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Original Article

Approach of resource expenditure estimation toward mechanization in the manufacturing of cell-based products

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ABSTRACT

Recent developments for the manufacturing of cell-based products have focused on the advancement of products to clinical trials or commercialization, with awareness of the importance of cost-based effectiveness in cell manufacturing. The mechanization of cell-processing operations is advantageous for the reproducibility and stability of product quality and is thought to reduce the cost-of-goods through the life cycle of the product in a scale-up system; however, few cases of the implementation exist. This study developed an estimation method for the resource expenditure of cell-processing operations in the manufacturing of cell-based products. To estimate resource expenditures, we evaluated the manufacturing processes by operations involving entering into the surrounding area of cell processing zone, materials loading, cell-processing operation, cleaning, and leaving from the surrounding area. The cell-processing operation is applicable to manual or robotic cell manufacturing system in a biosafety cabinet or an isolator system. In cases of low annual batch numbers of manufacturing (batch number <33), the resource expenditure of cell-processing operations in a robotic operation system installed in the isolator system is estimated to be higher compared with a manual operation system in the isolator system due to additional initial costs for design and fabrication of the robotic operation system containing robot arms. With increasing numbers of annual batches, the resource expenditure decreases for robotic operating system, leading to an advantageous juncture where the resource expenditure of a robotic operation system is equivalent to that of a manually operated system, whereby the labor cost for cell-processing operations rises. In addition, the expertise of operations required for cell manufacturing is suggested to foster potential risks associated with the operation skills or turnover of operators, and the cost of education and training increases due to the necessity of persistent human resource development. Collectively, revealing the approach for installation of robotic operation system in cell manufacturing.

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Nomenclature

C_{manu}	expenditure for manual operation system of a product [JPY·(product)$^{-1}$]
C_{robo}	expenditure for robotic operation system of a product [JPY·(product)$^{-1}$]
$c_{wor,A}$	actual hourly rate of operator A [JPY·h^{-1}]
$c_{wor,B}$	actual hourly rate of operator B [JPY·h^{-1}]
n_{bat}	annual number of batches required for production [batch·(year)$^{-1}$]
n_{manu}	number of batches performable by operator B [batch·(operator)$^{-1}$]
$n_{nec,ope}$	number of operator B required during the life cycle of production [operator]
$n_{nec.robo}$	necessary number of the robotic operation system [unit]
n_{robo}	maximum number of batches per a robotic operation system [batch·(unit)$^{-1}$]
t_{proc}	time required for each process [h]
$t_{tra,cell}$	education and training time for cell-processing operation skills [h·(operator)$^{-1}$]

1. Introduction

Regenerative medicine, or therapy using cell-based products, has begun to cure many patients through growing commercialization of products made from autologous or allogeneic cells or tissue [1–3]. Recent advances in the research and development of pluripotent stem cell-based products using human embryonic stem cells (ESC) or induced pluripotent stem cells (iPSC) have resulted in the commencement of clinical trials [4–6]. Using pluripotent stem cells, it is theoretically feasible to produce all differentiated therapeutic cell sources that are difficult to obtain from patients or volunteer healthy donors, thus representing an essential technique for expanding therapeutic applications.

When manufacturing cell-based products for therapeutic, it is necessary to design of cell manufacturability [7]. The fundamental feature for the manufacturability is in terms of maintenance of aseptic environment, assurance of processing independence, containment against contaminants and robust management, whereas the concept of cell manufacturability requires that the attainment of the desired capability of a cell manufacturing process by bridging the gap between its biological and engineering aspects. The quality of cell-based products as the output of the process is sensitive to fluctuations derived from several factors, for example, environmental noise, fluctuations in the process operation or intrinsic biological disorders. Notably, the quality of cell-based products is sensitive to fluctuations derived from the factors of operation in manufacturing processes. These intrinsic disorders lead to a compounded impact on the stability of the process. So manufacturers must have proper operational parameters in the manufacturing process and ensure maintained to deliver the required level of stability. And these design for manufacturability mean not only to assist the design of cell manufacturing processes but also to deliver cost saving through process simplification based upon the governing principles of cell behavior.

As the raw materials for cell-based products shift from somatic cells or tissue to pluripotent stem cells, two major changes in the manufacturing process are anticipated. The first assumes that the source cells come from a master cell bank, thus allowing the same origin of cells to be supplied throughout the life cycle of the product. The second assumes that the main target of quality control in cell processing will shift from cell replication processes to cellular differentiation processes. Pluripotent stem cells can theoretically be amplified indefinitely and their expansion process has become relatively easy to manage in recent years [8–11]. However, controlling the conditions of differentiation processes is complicated, and it often takes a long time to obtain target cells [12,13]. These differences must be reflected in the process and quality control requirements for production of cell-based products. The quality of cell-based products is prone to variability due to cell-processing operation of the manufacturing process, which causes intrinsic disorder of cells, described above. To ensure the reproducibility of process controls for cell manufacturing, it is important to design accelerations for the motion control of cell-processing operations in addition to controlling the cultivation conditions [14]. Therefore, a long education and training period will be required to maintain the quality of cell operations when the manufacturing process is performed manually by human operators. To ensure the required quality level is stably maintained throughout the life cycle of production, it is necessary to secure sufficient operators with the required operation skills, which makes production activities extremely expensive. It is assumed that the tolerance for variations due to cell-processing operations is large because there are large variations in somatic cells and tissue as raw materials for conventional manufacturing [15]. However, manufacturing using stem cells with a master cell bank is expected to require operators with more sophisticated mastery of skills for cell-processing operations. To maintain a certain number of required skilled operators throughout the life cycle of production, it is necessary to constantly secure personnel, including reserves, with consideration of unexpected vacancies or retirement.

Extensive research and development of robotic operation system for the mechanization of manual cell-processing operations has been underway [16–19]. The robotic operation here is mechanization and intended for mechanized operations of skilled cell-processing that make it difficult to reproduce operational parameters in the medium exchange or the passaging, and it is also necessary to achieve aseptic operation. For manufacturing using a master cell bank as raw material, the mechanization of cell-processing operations is an advantage for both the reproducibility and stability of product quality [20]. Indeed, it is assumed that robotic operations can increase reproducibility of product quality while reducing the cost of manufacturing [21,22]. Evaluating the cost-based effectiveness of cell manufacturing leads to reduced cost-of-goods in the life cycle of the product. It is expected that during the scale-up system of cell manufacturing, the life cycle cost imposed by robotic operations can be lower than that of manual operations, which have additional costs of securing personnel and education and training. It is presumed that characteristics impacting quality during operation are quite different between upstream processes (cellular expansion or differentiation) and downstream processes (dispensing or freezing of cells); thus, these processes need to be discussed individually [23–25].

In this study, we attempted to develop an estimation method for the resource expenditure required for manual or robotic operation in a cell manufacturing system using an isolator system, which assumes the upstream process for a manufacturing model of cell-based products. Resources required to achieve process control by manual or robotic operation were analyzed to lead the availability of robotic operation system.

2. Methods

2.1. Layout pattern using isolator system for performing processes

It is premised that all the cell manufacturing processes modeled in this study must have proper operational parameters for manual

or robotic operation system that can be controlled within the design space to meet specified quality requirements for pharmaceutical production [26]. As shown in Fig. 1, a group of procedures for cell culture vessel-handling operation is adopted, and every process proceeds inside the sealed-chamber equipment such as a biosafety cabinet or an isolator system, referred to as the cell processing zone (CPZ), with a cleanness level of ISO class 5 (grade A) [16]. In this study, an isolator system is adopted. The surrounding area which is connected to the CPZ has a strong influence on the aseptic environment, so cleanliness level of ISO class 8 (grade C or D) is required for an isolator system to achieve aseptic processing, depending on the physical structure of CPZ. Operators need to gown when entering the surrounding area, which involves a series of procedures for washing and disinfecting hands, changing out of street clothes, and donning aseptic gowns. The required gowning level differs depending on the type or specifications of CPZ equipment, but it is assumed to be the same regardless of the equipment or operational specifications in this study.

2.2. Requirement time of operational cycle for a process

As shown in Fig. 1, the operational cycle for cell-processing process has 5 steps with each required time, which consists of 1st step for entering into the surrounding area, t_{ent} [h] where is the gowning time of operators, 2nd step for materials loading, t_{load} [h] where is the decontamination and setup time of materials, 3rd step for cell-processing operation, t_{cell} [h] where is the actual cell-processing time in the process, 4 step for cleaning, t_{clean} [h] where is the cleaning time for the processing area containing CPZ affecting next cycle, 5th step for leaving from the surrounding area, t_{leav} [h] where de-gowning and removal time of operators. In practice, this cycle is repeated when processes for vessel-handling operation are underway in the CPZ, regardless of process characteristics.

2.3. Resource factors required to achieve aseptic-processing operation skills

The manufacturing of a product can be represented by the accumulation of resource expenditure with time for series of repeated processes. Such processes require aseptic-processing operation skills, including gowning technique, materials loading and cleaning, and additional cell-processing operation skills. The requirements for approving the operator or robot arms to perform processes were defined as shown in Table 1. The robot arms are machinery included in the robotic operation system.

To secure the resource of operator or robot arms with necessary operation skills, it is assumed that expenditures are incurred during start-up for design and actualization (initial), during production (running) period, and during the breaking period for maintenance. The resource expenditure for start-up is once as an initial investment, whereas expenditures during production period and the breaking period are required annual continuously. During the breaking period, the resource expenditure to upkeep proper cell processing operation skills (upkeep cost) requires. These expenditures during start-up do not only be required when production starts since demand of human resources occurs multiple times during the life cycle of production as an example in this setting. In this study, the resource expenditure for additional demands of human resource through the life cycle of the product is defined as the initial cost.

Cell-processing operation work involves two tasks: controlled cell-processing operation and process monitoring to detect deviation, and two tasks cannot be done by one operator with cell-processing operation skills (operator B) in the same time. Therefore, manual operation is set to require two of the operator B. For robotic operation, robot arms with the operation system can combine the tasks of controlled cell operation and process monitoring, but requires only one operator with aseptic-processing operation skills (operator A) for materials loading and cleaning work, in this setting. The required resources for each process to maintain the required quality of manual or robotic operations are summarized in Fig. 2.

2.4. Personnel life cycle by considering the periods of education and training

It is difficult to utilize all the time of employees for processes due to spend a certain amount of time outside of production activities. As shown in Fig. 3, when an operator is employed for the personnel lifecycle of average employment period, t_{emp} [h·(operator)$^{-1}$], the period of education and training, $t_{tra.asep}$ [h·(operator)$^{-1}$] and/or $t_{tra.cell}$ [h·(operator)$^{-1}$] to secure the necessary operation skills for work cannot involve production activities. Therefore, the remaining period, which is obtained by subtracting the education and training period from the personnel

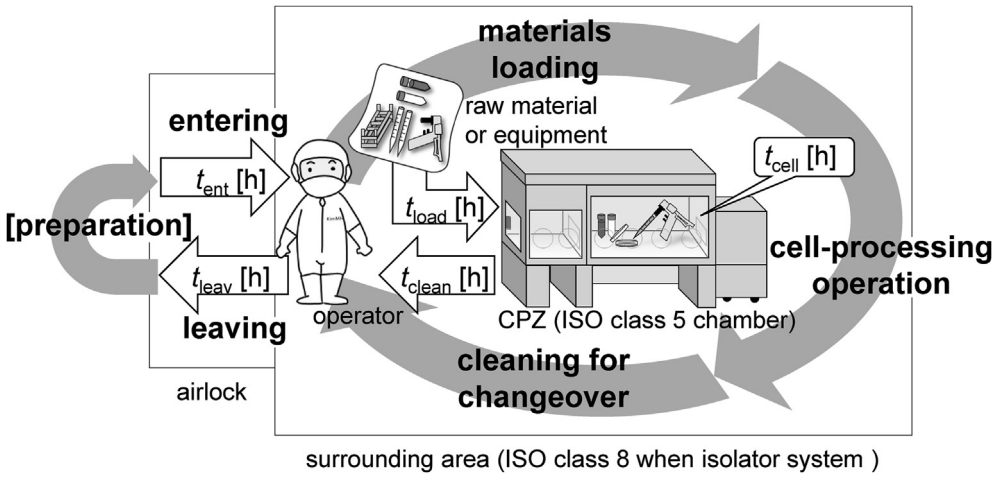

Fig. 1. Diagram of manufacturing process and time schedule for repetition in a sealed-chamber cell manufacturing system. The operational cycle time for a cell processing cycle consists of 1st step for entering into the surrounding area, t_{ent}, 2nd step for material loading, t_{load}, 3rd step for cell-processing operation, t_{cell}, 4 step for cleaning, t_{clean}, and 5th step for leaving from the surrounding area, t_{leav}.

Table 1
Essential factors for the formulation of resources in cell-processing operation.

resource	essential resource expenditure to achieve manufacturing process in production		
	during start-up to gain skills (initial costs)	during production period (running costs)	during the breaking period (upkeep costs)
operator with aseptic-processing operation skills (operator A)	1) education and training time and cost required for aseptic-processing operation skills	1) working time for processes in the manufacturing 2) consumables for maintaining the environment (gowning and other supplies material)	1) all other working time required for employees 2) affairs required to secure reserve personnel with aseptic-processing operation skills
operator with cell-processing operation skills (operator B)	1) education and training time and cost required for aseptic-processing operation skills 2) education and training time and cost required for cell-processing operation skills with process monitoring skills	1) working time for processes in the manufacturing 2) consumables for maintaining the environment (gowning and other supplies material)	1) all the other working time required for employees 2) affairs required to secure reserve personnel with cell-processing operation skills
robot arms for cell-processing operation system (robot arms)	1) design and assembly of equipment for cell manufacturing with aseptic-processing operation 2) programme of cell-processing operations and monitoring operations	1) utilities consumed (power and other supplies material) 2) cleaning and disinfection cost required for reuse	1) appropriate calibration and check at defined intervals with computer system validation 2) replacement of major parts at defined intervals

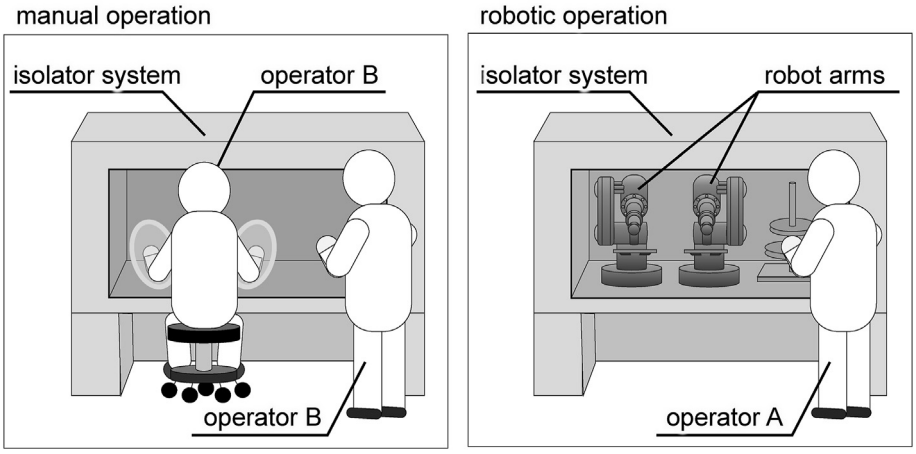

Fig. 2. Schematic image of required resources for manual operation and robotic operation in the cell-processing operation system.

life cycle, is period as performer of cell processing time for production. In addition, the practical manufacturing has to separate the periods of processing and non-processing. This consider that the available time for production, $\alpha_{\mathrm{rate}} \cdot t_{\mathrm{emp}}$ [h·(operator)$^{-1}$], which is the net time for the operation cycle, can be calculated from the working time ratio available for production, α_{rate} [-].

Furthermore, the period of education and training consumes human resources, as well as facility and equipment resources involving raw materials, to carry out training objectives. Since the t_{emp} may be shorter than the expected production period, t_{life} [year/production] where is the years of production corresponding to the product life cycle, it is necessary to always add maintenance expenditures (initial cost to demand human resources) that consider the replenishment or risk for unexpected retirements.

2.5. Machinery life cycle by considering the design and fabrication of manufacturing system

In this study, it is assumed that a machinery in the robotic operation system has a pair of robot arms and their operating system. At the start of production, the design and fabrication are required for the robot arms containing operating system of operational procedures, which is the first robotic operation system. With the increase in the number of annual batches, required unit number of the robot arms, $n_{\mathrm{nec.robo}}$ [unit], are additionally fabricated by the initial design. The value of $n_{\mathrm{nec.robo}}$ depends on the maximum available batch number per a robotic operation system, n_{robo} [batch·(unit)$^{-1}$]. The robot arms are assumed to use consistently throughout the production period, although additional annual upkeep operation, including operating system validation, is required.

2.6. Estimation method of resource expenditure for cell operation

Because the contents and timing requirements of resource expenditure differ between operators and robot arms, the estimation of costs for cell manufacturing is integrated throughout the life cycle of production. On the basis of these assumptions, we carried out our estimations of resource expenditure for cell-processing operations, which is the basis for calculating the cost of goods in future by manual or robotic operation system.

In this study, it is assumed that all procedures for the operation or management of facilities and equipment are common between manual and robotic operations. A series of upstream processes need to be carried out at prescribed intervals, and hence cannot be carried out continuously in the CPZ. Therefore, in this study, it is assumed that one CPZ is shared for processes of multiple batches proceeding in parallel to obtain an appropriate utilization rate of the CPZ.

The education and training times for operators to gain aseptic-processing operation skills or cell-processing operation skills are stipulated as $t_{\mathrm{tra,asep}}$ and $t_{\mathrm{tra,cell}}$, respectively. The model input for

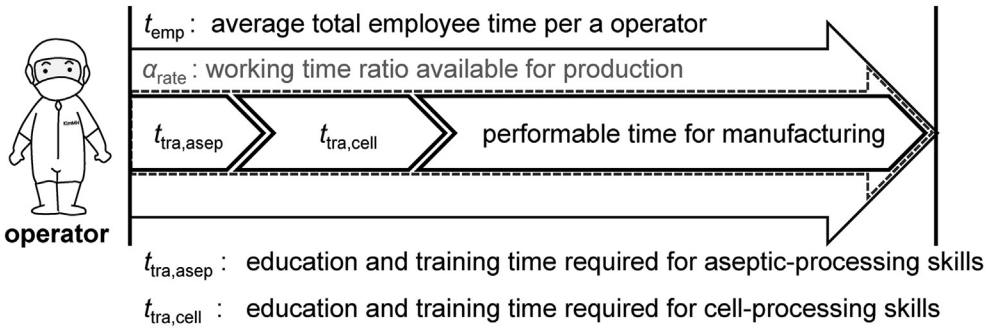

Fig. 3. Work timetable of one operator in the total employee time.

the cost estimation of manual operations is defined as $t_{tra,cell}$, since $t_{tra,asep}$ to gain aseptic-processing operation skills will be a common value regardless of the product. The costs for education and training to acquire or upkeep operation skills are classified as initial costs or upkeep costs, but it is considered running costs since they are incurred on the basis of each operator. When the $\alpha_{rate} \cdot t_{emp}$ can be calculated, it is considered that the actual hourly rate of operator A or B after acquiring operation skills, $c_{wor,A}$ [JPY·h^{-1}] or $c_{wor,B}$ [JPY·h^{-1}], can be estimated using the following equation:

$$c_{wor,A} = \frac{c_{tra}\left(t_{tra,asep} + t_{tra,cell}\right) + c_{emp}t_{emp} + c_{mai,A}}{\alpha_{rate}t_{emp} - t_{tra,asep} - t_{tra,cell}} \quad (1)$$

$$c_{wor,B} = \frac{c_{tra}\left(t_{tra,asep} + t_{tra,cell}\right) + c_{emp}t_{emp} + c_{mai,B}}{\alpha_{rate}t_{emp} - t_{tra,asep} - t_{tra,cell}} \quad (2)$$

where c_{emp} [JPY·h^{-1}] is the hourly personnel rate of the operator, c_{tra} [JPY·h^{-1}] is the hourly education and training rate, and $c_{mai,A}$ [JPY·(operator)$^{-1}$] or $c_{mai,B}$ [JPY·(operator)$^{-1}$] is the upkeep cost for operator A or B. $c_{mai,A}$ is only the upkeep cost for aseptic-processing operation skills while $c_{mai,B}$ also contains the resource expenditure for cell-processing operation skills, both are including re-education and training. According to the time schedule of the process shown in Fig. 1, the time required for each process, t_{proc} [h], can be expressed by the following equation:

$$t_{proc} = t_{ent} + t_{load} + t_{cell} + t_{clean} + t_{leav} \quad (3)$$

Next, the expenditure for manual operation systems of a product, C_{manu} [JPY·(product)$^{-1}$], is estimated using the following equation:

$$C_{manu} = \frac{2n_{proc}\left(c_{wor,B}t_{proc} + c_{gow}\right)}{n_{lot}} \quad (4)$$

where n_{proc} [(process)·(batch)$^{-1}$] is the number of processes per batch in production and n_{lot} [(product)·(batch)$^{-1}$] is the number of products included in a batch for lot production. It is defined that the gowning costs for operators are charged for each process. The initial or upkeep cost can be calculated according to the respective ratio in the $c_{wor,B}$ and other expenditures is considered to be the running cost.

In the model for cost estimation of robotic cell-processing operations, it is difficult to convert the initial design and fabrication of the robot arms into an hourly rate. Thus, the costs of initial design and fabrication, c_{des} [JPY] and fabrication and installation of robot arms with acquisition of operation skills, c_{fab} [JPY·(unit)$^{-1}$], are charged as the initial investment during start-up for production. Antithetically, it is assumed that robot arms can be used consistently throughout the production period, although c_{des} and c_{fab} are required when production starts. The c_{des} is regarded as a one-time cost through the life cycle of production. The maximum number of batches, n_{robo} [batch·(unit)$^{-1}$], that can be generated with one robotic operation system is appraised. When the annual number of batches required for production, n_{bat} [batch·(year)$^{-1}$], is used as the input value, the necessary unit number of robotic operation systems, $n_{nec.robo}$ [unit], is defined using the following equations:

$$n_{robo} = \frac{\alpha_{capa}t_{prod}}{n_{proc}t_{proc}} \quad (5)$$

$$n_{nec,robo} = \frac{n_{bat}}{n_{robo}} \quad (6)$$

where α_{capa} [-] is the utilization rate of the CPZ including the robot arms, and t_{prod} [h·(year)$^{-1}$] reflects the annual business hours available for production. He expenditure for robotic operation system of a product, C_{robo} [JPY·(product)$^{-1}$], is estimated using the following equation:

$$C_{robo} = \frac{c_{des} + n_{nec,robo}\left[c_{fab} + t_{life}(c_{rsm} + c_{rse})\right] + t_{life}n_{bat}n_{proc}\left(c_{wor,A}t_{proc} + c_{gow}\right)}{t_{life}n_{lot}n_{bat}} \quad (7)$$

where c_{rsm} [JPY·(unit·year)$^{-1}$] is the upkeep cost of the robot arms including the operation verifying or computer system validation during the breaking period, and c_{rse} [JPY·(unit·year)$^{-1}$] is the essential cost to maintain of the robotic operation system during production period. It is assumed that c_{rsm} and c_{rse} are defined as the upkeep cost to be charged annually, including the expenditure of operator A in the breaking period. The initial cost includes c_{des} and c_{fab}, as well as the expenditures for demand of the human resource.

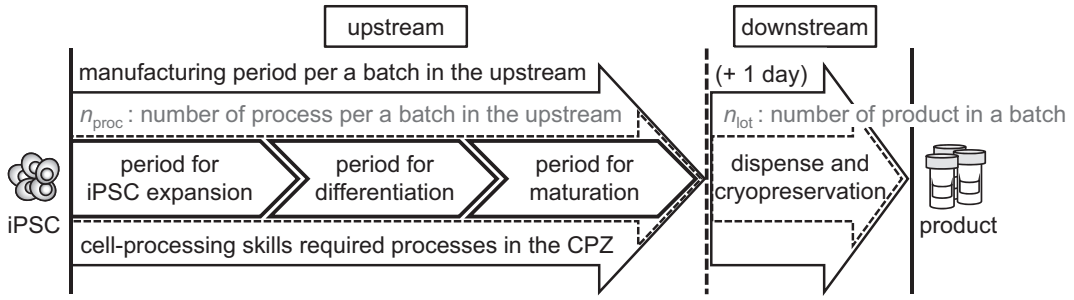

Fig. 4. Overview of a production model for iPSC-derived products.

2.7. Production model conditions toward estimation

To estimate the resource expenditure for cell manufacturing, a life cycle of the production model was constructed for an iPSC-derived retinal pigment epithelial (RPE) cell manufactured using an isolator system [27]. As shown in Fig. 4, n_{proc} was set to 90 in a production period of 91 days per a batch in the range of upstream processes, which involve iPSC expansion, differentiation, and maturation. The resource expenditure, C_{manu} or C_{robo}, is estimated on the basis of the parameter values defined in Table 2, with n_{bat} as the variable input value and t_{life} fixed to 10. Each value in Table 2 is empirically set on the basis of the common or the measured value from operational procedures in the model manufacturing, only to calculate the resource expenditure in this study. All values would need to be reviewed when another production model is developed for other organizations.

C_{manu} is estimated only from the cost of maintaining skilled operators and time associated with processes, whereas the number of batches performable by operator B, n_{manu} [batch·(operator)$^{-1}$], is limited in reality. Therefore, the number of operator B required during the life cycle of production, $n_{nec,ope}$ [operator], is calculated using the following equations:

$$n_{manu} = \frac{\alpha_{rate} t_{emp} - t_{tra,asep} - t_{tra,cell}}{2 n_{proc} t_{pro}} \quad (8)$$

$$n_{nec,ope} = \frac{n_{bat} t_{life}}{n_{manu}} \quad (9)$$

3. Results and discussion

When education and training time to gain required cell-processing operation skills of operator B were employed, the $t_{tra,cell}$, was provided and the hourly rate of operator A or B, $c_{wor,A}$ or $c_{wor,B}$, respectively, was estimated as shown in Fig. 5. As a matter of course, the $c_{wor,B}$ increased depending on $t_{tra,cell}$, whereas $c_{wor,A}$ was constant. During cell manufacturing processes, constant quality can be ensured by acquiring both aseptic-processing operation skills and cell-processing operation skills, and $t_{tra,cell}$ for the latter would be unique for each product. Notably, the designed $t_{tra,cell}$ is expected to increase enormously if there are any complicated operations that are difficult to accrue for operators, which also depends on the cell manufacturability of the product model. Furthermore, the hourly rates in this production model are calculated by fixing the α_{rate} at 0.7, but the decrease of α_{rate}, which depends on decreasing the work engagement time for cell-processing of operators, will lead increase of the hourly rates. It is desirable that the α_{rate} is higher in order to decrease the hourly rate, but it is assumed that the value of α_{rate} is to be decrease when the number of personnel is secured in consideration of the retirement or other risks.

Table 2
Nomenclature and values used for calculation.

symbol	value	unit	explanation
α_{capa}	0.80	–	capacity operating ratio of the CPZ
α_{rate}	0.80	–	working time ratio available for the production
c_{des}	1.0 × 108	JPY	initial design cost of robotic operation system
c_{emp}	3.0 × 103	JPY·(hour)-1	basal hourly rate of operator
c_{fab}	1.0 × 108	JPY·(unit)-1	fabrication cost of robot arms and the operating system
c_{gow}	4.0 × 103	JPY·(process)-1	cost for materials of gowning
$c_{mai,A}$	5.0 × 105	JPY·(operator)-1	upkeep cost for operator A
$c_{mai,B}$	2.0 × 106	JPY·(operator)-1	upkeep cost for operator B
c_{rse}	5.0 × 104	JPY·(year)-1	essential costs to maintain robotic operation system
c_{rsm}	1.0 × 106	JPY·(year)-1	maintenance cost of robotic operation system
c_{tra}	6.0 × 103	JPY·(hour)-1	hourly cost preparing for education and training
n_{lot}	100	product·(batch)-1	number of product in a batch of manufacturing
n_{proc}	90	process·(batch)-1	number of process per batch in the manufacturing
t_{cell}	0.60	hour·(process)-1	working time for cell-processing operation
t_{clean}	0.50	hour·(process)-1	working time for cleaning
t_{ent}	0.40	hour·(process)-1	working time for entering of operator
t_{emp}	1.0 × 104	hour·(operator)-1	average total employee time of operator
t_{leav}	0.30	hour·(process)-1	working time for leaving of operator
t_{life}	10	year/production	life cycle period of the production
t_{load}	0.50	hour·(process)-1	working time for materials loading
t_{prod}	1.6 × 103	hour·(year)-1	manufacturing time in the facility
$t_{tra,asep}$	1.3 × 102	hour·(process)-1	education and training time for aseptic-processing

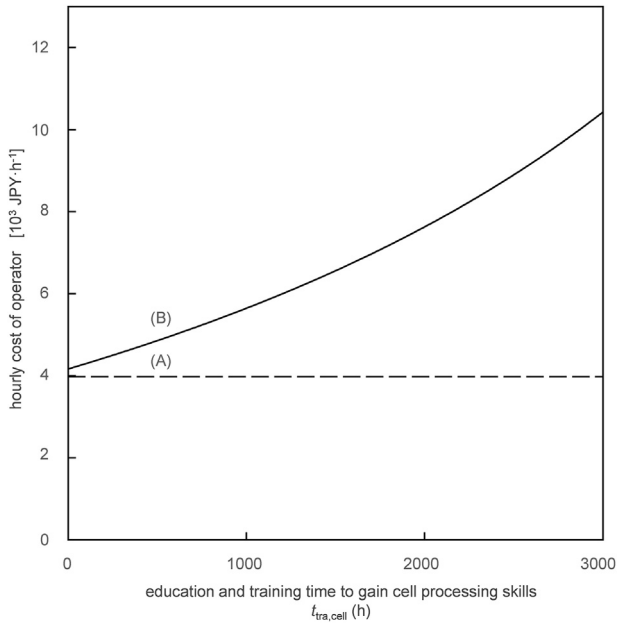

Fig. 5. Estimated hourly cost of a human operator considering the practical performance time for manufacturing processes depending on education and training time. (A) Operator with aseptic-processing operation skills (operator A), $c_{wor,A}$. (B) Operator with cell-processing operation skills (operator B), $c_{wor,B}$.

The resource expenditure adopted a manual cell-processing operation, C_{manu}, in the production model that increased depending on $t_{tra,cell}$, as shown in Fig. 6. C_{manu} did not change with the value of n_{bat}. C_{manu} was 2.4×10^4 when $t_{tra,cell}$ was zero, whereas 2.9×10^4 when $t_{tra,cell}$ was 8.0×10^2 or 3.5×10^4 when $t_{tra,cell}$ was 1.6×10^3, which is the guidepost for half a year and one year of education and training period. Most of resource expenditures in the manual cell-processing operation was running cost, and the value was 2.2×10^4 when $t_{tra,cell}$ was zero, which was 91% in the C_{manu}. The percentage of initial cost was as small as 2.5% when $t_{tra,cell}$ was zero, but it raised with the increase of $t_{tra,cell}$. The initial cost became to be 2.2×10^4 when $t_{tra,cell}$ was 2.9×10^3, and the percentage of running costs in the C_{manu} decreased to 49%. Since the work time of skilled operators is not occupied in certain processes and considered to be controlled by the value of α_{rate} optionally, the operator costs in the running costs did not have marked increase.

In contrast, the resource expenditure adopted a robotic cell-processing operation, C_{robo}, that decreased with increasing n_{bat}, because initial costs for design and fabrication of the robot arms are necessary, as shown in Fig. 7. The required number of robotic operation systems, $n_{nec.robo}$ [unit], fluctuated step by step relative to n_{bat} and the decrease of C_{robo} value undulated because the robot arms needs to be occupied by certain processes. That is the trend of decrease contains the utilization rate change-related multiple lines of discontinuity when the $n_{nec.robo}$ increase with increasing n_{bat}. Notably, this value settled around 3.0×10^4, when equilibrium with the increase in n_{bat} was reached. The running cost was around 1.1×10^4 and constant regardless of n_{bat}, the percentage was around 37% when C_{robo} reached in equilibrium. Although the initial cost was high when n_{bat} was low, it decreased with increasing n_{bat}, and the value settled around 1.7×10^4 when C_{robo} reached in equilibrium.

To compare manual and robotic operation system, C_{manu} with $t_{tra,cell}$ of 8.0×10^2 or 1.6×10^3 and C_{robo} were evaluated. The results were exhibited with the number of operator B or robot arms required for the production model, as shown in Fig. 8. C_{manu} was constant regardless of n_{bat}. It was always 2.9×10^4 when $t_{tra,cell}$ was 8.0×10^2 and 3.5×10^4 when $t_{tra,cell}$ was 1.6×10^3. When $t_{tra,cell}$ was 8.0×10^2 or less, C_{robo} was higher than C_{manu}. Compared with C_{manu} when $t_{tra,cell}$ are 1.6×10^3, the value of C_{robo} was lower than C_{manu} when n_{bat} was 33 or more, but the reduction of C_{robo} was not remarkable even when n_{bat} was increased further, because n_{bat} has reached in equilibrium. Since these results of estimation are case study from parameters of a production model, the superiority of the certain operation method cannot be considered. Though it is suggested that comparison of different cell-processing operation methods is available by life cycle costing, which estimates the sum of running costs, upkeep costs and initial costs.

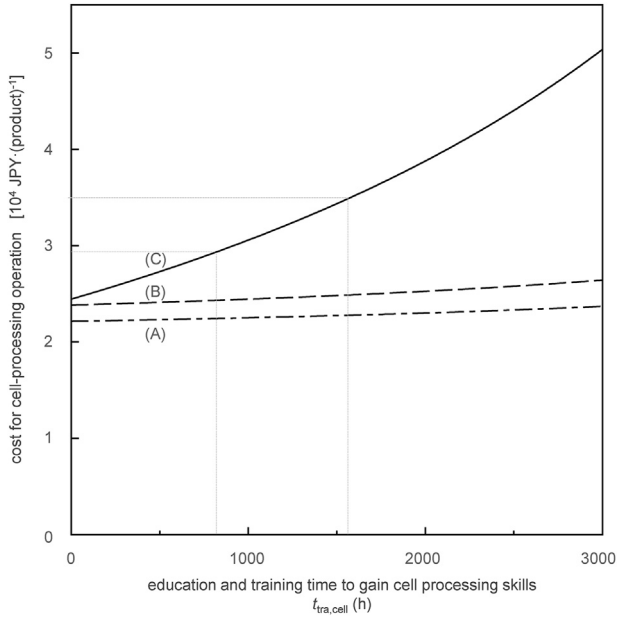

Fig. 6. Estimated resource expenditure for cell manufacturing by the manual operation system, C_{manu}. (A) Running costs in C_{manu}. (B) Sum of running costs and upkeep costs in C_{manu}. (C) C_{manu} which is the sum of running costs, upkeep costs and initial costs.

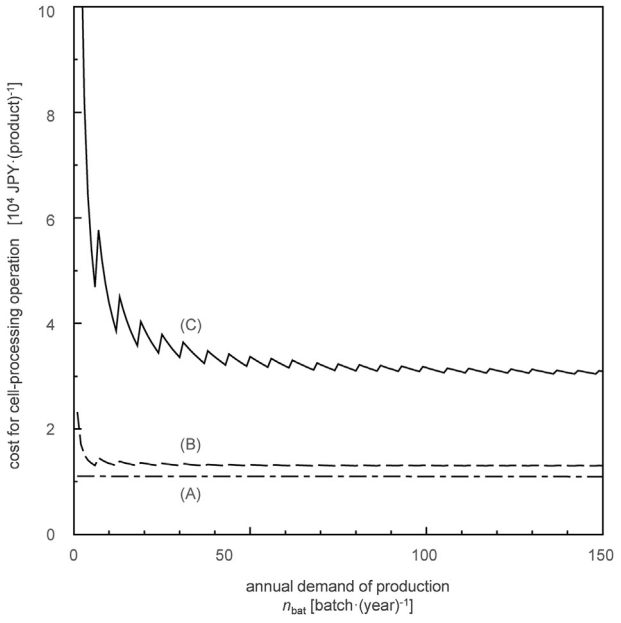

Fig. 7. Estimated resource expenditure for cell manufacturing by the robotic operation system, C_{robo}. (A) Running costs in C_{robo}. (B) Sum of running costs and upkeep costs in C_{robo}. (C) C_{robo} which is the sum of running costs, upkeep costs and initial costs.

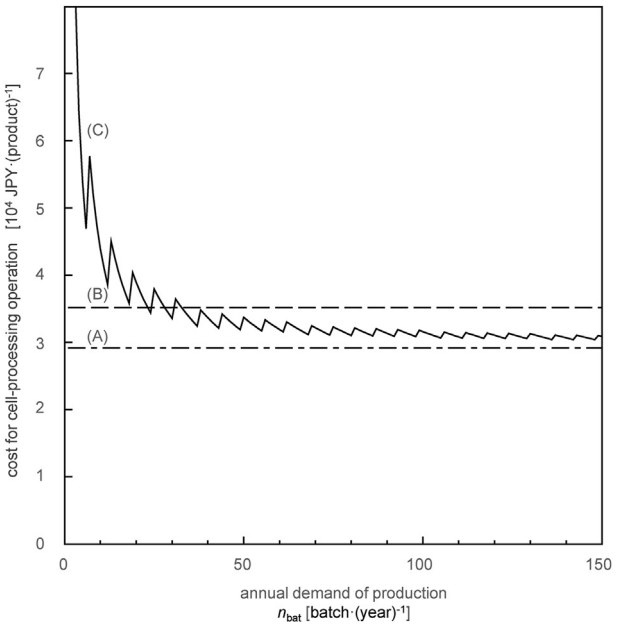

Fig. 8. Comparison of resource expenditure and required operators for manual and robotic cell-processing operation systems. (A) Cost for manual operation system, C_{manu} when $t_{tra.cell}$ is 8.0×10^2. (B) Cost for manual operation, C_{manu} when $t_{tra.cell}$ is 1.6×10^3. (C) Cost for robotic operation system, C_{robo}.

For manufacturing adopting a manual operation system, it was necessary to secure many workers with the required operation skills as n_{bat} increased. This result implies that the increase of operator numbers is a serious potential risk in formulating a robust production plan. Indeed, manual operation systems need to consider that a certain percentage of operators will retire during the production period, so reserve employment and additional education or training will be required continuously to ensure the required number of operators are available throughout the life cycle of production. When the number of operators required increases depending on higher production demands, it is considered that the initial costs for the unit cost of each operator increase due to activities related to securing human resources, which occur irregularly. Furthermore, suppressing variations among operators is an important factor to assure the quality of products, especially when the process requires fine motion controls during cell-processing operations; accordingly, an increase in operator numbers becomes a great potential risk to carry out proper education and training. Thus, we assumed that these potential risks would increase C_{manu}, yielding a higher than the expected cost-of-goods.

The running cost in the robotic cell-processing operation was half of the running cost in the manual cell-processing operation. It is suggested that the number of operators, which is one in the robotic operation system compared to two in the manual operation system, led this result. On the other hand, C_{robo} was not sufficiently lower than C_{manu}, even when n_{bat} was greatly increased. Though we considered that the initial cost assumed is not much high, the percentage of initial cost didn't decrease enough with the increase of n_{bat}. Unlike conventional processes for other medicinal products, the cell manufacturing processes in this method cannot be continuously performed by simply repeating the same cell-processing operation (t_{cell}). Rather, the operation time of processes and accumulation of estimated resource expenditures in this study do not require the repetition of t_{cell} by cell-processing operation but instead the repetition of t_{proc} by combining times for activities such as materials loading, cleaning, and operators entering/leaving the CPZ. These results suggest that the reduction of C_{robo} is restricted when the process cycle induces a low utilization rate of the robot arms. Reportedly, robotic operation and closed systems can effectively reduce the cost-of-goods [22,28]. Closed systems involve a liquid-handling operation system adopting sealed vessels, such as a culture tank, and do not require extended occupation of the CPZ in which the robot arms are installed. These findings suggest that a reduction of t_{proc} by shortening the time other than t_{cell} in Equation (3), improves the utilization rate of robot arms, and reduces the cost-of-goods for manufacturing systems adopting robotic cell culture vessel-handling operations.

There are two possible methods to reduce t_{proc} relative to the improvement of the substantial utilization rate of CPZ and robot arms. One is to have a repetition of t_{cell} in a cycle of the process, while the other is to shorten t_{proc} while keeping t_{cell} constant as mentioned above. However, it is suggested that the former is difficult or limited when considering cell manufacturability because the amounts of cells per batch increase [7]. Therefore, we have concluded that it is effective to shorten times for materials loading and/or cleaning to immediately improve the substantial utilization rate of CPZ and robot arms in manufacturing systems using cell culture vessel-handling operations.

As a technical example, rapid loading methods employing a new decontamination technology permit operations in which the CPZ is continuously aseptic or maintained aseptic by cleaning without decontamination is assumed [29,30]. Furthermore, omitting the intervention of human operators with such methods is also profitable due to reduce the resource expenditure.

4. Conclusion

We developed an estimation method for the resource expenditure of cell-processing operations applied in cell manufacturing systems that involve vessel-handling procedures performed in a biosafety cabinet or an isolator system. The estimation method reported in this study adopted a life-cycle costing technique focused on cell-processing operations of the upstream process. Because procedures in the upstream process involve work such as entering the CPZ, loading materials, cell-processing operation, cleaning, and leaving the CPZ, reducing the time required for loading materials or cleaning can effectively improve the resource expenditure for cell-processing operations, thus reducing the cost of goods or products.

In addition, a large number of operators is required for manually operated cell manufacturing systems when the number of batches in production is increased. The requirement to secure operators with appropriate operation skills is a great potential risk to the reproducibility of manufacturing processes. Therefore, it is suggested that cell manufacturing systems adopt robotic cell-processing operations for their advantages in stabilizing the production of cell-based products. Indeed, increasing the substantial utilization rate of robot arms can effectively reduce the resource expenditure of cell-processing operations. To increase the substantial utilization rate of robot arms, technologies that reduce the times required for materials loading or cleaning during each process are expected in the future.

Declaration of competing interest

None.

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