No	Article of the Ministerial Ordinance	Question
		retain the records thereof. (2) When making the changes upon approval of the Quality Department pursuant to the provision of the preceding item, to revise relevant documents, give training to personnel and take other required measures.

14. Deviation control (related to Article 17)

No	Article of the Ministerial Ordinance	Question
34	Article 17, Paragraph 1	When there are deviations from the manufacturing procedures, etc., are manufacturers, etc. having a person, designated beforehand, implement the following duties in accordance with the operating procedures? (1) That the details of deviations shall be recorded. (2) That the following duties shall be performed when major deviations occurred: (a) To evaluate the effect of deviations on the quality of products, and take required measures; (b) To prepare and retain the records on the results of the evaluation and the measures specified in Item (a), and report them in writing to the Quality Department; and (c) To have confirmation of the Quality Department on the results of the evaluation and the measures reported pursuant to the provision of Item (b).

No	Article of the Ministerial Ordinance	Question
35	Article 17, Paragraph 2	Are manufacturers, etc. having the Quality Department prepare and retain the records on the confirmation pursuant to the provision of Item 2 (c) of the preceding paragraph in accordance with the operating procedures and properly report in writing with the records set forth in Item 2 (b) to the Manufacturing Manager?

15. Handling of quality information and quality defects (related to Article 18)

No	Article of the Ministerial Ordinance	Question
36	Article 18, Paragraph 1	When receiving information on the quality and other relevant matters of products (hereinafter referred to as the "quality information"), are manufacturers, etc. having a person, designated beforehand, implement the following duties in accordance with the operating procedures excluding the case where matters concerning the quality information are clearly not attributable to the manufacturing site? (1) To investigate into the cause of the matter concerning the quality information, and take required measures when improvement in manufacturing control or quality control is needed. (2) To prepare and retain records describing the details of the quality information, the results of the investigation into the cause and corrective measures taken, and promptly report them in writing to the Quality Department. (3) To have confirmation of the Quality Department for the report set forth in the preceding item.

No	Article of the Ministerial Ordinance	Question
37	Article 18, Paragraph 2	When quality defects or suspected quality defects are identified as a result of the confirmation set forth in Item 3 of the preceding paragraph, are manufacturers, etc. having the Quality Department report the said matter in writing to the Manufacturing Manager in accordance with the operating procedures?

16. Recall action (related to Article 19)

No	Article of the Ministerial Ordinance	Question
38	Article 19	When recall is implemented because of reasons on the quality, etc. of products, are manufacturers, etc. having a person, designated beforehand, implement the following duties in accordance with the operating procedures? (1) To appropriately dispose recalled products after separately storing them for a certain period if the recalled products are to be stored. (2) To prepare and retain records on a recall action describing the details of the recall, and report them in writing to the Quality Department and Manufacturing Manager, provided, however, that this provision shall not apply to the case where the reason for implementing the recall is revealed to be not attributable to the concerned manufacturing site.

17. Self-inspections (related to Article 20)

No	Article of the Ministerial Ordinance	Question
39	Article 20, Paragraph 1	Are manufacturers, etc. having a person, designated beforehand, implement the following duties in accordance with the operating procedures? (1) To perform the periodic self-inspections on the manufacturing control and quality control of products at the manufacturing site. (2) To report the results of the self-inspections in writing to the Manufacturing Manager. (3) To prepare and retain records of the self-inspection results.

No	Article of the Ministerial Ordinance	Question
40	Article 20, Paragraph 2	Are manufacturers, etc. taking required measures when it is found necessary to improve manufacturing control or quality control based on the results of the self-inspections set forth in Item 1 of the preceding paragraph, as well as prepare and retain the records of the said measures?

18. Training (related to Article 21)

No	Article of the Ministerial Ordinance	Question
41	Article 21	Are manufacturers, etc. having a person, designated beforehand, implement the following duties in accordance with the operating procedures? (1) To systematically implement necessary training on manufacturing

No	Article of the Ministerial Ordinance	Question
		control and quality control for personnel engaged in the manufacturing and quality control duties. (2) To provide personnel engaged in manufacturing or inspection and testing with training on sanitary control, microbiology, medicine, veterinary medicine and other necessary matters for the manufacturing of products. (3) To give training on measures necessary for preventing contamination by microorganisms, etc. to personnel who are engaged in duties in the controlled clean area, aseptic operation area, etc. and duties related to the culture or other processing of human or animal cells or microorganisms, etc. used for the manufacturing of products. (4) To report the status of implementation of training in writing to the Manufacturing Manager. (5) To prepare and retain records on the implementation of training.

19. Document and record control (related to Article 22)

No	Article of the Ministerial Ordinance	Question
42	Article 22	Are manufacturers, etc. a person, designated beforehand, implementing the following duties concerning documents and records specified in this Ordinance in accordance with the operating procedures? (1) When preparing or revising documents, to implement approval, distribution, retention and other relevant matters in accordance with the operating procedures. (2) When preparing or revising the operating procedures, to record its date in the operating procedures, and to keep a history of the previous revisions. (3) To retain documents and records specified in this Ordinance for the following periods (5 years for records on training) from the date of preparation (date when documents are no longer used for the operating procedures): (a) A period of the expiry date plus 30 years for specified regenerative medicine products; and (b) A period of the expiry date plus 10 years for regenerative medicine products (excluding those mentioned in Item (a)).

20. Exceptions for retention of records (related to Article 23)

No	Article of the Ministerial Ordinance	Question
43	Article 23	Notwithstanding the provisions of the preceding article, are the manufacturers, etc. having a person, designated beforehand, retain records specified in the preceding article for regenerative medicine products designated by the Minister of Health, Labour and Welfare, for the period stipulated by the Minister of Health, Labour and Welfare? Provided, however, this provision shall not apply to the case where a contract has been closed between the manufacturers, etc. and raw materials collecting firms, etc., and these records shall be appropriately retained for the concerned period by the raw materials collecting firms, etc.

[Attachment 3]

Qualification Criteria for Each Article of the GQP Ordinance
(Cellular and Tissue-based Products)

1. Operations of the marketing supervisor-general of cellular and tissue-based products (related to Article 3 as applied mutatis mutandis to Article 21)

No	Article of the Ministerial Ordinance	Question
1	Article 3 as applied mutatis mutandis to Article 21	Is the marketing authorization holder of cellular and tissue-based products requiring the marketing supervisor-general of cellular and tissue-based products to carry out operations indicated in the following Items? (1) To supervise the quality assurance supervisor prescribed in Paragraph 3 of the next Article. (2) To conduct the operation prescribed in Article 11, Paragraph 2, Item 2 as applied mutatis mutandis to Article 21, as well as to determine necessary measures based on reports, etc., from the quality assurance supervisor prescribed in the preceding Item, and to order the quality assurance division prescribed in Paragraph 2 of the next Article and other divisions and responsible persons relevant to the quality control operation to conduct these measures. (3) To value the opinion of the quality assurance supervisor prescribed in Item 1. (4) To require close cooperation between the quality assurance division prescribed in Item 2 and the safety control supervisory division prescribed in post-marketing safety control standards and other relevant divisions of quality control operation.

2. Organization and personnel pertaining to quality control operation (related to Article 4 as applied mutatis mutandis to Article 21)

No	Article of the Ministerial Ordinance	Question
2	Article 4, Paragraph 1 as applied mutatis mutandis to Article 21	Does the marketing authorization holder of cellular and tissue-based products have a sufficient number of personnel with the capacity to appropriately and smoothly execute quality control operations?

No	Article of the Ministerial Ordinance	Question
3	Article 4, Paragraph 2 as applied mutatis mutandis to Article 21	Has the marketing authorization holder of cellular and tissue-based products placed a quality assurance division that meets the following requirements as a division pertaining to integration of quality control operations? (1) Shall be placed under the supervision of the marketing supervisor-general of cellular and tissue-based products. (2) Shall have a sufficient number of personnel with the capacity to appropriately and smoothly execute operations at the quality assurance division.

No	Article of the Ministerial Ordinance	Question
		(3) Shall be independent from the division pertaining to sales and from other divisions that influence appropriate and smooth execution of the quality control operation.

No	Article of the Ministerial Ordinance	Question
4	Article 4, Paragraph 3 as applied mutatis mutandis to Article 21	Has the marketing authorization holder of cellular and tissue-based products placed a quality assurance supervisor who meets the following requirements? (1) Shall be a responsible person for the quality assurance division. (2) Shall be a person who has engaged in the quality control operation and other similar operations for 3 or more years. (3) Shall have the capacity to appropriately and smoothly execute quality control operations. (4) Shall be a person who is not affiliated to any of the divisions pertaining to sales and shall be a person with no possibility of posing any impediment in appropriate and smooth execution of the quality control operation.

No	Article of the Ministerial Ordinance	Question
5	Article 4, Paragraph 4 as applied mutatis mutandis to Article 21	The marketing authorization holder of cellular and tissue-based products are required to appropriately prescribe in document the responsibilities and the management system of persons engaged in the quality control operation (including the marketing supervisor-general of cellular and tissue-based products and the quality assurance supervisor; the same shall apply hereinafter).

3. Quality standards (related to Article 5 as applied mutatis mutandis to Article 21)

No	Article of the Ministerial Ordinance	Question
6	Article 5 as applied mutatis mutandis to Article 21	Is the marketing authorization holder of cellular and tissue-based products conducting the operation of preparing quality standards according to each drug item?

4. Documents regarding procedures for quality control operations (related to Article 6 as applied mutatis mutandis to Article 21)

No	Article of the Ministerial Ordinance	Question
7	Article 6, Paragraph 1 as applied mutatis mutandis to Article 21	Is the marketing authorization holder of cellular and tissue-based products conducting the operation of preparing the following procedures for quality control operation in order for their appropriate and smooth conduct? (1) Procedures for control of release into the market (2) Procedures for ensuring appropriate manufacturing control and quality control (3) Procedures for information on quality, etc., and measures for quality defect, etc. (4) Procedures for management of recalls (5) Procedures for self-inspection

No	Article of the Ministerial Ordinance	Question
		(6) Procedures for training and education (7) Procedures for control of storage, etc., of cellular and tissue-based products (8) Procedures for control of documents and records (9) Procedures for mutual cooperation with the safety control supervisory division and other divisions and responsible persons relevant to the quality control operation (10) Other necessary procedures for appropriate and smooth quality control operations

No	Article of the Ministerial Ordinance	Question
8	Article 6, Paragraph 2 as applied mutatis mutandis to Article 21	Has the marketing authorization holder of cellular and tissue-based products furnished procedures for quality control operation at the office in which the marketing supervisor-general of cellular and tissue-based products conduct his/her operation, as well as a copy of those procedures at other offices in which quality control operations are conducted?

5. Agreements with the manufacturers (related to Article 7 as applied mutatis mutandis to Article 21)

No	Article of the Ministerial Ordinance	Question
9	Article 7 as applied mutatis mutandis to Article 21	Has the marketing authorization holder of cellular and tissue-based products concluded agreements with product manufacturers on the following matters in order to ensure appropriate and smooth manufacturing control and quality control, and indicated them in the procedures, etc., for quality control operations? (1) Extent of manufacturing at the manufacturers and of other operations related to manufacturing (hereinafter referred to as "manufacturing operation" in this article), manufacturing control and quality control pertaining to these manufacturing operations, and procedures for release (2) Technical condition such as on manufacturing methods and testing methods (3) Periodic confirmation by the marketing authorization holder on whether the manufacturing operation is conducted under appropriate and smooth manufacturing control and quality control (4) Method of quality control during shipping and at receipt of the product (5) Method and the responsible person for taking prior contact with the marketing authorization holder in cases where change in manufacturing method, testing method, etc., may influence the product quality (6) Method and the responsible person for promptly contacting the marketing authorization holder regarding the following information obtained on the product (a) Information pertaining to the product on discontinuation of manufacturing, import, or sales; recall; disposal; and other measures that were taken to prevent occurrence or spread of sanitary hazard

No	Article of the Ministerial Ordinance	Question
		(b) Other information on quality, etc., of the product (7) Other necessary matters

6. Operation of the quality assurance supervisor (related to Article 8 as applied mutatis mutandis to Article 21)

No	Article of the Ministerial Ordinance	Question
10	Article 8 as applied mutatis mutandis to Article 21	Is the marketing authorization holder of cellular and tissue-based products requiring the quality assurance supervisor to conduct the following operations in accordance to procedures, etc., for quality control operations? (1) To integrate quality control operations. (2) To confirm that the quality control operations are appropriately and smoothly conducted. (3) To submit reports in document to the marketing supervisor-general of cellular and tissue-based products in cases where reporting was considered necessary for executing quality control operation, besides the prescribed reporting required to be made to the marketing supervisor-general of cellular and tissue-based products. (4) To contact and provide instructions in document to manufacturers, distributors, founders of hospitals and clinics, and other relevant persons, as necessary, when conducting quality control operations.

7. Control of release into the market (related to Article 9 as applied mutatis mutandis to Article 21)

No	Article of the Ministerial Ordinance	Question
11	Article 9, Paragraph 1 as applied mutatis mutandis to Article 21	Is the marketing authorization holder of cellular and tissue-based products ensuring that manufacturing control and quality control results are appropriately evaluated and that release into the market is appropriately and smoothly determined in accordance to procedures, etc., for quality control operations, and is it not releasing drugs into the market before this release acceptance has been appropriately determined?

No	Article of the Ministerial Ordinance	Question
12	Article 9, Paragraph 2 as applied mutatis mutandis to Article 21	Is the marketing authorization holder of cellular and tissue-based products requiring a person, designated beforehand, from the quality assurance division or the manufacturer of the product to appropriately evaluate manufacturing control and quality control results, to determine release into the market according to each lot (or according to each manufacturing number for those drugs that do not compose a lot; the same shall apply hereinafter), and to prepare records on release into the market, such as on the results of release determination and on the destination of shipping, in accordance to procedures, etc., for quality control operations?

No	Article of the Ministerial Ordinance	Question
13	Article 9, Paragraph 3 as applied mutatis mutandis to Article 21	Is the person who conducts operation such as determining release into the market prescribed in the preceding Paragraph a person with the capacity to appropriately and smoothly execute this operation?

No	Article of the Ministerial Ordinance	Question
14	Article 9, Paragraph 4 as applied mutatis mutandis to Article 21	In cases where a person other than the quality assurance supervisor is to determine release into the market, is the marketing authorization holder of cellular and tissue-based products requiring that person to appropriately report to the quality assurance supervisor the results, etc., of the determination of release into the market?

No	Article of the Ministerial Ordinance	Question
15	Article 9, Paragraph 5 as applied mutatis mutandis to Article 21	Are the following requirements being met when the marketing authorization holder of cellular and tissue-based products have the manufacturers conduct the operations prescribed in Paragraph 2? (1) To conclude agreements with the manufacturer in advance on the following matters. (a) Procedures for control of release into the market that manufacturers conduct (b) To designate a person within the manufacturing site in advance to conduct the operation prescribed in Paragraph 2. (c) To require the manufacturer to promptly report in document to the quality assurance supervisor in cases of deviation, etc., from the procedures prescribed in "(a)", and to determine release into the market and to release based on the instructions of the quality assurance supervisor. (d) To require the manufacturer to periodically receive confirmation from the marketing authorization holder that operations pertaining to release into the market is being appropriately and smoothly conducted. (2) To require a person, designated beforehand, from the quality assurance division to appropriately conduct the confirmation prescribed in "(d)" of the preceding Item and prepare records on those results. (3) To require the quality assurance supervisor to conduct the following operations in cases where improvement is necessary in the operation of the manufacturer pertaining to release into the market. (a) To order the manufacturer in document to take necessary measures. (b) To require the manufacturer to report the results of those measures that were taken, to appropriately evaluate those reports, to confirm on-site at the manufacturing site as necessary, and to prepare records of those results. (c) To report in document to the marketing supervisor-general of cellular and tissue-based products the evaluation of "(b)" and the confirmation results. (4) To report in document to the quality assurance supervisor the results of the confirmation and preparation of records prescribed in Item (2) if these operations were to be conducted by a person

No	Article of the Ministerial Ordinance	Question
		other than the quality assurance supervisor.

No	Article of the Ministerial Ordinance	Question
16	Article 9, Paragraph 6 as applied mutatis mutandis to Article 21	Is the marketing authorization holder of cellular and tissue-based products appropriately providing the person who determines release into the market information on quality, efficacy, and safety of the drug necessary for appropriately and smoothly determining release into the market, in accordance to procedures, etc., for quality control operations?

8. Securing appropriate manufacturing control and quality control (related to Article 10 as applied mutatis mutandis to Article 21)

No	Article of the Ministerial Ordinance	Question
17	Article 10, Paragraph 1 as applied mutatis mutandis to Article 21	Is the marketing authorization holder of cellular and tissue-based products requiring a person, designated beforehand, from the quality assurance division to conduct the following operations, in accordance to procedures, etc., for quality control operations? (1) To periodically confirm that the manufacturing control and quality control at the manufacturers is appropriately and smoothly conducted pursuant to the standards and matters prescribed in Ministerial Ordinances based on the provisions in Article 23-25, Paragraph 2, Item 4 and Article 23-35, Paragraph 2 of the Act, and pursuant to the agreement prescribed in Article 7, and to prepare records of those results. (2) To report in document to the quality assurance supervisor the results of the confirmation and preparation of records prescribed in the preceding Item if these operations were to be conducted by a person other than the quality assurance supervisor.

No	Article of the Ministerial Ordinance	Question
18	Article 10, Paragraph 2 as applied mutatis mutandis to Article 21	Is the marketing authorization holder of cellular and tissue-based products requiring the quality assurance supervisor to conduct the following operations in accordance to procedures, etc., for quality control operations in cases where improvement is necessary in manufacturing control and quality control of the manufacturers? (1) To order the manufacturer in document to take necessary measures. (2) To require the manufacturers to report the results of the measures that were taken, to appropriately evaluate those reports, to confirm on-site at the manufacturing site, etc., as necessary, and to prepare records of those results. (3) To report in document to the marketing supervisor-general of cellular and tissue-based products the evaluation and confirmation results prescribed in the preceding Item.

No	Article of the Ministerial Ordinance	Question
19	Article 10, Paragraph 3 as applied mutatis mutandis to Article 21	Is the marketing authorization holder of cellular and tissue-based products requiring a person, designated beforehand, from the quality assurance division to conduct the following operations in accordance to the procedures, etc., for quality control operations upon receiving report from the manufacturers regarding any change, such as in manufacturing methods and testing methods that may influence product quality? (1) To evaluate the content of the report from the manufacturers, to confirm that the change will not seriously influence product quality, to confirm on-site as necessary that manufacturing control and quality control are being appropriately and smoothly conducted at the manufacturing site, etc., and to prepare records of those results. (2) To report in document to the quality assurance supervisor the results of the evaluation and confirmation prescribed in the preceding Item if these operations were to be conducted by a person other than the quality assurance supervisor.

No	Article of the Ministerial Ordinance	Question
20	Article 10, Paragraph 4 as applied mutatis mutandis to Article 21	In cases where the change was considered to have the possibility of seriously influencing product quality as a result of the evaluation prescribed in Item 1 of the preceding Paragraph, is the marketing authorization holder of cellular and tissue-based products requiring the quality assurance supervisor to promptly order the manufacturers in document to take necessary measures, such as of improvement, in accordance to procedures, etc., for quality control operations.

No	Article of the Ministerial Ordinance	Question
21	Article 10, Paragraph 5 as applied mutatis mutandis to Article 21	Is the marketing authorization holder of cellular and tissue-based products providing manufacturers necessary quality information to enable appropriate and smooth manufacturing control and quality control?

9. Information on quality, etc., and measures for quality defect, etc., (related to Article 11 as applied mutatis mutandis to Article 21)

No	Article of the Ministerial Ordinance	Question
22	Article 11, Paragraph 1 as applied mutatis mutandis to Article 21	Is the marketing authorization holder of cellular and tissue-based products requiring the quality assurance supervisor to conduct the following operations in accordance to procedures, etc., for quality control operations upon obtaining quality information? (1) To investigate the quality information, and to appropriately evaluate the effect on the quality, efficacy, and safety of the cellular and tissue-based product and the effect on human health. (2) To investigate the cause of the matter pertaining to the quality information. (3) To take necessary measures in cases where improvement was considered necessary in the quality control operation or in the manufacturing control and quality control at the manufacturers

No	Article of the Ministerial Ordinance	Question
		based on the results of the evaluation and investigation prescribed in the preceding two Items. (4) To prepare records regarding the preceding three Items, indicating the content of information, evaluation results, investigation results on the cause, and improvement measures, and to promptly report them in document to the marketing supervisor-general of cellular and tissue-based products. (5) To provide instructions in document to the manufacturers if considered necessary for the investigation prescribed in Item (2) or for the improvement measures prescribed in Item (3); to require manufacturers to report in document these results; to appropriately evaluate them; to confirm on-site as necessary regarding the improvement status at the manufacturers; and to prepare records of those results. (6) To provide in document quality information regarding safety assurance measures to the safety control supervisory division without delay.

No	Article of the Ministerial Ordinance	Question
23	Article 11, Paragraph 2 as applied mutatis mutandis to Article 21	Is the marketing authorization holder of cellular and tissue-based products requiring the drug marketing supervisor-general and the quality assurance supervisor to conduct the following operations in accordance to procedures, etc., for quality control operations in cases where quality defect or suspected quality defect was found after the operation prescribed in the preceding Paragraph? (1) The quality assurance supervisor shall promptly report to the marketing supervisor-general of cellular and tissue-based products any matters pertaining to quality defect or suspected quality defect, and shall make records of this. (2) Upon receiving the report prescribed in the preceding Item, the marketing supervisor-general of cellular and tissue-based products shall promptly determine necessary measures, such as of recall, to prevent any hazard, and shall provide instructions to the quality assurance supervisor and other relevant divisions. (3) The quality assurance supervisor shall promptly take necessary measures upon receiving the instructions from the marketing supervisor-general of cellular and tissue-based products prescribed in the preceding Item. (4) The quality assurance supervisor shall create close cooperation with the safety control supervisory division and other relevant divisions to enable appropriate and smooth measures prescribed in the preceding Item. (5) The quality assurance supervisor shall report in document to the marketing supervisor-general of cellular and tissue-based products the status of progress of the measures prescribed in Item (3) as well as those results.

10. Management of recalls (related to Article 12 as applied mutatis mutandis to Article 21)

No	Article of the Ministerial Ordinance	Question
24	Article 12 as applied	Is the marketing authorization holder of cellular and tissue-based

No	Article of the Ministerial Ordinance	Question
	mutatis mutandis to Article 21	products requiring the quality assurance supervisor to conduct the following operations in accordance to procedures, etc., for quality control operations when making recalls of cellular and tissue-based products? (1) To separately store the recalled cellular and tissue-based products for a certain period, and to dispose them appropriately. (2) To prepare a record indicating the details of the recall, and to report them in document to the marketing supervisor-general of cellular and tissue-based products.

11. Self-inspection (related to Article 13 as applied mutatis mutandis to Article 21)

No	Article of the Ministerial Ordinance	Question
25	Article 13, Paragraph 1 as applied mutatis mutandis to Article 21	Is the marketing authorization holder of cellular and tissue-based products requiring a person, designated beforehand, to conduct the following operations in accordance to procedures, etc., for quality control operations? (1) To conduct periodic self-inspections on quality control operation, and to prepare records of those results. (2) To report in document to the quality assurance supervisor the results of self-inspection if conducted by a person other than the quality assurance supervisor.

No	Article of the Ministerial Ordinance	Question
26	Article 13, Paragraph 2 as applied mutatis mutandis to Article 21	The marketing authorization holder of cellular and tissue-based products shall require the quality assurance supervisor to take necessary measures if improvement was considered necessary based on the results of self-inspection, and shall report in document to the marketing supervisor-general of cellular and tissue-based products the results of those measures.

12. Training and education (related to Article 14 as applied mutatis mutandis to Article 21)

No	Article of the Ministerial Ordinance	Question
27	Article 14, Paragraph 1 as applied mutatis mutandis to Article 21	Is the marketing authorization holder of cellular and tissue-based products requiring a person, designated beforehand, to prepare plans for training and education aimed at those engaged in the quality control operation?

No	Article of the Ministerial Ordinance	Question
28	Article 14, Paragraph 2 as applied mutatis mutandis to Article 21	Is the marketing authorization holder of cellular and tissue-based products requiring a person, designated beforehand, to conduct the following operations in accordance to procedures, etc., for quality control operations and in accordance to training and education plans prescribed in the preceding Item? (1) To conduct systematic training and education on quality control operation for those engaged in this quality control operation, and to prepare records of this.

No	Article of the Ministerial Ordinance	Question
		(2) To report in document to the quality assurance supervisor on the status of training and education in cases where this operation is conducted by a person other than the quality assurance supervisor.

13. Control of storage, etc., of cellular and tissue-based products (related to Article 15 as applied mutatis mutandis to Article 21)

No	Article of the Ministerial Ordinance	Question
29	Article 15 as applied mutatis mutandis to Article 21	Is the marketing authorization holder of cellular and tissue-based products meeting the following requirements if it were to manufacture, etc., or store or display imported drugs intended for marketing? (1) A responsible person pertaining to the operation shall be allocated. (2) The person engaged in this operation (including the responsible person) shall meet the following requirements: (a) Shall not be affiliated to the quality assurance division. (b) Shall have necessary capacity for the operation and shall have received necessary training and education. (3) Buildings and facilities shall be located at the office at which the marketing supervisor-general of cellular and tissue-based products conduct these operations, and shall be appropriately maintained and controlled. (a) To have necessary facilities to sanitarily and safely store cellular and tissue-based products. (b) To have a necessary amount of area to appropriately and smoothly carry out operations. (4) Records pertaining to the operation, such as of receipt and distribution of the cellular and tissue-based products, shall be prepared.

14. Control of documents and records (related to Article 16 as applied mutatis mutandis to Article 21)

No	Article of the Ministerial Ordinance	Question
30	Article 16 as applied mutatis mutandis to Article 21	Is the marketing authorization holder of cellular and tissue-based products controlling documents and records in accordance to the following requirements for those prescribed in this Chapter? (1) When a document was prepared or revised, this document shall be approved, distributed, stored, etc., in accordance to procedures, etc., for quality control operations. (2) When the procedures, etc., for quality control operations were prepared or revised, the date of preparation or revision shall be indicated in these procedures for quality control operations, and past records pertaining to this revision shall be stored. (3) Documents and records prescribed in this Chapter shall be stored for the following period from the date on which they were prepared (or, for procedures for quality control operations, from the date on which their use was discontinued; the same shall apply hereinafter):

No	Article of the Ministerial Ordinance	Question
		(a) A period of 30 years plus shelf-life for specified regenerative medicine products prescribed in Article 68-7, Paragraph 3 of the Act (b) A period of 10 years plus shelf-life for cellular and tissue-based products (excluding those indicated in "(a)") (c) A period of 5 years for documents and records pertaining to training and education regardless of the period prescribed in "(a)" and "(b)"

Ⅱ．委託業務成果報告（業務項目）

厚生労働科学研究委託費（再生医療実用化研究事業）
委託業務成果報告
特定細胞加工物／再生医療等製品の品質確保に関する研究

一般的な滅菌・濾過滅菌等の無菌化手法の適用が困難な細胞加工物の製造における無菌操作、バリデーション、環境モニタリング、清浄化等を通じた無菌性保証及び工程等の微生物等汚染リスク低減のあり方に関する研究

担当責任者　紀ノ岡　正博　大阪大学　大学院工学研究科　教授
担当協力者　篠塚　より子　大阪大学 大学院工学研究科　研究員
西田　幸二　大阪大学　大学院医学研究科　教授

研究要旨　最終的な滅菌ができない医薬品の基準は、平成22年度厚生科研にて『無菌操作法による無菌医薬品の製造に関する指針』として公開されている。しかしながら、特定細胞加工物/再生医療等製品（以下、細胞加工物と略す）は、一般的な滅菌、無菌化ができない、製造スケールが小さい、製品の種類が多岐、製造設備に関する新技術（自動化等）も開発中、などの特徴があるため、新たなガイドラインや科学論文を作成することが必要とされる。本研究では再生医療等製品の無菌操作法に関するガイドラインを作成すると共に実験を通した細胞加工物の無菌操作法の考え方を示していく。これらの考え方の提示は、今後、細胞加工物の実用化を促進するのに大きく寄与するものとなろう。

A．研究目的

一般的な滅菌・濾過滅菌等の無菌化手法の適用が困難な細胞加工物の製造における無菌操作、バリデーション、環境モニタリング、清浄化等を通じた無菌性保証及び工程等の微生物等汚染リスク低減のあり方の提言を行い、これらの結果を取りまとめることにより、細胞加工物の実用化を促進することを目的としている。

B．研究方法

1) ガイドライン作成

再生医療等製品における無菌操作法のガイドラインを作成するために会議を立ち上げた。『無菌操作法による無菌医薬品の製造に関する指針』をベースとし、再生医療等製品と医薬品製品の違いを議論しながら、企業専門家を主体として進めていく。

2) 無菌操作法に関する実験

細胞加工物における無菌操作法の考え方を、実験を通して示していく。実験は、大阪大学内にある細胞培養加工施設 (以下、CPCと略す)と、アイソレーターを使って行う。CPC は、本実験に使用できる性能を有しているかを調べるために、環境検証を外注した。

（倫理面への配慮）

該当事項なし

C．研究結果

1) ガイドライン作成

2015 年 2 月 9 日に第一回全体会議を行い、再生医療等製品に携わる企業 18 社を集め、再生医療等製品の無菌操作法のガイドライン作成の趣旨・今後の進め方について説明した【ガイドライン会議関係資料添付】。現在、各社の代表者及び各項目の主担当者について選定を進めている。

2) 無菌操作法に関する実験

・CPC において、清掃後、風量・換気回数、空間差圧、微粒子清浄度、気流可視化評価などを行った。

・本評価は、主に操作室（ISO クラス 7)、操作室に設置された安全キャビネット (ISO クラス 5)、および操作室に隣接した着衣室（ISO クラス 7）にて実施した。

・気流可視化評価は、可視化しやすいように黒色の軟質ビニールシートを背景になるように貼付し、水蒸気を利用した気流可視化装置を用いて行った。

・安全キャビネット（以下、BHC とする）シャッター開口部はエアーバリアにて保護されており、操作室から BHC 内、BHC 内から操作室への気流漏洩はなかった【写真 1】。

・清浄度検査では、着衣室に薄型クリーンユニット（以下 ACP と略す）を設置し、着衣室内の清浄度と回復度を測定器（A2400LL, HACH）にて測定した。この結果、通常では微粒子清浄度が回復するのに ISO クラス 7 (0.5μm 以上の微粒子が作業時 10,000 個/cft、非作業時 100 個/cft。以内を想定。グラフでは 10,000 個/cft ≒1000 個/0.166 cft) に低減するまで 2 分ほどかかるが、ACP を使うと 30 秒以内に同クラスにまで清浄度が回復した【グラフ】。

・次年度の CPC 環境検証の準備として風量（換気回数）と室圧の評価パターンを確認し、清浄度と気流を測定した【表】。

D．考察

＜操作室内気流の確認＞【図 1】

・天井部に設置されたファンフィルターユニット(以下 FFU と略す)から清浄気流が操作室に供給され、天井部 2 箇所の排気口で吸い込まれている。FFU 吹出し部から直接排気口へ向かう気流は無く、その他のエリアでも目視にて確認できるような乱れた気流はなかったことから、FFU から供給された正常な気流は徐々に室内に拡散し、排気口にて吸い込まれると考える。清浄度の測定結果からも清浄空気が室内に拡散していることが推定された。

・BHC の運転/停止にて BHC 天井排気部近傍の気流に変化が生じる。しかし BHC 上の HEPA フィルターを通過した気流であるため汚染などの影響は少ないと考えるが、それは次回、環境モニタリング等を通して示していく。

・パスボックス、インキュベーターの扉開閉時には操作室内の気流がパスボックスやインキュベーター内に影響を与えることはない。しかし扉開閉時には、扉の動作により操作室内の気流が誘引されることが確認できたことから、操作室内が汚染されている場合、開閉時に内部も汚染する可能性はある。扉開閉の動作が早いほどその影響が大きくなるため、扉開閉はゆっくりとした動作が望ましい。これについても次回、菌の散布試験による検証実験を行う予定である。

＜風量・室圧による環境検証パターンの検

討＞

・操作室の微粒子清浄度仕様値は、Grade B 相当であり、非作業時では 0.5μm 以上の微粒子が 100 個/cft 以内が妥当と考える。【表】に非作業時、BHC 停止条件下の測定結果を示す。測定結果は全条件において仕様値以内であり、適切であった。しかし測定を実施するに当たり、風量（換気回数）条件や測定位置により粒子濃度が減衰する時間（清浄度回復性能）に差があることを確認した。今後は実作業時の動線域における清浄度回復性能を考慮した換気回数の決定方法を検討する。

・今回の CPC における測定条件下において、室圧による清浄度、気流の影響（変化）はなかった。ただし、操作室への外気導入量（以下 OA と略す）が少量のため、隣接する着衣室、脱衣室からの出入りの際に各室からの誘引が発生することが推定される。操作室への OA 量を増加させれば改善可能だが、初期費用、運転費用が増大するという問題がある。OA 量を増加させずに操作室と隣接する着衣室の清浄度回復性能を向上させることが重要と考える。取りうるべき対策としては、教育指導により、更衣後、粒子が落ち着いてから操作室に入るということで対応する。または粘着テープにて着衣表面の粒子を減少させた後、ガウニングを行うというのも有効であろう。【グラフ】は故意に空中に粒子を拡散させた後、ACP 停止/運転条件下で経過時間と共に粒子濃度を測定した結果である。更衣時に発生すると想定する微粒子は、ISO クラス 7 に低減するまでおよそ 2 分かかる。一方、ACP 運転条件下では 30 秒で同クラスに低減することから、ACP の活用が有効となる場合もあると考える。人体から発生する粒子と生物学的な汚染がどれほど相関するかについては、次回環境モニタリング等によって示していく。

＜その他＞

・室内気流の検証は非単一方向流方式の部屋の場合、目視にて確認することは作業量が膨大となる上、検証の妥当性が不十分であり、非現実的である。よって FFU からの清浄気流が室内を循環していることの確認方法は清浄度の測定が良いと思われる。

・【図 1】は、操作室における気流可視化試験結果と、清浄度測定結果を照らし合わせて推察される気流の流れを示したものである。

今回、気流可視化試験で遠心分離機の運転時、背面より排気エアーが吹き出しそれが天井部まで上昇して、本来の気流の流れを乱していることを確認した。機器の特性、使用上、作業動線には該当せぬ区域であるが、設置場所、排気位置、方向には考慮する必要がある。また施設設計時に機器レイアウトが分かっていれば、排気空気をスムーズに排気口に流す配慮を行うことが望ましい。

・気流可視化試験で、BHC シャッター部のエアーバリアは、作業者の腕、資材等の搬入時にも十分に機能していることを改めて確認した。しかし急激な動作の場合は、気流を乱すようである。BHC ON の時、外部からの風は BHC 入口で遮蔽される【写真 1】。また、内部からの風も手元付近と奥にある通気口を通じて吸われており、風のバリアーが形成されている。しかしながら、それらの通気口をピペットの包装部や手などでふさぐと風流が乱れ、風のバリアーが弱ま

る【写真2】。気流吸込部を腕や資材にて塞ぐことがないようSOP策定や教育指導が必要である。BHC内の気流は上流より下流へ作業室中央を境目に前後吸込部に流れている【図2】。左右方向には吸込口はないので、資材は左右に吹込口を塞がないように配置して作業を行うのが望ましい。

E．結論

・再生医療等製品の無菌操作法に関するガイドライン作成を行うべく、各分野の専門家を集めた会議を立ち上げた。

・CPCにおいて、風量・換気回数、空間差圧の様々な条件検討や気流可視化試験、清浄度検証などを行った。今回の検証の結果、当CPCは、今後行う予定の無菌性保証及び工程等の微生物汚染リスク低減のあり方を提言するための諸実験計画を行うのに適した性能を持つ細胞加工施設であることが分かった。

F．研究発表

1. 論文発表

なし

2. 学会発表

1) KFCホール、日本PDA製薬学会 第4回微生物シンポジウム「最新の迅速微生物測定法」、『再生医療における微生物管理の現状』、水谷 学、紀ノ岡 正博

2) パシフィコ横浜、第14回日本再生医療学会総会「培養工学観点から見たiPS細胞培養技術の展開」紀ノ岡 正博

G．知的財産権の出願・登録状況

（予定を含む。）

1. 特許取得

なし

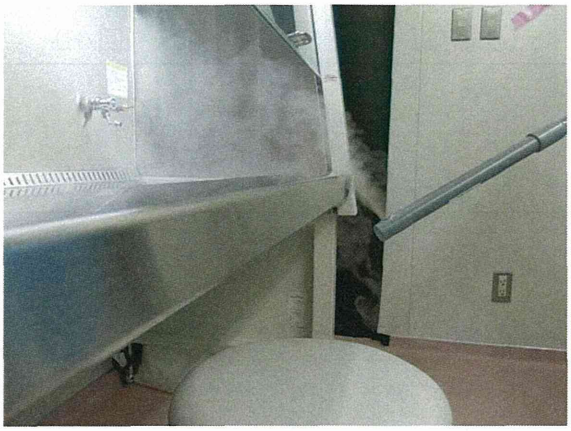
2. 実用新案登録

なし

3.その他

なし

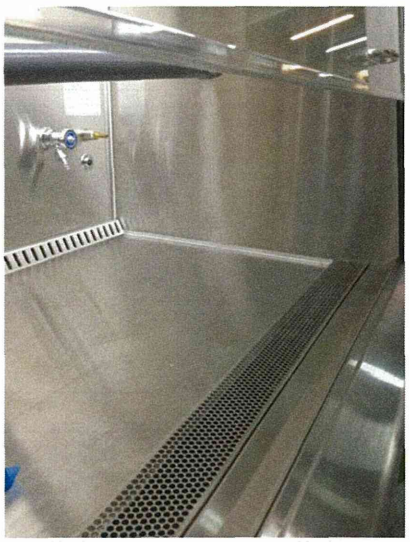
【写真1】BHC 外部の風のバリアー



BHC OFF

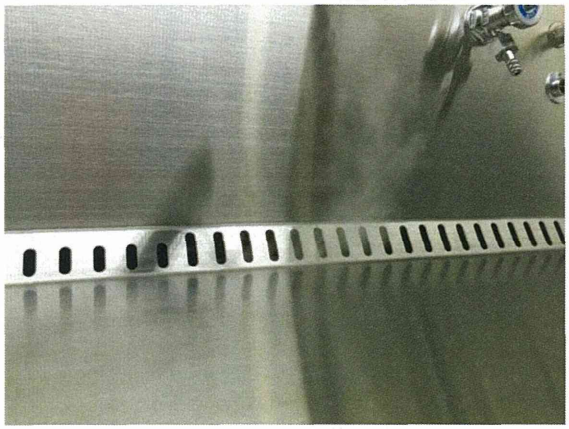
BHC ON

【写真 2】BHC 内における気流吸込部確保の重要性

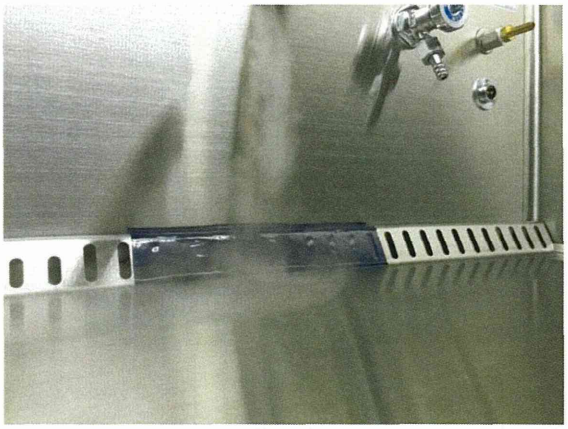


BHC 全面吸込部　正常運転中

腕で吸込部を塞いだ時



BHC 奥側吸込部　正常運転中



テープにて吸込部を防いだ状態(テープ幅 200mm)