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Case report

Remote audit practice for inspection of structural and equipment standards for cell processing facilities under the act on the safety of regenerative medicine in Japan

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ABSTRACT

Introduction: The Act on the Safety of Regenerative Medicine enforced in Japan in 2014, regulates the manufacture of cellular processed products. However, with regards to the manufacturing facilities at medical institutions, only the submission of necessary documents is required for a license, and the need for third-party inspection has been highlighted. Remote activities are becoming more prominent with the spread of the Severe Acute Respiratory Syndrome Coronavirus 2 infection; therefore, the current assessment of compliance with structural facility standards was conducted remotely.
Methods: The entire process, including start-up meetings, preparation of the survey schedule, submission and review of preliminary materials, audits, and reporting of results, was conducted via e-mail and web conferencing systems. The survey was conducted remotely, to minimize the risk of contamination of the cell processing facility (CPF) and reduce the burden on surveyors, while contributing to the establishment of suitable structural facilities by identifying and highlighting the areas or items that were considered to be non-compliant with the regulations. The series of audits were completed in ten weeks, with a period of six weeks between the start-up meeting and the audit implementation. The audit was completed in approximately 3 h on the day of the inspection.
Results: The audit results were delivered in the report, with four items requiring improvement and several other recommended items listed as non-conformities.
Conclusions: We believe that this remote method allows the effective inspection of regenerative medicine manufacturing facilities and assessment of more cell culture processing facilities than the current in-person audit method, with limited human resources.

1. Introduction

In Japan, the Act on the Safety of Regenerative Medicine (Safety Act) was enforced in 2014, to establish regulations regarding the provision of medical care using human cell-processed therapeutic products [1]. Additionally, the Act on Pharmaceutical and Medical Devices, which regulates pharmaceuticals and medical devices, has been revised to the Pharmaceutical Affairs Law, to define regenerative and cellular therapeutic products [2,3]. This was a major turning point in the provision of regenerative medicine in Japan. Nine years since its enforcement, the Safety Act is now under

Abbreviations: CPF, cell processing facility.

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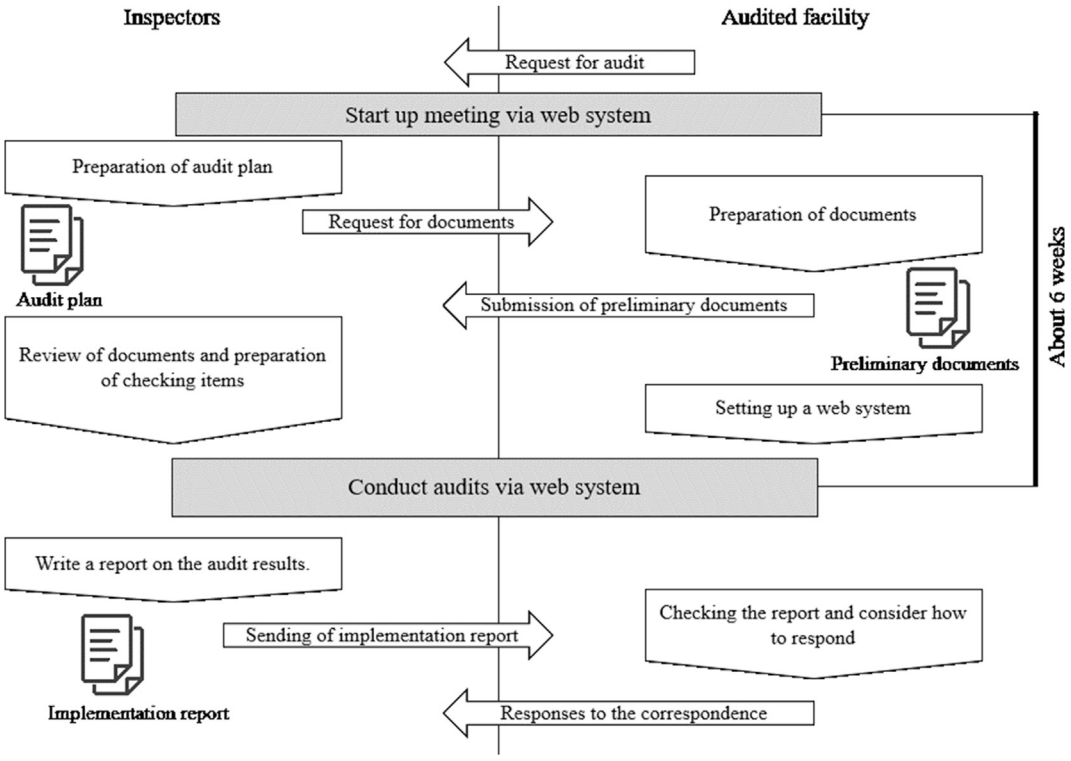

Fig. 1. Scheme for conducting the remote audit. The direction of the contact is indicated by a graphic, divided into the investigation side and the non-supervisory facility. The requirements, information and documents pass from the base towards the arrowhead. The main contents to be implemented upon receiving the contact are indicated. Start-up meetings and audits were conducted online.

consideration for revision, and one of the points of contention is the investigation of cell processing facilities (CPFs) that manufacture cell-processed therapeutic products. One of the major reasons for the dispute is that although CPFs are required to obtain a license under Article 35 of the Safety Act, medical institutions can fulfill the requisite administrative procedures merely by submitting an application, whereby the license can be obtained by just preparing the necessary documents, without any investigation by a third party. According to information published by the Ministry of Health, Labour and Welfare, there are more than 3400 registered CPFs that are not subject to inspection. Therefore, the Health Sciences Council has highlighted that other modes of confirmation apart from the documentation are required for a CPF license, which allows the production of cellular processed products [4].

Recently, with the spread of Severe Acute Respiratory Syndrome Coronavirus Type 2 infection, many operations have been carried out remotely and attempts have also been made to carry out document compliance inspections under the Act on Pharmaceutical

Table 1
Audit action plan.

Sponsor	Facility Manager	Date of request	May 18, 2021
Writer	Person responsible for auditing	Date of creation	June 3, 2021
Confirmer	Director	Date of confirmation	June 3, 2021
Authorizer	Facility Manager	Date of authorization	June 4, 2021
Number of the audit	2021-E01		
Audited facility	Cell Processing Facility at Hiroshima University Hospital		
Objective			
Check whether there is any problematic non-compliance with the “Act on Safety of Regenerative Medicine. (Act No. 85 of 2013)" with respect to structural facilities and methods of manufacturing and quality control of the cellular and tissue-based products.			
Scope of Inspection			
Structural equipment of the Cell Processing Facility of Hiroshima University Hospital.			
[Relevant to Article 42 of the Safety Act and Article 89 of the Ministerial Ordinance]			
Methods of manufacturing and quality control.			
[Relevant to Article 44 of the Safety Act and Article 92 to 110 of the Ministerial Ordinance]			
Priority items			
☐ Status of compliance with structural equipment standards related to each item of Article 89 of the Ministerial Ordinance			
☐ Status of maintenance of procedure manuals as stipulated in Article 97, Item 4 of the Ministerial Ordinance.			
☐ Status of Response to Opinion Letter, which was prepared by Consulting Corporation, March 8, 2021., on Serious Incident Occurrence			
☐ Records pertaining to the operation of the CPF			
Schedules			
Period to review written documents in advance: June 7, 2021 to June 10, 2021			
Date of conducting online inspection: June 11, 2021.			

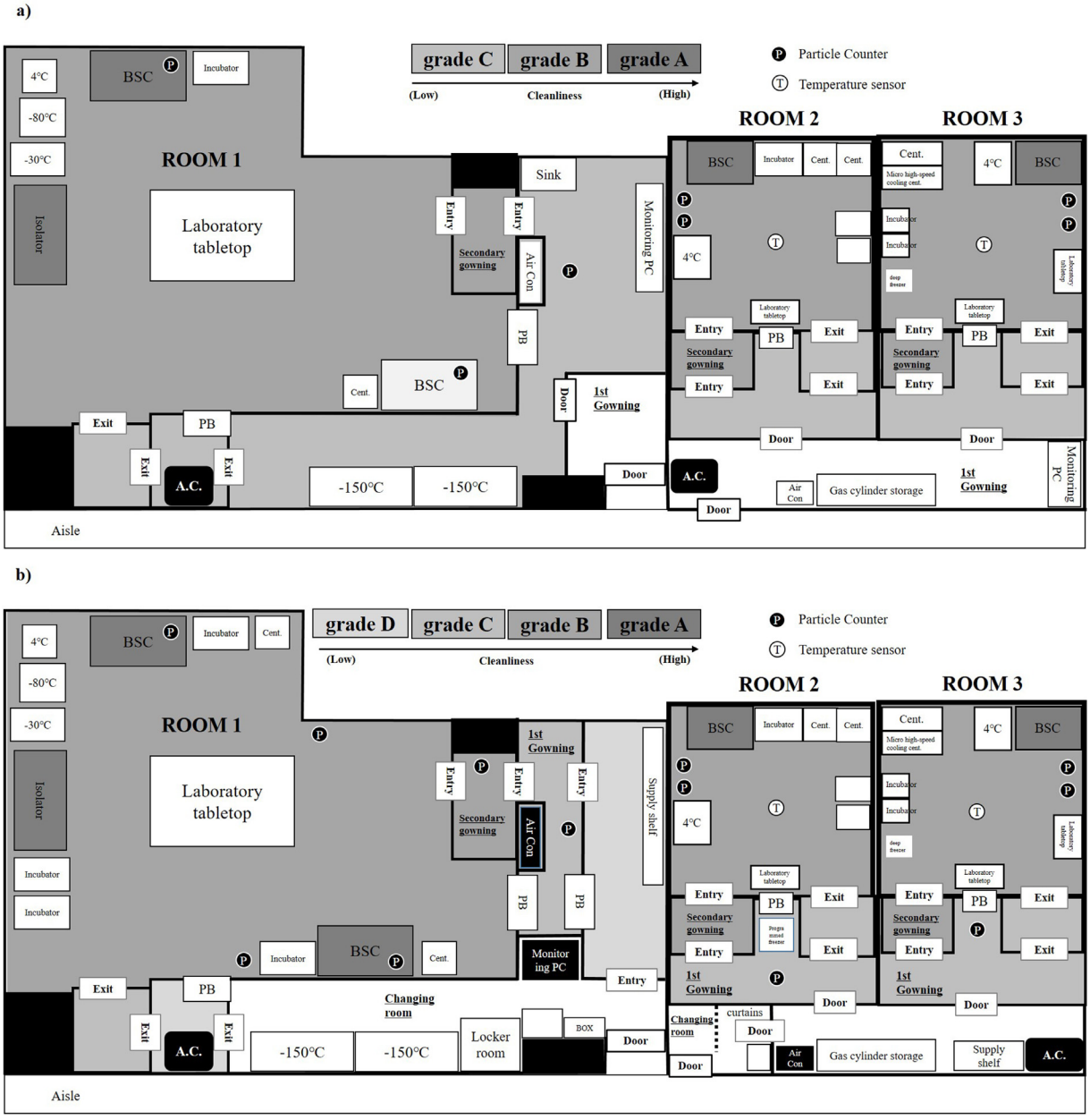

Fig. 2. Drawing of facility, before and after renovation. a) Drawing of the facility before renovation. b) Drawings of renovated facilities. BSC; Biosafety cabinet, Cent.; Centrifuge, PB; Pass box, A.C.; Autoclave, PC; Personal computer. The temperature indicates the setting of the cold storage system.

and Medical Devices by the Pharmaceutical and Medical Devices Agency [5]. In this report, we conducted a remote audit of the Hiroshima University CPF, which had undergone renovations voluntarily considering the Safety Act.

2. Methods

An overview of the survey procedure is provided in the scheme in Fig. 1. First, a table of implementation items and schedule was prepared by the parties involved. The following seven items were identified for implementation: (1) preparation of audit plan; (2) submission of documents about CPF; (3) Document confirmation by auditor; (4) notification of search contents; (5) audit; (6) report of results and conveyance of findings; (7) response to results and findings. The start-up meeting was held using zoom, a web conferencing system (https://zoomgov.com/jp-jp/meetings.html). An audit action plan was prepared, where we listed the provisions of the laws and regulations on which the plan was based and designated the points of emphasis to be checked (Table 1).

The facility floor map (Fig. 2), document master list, and documents of manufacturing control standards, sanitation control standards, and quality control standards were requested and obtained via email. List of pre-submission documents included: (1) organizational structure chart; (2) document master list; (3) management standards document; (4) standard operating procedures defined in each item of Article 97, item 4 of the Ministerial

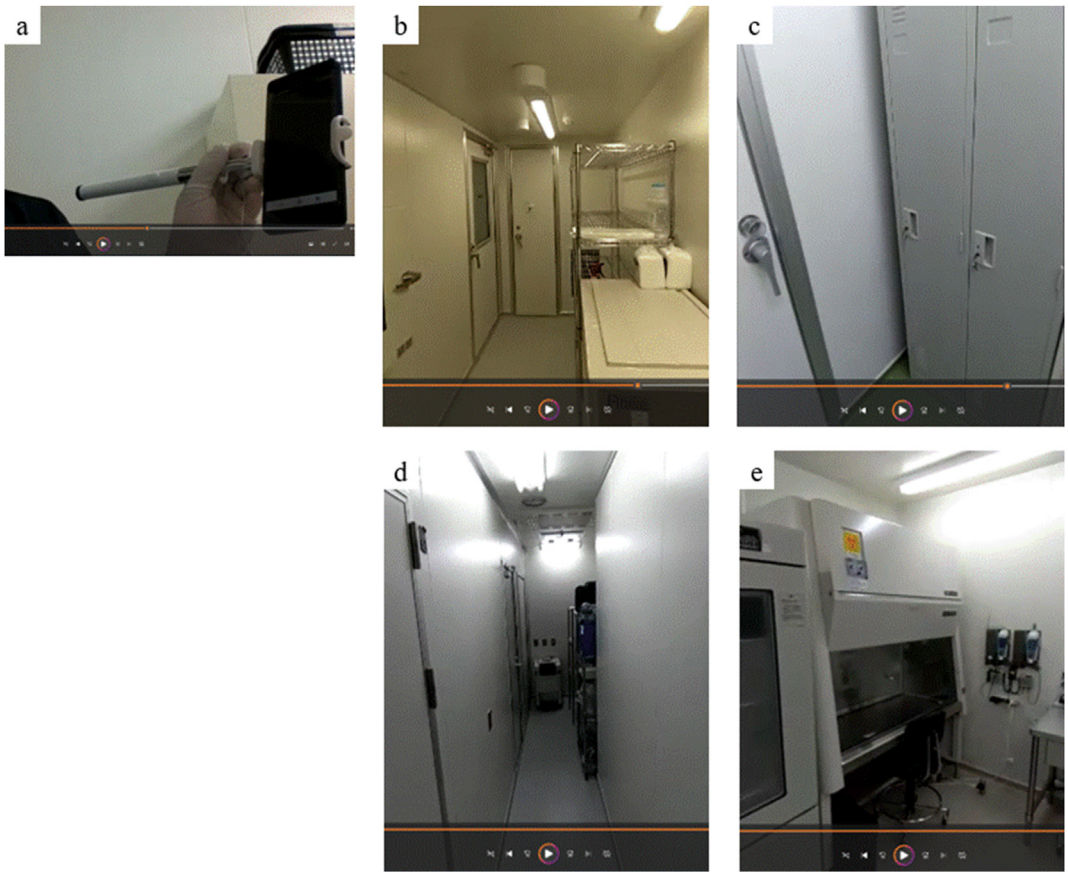

Fig. 3. Camera image of the Zoom videoconferencing screen during facility audit. a) Smartphones and tool used to capture on-site footage of the facility. b) View after entering Grade D from the changing room in ROOM1. c) Lockers in secondary gowning room. d) View after entering the room leading to ROOM2 and ROOM3. e) Equipment installed in ROOM3.

Ordinance; (5) CPF Floor Plan – before and after renovation; (6) air conditioning system diagram of the CPF (indicating room pressure and ventilation frequency); (7) drawings of air piping and drains.

After reviewing the facility floor plan and documents, a checklist of items (Supplementary data 1) to be examined on the day of the inspection was prepared and submitted to the party being investigated. The checklist was prepared in accordance with the 2014 Ministry of Health, Labor, and Welfare Ministerial Ordinance No.110 [6] and ISO 15189 (accreditation for clinical laboratories) checklist.

On the day of the inspection, the concerned team from Osaka University gathered in one of the hospital's conference rooms and used the Zoom videoconferencing application. Osaka University teams kept in touch with Hiroshima University teams during the Zoom videoconference. The Hiroshima University team consisted of one member who remained present in the conference room and two persons paired up to take video recordings and pictures of the CPF (all facilities, including ROOM1, ROOM2 and ROOM3), with a smartphone camera, as they moved around (Fig. 3). Additionally, a question and answer session was held. For video recording, an approximately 2 MP (full high definition) camera was used.

3. Results

The audit was completed in 3 h. The audit results revealed noncompliance with structural equipment standards. Table 2 lists the areas that require improvement and those that are recommended.

Post declaration of the audit result, a follow-up survey was conducted at the Hiroshima University Hospital CPF to confirm whether the actions listed in Table 3 had been taken. Based on the effective implementation of the plan of action provided in Table 3, the improvements were communicated to the Chugoku Shikoku Public Welfare Bureau, the respective regulatory authority, following which the facility was reopened. In ROOM1, one and five products were manufactured and shipped in 2021 and 2022, respectively. In ROOM2, medical support was provided to Kymriah®, which received approval for institutional accreditation on June 28, 2022. In ROOM3, validation of clinical research on regenerative medicine, which is scheduled to begin in 2023, was being conducted.

4. Discussion

We successfully remotely investigated the status of compliance with the structural equipment standards of the Safety Act at the Hiroshima University Cell Culture and Processing Facility. From advance preparation to the day-of-work response and declaration of the results, the project was completed within the standard five-month period required for a permit application. Although the survey was carried out using submitted documents and images

Table 2
Audit results and required improvements and recommendations based on it.

Result: Nonconforming items exist.
Items that need to be addressed
Document management
1) Article 96 of the Ministerial Ordinance stipulates that the standard document for cellular and tissue-based products shall be approved by the Quality Division. Please keep this in mind and manage and utilize it as a document for CPF in the future.
2) Article 99 of the Ministerial Ordinance stipulates that the manufacturing control is properly conducted and the results are to be reported in writing to the Quality Division, and this should be stated in the manufacturing control standards.
Structural equipment (workshop)
3) The lockers in the secondary gowning room of cell culture ROOM1 are difficult to move and the gaps between the lockers and the walls are not in a position to be easily cleaned, so they should be removed and another material rack should be installed where cleaning can be properly implemented.
4) With regards to dustproofing, insect-proofing, and the structure or equipment for such, the facility is located on the second floor of a hospital; therefore, we expected relatively little impact. However, the windows in the corridor can be opened; therefore we believe it is necessary to conduct insect monitoring and evaluate the environmental impact on the manufacturing facility from the perspective of insect-proofing.
Recommendations
Document management
5) Please consider creating a list that will allow us to track the status of document revision, abolition, and distribution.
6) When constructing an operation in which only the currently applicable approved version of the document is available at the point of use, please consider the use of electronic devices, such as tablets for viewing documents in the cell culture room, etc., considering the risk of contamination of structural equipment.
Records Management
7) Document storage will likely need to be expanded to accommodate the operating needs.
Structural equipment (workshop)
8) The change of footwear from outer shoes to indoor shoes should be performed outside the entrance of the workshop, not inside the entrance, as feet are a source of contamination.
9) Zoning was not indicated for areas where cleanliness changes, but please consider clearly indicating zoning if you think it would be difficult to accommodate this in operations.
Construction equipment (cleanliness management area)
10) The fluorescent lamps installed on the ceiling of the cell culture room are exposed, and we were concerned that dust and other contaminants could accumulate in that area, posing a contamination risk. Please consider installing covers.
Structural equipment (storage facilities)
11) The system was designed to notify the person in charge by e-mail of an alarm when the incubator, cold storage, etc. showed abnormal values, but it was explained that the system was to be handled by a small number of personnel. In order to reduce the excessive burden on the person in charge, we believe that the e-mail notification range should be set (including the department in charge), and the primary response personnel should be set. We believe that operational settings for primary and secondary response should be made accordingly. We also believe that efforts should be made to reduce risk by increasing the number of personnel to respond.

captured by a camera, the real-time operation of the camera allowed the surveyor to inspect the areas he/she wanted to check. Although this method may not be as effective as an actual on-site survey, it allowed the surveyor to check every detail.

The risk assessment focused on the maintenance of an appropriate environment in the CPF, and evaluated the risk of contamination due to different auditing methods, such as defining areas where third parties should be prevented from entering and conducting audits, either on-site or remotely. The area requiring the most cleanliness was designated Grade A (equivalent to ISO Class 5), while the areas requiring high, relatively high, and lowest levels of cleanliness among the controlled areas were designated Grade B (equivalent to ISO Class 7), Grade C (equivalent to ISO Class 8), and Grade D, respectively [7]. The number of particles measured as a possible source of contamination in the Grade B control area should be minimized, because it has been reported that the number of particulates increases in correlation with the number of people entering the clean controlled area [8]. Since several auditors with no training are expected to enter Grade B areas during on-site audits, remote audits offer a major advantage of avoiding external personnel from entering the Grade B area. As it is essential for persons to enter the facility to show video footage of the facility, this could be solved by making this area unmanned, e.g. by using robots. However, it is difficult to inspect areas or items that are difficult to confirm from videos, such as the materials of the floors and walls of the structural facilities and the condition of caulking between the materials. For items that are difficult to confirm with video images, a combination with non-destructive testing methods may be promising and requires further verification.

Another perspective involves accounting for the travel-related burden on investigators. Travel between Osaka University and Hiroshima University takes at least 200 minutes, one way, including the Shinkansen bullet train as the mode of public transportation. The option of removing travel and recovering that time is a major advantage. Additionally, since 3427 facilities nationwide have submitted reports under regenerative medicine therapy, as of August 31, 2023, we believe that eliminating travel time is essential to check more facilities within a certain period of time and with limited human resources.

Therefore, while on-site verification is recommended for facilities before the start of operation (or for the initial survey), remote audits are considered to be advantageous for the periodic survey of facilities in operation. In addition to structural facilities, materials to be submitted in advance should be considered during audits, including electronic documentation of manufacturing records and manufacturing records of specific cellular processed products. The facility that underwent this audit has resumed operations, with no contamination or non-conformity of manufactured products for more than a year, demonstrating the usefulness of the audit.

Table 3
Requisite actions based on audit results.

Findings of the Audit			
Items that need to be addressed			
No.	Category	Plan of action	Outcome of action
1)	Procedure	Article 96 of the Ministerial Ordinance stipulates that the Standard Document for specified cell processed products shall be approved by the Quality Division. With this in mind, the document should be managed and operated as a document for cell culture processing facilities in the future.	The CPF department established an operational rule to check and approve the standard documents, procedure manuals, and instruction manuals for specified cellular processed products related to research, and to manage the originals and the number of versions.
2)	Procedure	Article 99 of the Ministerial Ordinance stipulates that the manufacturing control is to be checked for proper implementation and the results are to be reported in writing to the quality department. This should be stated in the manufacturing control standards.	Revision of the manufacturing control standard was implemented as of December 8, 2021, with the addition of an item to confirm that the manufacturing process is properly controlled and report the results to the facility manager.
3)	Facilities	The lockers in the secondary gowning room of ROOM1 are difficult to move and are not in a position to allow easy cleaning of the gaps between lockers and the walls, therefore they should be removed and another material rack installed where cleaning can be properly implemented.	Lockers were removed and aluminum racks were installed in the gowning room of ROOM1 for easy cleaning.
4)	Facilities	With regard to dustproofing, insect-proofing, and the structure or equipment for such, since the facility is located on the second floor of a hospital, the impact is expected to be relatively small; however, since the windows in the corridor can be opened, insect monitoring should be conducted from the perspective of insect control, and an environmental assessment of the impact on the manufacturing facility should be conducted.	Insect monitoring was outsourced in March 2022. However, a risk assessment was conducted, and for the risks extracted, measures, such as reinforced caulking, were implemented during the annual validation.
Recommendations			
No.		Plan of action	Outcome of action
5)	Procedure	We will consider creating a list that will allow us to track the status of document revision, abolition, and distribution.	Under consideration.
6)	Procedure	When constructing an operation in which only the currently applicable approved version of the document is available at the point of use, we will consider the use of electronic devices, such as tablet terminals for viewing documents in the cell culture room, considering the risk of contamination of structural equipment.	The procedure documents were placed in the front room of the cell culture processing facility for viewing.
7)	Facilities	In areas where cleanliness changes, zoning is not indicated. Therefore, if it is considered difficult to deal with this issue through operation, clearly indicate the zoning.	Zoning tapes were purchased and zoning areas were set up in the gowning room of each CPF, and CPF users were briefed during education and training (on-the-job training).
8)	Facilities	The storage facility will be expanded according to the operation.	Older documents are stored in the new stacks, while documents from the past three years are stored in the same way as before, in the stacks in the residence.
9)	Facilities	Consider changing from outer shoes to indoor shoes outside the entrance of the workshop, rather than inside the entrance, as footwear is a source of contamination.	Urethane mats and indoor shoes were installed at the entrances, and operational rules were set so that personnel remove their shoes outside the CPF entrance and change into indoor shoes inside the entrance. Additionally, the storage shelves for indoor shoes storage are wiped and cleaned regularly.
10)	Facilities	Fluorescent lamps installed in the ceiling of the cell culture room are exposed, therefore there is concern that dust and other contaminants may accumulate in these areas, posing a contamination risk.	Regarding the fluorescent lamps installed, we confirmed that they are for clean room use, but we are considering the installation of covers.
11)	Procedure	The system was designed to notify the person in charge by e-mail of alarms when the equipment showed abnormal values, but since it was explained that the person in charge would be dealing with a small number of personnel, to reduce the excessive burden on the person in charge, the e-mail notification range should be set (e.g., include the department in charge) and the operation of primary and secondary response should be set according to the project status.	The number of CPF staff was increased, and the operational procedures for primary response (CPF users) and secondary response (CPF staff) were decided at the department meeting. (October 14, 2021)

5. Conclusions

To confirm adherence to structural facility standards required by the Safety Act for manufacturing facilities with specified cellular processed products, we conducted the audit remotely, to avoid contamination of the CPF as much as possible and reduce the burden on investigators, by ascertaining and highlighting points that indicated non-compliance of the law. By responding to the issues raised and recommendations made based on the audit, the inspected facility achieved the construction of a suitable structural facility, which allowed the production of cellular processed products. Hence, we believe that remote CPF inspection can be achieved with limited human resources, sanctioning the production of regenerative medicine at such facilities. In this report, the facility was filmed by humans, but it is hoped that unmanned robotic systems will make remote auditing a more effective tool in the future.

Declarations of competing interest

All authors have nothing of COI.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.reth.2023.12.001.

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