EU-Japan Centre
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The Biopharmaceuticals sector in Japan: Government regulations, the competitive situation and how to find an entry point - A primer for European SMEs.

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Contents

Abbreviations

$	US-Dollars
AMED	Agency for Medical Research and Development R&D Agency of the MHLW
API	Active pharmaceutical ingredient Active pharmaceutical ingredient
ATMP	Advanced therapy medicinal product (advanced therapy product)
CRO	Contract research organisation
CTD	Common technical document. All the documents required for a marketing authorisation for a medicinal product
DMF	Drug master file Confidential information of an API manufacturer on the manufacturing process
eCDTD	Electronic common technical document. The entirety of the documentation for a marketing authorisation for medicinal products in digital form.
EMA	European Medicines Agency European Medicines Agency
FDA	Food and Drug Administration American health authority
FMR	Foreign manufacturer registration
FY	Fiscal year (April 1 – March 31
G-CSF	Granulocyte cell-growth factor
GCP	Good clinical practice
GMP	Good manufacturing practice
GPSP	Good post-marketing study practice
GQP	Good quality practice
GVP	Good vigilance practice
IB	Investigator brochure central document for approval procedure
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICH-GCP	Good clinical practice in accordance with the ICH
IND	Investigational new drug new, not yet approved drug
IRB	Institutional review board protects patients' interests, required for clinical trials
J-GCP	Good clinical practice, Japanese prescription
JETRO	Japan External Trade Organization Foreign Trade Organisation of METI
JST	Japan Agency for Science and Technology Project Management Agency of MEXT
MAH	Marketing authorization holder binding certificate for one applicant
METI	Ministry of Economy, Trade and Industry Ministry
MEXT	Ministry of Education, Culture, Sports, Science and Technology Ministry
MHLW	Ministry of Health, Labour and Welfare Ministry
NEDO	New Energy and Industrial Technology Development Organization Project executing agency of METI
NHI	National Health Insurance
NME	New molecular entity
OTC	"Over the counter", non-prescription drug
PAFC	Pharmaceutical Affairs and Food Council Approval Committee of the MHLW
PIC/S	Pharmaceutical Inspection Cooperation Scheme International Association for the Harmonization of GMP Regulations
PMDA	Pharmaceutical and Medical Device Agency Approval Agency of the MHLW
QMS	Quality management system
R&D	Research and development
SMO	Site management organisation

1 Executive summary

Japan is a highly industrialised nation with a large population, but limited space and few natural resources. National budget deficits for the import of food and energy are compensated by the manufacture and export of industrial products such as automobiles, machines, optical and IT equipment, chemicals or pharmaceuticals. Innovation plays a dominant role in order to stand national competition and be successful in the international markets.

For most of its history, Japan was ruled by central government and confined to its insular boundaries. As a consequence, laws and regulations tend to follow top-down principles and are generally followed. Limited space and Confucian ethics have led to a social conduct which offers respect towards one's seniors and senior people in general. In return, superiors, including the government, are expected to mediate conflicts and care for the general welfare.

In a society composed for over 98% of ethnic Japanese, these attitudes have led to a welfare state where state and company insurance systems largely cover disease risks. In return, the state controls the cost structure of health services, e. g., through setting the prices for drugs and medical services. In this system, prices of established products are successively curbed, whereas innovative drugs or services receive a bonus price.

This well-balanced system is challenged threefold: First, by the "bubble economy" of the mid-1980s, which drew much capital from Japan's economy and has left the nation with a national debt of over 250% of its GDP. Second by the economical rise of China, which has become a fierce competitor for innovation and markets at the global level. Third by the ripples of an over-ageing society, which menaces not only Japan's healthcare system but also leads to an increasing shortage of labour.

The Japanese government under Prime Minister Shinzo Abe has answered to these challenges with a Strategic Innovation Promotion Program (SIP)[1] initiated in 2014. Its objective is to promote innovative science and technology, to accelerate national economic development and to open up new markets for the Japanese industry overseas. Five amongst its 11 projects are related to biotechnology, and one of the targets is the pharmaceuticals industry.

The Japanese market for pharmaceuticals is amongst the largest in the world and, through many international networks opened to innovative products and services. In 2016, nearly one fifth of all drugs came from abroad, and foreign companies served about 70% of the particularly innovative market for biopharmaceuticals. Although Japanese pharmaceutical companies generate 70% of sales and are expanding internationally, they are not amongst the global industry leaders. The Japanese market thus offers good opportunities for European SMEs with innovative biopharmaceutical products or services such as blood products, therapeutic antibodies, vectors for gene therapy or cell products. In the latter category in particular, Japan aims at international leadership, readily integrating innovation from abroad.

Drugs are heavily regulated in Japan, and even more stringent rules apply to biopharmaceuticals. This concerns approval procedures, quality control, distribution and price maintenance. Although the regulatory authority PMDA is increasingly following international rules, it requires pharmacodynamic and clinical studies with a reference to the Japanese population. Some documents and many consultations require knowledge of the Japanese language and business culture. Japanese service providers are therefore indispensable.

The National Health Insurance (NHI) sets the prices for pharmaceutical products. Its primary task is to curb the increase in healthcare costs for the rapidly ageing population, in particular by increasing the approval of generics and biosimilars. In fiscal 2017, these were already 70% of all prescribed drugs, and the target for 2020 is 80%. The NHI is also continuously reducing prices for products that have already been on the market for some time, and the overall size of

[1] https://www8.cao.go.jp/cstp/panhu/sip_english/sip_en.html

the pharmaceutical market could therefore stagnate. Subsidies and accelerated approval procedures, on the other hand, support novel drugs ("forerunners = 先駆け Sakigake"), in the sense of "first-in-class" pharmaceutical entities, if they show high efficacy, and especially if they were first developed in Japan. This also applies to new drugs for the treatment of rare diseases (orphan drugs), paediatrics and regenerative medicine.

90% of all drugs require a prescription, and the prescribing physician may charge a "physician bonus" for this. The brand loyalty of Japanese patients and the distribution channel make market access difficult for foreign companies. In fact, more than 80% of all medication is distributed by the channels of only four companies, and marketing of drugs by the internet is limited to over-the-counter drugs (OTC), and even then burdened by severe regulations. As a consequence, a partnership with a well-chosen Japanese contract research organisation (CRO), a Japanese company, or an international company already operating in Japan as a "marketing authorization holder" (MAH) is therefore strongly recommended. Over 50 CROs offer such kind of services, and license scouts of Japanese or international pharmaceutical companies can be met at international trade fairs such as BioEurope or BioJapan.

2 Scope of the report

This report covers an introduction to the Japanese healthcare system and to the healthcare market, one of the largest in the world. Special attention is given to the market of biopharmaceuticals. Major players such as the pharmaceutical industry and the Japan Agency for Medical Research and Development (AMED), the "NIH of Japan", are shortly described.

This introduction is followed by a description of pharmaceutical products, with special reference to biopharmaceuticals and biosimilars. It is outlined, that therapeutic antibodies, which constitute the major part of the biopharmaceutical market both in value and weight, are mostly introduced from abroad, and that Japan's share in innovation in this field is below average of other industrial nations. However, Japan is an international leader in the development of cellular medicines.

The second part of this report deals with the regulations for marketing or producing pharmaceuticals and biopharmaceuticals for the Japanese market, governed by the Pharmaceutical Affairs law and overseen by PMDA, the Pharmaceuticals and Medical Devices Agency. Among standard procedures, which to a considerable part are already based on international regulations, Japan supports the introduction of innovative drugs through a "first-in-class" process ("Sakigake process"), offering opportunities to European SMEs or start-ups with highly innovative products.

It is further illustrated, how the National Health Insurance (NHI) regulates prices and promotes the use of generics, and which measures need to be taken for the marketing and sales of pharmaceuticals on the Japanese market.

Special emphasis is put on what European SMEs and start-ups should consider to best prepare for an entry into the huge, growing but sophisticated Japanese market for biopharmaceuticals.

Part of this report is based on an earlier account on this subject in German language, published in October 2018[2].

[2] Rolf Schmid, Gesundheitsmarkt Japan - Arzneimittel und Biopharmazeutika, Germany Trade and Invest (GTAI), October 2018

3 Introduction

Japan is a highly industrialised nation whose economy is largely based on science and technology (S&T). In 2017, the country had one of the biggest technology pools in the world, with over 1,060 million scientists and engineers; business enterprises, including the pharmaceutical industry, employed > 586,000 researchers and technicians[3]. For many decades, Japan has been amongst the world leaders in spending on R&D (2017: 3.48% of GDP), patent applications and scientific publications. Typical for Japan are the so-called research associations, temporary and government-co-funded collaborative research partnerships amongst industry, universities and government research centres. As we will see in chapter 4.7, this approach has also been chosen for Japan's biopharmaceutical industry.

Increasing competition with its Asian neighbours, especially China, is threatening Japan's economic and technological supremacy in Asia. With more than five million people in S&T, China's technology pool is already five times larger than Japan's, and China continues to increase its R&D expenditure from currently 2.1% of GDP.

Among Japan's specific problems are a high public debt (2018: 253% of GDP) [4] which limits public expenditures, and a rapidly ageing population (Table 1). As a result of high life expectancy, a persistently low fertility rate of 1.45 births per woman and negligible immigration, one in four Japanese (almost 28% of the population) was over 65 by 2017; by 2050, the proportion could rise to over 35%[5]. As a result, there is already a shortage of labour in many sectors: health and social expenditures for the elderly are on the rise, and so is national debt.

Table 1: Population development in Japan[5]

	2016	2018	Forecast 2020
Total population (million)	126,9	126,2	125,3
Population growth: -0.10%			
Life expectancy at birth (2015): women 87.05, men 80.79			
Age structure (2017) ▪ 0-14 years: 12.8% ▪ 15-24 years: 9.6% ▪ 25-54 years: 37.5% ▪ 55-64 years: 12.2% ▪ 65 years and over: 27.9%			

[3] https://www.stat.go.jp/data/nenkan/index1.html
[4] https://tradingeconomics.com/japan/government-debt-to-gdp
[5] https://www.stat.go.jp/english/data/handbook/pdf/2017all.pdf

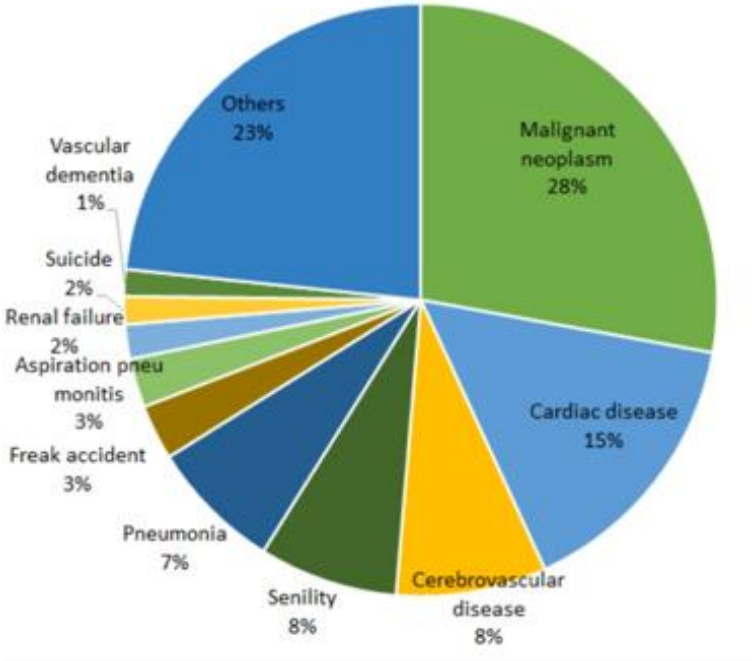
4 Japan's healthcare system

4.1 Introduction

Japan's ageing population has a high purchasing power and is health-conscious. The state reimbursement system follows the principle of public welfare and protects its citizens well against the risk of illness. In 2016, pharmaceuticals generated sales of around $108 billion (section 4.6). This makes Japan's pharmaceutical market the third largest in the world. Between 2008 and 2015, it grew at an average annual rate of 3.4%, stronger than Japan's GDP[6].

Amongst the causes of death of the Japanese, nearly one third relate to malignant neoplasms (Figure 1). Cardiac diseases are less frequent compared to Western industrialised countries. A relatively high proportion of cerebrovascular diseases and pneumonia is noticeable (2017: 8% and 7% of all deaths, respectively)[7]. Lifestyle diseases are also on the rise: research by Japan's Ministry of Health, Labour and Welfare (MHLW) at the end of 2016 suggests that 10 million Japanese adults have diabetes[8].

Fig. 1: Causes of death in Japan, 2017[8]



4.2 Healthcare expenditure

Japan's healthcare system is highly developed and based on the concept of public welfare. Public health spending accounted for over 11% of GDP in 2017 (Table 2).

Table 2: Health expenditure and health-related facilities[9]

[6] https://www.jetro.go.jp/ext_images/en/invest/attract/pdf/en_2016_life.pdf
[7] http://nbakki.hatenablog.com/entry/Top_10_Causes_of_Death_in_Japan_2017
[8] https://www.japantimes.co.jp/news/2017/09/21/national/science-health/diabetes-continues-trend-japan-10-million-suspected-adult-cases/#.WvxSXy_qhBw
[9] https://www.exportinitiative-gesundheitswirtschaft.de/EIG/Redaktion/DE/Publikationen/PDF/gesundheitsmarkt-japan.html

	2015	2017
Total health care expenditure ($ billion)	418.3	467.9
Health expenditure per capita ($)	3,268.4	3,669.9
Share of GDP (%)	10.9	11.1
Share of government expenditure (%)	84.0	84.2
Share of private expenditure (%)	16.0	15.8
Hospitals with > 20 beds	8,596	8,481
Number of doctors (about 2/3 of them work in hospitals)	316,199	326,430
per 100,000 inhabitants	247	256
Number of pharmacists	294,855	308,735

According to estimates by the consulting firm McKinsey, higher spending on the elderly could drive this share up to 13.5% by 2035[10]. The government is responding with cost containment measures, such as government intervention on pricing and the approval of more generic prescription drugs. It also supports innovation by inviting new technologies, services and regulations to turn the healthcare market into a growth industry. IT-supported health care, scientifically optimised nutrition, age-appropriate medicine, care by robots and prosthetic products are booming fields of industrial development, which the Ministry of Economy Trade and Industry METI also frequently supports in research associations with universities and state research centres. A focus lies on improving the quality of life of the elderly which aims to maintain the state of not-yet-ill-being as far as possible into old age[11].

Japan's state and company insurance systems largely cover disease risks. The state controls the cost structure and thus favours laboratory tests, equipment-based medicine and prescription drugs. Employers are obliged to send their employees to preventive medical check-ups every year. There are weaknesses in the scarcity of medical personnel and in excessively long hospital stays.

More than 90% of all clinics are private day clinics without a state license (medical practices). They are run as a family business. In contrast, two thirds of the 300,000 doctors work in Japan's 8,500 hospitals. According to WHO surveys, the Japanese spent about $75 billion privately on their health in 2016. Mild drugs with a low concentration of active ingredients such as vitamins or plant preparations for the treatment of colds, pain or stress are popular - they allow people to continue working even if considered ill according to Western standards.

Typical for Japan are the many food products with state-registered health or functional claims (FOSHU, food of specified health use, and FFC, food with function claims). At the end of 2016, 1,271 food items carried an FOSHU label and about 500 an FFC label, and their market volume was estimated at over $20 billion[12,13].

[10] https://www.mckinsey.com/industries/healthcare-systems-and-services/our-insights/improving-japans-health-care-system
[11] https://www.j-mibyou.or.jp/mibyotowa.htm
[12] https://www.nutraingredients-asia.com/Article/2016/10/10/Japan-moves-beyond-Foshu-Over-400-products-approved-under-new-health-claims-regime-in-last-year
[13] https://www.wysiwyg.co.jp/service/systematicreview/systematicreview-e/

4.3 Japan's Pharmaceutical and Biopharmaceutical Industry

In an international comparison, Japan's pharmaceutical companies have not yet reached the top ranks of international pharmaceutical manufacturers (Table 3). However, the leading companies are networked worldwide, execute mergers and acquisitions worldwide[14] and usually operate R&D centres in the US and Europe.

Table 3: Japan's largest pharmaceutical companies[15]

Market Capitalisation on March 16, 2019	**(US$ bn)**	**Ranking (World)**
Takeda Pharmaceutical Industries Co Ltd	65.77	15
Chugai Pharmaceutical Co Ltd	37.67	27
Astellas Pharma Inc.	29,97	29
Daiichi Sankyo Co Ltd	25.75	30
Eisei Co. Ltd.	23.51	31
Otsuka Holdings Co Ltd	22.86	34
Shionogi & Co. Ltd.	19.20	38
for comparison		
Johnson & Johnson (J&J)	366.40	1
Roche	231.99	2
Pfizer Inc.	231.95	3

Amongst over 300 pharmaceutical companies in Japan, the largest have formed the Japan Pharmaceutical Manufacturer Association (JPMA)[16]. The top twenty of these companies spent over $13 billion on R&D in 2017[17]. Japan's pharmaceutical industry has long been familiar with the development of biological active ingredients: as early as 1945, more than 80 Japanese companies produced penicillin[18]. Today, many JPMA members do research on and manufacture biopharmaceuticals. They are organised in the Japan Bioindustry Association (JBA)[19], an association close to the Ministry of Economics and Trade METI. The JBA organises BioJapan in Yokohama, Japan's largest pharmaceutical and biotech trade fair. It takes place annually and offers European companies a good opportunity to get to know the market and its players (see section 8.3).

Beyond "big pharma", there is a sizeable group of Japanese venture companies and start-ups targeting new biopharmaceuticals. A full review is beyond the format of this report, but a small selection of such companies and their targets is provided in Table 4[20].

Table 4: Japanese venture companies and start-ups targeting biopharmaceuticals

Company name	Target	URL
EdiGENE Inc.	Therapeutics for genetic disorders based on gene editing	http://www.edi-gene.com

[14] https://asia.nikkei.com/Business/Business-trends/Japan-Inc-signed-record-777-overseas-M-A-deals-in-2018
[15] https://www.value.today/world-top-companies/pharmaceutical
[16] http://www.jpma.or.jp/english/
[17] https://eolas-bio.com/market/
[18] https://www.eubusinessinjapan.eu/sectors/healthcare-medical/pharmaceuticals
[19] https://www.jba.or.jp/en/
[20] https://www.j-startup.go.jp/en/about/

Quantum Biosystems Inc.	Semiconductor-based single-molecule gene sequence analyser	http://quantumbiosystems.com
PeptidDream Inc.	Peptide discovery platform for identification of drug targets	https://www.peptidream.com
Megakaryon Corporation	Blood platelets from iPS cells	http://www.megakaryon.com/en/
ReproCELL Inc.	Regenerative cell products starting from iPS cells including gene editing	https://www.reprocell.com
RegCell Co., Ltd.	Immunotherapies bysed on antigen-specific regulatory T-cells (Tregs)	http://regcell.jp/home_en

4.4 Public R&D in biomedicine

Japanese academia has an excellent research infrastructure for life sciences and pharmaceuticals. A detailed description of universities and public research institutes involved in biomedical R&D is beyond the scope of this review. Table 5 contains a selection of major players.

Table 5: Some major players in Japanese public biomedicine R&D

RIKEN	Center for Integrative Medical Science	http://www.riken.jp/~/media/riken/about/organization/ims-e-20190701.pdf
NIBIO	National Institute of Biomedical Innovation	http://www.nibiohn.go.jp/nibio/english/index.html, https://www.nibiohn.go.jp/en/activities/biodrug-development.html
University of Tokyo	Institute of Medical Science	http://www.ims.u-tokyo.ac.jp/imsut/en/
Kyoto University Hospital	Kyoto University Hospital	http://www.kuhp.kyoto-u.ac.jp/english/index.html
Kyoto University	Center for iPS Cell Research and Application	http://www.cira.kyoto-u.ac.jp/e/
Kobe University	School of Medicine, Dept. of iPS cell applications	http://www.lab.kobe-u.ac.jp/gmed-ipsc/en/member/index.html
Osaka University	Center of Medical Innovation and Translational Research	http://www.comit.med.osaka-u.ac.jp/en/
Keio University	Institute of Advanced Biosciences	http://www.iab.keio.ac.jp/en/about/index.html
Tokyo University of Science	Research Institute for Biomedical Sciences	https://www.tus.ac.jp/en/labo/research_life.html

4.5 Japan Agency for Medical Research and Development (AMED)

In acknowledgement of the leadership of the US National Institute of Health (NIH), the Japanese government decided in 2015 to strategically align drug research, forming the Japan Agency for Medical Research and Development (AMED)[21]. Thanks to generous budgets, AMED has already managed to bundle research priorities that were previously

[21] https://www.amed.go.jp/en/index.html

scattered across academia, and to network them with projects in the pharmaceutical industry. Examples in biopharmaceutical-related fields are a large national project on genomic medicine (see section 4.11), and national programmes for the treatment of rare diseases, cancer therapy or the therapy of psychiatric and neurological disorders[22].

4.6 Japan's market for pharmaceuticals and biopharmaceuticals

Japan's pharmaceutical market is the world's third largest, behind the USA and China, and shows a steady growth. Its market size reached ~$104 billion in 2018[23].

More than 90% of all medications are prescription-only. Almost 90% of them are protected by patents, but important blockbusters will become patent-free in the next few years. In 2016, generic drugs accounted for only about 14% (value-based) of total pharmaceutical sales. However, their share is steadily growing. Imports of foreign drugs accounted for around 18% in 2016. In 2017, the EU exported pharmaceutical products worth EUR 8.1 billion to Japan, corresponding to a market share of around 8% (Table 6).

Table 6: The Japanese pharmaceutical market[24]

	2014	2016	2018*	2022*
Pharmaceuticals sales ($ billion)	106,137	107,805	104,005	104,818
Pharmaceutical sales per capita ($)	828.	843.9	817.7	833.9
Of which were prescription drugs (%)	94	94.1	94.1	94
Of which were patented (%)	87.8	86.4	84.9	81.9
Generics (% of pharmaceutical sales)	12.2	13.6	15.1	18.1
OTC drugs (% of pharmaceutical sales)	6	6.1	6.2	6.4
Imports ($ billion)	19,843	19,135	19,440	
Imports as a share of pharmaceutical sales (%)	18.4	18.3	18.5	

*forecasts

4.7 Japan's biopharmaceutical market: the competitive situation

Biologically active substances are considered the driving force behind innovation in the pharmaceutical industry. In this aspect, Japan is lagging behind the USA and Europe (Figure 2).

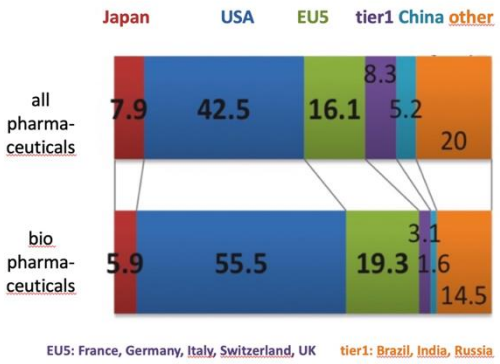


Fig. 2: Share of biopharmaceutical sales 2016[25]

[22] https://www.amed.go.jp/content/000002892.pdf
[23] https://www.export.gov/article?id=Japan-Pharmaceutical
[24] https://www.exportinitiative-gesundheitswirtschaft.de/EIG/Redaktion/DE/Publikationen/PDF/gesundheitsmarkt-japan.pdf?__blob=publicationFile&v=8
[25] http://www.jpma.or.jp/opir/research/rs_071/paper_71.pdf

According to a survey by the Japan External Trade Organization (JETRO), biopharmaceuticals accounted for only 12% of Japanese pharmaceutical sales in 2014, compared with 30% on the world market. By the end of 2016, foreign companies such as Sanofi, Pfizer, Roche, MSD and Novo Nordisk dominated over 71% of the Japanese biopharmaceutical market with 95 products, and four out of the ten biosimilars approved in Japan until July 2017 came from foreign companies (see section 4.9). JETRO expects that the turnover of biotechnologically produced pharmaceutical products in Japan will increase by more than 8% annually and reach a value of 47 billion $ in 2020. The market for biosimilars is expected to grow even faster, by as much as 35% and generate sales of 4 billion $ (see section 4.9)[26].

4.8 Biopharmaceuticals

A recent discussion paper from the Japanese Pharmaceutical Manufacturers Association (JPMA) provides a detailed analysis of sales values and production quantities of biopharmaceuticals in Japan over time (Figures 3 and 4, for details see ref. 21). As can be seen from these graphs, market growth is driven mostly by antibody drugs.

Fig. 3 Sales volume of biopharmaceuticals in Japan, 2001 - 2016

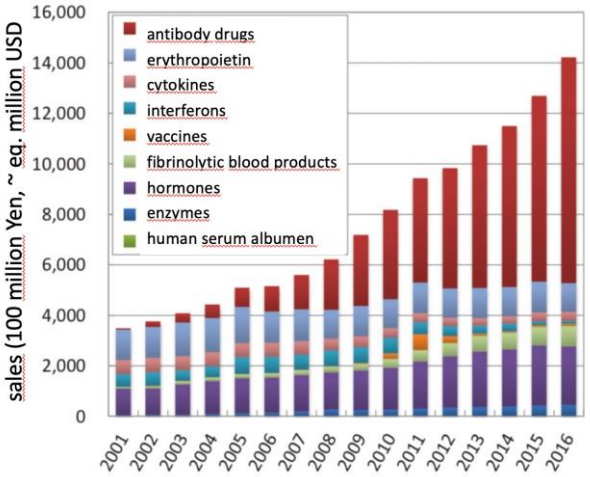
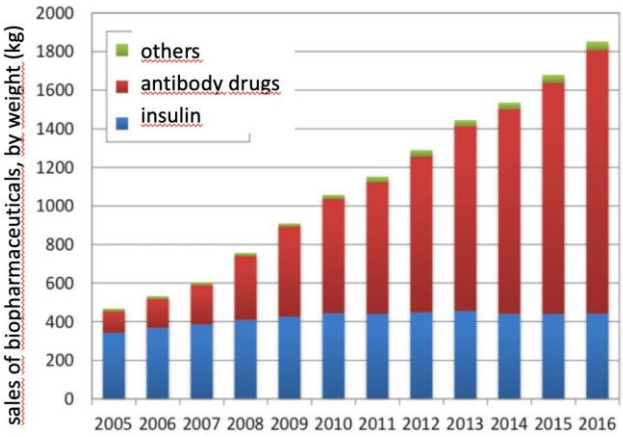


Fig. 4: Sales volume of biopharmaceuticals in Japan by weight, 2005 - 2016



[26] https://www.jetro.go.jp/ext_images/en/invest/attract/pdf/mr_bio_en201712.pdf

About 80% of the antibody drugs were produced by Chinese Hamster Ovary cells (CHO).

Recent activities of Japanese companies in the field, based on company press releases, are provided in Table 7. This summary provides evidence that Japanese companies are actively attempting to break the dominance of foreign companies which yet dominate Japan's biopharmaceutical market.

Table 7 Recent activities of Japanese companies related to biopharmaceutical production[26]

Press release of company	Activity	Details
Within Japan		
2014/4/8 Kyowa Hakko Kirin	Completion of biopharmaceutical drug substance manufacturing facilities in Takasaki plant	Purification facility incorporating a large-scale column and a culture facility (12,000 L culture tank) for recombinant animal cells, the largest class in Japan. Investment: about 6 billion yen
2014/10/30 Kyowa Hakko Kirin	New pharmaceutical building completed in Takasaki Plant	Can produce many kinds of products such as lyophilizers and solutions mainly for biopharmaceuticals. Investment: about 4.6 billion yen
2015/10/22 Chugai Pharma	Establishment of a bioantibody drug substance production plant in the Ukima Plant	Six 6,000 L culture vessels are newly established. Seamless production of large-quantity, small-lot varieties of clinical trials for late-stage development and early-stage commercial bio-drugs. Total investment: about 37.2 billion yen
2016/6/7 Mitsubishi Gas Chemical, Nihon Kayaku	Establishment of Kartivex, an antibody drug manufacturing company	Joint venture for domestic production of antibody drugs including biosimilars. Will operate production facilities for antibody drugs within two years
2016/8/2 Kyowa Hakko Kirin	Completed biopharmaceutical drug substance manufacturing building in Takasaki plant	Facility for cultivating recombinant animal cells, the largest class in Japan (12,000 L cell reactors). Investment about 7.1 billion yen
2017/2/17 Zenyaku Kogyo	Joined the Next-Generation Biopharmaceutical Manufacturing Research Association	Will promote business of next-generation biopharmaceutical manufacturing technology
2017/2/22 Daiichi Sankyo	Invests 40 billion yen in biopharmaceutical production, expands three domestic plants	Full-scale production of antibody-drug complex (ADC) in which an anticancer drug is fused to an antibody
outside Japan		
2016/1/6 Takeda Pharmaceuticals	Acquisition of a biopharmaceutical manufacturing facility in the United States	Acquired a biopharmaceutical manufacturing facility located in Minnesota from Baxalta US Inc. Used as a manufacturing facility for vedolizumab and other bio-products
2016/6/7 Fuji Film	Increase of production capacity for biopharmaceuticals contract manufacturing	Takes advantage 20,000 L culture facility for microorganisms owned by Merck US, located in Ireland. Investment $ 60 million
2018/9/6 AGC Asahi Glass	Acquired German biopharmaceutical manufacturing company Biomeva	Development and manufacturing service of biopharmaceuticals using a microbial expression system
2016/12/20 AGC Asahi Glass	Acquired CMC Biologics, a US/Danish CDMO	CDMO using animal cells and microorganisms. Covers drug development and commercial drug product development, scale-up and commercial manufacturing. Acquired all shares for about 60 billion yen
2017/3/22 Meiji Seika Pharma	Establishment of antibody drug manufacturing process at DM Bio in Korea. Start of CMO service of biopharmaceuticals	Establish commercial-scale antibody drug manufacturing and start contract manufacturing (CMO) service of biopharmaceuticals
2017/4/18 Fuji Film	Expand biopharmaceutical development and manufacturing contract business	Enhance US-based biopharmaceutical production capacity: introduce three 2,000 L animal cell culture tanks (expansion to a maximum of 12). Production and development bases in the

		United Kingdom will also be expanded. Total investment: about 14 billion yen
2017/5/9 Kaneka	New Belgium facility quadruples biopharmaceutical production capacity	New large-scale manufacturing facility including a 2,200-liter large-scale culture tank for contract manufacturing. Capital investment: approximately 5 billion yen
2017/5/22 JSR	Expanded biopharmaceutical manufacturing facilities in the US	At KBI Biopharma, Inc., a consolidated subsidiary, two animal cell culture facilities (2000 L bioreactors) and one microbial culture facility (300 L) added. Investment: about 30 million USD
2017/9/25 AGC Asahi Glass	Subsidiary CMC Biologics in Denmark to increase biopharmaceutical production capacity	Five single-use 2,000-liter animal cell culture tanks were added. Supports a wide range of culture sizes from existing 2,000 liters to up to 12,000 liters
2017/11/6 Fuji Film	Expanded process development and production facilities for antibody drugs at US and UK bases	Three more single-use 2,000 L animal cell culture tanks were introduced at the US base, investment approximately 2.2 billion yen. Expanded production process development bases and facilities in the United Kingdom: investment approximately 1 billion yen
2018/3/6 AGC Asahi Glass	Augmented biopharmaceutical culture capabilities of AGC Biologics (US)	Introduction of a new single-use culture vessel of 2,000 L. Covers a wide range of phase II requests, prompt response to scale-up and production
2018/3/7 JSR	KBI Biopharma Inc. (US)	Concluded co-marketing agreement on outsourcing of biopharmaceutical development and manufacturing (CDMO) services in Japan

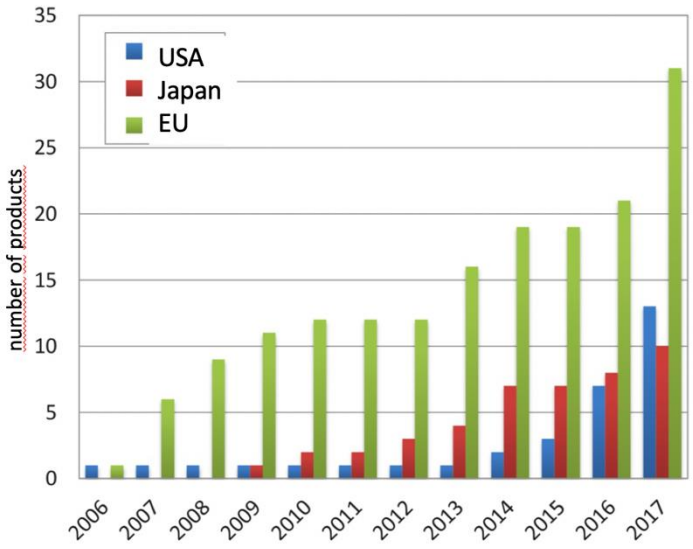
On the initiative of the Japan Bioindustry Association JBA, companies, universities and public research institutes established in 2013 a "Manufacturing Technology Association of Biologics"[27] which presently comprises 32 companies and startups, 4 national universities and several public research institutes. It aims to help members upgrade advanced manufacturing technologies for biopharmaceuticals in order to become internationally competitive. Companies such as Daiichi Sankyo, JNC, Asahi Kasei, Kaneka, Toray and Takara Bio are members, but also equipment manufacturers like Able, Hitachi, Yokogawa or Shimadzu.

4.9 Biosimilars

Biosimilars are the generic versions of biopharmaceuticals[28]. In order to keep health-related costs under control, the development of biosimilars and of generics, is strongly supported by governments all over the world, and also by the Japanese government (Figure 5). JETRO expects that the market of biosimilars will show strong growth over the next years[27] and JPMA estimates the sales of biosimilars in Japan at 18.4 billion Yen ($170 million) in 2016[26].

[27] http://cho-mab.or.jp
[28] https://www.pfizerbiosimilars.com/node/37

Fig. 5: Number of approved biosimilars in the USA, Japan and the EU[26]



As shown in Table 8, at present 15 biosimilars have been approved for manufacturing and sales in Japan.

Table 8: Approved biosimilars in Japan

Company	Name of biosimilar	Reference product/generic name	original registration	approved in Japan
Sandoz	Somatropin BS	Human growth hormone	1987	2009
JCR Pharma	Epoetin Alfa BS	Epoetin kappa	1990	2010
Mochida Pharmaceuticals	Filgrastim BS	Filgrastim/G-CSF	1992	2012
Fuji Pharma	Filgrastim BS	Filgrastim/G-CSF	1992	2012
Teva	Filgrastim BS	Filgrastim/G-CSF	1992	2013
Nippon Kayaku	Filgrastim BS	Filgrastim/G-CSF	1992	2014
Sandoz	Filgrastim BS	Filgrastim/G-CSF	1992	2014
Eli Lilly	Insulin glargine BS	Lantus/Insulin glargine	2003	2014
Nippon Kayaku	Infliximab BS	Infliximab/Remicade, TNFa antibody	2002	2014
Fujifilm Pharma	Insulin glargine BS	Lantus/Insulin glargine	2003	2016
Sandoz/Kyowa Hakko Kirin	Rituximab BS	Rituximab, CD20 antibody	2001	2016
Kyowa Hakko Kirin	Darbepoetin alfa BS	Darbepoetin alfa, engineered EPO	2001	2018
Daiichi Sankyo	Trastuzumab BS	Trastuzumab/Herceptin	1998	2018
Mochida Pharmaceuticals	Etanercept BS	Etanercept/TNFR2/p75 fusion protein	2000	2018
Lupin/ YL Biologics	Etanercept BS	Etanercept/ TNFR2/p75 fusion protein	2000	2019

According to the survey by JPMA[26], there were 144 biosimilars in clinical development or pre-application stages in early 2018, and another 176 biosimilars in the preclinical stage. On the other hand, the development of 290

biosimilars was discontinued, showing the difficulty of developing biosimilars such as proof of their "bio-equivalence". Table 9 provides examples for specific products.

Table 9: Status of biosimilar development in Japan, early 2018

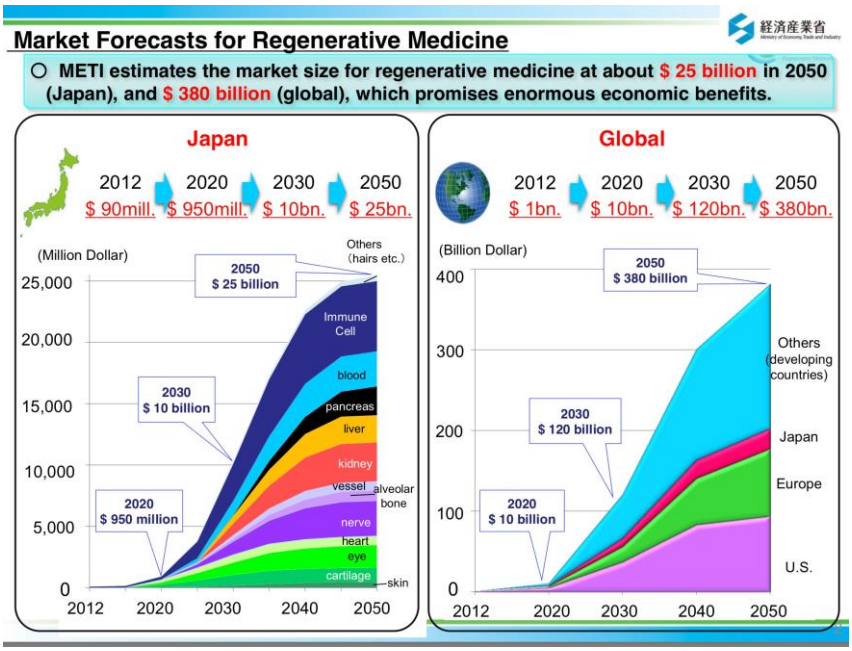
	under development	preclinical stage	discontinued
adalimumab	20	11	9
filgrastim	13	10	16
rituximab	13	3	26
bevacizumab	19	13	13
trastuzumab	12	11	16
Interferon	6	5	16
etanercept	7	4	12
insulin	6	9	13
infliximab	7	4	8
darbepoetin	6	0	3

4.10 Cell products

In 2012, Shinya Yamanaka, a researcher at Kyoto University, received the Nobel Prize for Medicine for a method in which cells taken from human skin can be transformed in the laboratory into organ-typical cells of the heart muscle, eye or liver in order to heal aging and degenerated organs[29]. This discovery has led Japan to a national focus on regenerative medicine[30] (Figure 6) with strong impact on the pharmaceutical industry: out of 43 clinical trials registered in May 2018, 25 were initiated by companies, and three cell products had already been approved. Apart from pharmaceutical firms, medical technology companies such as Terumo, and camera manufacturers such as Fujifilm, Nikon and Konika-Minolta, have entered this new field as they are under pressure due to disruptive innovations in their traditional market segments.

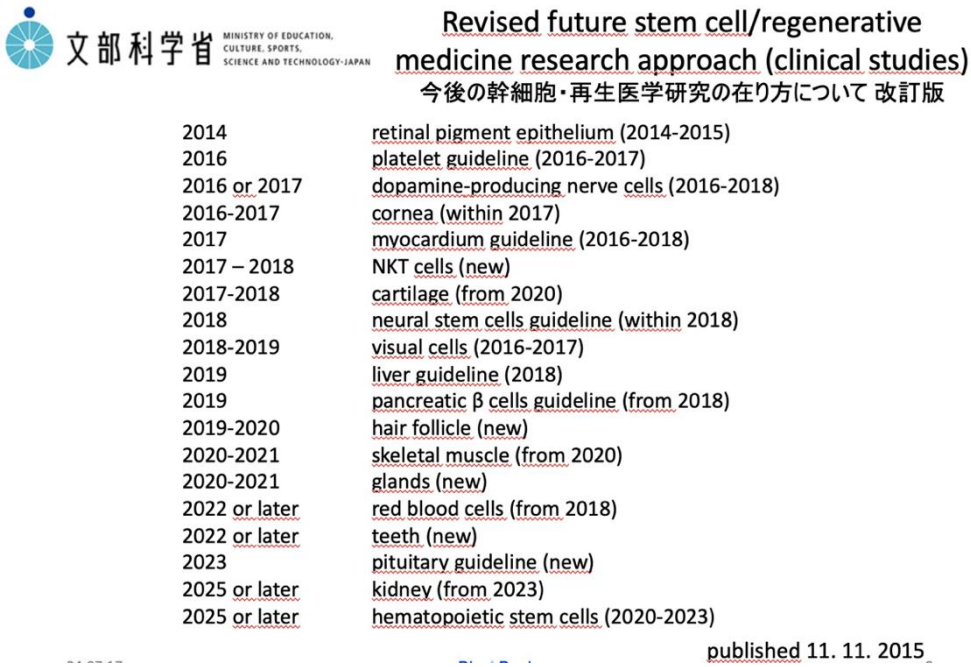
[29] Rolf Schmid: Stammzelltechnik: Japans systematischer Ansatz, Nachrichten aus der Chemie, Mai 2018
[30] https://www.jetro.go.jp/ext_images/australia/JVBFPresentations/FIRM.pdf

Fig. 6 Market Forecast of METI for Regenerative Medicine[31]



A pertinent R&D organisation, the Forum for Innovative Regenerative Medicine (FIRM)[31], has more than 150 member companies working together on R&D, standardisation and safety. The Japanese government is supporting these developments with research initiatives and has created guidelines and regulatory measures since 2014 to accelerate clinical testing and market introduction of cell products (Figure 7).

Fig. 7 Survey of guidelines for R&D on regenerative medicines[30]



[31] https://firm.or.jp/en/about3

4.11 Genomic medicine and gene therapy

Another important direction of biomedical innovation is in genomic medicine (other term: personalised medicine). It involves using genomic information about an individual as part of clinical care (e.g. for diagnostic or therapeutic decision-making). Already, genomic medicine is making an impact in the fields of oncology, pharmacology, rare and undiagnosed diseases, and infectious diseases[32].

In Japan, the Tohoku Medical Megabank Organization[33] which was established after the Great Western Earthquake in 2011 collects genomic and post-genomic data from 70,000 individuals and their blood relatives, provided they represent at least three generations. The data are used to determine markers for hereditary, genetically coded diseases as well as genetic criteria for the individual tolerance of drugs and foods.

Japan is also among the global leaders of R&D on gene therapy[34]. Several Japanese companies who develop gene therapies for the treatment of diseases are presented in Table 10.

Table 10: Some Japanese companies involved in R&D on gene therapy

Company	topics
Anges MD[35]	• Gene medicine for the treatment of critical limb ischemia • NF-kappaB decoy oligonucleotide for suppression of inflammation
Takara Bio[36]	• Oncolytic virus HF10 for co-treatment of unresectable malignant melanoma • Antigen-specific transgenic T-lymphocytes • Retro-nectin therapy of lymphocytes
Gene Therapy Research Institution[37]	Adeno-associated virus (AAV)-based treatment of • Parkinson's disease • Amyotrophic lateral sclerosis (ALS) • Aromatic amino acid decarboxylase deficiency (ADCC), and • Alzheimer's disease
Astellas[38]	AAV-based therapy of rhodopsin diseases
Bonac[39]	"Bonac RNA" as a stable form of RNA

5 Market access

5.1 Categories of pharmaceutical and biopharmaceutical products

The Japanese pharmaceutical market distinguishes three categories of products, for which different approval and sales conditions apply: prescription drugs, non-prescription drugs (OTC) and quasi drugs (e.g. ointments) (Table 11).

[32] https://www.genome.gov/health/Genomics-and-Medicine
[33] https://www.megabank.tohoku.ac.jp/english/
[34] EU-Japan Centre's report on "Update on cell technology, cell therapy, tissue engineering and gene therapy in Japan", March 2017
[35] https://www.anges.co.jp/en/
[36] http://www.takara-bio.com
[37] http://www.genetherapy-ri.com
[38] https://www.astellas.com
[39] http://www.bonac.com/global/en/

Prescription drugs make up over 90% of the Japanese pharmaceutical market. While the market as a whole is stagnating, the share of generics is growing.

Table 11: Categories of pharmaceutical products

Category	Approval procedure	Sale (see section 5.10)
Prescription-only medicines (over 90%), including all biopharmaceuticals and about 60% generic drugs/biosimilars	• Standard authorisation procedures • Generic medicines subject to special prescription rules (see section 5.6)	No online sales
Non-prescription drugs (over-the-counter/OTC drugs)	Special case: "switch drugs"*	May only be sold after advice from the pharmacist, but also online

*weaker drugs that showed no unexpected side effects three years after market launch;
before sale, a pharmacist must give personal advice ("patient must be informed").

- Class 1 (contain highly active substances)
- Class 2 (moderate risks and side effects; examples: cough medicine, painkillers)
- Class 3 (low risks and side effects; example: vitamins). Advice from the pharmacist is recommended.

5.2 The Pharmaceutical Affairs Law and the Pharmaceutical and Medical Devices Agency (PMDA)

The Pharmaceutical Affairs Law contains all relevant rules and regulations for domestic and foreign companies seeking a license to manufacture and sell pharmaceutical products. First adopted in 1943, the current version came into force on 25 November 2014. The Ministry of Health, Labour and Welfare (MHLW) is the responsible ministry.

The approval of pharmaceutical products is carried out by the Pharmaceutical Affairs and Food Council (PAFC) of the MHLW. The regulatory authority is the Pharmaceutical and Medical Devices Agency (PMDA)[40]. It controls the efficacy, safety and quality of pharmaceutical products in advance. This term covers not only medicines, but also medical aids ("quasi drugs", for example ointments), cosmetics, medical devices and regenerative medical products. The core tasks of PMDA are: inspection, safety precautions and compensation (Figure 8).

Fig. 8: Tasks of the Pharmaceutical and Medical Devices Agency (PMDA)[41]

[40] https://www.pmda.go.jp/files/000218744.pdf
[41] https://www.pacificbridgemedical.com/wp-content/uploads/2015/04/Japan-Drug-Regulatory-Overview-2014.pdf

Inspection: The PMDA conducts the regulatory review for approval and checks whether a manufacturing plant produces according to international standards (Good Manufacturing Practice, GMP). It advises on clinical studies, reviews participating clinics (Good Clinical Practice, GCP) and finally examines the documents submitted by the manufacturer for a manufacturing and sales permit by the MHLW.

Safety precautions: The PMDA systematically collects safety information on adverse drug reactions and stores it in a Medical Information Database. To this end, it requires companies to implement Good Post-Marketing Study Practice (GPSP) and Good Pharmacovigilance Practice (GVP). Using the Medical Information Database Network MID-NET, it analyses anonymous patient data in order to predict security problems. Doctors and pharmacists receive up-to-date safety information via a free e-mail information service.

Compensation: As a consequence of court rulings on thalidomide and quinoform disease with nearly 7,000 cases in Japan alone, the government established the Fund for Relief Services for Adverse Drug Reactions in 1979, which is invested by industry and government grants. Since 1979, the fund has provided more than $18 million in compensation for adverse drug reactions (as of 2015). Since 2004, the Relief Fund has also covered benefits for infections caused by taking biological drugs - a consequence of the BSE scandal. Since 2014, the benefits catalogue has also included compensation for undesired side effects of regenerative medical products[42].

A particular feature of PMDA is that the agency has set up a profound consultation system, which provides advice to applicants at all levels of the regulatory process[43].

5.3 Authorisation requirements for marketing

Every domestic and foreign company marketing a pharmaceutical or biopharmaceutical product in Japan must be registered with the PMDA as a "Marketing Authorisation Holder" (MAH)[44]. Foreign companies without their own branch in Japan can appoint a Japanese MAH for this purpose. In the application for approval, a competent partner with Japanese knowledge must be named who will conduct the negotiations with the PMDA and, after market approval, assume responsibility for the reliability of the applicant and his data material[45]. More than forty Contract Research Organisations (CROs) are available for such services; they are organised in the Japan CRO Association[46]. Reliability testing includes Good Quality Practice (GQP), quality assurance, Good Vigilance Practice (GVP) sales assurance and Good Vigilance Practice (GVP) safety management[47].

The PMDA distinguishes between prescription (MAH type 1) and non-prescription (MAH type 2) drugs, and, in the case of foreign applicants, whether the registration is for biological or radioactive preparations, for non-sterile or sterile drugs, or only for the packaging, labelling or storage of pharmaceutical products. Each company needs only one MAH license. This is limited to five years. An application costs approximately $1,300 and takes 35 days to process (see ref. 26). PMDA offers a comprehensive personal consulting service for the approval of pharmaceutical products. This leads to short approval periods, and innovative products are ahead of the field[48].

[42] https://www.pmda.go.jp/files/000214750.pdf
[43] https://www.pmda.go.jp/files/000157641.pdf
[44] https://www.pmda.go.jp/english/review-services/reviews/foreign-mfr/0001.html
[45] https://www.pmda.go.jp/files/000163838.pdf
[46] https://www.google.com/search?client=safari&rls=en&q=japan+cro+association&ie=UTF-8&oe=UTF-8
[47] https://www.pmda.go.jp/files/000204341.pdf
[48] https://ec.europa.eu/futurium/en/system/files/ged/future_plan_of_pmda_japan.pdf

5.4 Authorisation requirements for manufacturing

Foreign manufacturers of active pharmaceutical ingredients, including biopharmaceuticals (APIs) must register in Japan and obtain a letter of access from a Marketing Authorization Holder (MAH)[49]. In the application, the manufacturer must name an expert advisor based in Japan, who is responsible for all discussions with the authority (in Japanese language); direct contact with the PMDA is not possible.

In the case of manufacturing companies abroad, the PMDA grants this licence (Foreign Manufacturer Registration, FMR) for a period of five years, usually after document examination; often, however, an inspector from the PMDA also arrives for an GMP audit (expert interpreters recommended!). Such GMP audit covers all production sites described in the application for approval[50]. In the case of prescription drugs, the facilities for the manufacture of active substances, intermediate products, packaging, labelling and storage as well as external testing and inspection bodies are also audited.

An FMR license costs approximately $1,400 for document review and is limited to five years. The official processing time is five months, but partial change approval applications can also take two years. If a foreign company wants to register a masterfile, it needs a letter of access from an MAH. For certified master files, PMDA only publishes global information. The most common problems for granting an FMR license are changes in manufacturing conditions, deficiencies in the agreement of technical conditions and change controls (QVP), and insufficient minimum requirements for biological raw materials and retention periods. This also applies to the manufacturing of biopharmaceuticals.

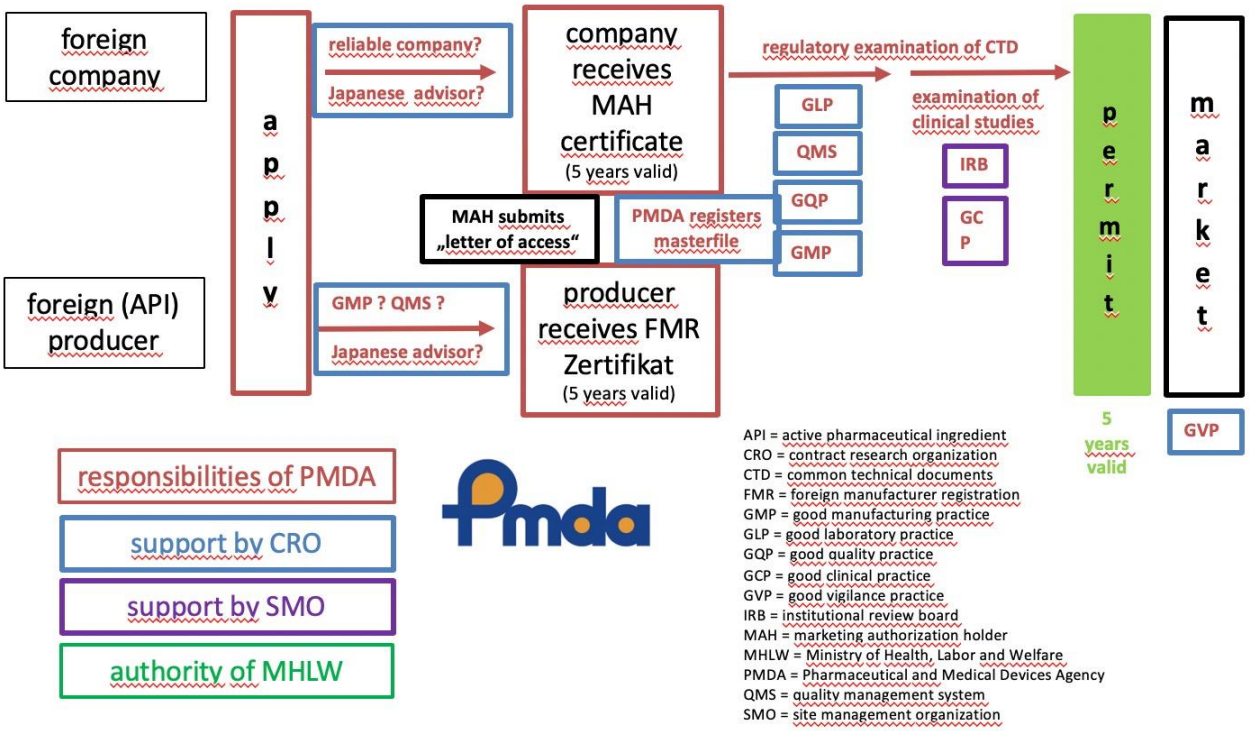
If a European company concludes a license deal or a development contract with an MAH that has already been licensed, the MAH may also take over the approval of the product by PMDA. The MAH can be both Japanese or international companies. Sales partnerships often follow the pattern of co-promotion, in which lower transfer prices are accepted in return for a sales monopoly in Japan. Technical partnerships are the rule for foreign start-ups. In this case, the partner in Japan assumes responsibility for creating all the prerequisites for market approval and for manufacturing the product within the framework of a license and development agreement.

5.5 Regulatory review and clinical trials

Thanks to the work of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH)[51], the PIC/S and other agreements, the Japanese rules of the regulatory review already comply with US and European standards in many areas (Figure 9).

[49] https://www.pmda.go.jp/english/review-services/reviews/foreign-mfr/0001.html
[50] https://www.jetro.go.jp/ext_images/brazil/topics/20140806962-topics/Sessao4-2_Tawaragi.pdf
[51] http://www.ich.org/home.html

Fig. 9 General scheme for registration of a drug or API



At the heart of the system is the Common Technical Document (CTD). It contains all quality, safety and efficacy information. Out of its five modules, only module 1 is Japan-specific - for example, it must contain a draft package insert in Japanese. Clinical trials are governed by country-specific Good Clinical Practice (J-GCP) standards. These contain additional requirements compared to the international standards (ICH-GCP), such as a site-specific institutional review board (IRB). International clinical trials are in vogue for new active substances aimed at international markets. They have larger patient populations and often achieve results more quickly[52]. More than 40 Japanese Site Management Organisations (SMOs) offer consulting services here[53]. PMDA also offers individual consultations in Japanese before each new phase of the regulatory review and clinical trials begins. Depending on the approval phase and drug type, the fees range between approximately $18,000 and $54,000.

Biological products require special attention due to infection risks. Many of the ICH regulations for biotechnologically manufactured drugs have already been incorporated into the Pharmaceutical Affairs Law, for example the Q5A guideline for testing for the absence of viruses. The manufacture of cellular drugs requires ministerial approval. For clinical trials with recombinant and gene therapy products, the Cartagena Protocol applies to the strictly controlled release of genetically modified material. Here too, special permits are required[54]. Cell products are biological products from processed human or animal cells or tissues intended for the reconstruction or repair of structures or functions of the human body (regenerative medicine). Their development to market maturity is particularly promoted, for example through accelerated testing procedures and provisional approvals (see section 5.8).

[52] http://www.mhlw.go.jp/file/04-Houdouhappyou-11123000-Iyakushokuhinkyoku-Shinsakanrika/GCPclinicaltrials.pdf
[53] http://jasmo.org
[54] https://www.biodic.go.jp/bch/english/cartagena/images/e_cartagena.pdf

5.6 Approval criteria for generics

In order to control the cost of the healthcare system, the government plans that, by 2020, sales of generic products should account for 80% of all drugs (value-based). This includes sales of biosimilars.

Approval criteria for generics are

- GMP-compliant manufacturing processes,
- conformity to Japanese standard specifications including standards and test methods used,
- good stability data from accelerated tests (stability of three samples over six months at 40°C (±1) and 75% (±5%) relative humidity),
- good absorption, distribution, metabolism and excretion (ADME) data for bioequivalence assessment.

They can be approved without clinical testing, if efficacy and safety are demonstrated in other ways[55]. However, if no data obtained on Japanese are available, such studies may be extensive in practice.

On average, 20% of all applications are rejected. The approval period is approximately 12 months for new applications and 6 - 12 months for changes on existing applications (see ref. 26).

For biopharmaceutical generics (biosimilars), special rules of MHLW to ensure bio-equivalence apply[56]. Details can be retrieved from the website of the Japan Generics Medicine Association (JGA)[57].

5.7 Orphan drugs

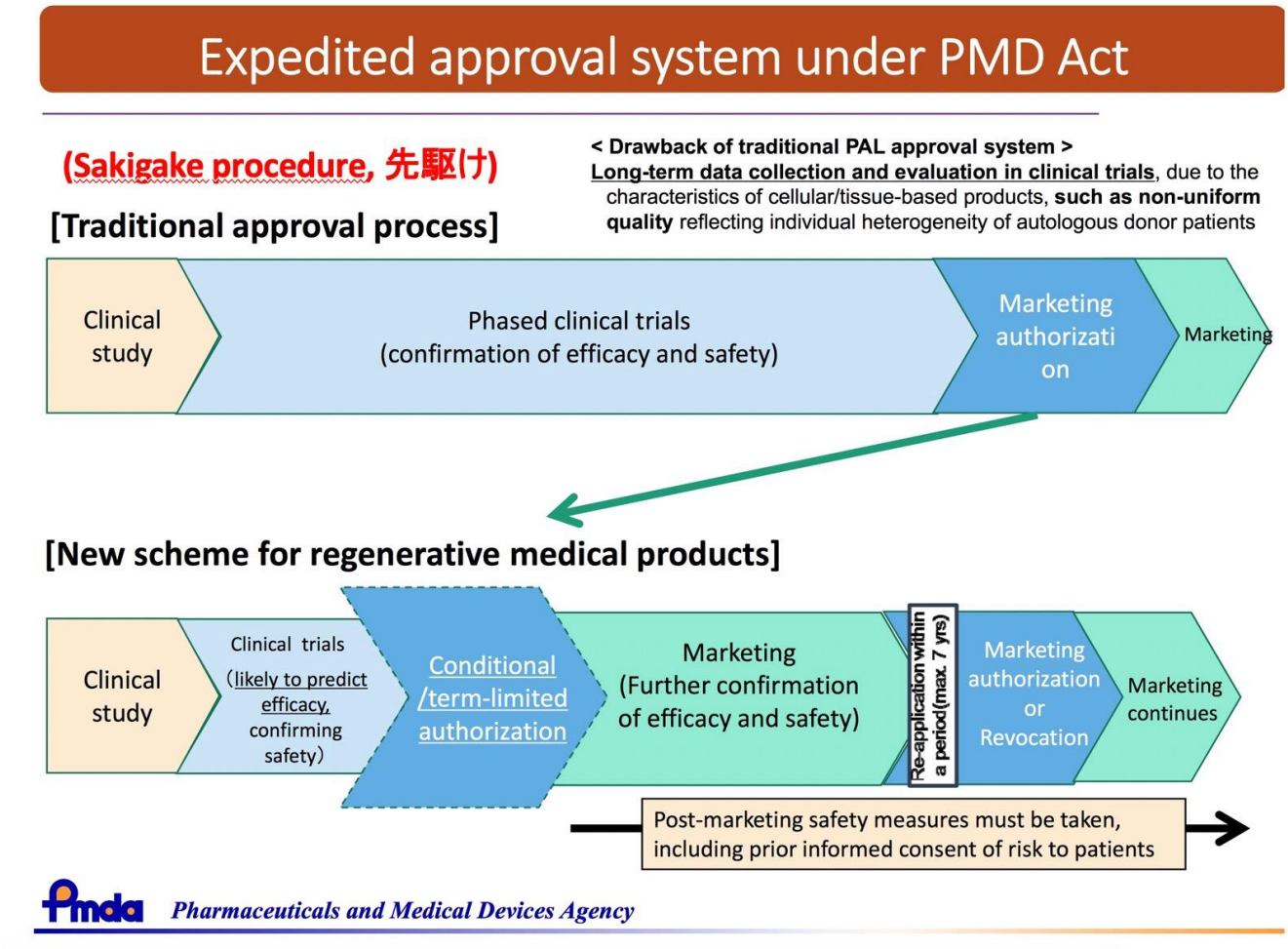
Orphan drugs are active pharmaceutical ingredients for severe or chronic diseases for which there is no drug or medical treatment and which affect less than 50,000 people, in the case of chronic diseases less than 180,000 people. Orphan drugs are expected to be significantly effective and safe. For such drugs, the Japanese government offers priority advice from the PMDA, priority checks, tax relief, government grants and exclusive marketing periods[58].

5.8 Innovative products and bio-products: the forerunner (“Sakigake”) procedure

The Japanese government has recently emphasized the aim to accelerate the approval of innovative drugs, roughly corresponding to the American "first-in-class" label. If a pharmaceutical product, including a biopharmaceutical, meets a therapeutic gap, shows high efficacy and safety in initial clinical studies and was first developed in Japan, it can be rated "innovative" through consultations with the PMDA[59]. In such case, accelerated regulatory reviews are carried out according to the so-called Sakigake procedure, leading to provisional approval (Figure 10). Such approval is conditional and limited in time, pharmacovigilance is subject to stricter rules, and a final evaluation of the product must be carried out after seven years at the latest.

[55] https://www.pmda.go.jp/files/000221883.pdf
[56] https://www.jga.gr.jp/library/old/www.jga.gr.jp/english/wp-content/uploads/sites/4/2015/03/Interim-Translation1.pdf
[57] https://www.jga.gr.jp/english/country-overview/biosimilar-products.html
[58] https://www.pacificbridgemedical.com/publication/japan-orphan-drug-update-2017/
[59] http://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/dl/140729-01-02.pdf

Fig. 10 Expedited approval system for innovative drugs[60]



5.9 Pricing

The pricing of medicines is carried out by the National Health Insurance (NHI) and published by the MHLW. The NHI establishes a price list four times a year, which has been drawn up by a committee (中医協 Chuikyo, Central Social Insurance Medical Council) and is binding for hospitals and pharmacies[60]. The prices for medicines are set by the Japanese government. Innovative products, especially biologics, have an advantage. State pricing includes: the proven costs of the manufacturer, "daily price equivalents" for domestic and foreign reference products (if available), discounts for high sales ("huge-seller repricing rule"), but also the degree of innovation (first-in-class labelling), which can lead to price premiums of more than 100% according to Sakigake rules for particularly eligible products such as orphan drugs, medicines for paediatrics or pharmaceuticals developed on behalf of the state[61]. Biologics, especially biosimilars, have an advantage here - Japan still needs to catch up by international standards. However, the market volume for drugs as a whole is likely to stabilise due to the declining population and ever stricter price controls. The prices of generic products such as biosimilars are being curbed particularly sharply.

[60] https://www.pacificbridgemedical.com/wp-content/uploads/2015/04/Japan-Drug-Regulatory-Overview-2014.pdf
[61] https://www.pmda.go.jp/files/000221888.pdf

For biosimilars, the fixed price is 60% to 70% of the original. As already mentioned, the government, through NHI, wants to achieve that 80% or more (in value) of all pharmaceuticals prescribed by doctors are generic by 2020 at the latest; by September 2017 their share was already 66%[62], so the country is on course. The switch from branded drugs to generics reduced health care costs already by an estimated $12 billion in fiscal year 2017. This trend is reinforced by Japan's growing trade relations with the ASEAN countries and above all with India, a leading manufacturer of generics.

5.10 Marketing and sales

The distribution channel for pharmaceutical and biopharmaceutical products in Japan is short. Almost all medicines are delivered by only four wholesalers and their regional distributors[63] (Table 12). As a consequence, there are hardly any bottlenecks, control is high and there are practically no counterfeit products.

Table 12 Four pharmaceutical wholesalers dominating distribution

Company net sales FY 2017	**($ billion)**
Medipal Holdings	29.6
Alfresa Holdings Corp	24.9
Suzuken Co. Ltd.	20.0
Toho Holdings	11.9
Total	86.4

The wholesalers supply hospitals, private clinics and pharmacies up to twice a day and employ around 30,000 marketing specialists as medical consultants. Direct sales bypassing these wholesalers usually fail due to lack of space in pharmacies.

The most important target group for pharmaceutical and biopharmaceutical marketing is not patients, but doctors and pharmacists. The Japanese are characterised by a high level of brand loyalty when it comes to pharmaceuticals. Doctors and pharmacists therefore play a decisive role in the marketing of a new medicine, because 90% of all pharmaceutical products sold in Japan are subject to prescription, and even for over-the-counter medicines the laws provide for expert advice on effects and side effects. Doctors often prefer sponsored branded products. They may charge a premium of up to 25% on the government-fixed selling price ("medical margin")[64].

In Japan, prescription drugs cannot be ordered over the Internet. The sale of more than 11,000 over-the-counter (OTC) medicines, on the other hand, is available online, but not without information from both the patient and the retailer: OTC type 1 requires a pharmacist to explain the product, type 2 requires a pharmacist or qualified salesperson to provide advice, and even the online sale of type 3 products requires the patient to be available for queries[65]. As a general rule, prescription medicines cannot be sold on the Internet in Japan, and no licensed Japanese pharmacy is permitted to sell prescription drugs online or to market unapproved drugs via the internet.

[62] https://www.pacificbridgemedical.com/news-brief/japan-expands-share-of-generic-drugs/
[63] http://www.ial-japan.com/PA-Aug.29,2013.pdf
[64] https://www.eubusinessinjapan.eu/sectors/healthcare-medical/pharmaceuticals
[65] https://www.pmda.go.jp/files/000152069.pdf

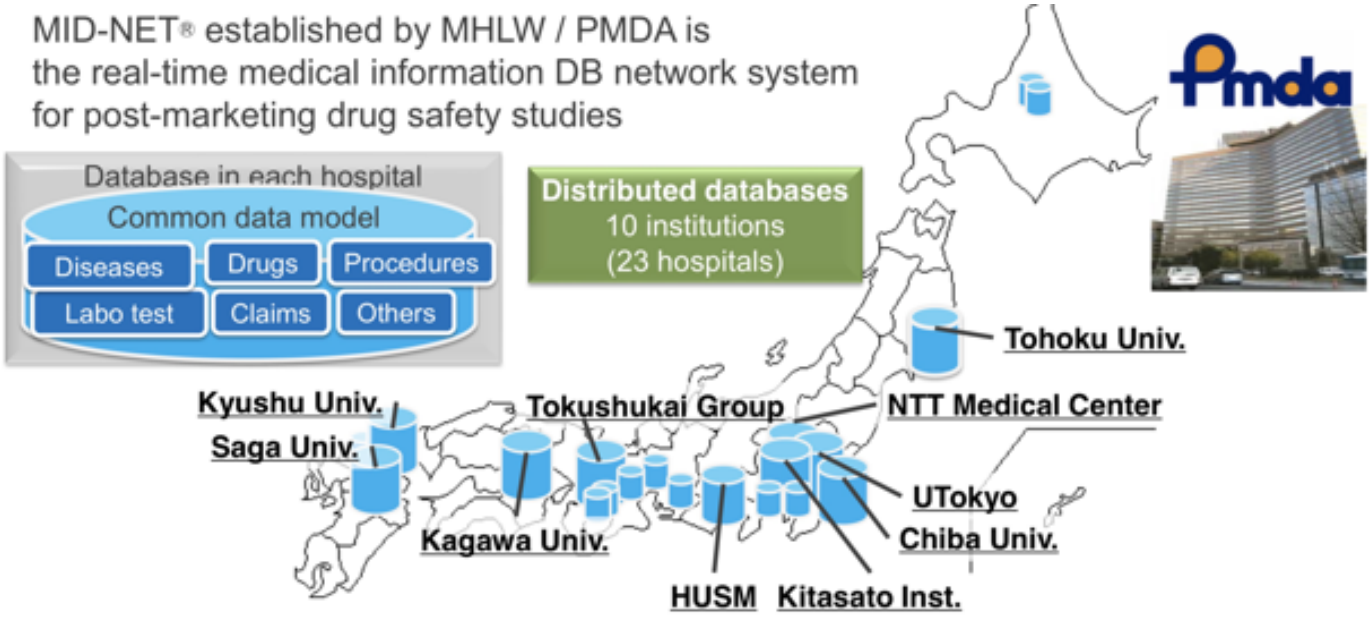
Digital marketing, on the other hand, is on the increase. Public advertising is only permitted for non-prescription medicines. Doctors are therefore a preferred target group for new prescription drugs. According to studies by the Japanese pharmaceutical industry, 85% of them use specialist information from the Internet and now spend up to 20% of their business hours doing so. The pharmaceutical industry is responding with electronic product advertising (e-detailing). Consultation portals for doctors such as MedPeer, Carenet or m3 offer assistance. Interestingly, however, the desire for personal consultation by physician visitors is not diminishing - in 2013, Japan's 308,000 physicians were served by 66,000 of these "marketing specialists"[66].

5.11 Postmarketing and Good Vigilance Practice (GVP)

The Japanese Pharmaceutical Affairs Law supports a fairly rapid market launch of products, but emphasises the manufacturer's responsibility after market entry even more strongly than the European law[67]. With the recommended Good Post-Marketing Study Practice (GPSP) and the binding Good Vigilance Practice (GVP), a Marketing Authorization Holder (MAH) must permanently collect information about their pharmaceutical or biopharmaceutical product, including information from the Internet. They must point out undesirable events and countermeasures and, if necessary, carry out a reassessment. Depending on the type of drug, there are different GMP requirements, for example for standard operating procedures (SOPs), safety information and training. Only some of these responsibilities can be delegated to third parties. All data records must be archived for at least 10 years, in special cases up to 30 years. Since 2018, such data flow into the Medical Information Database (MID-NET) of JDMA, a nationwide surveillance network of 23 hospitals and 10 other medical centres[68] (Figure 11).

Figure 11: MID-NET, Japans medical information system for pharma vigilance[69]

[66] https://www2.deloitte.com/content/dam/Deloitte/global/Documents/Life-Sciences-Health-Care/gx-lshc-2015-life-sciences-report-japan.pdf
[67] https://www.pmda.go.jp/files/000218744.pdf
[68] https://www.fda.gov/media/107784/download



Since July 2018, suppliers of pharmaceutical or biopharmaceutical products, which have already been approved in Japan, are expected to include information from MID-NET for up to 10 years in their safety assessment and to conduct new clinical studies if any side effects are observed. In this context, risk groups, such as older people, pregnant women, children, etc. must be given special consideration.

6 Cultural business practice

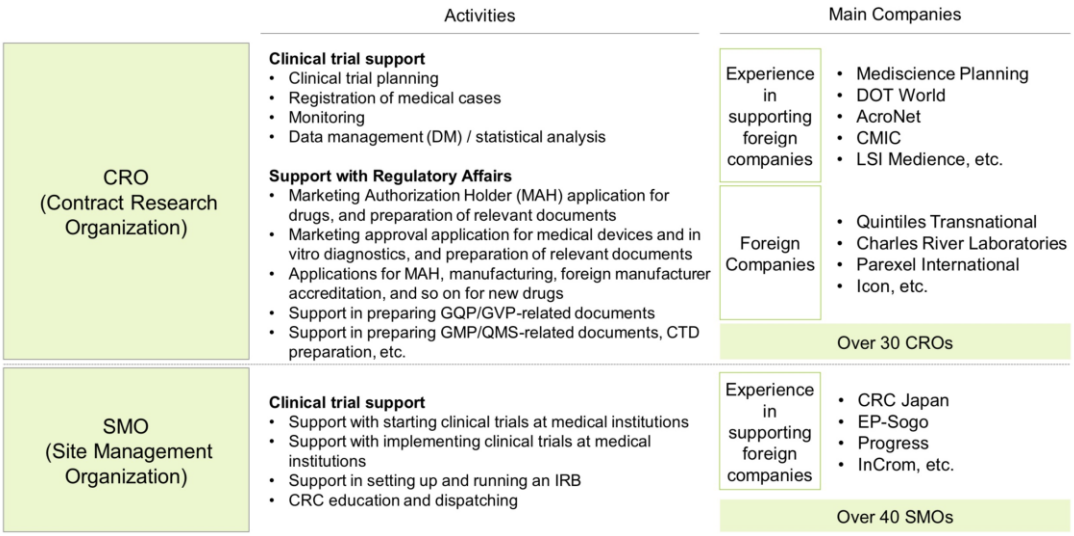
The Japanese are a homogeneous, closely networked community. 125 million people live in the limited settlement area of the Japanese islands, two thirds of them in five metropolitan regions. More than 98% are ethnic Japanese, characterised by a respectful conduct in a confined space, a unique culture with 2,000 years of history and constant challenges posed by nature, such as volcanic eruptions, typhoons, earthquakes and tsunamis. These experiences and the island's isolation over centuries have given rise to a personality type with its own culture of interaction and business. Japanese society is largely built on 系列 keiretsu, informal business groups with interlocking business relationships, and 義理 giri, mutual dependence through obligations and duty. Networks also permeate the Japanese economy like a spider web. 99.7% of all Japanese companies are SMEs with less than 300 employees, but often part of manufacturing networks of world-famous companies, such as Toyota, NEC, Fujifilm or Takeda, or of trading houses, such as Mitsubishi, Mitsui or Sumitomo.

Not only personal networks, but also long traditions shape the Japanese business world. The history of the trading house Sumitomo goes back to 1630, and many companies have been family-owned for more than a hundred years. They see themselves as a community of interests between owners, family members, employees, suppliers and customers. If there is no suitable successor in the company, it is better to "adopt" a non-family member rather than sell to a non-Japanese owner: that would not only be entrepreneurial failure, but an abandonment of Japanese traditions.

In view of these characteristics, which translate into the specificities in the Japanese regulatory practice, including the requirement to complete many steps in Japanese language, SMEs or start-ups who want to do enter the Japanese market are strongly advised to contract with a CRO or SMO. There are over 70 CRO/SMOs in Japan supporting new

foreign players in carrying out the necessary clinical trials and approval procedures, as shown in a recent shortlist of JETRO reproduced in Fig. 12.

Fig. 12 CROs or SMOs and their services for entry into the Japanese market[25]



7 Opportunities and access points

7.1 General remarks

The Japanese market is large, highly regulated and far away in a different culture. Large European life science companies, such as Aventis, Bayer, Glaxo-Smith-Kline or L'Oréal deploy considerable investments to be successful in this market. SMEs and start-ups have less resources and thus should consider the following options:

Variant 1: Import, approval, market launch by own efforts

Variant 2: Contract production by a manufacturer in Japan, approval, market launch by own efforts

Variant 3: Production in Europe, sales partnership in Japan

Variant 4: Technical production and sales partnership with companies in Japan

Variants 1 and 2 mean a very high expenditure of time, organisation and money, not only for registration, but also for marketing and sales. SMEs should therefore carefully examine if they are able to bear such expenditure. Most likely, variant 3 is better suited for European SMEs, and variant 4 for start-ups.

7.2 Access points

The Japanese pharmaceutical market offers European SMEs and start-ups a considerable number of entry opportunities, particularly in the field of innovative biopharmaceuticals, which have a unique selling proposition. It is a mature market with particularly demanding customers and many established suppliers. In order to examine the market niche, which might be reached with a new product, it is proposed to network at trade fairs with strong Japanese participation (e. g., BIO International Convention, BIO-Europe) or even better at Japanese trade fairs, such as BioJapan and CPhI - preferably with documents about one's product or service in Japanese translation.

For market access and marketing, country-specific rules must be observed, which can hardly be mastered without the support of Japanese partners. Although the regulations are clear and the procedures well structured, communication with Japanese authorities such as the PMDA are a major hurdle; many documents and discussions during advisory meetings require a very good knowledge of spoken and written Japanese language. Cooperation with a Japanese consulting firm is therefore indispensable and is also favoured by the Japanese side, as shown in a graph by JETRO (Figure 13). Such kind of services are offered by more than 70 CROs and SMOs, including international companies. They can effectively advise on consensus building with PMDA, NHI, or sales and marketing experts.

Figure 13: Partnerships for sales of biopharmaceuticals in Japan (see ref. 20)

Types of Partnerships and Advantages		Potential Partners
Technical partnership	• Licensing agreements and joint development contracts between multiple companies, and centering on intellectual property rights (technical patents, know-how, etc.).	• Pharmaceutical companies • Chemical producers • Research institutions
Production partnership	• Supplementation of production capacity by outsourcing a portion of production or the manufacturing process.	• Pharmaceutical companies • Chemical producers • CMOs
Sales partnership	• Partnership which utilizes sales channels, a partner's brand, or other sales resources. • Partnering with a Marketing Authorization Holder (MAH) can lessen the burden imposed by Pharmaceuticals and Medical Devices Law procedures.	• Pharmaceutical companies • CSOs

7.3 PMDA' consulting services are indispensable

PMDA offers consulting services throughout the entire approval process as well. These are not free of charge, but are indispensable. PMDA evaluates documents and provides advice on the adequacy of study design and protocols before starting clinical trials. As an example, if the tests for a CTDs are conducted according to ICH and PIC/S guidelines, English files may be submitted for Modules 3, 4 and 5 (although the table of contents should be in Japanese)[69], but modules 1 and 2 require a Japanese translation, whereas English is accepted for figures and tables. If there are only minor differences between non-Japanese and Japanese in the pharmacodynamic investigations in Module 3, the size of the clinical trial in Japan can be significantly reduced and, after consultation with PMDA, data collected in international clinical trials can be used. For clinical trials in Japan, a government-licensed clinic may be preferable as it is already experienced in conducting clinical trials; there might be fewer deviations from standard protocols, making the study duration shorter and lowering the costs.

7.4 Further recommendations to SMEs

- The National Health Insurance (NHI) sets prices for all pharmaceutical products several times a year, taking into account the life cycle of a drug with annual price reductions. Even if there is no drug similar to your product in

[69] https://www.pacificbridgemedical.com/wp-content/uploads/2015/04/Japan-Drug-Regulatory-Overview-2014.pdf

Japan yet, this may be the case at the time of approval. Then there would already be an NHI price standard and the launch price of your product would be set at that price. Thus, check to see if any competing products are being developed. Are you working on a particularly innovative compound according to a first-in-class FDA definition, a rare disease compound or a paediatric drug? Then you can negotiate price surcharges[70].

- Consider carefully whether you can shoulder the great expense of registering your pharmaceutical product yourself as a foreign company. Consider also the high costs for sales and marketing: doctors and medical representatives are not only to be convinced of the medical, but also of the economic advantages of your product. SMEs rarely have the capital they need to register a new active ingredient in Japan on their own. It is much easier to work with a Japanese pharmaceutical company. All international and large Japanese pharmaceutical companies analyse interesting drug candidates worldwide and maintain licensing offices. Some of them have specialised in licensing business from abroad, for example the Sumitomo subsidiary Summit with European offices in Düsseldorf, London, Milan and Madrid[71]. For European SMEs that are already in the approval process for a new molecular entity (NME) with EMA or FDA, an exclusive licensing agreement for the Japanese market may offer significant advantages.

- Takeovers are also not uncommon: leading Japanese pharmaceutical companies do corporate venture investments and are constantly expanding their strategic portfolio, also in Europe (in 2016, Japanese companies took over 156 European companies, 41 of them in Great Britain and 26 in France)[72].

- The large Internationals in pharma all hold market approvals (MAH) for drugs in Japan and cooperate in many ways with the Japanese pharmaceutical industry. Some have Japanese subsidiaries, such as MSD (Banyu Pharmaceuticals) or Roche (Chugai Pharma). Bayer, Boehringer-Ingelheim, Sanofi and others operate laboratories and innovation networks in Japan. If your pharmaceutical product or service addresses an interesting market niche in Japan, cooperation with an International with a presence in the Japanese market can also be promising.

- Manufacturers of biosimilars might want to check if their innovative product fits into the portfolio of generic drug manufacturers from emerging markets exporting to Japan. Indian manufacturers, for example, have successfully established themselves in Japan's pharmaceutical market - either as suppliers or by acquiring Japanese companies[73].

- Take part in international trade fairs such as BIO-Europe, BIO International Convention or BioJapan, and you will have a good opportunity to talk to licence scouts from Japanese and international pharmaceutical companies.

- If you are an SME or start-up, the EU-Japan Centre for Industrial Cooperation in Brussels organises every year its “biotech cluster SME mission”[74].

- If you are a start-up in the life sciences field, the GoGlobal programmes of the European Institute of Technology (EIT) offer support to introduce your product or service to the Japanese market. The programme is operated by BioM Biotech Cluster Development, a public scouting and partnering agency in Munich, Germany[75].

[70] https://www.mhlw.go.jp/content/11123000/000335149.pdf
[71] http://www.summitpharma.co.jp/english/about/network.html
[72] Nikkei Asia Review, April 2017
[73] https://www.manufacturingchemist.com/news/article_page/Indian_generic_manufacturers_aim_to_enter_the_Japanese_market/114151
[74] https://www.eu-japan.eu/events/biotech-cluster-sme-mission
[75] https://www.bio-m.org/start.smart.global/; https://www.bio-m.org/startsmartjapan

8 Actors, clusters, fairs

8.1 in Japan

Pharmaceuticals and Medical Devices Agency PMDA
独立行政法人医薬品医療機器総合機構 Dokuritsugyōsei hōjin iyakuhin'iryōkikisōgōkikō is Japan's regulatory body under the Ministry of Health MHLW. It is responsible for protecting public health by ensuring the safety, efficacy and quality of medicines and medical devices. It conducts scientific reviews of marketing applications for drugs and medical devices and monitors their safety after approval. It is also responsible for providing compensation to patients affected by adverse drug reactions or infections caused by drugs or biological products.
https://www.pmda.go.jp/english/index.html

Ministry of Health, Labor and Welfare MHLW
厚生労働省 Kōsei-rōdō-shō. The Ministry of Health, Labour and Welfare is responsible for the wide range of areas from medicine and long-term care, childcare, pension reform, employment and labour to social affairs. Its budget of around 31 trillion yen ($290 billion) in fiscal year 2017 represented almost a third of total national spending.
http://www.mhlw.go.jp/english/

National Health Insurance
国民健康保険 Kokumin-Kenkō-Hoken and the **Employee Health Insurances** 健康保険 Kenkō-Hoken are the two mainstays of Japanese health insurance. Joining the national health insurance is compulsory for all Japanese who do not have an employee health insurance and for all foreigners resident in Japan with visas valid for longer than 3 months.
https://5kuho.com

Japan Agency for Medical Research and Development, AMED
国立研究開発法人日本医療研究開発機構 Kokuritsu kenkyū kaihatsu hōjin Nihon iryō kenkyū kaihatsu kikō was founded in 2015. Modelled after the National Institute of Health of the USA, it aims to integrate Japan's basic research with practical application, creating the world's most advanced medical technologies and services. As an agency under the Ministry of Health MHLW, the Ministry of Science MEXT, the Ministry of Industry and Trade METI and chaired by the Prime Minister, it aims to advance Japan's industry in the field of medicine, pharmaceuticals and medical devices.
https://www.amed.go.jp/en/index.html

Japan Pharmaceutical Manufacturers Association JPMA
日本製薬工業協会 Nihon-seiyaku-kōgyō-kyōkai The Japan Pharmaceutical Manufacturers Association (JPMA) is an association of 71 research-based pharmaceutical companies (as of May 2018) and celebrates its 50th anniversary in 2018. Through the development of innovative ethical medicines, it aims to help advance global healthcare and promote healthy development of the pharmaceutical industry by developing proactive strategies and recommendations in response to globalisation and improving public understanding of medicines.
http://www.jpma.or.jp/english/

Manufacturing Technology Association of Biologics MAB
次世代バイオ医薬品製造技術研究組合 Jisedai baioiyakuhinseisaku-gijutsu-kenkyu-sougo
An association of some 50 companies, universities and research centres to drive improved manufacturing processes for biopharmaceuticals.
http://cho-mab.or.jp

Japan Generic Medicines Association JGA

日本ジェネリック製薬協会 Nihon djeneriku seiyaku kyōkai is an association of MAH (Market Authorization Holders) for generics, and since its foundation in 1965 has contributed to a sustainable supply of generics at affordable prices and high quality. It is a member of the International Generic and Biosimilar Medicines Association IGBA.
http://www.jga.gr.jp/english.html

Forum for Innovative Regenerative Medicine FIRM
一般社団法人再生医療イノベーションフォーラム Saisei-iryō-Inobēshon-fōram was founded in 2011 by fourteen companies conducting R&D in the field of regenerative medicine, and in 2017 already had approximately 150 member companies.
https://firm.or.jp/en/about3

SPI - Summit Pharmaceutical International
is a service company that belongs to the wide network of the trading house Sumitomo and offers contract research and other services when entering the Japanese market.
http://www.summitpharma.co.jp/english/index.html

Japan External Trade Organisation JETRO
ジェトロ is the foreign trade agency under the Ministry for Economy, Trade and Industry METI. With 74 offices in 54 countries (as of November 2017) and about 1,800 employees, many of whom are temporarily seconded from industrial companies, it supports trade and investment between Japan and the rest of the world. Originally established to support Japanese exports, the focus has shifted to promoting foreign direct investment in Japan and helping small and medium-sized Japanese companies maximize their global export potential.
https://www.jetro.go.jp/en/

New Energy and Industrial Technology Development Organisation NEDO
国立研究開発法人新エネルギー・産業技術総合開発機構 Kokuritsu kenkyū kaihatsu hōjin shin enerugī sangyō sangyō gijutsusōgō kaihatsu kikō plays an important role in Japanese economic and industrial policy as project house of the Ministry for Economy, Trade and Industry METI. It has two main tasks: to address energy and global environmental problems, and to promote and develop new cutting-edge technologies. NEDO's projects are usually carried out in cooperation with industrial companies and public research institutions, and are intended to form the basis for industrial development and technological change in the medium to long term. Amongst other targets, NEDO supports large projects in medical and cell technology.
http://www.nedo.go.jp/english/index.html

Japan Bioindustry Association JBA
バイオインダストリー協会 Bioindasutori-kyōkai was founded in 1987 and is affiliated with the Ministry for Economy, Trade and Industry METI. Its more than 200 members include a broad spectrum of companies using biotechnology in sectors, such as pharmaceuticals, medical equipment, food and cosmetics, chemicals, information technology, engineering, construction, and energy and natural resources. In addition, JBA members include public organisations, universities, public research institutions and a variety of individuals. Since 1999, JBA is organising Japan's leading annual biotechnology exhibition BioJapan
https://www.jba.or.jp/en/

8.2 in Europe

European Federation of Pharmaceutical Industries and Associations (EFPIA) Japan
was founded in 2002 and, with 24 member companies, is the voice of the research-based European pharmaceutical industry in Japan.
https://www.efpia.eu/about-us/efpia-japan/

Start.Smart.Japan and Start.Smart.Global

are “GoGlobal” initiatives of the European Institute of Innovation and Technology (EIT Health) to initiate business with Japanese partners for small and medium-sized European life science companies.
https://www.bio-m.org/start.smart.global/; https://www.bio-m.org/startsmartjapan

8.3 Pharmaceuticals-related Trade Fairs in Japan

CPhI Japan 2019
March 16 - 18, 2020
Venue: Tokyo Big Sight
https://www.cphi.com/japan/visit/news-and-updates/2020

Medical Japan
October 23 – 25, 2019
Venue: INTEX Osaka
https://www.medical-jpn.jp/en-gb.html

BioJapan 2019
October 9-11, 2019
Venue: Pacifico Yokohama
https://www.ics-expo.jp/biojapan/en/

9 Literature

JETRO Invest Japan: Market Report Biopharmaceuticals and Biosimilars, December 2017
https://www.jetro.go.jp/ext_images/en/invest/attract/pdf/mr_bio_en201712.pdf
A short report worth reading in English language about trends in the Japanese biopharmaceutical market, government support measures and how to gain a foothold.

JETRO Invest Japan: Attractive Sectors - Life Science, July 2016
https://www.jetro.go.jp/ext_images/en/invest/attract/pdf/en_2016_life.pdf
Information in English about the Japanese pharmaceutical market and its future development. The government strategies for accelerating the approval process are being described.

Pharmaceutical and Medical Devices Agency (PMDA) Review Reports: Drugs
https://www.pmda.go.jp/english/review-services/reviews/approved-information/drugs/0001.html
PMDA, the Japanese regulatory authority, has published numerous presentations and reports in English on the approval of active pharmaceutical ingredients, import, safeguards and other relevant topics.

Ministry of Health, Labour and Welfare: Update of Drug Pricing System in Japan, November 2016
https://www.pmda.go.jp/files/000221888.pdf
A 40-page presentation in English, which describes the Japanese pricing system for all types of active pharmaceutical ingredients in considerable detail.

EU-Japan Centre for Industrial Cooperation, Keith Jackson: The pharmaceuticals industry in Japan: current trends and emerging business opportunities for EU-based small- and medium-sized enterprises, March 2018
https://www.eubusinessinjapan.eu/sectors/healthcare-medical/pharmaceuticals, registration required.
A comprehensive report on 75 pages in English with over 100 references. The author teaches at the Doshisha Business School in Kyoto and has compiled extensive material on the structure of the medical market in Japan. However, the report is somewhat academic and gives little practical guidance.

Pacific Bridge Medical Inc.: Japan Drug Regulatory Overview 2014
https://www.pacificbridgemedical.com/wp-content/uploads/2015/04/Japan-Drug-Regulatory-Overview-2014.pdf
The company, which is based in Bethesda, Maryland, offers news on the Japanese (and Asian) pharmaceutical markets, including this detailed report on the approval process of active pharmaceutical ingredients in Japan, which comprises more than 80 pages and is still largely up to date. Pacific Bridge Medical also offers an online resource centre with valuable news on Japan's pharmaceutical market.

CPhI Pharma Insights: Japan Report 2018 - a big year for Japanese pharma
https://ubmemeaensoprod.s3.amazonaws.com/CPHI_JAPAN/cphi_pharma_insights_japan-2018-mp-v6.pdf ,
registration required.
Results of the surveys of visitors of the annual CPhI Pharma fairs in Tokyo

Hiromoto AKABANE, Institute of Pharmaceutical Industry Policy Research: Challenges for the biopharmaceutical industry and recommendations for further development – research paper No. 71 (March 2018)
http://www.jpma.or.jp/opir/research/rs_071/paper_71.pdf
A 79-page study on this topic with many data and summaries, in Japanese language.