abbreviated presentation package which includes key points (description of the product, description of clinical indication and approach), identification of specific issues and various questions to be addressed by FDA at free of charge.

Taking a gene therapy as an example, review will be done by three review divisions under Office of Cellular, Tissue, and Gene Therapies (OCTGT) at CBER as shown in **Fig. 1**.

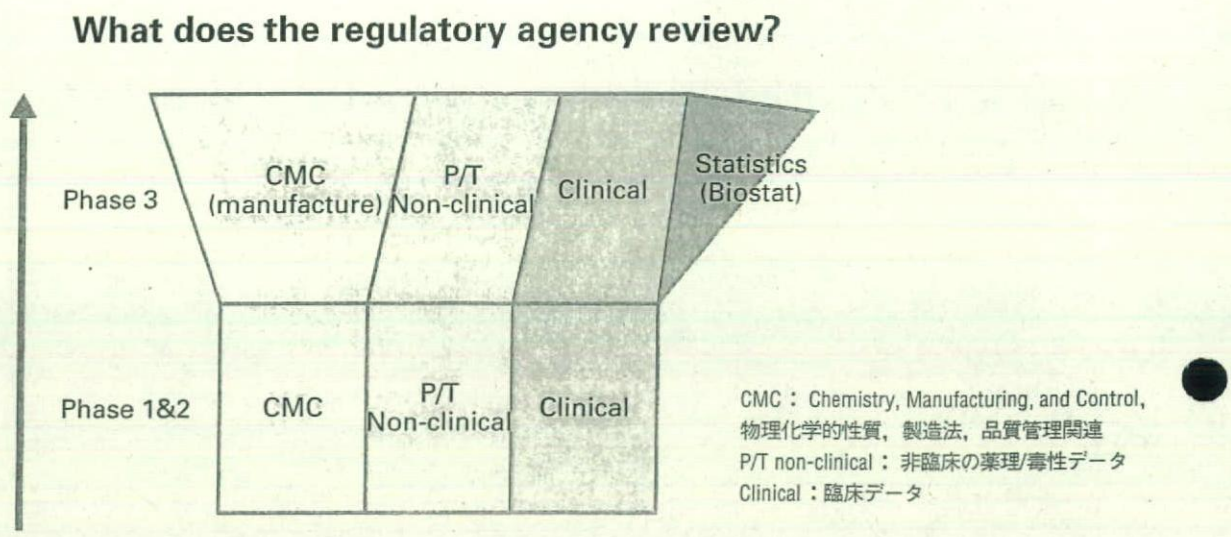

Fig. 1 Evaluation Process of CBER (FDA)

IND申請後，FDAは30日以内に審査結果をスポンサーに通知する。先端医療の場合は院内・研究室内製造であることが多いため，製造工程や製造場所が変わった場合，どのように品質を確保するかなどのcomparability も非常に重要になってくる。

生物製剤の場合は従来の合成化合物と異なり，最初に臨床試験を実施してみないとわからない点が多々あるため，開発を進行しながら製剤の規格化(characterization)やGMPの準備を行うことになる(**Fig. 2**)。生物製剤の審査で特に重要視される事項を**Table 3**に示す。

After submission of IND, FDA is supposed to inform the review results to the sponsor within 30 days. In the case of advanced therapy, the product is usually manufactured in the hospital/university lab, comparability tests are also very important to ensure the quality and homogeneity of the product when it is manufactured by different manufacturing processes at different laboratories.

Unlike the conventional chemically synthesized compounds, there are various unknown matters. Therefore, its clinical trial will be eventually done

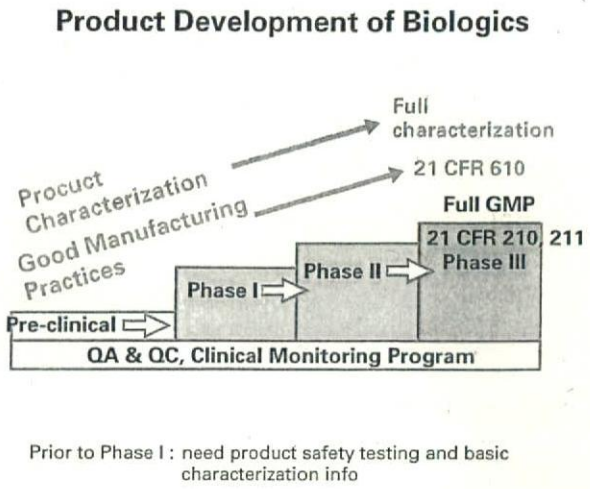

Fig. 2 Product Development of Biologics　医薬品候補としての生物製剤の開発

表3　生物製剤の審査で特に重要視される事項
Table 3. Regulatory Concerns Common to All Biologicals

- 安全性—Product Safety
  細菌，エンドトキシン，マイコプラズマなどの混入やウィルスなどの感染の有無
  Sterility, endotoxin, mycoplasma, adventitious agents
- 製品の特性—Product Characterization
  製剤そのものの特徴，力価，純度，その他
  Identity, potency, purity, other assessments
- 製造工程の管理法—Control of the Manufacturing Process
  品質，プロセス内の試験，施設，標準手順書，記録管理，QA/QC
  Quality of materials and in-process tests, facility, SOPs, record keeping, QA/QC
- 再現性/ロット間の均一性—Reproducibility/consistency of product lots
  各ロットにおける候補物の放出試験
  Lot release testing of the final product

日本における審査の流れ：臨床試験と臨床研究

日本の審査機関としての医薬品医療機器総合機構(PMDA；Pharmaceuticals and Medical Devices Agency)では2007年までに350名のスタッフを擁することを計画しており，そのうち生物製剤の担当官数は2006年の19人から29人への増員が決定されている。ちなみにFDAはスタッフ総勢約9000人，CBERは約800人体制である。

日本では，製薬企業が規制当局への新薬承認申請を前提として実施する臨床試験(すなわち「治験」)と，病院の医師・研究者が製薬企業からの依頼とは無関係に，企業から医薬品等の供与を受けずに実施する医師・研究者による「臨床研究」(意味的にはpatient-oriented research)という道がある。前者は新薬の有効性と副作用を調べることを目的としており，薬事法に則って行なわれ，治験を実施しない限り規制当局の承認は得られない。一方，後者は医療行為として医療法(Medical Affairs Law)の下で実施されるもので，臨床研究終了後のゴールとしては，当該病院の中だけの「先進医療」あるいは「高度先進医療」として認められてきた(**Fig. 3**)。

しかし2006年7月，従来の高度先進医療と先進医療が統合され，同年10月より特定療養費制度が廃止され，保険導入を前提とする新たな制度(新たな枠での先進医療)が導入されることになった。したがって，今後は臨床研究であっても申請要件が治験なみに厳しくなることが予想され，結局は治験として申請するほうがよいのではないかと考えられている。いずれにしても，米国の臨床試験がFDAへのIND申請という形で一元化されていin parallel with the product's characterization and GMP preparation processes (**Fig. 2**). Especially important matters for biologics during the FDA review are shown in **Table 3**.

Review Pathway in Japan: Clinical Trials and Clinical Research by Academia

PMDA (Pharmaceuticals and Medical Devices Agency) is the regulatory agency in Japan, according to them, 350 officers will be secured during 2007. Among them, officers in charge of biologics department will be increased from 19 in 2006 to 29. In comparison, number of officers at FDA is approx. 9,000, and 800 for CBER.

In Japan, clinical trials to be sponsored by pharmaceutical companies is called "Chiken (clinical trials)" in Japanese (be careful not "chicken" in English!!), and clinical trials to be performed by academia (physicians/researchers), which is not requested by pharmaceutical companies nor received any funds from companies is called "Clinical Research", meaning "patient-oriented research" in another word. Purposes of the former is to assess the efficacy and adverse events of the product, and the latter is to be performed as a part of medical treatment. Approval from the regulatory agency will not be given to the latter case, as it is regarded as advanced therapy as a goal at the performing hospital, and therefore, the application is limited to the hospital only (**Fig. 3**).

In July 2006, however, the "advanced therapy" and "highly advanced therapy" were combined to a new system, which will lead to make the clinical research more rigid just like "Chiken" by com-

るのに比べ，日本では製薬企業による臨床試験と，医師・研究者によって実施される臨床研究の2つの方法があり，システムが複雑である。

panies, or, completely the same system might be introduced in the near future. As such, unlike centrally controled system by FDA, the current system in Japan is much more complicated.

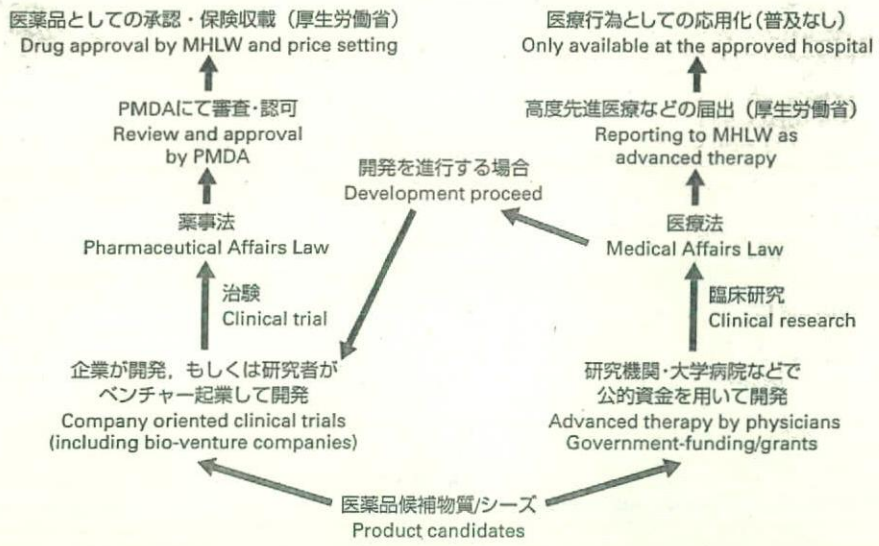

Fig. 3　日本における臨床試験（治験および臨床研究）の現状
Pathways of Clinical Trials (by company or academia) in Japan

日本における臨床試験実施に関する問題点

以上，日本における問題点をまとめると次のとおりである：

1) 大学の研究者にとってしくみが複雑。臨床研究として実施したとしても，いつかはベンチャー企業をつくるかライセンスアウトして臨床試験をやり直さなければ承認は得られない。
2) PMDAは医師による臨床研究の審査を行って来なかったため，生物製剤のような先端医療に関わる医薬品を扱った経験がない。したがって審査に時間がかかる。
3) 米国では臨床試験が一元管理され，ウェブなどで公開・宣伝されて普及しているが，日本では規制当局に臨床試験データベースが構築されておらず，宣伝・普及していない。

近年，日本の製薬企業による臨床試験の海外実施が急増している。このような状況を打破するため，経済産業省も治験体制の改革に向けて厚生労働省に働きかけており（第6回ライフサイ

Problems in Japan Towards Performance of Clinical Trials

Problems in Japan can be summarized as follows:

1) Because of the double pathways in Japan, the system itself is complicated procedure for academic researchers.
2) The agency (PMDA) lacks experience on the advanced products (such as biologics) because they have not reviewed academic researchers-sponsored clinical trials so far.
3) In the US, database of clinical trials has been set up, and promoted on the web for public. However, the formalized database of clinical trials is not set up by the authority in Japan, so, promotion has not been done properly.

In recent years, clinical trials by Japanese pharmaceutical companies are increasingly performed overseas. In order to put an end to such situations, the Japanese Ministry of Economy, Trade and Industry (METI) recently worked on and urged the need for urgent improvement towards the MHLW. It's now or never.