CDMOs for pharmaceutical **chemicals in Japan**

Kazuya Okano of **Juzen Chemical** shares a general overview of Japanese CDMO businesses for pharmaceutical chemicals

Large Japanese pharmaceutical firms are significant players in the global pharmaceutical industry. Since the 1980s, they have emerged as premier drug discovery companies worldwide through the creation of blockbusters. Japan's world-class innovations include the discovery of quinolone antibiotics (levofloxacin), cholesterol-lowering drugs (pravastatin and rosuvastatin), immunosuppressive drugs (tacrolimus), drugs for Alzheimer's disease (donepezil), diabetes drugs (pioglitazone, canagliflozin and ipragliflozin), proton pump inhibitors (lansoprazole and rabeprazole), and antihypertensive drugs (diltiazem, candesartan, azilsartan and olmesartan).

As innovators, Japanese pharmaceutical firms are working on many clinical projects in various modalities and are world leaders in developing cutting-edge therapeutics, such as antibody-drug conjugates. According to a CPhI Pharma Insights report, the Japanese pharmaceutical industry is expected to keep its strong position as an innovator in the 2020s. Over 100 domestic Japanese biopharma companies, including many start-ups, are supporting the continuation of Japanese pharmaceutical innovations in the global market.[1]

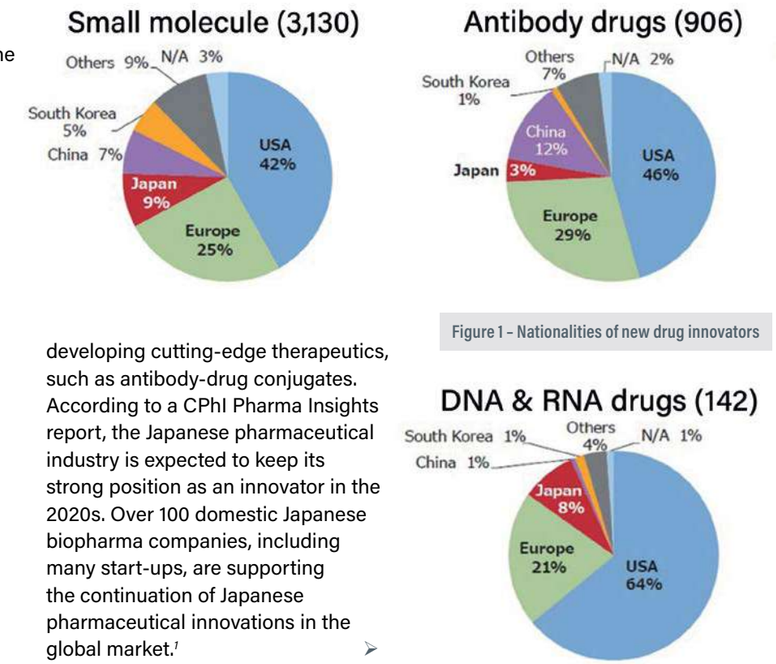


Figure 1 – Nationalities of new drug innovators

The Ministry of Health, Labour & Welfare released the strategic 'Pharma Industry Vision 2021' report in September 2021, eight years after the previous vision was formulated.[2] The report focused on changing business circumstances in recent years, such as drug discovery using genome technology and Big Data, market penetration by generic drugs and the globalisation of the drug market.

Based on the external trends surrounding the industry, the report advocated a policy that supports innovative drug discovery by the development of genome data infrastructure and the vitalisation of collaboration between academia and start-ups throughout the pharmaceutical ecosystem.

Small molecule revival

One recent remarkable trend in pharmaceutical R&D is the revival of the investigation of small molecule drugs. This is particularly obvious in the field of oncology.[3] The US FDA approved 53 new drugs in 2020, 40 small molecules and 13 biological drugs. Chemotherapeutic agents accounted for 23 new approvals, including 13 new chemical entities.

Small molecules represent approximately 75% of all drugs approved by the FDA and they are expected to continue to play a key role in innovative treatments. Owing to an increased development of small molecule drugs, the global production capacity for small molecules in CDMOs is becoming tighter.[4]

A report from the Office of Pharmaceutical Industry Research, a Japanese think tank for the pharmaceutical industry, reviewed the nationality of the innovators of novel molecular entities worldwide in 2020.[5] The proportion of Japanese companies in the nationalities of project owners was only 3% for antibody drugs but approximately 10% for small and medium-sized molecule (DNA and RNA) drugs (Figure 1).

This indicates that a credible and sustainable cycle has been realised in Japan in which strong demand for small and medium-sized molecule projects has revitalised the CDMO business. This in turn has helped the development of new drugs by pharmaceutical companies, including start-ups.

CDMOs in Japan

When 'Western' drugs were first introduced to Japan in the 19th century, API sourcing depended upon the import from foreign pharmaceutical companies. During the strong economic recovery in the 1950s, many pharmaceutical companies were established with the aim of manufacturing APIs in Japan.

At that time, API manufacturers focused on the production of antibiotics and antihistamines, which became big markets in Japan. Juzen Chemical was established in 1950 to produce diphenhydramine.

In the 1960s, GMP for pharmaceutical production was enacted in the US and other countries followed suit. The manufacturing standards in Japan were established approximately a decade later.

Since its establishment in 1975, the Japan Bulk Pharmaceutical Manufacturing Association (JBPMA) has been working on the introduction and improvement of GMP systems

Juzen Chemical's facility in Japan

in the API manufacturing industry. Currently, 101 API manufacturers are members of the JBPMA.

In the 1980s, several global blockbuster drugs were developed and launched by Japanese pharmaceutical firms and they began to outsource the manufacturing to third parties because of growing global demand for APIs. To meet these new demands, API manufacturers have made capital investments in new facilities and expanded GMP production capabilities. Japanese API manufacturers also grew with the success of blockbuster drugs.

In the 1990s, the outsourcing of pharmaceutical chemicals expanded to more nations worldwide. Both types of businesses, pharmaceutical intermediates by specific technology and exclusive API synthesis using GMP, progressed. Major Japanese chemical companies, such as Mitsubishi Chemical, Sumitomo Chemical and AGC, have entered the market through the application of their chemical technology and production capabilities.

The expansion of API sales outside Japan provided the US FDA and the European Medicines Agency (EMA) the opportunity to inspect Japanese API manufacturers. Since the 2000s, many API manufacturers have obtained approval from the US FDA and other authorities.

In 2004, the Japanese government established the Pharmaceuticals & Medical Devices Agency (PMDA) with the aim of integrating the policies for pharmaceutical regulation in Japan. The PMDA has been a member of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme for GMP cooperation between the regulatory authorities and pharmaceutical industry since 2014. The three major regulatory agencies (FDA, EMA and PMDA) are working together to harmonise GMP worldwide.

In recent years, support services for drug development have become another important business sector in the pharmaceutical industry. This concept has been implemented in the context of CDMOs, and the number of global CDMOs has been rising since the 2010s, due to the historical accumulation of technology and abundant opportunities for new drug projects.[6]

Technology advances

Japan has a strong tradition of and aptitude for chemistry in academia, with seven Nobel laureates in chemistry. In the 1980s, common chiral intermediates for blockbuster pharmaceuticals, such as the novel carbapenems, cholesterol-lowering drugs, and HIV drugs, became the targets of pharmaceutical intermediate businesses.

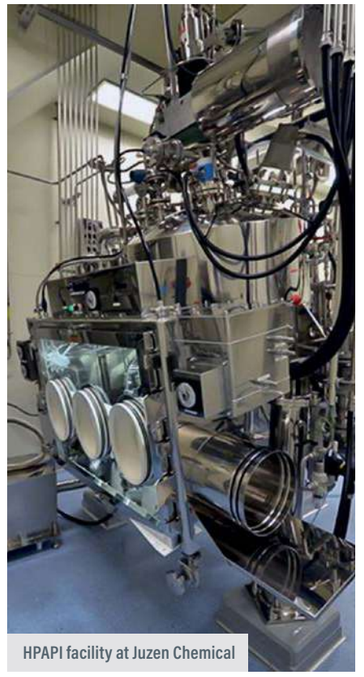
Many companies have joined the chiral intermediate market using chiral technologies. Takasago industrialised the asymmetric transition metal catalyst explored by Noyori, while Kaneka and API Corporation developed the enzymatic transformation examined by Shimizu as a commercial manufacturing method.

Japan is one of the leading countries in flow chemistry. Yoshida and Nagaki established the concept of 'flash chemistry', which facilitates chemical reactions not amenable to the usual batch process.[7] Kobayashi established the concept of flow 'fine' synthesis and achieved the flow total synthesis of several APIs using a heterogeneous column catalyst.[8]

Several industrial consortia are working on the installation of continuous production for commercial processes. Fujifilm Wako Chemicals has a large-scale continuous GMP production capability, which reduces costs in the BuLi process.

Continuous stirred-tank reactor (CSTR) technology also plays an important role in chemical production innovation, and various chemical companies in Japan have announced the application of CSTR technology for fine chemical production. Juzen Chemical recently started to develop the CSTR process for the Grignard reaction, which has a low yield in batch processing but was still successfully scaled up at a GMP production plant using this technology.

The demand for highly potent APIs (HPAPIs) is increasing due to the advances in anticancer drug discovery. The total number of new drugs in the oncology pipeline reached almost 3,500 in 2020, increasing by 75% since 2015, marking a large investment and research focus to address many clinical needs. [9]



HPAPI facility at Juzen Chemical

The number of dedicated containment facilities for HPAPIs is also increasing for many API manufacturers in Japan. Juzen Chemical, for instance, constructed a multi-purpose HPAPI plant in 2015 *(pictured)* and several anticancer drugs have been commercially produced.

Along with the expansion of modalities in pharmaceutical research, business opportunities for the manufacturers of medium-sized drugs, such as peptide and nucleic acid drugs, are increasing. In particular, the development of RNA vaccines against COVID-19 has become a driving force for expanding the medium-sized drugs sector and has accelerated the development of therapeutic tools that target the RNA.

Many CDMOs in Japan, such as Nitto Denko, Ajinomoto and Nippon Shokubai, are working on peptide or nucleic acid synthesis at a commercial scale. Juzen Chemical is also working on efficient synthesis of new amidites and oligonucleotides.

Currently, many pharmaceutical start-ups have been established in Japan. As they focus on drug discovery, the demand for chemistry, manufacturing, and control (CMC) solution services, such as route selection, process refinement, analytical development, and formulation, is increasing.

Large pharmaceutical companies are also following the trend to save the resources devoted to CMC functions, and the expectation from CDMOs for CMC support is increasing. Juzen Chemical began its CMC solutions service in 2017.

Recently, the 'ecosystem' that accelerates open innovation among pharmaceutical companies, start-ups, and academia has been recognised as a key factor in drug discovery. Shonan iPark, a research hub established around Takeda's Shonan Laboratory, now houses 120 companies that specialise in various domains of pharmaceutical production and next-generation biotechnology. Juzen Chemical became the first CDMO to establish a laboratory there in 2020. ●

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