	でしょうか。	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1 2,(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針の記載参照が指している	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。

	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。	「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。
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いるわけではない。製造販	重要な記載と考えますので、修正は不要と考えます。

	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。	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続される場合もあると思い	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）

	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

		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

		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

		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されているでしょうか？体	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、製造される製品の品質の恒常性の確保です。そ

	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。	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 製造方法を変更する場合、	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

	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。	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。
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「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。	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。
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

C.12.1 国際学会等での発表

国際社会への情報発信については、第11回日本再生医療学会国際規制WS(2012年6月)、第3回国際組織再生工学・再生医療会議（2012年9月）及び世界幹細胞サミット2012（2012年12月）において、５指針(案)の概要を発表するとともに、米国FDAやEUの規制担当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指針全文の英文版を作成し、国際社会に発表すべく完成度を高めつつある。英文版作成にあたっては、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ない。通知の概念、内容、趣旨を最も正確に英語で伝えようとした、それ自体独立したものとしての完成度を高めつつある、ということである。

以下に、そのドラフトを示す。

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英文版

Guidelines on Ensuring the Safety and Quality of Pharmaceuticals and Medical Devices Derived from Processing of Human (Autologous) Induced Pluripotent Stem(-Like) Cells

(September 7, 2012)

Introduction

1. The present guidelines outline the basic technical elements to ensure the quality and safety of pharmaceuticals and medical devices derived from processing of human (autologous) induced pluripotent stem (iPS) cells or human (autologous) iPS-like cells. These products are hereinafter referred to as human (autologous) iPS(-like)cell-based products or merely as "desired cell products".
Human (autologous) iPS(-like) cell-based products are obtained either by artificially inducing the differentiation of various types of iPS(-like) cells generated artificially from human somatic cells and are then used directly or after further processing. There are many different types of manufacturing methods, intermediates, types and characteristics of desired cell products, and methods of clinical applications. On the other hand, the scientific progress and accumulation of experience and knowledge in this field are constantly advancing. Therefore, it is not always appropriate to consider that the contents of the present guidelines *are all inclusive and all definitive*). Consequently, when testing and evaluating each individual product, it is necessary to take flexible approaches, on a case-by-case basis, based on rationale that reflects scientific and technological advances at that specific point in time.

2. The main purpose of evaluation of quality and safety of the desired cell products prior to conducting investigational clinical trials (e.g., at the time of "clinical trial consultation") is to confirm whether or not there are any quality and/or safety problems that would obviously be a hindrance to initiating human clinical trials on iPS(-like) cell-based products in question, whether certain quality attributes (QA) of the product are grasped enough to check the relationship between clinical findings and the QA, and whether consistency of the QA are ensured within a definite range. At that time, it is also important at first to eliminate any presumed known risk factors associated with the product quality and safety as much as possible 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 suffering from diseases that are serious and life-threatening, involve marked functional impairment, or a marked loss of quality of life (QOL) due to the loss of a certain degree of physical function or form, and for diseases in which existing therapies have limitations and do not provide cures. Furthermore, it is also

important to entrust the right to making a decision to the patient after making all of this information available. In applying for investigational clinical trials, applicants can submit reasonably-prepared provisional data package, which fulfill conditions to meet the purpose as aforementioned, on the premise that data package for ensuring quality and safety at the time of marketing application/registration are enriched and developed along with the progress of clinical trials in line with the guidelines.
Finally, applicant are encouraged to discuss with the Pharmaceuticals and Medical Devices Agency (PMDA) with respect to the type and extent of data that may need for initiating individual clinical trials. There may be numerous variations in individual data package that could not be definitively clarified in the present guidelines due to differences such as in the origin of the product, target disease, target patients, sites of application, methods of application, and methods of processing.

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

Chapter I. General Principles

I. Objective

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

II. Definitions

The definitions of the technical terms used in this guideline are as follows:
1. "Human induced pluripotent stem cells (iPS cells)": Cells that are generated from somatic cells through artificial reprogramming by introducing genes or proteins, or by chemical or drug treatment, or cells that are obtained from such cells through cell division, and that possess the ability to differentiate into endoderm, mesoderm, and ectoderm, and furthermore, maintain the ability to self-renew or the similar ability.
2. "Human induced pluripotent stem-like cells (iPS-like cells)": Cells that are generated from somatic cells through artificial dedifferentiation by introducing genes or proteins, or by chemical or drug treatment, or cells that are obtained from such cells through cell division, and that at least possess the ability to differentiate into some type of endoderm, mesoderm, or ectoderm, and furthermore,

maintain the ability to self-renew or similar ability.

3. "Processing of cells and tissues": Any processing of a cell or tissue, such as pharmaceutical or chemical treatment, altering a biological characteristic, combining with a noncellular component, manipulation by genetic engineering, and so on, with the objective of propagation and/or differentiation of a cell or tissue, cell activation, and production of a cell line, with the aim of treating a patient, or repairing or regenerating tissue.

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

4. "Manufacture": Actions undertaken up until the final product (a human (autologous) iPS(-like) cell-based product) is released to market. This includes in addition to processing of cells and tissues, minimal manipulations such as the separation of tissue, disintegration of tissue, separation of cells, isolation of a specific cell, treatment with antibiotics, sterilization by washing or gamma irradiation, freezing, thawing, and other procedures that are performed without any change in the original properties of the cells or tissues.

5. "Phenotype": A morphological or physiological characteristic that is expressed by a certain gene under constant environmental conditions.

6. "Donor": persons who donate their own somatic cells that serve as the raw material of a human (autologous) iPS(-like) cell-based product. As for a human (autologous) iPS(-like) cell-based product, a patient is difinitely a donor. (Note: A patient is identified as a donor for actual treatment. It is also presumed that cells/tissues obtained from a donor besides a patient are used for a purpose of test production at the development or other stages.)

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

8. "Protein transductant": A construct which contains a target protein and elements like reagents necessary for introducing the target protein into a target cell.

Chapter II Manufacturing Methods

Describe all important and relevant information concerning the manufacturing method, taking into account the items listed below. This information will contribute to ensuring the quality, safety, and efficacy of the final product, and is important for guaranteeing the consistency of the quality from a manufacturing perspective. It should be noted that assurance of the quality and safety, and their consistency, is achieved by mutual complementary measures throughout the manufacturing method as a whole, and it is most important that the

measures are rational and serve the intended purpose. It may be acceptable to omit a portion of the items listed below, after providing the appropriate scientific basis, with respect to the quality tests or controls of the final product or intermediates, or control of the manufacturing process, if the quality and safety, and their constancy, can be assured.

I. Raw Materials and Materials Used in Manufacturing

1. Human somatic cells that serve as raw materials

(1) Characteristics of biological structure and function, and justification of their selection

Explain and justify the reasons for selecting the somatic cells used as raw materials based on the characteristics of their biological structure and function, such as for example, morphological characteristics, growth characteristics, biochemical indicators, immunological indicators, specific substances produced, and other suitably chosen and appropriate genotype or phenotype indicators. It is acceptable to use studies that used test samples prior to initiation of clinical trials.

This should lead to the identification of the main cell characteristic indicators that are to be employed when applying the cells to the patient. It is recognized that such study can only be performed to a reasonably possible extent since there are quantitative limits to samples as well as technological limits.

(2) Considerations with respect to the donor

From the perspective of ensuring the safety of the patient as well as personnel involved in manufacturing the product or health care workers who treat a patient, establish test parameters related to any type of possible infections that may occur via the somatic cells collected, 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 account the genetic characteristics, history of the patient, the condition of their health, and others and justify their appropriateness as donors. If donor genome or gene analysis is undertaken, they shall be done in accordance with "Ethical Guidelines for Human Genome and Gene Analysis Research" published jointly on December 28, 2004 by the Japanese Ministry of Education, Culture, Sports, Science, and Technology, Ministry of Health, Labor and Welfare, and Ministry of Economy, Trade and Industry.

(3) Records related to the donor

All records related to the donor shall be complete and kept so that any information necessary with respect to ensuring the safety of somatic cells used as raw materials can be verified. Concrete measures shall be described. For patients and donors of test samples, it is enough to only prepare and keep each specific information corresponding to the intended use of individual 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 sampling site and sampling method

Describe the rationale for selecting the cell and tissue sampling sites as well as the sampling method, and clearly state how these sites selected are both scientifically and ethically appropriate. For the 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 of the donor of the cells or tissue.

(iv) Protection of donor privacy

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

(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 undertaken for test results that indicated a problem existed.

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

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

(vii) Transportation methods

If cells and/or tissues or iPS(-like) cells collected 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 keeping procedures

Written records for (i) through (vii) above shall be prepared and proper keeping procedures for the records shall be described in detail.

2. Raw materials other than target cells and tissues as well as materials used in manufacturing

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

When so called 'Biological Products' or 'Specific Biological Products' (refer to Article 2.9 and 2.10 of Pharmaceutical Affairs Law) are used as raw materials, the amounts used should be kept to the minimum

amount required and should strictly obey the relevant laws and notifications, such as "Standards for Biological Raw Materials" (Notification Number 210, Japanese Ministry of Health, Labor, and Welfare, 2003). It is particularly important to sufficiently evaluate information related to the inactivation and elimination of viruses, as well as to indicate measures for ensuring retrospective and other studies.
The technical requirements described in this paragraph should be taken into consideration when the process of reprogramming or dedifferentiation from the raw materials into iPS(-like) cells, and of directed differentiation from iPS(-like) cells into the final products in question include any relevant elements/concerns be applied.

(1) When culturing cells
(i) Indicate the appropriateness of all the components of any media, additives (serum, growth factors, antibiotics, etc.) and reagents, etc. used in the treatment of cells, and set specification if necessary. Give consideration to the route of clinical application, etc. of the final product when setting specifications concerning the appropriateness of each component.

(ii) Take into consideration the following points with respect to media components
(a) The ingredients and water used in media should be of high quality and high biological purity, and whose quality is controlled at standards equivalent to those for pharmaceuticals and pharmaceutical raw materials.
(b) Provide information on not only the main ingredients used in media, but all components, as well as the rationale for their selection, and if necessary, the quality control and other procedures. However, widely known and commercially available media products such as DMEM, MCDB, HAM, and RPMI are regarded as one raw material.
(c) Conduct sterile tests and performance tests on media that contain all components in order to determine whether they are suitable as target media. Set specifications for any other relevant parameters believed to be controlled in process and perform proper quality control.

(iii) Heterologous serum or components derived from heterologous or homologous serum shall not be used unless they are essential for processes such as cell activation or cell growth. For products that may be used repeatedly in particular, investigate as much as possible ways to avoid using these serum components. If the use of serum or other such material is unavoidable, give consideration to the following points, and investigate ways to prevent the contamination and spread of bacteria, fungi, viruses, and abnormal prions from the serum and other products, as well as treatment methods for their elimination, to the greatest extent possible, from the final product.
(a) Clarify the origin of the serum or other component.
(b) Make strenuous efforts to minimize the risk of prion

infection, such as by strictly avoiding the use of serum from areas or regions with known outbreaks of bovine spongiform encephalopathy (BSE).

(c) Only use these sera after having confirmed that they are not contaminated with viruses or other pathogens by conducting appropriate tests to prove the absence of specific viruses and mycoplasma that originate in animal species.

(d) Conduct appropriate inactivation and elimination procedures for bacteria, fungi, and viruses to an extent that does not impact the activation and growth of the cells. For example, to avoid the risks associated with latent viral contamination, perform combinations of heat treatment, filtration, irradiation, and/or UV treatment, if needed.

(e) Preserve and store a portion of the serum used in order to be able to monitor for viral infections in cultured cells, monitor for outbreaks of viral diseases at the patient, and measure antigen production in response to a component of the heterologous serum used.

(iv) When using feeder cells, conduct quality evaluation while referring to "Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products" (Pharmaceutical Notification Number 873, Ministry of Health, Labor, and Welfare, July 14, 2000), "Guidelines on Public Health Infection Issues Accompanying Xenotransplantations" (Notification 0709001, Research and Development Division, Health Policy Bureau, Japanese Ministry of Health, Labor, and Welfare, issued July 9, 2002), and "Guidelines on Epithelial Regenerative Therapy Using 3T3J2 Strain or 3T3NIH Strain Cells as Feeder Cells" based on "Guidelines on Public Health Infection Issues Accompanying Xenotransplantations" (Notification 0702001, Research and Development Division, Health Policy Bureau, Japanese Ministry of Health, Labor, and Welfare, issued July 2, 2004) in order to prevent the contamination and spread of bacteria, fungi, viruses, and abnormal prions from the feeder cells, and indicate the methods for the inactivation of cell division potential and conditions such as cell density when using the feeder cells. However, for example, if the feeder cells or equivalent cells are being used in the manufacture of a cell or tissue product that has already been used clinically and whose characteristics and microbiological safety have already been assessed and confirmed, it may be possible to omit the virus tests or parts of other tests by demonstrating the appropriateness of using these cells.

(v) The use of antibiotics should be avoided as much as possible. However, if it is thought the use of antibiotics in the initial stages of processing is indispensable, attempt to decrease their use in subsequent steps as much as possible, and clearly state the appropriateness of their use from perspectives such as the scientific rationale, estimated residual amounts in the final product, and the effects on the patient. If it has been verified that an antibiotic can be adequately eliminated, its use need

not be restricted. On the other hand, if a patient has a past history of allergy to the antibiotic used, in principle, this therapeutic method should not be used. If there is no way to avoid the use of antibiotics, administer them very carefully and make sure informed consent is obtained from the patient.

(vi) If growth factors are used, show the appropriate quality control methods with established acceptance criteria and assay methods, such as for example purity and potency, in order to guarantee the reproducibility of the cell culture characteristics.

(vii) For media components that may be contained in the final product and other components that are used in manipulation, choose components that do have any harmful biological effects.

(viii) When using cells derived from a different species (heterologous cells) as feeder cells, ensure the safety of the cells from the viewpoint of the risk of infection of heterologous-derived cells.

(2) When combining with noncellular components

(i) Quality and safety of noncellular raw materials

If the final product consists of cells together with noncellular components such as matrix, medical materials, scaffolds, support membranes, fibers, and beads, describe in details the quality and safety of the noncellular components.

Provide any relevant information concerning the noncellular raw materials, taking into consideration their type and characteristics, form and function in the final product, and evaluation of the quality, safety, and efficacy from the perspective of the presumed clinical indication. When using materials that are absorbed by the body, perform the necessary tests on any degradation products.

With respect to the tests that should be carried out, refer to "Basic Views on Biological Tests Necessary for Regulatory Approval for Manufactured or Imported Medical Devices" (Notification No. 02013001, Pharmaceutical and Food Safety Bureau, Japanese Ministry of Health, Labor, and Welfare, issued February 13, 2003), and describe the test results and justify the use of such raw materials. It is encouraged to use rationally knowledge and information obtained from the literature as well.

(ii) Interactions with target(desired?) cells

Demonstrate the validity of test methods used and justify the results obtained for the following three items with respect to the interactions between noncellular components and the cells in the final product as well as in any intermediate products.

(a) The noncellular components do not have any deleterious effects on the function, growth capability, activity, or stability of cells in the final product required for the presumed clinical indication or the cells in any intermediate products.

(b) Evaluate to the greatest extent possible any potential interactions between the cells and noncellular components, taking into consideration for example the mutation, transformation,

and/or dedifferentiation of cells in the final product or cells in intermediate products.

(c) Show there is no loss of the expected properties of the noncellular components in the presumed clinical indication due to any interactions between the noncellular components and the cells in the final and intermediate products.

(iii) When using noncellular components with the objective of segregating the cells from the application site.

When using noncellular components with the objective of segregating the cells from the application site, confirm their efficacy and safety by referring to (a) through (d) below.

(a) Membrane permeability kinetics and pharmacological effect of target physiologically active substances derived from cells in the final product.

(b) Diffusion of nutritional components and excretory products

(c) Effects of noncellular components on the area near the application site.

(d) When a pharmacological effect of a target physiologicallly active substance derived from a desired cell is anticipated and the objective is segregation of the application site and the desired cells or undifferentiated cells, confirm that the cells do not leak out caused by the degradation, etc. of noncellular components.

(3) When cells undergo genetic modifications

When genes are introduced into cells, provide the details concerning the following items.

(i) For the target gene (specific gene encoding a desired protein or RNA), information related to its structure, origin, method by which it was obtained, cloning methods, and for cell bank of the target gene, methods of preparation of its cell bank, control, and renewal, and so on.

(ii) Nature of the transgene.

(iii) Structure, biological activity, and properties of the desired gene products

(iv) All raw materials, properties, and procedures (transgenic method, and origin, properties, and method of obtaining vector used in gene introduction) needed to produce the transgenic construct.

(v) Structure and characteristics of the transgene construct.

(vi) Control and preparation methods for cell and virus banks in order to prepare vectors and transgenic constructs.

For the manufacturing methods for transgenic cells, refer to Chapter 2 and other sections of "Guidelines for Ensuring the Quality and Safety of Gene Therapy Pharmaceuticals", which is an appendix of "Concerning Guidelines for Ensuring the Quality and Safety of Gene Therapy Pharmaceuticals" (hereinafter referred to as "Gene Therapy Pharmaceutical Guidelines"), published as Notification 1062 by the Ministry of Health and Welfare on November 15, 1995. Also, state clearly the appropriateness of the establishment in accordance with the appendix of the same notification.

Be aware that, based on the law (Law

No. 97, 2003) concerning ensuring the biodiversity of living organisms by regulating the use, etc. of genetic recombination organisms, etc., a separate application procedure will be required when living organisms including certain cells, as well "viruses", and "viroids" are genetically modified. The following cells are not regarded as living organism: "human cells, etc." or "cells that have the ability to differentiate, or differentiated cells but are not viable when alone under natural conditions".

Regardless of what is mentioned above, if a gene introduced into cells is used as a reagent in the manufacturing process and does not either chemically or functionally make up part of the final product, it is acceptable to just describe how the quality and safety of the gene conform to the intended use, based on the most up-dated knowledge.

(4) When proteins are introduced into cells

When proteins are introduced into cells, provide the details of the items listed below.

(i) Origin, and quality attributes including structure, biological activity and the physicochemical properties of the proteins.

(ii) Information concerning the procurement, manufacturing, quality control, and renewal methods for the proteins

(iii) Methods for introducing the proteins into the cells

(iv) Ouality attributes including the structure, biological activity, and the physicochemical properties of the chemical substances used to introduce the proteins into the cells

(v) When preparing a construct for introducing the protein in question into the cells, provide information related to its preparation, quality control, and renewal methods.

(vi) Preparation of cell banks and cell bank control methods in order to produce introduced proteins

Regardless of what is mentioned above, if a protein introduced into cells is used as a reagent in the manufacturing process and does not either chemically or functionally make up part of the final product, it is acceptable to just describe how the quality and safety of the protein conform to the intended use.

(5) When reprogramming or dedifferentiating, and/or differentiating cells by drugs or any chemicals

When reprogramming or dedifferentiating, and/or differentiating by drugs or any other chemicals, provide the details related to the following items.

(i) Origin, and quality attributes including the structure, and biological activity, if any and the physicochemical properties of the drugs or chemicals in question.

(ii) Information concerning the procurement, manufacturing, quality control, and renewal methods for the target drugs or chemicals.

(iii) Cell treatment methods using target drugs, etc.

(6) When performing cell reprogramming or dedifferentiation, and/or differentiation using physical methods

Describe the details of the methods used when performing cell

reprogramming or dedifferentiation, and/or differentiation using physical methods in question.

(7) When performing cell cell reprogramming or dedifferentiation, and/or differentiation using a combination of methods
Describe the details of the methods when using any combination consisting of genetic modification, the introduction of a protein, drug/chemical treatment, or physical methods to conduct cell reprogramming or dedifferentiation, and/or differentiation.

3. Establishment of human iPS(-like) cell line
Describe the methods used up until the establishment of iPS(-like) cells from somatic cells that serve as the raw material, and indicate, to the greatest extent possible, the appropriateness of the methods. These include the methods for obtaining the human somatic cells, the separation and culturing of somatic cells, the reprogramming or dedifferentiation of the somatic cells, methods for the isolation and preparation of cell lines of the reprogrammed or dedifferentiated cells, as well as the media, culture conditions, culture period, yield, and so on at each step in the process until establishment of the human iPS(-like) cell line.

In order to maintain the stability and consistency of the quality of human iPS(-like) cell line, identify critical quality attributes of the cells from among the various cell characteristics (for example; cell purity, morphological features, phenotype specific markers, karyotype, cell growth properties, pluripotency, etc.) and set acceptance criteria for them. Also demonstrate the potent number of passages or of cell divisions within which cells can be proliferated with keeping their quality in terms of the criteria specified.

4. Storage and transport of human iPS(-like) cell line
For human iPS(-like) cell line, perform appropriate stability tests based on cell viability and potency etc., of the cells, establish storage method and validity period, and make clear their appropriateness, taking into the due consideration duration of storage and distribution and storage form. In particular, when freezing and thawing, confirm whether the process of freezing and thawing have effect on stability and any criterion of the cell line, if needed. Evaluate storage over standard storage period, and confirm the margin of stability to the extent possible. However what are mentioned above are not adopted when using the cells immediately following establishment.
When transporting human iPS(-like) cells, the containers used for transport and the transportation procedure (including temperature control, etc.) shall be determined and their appropriateness clearly indicated.

5. Preparation of records and keeping procedures
Written records for 2. through 4. above shall be prepared and proper keeping procedures for the records shall be clearly described.

II. Manufacturing Process

When manufacturing pharmaceuticals

and medical devices derived from processing of human (autologous) iPS cells or human (autologous) iPS-like cells (i.e., human iPS(-like) cell-based products), describe in detail the manufacturing method and verify, to the greatest extent possible, the appropriateness of the method using the items listed below in order to maintain consistency of the quality of the product.

1. Lot composition and lot control
Indicate whether or not a lot is made up of final products and intermediate products. If a lot is composed of both final and intermediate products, establish standardized procedures concerning the make up and control of the lot.

2. Manufacturing method
Provide an outline of the manufacturing method from the time of receipt of the cells and tissues or somatic cells that serve as the raw materials through to the establishment of human iPS(-like) cells and cells that have progressed to the differentiation stage and then to the final product, and describe the technical details of the process and necessary process control and product quality control.

(1) Tests upon receipt
Establish a battery of tests as well as acceptance criteria to assess appropriateness of the cells and tissues or somatic cells, respectively that will serve as the raw materials, taking into account the nature of the cells and its intended use. These may include, for example, visual test, microscopic examination, recovery factor of target cells, cell viability, characterization of cells and tissues, microbiological tests, and so on. At the stage of initiating clinical trials, provide the actual measured values obtained up until that point with test samples, and propose provisional a set of acceptance criteria based on these values.

(2) Inactivation and elimination of bacteria, fungi, viruses, and other microorganisms
For cells and tissues or human somatic cells that serve as raw materials, carry out the inactivation and elimination of bacteria, fungi, viruses, and other microorganisms if needed and whenever possible, to such an extent that the procedures do not have any effect on the cell viability, phenotype, genetic traits, specific functions, or other characteristics and quality of the cells and tissues serving as raw materials. State the appropriateness of measures, procedures and evaluation methods taken, if any.

(3) Tissue disintegration, cell separation, isolation of specific cells, etc.
Describe the methods for the disintegration of tissue, separation of somatic cells, the isolation of specific somatic cells, as well as the methods for washing, etc. of these cells and tissues in order to generate the iPS(-like) cells, that is performed in the early stages of manufacture of the iPS(-like) cell-based products from collected cells and tissues. When isolating specific somatic cells, establish identification methods for the cells.

(4) Establishment of human iPS(-like)