Featured Articles

Plant Solutions for Next Generation Biopharmaceuticals and Regenerative Medicine

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OVERVIEW: There has been an increase in plans for new facilities in the pharmaceutical manufacturing industry over recent years in anticipation of developments such as the rising level of capital investment prompted by ongoing technical innovation and rapid growth in the market for biopharmaceuticals, and the introduction of regenerative medicine using iPS cells and similar on a commercial scale. Hitachi is contributing to the supply of equipment that delivers a high level of safety and security, having gained many years of experience in optimizing and enhancing the efficiency of such facilities and improving their productivity and quality.

INTRODUCTION

BIOPHARMACEUTICALS with more sophisticated functions than low-molecular-weight drugs have been an active area of development in recent years, accounting for the largest share of per-drug sales by value. Regenerative medicine, meanwhile, which uses cells directly, is being put to a wider range of uses and the field is recognized for its potential applications in treating illnesses that do not respond well to drugs.

Hitachi's plant solutions business has a large share of the market for biopharmaceutical and regenerative medicine plants in Japan, with these being the mainstays of Hitachi's pharmaceutical plant business.

This article gives an overview of the equipment used in these plants and describes Hitachi's activities in the field.

PLANT SOLUTIONS FOR HEALTHCARE SECTOR

Hitachi's industrial equipment business has experience supplying a wide variety of equipment for chemical, chemical synthesis, food, gas, and other plants. The pharmaceutical plant business supplies important solutions by building the equipment used to produce pharmaceuticals that account for a large part of the healthcare market. The pharmaceutical market is valued at 10 trillion yen in Japan and 100 trillion yen globally, with the manufacture and sale of pharmaceuticals continuing to rise in both markets, and with further growth anticipated.

The pharmaceutical plants supplied by Hitachi include plants for biopharmaceuticals, synthetic pharmaceuticals, solid preparations, aseptic pharmaceutical production, and regenerative medicine. Among these, Hitachi has held a large share of the Japanese market for biopharmaceutical and regenerative medicine plants in recent years, both markets where further growth is anticipated, and it is in these types of pharmaceutical plants that Hitachi sees itself as having particular expertise. These plants have the following four characteristics.

(1) Even small variations in the production process or small deviations from standard conditions can influence the quality, yield, and level of impurities in the pharmaceuticals produced.

(2) Because many of the drugs have large molecular structures compared to the sort of pharmaceuticals produced by chemical synthesis, or a large degree of structural variability, there is a limit to how far consistency can be verified.

(3) Side effects or other problems may occur unless adequate measures are taken to prevent or eliminate impurities and contamination.

(4) A high level of investment in production equipment is needed to ensure high quality.

As a variety of technologies are needed to overcome these problems, considerable research, development, and other work is being undertaken.

Hitachi has been engaged for many years in research and development and in the acquisition of know-how about how to deal with these problems. The results of this work are incorporated into the plants it supplies, with many such examples in operation. Hitachi is also pressing ahead with further research and development to acquire new technologies. The following 10 technologies are past examples of such work:

(1) Technologies for achieving and maintaining sterile conditions
(2) Cleaning techniques
(3) Culture productivity improvement techniques
(4) Culture process simulation techniques
(5) Technologies for metabolic analysis of culture processes
(6) Technologies for virus inactivation
(7) Development of technology for improvements to purification equipment
(8) Development of technology for single-use equipment
(9) Technology for containment and maintaining a clean environment
(10) Modularized equipment configuration techniques

Hitachi is seeking to use these technologies for things like making enhancements and improving accuracy.

WORK ON BIOPHARMACEUTICAL PLANTS

Hitachi has supplied more than 200 pharmaceutical plants to date, including the fabrication of more than 500 fermenters, a key item of equipment in biopharmaceutical plants.

The production of biopharmaceuticals (antibody medicines and vaccines) consists of a culturing step that uses animal or other cells in which the desired product is produced by biological reactions, and a purification step during which the purity of the product is improved. Because the fermenter has a major influence on plant productivity, its design and manufacture is crucial.

The culturing step typically starts with the cells being cultured in flasks and then gradually scaled up to the scale of 5,000 to 10,000 L. As this up-scaling results in significant changes to the culture environment in the fermenter, when building commercial-level production equipment, it is essential that the design gives adequate consideration to the factors that influence productivity. Fig. 1 shows a high-volume cell culture system in the 10,000-L range.

Hitachi uses computational fluid dynamics (CFD) for fermenter simulation in order to design suitable fermenters. The simulation performs a predictive analysis of factors that influence cell multiplication, such as the stirrer shear force, uniformity of mixing, and the appropriate gas exchange in the fermenter, and compares the results against the flask-scale experimental data provided by the customer to determine the cell multiplication characteristics and appropriate culturing conditions so that this information can be incorporated into the equipment design to improve productivity.

Furthermore, a high level of sterilization and cleaning are needed to ensure process stability during the culturing step. In the case of a large biopharmaceutical plant, there may be upwards of 1,000 valves that need to be operated correctly to perform sterilization and cleaning. To achieve this operation, Hitachi uses control techniques based on the use of a distributed control system (DCS). When developing the software, Hitachi automates the process and maintains product quality without cross contamination by ensuring it fully understands things like equipment characteristics and customer cleaning procedures, and offers operating practices that are based on sterilization and cleaning mechanisms that derive from scientific principles.

Given the innovative nature of biopharmaceuticals, they are increasingly becoming recognized throughout the world for their potential to protect people's health through benefits such as treating difficult diseases and preventing infection. Hitachi intends to continue contributing to the enhancement of plants through work on improving the productivity and quality of biopharmaceutical manufacturing technology.

Fig. 1—High-volume Cell Culture System.
This high-volume cell culture system (supplied by Hitachi, Ltd.) is used for the production of antibody drugs.

TECHNOLOGY DEVELOPMENT BY MAB

The Manufacturing Technology Association of Biologics (MAB) was established in September 2013. Initially made up of 29 organizations (24 companies, two associations, one independent administrative corporation, and two universities), another company has since joined, giving it a current make up of 25 companies, two associations, one national research and development agency, and two universities. Toshiaki Higashihara, President & COO of Hitachi, Ltd. has served as director since the association was formed.

MAB is an "all-Japan" organization that consolidates Japanese know-how for the manufacture of the next generation of biopharmaceuticals and other products. Its aims are to establish the industrial technology for the manufacture of the next generation of antibody drugs and other products in accordance with international standards and to deploy international business models for personalized medicine.

The main research topics being worked on by MAB fall into the following five categories.

(1) Development of technology for establishing production cell cultures

(2) Development of high-performance cell culturing techniques

(3) Development of advanced downstream technologies

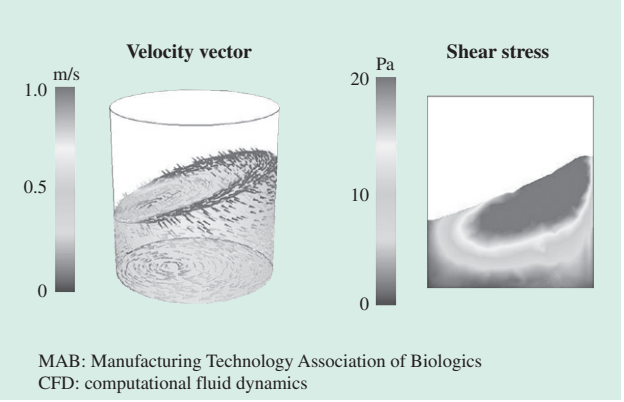
(4) Development of advanced quality assessment techniques

(5) Establishment of technologies for creating the next generation of platforms that comply with international standards

Hitachi plays a central role in the association, working on the second and third of these categories.

In the case of high-performance cell culturing techniques in particular, Hitachi is working in collaboration with its own Research & Development Group (previously the Hitachi Research Laboratory) to utilize its expertise in CFD analysis (see Fig. 2) to participate in the design stage of the next generation of single-use culturing systems being built by other association members for screening, process investigation, and production, making a major contribution to improving the performance and reliability of the products being developed.

MAB has set up the Kobe Good Manufacturing Practice (GMP) facility in an annex building at the Integrated Research Center of Kobe University, Kobe City, and is working on product developments that outperform products from overseas suppliers like "Company G," "Company M," and "Company Z" that are already on the market. Hitachi is the only member of MAB that is a pharmaceutical plant manufacturer and, through the provision of its know-how, is making a major contribution to these activities, which are being conducted under an "all-Japan" organizational structure. In the future, Hitachi aims to expand its plant solutions business by utilizing the various forms of knowledge acquired at MAB and the strong "pipes" that connect it with association members.



MAB: Manufacturing Technology Association of Biologics
CFD: computational fluid dynamics

Fig. 2—CFD Analysis of Production Fermenter.
As part of the development of the next generation of 200-L class single-use production fermenters in collaboration with other companies that belong to the MAB, Hitachi used CFD analysis to verify product performance and reliability improvements.

WORK ON REGENERATIVE MEDICINE PLANTS (CPCs)

Regenerative medicine involves the process of culturing cells or tissue for transplanting into a patient and is recognized for its potential to treat conditions that do not respond well to drugs. Until recently, regenerative medicine in Japan involved providing treatment under the Medical Practitioners Law and production under the Pharmaceutical Affairs Act, but the number of manufacturing facilities has been growing since the passing of the Act on the Safety of Regenerative Medicine and the Pharmaceutical and Medical Device Act in November 2014, establishing the conditions for cell and tissue production. While the market is a small one compared to that for pharmaceutical plants, Hitachi has been supplying plants and equipment for production and research use since 2004.

The plants that produce regenerative medicine products are called cell processing centers (CPCs). A CPC cultures harvested cells over a period of several weeks or months in an incubator kept at a temperature of around 37ºC. During this period,

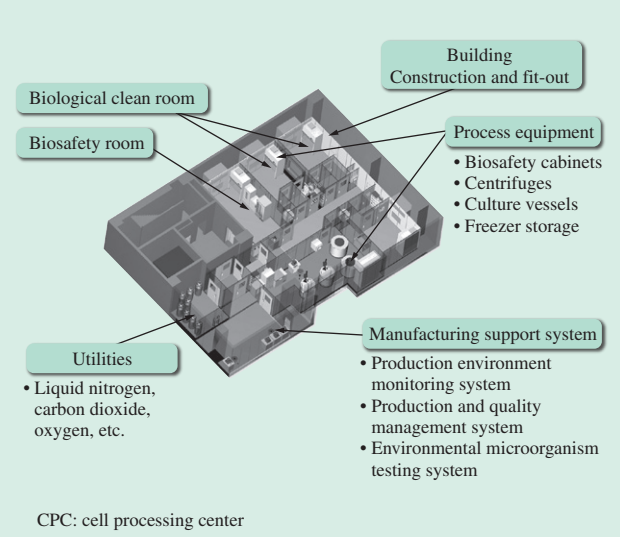


Fig. 3—Example CPC Layout.
CPCs have a large number of rooms. It is important to manage things like cleanliness and air pressure to maintain the environment in the cell handling laboratory (biological clean room).

Fig. 4—CPC Test Facility at Matsudo Research Center.
A variety of development work is conducted to reduce the risk of product contamination and improve staff work environments.

culture vessels are taken out of the incubator for cell processing operations such as replacing the culture medium, sub-culturing (transferring a portion of cells to a different vessel), or selection. The cells or tissue cultured by this process (in the form of tissue sheets, for example) are cleaned and then packaged in a sterile container for delivery. This end product is sent to a medical institution for transplanting into the patient. These processes need to be performed in a controlled environment to minimize the risk of contamination by microorganisms or other sources.

However, many cell processing operations depend on manual techniques such as the use of pipettes and are often performed inside a biosafety cabinet. Accordingly, cell handling laboratories fitted with biosafety cabinets are commonly set up as ISO 6 biological clean rooms. CPCs are made up of a number of rooms. In addition to the cell handling laboratory, these include a cell storage facility, a packaging room, a sterile room, a gowning room, and an airlock to prevent the entry of contaminated air. They are also augmented by utilities such as a carbon dioxide supply, for example (see Fig. 3). A key factor in the design of these facilities is to prevent staff, materials, and air from acting as carriers, bringing contaminants such as microorganisms into the cell handling laboratory.

Hitachi Plant Services Co., Ltd. has supplied numerous CPCs to universities, organizations, private companies, and medical institutions since delivering its first CPC to the Donated Blood Distribution Foundation in 2004. These customers include medical institutions that transplant cells cultured in a CPC into patients. With regenerative medicine having become a recognized industry over the last few years, there are examples of private companies conducting clinical trials of regenerative medicine and related products and obtaining preliminary approval for their use. Hitachi has provided support to companies that have purchased its equipment to help them obtain the approvals they need for production.

Technology development aimed at minimizing the risks associated with CPCs is also ongoing. Fig. 4 shows a CPC constructed at the Matsudo Research Center of the Infrastructure Systems Company of Hitachi, Ltd. This CPC is equipped with the ability to spray microbes or admit contaminated air, enabling its use for risk assessment in various different situations. One risk with a particularly large impact is the entry of contaminated air into the cell handling laboratory due to a fault in the air conditioning used to control the air pressure in various rooms. Disruption of air pressure can also occur due to switching over to the backup system in the event of a power outage. Hitachi is developing a pressure differential simulator that can consider a wide variety of situations, such as low external air pressure during a typhoon. This ensures that ducting, equipment, door interlocks, and so on are designed correctly.

While this article has focused on production facilities, Hitachi is active in a wide range of areas aimed at ensuring the success of customer businesses, supplying comprehensive solutions that include biosafety cabinets, isolators, and other production equipment; production management systems that minimize human error and facilitate management; and cell transportation.

CONCLUSIONS

The healthcare sector is anticipating significant growth in the market for biopharmaceutical and regenerative medicine plants, a field that can contribute to the safety and security of society through the supply of high quality products. Hitachi intends to continue paying close attention to the requirements for these plant solutions as it aspires to deliver the best possible equipment.

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