10. 無菌中間製品の保管及び輸送の管理 10.1 一般要件 10.2 保管及び輸送のための容器 10.3 容器への投入, 容器からの取出し作業 10.4 保管及び輸送の条件	➢ “無菌操作法”を参考に、“再生”に関連した事項を加える。 無菌中間製品は、凍結された状態が前提でしょうか？ 温度により場合分けを行なうべきなのか？ （温度により菌が増殖するリスク考慮必要か？ → 無菌だから必要ない？） 中間製品の無菌性をどのように確認、担保するのか？	
11. 環境モニタリング 11.2 一般要求事項 11.2 日常管理要求事項 11.3 環境モニタリング判定基準例	➢ クリーンルーム（安全キャビネット）及びアイソレータ（RABS）における環境モニタリングの在り方について具体的に記載する。	
12. 製造設備及びユーティリティの適格性評価 12.1 一般要件 12.3 維持管理 12.3 校正 12.4 変更管理	必要なら、“無菌操作法”を引用する記載にする 作業者のスキルが絡むものの適格性評価（OQ、PQ）はどのように考慮するのか？ 例えば、安全キャビネット。作業者の人数（ギャラリーが多いとリスクが増す）等で個別に評価するのか、上限条件のようなものを設定するのか...など。	
13. 滅菌工程 13.2 一般要件	必要なら、“無菌操作法”を引用する記載にする ➢ 滅菌済み製品（デスポーザル製品）の選択要件に	

13.2　高圧蒸気滅菌 13.3　乾熱滅菌 13.4　電子線，γ線滅菌 13.5　その他の滅菌法	ついて記載する	
14. 無菌製造設備の定置清浄化(CIP) 14.1　CIP 対応の設計要点 14.2　洗浄剤の選定 14.3　CIP 工程パラメータ 14.5 日常管理 14.5　保守・管理 14.6　職員の教育訓練	必要なら、“無菌操作法”を引用する記載にする	
15. 無菌製造設備の定置蒸気滅菌(SIP) 15.1　一般要件 15.2　装置設計の要点 15.3　日常管理 15.4　保守・管理 15.5　職員の教育訓練	必要なら、“無菌操作法”を引用する記載にする	
16. 無菌充てん工程 16.2 一般要件 16.2　液体充てん工程 16.3　粉末充てん工程	必要なら、“無菌操作法”を引用する記載にする。ただし、最終製品化と輸送容器については、記載する必要があるかもしれない。	
17. ろ過滅菌工程 17.1 液体ろ過滅菌工程	➢　培地や試薬のろ過滅菌については記載する必要がある。	

17.2 空気その他ガス		
18. 凍結乾燥工程 18.1　一般要件 18.3 バリデーション 18.3　凍結乾燥装置の洗浄及び滅菌 18.4　日常管理と維持管理事項	必要なら、“無菌操作法”を引用する記載にする	
19. アイソレータ／バリアシステム／ブローフィルシール 19.1 アイソレータシステム 19.1.1　一般要件 19.1.2　アイソレータシステムの設計 19.1.3　空調システム 19.1.4　除染 19.1.5　教育訓練 19.1.6　日常管理 19.2 アクセス制限バリアシステム（RABS） 19.2.1　一般要件 19.2.2　教育訓練 19.3 ブローフィルシール 19.3.1　ブローフィルシールの範囲及び対象工程 19.3.3　容器の成型及び製品充てんの工程のフロー及びその環境	➢ アイソレータと RABS の使用要件については、詳細に記載する。 ・除染方法 ・リーク試験 ・微粒子計測計の規格 ・風速 ・各種インターフェースに対する要件 ・	

19.3.3　プラスチック容器の無菌性保証 19.3.4　ブローフィルシール工程の重要管理項目		
20. プロセスシミュレーション 20.1　概要と範囲 20.2　実施要領 20.3　プロセスシミュレーションの留意事項 20.4　培養及び観察 20.5　プロセスシミュレーションの許容基準 20.6　アイソレータシステムを採用している製造ラインのプロセスシミュレーション	➢ ロットを構成しない“再生”のプロセスシミュレーションについては、以下のことについて詳細に記載する。 ・使用培地、培養条件 ・初期評価、定期評価 ・シミュレートする範囲 ・サロゲート 評価する検体は、引き抜き試験か全量試験かについて、モデル例（分類）で示すのか？ （全量の場合、同時に A6 の複数の試験は難しいと考えます。全て最終加工物で評価するのか？）	
A1. 細胞培養／発酵により製造する原薬 A1.1　一般要件 A1.2　細胞培養又は発酵 A1.3　ハーベスト, 分離及び精製	➢ 細胞培養については詳細かつ具体的に記載する。本項は、参考情報から本体に移動。 ・細胞培養、ハーベスト、誘導、分離及び精製 ・MCB 及び WCB の確立	
A2. 製薬用水 A2.1　製薬用水設備の基本設計の留意点 A2.2　製薬用水のバリデーション	➢ 製薬用水を自家製造する際には、“無菌操作法”を引用する記載にするが、培地調製や試薬調製等に使用する製薬用水を購入して使用する場合の	

A2.3　製薬用水の日常管理 A2.4　製薬用水設備に係る職員の教育訓練 A2.5　製薬用設備の維持管理 A2.6　変更管理 A2.7　逸脱管理	要件は記載する	
A3. 無菌医薬品製造所の防虫管理 A3.1　一般要件 A3.2　昆虫類管理プログラム A3.3　防虫対策	必要なら、“無菌操作法”を引用する記載にする	
A4. バイオセーフティ及びバイオセキュリティ対策 A4.1　バイオセーフティレベル A4.2　バイオセキュリティ対策 A4.3　微生物等安全管理区域(管理区域) A4.4　BSL1施設に対する一般要件 A4.5　BSL2 施設に対する一般要件 A4.6　BSL3 施設に対する一般要件 A4.7　緊急時の対策 A4.8　教育訓練	➢ 感染症法の対象疾患に感染している患者検体を取り扱う際のバイオセーフティを中心に詳細かつ具体的に記載する。本項は、参考情報から本体に移動。 ・構造設備要件 ・廃棄物、廃水物の管理 ・感染症法の対象疾患を表形式で提示する	
A5. ケミカルハザード対策 A5.1　原則 A5.2　リスクマネジメントプロセス A5.3　教育訓練	必要なら、“無菌操作法”を引用する記載にする	
A6. 試験検査	➢ 代替微生物試験法を含め、詳細かつ具体的に記載	

A6.1　エンドトキシン A6.2　不溶性微粒子 A6.3　容器完全性 A6.4　外観検査	する。本項は、参考情報から本体に移動。 ・無菌試験 ・マイコプラズマ否定試験 ・エンドトキシン試験 ・外来性ウイルス否定試験が必要かどうか？ それぞれにおいて、どのようなもの（細胞、培地上清）が検体として適切なのかまで言及するのか？	

最終製品の保管および輸送の条件は不要という認識？

再生医療等製品の無菌製造法に関する指針作成における考慮点
（佐々木）

【使用語】

無菌操作法指針	GCTP、構造設備規則（再生医療等製品）	コメント
無菌操作区域、直接支援区域、その他の支援区域、清浄区域、作業室	無菌操作区域、清浄度管理区域、作業管理区域、作業室	使用語の統一は不要であるが、各区域の理解に誤りのないように
バリデーション	バリデーション又はベリフィケーション	ベリフィケーションの言及が必要か？
	品質リスクマネジメント、回収処理、管理単位、ドナー、外部試験検査機関等、生物由来原料基準、参考品及び保存品の保管管理、原料及び資材の供給者管理、	GCTP で使用している言葉の概念をどこまで盛り込むべきか？
バイオセーフティ対策	職員の感染防止措置	同一要件か？
一方向気流装置	層流装置	

【要議論点】

≪病原性を持つ微生物等による職員の感染防止措置に関する構造設備≫

・構造設備規則の逐条解説（１６）で「病原性を持つ微生物を取り扱う区域」には、病原性を持つ微生物等が混入しているおそれのある物を取り扱う区域であって封じ込めを行わなければ製品等の汚染又は交叉汚染のおそれがある場所も含むとある。BSL 3 該当病原体を使用する場合は、P3 施設が必要であるが、BSL 2 の肝炎ウイルス（B 型、C 型）を取り扱う構造設備を封じ込めにする必要があるかどうか。

《アイソレータに対する要件》

・一般無菌医薬品製造用アイソレータは、One-way 方式で、全て滅菌された原料、資材が搬入され、マウスホールを通して外部に搬送される。再生医療用アイソレータは、Working cell の消毒、プロセッシング後の使用器材、必要に応じて製品が搬入口に戻る。それ故、作業員が直接介在できない高度な清浄装置であり、一般無菌医薬品製造用アイソレータとは異なるので、過度な要件を課さないこと。
・USP<1116>要件やこれまでの実績データからみても、アイソレータ使用の場合、環境モニタリングは微粒子測定を主とし、微生物のモニタリングは従にしてよい。環境モニタリングの記載ぶりを考えること。

《使用培地の性能試験》

・種々の培地が、製造用、環境モニタリング、無菌試験、出荷試験等に使用される。製造用（細胞培養用）培地の性能試験は必須であるが、その他の市販培地については、製造所が品質システム（ISO 9001 等）を有し、適切な COA を提出し、使用者までの輸送システムに問題ないなら、受け入れロットごとの培地性能試験を省略できるようにしなければ再生医療等製造所では対応ができない。必要に応じては、培地製造者もしくは販売代理店と Quality agreement を締結させることでもよい。

《出荷時試験：無菌試験》

・出荷時製品の培養液、洗浄液等について MF 法でろ過し、可能な限り、迅速無菌試験法を採用すること。迅速無菌試験法としては、米国 FDA の評価研究で好成績を得た、ノバルティス社が開発し、かつ PMDA でも承認されている Shaedler Blood Agar を用いた方法が推奨される。出荷時製品の培養液、洗浄液等が使えるなら、製品そのものを試験に供する必要はない。

《出荷時試験：マイコプラズマ試験》

・マスターセルバンクやワーキングセルバンク確立の場合には、培養法や DNA 染色法での確認も必要ではあるが、製品出荷時においては PCR 法のみでよい。マイコプラズマの多くは細胞表面に付着し、表面で増殖後、上清に移行する。Late phase の培養物の場合、細胞破片に付着したマイコプラズマが上清に存在するので、上清を遠心処理し、沈渣から DNA を抽出し、日局参考情報に収載されている改正「マイコプラズマ否定試験法」で PCR を行う。

《出荷時試験：エンドトキシン試験》

・特に問題なく実施可能

《プロセスシミュレーション：培地充填試験》

・無菌性検証手段として、何らかのプロセスシミュレーションが必要ではあるが、サロゲートの選択、実施回数（初期評価、定期評価）、実施容器数、シミュレート範囲等、難しい問題である。

《重要な原料及び資材の供給者管理》

・製造元の監査は難しいので、基本は Quality agreement 締結で十分と考えられるが、agreement の具体的内容を例示した方がよいのでは。

《生物由来原料基準への準拠》

・特殊な試薬や原料の中には、生物由来原料基準への適合の難しいものもある。規制当局との個別協議内容か？

《外部試験検査機関》

・ＧＭＰ上の製造所に相当するのか？　例えば、環境モニタリングの培地の培養と観察を委託する場合、当該機関はＧＭＰ適合機関でなければならないのか？

《原料や資材の受入れ管理試験》

・原料（培地や試薬類を含む）の受入れ試験として、バイオバーデンやエンドトキシン試験実施は必須か？

《市販滅菌器材》

・一般無菌医薬品の製造には、SAL<10^{-6} で滅菌した器材の使用が求められている。市販プラスチック製品の中には、滅菌水準の分からないものもある。どうすべきか？

○ Ordinance No. 93 of the Ministry of Health, Labour and Welfare

Pursuant to the provisions of Article 23-25, Paragraph 2, Item 4 (including the cases where it is applied *mutatis mutandis* pursuant to Article 23-37, Paragraph 5) of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (Law No, 145 in 1960), the Ministerial Ordinance on Good Manufacturing Practice (GMP) for Regenerative Medicine Products is stipulated as below.

August 6, 2014

Norihisa Tamura, Minister of Health, Labour and Welfare

Ministerial Ordinance on Good Manufacturing Practice (GMP) for Regenerative Medicine Products

(Purpose)

Article 1 This Ministerial Ordinance specifies standards stipulated by the Ordinance of the Ministry of Health, Labour and Welfare set forth in Article 23-25, Paragraph 2, Item 4 (including the cases where it is applied *mutatis mutandis* pursuant to Article 23-37, Paragraph 5; the same applies hereinafter) of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (hereinafter referred to as the "Act").

(Definitions)

Article 2 The term "products" used in this Ordinance means materials which underwent manufacturing processes in a manufacturing site (including materials manufactured in the intermediate manufacturing process which must undergo further manufacture processes before the formulation of a product (hereinafter referred to as "intermediate products"); the same applies hereinafter).

2. The term "packaging and labelling materials" used in this Ordinance means containers, wrappers and labels (including package inserts; the same applies hereinafter) of a product.
3. The term "lot" used in this Ordinance means a batch of products manufactured so as to have uniform quality in a series of manufacturing processes in a unit of manufacturing period, and raw materials (hereinafter referred to as "products, etc.").
4. The term "control unit" used in this Ordinance means a batch of labeling and packaging materials confirmed to have uniform quality.
5. The term "validation" used in this Ordinance means to validate and document that anticipated results yield from the buildings and facilities at manufacturing sites as well as procedures, processes and other methods of manufacturing control and quality control (hereinafter referred to as the "manufacturing procedures, etc.").
6. The term "verification" used in this Ordinance means to confirm and document that anticipated results are obtained from the manufacturing procedures, etc.
7. The term "controlled clean area" used in this Ordinance means among the areas for performing manufacturing operations (hereinafter referred to as "work area"), a place for carrying out the preparing

operations of products, etc. (excluding those which must be handled by aseptic operations), and a place where containers, etc. before sterilization are exposed to the air in the work area.

8. The term "aseptic operation area" used in this Ordinance means among the work areas, a place for performing the preparing operations of products, etc., which must be handled by aseptic operations, a place where sterilized containers, etc. are exposed to the air in the work area, as well as a place for carrying out aseptic operations such as sterility tests.
9. The term "donor" used in this Ordinance means an individual providing his or her cells or tissues as the raw materials of regenerative medicine products (excluding cells or tissues derived from the human body with brain death as specified in Article 6, Paragraph 2 of the Law on Organ Transplantation (Law No. 104 in 1997)).
10. The term "donor animal" used in this Ordinance means an animal providing its cells or tissues as the source materials of regenerative medicine products.
11. The term "quality risk management" used in this Ordinance means to assess and control risk for product quality throughout processes from the early development to the completion of marketing of a product in accordance with appropriate procedures.
12. The term "review" used in this Ordinance means to assess the appropriateness and efficacy for achieving specified goals.

(Scope of application)

Article 3 The marketing authorization holders of regenerative medicine products or the marketing authorization holders of products such as appointed foreign manufactured regenerative medicine products specified in Article 23-37, Paragraph 4 of the Act shall have manufacturers and foreign manufacturers of regenerative medicine products (hereinafter simply referred to as "foreign manufacturers of regenerative medicine products") stipulated in Article 23-24, Paragraph 1 of the Act (hereinafter referred to as "manufacturers, etc.") perform the manufacturing control and quality control of the products at manufacturing sites pursuant to the provisions of this Ordinance.

2. The manufacturers, etc. shall implement the manufacturing control and quality control of products at manufacturing sites specified in Article 137-58 of the Enforcement Regulations of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (Ordinance No. 1 of the Ministry of Health and Welfare in 1961; hereinafter referred to as the "Enforcement Regulations") pursuant to the provisions of this Ordinance.
3. The manufacturers of regenerative medicine products for export set forth in Article 80, Paragraph 3 of the Act shall implement the manufacturing control and quality control of products at the manufacturing sites of regenerative medicine products for export pursuant to the provisions of this Ordinance.

(Quality risk management)

Article 4 The manufacturers, etc. shall consider the use of quality risk management when implementing manufacturing control and quality control of products at manufacturing sites.

(Manufacturing Department and Quality Department)

Article 5 The manufacturers, etc. shall establish a department for controlling manufacturing (hereinafter referred to as the "Manufacturing Department") and a department for controlling quality (hereinafter referred to as the "Quality Department") for each manufacturing site under the supervision of a Manufacturing Manager of regenerative medicine products specified in Article 23-34, Paragraph 4 of the Act (for foreign manufacturers of regenerative medicine products, a responsible person of a manufacturing site authorized pursuant to the provisions of Article 23-24, Paragraph 1 of the Act or a person appointed beforehand by the foreign manufacturers of regenerative medicine products; hereinafter referred to as the "Manufacturing Manager").

2 The Quality Department shall be independent from the Manufacturing Department.

(Manufacturing Manager)

Article 6 The Manufacturing Manager shall carry out the following duties:

(1) To supervise activities for manufacturing control and quality control (hereinafter referred to as the "manufacturing and quality control duties") and manage/ direct so that they can be properly and smoothly implemented.

(2) When there are risks of quality defects and other significant effects on product quality, to confirm required measures being promptly taken and the status of their progress, and as necessary to instruct to implement necessary measures such as improvement.

2. The manufacturers, etc. shall make efforts for the effective performance of the duties assigned to the Manufacturing Manager.

(Personnel)

Article 7 The manufacturers, etc. shall appropriately appoint a responsible person who is capable of properly and smoothly carrying out the manufacturing and quality control duties (hereinafter simply referred to as the "Manager") according to the organization and scale of the manufacturing site as well as types of duties.

2. The manufacturers, etc. shall appoint an appropriate number of Managers according to the organization and scale of the manufacturing site as well as types of duties.

3. The manufacturers, etc. shall secure an adequate number of personnel who are capable of properly implementing the manufacturing and quality control duties.

4. The manufacturers, etc. shall properly document responsibilities and a management system for personnel (including Manufacturing Manager and Managers) engaged in the manufacturing and quality control duties.

(Product master formula)

Article 8 The manufacturers, etc. shall prepare and retain a product master formula for each product (excluding intermediate products; the same applies hereinafter in this article) describing the belowmentioned matters at each manufacturing site involved in the manufacture of the product, and receive approval of the Quality Department:

(1) Terms concerning manufacturing approval;
(2) The standards specified pursuant to the provisions of Article 42, Paragraph 1 of the Act, other pharmaceutical affairs-related laws and regulations, or matters concerning quality among orders or dispositions based on these;
(3) Manufacturing procedures (excluding the matter set forth in Item (1));
(4) Name, essence, description, ingredients and their contents, and other specifications of a material obtained from humans, animals, plants or microorganisms provides as the source material;
(5) Specifications of animals used for manufacturing or inspection and testing (including donor animals; hereinafter referred to as "utilized animals"); and
(6) Other necessary matters.

(Procedures)

Article 9 The manufacturers, etc. shall, at each manufacturing site, prepare and retain a sanitation control standard code presenting hygienic control of buildings and facilities as well as personnel and other necessary matters.

2. The manufacturers, etc. shall, at each manufacturing site, prepare and retain a manufacturing control standard code describing the storage of products, etc., the control of manufacturing processes and other necessary matters.
3. The manufacturers, etc. shall, at each manufacturing site, prepare and retain a quality control standard code mentioning a method for sample collection, a method for assessing inspection and testing results, and other necessary matters.
4. The manufacturers, etc. shall, at each manufacturing site, prepare and retain the following documents concerning procedures (hereinafter referred to as the "Procedures") for properly and smoothly implementing manufacturing control and quality control in addition to those set forth in the preceding three paragraphs:
   (1) Procedures for control of release from a manufacturing site
   (2) Procedures for validation or verification
   (3) Procedures for review of product quality
   (4) Procedures for change control set forth in Article 16
   (5) Procedures for deviation control set forth in Article 17
   (6) Procedures for handling quality information and quality defects
   (7) Procedures for recall action
   (8) Procedures for self-inspections
   (9) Procedures for training
   (10) Procedures for document and record control
   (11) Other procedures necessary for properly and smoothly implementing manufacturing control and quality control.

5. The manufacturers, etc. shall retain the product master formula, sanitation control standard code, manufacturing control standard code, quality control standard code and Procedures (hereinafter referred to as the "operating procedures") at the manufacturing sites.

(Buildings and facilities)

Article 10 Buildings and facilities at the manufacturing sites of products shall meet the following requirements:

(1) That cleaning and maintenance are properly carried out according to their usage, and as necessary, sterilization is implemented in accordance with the operating procedures, and their records are prepared and retained.

(2) That facilities for the disposal of poisonous gases, if handled depending on products, etc., are equipped.

(3) That among the work areas, a work room or working control area (the area consisting of work rooms, passage, etc. that are controlled so as to maintain the uniform quality of cleanliness; the same applies hereinafter) shall be provided with adequate buildings and facilities for maintaining and controlling cleanliness according to the types, structures, characteristics and manufacturing processes of products.

(4) That the work room shall meet the following requirements:

A. The work room shall be provided with buildings and facilities for preventing contamination by dust or microorganisms according to the types, structures and manufacturing processes of products, provided, however, that this provision shall not apply to the case where the same effects are obtained from the functions of the manufacturing facilities;

B. The work room shall have facilities necessary for properly drying and storing containers after washing;

C. The work room shall have sterilization equipment necessary for manufacturing according to the types of products;

D. An area for performing aseptic operations shall be provided with clean air processed through a filter and have buildings and facilities necessary for properly controlling differential pressure; and

E. When manufacturing products related to injections, the liquid-contacting piping of pipes and other relevant materials affecting sterility assurance shall be constructed so as to facilitate cleaning and enable sterilization.

(5) That the work room for the drying and sterilization operations of containers after washing shall be used exclusively for that purpose, provided, however, that this provision shall not apply to the case where there is no risk of contamination of containers after washing.

(6) That work rooms for the weighing operations of raw materials, the formulating operations of products, and the filling operations of products or sealing operations of containers shall be constructed so as not to allow passage for personnel other than those working in the room,

provided, however, that this provision shall not apply to the case where there is no risk of contamination to products by personnel other than those working in the room.

(7) That work rooms for the formulating operations or the filling operations of products or sealing operations of containers shall be separated from work rooms other than these or the working control area but used exclusively for those purposes. Also, the working rooms shall have dressing rooms for exclusive use by personnel engaged in these operations.

(8) That when products, etc. which are suspected to have serious effects on other products by cross-contamination are manufactured, work rooms related to the products, etc. shall be exclusively for them, and the air-treatment system shall be separated, provided, however, that this provision shall not apply to the case where validated inactivation processes and cleaning procedures or either one of them is established or maintained.

(9) That facilities for supply of water of the quality and quantity needed for the manufacturing of products (including cleaning water for facilities, apparatuses and containers) shall be equipped.

(10) That facilities to supply distilled water, etc. for the manufacturing of products shall be constructed so as to prevent contamination of distilled water, etc. by foreign matters or microorganisms.

(11) That the work area shall be provided with the following facilities in rooms clearly separated from other rooms, provided, however that the facilities found to be unnecessary for the manufacturing of the product according to the types, manufacturing methods, etc. of products are excluded:

A. Storage facilities for cells or microorganisms, etc.;

B. Facilities for keeping animals for use in manufacturing or inspection and testing after inoculation of microorganisms, etc.;

C. Facilities for treating animals for use in manufacturing or inspection and testing;

D. Facilities for inoculating cells or microorganisms, etc. into culture media, etc.;

E. Facilities for cultivating cells or microorganisms, etc.;

F. Facilities for collecting, inactivating, sterilizing, etc. cultured cells or microorganisms, etc.; and

G. Facilities for disinfecting apparatus and appliances that have been used in manufacturing or inspection and testing.

(12) That the room provided with the facilities mentioned in Items D and F of the preceding item and the room provided with the facilities for sterility tests among the facilities necessary for inspecting and testing products, etc. and packaging and labelling materials shall meet the following requirements:

A. Work rooms shall be aseptic, provided, however, that this provision shall not apply to the case where the work room is provided with facilities having function enabling to perform aseptic operations without problem according to the types, manufacturing methods, etc. of products; and

B. The aseptic room set forth in Item A shall have an adjacent anteroom which usually allows exclusive passage of personnel to and from the work room and whose entrances and exits are not opening directly to the exterior.

(13) That the work area shall be provided with the following facilities in addition to those specified in Item (11):

A. Facilities necessary for breeding and managing animals for use in manufacturing or inspection and testing;

B. Facilities for preparing culture media and diluents for the media;

C. Facilities for washing and sterilizing in advance apparatus and appliances, containers, etc. which are used in manufacturing or inspection and testing; and

D. Facilities for properly treating animal carcasses and other wastes as well as for purifying sewage.

(Manufacturing control)

Article 11 The manufacturers, etc. shall have the Manufacturing Department properly carry out the following duties related to manufacturing control in accordance with the operating procedures:

(1) That the manufacturing order describing instructions, precautions and other necessary matters during manufacturing processes shall be prepared and retained.

(2) That products shall be manufactured in accordance with the manufacturing order.

(3) That records on the manufacturing of products shall be prepared and retained by lot (by manufacturing number for products not constituting a lot; the same applies hereinafter).

(4) That whether or not the packaging and labelling materials of products are appropriate shall be checked by lot, and the records of its results shall be prepared and retained.

(5) The products, etc. by lot, and packaging and labelling materials by control unit shall be appropriately stored and released, and the records thereof shall be prepared and retained.

(6) That the cleanliness of the buildings and facilities shall be checked, and the records of its results shall be prepared and retained.

(7) That periodic inspection and maintenance of the buildings and facilities shall be performed, and the records thereof shall be prepared and retained. Also, meters shall be properly calibrated, and the records thereof shall be prepared and retained.

(8) That it shall be checked through records of manufacturing, storage, release and hygienic control that manufacturing control is properly implemented, and its results shall be reported in writing to the Quality Department.

(9) That for work rooms or working control areas, according to the types, structures, characteristics and manufacturing processes of products to be manufactured, as well as the contents of operations to be carried out in the work rooms or working control areas, the control level of work environment such as cleanliness shall be appropriately set and managed.

(10) That for the products, etc., and packaging and labelling materials, according to the types, structures, characteristics, manufacturing processes, etc. of products to be manufactured, necessary control items such as the counts of microorganisms, etc. shall be appropriately set and managed.

(11) That necessary measures for preventing contamination of the products, etc. and packaging and labelling materials by microorganisms, etc. during manufacturing processes shall be taken.

(12) That for critical processes for ensuring the sterility of products, according to the types, structures, characteristics, manufacturing processes, etc. of products to be manufactured, control values necessary for process control shall be appropriately set and managed.

(13) That for manufacturing water, according to its usage, control values related to necessary microbial and physicochemical items shall be appropriately set and managed.

(14) That when microorganisms, etc. contained in the products, etc. are inactivated or eliminated during the manufacturing processes, measures necessary for preventing contamination by the products, etc., which do not undergo the said inactivation or elimination shall be taken.

(15) That when biochemical technology is applied during the manufacturing processes, continuous measurements of temperature, a hydrogen ion index, etc. necessary for the control of the manufacturing processes shall be performed.

(16) That when equipment for column chromatography is used during the manufacturing processes, measures necessary for preventing contamination of the equipment by microorganisms, etc. shall be taken, and measurements of endotoxins, if needed, shall be carried out.

(17) That in employing the culture method to provide a continuous supply of culture media to an incubation tank and to perform continuous discharge of liquid media during the manufacturing processes, measures necessary for maintaining incubation conditions in the incubation tank during the incubation period shall be taken.

(18) That all the articles, which have been contaminated by microorganisms, etc. (limited to those contaminated during the manufacturing processes), shall be disposed of so as not to cause hazards to the public health and hygiene.

(19) That records on the handling of cell strains to be used for manufacturing shall be prepared for the following matters, and the records shall be retained:

A. Name of cell strain and number given to each container;

B. Date of being transferred, and the name and address of a person who has transferred (in case of a corporation, name and address);

C. Biological properties and date of testing; and

D. Status of subculture.

(20) That for raw materials derived from organisms (excluding plants) (hereinafter referred to as "biological-origin raw materials for regenerative medicine products") to be used for manufacturing, it shall be confirmed that the biological-origin raw materials for regenerative medicine products are appropriate by reference to the product master formula of the product, and records of the confirmation shall be prepared and retained.

(21) That the manufacturers, etc. shall retain themselves the records of biological-origin raw materials for regenerative medicine products to be used for manufacturing of the product with respect to matters as specified by the Minister of Health, Labour and Welfare for a period set forth in Article 22, Item 3, A or B, or close a contract with a firm collecting raw materials of the biological-origin raw materials for regenerative medicine products (referring to the origins of raw materials or materials (including those used during the manufacturing processes) to be used for manufacturing) (hereinafter referred to as the "raw materials collecting firms, etc."), and the records shall be properly retained by the raw materials collecting firms, etc. based on the contract.

(22) That records set forth in Item (8) and the preceding two items shall be prepared for each lot of products to be manufactured, and the records thereof shall be retained.

(23) That in handling of the cells or tissues collected from different donors or donor animals, measures necessary for preventing mixture and cross-contamination of the cells or tissues shall be taken.

(24) That it shall be confirmed based on records on the following matters that cells or tissues as raw materials are appropriate, when received, by reference to the product master formula of the product, and the records of the confirmation results shall be prepared and retained:

A. Facilities where the cells or tissues have been collected;

B. Date on which the cells or tissues have been collected;

C. When the cells or tissues are derived from humans, the status of diagnosing donors based on their interview and tests for the donor screening (referring to performing a diagnosis based on interview and tests of donors to decide whether or not they are fully eligible to provide their cells or tissues as the raw materials of products);

D. When the cells or tissues are derived from animals, the status of receiving donor animals as well as conditions of the inspection and testing, and breeding and keeping of such animals for the donor screening (referring to performing inspection/ testing and breeding/ keeping of donor animals to decide whether or not they are fully eligible to provide their cells or tissues as the raw materials of products);

E. Course of operations to collect the cells or tissues;

F. Course of transporting the cells or tissues; and

G. Requirements for ensuring the quality of the products in addition to those mentioned in Items A to F.

(25) That when collecting cells or tissues as raw materials from donor animals, measures necessary for preventing contamination by microorganisms, etc. during the collection shall be taken, and records of such measures shall be prepared and retained.

(26) That for products, the names of the destination facilities, date of distribution and lot shall be understood for each product, and the records thereof shall be prepared and retained.

(27) That for distribution, measures necessary for ensuring the quality of products shall be taken, and records of such measures shall be prepared and retained.

(28) That records set forth from Item (24) to the preceding item shall be prepared by lot (product for the records in Item (26)) and retained.

(29) That the hygienic control of personnel shall be implemented in accordance with the following requirements:

A. To restrict as much as possible for persons other than personnel engaged in manufacturing operations to go in or out of the work area;

B. To restrict as much as possible for personnel to go in or out of the controlled clean area or aseptic operation area where actual operations are carried out;

C. To specify strict procedures for preventing contamination by personnel engaged in duties related to culture of human or animal cells or microorganisms, etc. and other processing (excluding those actually used as raw materials in the manufacturing), and not to allow the personnel to go in or out of the work room or working control area for products except for the case where such procedures are compiled; and

D. To have personnel engaged in manufacturing operations not assigned to activities related to controlling utilized animals (excluding those actually used for the manufacturing process).

(30) That the hygienic control of personnel working in the controlled clean area or aseptic operation area shall be implemented in accordance with the following requirements:

A. To have personnel engaged in manufacturing operations wear work clothes, shoes, caps, masks and gloves that have been disinfected;

B. To have personnel engaged in manufacturing operations properly change clothing according to the level of control of the concerned area when entering in the controlled clean area or aseptic operation area;

C. To have personnel undergo medical checkups at intervals not exceeding 6 months in order to confirm that they do not have diseases that are suspected to contaminate the products, etc. by microorganisms, etc.;

D. When personnel having their health conditions that are suspected to contaminate the products, etc. with microorganisms, etc. (including infectious diseases such as skin or hair, cold, wound, or symptoms such as diarrhea or fevers without causes), to have the personnel not engage in operations in the controlled clean area or aseptic operation area;

E. When personnel handle microorganisms, etc. that may contaminate cells or tissues immediately before collecting or treating the cells or tissues, to have the personnel not engage in operations in the controlled clean area or aseptic operation area; and

F. To prepare and retain records on the preceding Item and Items A to E.

(31) Other duties necessary for manufacturing control.

2. Records on products specified in the preceding paragraph shall be retained so as to appropriately confirm a series of records from biological-origin raw materials for regenerative medicine products provided in manufacturing to a product manufactured with the biological-origin raw materials for regenerative medicine products.

(Quality control)

Article 12 For products, from each lot of product (in the case of specified regenerative medicine products stipulated in Article 68-7, Paragraph 3 of the Act (hereinafter simply referred to as "specified regenerative medicine products") not constituting a lot, for biological-origin raw materials for regenerative medicine products used in the manufacturing, for each manufacturing number of the product or from each lot of the biological-origin raw materials for regenerative medicine products), consisting of at least twice the quantity needed for all the required inspection and testing (however, an appropriate quantity if the quantity cannot be secured), the manufacturers, etc. shall store a reserve sample under proper conditions of storage for periods set forth in each of the following items from the date of manufacturing, provided, however, that this provision shall not apply to specified regenerative medicine products not constituting a lot under a contract, already closed between the manufacturers, etc. and raw materials collecting firms, etc. specifying that the raw materials collecting firms, etc. shall store a reserve sample for periods set forth in each of the following items. For products constituting a lot, after a period of the expiry date plus one year, the storage of the biological-origin raw materials for regenerative medicine products, which have been provided in manufacturing the product, may be substituted for storage of the product:

(1) A period of the expiry date plus 10 years for specified regenerative medicine products; and

(2) Appropriate duration for regenerative medicine products (excluding products set forth in the preceding item).

2. The manufacturers, etc. shall have the Quality Department systematically and appropriately perform the following duties related to the quality control of products in accordance with the operating procedures:

(1) That samples necessary for carrying out inspection and testing shall be collected by lot for products, etc. and by control unit for packaging and labelling materials as well as the records thereof shall be prepared and retained.

(2) That the inspection and testing (including inspection and testing implemented on the responsibilities of the manufacturers, etc. using other inspection and testing facilities of the manufacturers, etc. or other inspection and testing institutions, and such use is found to be acceptable; the same applies hereinafter) of the collected samples shall be conducted by lot or control unit as well as the records thereof shall be prepared and retained.

(3) That the periodic inspection and maintenance of the facilities and apparatuses for inspection and testing shall be carried out as well as the records thereof shall be prepared and retained. Also, meters for inspection and testing shall be properly calibrated as well as the records thereof shall be prepared and retained.

(4) That the results of the inspection and testing set forth in Item (2) shall be assessed, and the results shall be reported in writing to the Manufacturing Department.

(5) That samples shall be separated by the proper labeling of identification in order to prevent mixture and cross-contamination of the samples.