DRUG DEVELOPMENT IN THE AGE OF PRECISION MEDICINE —PHARMACEUTICAL COMPANIES BETTING ON DIGITAL TRANSFORMATION—

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THE PHARMACEUTICAL MARKET IN THE AGE OF PRECISION MEDICINE

The scale of the global pharmaceutical market was $774 billion in 2017 and is expected to reach $1,060 billion by 2022 (EvaluatePharma forecast, average annual growth rate of 6.5%). Furthermore, pharmaceutical research and development costs are also rising, totaling $157 billion in 2016 and forecast to reach $181 billion in 2022 (average annual growth rate of 2.4%). Development of drugs used in "precision medicine" is now moving forward in the pharmaceuticals market. As opposed to the conventional "one-size-fits-all-type" treatment targeting an average patient, precision medicine aims to provide a highly segmented treatment plan for each patient using the individual's genetic and diagnostic information. Because drug development that responds to segmented needs is both very difficult and time-consuming, and given the increasing pressure to reduce medical costs, with the survival of pharmaceutical companies at stake, they are striving to revolutionize their operations to reduce costs. In this report, using leading examples, we will introduce the latest trends and new business opportunities in the pharmaceutical industry, which has been rapidly advancing digital transformation (DT) initiatives in recent years.

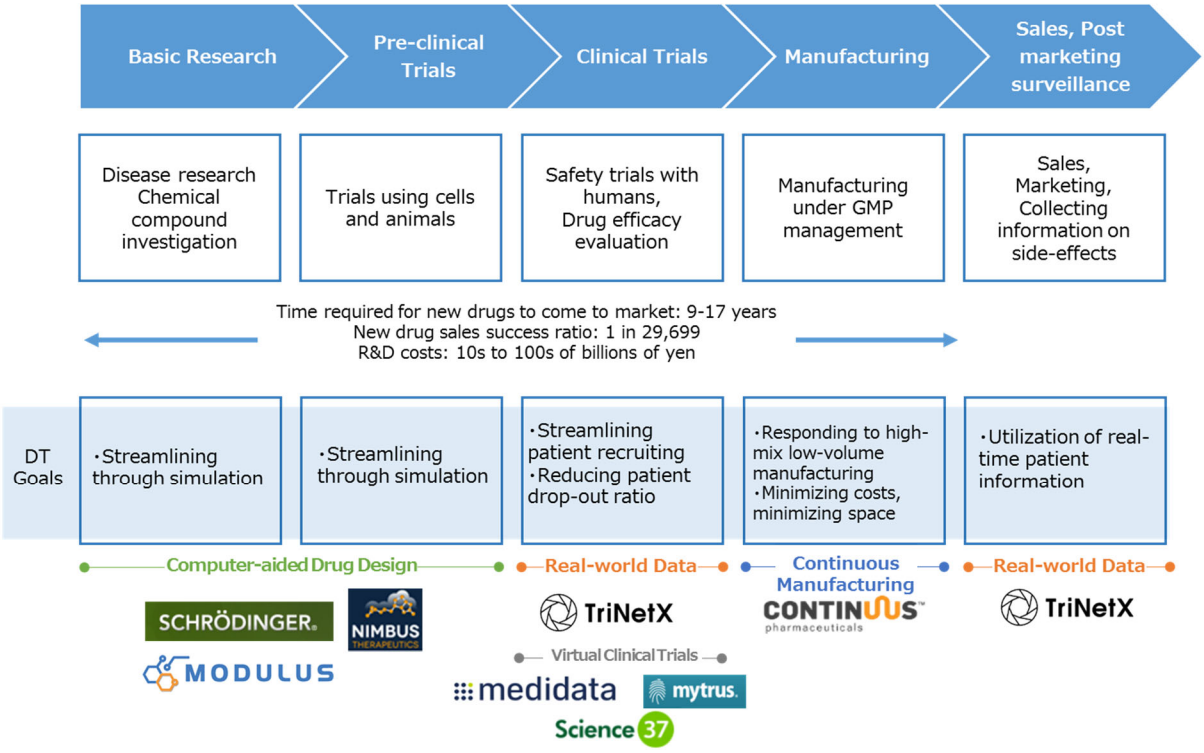
DT INITIATIVES IN THE PHARMACEUTICAL VALUE CHAIN

In new drug development, efficacy and safety are verified through a long and complicated series of steps to receive government approval before drugs finally see the light of day anywhere in the world. That process can take 9 to 17 years, and the rate for a new drug to successfully reach the sales stage is extremely low at only one out of 29,699. The process also requires enormous research and development costs (tens to hundreds of billions of yen per product)[1]. A rough breakdown of the costs of new drugs is 30% research and development, 40% manufacturing costs, and 30% general administrative expenses. Among these, there appears to be ample room for streamlining the research and development and manufacturing processes through the utilization of IT and outsourcing.

Challenges in research and development in the age of precision medicine include 1) efficient discovery of drug candidates (seeds) in a short amount of time, 2) efficient patient recruitment for clinical trials, and 3) securing the continuous cooperation of patients until the trial results are produced by avoiding patients dropping out during the trial due to the trouble of visiting the hospital, etc. Furthermore, on the manufacturing front, as there are increasingly fewer target patients per drug, high-mix, low-volume drug manufacturing is required. To resolve these issues, pharmaceutical companies are evaluating and introducing new DT-based research and development processes and manufacturing processes, including "computer-aided drug design," "real-world data," "virtual clinical trials," and "continuous manufacturing" (Image 1).

*1 Japan Pharmaceutical Manufacturers Association (JPMA), Vice President Yoshihiko Hatanaka, "Toward the Creation of Revolutionary New Medicines," Expenditure Innovation Working Group, Important Issue Evaluation Sub-group (#5), Materials, May 29, 2015

Image 1: Pharmaceutical Value Chain and Digital Transformation Initiatives



Computer-aided Drug Design

Computer-aided simulation technology (in-silico drug discovery) is gaining attention as a means of streamlining the basic research and pre-clinical trial stages of drug development process. Traditionally, how the chemical compounds bind the therapeutic target of disease was verified only through experiments and evaluations in the laboratory. However, with computer-aided drug design, by conducting computerized simulations on a molecular level, compounds for drug candidates can be efficiently screened and designed while reducing the number of experiments. Furthermore, simulations in the bodies of animals are also becoming possible and are expected to greatly reduce the time required for animal experiments.

Expectations for computer-aided drug design surged in 2016 when Gilead Sciences (US) acquired Nimbus, a subsidiary of Schrödinger (US), which owns chemical compounds developed through simulation, for $1.2 billion. Using its overwhelmingly powerful supercomputer Anton and unique analysis algorithms, Schrödinger has reduced the process required to optimize compound for drug candidates from two years to one year. The company announced the establishment of the joint venture Faxian Therapeutics with China's major contracting research organization (CRO) WuXi App Tec in October 2018, and is expanding its business. In Japan, Modulus Discovery, Inc., an in-silico drug discovery venture company established in 2016, is gaining attention for partnering immediately after its foundation in 2017 with PeptiDream, a venture company coming out of the University of Tokyo and offering a revolutionary drug discovery platform. Modulus aims to become a virtual pharmaceutical company by outsourcing most of its operations in drug development processes, except for the processes using computational science, to CROs and other organizations.

Real-world Data

In clinical trials of precision medicine, it is necessary to identify very peculiar types of patients, which has created increasing difficulty in patient recruiting (for example, 2,000 patients must be screened to find 100 patients with a gene that is only present in 5% of lung cancer patients). Disease registry systems, which collect real-time patient information from networked hospitals (real-world data), are gaining attention as a technology to streamline patient recruiting.

The US's TriNetX, established in 2013, is noteworthy for having built a network covering 16 countries and 135 million total patients in only five years since going into business. With hardware servers and software provided to hospitals free of charge, TriNetX offers the system that is accessible to electronic medical records (EMR) in hospitals connected by networked servers. Through this system, hospital's data always remains within the internal system, and only aggregate results can be obtained by pharmaceutical companies and CROs for clinical trials. Using the system, mismatches for patient recruitment were reduced by 10%, and the successful ratio for patient recruitment by each hospitals has increased by 37%. From the standpoint of hospital operations as well, the system is also beneficial because participation in clinical trials has a positive effect on earnings. The real-world data collected from the TriNetX network is also expected to be utilized for pharmaceutical sales strategies and post marketing surveillance.

Virtual Clinical Trials

Virtual clinical trials refer to at-home clinical trials which patients can join from home using mobile devices, telemedicine, wearable technologies, etc. Normally, patients must visit the hospital multiple times for medications and examinations (the average in the US is said to be 11 hospital visits every six months), and one in four patients agreeing to participate in trials drops out during the trial. By using IT, virtual clinical trials reduce the burden of visiting the hospital for patients while decreasing the drop-out ratio, helping to avoid inefficiency and save time and costs.

A virtual clinical trial, "ADAPTABLE," which makes comparative decisions on the optimal amount of aspirin for heart disease patients, is currently underway in the US with around 15,000 targeted registered patients. Medidata, which acquired the US venture company Mytrus, which held the world's first virtual clinical trial, is leading the ADAPTABLE virtual clinical trial. Science 37 (US), which provides similar services to Mytrus, is another company gaining attention for its successive announcements of partnerships with companies such as Novartis (Switzerland), Sanofi (France), and Otsuka Pharmaceutical (Japan). Virtual clinical trials are not suitable for drugs with serious side effects expected. On the other hand, because wearable electrocardiograms (ECGs) and heart-rate monitors can be connected to mobile devices, a different quality of real-time data can be collected as compared to traditional clinical trials. At the same time, the chance to visualize the novel mode of action of drugs is also expected.

Continuous Manufacturing

In the manufacturing of pharmaceuticals used in precision medicine, continuous manufacturing is gaining attention for its ability to produce high-mix, low-volume pharmaceutical drugs (only the required amount produced at the required time). In the pharmaceutical field, batch manufacturing in which large-scale tanks are lined up and managed by individual process has been the standard, and continuous manufacturing has not been introduced. 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 continuous manufacturing of pharmaceuticals, research is advancing in "Soft Sensors", which use a range of sensing data to estimate the operating status while the flow is in process, and controls the quality of the product. In addition to its ability to handle high-mix, low-volume production, continuous manufacturing can save space, taking up a space comparable to only two convenience stores for its plant. This naturally increases expectations for reduced costs.

Continuous manufacturing in the pharmaceutical field began in 2007 when Novartis (Switzerland) and Massachusetts Institute of Technology (MIT) of the US established the Novartis-MIT Center for Continuous Manufacturing and launched joint research into continuous manufacturing. From 2014, more active discussions have been made on the social applications of continuous manufacturing, with the Center at the core, among the US FDA, businesses, and academia. In the US and EU, major projects to realize continuous manufacturing that thoroughly covers every step from the introduction of raw materials to drug formulation are underway. Examples include the "Make-It Program" (US Defense Advanced Research Projects Agency/DARPA) and "ONE-FLOW Project" (EU). In Japan, the "Flow Science & Technology Consortium (FlowST)" was established, led by the National Institute of Advanced Industrial Science and Technology and the University of Tokyo, with 74

participating companies. FlowST aims to build a convenience-store sized “iFactory” module, (Image 2) which will make each process cube-sized and rearrangeable (NEDO-supported program).

Image 2: NEDO Strategic Innovation Program for Energy Conservation Technologies -- “iFactory”

Image provided by Takasago Chemical Corporation’s President and CEO Takao Saito

Among private-sector companies, CONTINUUS Pharmaceuticals (US), a venture company spun off from the Novartis-MIT Center for Continuous Manufacturing in 2013, is gaining attention for its operation of a pilot plant called Integrated Continuous Manufacturing (ICM), which reduces manufacturing facility space by 90% and costs by 50%, with the support of the US FDA. Furthermore, in Japan, Chugai Pharmaceutical announced a “Next Generation Factory” concept, which envisions establishing a technological platform for continuous manufacturing capable of reducing the manufacturing costs of bio-pharmaceuticals to one tenth that of current costs by 2021. At present, the technological hurdles for completely integrated continuous manufacturing are high, and mainly a hybrid form of combined continuous manufacturing and batch manufacturing is being pursued. However, in the future, sensing technology including soft sensors will likely support the realization of thoroughly integrated continuous manufacturing. Moreover, if small-scale continuous manufacturing facilities such as the “iFactory” can be realized, local-production/local-consumption-type plants and shipboard plants may also become possible.

MANUFACTURING COMPANIES AT THE TURNING POINT FROM HARD TO SOFT AND NEW BUSINESS OPPORTUNITIES

With respect to DT aimed at pharmaceutical companies, various venture companies like those introduced in this report are trying to create new business opportunities. Major IT companies such as Google and Apple have also begun real evaluations aimed at expanding into this field, leveraging their connections with consumers. However, partly due to the high level of expertise required and the regulatory barrier, at present no notable acquisition deals can be seen, and their influence on the overall pharmaceutical value chain is limited.

Pharmaceutical companies are well-versed in life sciences. However, when it comes to DT initiatives, there are many cases that are limited to individual optimization or where existing facilities have been maintained. What is needed is makeover of the entire operational process, not bound by conventional ideas, and the realization of high added value through DT. In addition, it is necessary to visualize the efficiencies of various

processes through digitalization and identify fields to focus on and fields to abandon. Going forward, the pharmaceutical companies that survive in the age of precision medicine will be those that can combine their own strengths with outsourcing to further sophisticate their capabilities. Ireland's Shire (sales of approx. ¥1.7 trillion in the fiscal year ended Dec 2017) is an example of a company which has realized specialization through outsourcing. (Takeda Pharmaceutical Company (Japan) proposed to acquire Shire in May 2018.) Shire has virtualized the pharmaceutical development process by outsourcing its basic research, clinical trials, manufacturing, and sales processes. The company itself focuses on building relationships with physicians and patient groups based on its product strategy and negotiating drug prices, and functions as a decision-making body in the efficient use of its external contractors.

Going forward, with increasing outsourcing by pharmaceutical companies, the creation of "network-type drug discovery support platforms" will be required to consolidate outsourcing contractors and provide tailored support for individual drug discovery responding to pharmaceutical companies' needs (Image 3). Moreover, by providing DT solutions that contribute to total optimization, this platform is expected to connect the fragmented pharmaceutical value chain. Japanese trading companies (Sogo Shosha) have traditionally provided a range of support from upstream to downstream in the pharmaceutical industry from a global, neutral position. Sogo Shosya are well-versed in coordinating with partner companies and will now be expected to function as the facilitator for the optimization of the value chain while becoming the developer of this platform. Additionally, precision medicine is expected to expand not only in developed countries, but also in the developing world. Sogo Shosya carry the weight of expectations for Asian expansion of companies leading DT.

Image 3: Image of Network-type Drug Discovery Support Platform