(FD&C) act といった法律を行使する機関であり，その法の解釈として，より具体的な規制である Code of Federal Regulations（CFR，うち第21項が IND 制度や認可についての項目）が運用されている。

2. 細胞・組織を利用した生物製剤および医療機器の審査について

FDA は，7つのセンター・部署から構成されている。このうち医薬品などの認可行政機関としては，薬品を扱う Center for Drug Evaluation and Research（CDER），生物製剤を扱う Center for Biologics Evaluation and Research（CBER），医療機材や機器などを扱う Center for Devices and Radiological Health（CDRH）の3つが存在する。CBER の扱う生物製剤には，

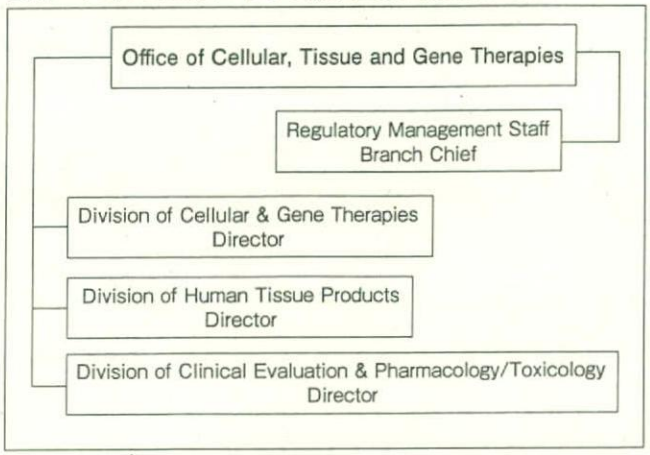
- 遺伝子治療
- 細胞治療（再生医療を含む）
- 異種間移植（組織移植）
- 癌ワクチン
- アレルゲンパッチテスト，診断用アレルゲン
- 抗毒素各種
- 感染症予防ワクチン
- トキソイド，免疫用毒素
- 血液製剤，血液代替物

が挙げられる。特に細胞医薬，組織医療品に関しては，CBER 内の Office of Cellular, Tissue, and Gene Therapies（OCTGT）が審査・認可を担当している。OCTGT は3つの division により構成されるが，製剤としての chemistry, manufacturing, and control（CMC= 物理化学的性質・製造・品質つまり規格および試験方法，安定性）を担当する Division of Cellular and Gene Therapies（DCGT），clinical trial のプロトコルや IRB，非臨床データを担当する Division of Clinical Evaluation and Pharmacology/Toxicology（DCEPT）が細胞医薬の審査と行政指導に，また Division of Human Tissue Products（DTP）が組織医療品や臍帯血などに関係する部署である（図❶）。

3. 細胞製剤を用いた臨床試験の初回申請と審査の流れ

まず，アメリカ国内で新規の医薬品候補物あるいは生物製剤の clinical trial を実施したい企業，大学の研究者など（sponsor）は，IND 申請のパッケージを用意しなければならない。IND パッケージには製剤の説明，製剤および臨床試験の科学的な意義，製造法と品質管理関連（CMC），試験のプロトコル，IRB やインフォームドコンセントなどの整備・取得，薬物動態・毒性・安全性のデータ，実施医師（PI：principal investigator）の履歴書・業績集などが含まれる。IND 申請に先立って，申請者は pre-IND と呼ばれる予備審査を受けることができる。引き続いて IND 申請となる。FDA は申請パッケージを受理し，IND ナンバーを付けた後，当該審査部署の割り振り担当の事務官（あるいは審査官）の指定した審査官（製剤，非臨床，および臨床の3人の審査官）にパッケージを送付する（図❷）。当該申請に pre-IND が行われていた場合は，通常同じ審査官が IND 審査を担当する。初回申請（original IND）の審査期間は原則 30 日以内となっている（30-day rule）。もし審査期間内に IND 申請者への質問事項，確認事項などがある場合，電話あるいは Fax にて連絡がなされる。申請者である企業あるいは研究機関の regulatory affairs（薬事担当者）との連絡が審査期間内に取れない場合や，質問事項に対する回答に審査官が納得しなかった場合には，その IND は clinical hold（治験のスタートを認めない）との扱いになる。審査期間後，電話にて事務官あるいは必要に応じて審査官が審査結果を申請者に伝え，その後，上官の認証（concurrence），公

図❶　FDA-CBER における細胞医薬の規制関連部局



文書作成がなされる。公文書作成の際には，担当事務官によってCFR（code of federal regulations）からの規制事項の引用が行われる。

IND申請が受諾されると，申請者（あるいは臨床試験実施医師）は患者のenrollmentを開始することができる。FDAによるoriginal reviewに際してminor commentsの枠(clinical hold issueに至らない範囲)で疑問点・照会事項があった場合は，それに対する回答文，データなどをamendmentとしてINDを担当する審査官に提出することが望まれる。また，治験中に何か重篤な副作用や安全性情報（SAE：severe adverse events）があった場合，製造方法に変更があった場合，治験医師に変更があった場合，年度末報告なども，FDAにamendmentを提出する義務がある。

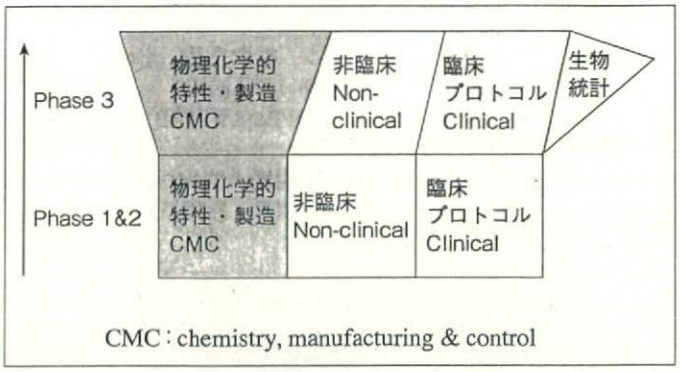
4. 細胞医薬の審査および認可の現状

通常のIND申請を行っての臨床試験におけるCMC水準は，連邦政府の規制集（CFR），特に21CFR 312.23 (a)(7)(i)に従う必要がある。しかしながら，特に再生医療用途や癌ワクチンなどに用いられる細胞医薬に関しては，"Guidance for reviewers: Instructions and template for chemistry, manufacturing, and control（CMC）reviewers of human somatic cell therapy INDs"（draft guidance, 2003年8月）が発表され，規制側（FDA審査官）および開発者（大学や製薬企業）双方に対しての基本的な安全性評価の考え方について記されている。本ガイドラインにおいては，表に示すように細胞医薬としての特徴（**表❶**），製造（**表❷**），評価（**表❸**），その他（**表❹**）の各項目において審査が行われることが明記されている[1]。

5. Phase 1 cGMPについて

細胞医薬を含む昨今のバイオテクノロジー技術を応用した創薬を行う大学などアカデミアの研究機関やバイオベンチャーの施設，資金，経験，知識では，市販後製造を念頭においた1978年9月の医薬品・生物製剤に関するcGMP（good manufacturing practice）基準を定めた連邦行政規則（21CFR 210/211），あるいは1991年のGuidance on the Preparation of Investigational New Drug Products（Human and Animal）への対応が困難になってきている。そこで，2006年1月，米国FDAのCDERおよびCBERから"Guidance for Industry: INDs - Approaches to Complying with CGMP During Phase 1"（以下，Phase 1 cGMP）がドラフトガイダンスとして発表された。CDERとCBERの連名となっていることからわかるように，低分子化合物などの医薬品のみならず生物製剤（バイオロジクス）をも対象として，Phase 1臨床試験の試験物質（治験薬）製造のcGMPに関する当局の考え方を広く示したものである[2]。

図❷ 米国におけるバイオ医薬品を用いた臨床試験の審査項目と開発段階



Phase 1 cGMPガイダンスにおいては，大学などアカデミアにおける研究室レベルで製造される試験物，マイクロドーズなどのexploratory studiesで使用される試験物・生物製剤などへの適用が想定されている。このうち，生物製剤にはワクチン，アレルゲン，体内診断用製剤，血漿由来製剤，血液・血液成分，遺伝子製剤，細胞医薬，異種間移植も含まれている。逆に，適用外となるのはPHS act（section 361）に限定的に規定されるヒト細胞あるいは組織治療用品，医療機器，Phase 2あるいはPhase 3にて使用される医薬品あるいは生物製剤，またすでに承認を受けている医薬品や生物製剤の適応拡大のためのPhase 1試験である。なお，ガイダンスに記されているように，臨床試験の被験者の安全性を担保するという基本的なCMC審査の精神に則り，試験物の同一性（identity），品質（quality），精製度（purity），力価（strength），生物学的機能（potency）はこれまでどおり審査

表❶　細胞医薬としての特徴につき臨床試験申請に含まれるべきこと

1. 細胞 - allogenic，autologous
   → 細胞ソース，修飾プロトコル，採取方法，ドナースクリーニング，病原体検査（allogenic）
2. 細胞バンクシステム - Master Cell Bank（MCB），Working Cell Bank（WCB）
   → 安全性，アイデンティティ，純度，安定性
   → 細胞の活性度，培養条件，保存条件，継代後のフェノタイプの安定性
3. 試薬
   → 最終製剤に含まれないこと（FBS，トリプシン，成長因子，サイトカイン，抗体，抗生物質など）
   → ソース，質，品質保証（CoA）
4. コンビネーションプロダクト
   → SOP（standard operating procedure：標準作業手続書）ガイドラインが公布済み
   → Office of Combination Products によるコーディネイト

表❷　細胞医薬としての製造につき臨床試験申請に含まれるべきこと

1. 細胞の準備
   → 採取方法，閉鎖系システムか否か，放射線により増殖不能にしても必要な特性を維持しているか，1つ1つのプロセスにかかる時間
2. 最終段階での回収
   → 遠心，洗浄の状態と方法
3. 最終製剤の組成
   → 細胞の濃度，運搬データ

表❸　細胞医薬としての評価につき臨床試験申請に含まれるべきこと

1. 微生物の混在
   → Sterility テスト，テスト時期，マイコプラズマ
   → 外来性病原体については *in vitro*（ウイルスによる細胞感作），*in vivo*（マウス，卵）
2. アイデンティティ
   → 複数の細胞が使用されている場合，区別が必要，細胞表面マーカー，遺伝子多型
3. 純度
   → 製造に使用した試薬の混在，エンドトキシンレベル（pyrogenicity）< 5 EU/kg 体重 /dose
4. 力価・活性
   → 相対的生物学的機能の評価，Phase 2 終了時までに測定法を開発すること
5. その他
   → 細胞治療薬に general safety は不要，バイアビリティ（> 70%），細胞数（ドーズ）の最小量，最大量とその理由

表❹　細胞医薬としての臨床試験申請に含まれるべきこと（その他）

1. 製剤の追跡（autologous- 採取から投与まで）
2. ラベリング
   → 製造中途および最終製剤の記載事項の遵守，患者の 2-ID が必要（autologous）
   → autologous でドナースクリーニングをしていない場合はその旨を明記
3. 容器，キャップ
4. 環境要因（製造）
5. バリデーションと品質管理
   → 施設，cGMP，QA/QC，無菌状態での製造
6. 生物統計

される。また，必要に応じて，当局からの査察対応もありうることが明記されている。

Phase 1 製剤の製造に際しての品質管理の要件としては，明確な製造手順の記載，適切にコントロールされた設備，そして正確かつわかりやすく記録された製造とテストのデータが望まれる。また，cGMP 製造の要件としては，ディスポーザル器具を使用すること，容器に装填されて販売される試薬の水（water for injection：WFI）を使用すること，閉鎖系の製造システムを利用すること，特に大学などの研究機関においては外部受託機関や共同施設などを利用することなどが例として示されている。いずれにせよ，製造環境における有害物質の可能性を同定して評価すること，そして試験物の品質の安全性を確保しリスクを最小限にするために製造前・製造時に適切な対処をとることが肝要である。

なお，組織医療品に関しては，医薬品や細胞製剤の GMP 基準よりもさらに規格の設定が困難であることがあり，弾力的かつ個々の事例に応じた対応が必要と考えられるようになった。そこで，医療や移植に用いられる組織（臍帯血も含む）について，2004 年 11 月に current Good Tissue Practice（cGTP）基準が公表され，現在は本基準に基づいた規制と行政対応が行われている。

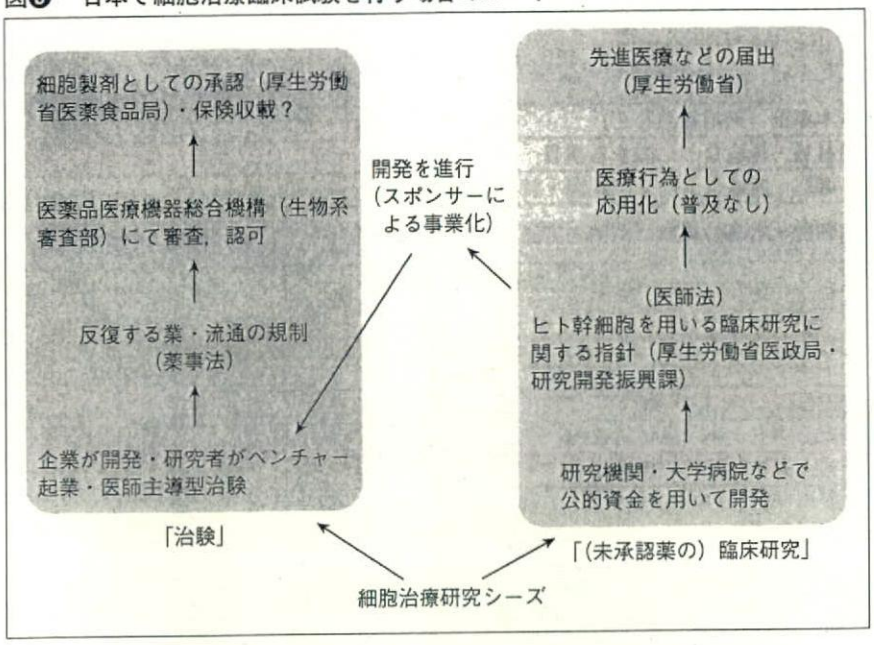
Ⅱ．日本における細胞医薬の規制の考え方

1.　日本における細胞医薬の臨床試験について

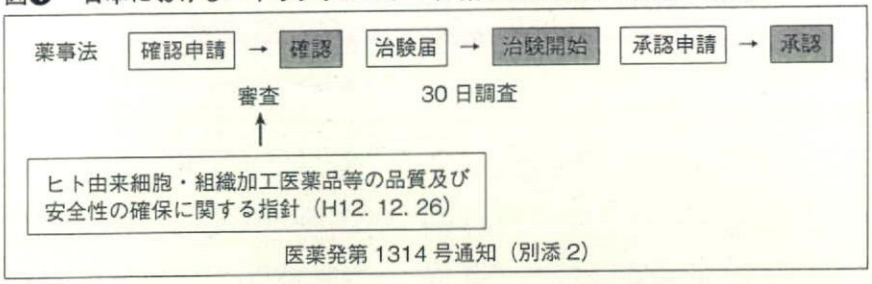
日本における医薬品審査・認可行政においては，原則として薬事法の規定内での「治験」（基本的に企業が主体）という枠組みでヒトを対象とした臨床試験を行う場合には，厚生労働省から委託を

受けて行政対応を行う独立行政法人 医薬品医療機器総合機構（以下，医薬品機構）での審査・認可を経ることになっている。近年の薬事法改正で，企業のみならず大学病院などの医療機関が医師主導型治験として医薬品機構に届出と審査を求めることもできるようになった。しかしながら，新規の医薬品候補物質であっても，薬事法外の医療行為として大学などが「臨床研究」として実施する場合には，行政への届出や審査を受けない（図❸）。医薬品機構での審査・認可を受けて開発を進める場合は，臨床試験（治験）が終了し，厚生労働省からの承認が得られると，最終的には保険収載となり，国内の医療機関での当該医薬品の使用が可能となる。一方，「臨床研究」として，治験をせずに開発を行った場合のゴールは，先進医療のように当該医療施設だけで国からの医療費が受けられる可能性がある。

図❸　日本で細胞治療臨床試験を行う場合のルート



図❹　日本におけるバイオテクノロジー医薬の臨床試験（治験）の流れ



2. 医薬発906号と医薬発1314号通知

現時点で，わが国では再生医療などに使用する細胞医薬，組織製品は医療機器の範疇で規制を受けている。薬事法下の治験として臨床試験を企画する場合，1999年の医薬発第906号「細胞・組織を利用した医療用具又は医薬品の品質及び安全性の確保について」，2000年の医薬発第1314号「ヒト又は動物由来成分を原料として製造される医薬品等の品質及び安全性確保について」といったガイドラインを遵守して，治験計画の届出と審査に先立って厚生労働大臣に確認申請を行い，医薬品機構による審査を受ける必要がある（図❹）。

一方で，治験外とはいえ，（新規医薬品候補の）臨床研究においても，遺伝子治療や，また2006年9月1日からは体性幹細胞を用いる臨床研究に際しては，厚生労働省に申請，審査を受け，その実施にあたって大臣からの許可が必要になった。特に「ヒト幹細胞を用いる臨床研究に関する指針」には，細胞製剤の準備過程や規格の設定，製造にあたって治験における確認申請と同様に医薬発第1314号通知（「別添2」）を参照し遵守することが明示されており，原則として治験と臨床研究とで同様の安全性にかかる規制の評価基準が設置されたことになる。

おわりに

細胞医薬を用いた臨床試験を実施する際の安全性の担保については，規格の設定，適用範囲などについて日米に大きな差異はなく，基本的な評価項目のフレームワークは同様である（表❺）。しかしながら，前述のように臨床試験をめぐる行政

表❺　日本および米国の細胞医薬関連の製造ガイドラインの比較

項目	日本			米国
	医薬発第1314号	医薬発第906号	ヒト幹細胞臨床研究の指針	ヒト体細胞INDsのガイドライン
基本原則（適用範囲など）	○	○	○	○
原材料・採取などに関する項目				
細胞・組織について（起源・特性・適格性など）	○	○	○	○
細胞・組織の採取（機関・方法・安全対策など）	○	○	医薬発第1314号に準じる	○
細胞の保存・出荷・運搬など	○	○	医薬発第1314号に準じる	
ドナースクリーニング	○		○	○
ドナーへのインフォームドコンセント	○		○	
対価について	○		○	
記録（ドナー・原材料など）	○		○	
製造・調整に関する項目				
製造･調整方法/工程について(ロット構成の有無･妥当性･記録など)	○	○	医薬発第1314号に準じる	
培養について（条件・安定性・血清成分など）	○		医薬発第1314号に準じる	○
セルバンクについて	○	○		○
分離・加工方法などについて	○			○
同一性・均一性（細胞・組織など）の評価	○			
遺伝子工学的改変について	○	○		
細胞・組織以外の原材料について（特性・試験項目など）	○	○	○	○
SOP	○			
品質管理・安全対策に関する項目			医薬発第1314号に準じる	
システム構築・試験方法など	○	○		○
試験項目（微生物学的検査・同一性・純度・活性・ウイルス検査・力価など）	○			○
安定性について（試験の実施・限界・運搬方法など）	○	○		○
最終製品の出荷規格試験	○			○
受け入れ試験などについて（原材料・試薬）	○			○
検疫・出荷・配送などの要件について	○			○
製品・調整物および使用段階の安全対策に関する項目				
効果効能を裏づける試験について	○	○	○	
体内動態	○	○		
複合製品について				○
最終製品について（回収方法・組成・剤型など）				○
患者へのインフォームドコンセントなど	○		○	
製品の追跡				○
容器・表示	○			○

対応と手続きは複雑であり，細胞医薬の臨床応用という共通課題を促進するためには，今後わが国の認可行政において医薬品機構の抜本的なあり方の見直しと強化（あるいは日本版FDAの設立）などを含んだ改革が必要であると思われる。すなわち，科学的根拠に基づいて医療・医学・産業の目標を明確にもった省庁が国家の対応として臨床試験のIND申請と審査の一元管理により医薬品の審査・認可を行い，それが医薬品開発に対して強力な支援となることが望ましい。未承認薬の臨床研究と治験という区別をなくし，基本的には新規の医薬品候補物，細胞医薬を含む生物製剤の臨床試験を一本化し，行政当局による全面的な審査と開発の支援を企業のみならず大学などアカデミアに対しても行うような人員や制度の強化が必要と思われる[3)4)]。

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川上浩司

1997年　筑波大学医学専門学群卒業（医師免許）
1999年　米国連邦政府食品医薬品局（FDA）生物製剤評価研究センター（CBER）ポストドクターを経て細胞遺伝子治療部臨床試験（IND）審査官・研究官
2001年　横浜市立大学大学院医学研究科頭頸部外科学卒業（医学博士）
2004年　東京大学大学院医学系研究科先端臨床医学開発講座客員助教授
2006年　京都大学大学院医学研究科・医学部薬剤疫学分野教授

現在，独立行政法人科学技術振興機構研究開発戦略センターシニアフェロー（臨床医学副統括），慶應義塾大学医学部客員教授などを兼務。

Critical issues for effective collaboration between academia and industry in the field of regenerative medicine in Japan

Mina Tsubouchi[1], Ryuichi Morishita[2], Yasuhiko Tabata[3], Shigeyuki Matsui[1] & Koji Kawakami[1†]

[†]Author for correspondence
[1]Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University, Yoshidakonoecho, Sakyoku, Kyoto 606-8501, Japan
Tel.: +81 757 539 469; Fax: +81 757 534 469; E-mail: kawakami-k@umin.ac.jp
[2]Department of Clinical Gene Therapy, Graduate School of Medicine, Osaka University, Osaka, Japan
[3]Department of Biomaterials, Institute for Frontier Medical Sciences, Kyoto University, Kyoto, Japan

Aim: To identify which factors are important barriers to effective collaboration between Japanese academia and industry in the field of regenerative medicine. **Methods:** In November–December 2006, in-person semistructured interviews were conducted with representatives from nine Japanese companies that are engaged in developing regenerative medicine products in collaboration with academia and two academic scientists with the successful collaborative experiences with companies. **Results & conclusions:** The major barriers to collaboration relate to the inadequacy of particular systems in academic institutions (particularly technology licensing organizations and mobility between industry and academia), the knowledge deficit of academic personnel with respect to industry, the inadequacy of particular governmental support systems and the Japanese public's view of these collaborations, which has resulted in overly strict conflict of interest guidelines. We suggest some approaches to overcome these barriers.

In the field of life science, collaborations between academia and industry for the development of commercial products have become a topic of considerable interest [1–4]. Since 2004, Japan's national universities have become 'incorporated', meaning that each university now controls the intellectual property rights of inventions created there [5]. The aims of incorporation of national university are promotion of collaboration between academia and industry for progress of science technology, preparation of competitive environment of research and restoration of Japanese industry. With incorporation, the number of collaborations between academia and industry has increased greatly [6]. As of March 2007, a total of 1590 companies emerging from Japanese universities had been established, 39.5% of which were life science-related companies [6].

In Japan, research and development for high-risk biotechnology therapeutics such as regenerative medicine products (RMPs) tends to be carried out by researchers in receipt of governmental research grants or funds from venture capitals (VCs), not by established pharmaceutical companies. Once clinical development of a candidate product has proceeded to some extent, the product is likely to be bought by a pharmaceutical company. Therefore, close collaboration between academia and industry is important for the development of RMPs. However, the incorporation of national universities in Japan has caused difficulties in obtaining research grants. Operating funds supplied by the government have been much reduced, and most of the limited numbers of research grants are open to competition, such that only a limited number of institutions receive grants. Consequently, academic researchers have striven to obtain research funds from other sources, including VC. In many cases, start-up companies develop the RMP in Japan and investment of VCs is an important source of funds for these companies. However, recently, Japanese VCs prefer not to invest in companies developing medicinal products, because very few pharmaceuticals or medical devices that have been developed through collaboration between academia and industry have received official manufacturing and sales approval. Therefore, it is now becoming difficult for academic researchers to obtain funds from investors. The difficulty of raising funds may lead to difficulty of maintenance of intellectual property because maintenance costs are expensive.

In Japan, governmental agencies including the Ministry of Economy, Trade and Industry (METI), the Ministry of Education, Culture, Sports, Science and Technology (MEXT), and the Ministry of Health, Labour and Welfare (MHLW) support collaborations between academia and industry for the purposes of promoting the clinical application of RMP and driving the nation's economy [101–103]. Recently, the METI, MEXT and MHLW have begun to communicate amongst each other and promote applied science and technology projects, including clinical trials and translational research, to academia and industry [104]. However, the

Keywords: academia–industry collaboration, conflict of interest, Japanese government, regenerative medicine products, semistructured interview

future medicine part of fsg

collaborations between these organizations have not been fully successful because in addition to the total budget for the projects being limited, the agency staff who are in charge of interagency communication have a somewhat conflicting mindset, that is, the agency he or she originally belonged to, for example, the METI, MEXT or MHLW, sometimes has different policy strategies from those of coordination project, and in many cases these staff need to go back to their original agency in a few years.

A cultured epidermis, manufactured by using the technology developed by Green and colleagues in 1979 [7,8], that was developed with university researchers and is now produced by the company J-TEC in Japan, received official manufacturing and sales approval (JACE®) in the country in October 2007, thereby becoming the nation's first commercially available RMP [105]. However, it seems that companies and researchers in the field of regenerative medicine feel that the collaborations between academia and the private sector are not yet functioning optimally with respect to the development of RMPs.

To investigate the issues in collaboration between academia and industry with respect to the field of regenerative medicine, we conducted semistructured interviews with representatives from Japanese companies engaged in developing RMPs in collaboration with academia. Our aim was to identify the barriers to effective collaboration between academia and industry.

Methods

We first conducted an initial survey to investigate issues in the successful development of RMPs, 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 [9].

Subsequently, we conducted interviews with representatives of nine companies that responded to the questionnaire, which also had RMPs under clinical development in collaboration with academia. Semistructured in-person interviews were conducted in November and December 2006. Company presidents or persons responsible for the development of the RMPs were interviewed. In addition, we interviewed two academic scientists conducting their research programs in the field of regenerative medicine, with successful collaborative experiences with Japanese companies. The interviews were recorded. Each interview was transcribed verbatim and the responses were analyzed by sampling of the keyword from transcripts and categorizing segments including keyword into topic areas, that is, issues regarding academia and industry, governmental agency and infrastructure, and others [10]. This categorization process was independently performed by the first and last authors, and categorizations were adjusted by consensus to arrive at a final categorization. In the interview, participants were asked about their opinions on collaborations between academia and industry and the conflicts of interest (COI) issues that arise for academic researchers.

Questions include:

- What are the barriers in collaborating between academia and industry?
- What do you think about the COI issues that may arise for academic researchers?

Participants were given a list of questions 1 week prior to the interview. At the end of each interview, the interviewer reviewed the questions and answers with the interviewee to ensure that all questions were fully answered.

Results

Characteristics of company representatives

The characteristics of the companies involved and the number of respondent from each company are listed in Table 1. One company was a large, well-established pharmaceutical company, and the remainders were start-ups founded within the last 10 years. All companies had had relationships with academia at various phases of development of the product in question.

Issues relating to academia & industry

Box 1 summarizes the systemic issues that the company representatives believed to exist in collaborations between academia and industry. Six out of nine respondents suggested that the issues of inadequate university systems and the knowledge deficit of academic staff with respect to industry should be addressed to improve the efficiency of collaborations. Two respondents felt that academic researchers usually lack understanding of issues around public demands, concepts of risk and benefit and product manufacture. Moreover, these two respondents felt that academic researchers must, at least to some extent, understand and consider good laboratory practice (GLP) and good manufacturing practice, even in the early stages of development.

Table 1. Key characteristics and number of respondent of the nine companies involved in the study.

Nature of candidate product	Year founded	Capital (millions of US$)	Number of respondents
Autologous cells (epidermal cells, cartilage, epithelium)	1999	37.8 (June 2007)	1
Autologous cells (myoblasts)	1921	352 (March 2007)	1
Autologous cells (bone marrow stem cells)	1999	4.5 (July 2007)	2
Autologous cells (dendritic cells)	2001	0.91	1
Autologous cells (epithelium)	2001	12.4	1
Allogenic cells (epithelium)	2000	8.1 (August 2007)	1
Allogenic cells (somatic stem cells)	2002	6.7 (May 2007)	1
Plasmid gene	1999	51.8 (December 2006)	1
Peptide	2004	3.3 (August 2007)	3

Note: An exchange rate of 110 yen to the US dollar was used. Capital values are as of the dates given.

One respondent pointed out that there is also a misunderstanding specific to RMPs, whereby many researchers believe that research and development for allogenic cells is too complex, so few companies have attempted to develop these products, although in fact they are more suitable for manufacturing and distribution than autologous cells.

One respondent noted that technology licensing organizations (TLOs) in universities lack business experience. Two respondents felt that it is necessary for universities to establish a system whereby students or postdoctoral fellows are placed within companies so that they can clearly understand the issues around industrial manufacture of a product. These respondents also felt that it was necessary for individuals from the private sector to take up academic positions, to bring their experience into the university environment. Two respondents expressed concern that academic researchers utilize research funds from the private sector or VC in a way that is different from how the investors intended. One respondent pointed out that some academic researchers tend to use VC funds not for the development of products but for basic research. Another respondent felt that investment from VCs has tended to be overly focused on basic academic research at the beginning of collaborations, which might have caused researchers to misunderstand how the funds are intended to be used.

When asked about issues arising from industry, no respondent mentioned any problems relating to the private sector companies themselves, but one respondent stated that private sector companies that have a relationship with academia must attempt to develop more than one product arising from such collaborations so that there is a precedent, in order to further promote this type of collaborative relationship.

Issues relating to governmental agencies & infrastructure

Four of nine respondents felt that the systems of governmental support for the research and development of pharmaceuticals, including RMPs, were inadequate. Multiple issues were mentioned, relating to governmental agencies including the METI and MHLW. One respondent thought that the support system of the METI does not offer sufficient assistance for bridging the gap between a research project and a market product. Another respondent had concerns with the MHLW, relating to the cost of regulatory review for collaborations between academia and industry. The respondent pointed out that at the US FDA, the cost of review is based on the size of the company, whereas the size of the company is not a factor in the costing of the Japan Pharmaceuticals and Medical Devices Agency (PMDA). Furthermore, because the Japan PMDA does not conduct regulatory review of clinical trials initiated by academia, academic researchers do not have a good understanding of the actual review process. The support strategies of agencies with respect to collaborations between academia and industry were felt to be poorly harmonized because each agency's goal is different: that of MEXT is to promote basic academic research, that of the MHLW is to protect public health and promote drug development, and that of METI is to drive the nation's economy. One respondent considered that although the goals of the various agencies may differ, for efficient product development, any

Box 1. Quotes relating to collaboration between academia and industry.

Relating to academic researchers

"Academic researchers do not recognize the importance of issues around the industrial manufacture of products, for example risk and benefit, manufacturing issues, GLP and GMP."

Relating to academic institutions

"TLOs do not function adequately."
"A system for exposing students to industry is necessary."
"Positions in academia specifically for individuals with industry knowledge are necessary."

Regarding research funds

"Academic researchers tend to use VC research funds not for product development but for basic research."
"VCs are overly focused on basic research at the beginning of the collaboration between academia and industry."

Relating to governmental agencies

"The METI offers insufficient support for bridging the gap between a research project and a market product."
"The review fee for clinical trials is fixed regardless of company size."
"The aims of the METI, MEXT and MHLW are not harmonized."
"Official or semiofficial organizations are necessary to promote collaborations between academia and industry."

Other

"Senior staff members who are knowledgeable about and experienced in dealing with intellectual property issues in universities and semiofficial institutions are necessary."
"Academic researchers with industry knowledge are useful."
"A COI assessment system operated by a third party would be useful."

COI: Conflict of interest; GLP: Good laboratory practice; GMP: Good manufacturing practice; METI: Ministry of Economy, Trade and Industry; MEXT: Ministry of Education, Culture, Sports, Science and Technology; MHLW: Ministry of Health, Labour and Welfare; TLO: Technology licensing organization; VC: Venture capital.

parties involved in development must have the same ultimate goal with respect to the project.

One respondent suggested that a new official or semiofficial organization with the aim of promoting effective collaborations between academia and industry might be helpful in the field of medicinal products, including the development of RMPs.

Other issues

Two of nine respondents noted that they had experienced problems relating to academic staff lacking knowledge of various aspects of product development. One respondent felt that universities must appoint a senior staff member who is knowledgeable about and experienced in dealing with intellectual property issues. The other respondent pointed out the necessity of academic researchers understanding the role of industry for effective collaborations.

We asked the respondents about COI issues (defined as 'conflict between the private interest and the official responsibilities of a person in a position of trust [as a government official]' [11]) faced by academic researchers in the development of RMPs. All respondents consider that COI is currently managed well at academic institutions. However, COI is managed in different ways in different institutions, using different systems and procedures. Three respondents thought that there should be a centralized COI assessment system managed by a third party, such as a semiofficial organization, to ensure effective collaborations between academia and industry.

Issues obtained from academic scientists

We also conducted interviews with two academic scientists. Both of them felt difficulties in carrying out their activities in collaboration with companies. One of them pointed out that university has very inflexible rules regarding research and development activities with companies. Regarding the COI issue, both of the scientists considered it to be currently well controlled. However, one respondent referred to the necessity of a certain system to protect academic scientists from COI and advisory contact for intellectual property to academic scientists collaborating with companies. One scientist felt application and handling of intellectual property after incorporation of national university was not well done in the country.

Regarding industry, the necessity for academic scientists to take up industry positions was raised, because individuals who have knowledge about both academia and industry are necessary for effective collaborations between

academia and industry. In addition, individuals from the companies need to acquire knowledge of GLP and good clinical practice, which are not familiar to most scientists.

With respect to governmental agencies, both scientists pointed out the necessity for METI to encourage start-up companies, strong recommendation for collaborations between academia and industry by MEXT, and improvement of regulatory review for RMPs by PMDA and MHLW.

Discussion

To investigate the barriers to effective collaboration between academia and industry in the field of regenerative medicine, we conducted semi-structured interviews with representatives of nine Japanese companies that are engaged in developing RMP in collaboration with academic researchers and two academic scientists successfully collaborating with Japanese companies in the field of regenerative medicine. From the results of the interviews with company respondents, we found that the main barrier is that most academic researchers do not recognize the importance of factors relating to business, including intellectual property issues, time pressures, and the difference between basic academic research and applied research for product development, whereas most companies collaborate with academia in applied research with the aim of developing a product, and must consider the aforementioned factors. It was also pointed out that few companies have attempted to develop allogenic cellular products, although in fact they are more suitable for manufacturing and distribution than autologous cells. This problem has arisen because many academic researchers in the field of regenerative medicine consider that autologous cells are safer and more convenient for clinical use than allogenic cells. Therefore, for effective collaborations it is important to correct this misconception held by academic researchers, in an effort to initiate research and development relating to allogenic products, which are a promising RMPs in terms of quality control and distribution.

On the other hand, academic scientists interviewed in this study have had successful experience in collaboration with companies. Such scientists experience difficulties in carrying out research and development activities in collaboration with companies because universities have inflexible rules relating to activity with companies, which were established with researchers with little knowledge or experience of collaborations between academia and industry in mind, despite different levels of knowledge and experience existing in academia. These experienced academics feel that such inflexible rules mean that arranging agreements with companies is very time-consuming and hinders their effective collaboration. This suggests that academia should establish more flexible rules regarding collaboration with industry, and academic staff should be evaluated not only on the basis of the impact factors of the journals they publish their research in (as is the current situation), but also on the basis of their experience and knowledge of applied bioscience and industrial manufacturing. We believe that these changes would benefit collaborations between academia and industry for the development of RMPs.

In this study, respondents felt that few staff members at university TLOs have a good understanding of business. In fact, university TLOs are mainly staffed by scholars and researchers, but our results show that it would be much more effective for TLOs to be staffed by personnel who have had experience in the development of medicinal products. To improve staff mobility between academia and industry, professorial chairs could be established in university TLOs and other divisions, the incumbents of which would be specially appointed from industry. As respondents from university scientist mentioned, staff mobility between academia and industry is important in collaborations between academia and industry, not only for TLOs but also for companies. A system whereby students and post-doctoral fellows could be trained in matters of business and product development would address the concerns of the respondents.

Company respondents in this study suggested that academic researchers must change their view of VC funds invested in start-up companies. Also, academics and VCs should reach a mutual understanding of how research funding is to be used: academia must understand the intention behind the VC's investment and VCs must understand the needs of academia for research funds.

Some respondents asserted that more effective governmental support was needed for the development of RMP as a result of collaboration between academia and industry. Recently, the METI, MEXT and MHLW have initiated science and technology coordination projects for the promotion of clinical trials and translational research. However, unfortunately, it seems that

effective collaboration amongst these agencies has not been achieved yet. We believe that the major reasons for this are as follows:

- The persons in charge of the coordination projects, who are sent on special appointment from the various agencies, might have conflicted loyalties, since they need to go back to their original agency in a few years;
- Each research project is assigned only a small budget;
- The coordination project office has no power to prioritize particular research projects or to assess the progress of each project.

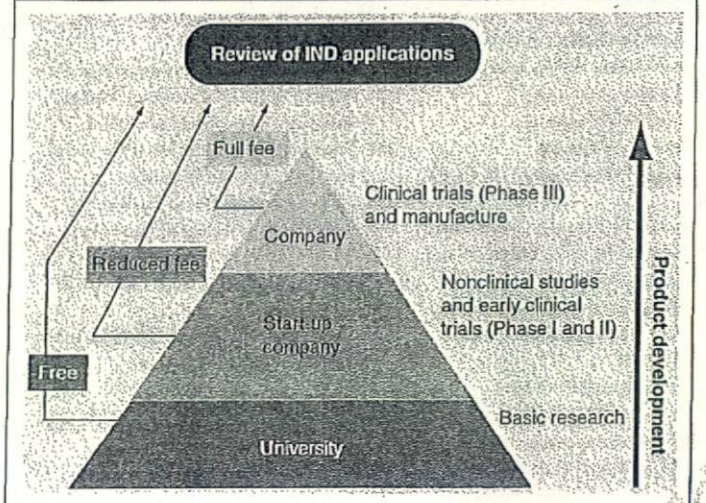
By contrast, in 2007 the UK government established a new organization, the Office for Strategic Co-ordination of Health Research (OSCHR), to unify, distribute and control clinical research funds from the Department of Health and the Department for Innovation, Universities and Skills [12]. The mission of the OSCHR is to facilitate more efficient translation of health research into health and economic benefits in the UK through better coordination of health research and more coherent funding arrangements to support translation. Our findings show that strong leadership and a support system that explicitly connects related agencies, as provided by the OSCHR, are critically needed in Japan to permit effective collaborations between academia and industry.

Issues relating to regulatory review fees were also mentioned in our study. In the USA, all applications, whether from academia or the private sector, must be submitted as an investigational new drug application to the FDA, and all protocols and applications are subject to the regulatory review of the FDA, with no exceptions. The review fee (user fee) is determined on the basis of company size: submissions from small or medium companies attract a lower fee than those from large companies, and submissions from universities are reviewed free of charge (Figure 1). In the EU, a central regulatory review system was adopted when European Commission directives came into force, and now all clinical trial applications from both universities and the private sector are subject to regulatory review [13]. In Japan, however, there is a fixed review fee that does not vary according to company size, and universities do not regularly submit all clinical research applications for regulatory review, because nonmarket clinical trials are regulated not under the pharmaceutical affairs law but under the medical affairs law, which is not subject to regulatory review by the PMDA [14]. In the field of regenerative medicine in Japan, start-up companies tend to develop products under a technology license from universities. Therefore, a new regulatory review system that would allow start-up companies to obtain regulatory approval without great expense, as exists in the USA, is highly desirable. We believe that such a system would contribute to smooth collaborations between academia and industry, resulting in expedited research and development for RMPs.

Finally, COI is an important topic when discussing collaborations between academia and industry. COI issues may arise in any field or situation, and we believe that the existence of COI is not necessarily problematic *per se*, but that control of COI is vital. However, although all respondents in our study believed that COI is currently well controlled, they felt that COI issues are barriers to smooth collaborations between academia and industry in Japan because the Japanese public tend to take a critical view of the existence of COI. This tendency may be caused by the Japanese cultural norm whereby 'suspects must always be punished'. Such norms might make the COI situation in Japan somehow different from other countries such as the USA. Similar to most scientific institutes in the USA, scientific institutes in Japan also take a critical review of COI. Even though the critical review is performed appropriately, Japanese journalists sometimes tend to indicate the possible private profit of the particular scientists upon their own research or opinion. To strengthen COI control, recently, the MHLW attempted to establish guidelines for the management of COI in clinical research collaborations between academia and industry [106]. However, there is a feeling in academia that these strict guidelines might obstruct product development. Thus, the key to successful collaboration between academia and industry may partially depend on overcoming the above-mentioned deeply entrenched cultural view. We suggest that the MHLW and other agencies (e.g., the METI and MEXT) cooperate to overcome these multiple barriers to effective collaborations between academia and industry.

A limitation of this study is that interviews were conducted with only nine companies that responded our first questionnaire survey and collaborate with academia and two academic scientists who have the successful experiences in collaboration with companies. In addition, we did not interview governmental agencies in this study. Therefore, result revealed in this study may lack generality. However, we consider the main

Figure 1. The US system for regulatory review of Investigational New Drug applications.



IND: Investigational new drug.

obstacles for effective collaborations between academia and industry are well included. We hope that the issues revealed in our study will be considered for the future effective collaborations between academia and industry.

Conclusion

In this study, we interviewed representatives from nine Japanese companies engaged in the development of RMP in collaboration with academia and two academic scientists who have successful experiences collaborating with companies to identify barriers to the success of such collaborations. We found that the major barriers related to inappropriate academic systems, poor understanding of industry issues in academia, inadequate governmental support systems and a problematic view of these collaborations by the Japanese public. We therefore propose that to overcome these barriers it is necessary to review particular governmental and academic systems, establish systems whereby individuals can move easily between academia and industry, and manage the Japanese public's view of these collaborations. We believe that these three major issues are critical for the prompt clinical application of advanced medicinal products, including RMPs, in Japan.

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Executive summary

- Respondents felt that major barriers to efficient collaboration between academia and industry in Japan are that academics lack an understanding of the business side of product development, and that there is no system permitting individuals to move between academia and industry.
- Some respondents felt that the Japanese governmental systems that support collaborations between academia and industry are inadequate.
- Potential conflicts of interest (COI) tend to be viewed extremely critically by the Japanese public; a number of respondents regard COI issues as barriers to successful collaborations between academia and industry.
- To permit effective collaboration between academia and industry in Japan, it is necessary to review particular governmental and academic systems, establish a system whereby individuals can move easily between academia and industry, and manage the Japanese public's view of these collaborations.

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Review

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

Takahiro Nakazawa[1], Misao Kurokawa[1], Kazuya Kimura[1], Akihiro Wakata[1], Shigeru Hisada[1], Tadashi Inoue[1], Fumio Sagami[1], Shawn M. Heidel[2], Koji Kawakami[3], Kazutoshi Shinoda[4], Hiroshi Onodera[4], Yuji Kumagai[5], Yasuo Ohno[6], Nobuyuki Kawamura[7], Tsuneyoshi Yamazaki[8] and Tohru Inoue[6]

[1]*Japan Pharmaceutical Manufacturers Association, Drug Evaluation Committee, Non-clinical Evaluation Subcommittee, Torii Nihonbashi Bldg., 3-4-1 Nihonbashi-Honcho, Chuo-ku, Tokyo, 103-0023, Japan*
[2]*Eli Lilly, Eli Lilly and Company, Indianapolis, IN 46285, USA*
[3]*Kyoto University, Yoshida Konoecho, Sakyoku, Kyoto 606-8501, Japan*
[4]*Pharmaceuticals and Medical Devices Agency, Shin-Kasumigaseki Building, 3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013, Japan*
[5]*Showa University, School of Pharmaceutical Sciences, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo, 142-8555, Japan*
[6]*National Institute of Health Sciences, 1-18-1, Kamiyoga Setagaya-ku, Tokyo, 158-8501, Japan*
[7]*European Federation of Pharmaceutical Industries and Associations, GSK Bldg., 4-6-15, Sendagaya, Shibuya-ku, Tokyo 151-8566, Japan*
[8]*Kyoritsu University of Pharmacy, Kyoritsu University of Pharmacy, 1-5-30, Shibakoen, Minato-ku, Tokyo 105-8512, Japan*

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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-

Correspondence: Takahiro Nakazawa (E-mail: nakazawa_takahiro@lilly.com)

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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