Mid-term Business Plan

Fiscal Year 2021 to Fiscal Year 2023

February 12, 2021

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1. Mid-term Business Plan for the Next 3 Years

(1). Summary of the previous consolidated fiscal year at the time of submission of this mid-term business plan

The Japanese economy and the global economy during the previous consolidated fiscal year suffered from the raging of the novel coronavirus (COVID-19) pandemic, restricting economic activities throughout the world. The economic picture has been extremely grim. The Japanese Government declared a state of emergency in March 2020, dealing a heavy blow to healthcare as well as economic activities. The third wave of COVID-19 arrived around November 2020 and infection spread to such an extent as to bring the second set of state of emergency declarations in January 2021. Fears of economic stagnation and recession are difficult to assuage and the future outlook still abounds in uncertainties.

Against this backdrop, CellSeed Group continued to pursue business activities in regenerative medicine supporting business and cell sheet regenerative medicine business while ensuring the health and safety of all employees by adopting such measures as teleworking from home as the basic rule for work.

As a result of the activities above, we recorded sales of JPY199,466 thousand (down JPY76,357 thousand year on year), and operating loss of JPY719,521 thousand (less in loss by JPY61,275 thousand year on year), with ordinary loss of JPY744,701 thousand (less in loss by JPY41,532 thousand year on year). Net loss attributable to owners of parent was JPY783,860 thousand (up JPY1,462 thousand year on year).

Performance results by segment is as follows:

(i). Regenerative medicine supporting business (Including cell cultureware business, OEM)

We continued to engage in R&D of new products so as to develop our cell cultureware business for the future. As for sales and marketing, we began product supply into new markets, which are expected to grow as mass culture of research cells will be on demand, with development activities increasing on prevention and therapies for infections including COVID-19 as well as for cancers. We continued to engage in sales promotion activities and reinforcing collaboration with existing agents in order to expand the sales of cultureware. As a result of these activities, we saw steady growth in overseas sales, achieving record-breaking sales in FY2020 as with the previous fiscal year.

In our Contract Development and Manufacturing Service that started as a new business supporting regenerative medicine through the effective use of our Cell Processing Facility, therapeutic clinical application of chondrocyte sheet has begun at Tokai University under Advanced Medicine B classification. Because we were impacted by the spread of COVID-19 causing delay in surgery, our initial sales plan was not achieved. However, with manufacturing orders received from Tokai University, we were able to post sales for three

cases during the fiscal year.
As a result of the activities above, we recorded sales of JPY147,314 thousand (up JPY30,179 thousand year on year), and operating loss of JPY38,901 thousand (less in loss by JPY5,043 thousand year on year).

(ii). Cell sheet regenerative medicine business
In the cell sheet regenerative medicine business, CellSeed is promoting research and development into epithelial cell sheet for esophageal regeneration, regenerated cartilage sheet and other cell sheet regenerative medicine products that are in its product development pipeline.
In the pipeline of cell sheet for esophageal regeneration, our effort has been focused on starting additional clinical trials.
To report on the clinical trials we had been conducting since August 2016, we completed case registration in trial facilities by April 2018. Although the safety of our product was confirmed, we could not obtain sufficient data to prove efficacy. The Pharmaceuticals and Medical Devices Agency (PMDA) required us to conduct an additional clinical trial.
Later, as steroids became recognized as an inexpensive and effective method of preventing stenosis after endoscopic therapy for esophageal cancer, we selected our additional trial patients to be those who were at risk if given steroids. We continued consultation with the PMDA on issues including the necessary case numbers. In July 2020 the decision was granted on our additional trial and in October we were able to submit trial notification.
Because of these reasons – the limiting of trial subjects to those who are at risk with steroid administration and the PMDA requirement for a larger number of cases than the initial trial – we have scheduled FY 2025 for the manufacture and sales approval application. However, we will continue to review the situation so as to shorten the trial timeframe by such actions as adding more institutions to our trial.
The development of epithelial cell sheet for esophageal regeneration in Europe based at our Swedish subsidiary has been halted. This is due to the diffusion in Europe of endoscopic therapy not being as advanced as we had initially assumed and as mentioned above, we decided to focus on obtaining manufacture and sales approval in Japan.
In the product pipeline for regenerated cartilage sheet and other products, we have been exploring the creation of a system to build cell stock for stocking up allogeneic cells.
However, cell stock creation for commercial application presented issues, in that the healthcare establishments and government bodies were not fully ready to create a system for collecting, storing and supplying cells. The acquisition of tissues was problematic for us as a private business. Therefore, we had been undertaking R&D for the time being by obtaining cartilage cells from the Nation Center for Child Health and Development (NCCHD) for the sole purpose of research activities.
In December 2020, we obtained approval from the Ethics Review Committee of NCCHD to be supplied cartilage tissue collected from patients with polydactyly (congenital condition of having more than five digits on a hand or foot). This ensured the stable supply of cartilage tissue that can be used for commercial application and means that we are in a position now to expedite R&D in order to conduct clinical trials of

allogeneic regenerated cell sheets and head for obtaining manufacture and sales approval.
In our overseas business, we posted JPY50,000 thousand in November 2020 for sales to MetaTech(AP)Inc. This sum is the milestone payment made to CellSeed from MetaTech(AP)Inc. under the agreement signed in April 2017 for the granting of exclusive development, manufacture and sales rights of cell sheet regenerative medicine business (epithelial cell sheet for esophageal regeneration/regenerated cartilage sheet) in Taiwan. Therapies using the regenerated cartilage sheets commenced under this agreement and after the completion of therapies given to ten cases, a milestone payment of JPY50,000 thousand was scheduled.
CellSeed will continue to provide support to MetaTech(AP)Inc. for their epithelial cell sheet for esophageal regeneration and regenerated cartilage sheet businesses.
As a result of the activities above, we recorded sales of JPY52,152 thousand (down JPY106,537 thousand year on year), and operating loss of JPY390,492 thousand (less in loss by JPY33,755 thousand year on year).

(2). Outline of the Mid-term Business Plan and Its Background

Outline of CellSeed Mid-Term Business Plan FY2021 - 23

Cell Sheet Regenerative Medicine Business

- ●Epithelial sheet for esophageal regeneration: Start additional trial, aimed at submission of application for manufacturing and sales approval in FY 2025.
- ●Allogeneic cartilage regeneration sheet: Expedite non-clinical study data gathering aimed at submission of clinical trial notification at the end of FY 2022.
- ●Collaboration: Rebuild collaboration with MetaTech and Taiwanese JV company, aimed at acquiring further income generating opportunities.
- ●Business alliance: Actively promote partnerships to globally develop cell sheet engineering originating in Japan and thereby generate increase in income.

Regenerative Medicine Supporting Business

- ●Cultureware: Push up cell cultureware product sales overseas by strengthening alliance with Thermo Fisher Scientific Inc.
- ●Cultureware: Expand business by developing/supplying cultureware to new markets for mass culture of cells for research needs
- ●Overseas sales: Improve and expand production system/capacity to enable us to expand overseas sales and cultureware supply to new markets, aimed at generating further increase in income.
- ●Other: Promote development, OEM and consulting operations, aimed at generating further increase in income.

CellSeed's business base is cell sheet engineering, an innovative regenerative medical technology made in Japan. We engage in the development of diverse cell sheet regenerative medical products and aim to diffuse them throughout the world.
Cell sheet engineering, the very pillar of Cellseed's technologies is a fundamental technology in regenerative medicine, producing artificially in vitro cell sheets that become the basic unit of human tissue and organs but generated from individual independent cells.

Regenerative medicine using cell sheets are already undergoing clinical research involving the regeneration of various tissues. Scientific evidence indicating basic safety and efficacy in actual therapies for human subjects is beginning to emerge.
November 2014 saw the coming into force of the Act on Pharmaceuticals and Medical Devices and the Act on the Safety of Regenerative Medicine. A sea-change followed in the environment surrounding regenerative medicine in Japan, leading to great progress in the commercialization of regenerative medicine products. Capitalizing on the momentous changes in our external environment, CellSeed will unwaveringly pursue development efforts as outlined in our plan above.

(3). Business Update and Outlook, with Preconditions

Cell Sheet Regenerative Medicine Business

Ongoing Pipeline Development Activities Led by CellSeed

● Epithelial Cell Sheet for Esophageal Regeneration
Special Features: Cell sheet produced from the autologous oral mucosal epithelial cells
Indications: Prevention of esophageal stricture that develops after removal of early esophageal cancer by endoscopic surgery

Early esophageal cancers are treated today using endoscopic submucosal dissection (ESD), the localized removal of the lesion under endoscopy. ESD produces less stress on the patient's body but often results in post-operative strictures where the cancer was resected. Esophageal stricture is treated by balloon stents to widen the affected area. However, patients suffer severe pain. Also, with repeated recurrence of strictures requiring balloon expansion therapy, patient QOL deteriorates. In order to address such issues of early esophageal cancer treatment, Tokyo Women's University developed treatment using cell sheets. In this treatment, the cell sheet is produced from tissue harvested from the patient's own mouth (oral mucosa) and pasted onto the resected section. Encouraging the healing of the resected section has the effect of decreasing the frequency of esophageal strictures, alleviating physical stress after surgery.
Regarding this pipeline effort, clinical trials were initiated in August 2016 and case registration in trial institutions was completed by April 2018. No side effect was reported in the clinical trials, meaning that no safety issues were confirmed; on the other hand, the efficacy rate of the "effectiveness of stricture prevention 8 weeks after endoscopic submucosal dissection (ESD)", which was an important evaluation item, did not show statistical significance to the threshold response rate (the rate of cases of non-stenosis in patients who did not receive any treatment after ESD). Although the Pharmaceuticals and Medical Devices Agency (PMDA) confirmed safety, it deemed data on efficacy was insufficient. Accordingly, before manufacturing and sales approval can be granted, we are required to conduct an additional clinical trial to obtain and provide data that confirm efficacy,
The Guideline for Diagnosis and Treatment of Carcinoma of the Esophagus 2017 (compiled by the Japan Esophageal Society) strongly recommends as a preventive measure for stenosis after endoscopic treatment of esophageal cancer either local injection or oral administration of steroids. Steroids are now the most common treatment method used to prevent stenosis.
Steroids are recognized as inexpensive and effective means of treatment. Therefore, for our additional clinical trial, we need to register patients at risk if given steroids. We had been in consultation with PMDA regarding details concerning the subjects and the number of cases required.
In July 2020, after due consultation with PMDA, decision was reached on conducting an additional clinical trial on patients at risk if given steroids. The notification for this additional trial was given in October 2020. Application for manufacture and sales approval is scheduled to be made in FY 2025. However, as mentioned above, because we have had to restrict the trial subjects and because a greater number of cases are required than in the original trial, we need to continue reviewing the situation so as to shorten the trial timeframe by adopting such action as increasing the number of trial institutions.

● Regenerated cartilage sheet
Special features: Cell sheet produced from autologous cartilage cells and allogeneic cartilage cells
Indications: cartilage defects, osteoarthritis

Osteoarthritis is a disease where wear or deformation of the cartilage surface of a joint caused by aging, obesity, heredity, external injury and other causes result in difficulty in bending and stretching a knee due to pain. In recent years, the number of osteoarthritis patients is on the rise and it is estimated that 10 million patients suffer from subjective symptoms. Conservative therapies such as rehabilitation, orthosis treatment including joint supporters, and pharmacotherapy including hyaluronic acid injection are carried out for minor symptoms, whereas operative treatment is performed for serious symptoms. Although these treatments have a certain degree of effect, they are not a fundamental therapeutic method.
Regarding the regenerated cartilage sheet using autologous cells, we succeeded in joint research with Tokai University, our partnering institution, in generating a regenerated cartilage sheet from the patient's own cartilage tissue. The cartilage cell sheet is harvested only by means of temperature alteration, without using enzymes. The cell sheet thus retains the adhesive proteins on the cell surface, allowing it to readily graft onto the intended area. The transplanted cartilage cell sheet is thought to protect the damaged areas and to secrete proteins needed for cartilage regeneration, thereby assisting with the cartilage's own tissue repair mechanism.
The Tokai University team applied for designation of this project as Advanced Medicine with the aim of extending the indication to be investigated beyond that of its clinical development so as to collect data that is useful to sponsor-initiated clinical trial, and to include more patients of osteoarthritis. In January 2019, the application was approved by the MHLW in the 71st Conference on Advanced Medicine, as "cartilage regeneration therapy using autologous cell sheet."
In the wake of this Advanced Medicine treatment taking effect, CellSeed began in FY2020 the contract manufacture for Tokai University of regenerated cartilage cell sheets using autologous cells and have posted income from this operation.
With regard to the allogeneic regenerated cartilage cell sheet, in June 2017, the R&D topic put forward by CellSeed as lead organization was selected for the 2017 Project Focused on Developing Key Evaluation Technology: Evaluation for Industrialization in the Field of Regenerative Medicine (Developing Evaluation Methods for Industrialization in the Field of Regenerative Medicine). This was a grant project publicly advertised and funded by the Japan Agency for Medical Research and Development (AMED). In September 2018, CellSeed's R&D proposal, the establishment of manufacturing methods for the commercialization of allogeneic regenerated cartilage cell sheet (CLS2901C), was selected for the FY2018 Project Focused on Developing Key Evaluation Technology: Evaluation for Industrialization in the Field of Regenerative Medicine (Accelerated Support Project for Regenerative Medicine Seeds Development). Utilizing the contract manufacture and development business described above, we have been pursuing the development of the allogeneic regenerated cartilage sheet and researching into a system of building up cell stock. Regrettably, issues exist in medical institutions and public sector bodies as to building up cell stock, with inadequate provision for a system for collecting, storing and supplying cells. This meant an unexpected delay in obtaining necessary tissue and it was only in January 2020 when tissues became available from the National Center for Child Health and Development (NCCHD) that we were able to move forward with our research. These cartilage tissues were provided only for use for research purposes.
In December 2020, we obtained approval from the Ethics Review Committee of NCCHD for the Center to supply us with cartilage tissues collected from patients with polydactyly (congenital condition of having more than five digits on a hand or foot), leading finally to a stable source of cartilage tissue for commercial application. We are now in a position to expedite our R&D activities to start clinical trials on allogeneic regenerated cartilage cell sheets and to head towards application for their manufacture and sales approval. We hope to be able to give clinical trial notification by the end of FY2022.

Business Alliances

● Business Alliances
In April 2017, CellSeed entered into an exclusive business alliance agreement with MetaTech of Taiwan, giving MetaTech exclusive rights in Taiwan on cell sheet regenerative medicine business. Under this agreement, CellSeed received and posted the milestone payment of JPY50,000 thousand when ten cases were completed of autologous cartilage cell sheet treatment under the Cell Therapy Technology

Implementation Plan (therapy program comparable to Advanced Medicine in Japan) approved by the Ministry of Health and Welfare of Taiwan (equivalent of the Ministry of Health, Labour and Welfare of Japan). Apart from the milestone payment, CellSeed is due to receive a royalty payment from MetaTech in the order of several percent in line with sales of autologous regenerated cartilage cell sheets.
We have been promoting new business partnerships and licensing agreements in Asia, especially in China. However, although some companies with whom we have been negotiating have shown interest in items under development as with MetaTech, none had reached the final agreement stage by the end of 2020 because of factors such as differences in regulatory environment. Alongside corporate value enhancement by promoting ongoing pipeline development, we will aim to diffuse our cell sheet regenerative medicine business in Japan as well as overseas. To this end we will promote business alliance and licensing activities.

Regenerative Medicine Supporting Business

● In the regenerative medicine supporting business, we will engage in reinforcing the development of new intelligent cell cultureware paying due attention to customer requirements and new market demands. In terms of marketing, we will aim to expand the sale of temperature responsive cell cultureware and other intelligent cell cultureware. To this end, we will conduct data gathering and analysis of sales and other information from key agents in Japan and engage in joint sales activities, aiming to increase not only sales in Japan but also overseas, which showed good results as represented by the case of Thermo Fisher Scientific Inc. in FY2019 and FY2020.
At present, we are outsourcing manufacture to Dai Nippon Printing Co., Ltd. of over-the-counter products. While maintaining stable product supply, we will be improving and expanding our production system so that we can supply our products to new markets requiring mass culture of cells for research and so that we can expand overseas sales as indicated above.

● Our regenerative medicine contracting business supports regenerative medicine using our Cell Processing Facility. We not only provide contract manufacture of cell sheets as consigned by academic institutions and private companies but also promote consulting on the strength of a wide variety of knowhow stockpiled through our cell sheet regeneration medicine business, thereby pushing for more income generating opportunities.

Other

● Joint Venture Company
The joint venture company we established will undertake the research and development of regenerative medicine products and therapies using cell sheet engineering based on seeds technology that we obtain from academic and research institutions in Japan and Taiwan. In order to commercialize products and therapies, we will review applicable indications and optimize manufacturing methods. The seeds developed by Professor Yuan-Kun Tu of the E-Da Hospital of E-Da Healthcare Group is an example of such a seeds candidate. CellSeed's regenerative medicine supporting business will engage in clinical development consulting as well as manufacturing and sales approval application support. As a result of the activities mentioned above, we will be posting sales from services rendered to the JV company such as technician training and other consulting fees.

● Epithelial Cell Sheet for Corneal Regeneration
CellSeed will continue discussing with parties concerned the future development in Japan of the epithelial cell sheet for corneal regeneration.

2. FY2020 Earnings Results and Future Performance Targets

(1) Profit and Loss Targets (FY Ending December 2021 to FY Ending December 2023)

	Sales	Operating Income	Ordinary Income	Net Profit Attributable to Owners of Parent
	million yen	million yen	million yen	million yen
FY 2021 (Plan)	213	-976	-998	-998
FY 2022 (Target)	1,400	20	19	10
FY 2023 (Target)	790	-590	-590	-590

*Share of sales by segment
Regenerative Medicine Supporting Business: FY21: 173 million yen; FY22: 330 million yen; FY23: 470 million yen
Cell Sheet Regenerative Medicine Business: FY21: 40 million yen; FY22: 1,070 million yen; FY23: 320 million yen

(2) Specific policies, preconditions, and numerical bases to achieve the business forecasts and planned targets

(i) Regenerative medicine supporting business
Promote development of new Intelligent cell cultureware, on the strength of good demand trends continuing and sales increasing overseas. Reinforce collaboration with Thermo Fisher Scientific Inc. and Dai Nippon Printing Co., Ltd. to strengthen supply chain to increase income. Supply cell cultureware to new markets seeking mass cell culture. Invest in manufacturing facilities, improve and expand production system to achieve supply to these new markets to further increase income generating opportunities.
Procure more orders for the regenerative medicine contracting service. Continue contract manufacture orders in advanced medicine from our partnering institution Tokai University (maximum 20 cases).

(ii) Cell sheet regenerative medicine business
● Regenerated cartilage sheet
Allogeneic cells
Complete technology transfer from clinical research partnering institution, Tokai University (completion of transfer scheduled in FY 2021).
Propel development effort to consolidate commercial cell stock manufacturing methods and to automate cell sheet manufacture.
Give clinical trial notification at the end of FY 2022.
● Epithelial cell sheet for esophageal regeneration
FY 2020 Clinical trials notification already given.
FY 2021 to FY 2024 Continue ongoing sponsor-initiated trial.
FY 2024 Complete sponsor-initiated trial (Submit manufacturing and sales approval application in FY 2025).
● Business alliances
Continue support of our partner MetaTech. JV company set up in Taiwan with MetaTech and CellSeed as key investors and step-up development activities for commercialization. Form new alliances with Asian companies including Japanese as well as European and American companies during the three years of this mid-term business plan.

(iii) Companywide issues
● Human resources
Regenerative medicine products R&D requires human resources with a wide range of expert skills. Cell sheet regenerative medicine is highly interdisciplinary, involving engineering, cell biology and

chemistry, making it essential to employ and train specialist and diverse human resources. Because CellSeed intends to intensify focus on joint development and business startup in Taiwan through setting up the Taiwanese JV company, in addition to our existing partnership with MetaTech, we will direct our effort into securing human resources who can be global players as well as be effective members in Japan.

- Financial resources

  As for capital necessary in the future, we will not only apply the existing funds in hand but also raise money flexibly using public financial support and subsidies, and deploy a wide range of measures such as financial approaches including equity finance and borrowing from financial institutions.

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