	について はじめに 2.について、患者の自己決定権があまりに強く出過ぎていないかと考えます。この挿入のため、「確認することにある。」から「したがって、治験開始の場合、」の流れを悪くしています。最終章で重複して述べられていることもあり、序文としては、削除してもよいと考えます。	らかにした上で、なお残る「未知のリスク」についての記載であり、過剰な表現ではないと考えます。本記載は重要な視点であるため、最終章にも同様の記載をしております。なお、治験への参加は患者の自由意志であることを申し添えます。 （研究班補足見解） 「自由意志」は「自由意思」と記載することが多いようです。文意も「意思」の方が適切と考えます。
3	（別添１～５）について はじめに 2.について、「薬事戦略相談あるいは治験相談における」の記載は不要かと考えます。	削除することで文章の意味が変わるものではございませんが、わかりやすさの観点から修正は不要と考えます。
4	（別添１～５）について はじめに 2.について、「治験開始の場合、その申請にあたって」の記載は「申請」ではなく、「届出」ではないでしょうか。また、	ご意見を踏まえ、修正いたします。

	「申請者」も、様々な開発段階が含まれることを踏まえて、適切な用語を選択するのがよいのではないでしょうか。	
5	（別添１～５）について 安全性の確保という点から外れてしまうのですが、「目的とする細胞・組織以外の原材料及び製造関連物質」(1) 細胞の培養を行う場合の培地成分についてに関して意見を述べます。 「DMEM、MCDB、HAM、RPMI のような培地は1つのものと考えてよい」と書かれていますが、是非種類を増やしていただきたいと思います。 例えば、FDAやヨーロッパで医薬品として認められているような培地に関しては、1つのものとまではいかないにして	培地の構成成分が周知のもので、市販品等が一般的に使用されるものの中で、DMEM、MCDB、HAM、RPMI と同等と判断されるものについては、本事例に該当するものと認識しております。

	も、準基準品のような取扱いにしていただきたいと考えます。	
6	（別添１～５）について 別添１～５に共通していますが、別添１の 12 ページにある「第３最終製品の品質管理　2 最終製品の品質管理法　(6) 無菌試験及びマイコプラズマ否定試験」の４行目、検証された核酸増幅法を用いることでもよい、について質問があります。 　この文の内容は、無菌試験とマイコプラズマ否定試験の両方にかかるものでしょうか？　また、検証された、の具体的な意味が明らかではないので説明していただきたいと思います。必ずしも日本薬局方に基づく必要はないという意味にもとれますが、	核酸増幅法はマイコプラズマ否定試験を対象としておりますので、修正させていただきます。 例えば、日本薬局方に規定されている最小の採取量を満たすことができない場合において、妥当性が説明できる試験等が該当いたします。試験法の検証については、平成 20 年 3 月 12 日付け医薬食品局審査管理課・医療機器審査管理室事務連絡「ヒト（自己）由来細胞・組織加工医薬品等の品質及び安全性の確保に関する指針に係る Q&A」の Q42 及び Q43 を参照下さい。 （研究班補足見解） なお、検証されたという意味は、薬局方など公定書に記載された方法で当該試験対象に適用することが合理的に説明できること、あるいは、公定書に記載された

	その場合の条件等はあるのでしょうか。	方法とは異なる方法や収載されていない方法でも、審査の際に科学的に妥当であると判断される内容であることが認められること、とご理解下さい。無菌試験法についても、そのような条件を満たした核酸増幅法が開発されれば門戸は開かれていると考えます。
7	（別添１）について 第２章第１２，（３）①～⑥は、昔の細胞指針を踏襲した記載であると理解していますが、最新の指針であることから、言葉の定義も含めて整備が必要と考えます。例えば、①目的遺伝子の項でセルバンクの意味するもの、遺伝子導入構成体・遺伝子導入用ベクター・ベクターの使い分け（第１章で定義されているのは、遺伝子導入構成体のみ）、遺伝子治療用医薬品指	用語定義の変更は他指針の範囲や内容に影響を与えるため今後慎重に検討させていただきます。例えば評価の対象が「目的遺伝子産物」を「導入遺伝子からの生成物」とすることであらゆる生成物について検討が必要となる可能性があります。

	針の記載参照が指している範囲の適切性等（第２章 第１が原材料や製造関連物質、第２が製造工程ですが、遺伝子導入細胞の製造方法について第１で説明するのが適切か）等。 ＜例＞ ①目的遺伝子の塩基配列及び入手方法 ②導入遺伝子の構築方法及び構造 ③導入遺伝子からの生成物の構造、性質（生物活性等） ④遺伝子導入構成体の構造（ただし②と同一の場合を除く）及び特性解析 ⑤遺伝子導入構成体の製造に用いる原材料、ウイルス・バンク、セル・バンク等の調製方法及び管理方法、遺伝子導入構成体の製造方法 ⑥（標的）細胞への遺伝子	

	導入方法、遺伝子導入細胞内での遺伝子導入構成体の存在状態及び残存性	
8	（別添１）について 第２章第１２.（３）の「上記の記述にかかわらず」については、遺伝子治療用医薬品指針とカルタヘナ法の事を指しているかと思います。医薬品の製造段階で、遺伝子導入に用いた組換えウイルス等の残存が否定されていれば、カルタヘナ法の「使用等」に該当しない可能性もありますが、組換えウイルスの使用する初期段階の範囲はどうしても「使用等」の定義に該当してしまうため、別途必要な手続きが必要とされるケースはありえます。この指針でどのように書いても、手続きを怠れ	「上記の記述」については、（３）全体を指しているもので、遺伝子治療用医薬品指針及びカルタヘナ法に該当するものについては、それぞれ別途手続きを必要とします。本記載により法律の範囲を越えることはありません。

	ば違法になってしまうケースがありうるので、別の法律の範囲であり、それに連なる通知等に従うべきとして、「上記の記述にかかわらず」の一文を削除したほうがよいと考えます。	
9	(別添１)について 第２章第１２.(３)の「最終製品の一部を構成していないか」という点は、最後には、その時点の科学技術に基づく検出可能性の話になり、検出感度によって結論が変わりうるため、議論になると思いますので、QA等が必要と考えます。	ご意見を踏まえ、QA等で対応させていただきます。
10	(別添１)について 本指針案の「はじめに」には、「治験開始段階で、本指針に記載された要件な内容をすべて充たすことを必ずしも求めて	重要な記載と考えますので、修正は不要と考えます。

	いるわけではない。製造販売承認申請時における品質及び安全性の確保のための資料は治験の進行とともに本指針に沿って充実整備されることを前提に、治験開始時点でその趣旨にかなう条件を満たし、合理的に作成された適切な資料を提出すること。」と記載されていることも踏まえ、第２章第１　２.（３）の「上記の記述にかかわらず」の一文を削除してもよいのではないかと考えています。	
11	(別添１)について 第４章　序文の「(注：例えば神経疾患ならばサル等)」の記載について、動物種の選択は製品の特性に合わせてケースバイケースで実施されること、また特に近年欧州などでは	本記載は、平成22年2月19日付け薬食審査発0219第4号 ICH-M3 を踏まえた非臨床試験における 3R の重要性を否定するものではありません。 （研究班補足見解） このケースにサル以外を挙げるのはかえって不適切であると考える。あ

	霊長類を用いた動物実験の規制大幅な強化（国際的な3Rの高まり）から、特にサルなど具体的な例示は避けた方がよいと考えます。	くまで例示であり、「適している場合がある。」と述べているにすぎないので、要求ではなく、現行でも差し支えないと考えられる。
12	（別添１）について 第４章　７．について、ベクターによって遺伝子挿入等のリスクは大小あれども皆無ではないと認識しておりますので、どのようなベクターを用いたにしても、その特性に応じた考察（必要に応じて試験）を、遺伝子治療用医薬品指針に定める項目について行うことは、科学的に適切な対応と考えます。なお、長期フォローアップについては、遺伝子改変の有無を問わず、製品のリスクに応じて、治験期間終了後も長期フォローアップが継	ご意見を踏まえ、ご指摘のとおり修正いたします。 なお、別添１以外にも同様の記載がございますので、併せて修正させていただきます。 （研究班補足見解） コメントされていることは、現行案にすべて網羅されており、修正の必要はないと思われます。修正例は文章としても充分練りきれていないと思います。さらに懸念があるようであればQ/A又は解説で対応すればと考えます）

	続される場合もあると思いますので、第7章で総合的に扱ってもよいかと考えます。また、染色体への挿入からの異常増殖性・造腫瘍性の他に、導入遺伝子（例：c-myc）の発現産物に起因する「細胞の異常増殖性や造腫瘍性」も重要な観点かと思います。 ＜例＞ 製造工程で外来遺伝子の導入が行われた場合は、遺伝子治療用医薬品指針に定めるところに準じて試験や考察を行い、臨床適用にあたっては長期フォローアップを考慮すること。染色体への挿入、導入遺伝子の発現産物、遺伝子導入に伴う培養条件等により腫瘍形成について特段の懸念がある場合には、細胞の異常増殖性	

	や造腫瘍性に関する詳細な評価や長期フォローアップにおける情報収集を考慮すること。	
13	（別添２）について ヒト体性幹細胞を、その分化能に直接関係のない性質を利用する場合でも、本指針第２章　第１　原材料及び製造関連物質　１　原材料となるヒト細胞・組織(2)原材料となる細胞・組織の特性と適格性に記載の「原材料となる体性幹細胞が有用な分化能を有することを明らかにする」必要はありますでしょうか。	分化能に直接関係のない性質を利用する場合も、本指針の「ヒト体性幹細胞」の定義に該当し、ヒト体性幹細胞加工医薬品等に該当する場合は対象となります。 （研究班補足見解） 1．この質問は、通知が「生体内での機能を期待する細胞への分化能を有することを示すことで良い。」と述べているところから発せられたものと推測される。この表記は前段の文章「特に原材料となる体性幹細胞が有用な分化能を有することを明らかにする」を受けているもので、分化能を示す際の考え得るさまざまな分化能を示すべきと解釈され、過剰なデータ要求となることを避け、合理的なアプローチでの特性解析の実施を推奨するためのものでありました。

		その一方で、幹細胞というものの本質的特性の一つは、分化能を有するということであることは論を待ちません。したがって用途の如何を問わず、幹細胞と称する細胞の固有の特性として適切な分化能を明らかにすることは非常に重要であると考えます。細胞特性解析の目的は、必ずしもその用途にのみ限定されるものではないということです。 2．また、質問はどのような具体例を想定しているか不明ですが、「分化能に直性関係のない製品」というのはGVHDを予防するために免疫調節効果を期待して投与される間葉系幹細胞のようなものをイメージされているのかもしれません。有効性からみた利用の仕方はどうあれ、分化能を有するという特性から、生体に移植された場合に生ずる安全性上の課題を考慮しなければならないということもあるかと思います。

		3．原材料として用いる細胞の特性指標として特定の分化能を挙げ、これを、規格化する場合もあると思います。 4．以上の観点から特性解析指標として何らかの分化能の提示は必須であると考えます。
14	（別添２）について ヒト線維芽細胞は、in vitro では適当な分化誘導をかけることで分化することが知られていますが、一般には幹細胞とは認識されていないと思います。このような細胞の利用はヒト体性幹細胞加工医薬品等の品質及び安全性の確保に関する指針の対象に入らないと考えてよいでしょうか。	ヒト線維芽細胞それ自身は一般的に幹細胞とはされず、このような細胞の利用は、2008年の指針での対応になると考えます。しかし、ヒト線維芽細胞を用いて幹細胞を作成する場合等は本指針の対象となりますのでご留意下さい。 （研究班補足見解） 1．細胞は一口に XX 細胞と言っても、前駆細胞や幹細胞を含むヘテロなものであります。また、意図的に初期化が可能であり、意図的でなくとも置かれた培養条件などで脱分化、分化転換などいろいろな潜在能力を持ちます。個別の素材と個別の製品という関係づけの中で、最も関

		係の深い指針及び該当項目を選択して対応していくのが基本的に望まれることであると思います。 2．原材料の細胞の細胞種と最終製品中の細胞の細胞種とが異なる場合、例えばヒト線維芽細胞を加工して別の細胞種を誘導することにより最終製品を製造する場合には、ヘテロな細胞中の前駆細胞や幹細胞が結果的に加工された可能性もあり、「ヒト体性幹細胞加工医薬品等の指針の対象となる」と考えます。なお、原材料の細胞を加工して一旦 iPS(様)細胞に誘導する工程が含まれる場合には、ヒト iPS(様)細胞加工医薬品等の指針の対象となると考えます。
15	（別添２）について ヒト（同種/自己）体性幹細胞加工医薬品等の品質及び安全性の確保に関する指針においてセル・バンクとは、どのようなものを想定	バンクの定義については、指針に記載のとおり、ICH-Q5D を参照下さい。 （研究班補足見解） そのとおりです。製品製造にあたっての最も重要な課題は、製造される

	されているでしょうか？体性幹細胞の場合、細胞分裂は有限でありバンクのスケールは比較的小規模で細胞によって異なります。また、バンクはドナー毎に作製することになり、バイオ医薬製造等で使用される不死化された細胞クローンを用いたバンクとはいろいろな観点で異なります。このような差異に関わらず、中間段階まで細胞を増殖させ、一様に小分けして凍結させたものがバンクと定義されるとの理解でよいでしょうか。	製品の品質の恒常性の確保です。そのための最も重要な方策の第一は原材料（から調製した医薬品製造基材）の品質特性のばらつきを可能な範囲でコントロールすること、第二は製造工程の一定性を維持することです。第一の医薬品製造基材の典型的なものがセル・バンクです。有限、無限にかかわらず、サイズのスケールにかかわらず特性解析された均質な医薬品製造基材として繰り返しの製造に供すべく安定に保管されているセル・バンクを確立することは、製品の品質の恒常性の確保にきわめて重要であると理解して頂ければと思います。なお、タンパク質性バイオ医薬品でも有限の正常２倍体線維芽細胞をセル・バンクとしている例があります。一方、ヒト（自己）体性幹細胞加工医薬品等の場合には、セル・バンクは一般に想定されていません。
16	（別添２）について	製造方法の変更については、変更内容により個別に判断されるべき事項であると考えます。 （研究班補足見解） 製造方法を変更する場合、変更前後の同等性/同質性の確認は、あらかじめ設定した製品規格の項目の範囲で確認することでよいとは限りません。どのような製法変更か、どの開発段階での変更か、旧製法で得られたどのデータを変更後も利用しようとしているかにより、変更前後の同等性/同質性の確認内容は変わってくると思います。逆に、治験届け出や承認申請の際のデータパッケージが新製法のものだけで構成されている場合は、変更前後の同等性/同質性の確認の必要はありません。詳細はICH-Q5Eを参照下さい。
	製造方法を変更する場合、変更前後の同等性/同質性の確認は、あらかじめ設定した製品規格の項目の範囲で確認することでよいでしょうか。	
17	（別添３）について 第１章　第２定義のiPS細胞の定義として、iPS様細胞の定義で	ご指摘のとおりですが、原案で同じ意味となっておりますので修正は不要と考えます。

	「少なくとも内胚葉、中胚葉及び外胚葉の一部の細胞」とされているのであれば、その対比として、「内胚葉、中胚葉及び外胚葉の全ての細胞に」が適当かと考えます。	
18	（別添３）について 第２章　第１「検体の量的制限」について、患者等から部分採取した体細胞（増幅させていないもの）なので、量的な制限があるという意味で記載されているという理解でよろしいでしょうか。	ご意見のとおりです。

C.10 ヒト幹細胞由来製品に関する５指針の発出

C.1からC.9の結果を受けて、平成24年9月7日に厚生労働省医薬食品局長名で下記に示すヒト幹細胞由来製品に関する５指針の発出に至った。

ヒト（自己）体性幹細胞加工医薬品等の品質及び安全性の確保について
（平成24年9月7日薬食発0907第2号）

ヒト（同種）体性幹細胞加工医薬品等の品質及び安全性の確保について
（平成24年9月7日薬食発0907第3号）

ヒト（自己）iPS（様）細胞加工医薬品等の品質及び安全性の確保について
（平成24年9月7日薬食発0907第4号）

ヒト（同種）iPS（様）細胞加工医薬品等の品質及び安全性の確保について
（平成24年9月7日薬食発0907第5号）

ヒトES細胞加工医薬品等の品質及び安全性の確保について
（平成24年9月7日薬食発0907第6号）

C.11 Q/A 作成

Q/Aについては、C.2からC.8の間で行政当局と研究班の間で議論の対象となった事項と内容及びパブコメに対する研究班見解の対象となった事項と内容について作成することが適切で必要と考えられた。その主な部分については、すでにパブコメの回答として公表され、またC.2からC.9において詳細に述べている。今後は、未公表部分の公表の仕方、すなわち、当局からのQ/Aを発出するのか、しかるべき学術雑誌等でより詳細な５指針解説として公表するのか、鋭意検討していく予定である。

C.12 国際社会への情報発信

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

C.12.1 国際学会等での発表

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

C.12.2 英文版作成

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

以下に、投稿原稿を示す。

C.12.3 ヒト（自己）体性幹細胞加工医薬品等の品質及び安全性の確保についての研究の経緯と視点及びガイドライン英文版

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

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Background (Chronology and Focus of the Study)

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

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

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

In Japan, there have been two main approaches to the research, development, and clinical application of cell-based regenerative medicine. The first one is aimed at the marketing authorization of cell- and tissue-based products under the Japanese Pharmaceutical Affairs Law. In other words, this first approach involves research and development initiated by a company and follows a stepwise process toward evaluation and approval of the product by the relevant regulatory authorities. These steps include: regulatory consultation with respect to the quality and safety of the products to ensure that there are no obstacles to its application to

humans in clinical trials; "clinical trials"; "product marketing authorization (manufacturing and import approval)"; and finally "clinical use". When adopting this kind of approach, researchers are encouraged to refer to certain official guidelines, such as Pharmaceutical Notification No. 1314 entitled "Ensuring the Quality and Safety of Pharmaceuticals and Medical Devices Manufactured Using Ingredients Derived from Humans and/or Animals," dated December 26, 2000. The second approach is "human stem cell clinical research" conducted, for the time being, according to the Medical Act. This is carried out in accordance with the Ministry of Health, Labor, and Welfare (MHLW) Notification No. 0703003, dated July 3, 2006 and entitled "Guideline Concerning Clinical Research Using Human Stem Cells," though the scientific contents are, on the whole, based on the aforementioned Pharmaceutical Notification No. 1314. Revised versions of MHLW Notification No. 0703003 were published in November 2010 and October 2013, although the Chemistry, Manufacturing and Control (CMC) parts therein are based on MHLW Notification No. 0208003 and MHLW Notification No. 0912006, described later. Whether "human stem cell clinical research" can proceed will depend on deliberations at the MHLW Scientific Committee Meeting (most reviews are conducted by competent expert committees) and a decision from the Minister of Health, Labor, and Welfare. As human stem cell clinical research proceeds, research will be eligible to receive public funding as a "high level/advanced therapy" if it is determined, from the standpoint of efficacy and safety, to be medical treatment within the public healthcare funding system. It is anticipated that human stem cell clinical research will lead to the smooth development of products by industry.

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

In fiscal year 2008, the Japanese MHLW convened a panel of experts entitled "Study Group on Ensuring the Quality and Safety of

Pharmaceuticals and Medical Devices Derived from the Processing of Human Stem Cells." The panel, chaired by Dr. Takao Hayakawa, was established as an MHLW scientific research project.

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

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

(i) From a scientific and technological perspective, the group assessed the current state of and future outlook on the manufacture and clinical application of cell and tissue-based products derived from the processing of human somatic stem cells, human ES cells, and/or human iPS cells, with reference to the most up-to-date research and information. In particular, the group presented the results of the study with respect to sources of human mesenchymal stem cells; the clinical application (including cellular therapy and gene therapy) for many different types of diseases; perspectives for the establishment and differentiation of iPS cells and clinical application of iPS cell-based products; and the current state of and views on therapeutic tissue engineering and its practical use in regenerative medicine.

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

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

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

(v) As a result of the analyses and discussions described in (i)–(iv), in accordance with the Pharmaceutical Affairs Law, and with the clinical application of products derived from human somatic stem cells, iPS cells, ES cells, and other cells as the goal,

the study group concluded that relevant guidelines should be tailored to specific cell sources and phenotypes (human autologous *vs.* human allogenic cells; somatic stem cells *vs.* iPS cells *vs.* ES cells *vs.* other cells) to facilitate efficient, effective, and rational research and development(R&D). Points to be considered include but are not limited to: technical details, the manufacturing process, characterization, quality control, stability evaluation, and the data necessary to guarantee the safety and efficacy of the products.

With this perspective in mind and with a desire for consistency in scientific principles and concepts, two interim reports on draft guidelines for products derived from the processing of autologous human somatic stem cells and autologous human iPS cells were prepared in 2009, on the basis of MHLW Notification No. 0208003. Three other interim reports on draft guidelines for products derived from the processing of allogenic human somatic stem cells, allogenic human iPS cells, and human ES cells, respectively, were also prepared, on the basis of MHLW Notification No. 0912006. These five sets of draft guidelines were thoroughly discussed from a variety of viewpoints. They were then widely circulated among interested parties as articles in a relevant scientific journal to allow readers to comment (Hayakawa T., et al.: Journal of the Japanese Society for Regenerative Medicine), 9, 116–180 (2010)). Thereafter, these articles were updated and published as eight articles (Hayakawa T., et al.: Journal of the Japanese Society for Regenerative Medicine, 10, 86–152 (2011)) that served as the basis for the final draft guidelines. After extensive discussions with the study group and public consultation, the Pharmaceutical and Food Safety Bureau of MHLW issued five notifications on September 17, 2012 entitled "Guideline on Ensuring the Quality and Safety of Pharmaceuticals and Medical Devices Derived from the Processing of Autologous Human Somatic Stem Cells," "Guideline on Ensuring the Quality and Safety of Pharmaceuticals and Medical Devices Derived from the Processing of Allogenic Human Somatic Stem Cells," "Guidelines on Ensuring the Quality and Safety of Pharmaceuticals and Medical Devices Derived from the Processing of Autologous Human Induced Pluripotent Stem(-Like) Cells," "Guidelines on Ensuring the Quality and Safety of Pharmaceuticals and Medical Devices Derived from the Processing of Allogenic Human Induced Pluripotent Stem(-Like) Cells," and "Guidelines on Ensuring the Quality and Safety of Pharmaceuticals and Medical Devices Derived from the Processing of Human Embryonic Stem Cells."

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

In this paper, we introduce guidelines that describe the basic technological requirements for ensuring the quality and safety of pharmaceuticals and medical devices derived from the processing of autologous human somatic stem cells. There may be cases where certain final products derived from the processing of somatic stem cells that are multipotent and retain the ability to self-replicate may be used in a non-homologous manner, even if they are autologously derived. In other words, as a result of cell processing, the product could exhibit cell characteristics different from those of the starting cells, and the product

might be applied and function at a site (cell environment) different from where the original cells localized. Concerns related to these points have been added to Notification No. 0208003, which serves as a basis for this guideline.

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

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

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

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

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

Introduction

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

There are many different types of cell products and methods of clinical application. In addition, the scientific progress in this field is constantly advancing and experience and knowledge are constantly accumulating. Therefore, it is not always appropriate to consider the present guidelines all inclusive and definitive. Consequently, when testing and evaluating each individual product, it is necessary to take, on a case-by-case basis, a flexible approach based on rationale that reflects the scientific and technological advances at that point in time.

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

Finally, applicants are encouraged to discuss with the Pharmaceuticals and

Medical Devices Agency (PMDA) the type and amount of data that may be needed to initiate an individual clinical trial. Because of differences in product origin, target disease, target patients, application sites, application methods, and processing methods, there may be numerous variations between individual data packages that cannot be definitively clarified in the present guidelines.

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

Chapter I General Principles

I. Objective

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

II. Definitions

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

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

and Safety of Pharmaceuticals and Medical Devices Derived from the Processing of Allogenic/Autologous Human iPS(-Like) Cells," respectively.)

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

Isolation of tissue, disintegration of tissue, separation of cells, isolation of a specific cell, treatment with antibiotics, washing, sterilization by gamma irradiation or other methods, freezing, thawing, and other such procedures regarded as minimal manipulations are not considered processing.

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

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

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

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

Chapter II Manufacturing Methods

Describe all important and relevant information concerning the manufacturing method, taking into account the items listed below. This information will help ensure the quality, safety, and efficacy of the final products, and it is important for guaranteeing consistency in quality from a manufacturing perspective. It should be noted that quality, safety, and consistency are assured by mutual complementary measures throughout the manufacturing process. It is most important that the measures are rational and that they serve the

intended purpose. It may be acceptable to omit a portion of the items listed below, if the quality, safety, and constancy of the final products can be established by suitably chosen quality tests, control of the final or intermediate products, or control of the manufacturing process.

I. Raw Materials and Materials Used in Manufacturing

1. Human cells and tissues used as raw materials

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

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

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

(2) Considerations with respect to the donor

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

Establish eligibility criteria that take into consideration the genetic characteristics, history, and health of the patient and others and justify the appropriateness of the patients as donors. Donor genome or gene analysis shall be performed in accordance with "Ethics Guidelines for Human Genome and Gene Analysis Research" issued jointly on

December 28, 2004 by the Japanese Ministry of Education, Culture, Sports, Science, and Technology, Ministry of Health, Labor, and Welfare, and the Ministry of Economy, Trade, and Industry.

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

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

(i) Eligibility of personnel and medical institutions collecting samples

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

(ii) Suitability of the sampling site and sampling method

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

(iii) Informed consent from donors

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

(iv) Protection of donor privacy

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

(v) Tests to ensure donor safety

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

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

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

(vii) Transportation methods

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

(viii) Preparation of records and record-keeping procedures