CONTINUOUS MANUFACTURING DEVELOPMENT IN PHARMACEUTICAL AND FINE CHEMICALS INDUSTRIES

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SUMMARY

- In the pharmaceutical and fine chemicals industries, the shift from the conventional batch manufacturing system to the continuous manufacturing method is gaining momentum. The advantages of continuous manufacturing include an increase in efficiency (productivity, economy), enabled through the maximized automation by the unit operations interconnection; enhanced product quality and safety by a continual automated monitoring of processes; environmental impact reduction by decreasing waste, through a high rate of reaction efficiency; and space saving owing to the compact size of the equipment.
- To realize continuous manufacturing, it is essential to develop new catalysts and processes to replace batch reactions with continuous ones, and to develop sensor technologies that help achieve advanced continual monitoring. Among sensors, drawing attention is the development of virtual measurement technologies, called soft sensors, which fully leverage simulation technology to estimate data that is difficult to obtain through actual measurements.

1. FACTORS BEHIND THE RISING MOMENTUM TOWARD CONTINUOUS MANUFACTURING

In the pharmaceutical and fine chemicals fields, the basic approach to production has been the batch manufacturing method, characterized by the sequential arrangement of large tanks that are managed individually for each process, while continuous manufacturing, such as that seen in large plants for manufacturing chemical products, had not been widely incorporated. Continuous manufacturing is a flow production method used to produce or process products without interruption by constantly supplying raw materials while the manufacturing process is underway.

In the pharmaceutical industry, the transition from batch to continuous manufacturing had not picked up momentum so far. This is because, in the high value-added pharmaceuticals domain, sufficient revenues can be ensured with batch methods, and there was little need to make the switch, which would require additional capital investment, as long as there were no problems with the product quality or manufacturing process.

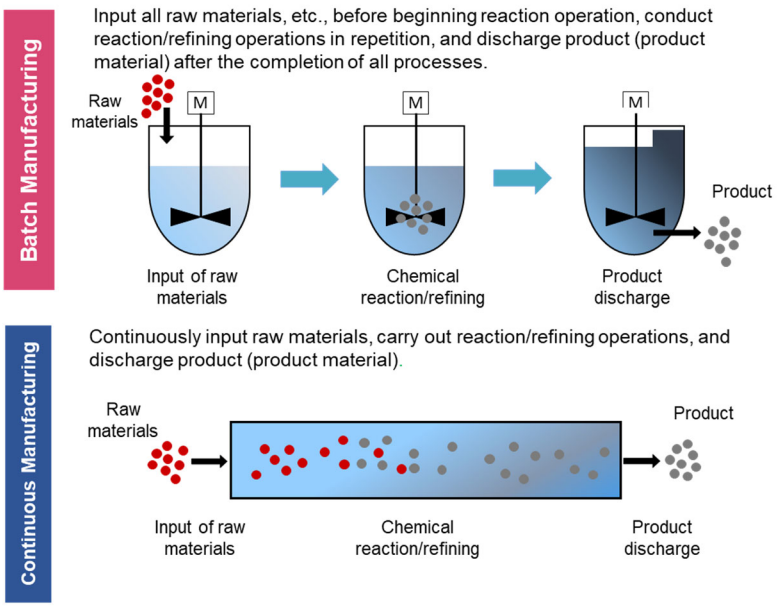
However, in the mid-1990s, a problem with product quality came to light in the US, where defective products of batch-produced pharmaceuticals were released into the market and developed into a public issue. In addition, the lack of production volume adjustment function has been pointed out as a disadvantage of batch manufacturing, and this fueled the momentum toward a switch to a continuous manufacturing system, which allows for the production of the required volume when needed. The US Food and Drug Administration's (FDA) industry guidance issued in 2004 included recommendations for the use of continuous manufacturing for pharmaceuticals, and in 2018, the adoption of continuous manufacturing by the pharmaceutical and fine chemicals industries went so far as to be mentioned as an important issue in its national strategy (Strategy for American Leadership in Advanced Manufacturing).

2. WHAT IS CONTINUOUS MANUFACTURING?

Advantages of Continuous Manufacturing

The conventional batch manufacturing method is one in which raw materials are input into a piece of production equipment, and the produced output is collected in one go after the completion of each specific unit production operation. In this method, since operations are stopped for each separate process, such as raw material input, manufacturing (chemical reactions, refining), and product discharge, operations tend to be complicated and labor intensive (Figure 1).

Figure 1: Schematic of batch and continuous manufacturing



Source: Created by MGSSI

On the other hand, continuous manufacturing is a production method in which raw materials are continuously injected into a manufacturing facility, and products are discharged continuously during the period in which the production processes are in operation. In this method, multiple processes are automatically controlled, contributing to simplifying the overall operation and reducing the workload requirements for human operators.

The advantages of continuous production include an increase in efficiency (productivity, economy), enabled through the maximized automation by the interconnection of unit operations (such as chemical reactions, refining, and crystallization); enhanced product quality and safety due to a continual automated monitoring of processes; environmental impact reduction by decreasing waste through a high rate of reaction efficiency; and space saving owing to the compact size of the equipment. Although the amount of capital investment will be higher than batch manufacturing, the operating costs reduction is expected to improve the overall economic efficiency of the business (Figure 2).

Figure 2: Features of batch production and continuous production

	Batch Manufacturing	Continuous Production
Raw material input/ Product output	Raw materials are injected into the process operation non-continuously, and the product (product material) is discharged collectively after the operation is completed.	Raw materials are injected into the process operation continuously, and the product (product material) is discharged continuously and sequentially after a certain time.
Production processes	Each operation is started and stopped repeatedly by operator handling.	Production is continuous through interconnected unit operations and automation without operator management.
Production facility area	Large space needed	Space saving
Scaling-up	Individual verification processes and dedicated equipment are needed for each scale at the stage of development and validation, and different equipment is needed for commercial production.	Equipment required for development can be designed in line with actual production, and a quick transition to commercial production is possible by simply adjusting the production time.

Source: Created by MGSSI based on the Pharmaceuticals and Medical Devices Agency's (PDMA) publication on its approaches to creating innovative technologies

In addition, by adjusting the production time, the required amount can be produced on demand without waste. The method thus offers significant advantages to the overall pharmaceutical product manufacturing operation, including product storage and distribution.

As the production volume can be adjusted, the same equipment can be used both for the development and production, meaning that, in general, scale up processes are unnecessary when moving on to the commercial production phase. This translates into a reduction of the time and costs involved in equipment development for new drugs.

Attention Turned to Elemental Technologies for the Realization of Continuous Manufacturing

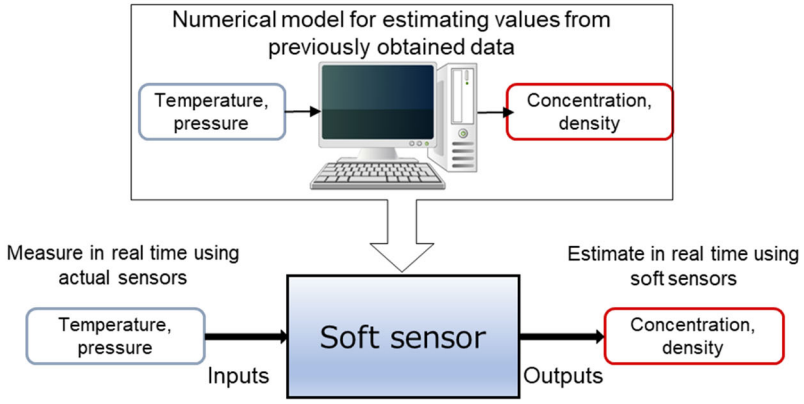
Given that batch and continuous manufacturing have different reaction mechanisms, the first step in achieving continuous manufacturing in pharmaceutical manufacturing is exploring process parameters, such as optimal catalysts for continuous manufacturing, temperature and pressure levels, and reaction vessel shapes that can maximize production efficiency.

Also, because production cannot be stopped in a continuous manufacturing system, measurement technologies for real-time monitoring of the reactions state during the processes play an important role. Back in the first half of the 2000s, when the pharmaceutical industry initially began to turn its attention to continuous manufacturing, the method did not spread widely because measurement technologies had some issues to be solved. Recently, however, technological advancements have made it more feasible to implement continuous manufacturing.

Process analytical technology (PAT) is a key technology for solving issues around real-time monitoring. PAT is a general term for technologies used for real-time monitoring of reaction behaviors during production processes, including the progress of reactions, temperature, and pressure.

Among PAT, the development of virtual measurement technology, called soft sensors, has become a focus of interest (Figure 3). Soft sensors enable the estimation of information that is difficult to actually measure in real time through a simulation technique. It is attracting a great deal of interest as an alternative to real measurements using actual sensors, and various manufacturers are promoting the development of soft sensor technologies.

Figure 3: Overview of soft sensor technology



Source: Created by MGSSI based on materials from the Laboratory of Chemoinformatics (Funatsu & Kotera Group), Department of Chemical System Engineering, Graduate School of Engineering, The University of Tokyo

Some variables such as temperature, pressure, and flow rate in the chemical reaction process can be measured in real time. But other variables, such as concentration and density cannot be measured unless a sample is taken and analyzed in the laboratory. Since such analysis takes time, its real-time property is lost, and a time-delay problem can occur in the process control.

With a soft sensor, a numerical model can be constructed, for example, based on previously obtained data on inputs (temperature, pressure) and outputs (concentration, density), and target output values can be estimated in real time. By collecting actual temperature and pressure information that changes every moment on-site using a real sensor, and inputting the obtained data into a soft sensor, it becomes possible to monitor real-time changes in concentration and density without going through time-consuming analysis. In addition, the technology can contribute to reducing the man-hours required for sample collection and analysis, and the cost of analytical equipment.

The development of soft sensors for monitoring processes with complex reactions is expected in the future, and is a vital elemental technology for the implementation of continuous manufacturing.

3. INITIATIVES IN VARIOUS COUNTRIES

Among national projects in Japan and other countries, under policies for strengthening industrial competitiveness, the EU, the US, Australia, and Japan, in particular, are actively pursuing the development of catalysts, equipment and prototypes that will enable the replacement of batch manufacturing with continuous manufacturing(Figure 4). Among them, the Pharmacy on Demand project in the US received particular attention for its ambitious aim to achieve continuous and automated operation of all processes from raw material inputs through medicinal tablet processing.

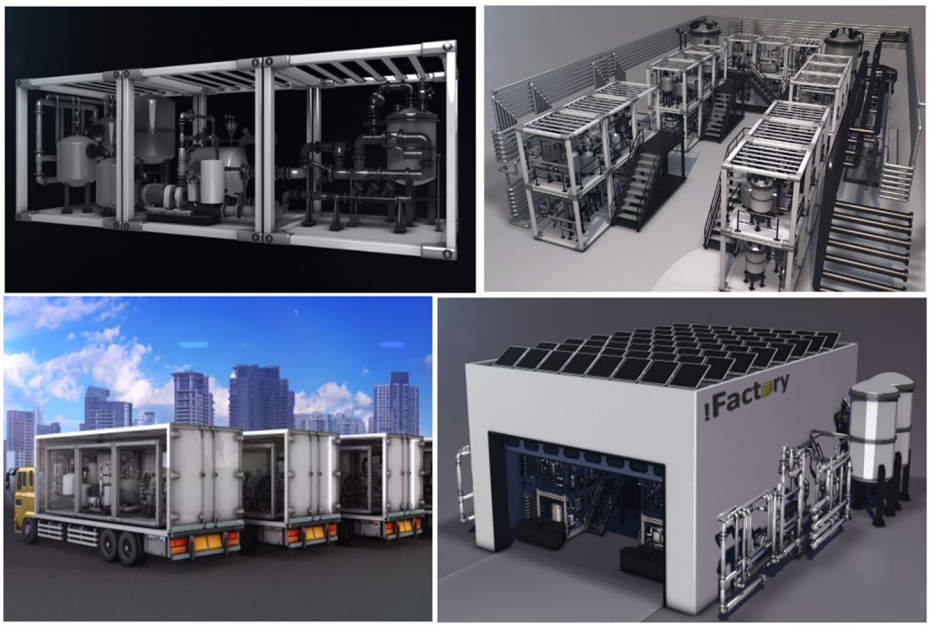
Figure 4: Continuous manufacturing-related projects in Japan and overseas

	Project name	Participating Countries, Organizations	Details
EU	F^3 Factory (FP7)	9 EU countries (2009–2013: EUR 30 million) Led by chemical companies	・Development of small-scale chemical production processes
	SPIRE (HORIZON 2020), COSMIC, ONE-FLOW project, others	UK, Germany, the Netherlands, etc. (2015–2020: EUR 58 million) University turned into an R&D center, conducting R&D in collaboration with chemical and pharmaceutical companies	・Development of catalysts, reactors, control equipment, etc. (approximately EUR 33.3 million) ・Technology development for process integration control and optimization (approximately EUR 24.3 million)
US	Pharmacy on Demand (Battlefield Medicine)	Since 2011: USD 10 million/yr MIT and other research organizations conducting R&D on consignment from the US Defense Advanced Research Projects Agency (DARPA)	・Development of compact drug ingredient manufacturing processes ・MIT succeeds with prototype
Australia	FloWorks	Australia's national science agency called the Commonwealth Scientific and Industrial Research Organisation (CSIRO) Total funding: AUD 200 million	・Development of continuous flow synthesis technologies for improving chemical processes
Japan	Flow Science & Technology Consortium (FlowST) iFactory	FlowST is a collaboration between industry and academia with over 90 participating organizations, and is led by AIST and the University of Tokyo. iFactory is a NEDO project involving a consortium of eight private companies	・Improvement and promotion of continuous manufacturing technologies ・Development of compact and reconfigurable modular systems

Source: Compiled by MGSSI based on materials from NEDO's Technology Strategy Center and other sources

In Japan, under the collaboration of industry, academia, and the government, the Flow Science & Technology Consortium (FlowST Consortium) was established in 2015. The Ministry of Economy, Trade and Industry and the New Energy and Industrial Technology Development Organization (NEDO) have been supporting the consortium's development activities. Currently, the development of iFactory is being promoted as a NEDO pilot project, led mainly by the efforts of eight private companies (Figure 5). iFactory features a production line that can be reconfigured according to the product, and aims to realize a flexible on-demand commercial production of needed products in only the needed quantities. Unit operations, such as chemical reactions, refining, and crystallization, are installed in each module, and when the process is changed or reconfigured according to the product, the connection of the modules can be rearranged. All processes are automated, from raw material input to product output, and the required space would only be roughly the size of a convenience store. In addition, a system is being proposed for storing the equipment in containers and transporting them by truck, thus allowing for easy on-site manufacturing of pharmaceuticals. The completion of a pilot plant is scheduled for fiscal 2022.

Figure 5: Reconfigurable Continuous Manufacturing Facility iFactory's Envisions



Source: iFactory

Among initiatives pursued by pharmaceutical companies, active adoption of continuous manufacturing can be seen primarily at companies in Europe and the US (Figure 6). US pharmaceutical majors Eli Lilly and Pfizer, which were among the earliest to take action, have obtained FDA approval for certain medicines produced through continuous manufacturing, and have already transitioned to commercial production for some of them. Novartis (Switzerland) has established CONTINUUS Pharmaceuticals, founded based on the results of joint research with MIT, to provide designing services for continuous manufacturing equipment. South Korea's SK biotek has introduced continuous manufacturing systems to replace many batch processes, leveraging its technological capabilities in catalyst and process development cultivated in the petrochemical business by applying it to the continuous manufacturing for pharmaceuticals.

Figure 6: Major Pharmaceuticals-Related Companies Pursuing Continuous Production

	Company	Initiatives
US	Eli Lilly and Company	Introduced continuous manufacturing systems for drug ingredients and pharmaceuticals. In 2017, obtained FDA approval for breast cancer medication produced using continuous manufacturing. Eli Lilly Japan became the first in Japan to obtain PMDA approval for continuous manufacturing of a new pharmaceutical product. Delivered a continuous-flow reactor to a Japanese pharmaceutical manufacturer.
	Pfizer Inc.	In 2018, obtained FDA approval for acute myeloid leukemia treatment agent produced using continuous manufacturing. In collaboration with GEA, developing portable facility for continuous manufacturing of solid dose preparations. Formed a consortium with GEA and G-CON to study designs for modular equipment that can be shipped by truck container.
Switzerland	Novartis International AG	Developing continuous manufacturing systems through joint research with MIT (Novartis-MIT Center for Continuous Manufacturing). Aiming to realize "end-to-end" facilities by systematizing processes, from raw material input through to synthesis and drug formulation, into a coherent whole. Established CONTINUUS Pharmaceuticals to promote the development and introduction of continuous manufacturing systems.
South Korea	SK biotek Co. Ltd.	Has the system for systematic and coherent implementation of catalyst development, process development, and engineering. Also in continuous manufacturing, pursuing development of pharmaceutical manufacturing processes through to commercial operation of facilities. Owns one of the world's leading continuous manufacturing facilities.
Japan	Shionogi Pharma	Promoting the introduction of continuous manufacturing for drug ingredients and pharmaceuticals by making the most of continuous manufacturing achievements and expertise accumulated by Shionogi & Co. Introduced continuous manufacturing beginning with solid preparation, aiming to adopt continuous manufacturing for other drug manufacturing processes by 2021.
	Takasago International Corp. Takasago Chemical Corp.	Takasago International succeeded in adopting continuous manufacturing for intermediates with the use of LAH reducing agent. Takasago Chemical has partnered with Eli Lilly to actively promote the transition from batch-type reactors to continuous manufacturing. Plays a central role in NEDO's iFactory development project.

Source: Compiled by MGSSI based on materials from NEDO's Technology Strategy Center and other sources

In Japan, Shionogi Pharma is planning and proceeding with capital investment to establish a continuous manufacturing system for solid preparations, investigational agents, and pharmaceutical ingredients, by the target year of 2021. Takasago International Corporation has succeeded in the continuous manufacturing of intermediates by applying its proprietary technology, and Takasago Chemical has partnered with Eli Lilly to install a continuous-flow reactor provided by Eli Lilly, thereby promoting the adoption of continuous manufacturing by incorporating advanced technologies from abroad.

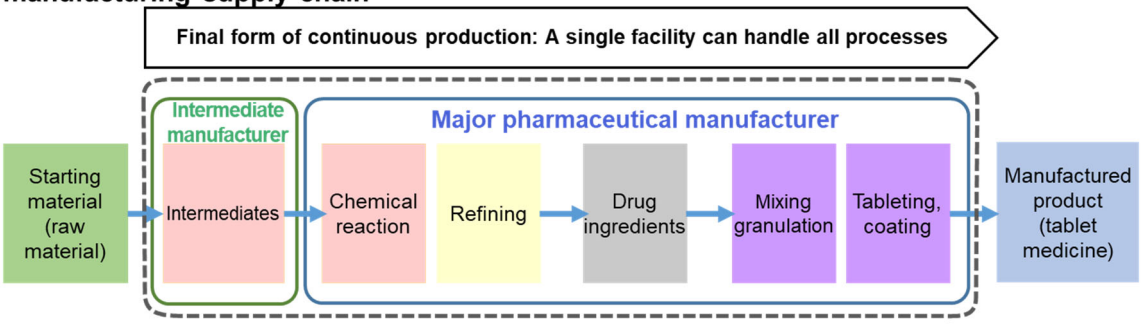
4. FUTURE PROSPECTS

Outlook for the Pharmaceutical Segment

At this time, companies are beginning to introduce continuous manufacturing systems for the production of some pharmaceutical products. Hybrid-type manufacturing systems that integrate both batch and continuous processes are being explored as well. This method combines the two systems, such as, for example, a conventional batch system for the reaction/refining operation (drug ingredient processing) and a continuous manufacturing system for the crystallization and tablet processing (pharmaceutical formulation). In the future, advancements in sensing technologies, such as for soft sensors, is expected to further promote hybrid-type systems and support the realization of comprehensive continuous manufacturing that integrates the entire manufacturing process.

In comprehensive continuous manufacturing, once the raw materials are input, only a single manufacturing facility is needed to produce the tablet medicine in one go, which means that the realization of such a system will allow the pharmaceutical manufacturer that owns the equipment to handle all of the pharmaceutical processes (Figure 7). As such, continuous production has the potential to revolutionize the value chain that has, until now, been consisted of divisions of labor between intermediate manufacturers and major pharmaceutical manufacturers.

Figure 7: Final form of continuous manufacturing and the pharmaceutical product manufacturing supply chain



Source: Created by MGSSI

Outlook for the Fine Chemicals Segment

Within the chemicals industry, many products in the fine chemicals segment are manufactured using the batch method, such as organic chemicals, synthetic resins, and agrochemicals.

The adoption of continuous manufacturing for these fine chemicals is expected to gain impetus in the future in the interest of reducing operator workload, enhancing safety, and downsizing equipment requirements.

For example, even for the agrochemicals production whose unit price is lower than that of pharmaceutical products, there has been a recent development in pursuing continuous manufacturing processes through industry-academia collaboration. Such efforts are underway as part of the National Agriculture and Food Research Organization's (NARO) research and development platform to develop innovative production processes for realizing low-cost agricultural chemicals.

Some are in the opinion that the introduction of continuous manufacturing in the fine chemicals segment will precede that of the pharmaceuticals segment, because of the more stringent regulations for the latter. In that case, repercussions of such development are also expected to extend to the business landscape of the engineering and equipment manufacturers involved in continuous manufacturing.