Featured Articles

Regenerative Medicine Solutions

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OVERVIEW: There are growing expectations throughout the world for the practical commercialization of regenerative medicine, a new field of medical technology that can cure or restore function to diseased parts of the body by transplanting tissue or cells processed using advanced cell culture techniques that use cells as raw materials. Encouragement for commercialization is also anticipated in Japan where regulations on regenerative medicine came into force in November 2014. Hitachi already offers a wide range of in-house resources for cell production, including equipment and facilities, information systems, and services. In the future, in addition to the marketing of resources from within the group, Hitachi will also consider joint development with customers or collaborating with other companies if needed, aiming to adopt a "One Hitachi" approach to deploying a wide range of regenerative medicine solutions that can take on the challenges faced by customers. Hitachi also plans to play a part in the development of the regenerative medicine industry through extensive collaboration with industry organizations, companies, and other groups associated with the field.

INTRODUCTION

CELLS are the basic units of the human body. Regenerative medicine is a new field of medical technology that makes it possible to restore function to diseased parts of the body by transplanting tissue or cells processed using advanced cell culture techniques that use cells as raw materials. There are growing expectations around the world for the commercialization of regenerative medicine, which can fully cure, at the cellular level, disease sites that have proven difficult to treat in the past, with numerous researchers having reported its highly therapeutic effects[(1)]. In Japan, cultured skin and cultured cartilage are already commercially available, being marketed as "regenerative medicine products," with extensive use of cancer immuno-therapy being led by doctors. Close to 90 regenerative medicine projects have reached the clinical research or clinical trial stage, and Japan is leading the world in establishing a legal framework that encourages commercialization.

The importance of cell culturing and other cell processing techniques will grow in the future as regenerative medicine enters wider clinical use. Hitachi is already involved in research, development, and manufacturing of equipment, facilities, and systems for cell culturing, utilizing technologies built up through its work in fields such as manufacturing equipment for medicine or semiconductors. This article describes the regenerative medicine solutions supplied by Hitachi, beginning with an overview of the field.

CHANGES IN CIRCUMSTANCES SURROUNDING REGENERATIVE MEDICINE

Act to Ensure Safety in Regenerative Medicine and Revised Japanese Pharmaceutical Affairs Law

Under the previous legal framework for regenerative medicine in Japan, clinical research and elective treatment were dealt with by the Medical Practitioners Law and Medical Service Law (human stem cell guidelines where applicable[(2)]), and regenerative medicine products by the Pharmaceutical Affairs Law[(3)] (use of medical devices). Since November 2014, this has changed such that clinical research and elective treatment are now regulated by the Act to Ensure Safety in Regenerative Medicine[(4)] and regenerative medicine products are now regulated by the Revised Japanese Pharmaceutical Affairs Law[(5)]. The changes give Japan a legal framework that is at the forefront globally (see Fig. 1).

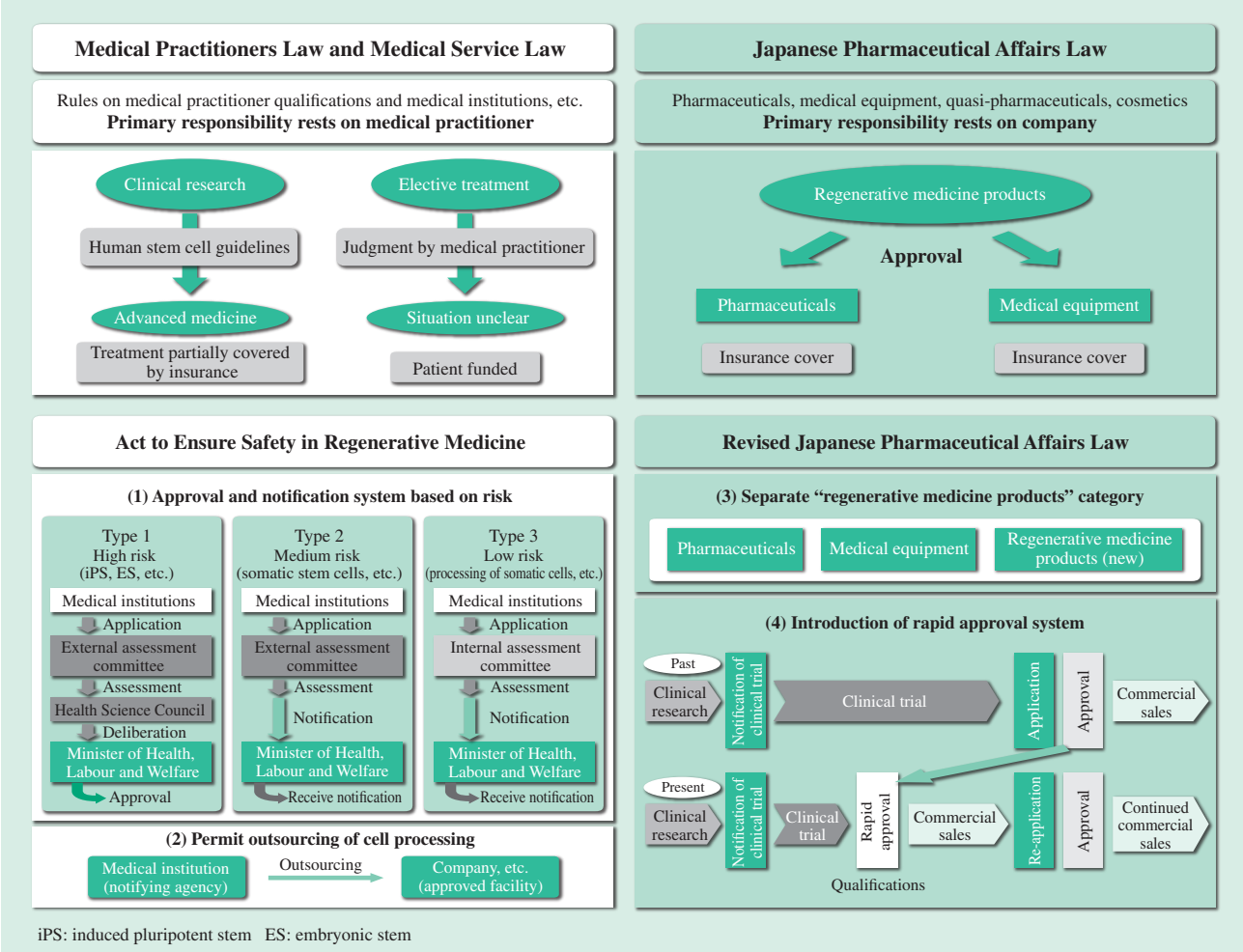

Fig. 1—Act to Ensure Safety in Regenerative Medicine and Revised Japanese Pharmaceutical Affairs Law.
The law on regenerative medicine in Japan came into force in November 2014. The key differences from the previous legal framework are: (1) steps to deal with risks, (2) outsourcing of cell processing, (3) a new "regenerative medicine products" category, and (4) a conditional approval system for clinical trials.

Major features of the Act to Ensure Safety in Regenerative Medicine include the following two provisions aimed at ensuring the safety of regenerative medicine in clinical research and elective treatment.
(1) An obligation to take steps to deal with the risks associated with the material (cells, tissue, etc.) used in transplants
(2) The ability to outsource cell processing

Similarly, the following two provisions are major features of the Revised Japanese Pharmaceutical Affairs Law.
(3) The addition of a "regenerative medicine products" category to the existing pharmaceuticals and medical equipment categories
(4) The creation of a conditional approval system for clinical trials

The first, third, and fourth of these provisions relate to the commercialization of regenerative medicine products. The second provision relates to the efficiency of cell processing, and because it allows medical institutions to outsource cell culturing, it is anticipated that the construction of a seamless infrastructure encompassing equipment and instruments, transportation, and information systems will become important in the future in order to ensure that medical institutions can obtain a reliable supply of cells, tissue, and other material produced for use in regenerative medicine.

Forum for Innovative Regenerative Medicine

The Forum for Innovative Regenerative Medicine (FIRM)[6] was formed in 2011 to get the regenerative medicine industry established. Interest in regenerative medicine within the Japanese industry is high, with the number of FIRM member companies growing rapidly to more than 100 companies (as of November

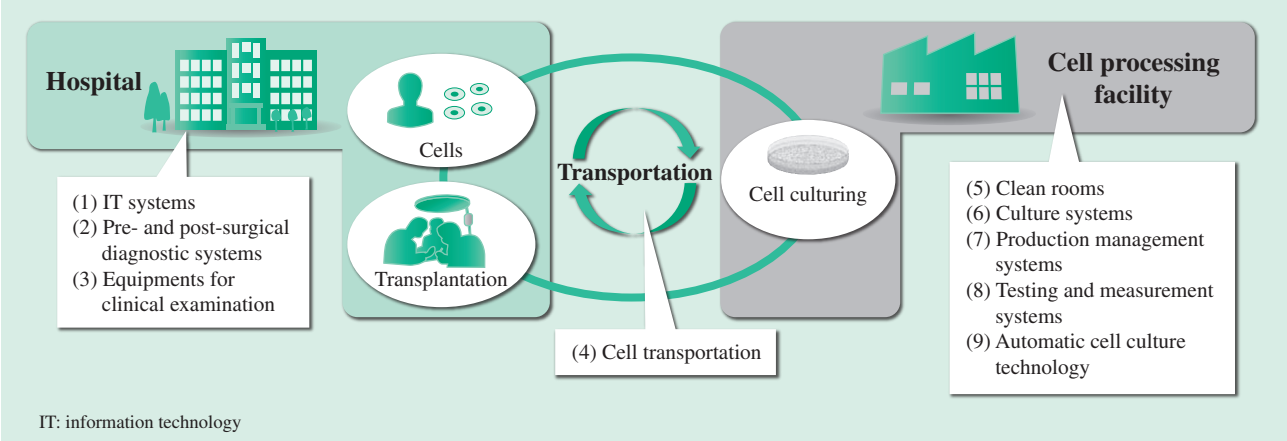

Fig. 2—Hitachi's Existing Involvement in Regenerative Medicine.
Hitachi has been engaged in a wide variety of businesses that relate to cell processing for regenerative medicine in the fields indicated by (1) to (9) in the figure. These activities have not included medical practices such as cell harvesting and transplantation.

2014). FIRM is divided into a Regulatory Committee, a Medical Economics Committee, a Public Relations Committee, a Business Planning Committee, a Standardization Committee, and a Supporting Industries Committee. As yet, regenerative medicine has few common standards (or guidelines), so the current practice is for each company to adopt its own. Accordingly, the Supporting Industries Committee has set up five working groups (equipment and instruments, automated cell culture systems, materials and samples, reagents and culture medium, and transportation), which are working toward equipment standardization. Hitachi is helping provide leadership to the regenerative medicine industry with a deputy chairmanship role at FIRM (as of November 2014).

PAST WORK BY HITACHI ON REGENERATIVE MEDICINE

Drawing on the capabilities of its group companies, Hitachi has been involved in work on regenerative medicine in a wide variety of areas (see Fig. 2).

Regenerative medical treatments typically involve the transportation of cells harvested from a patient or donor from the hospital to a cell processing facility (CPF)[*1]. At the CPF, the cells are cultured and processed by specialist technicians or automated cell culture systems in accordance with the legal requirements for cell processing, and subjected to the tests required for transplantation. The necessary cell processing equipment is used for this cell culturing and processing. The cells are then transported back to the hospital for transplanting into the waiting patient. After transplanting, the effect on the diseased body part is monitored using in vitro diagnostic systems.

Hitachi operates businesses that are associated with this sequence of steps, and conducts research and development into the required technology[(7)–(9)]. The following sections describe details of the CPF, equipment used at the CPF, a process management system for cell culturing, and cell transportation.

Cell Processing Facility (CPF)

Because cells, tissue, or other material processed at a CPF are inserted or transplanted directly into a patient's body, the products must be sterile. The regulations stipulate numerous requirements, including that facilities have the necessary mechanisms and equipment to supply clean air and maintain pressure differences where appropriate. There are also many regulations relating to operation and maintenance management. It is necessary to provide facilities that can comply with these requirements while also operating smoothly and controlling costs[(10), (11)].

The CPF includes rooms for cell preparation that enable work to be done aseptically, cell culturing, cell frozen storage, gowning rooms, instrument sterilization, and administration, and also utilities for supplying things like carbon dioxide gas and liquid nitrogen (see Fig. 3). At CPFs that handle cells that potentially contain pathogenic material, biosafety rooms are provided that are kept at negative pressure to prevent any escape of hazardous material. In addition to appropriate control of pressures in each of these many rooms to maintain cleanliness, it is also necessary to prevent the dispersal of contaminants.

*1 Also called a cell processing facility (CPF).

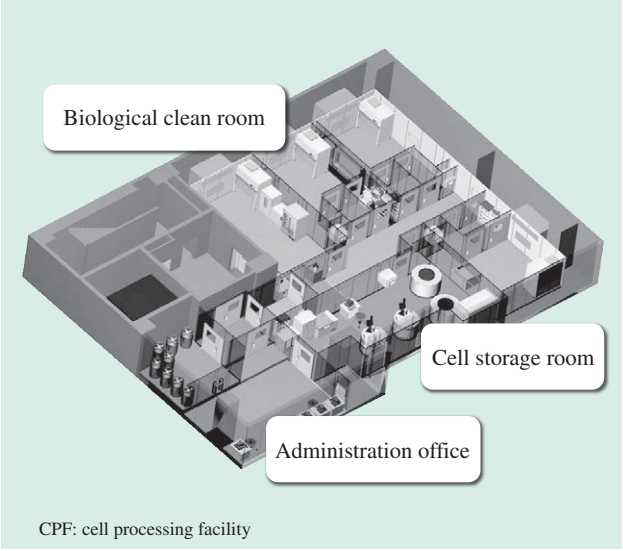

Fig. 3—Example Layout of CPF.
Efficient operation is combined with cost control and compliance with regulations.

With over 40 years of experience in the design and construction of medical and other facilities that require a high level of cleanliness, such as pharmaceutical and semiconductor plants, Hitachi Plant Services Co., Ltd. has a variety of technologies that are suitable for CPFs that possess the characteristics described above. For example, it provides reliable control of room air pressure using low air flow volumes thanks to the development of a simulator that accurately predicts fluctuations in the air pressure inside rooms resulting from factors such as changes in atmospheric pressure (such as during low-pressure weather systems) or the opening and closing of doors[12]. In the field of regenerative medicine, the company has further developed these technologies since supplying a CPF to the Donated Blood Distribution Foundation in 2004, during which time it has also supplied CPFs to numerous universities, organizations, private-sector companies, and medical institutions (see Fig. 4).

It also supplies solutions across the CPF life cycle, covering assistance with the preparation of documents for submission to regulatory agencies, equipment maintenance, and performance testing performed by conducting periodic re-validation.

Fig. 4—CPF Interior.
This scene from the Yotsugi CPF of the Donated Blood Distribution Foundation shows preparation work, which is performed in a safety cabinet in an environment-controlled room with 10 or fewer airborne microbes per cubic meter.

Equipment for Cell Processing

Cell manipulation (seeding, processing, passage, culture medium replacement, and so on) is an important process when culturing cells for regenerative medicine and must be performed in an environment that has an appropriate level of sterility (a "sterile environment"). Typically, regenerative medicine requires an environment that satisfies the International Organization for Standardization (ISO) class 5 level of sterility. The main items of equipment used to achieve this level of sterile environment at cell culture facilities are biohazard safety cabinets (see Fig. 5) and isolators.

Fig. 5—Equipment for Cell Processing.
Biohazard safety cabinets like this are used at cell processing facilities to support regenerative medicine.

A feature of both types of equipment is that they are designed to prevent air inside the equipment from leaking into the external environment while also maintaining a sterile environment to perform manual cell manipulation. Biohazard safety cabinets are open at the front and use an air barrier to keep the work environment sterile, while preventing cells, culture medium, and other material from leaking out of the cabinet. Hitachi Industrial Equipment Systems Co., Ltd. jointly developed the first biohazard safety cabinets in Japan with the National Institute of Infectious Diseases (previously the National Institute of Health), and currently supplies products that incorporate this technology according to customer needs for use in regenerative medicine. Isolators, on the other hand, enable cell manipulation to be performed in a sealed environment, using a clean air supply and disinfection (including decontamination) to maintain a sterile work environment and to prevent leaks into the surroundings.

Cell manipulation often involves using a centrifuge to separate and purify particular cells. Hitachi Koki Co., Ltd. produces centrifuges for use in regenerative medicine. It also supplies other cell processing equipment, including air conditioning systems such as pass boxes and air showers, and various testing equipment.

The Central Research Laboratory, Hitachi, Ltd. has developed an automated cell culture system for corneal and esophagus regeneration and a large-capacity culture system for heart muscle regeneration to automate the process of cell culturing, which is currently performed manually, and boost productivity by enabling 24-hour operation[13)–20)]. A feature of these automated cell culture systems is their advanced design that minimizes the risk of contamination or cross-contamination by unwanted microorganisms and enables cell culturing to be performed safely by using single-use closed designs for the culture vessels, flow paths, and other places where cell culturing takes place. The automated cell culture system for corneal and esophagus regeneration can produce cell sheets. The large-capacity culture system for heart muscle regeneration has a culture area of roughly 2.4 m^2 and a passage function (for sub-culturing cells to increase their number) that can achieve 1,000-fold growth in the number of cells. Utilizing the technologies developed through this research, Hitachi aims to achieve safe and reliable automated culturing that operates in tandem with CPF, cell processing management, and other systems.

Process Management System for Cell Culturing

Regenerative medicine facilities require production and quality management at a similar level to that provided by manufacturing management systems for pharmaceuticals. Most pharmaceutical manufacturers today make extensive use of manufacturing execution systems (MESs) to achieve rigor and efficiency in their production processes.

Hitachi Pharmaceutical Manufacturing Execution System (HITPHAMS), Hitachi's MES designed specifically for pharmaceutical manufacturing, has been installed at numerous sites since it was first released in 1995[21), 22)]. Intended to improve the efficiency of manufacturing management and the reliability of product quality at pharmaceutical manufacturers, the HITPHAMS system complies with not only current pharmaceutical regulations but also new regulations on regenerative medicine, companies involved in regenerative medicine have started to look at installing it. The following are some of the functions it provides (see Fig. 6).

The main functions of HITPHAMS are the management of manufacturing instructions and record-keeping. Other manufacturing-related functions include inventory management of cells and reagents, tracking and tracing, and storage management. Intended for a specific recipient only, regenerative medicine products require strict inventory management. Efficient record-keeping and the prevention of errors during production are achieved by providing interactive devices at the workplace to perform reliable on-the-spot checks during production.

The system is built on the Microsoft*2 .NET Framework and is not tied to any particular version of Windows*2. To satisfy customer needs, it can also be used from tablet computers and other portable devices. This means that it can adapt flexibly to processes that are specific to regenerative medicine by, for example, displaying detailed operating procedures and enabling the efficient on-site entry and recording of work records.

Cell Transportation

Hitachi has developed and trialed a constant-temperature cell transportation container for use in regenerative medicine[23)–26)]. The development was undertaken primarily by its research laboratories in collaboration with Hitachi Transport System, Ltd. With the adoption of the new law, Hitachi anticipates rapid growth in

*2 Microsoft and Windows are either registered trademarks or trademarks of Microsoft Corporation in the United States and/or other countries.

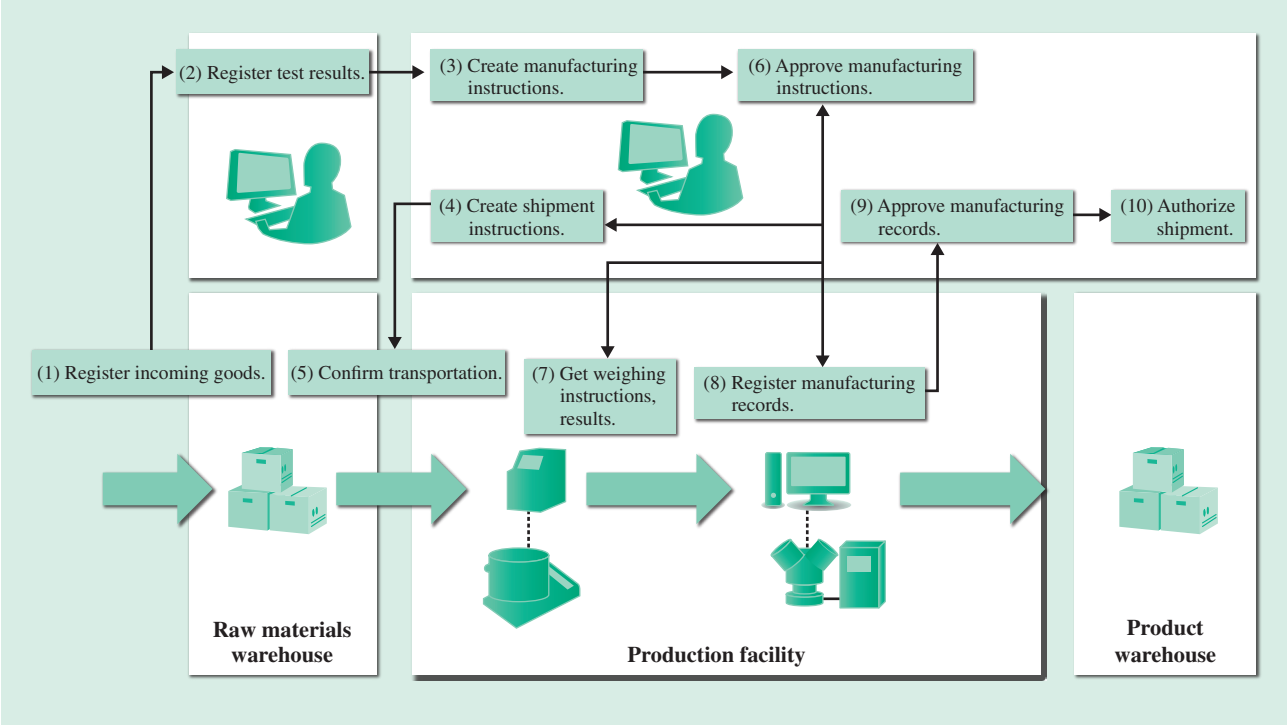

Fig. 6—Overview of HITPHAMS Functions.
Functions for managing incoming goods, manufacturing instructions, inventory, quality, test results, and shipment authorization ensure efficient production of regenerative medicine products with more reliable quality.

demand for reliable cell transportation from third party providers. However, because the transportation industry lacks standards (or guidelines) for cell transportation, each provider currently follows its own practices.

Hitachi plays a leadership role in the transportation working group of the Supporting Industries Committee of FIRM and is seeking to coordinate the formulation of guidelines by the transportation industry. Once in place, this should facilitate providing safer and less expensive cell transportation by enabling the resolution of issues of concern, such as quality assurance (minimizing changes in quality during transportation), preventing accidents (minimizing the risk of harm to transportation providers and others), and expanding the transportation market and the production of transportation goods (by ensuring consistent quality when activities are outsourced). Including these industry activities, Hitachi's aim is not just to supply its cell transportation containers, but also to establish a cell transportation service that suits customer needs.

REGENERATIVE MEDICINE SOLUTIONS THAT HITACHI AIMS TO SUPPLY

Hitachi's existing business consists primarily of equipment for the manufacturing of biopharmaceuticals (including antibody drugs and vaccines), equipment and instruments for regenerative medicine, and equipment for diagnosis, testing, and treatment at hospitals and other medical institutions. In the regenerative medicine sector in particular, Hitachi's past practice has been to market its equipment and instruments to customers as standalone products. Hitachi established its Healthcare Company in April 2014. In addition to taking a customer's perspective to marketing regenerative medicine resources from across the group (including equipment, systems, and services), Hitachi is also working on operation and maintenance services, joint development proposals, and collaborations with other companies. Based on its existing businesses, the company aims to take a "One Hitachi" approach to supplying pharmaceutical companies and others such as research institutions that work on regenerative medicine with a wide variety of regenerative medicine solutions designed to confront the issues customers face.

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