

Market Report

Biopharmaceuticals and Biosimilars

December, 2017



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Summary

1. Japan's Biopharmaceutical and Biosimilars Market

- Japan's pharmaceuticals market ranks 3rd globally, and is growing at a compound annual growth rate (CAGR) of 3.4%.
- The Japanese government has positioned healthcare as a growth industry, and has made the creation of technologies and services, and development of the supporting infrastructure as part of its growth strategies. To achieve these goals, the necessary regulations are also being developed.
- While biopharmaceuticals account for around 30% of overall global drug sales, the products only make up 10% of sales in Japan. As such, rapid growth is projected for the Japanese biopharmaceutical market.
- The biosimilars market is also a rapidly growing one, with a variety of products currently under development.

2. Market Entry Opportunities for Foreign Companies

- Over 70% of approved biopharmaceuticals in Japan are provided by foreign companies, indicating their status as major players in the domestic market.
- From among the 10 biosimilars approved in Japan by July 7, 2017, four are products developed by foreign companies.
- Foreign pharmaceutical companies entering the market could form development or manufacturing partnerships with domestic drug companies and research institutions.
- There are over 70 CRO/SMOs in Japan supporting new foreign players in carrying out the necessary clinical trials and approval procedures.
- Foreign companies can achieve smooth entry into the Japanese market in several ways, including shortening clinical trial periods by joining global clinical trials, using CROs to lessen the burden of drug approval procedures, and developing high value-added drugs which are not subject to Japan's biennial pricing revisions.

3. Business Environment in the Biopharmaceutical and Biosimilars Market

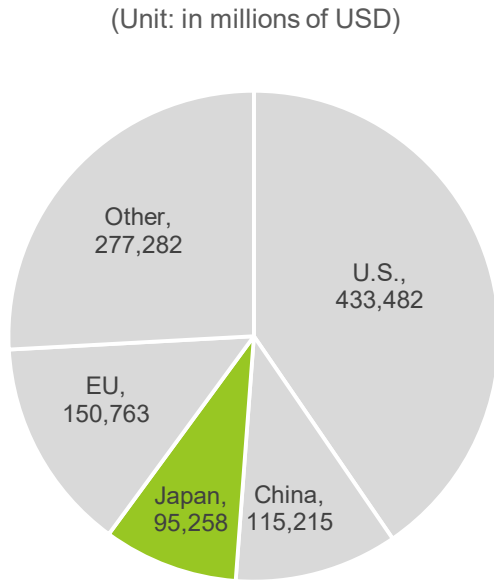
- Financial support for orphan drugs, tax breaks, and subsidies are available to new entrants in the market.
- The strong potential for drug discovery in Japan has seen the formation of numerous bio clusters that include world-class universities with cutting-edge technologies and know-how.
- Biopharmaceutical and biosimilar-related events are held throughout the year, providing chances to find out about trends in the Japanese market and meet with potential partners. Related trade associations are also working to further develop the biopharmaceuticals industry.

1. Japan's Biopharmaceutical and Biosimilars Market

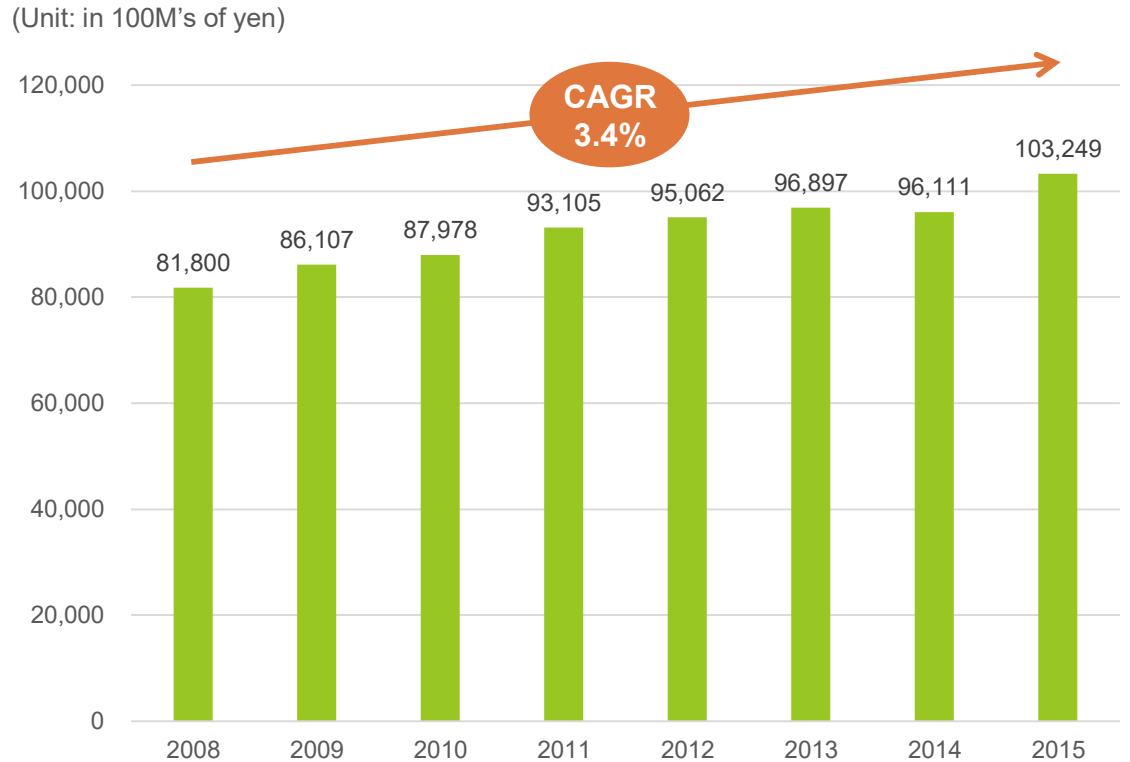
(1) Global Prominence of Japan's Pharmaceuticals Market

Japan's pharmaceuticals market ranks 3rd globally, and grew at a compound annual growth rate (CAGR) of 3.4% between 2008 – 2015.

Global Pharmaceuticals Market (2015)*1



Japan's Pharmaceuticals Market*2



*1 Source: Mizuho Bank

*2 Source: Ministry of Health, Labour and Welfare, *Statistics of Production by Pharmaceutical Industry 2015*

1. Japan's Biopharmaceutical and Biosimilars Market

(2) Government Initiatives to Develop the Healthcare Industry

The Japanese government has positioned healthcare as a growth industry, and has made the creation of technologies and services, and development of the supporting infrastructure as part of its growth strategies. To achieve these goals, the necessary regulations are also being developed.

Government Strategies in the Healthcare Sector*1

Regulatory Developments*2

Creating new services

- Building and utilizing various medical information databases.

Creating new technologies (R&D/commercialization)

- Set up the Japan Agency for Medical Research and Development (AMED) to centralize decision-making for strategies and budget allocations, and build a one-stop R&D system.
- Promote R&D among private sector.

Developing infrastructure

- Revision of legal systems and regulations based on characteristics of medical devices and regenerative medicine, etc.
- Development of an ICT environment for efficient promotion of the medical industry.
- Utilization and development of human resources.
- To trial services, arrange for platforms that utilize Special Zone systems.
- Drastic improvement of environment for conducting clinical research and trials.
- Address ethical issues such as protecting human subjects, and gaining citizens' trust toward clinical research.

The Law on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (November 2013)

Act to Promote Healthcare and Medical Strategy and Act on Japan Agency for Medical Research and Development (May 2014)

Medical Care Act (April 2015)

Clinical Research Law (April 2017)

- Expanded scope of third party certification system for medical devices.
- Establishment of regulations appropriate for the features of regenerative medicine products, etc.
- Established the Headquarters for Healthcare and Medical Strategy Promotion to act as a “control tower” for the Cabinet, and AMED, an institution for allocating research budgets and handling “one-stop” R&D (from basic research to practical application).
- To further development of innovative Japan-made drugs and medical devices, etc., definition for “Core Clinical Research Hospitals” (hospitals playing a central role in international standard clinical research) was prescribed under the Medical Care Act.
- Systems, etc., established for publishing information on procedures for carrying out clinical research, and announcing information on clinical research funding, etc.

*1 Source: Cabinet Secretariat, *Healthcare and Medical Strategy* (2013, 2014, 2017)

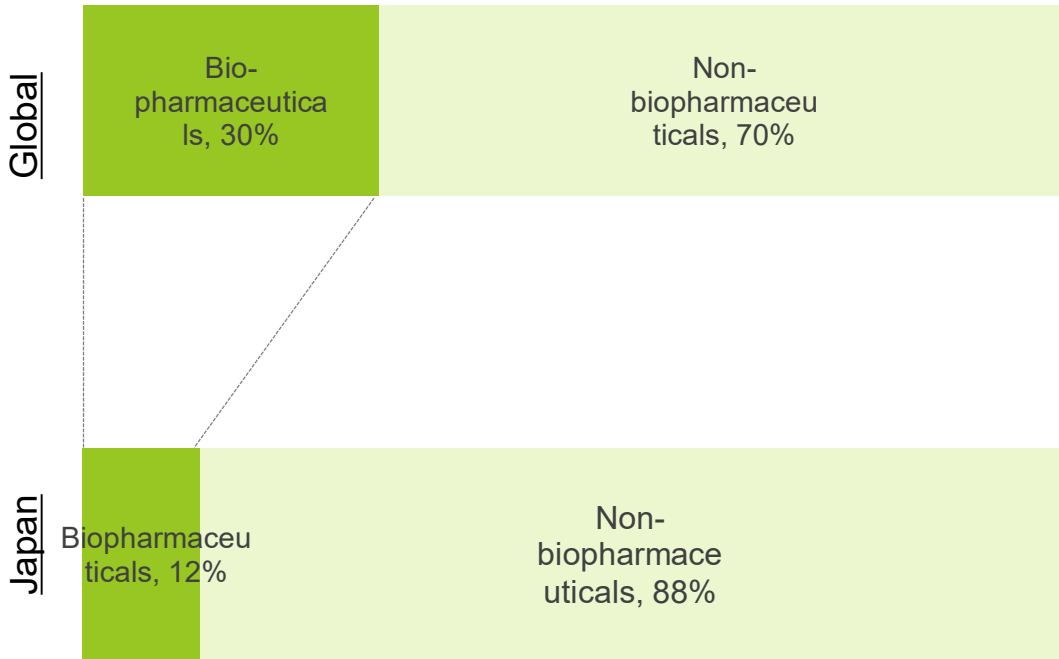
*2 Source: Cabinet Secretariat website, <http://japan.kantei.go.jp/index.html>

1. Japan's Biopharmaceutical and Biosimilars Market

(3) Japan's Biopharmaceutical Market

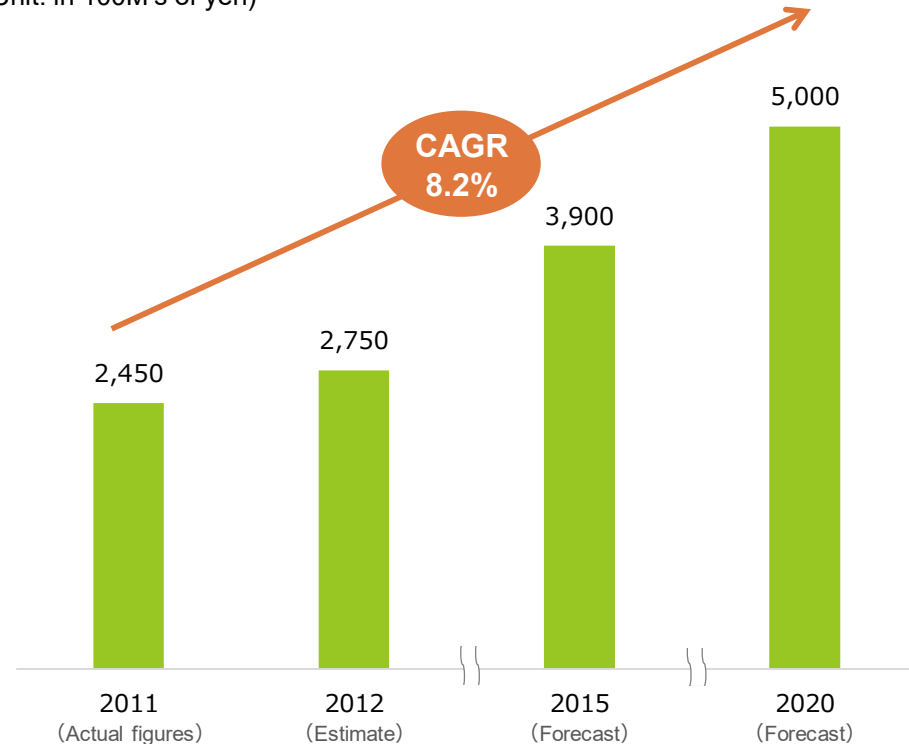
While biopharmaceuticals account for around 30% of overall global drug sales, the products only make up 10% of sales in Japan. As such, rapid growth is projected for the Japanese biopharmaceutical market.

Biopharmaceutical Sales in the Drug Market*1



Size of the Biopharmaceuticals Market in Japan*2

(Unit: in 100M's of yen)



*1 Sources: Evaluate Pharma as of July 2016, Mix Online (Nov. 13, 2015)
Global market figures are for 2015, Japanese market figures for 2014

*2 Source: Seed Planning

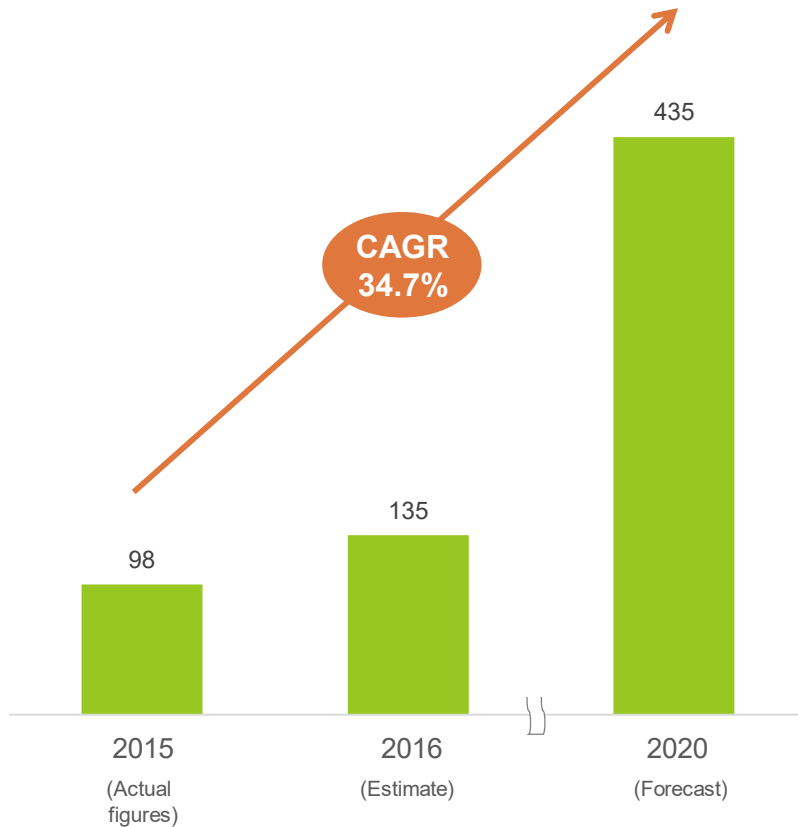
1. Japan's Biopharmaceutical and Biosimilars Market

(4) Japan's Biosimilars Market

The biosimilars market is also a rapidly growing one, with a variety of products currently under development.

Market Size of Biosimilars in Japan*1

(Unit: in 100M's of yen)



Status of Major Drug Developments*2

Drug Efficacy	Ingredient / Name of Original Drug	Drug Developer	Sales in Japan of Original Drug
Rheumatism	Enbrel (etanercept) Mochida Pharmaceutical/ Pfizer	Daiichi Sankyo, Mochida Pharmaceutical, Yoshindo	41.2 billion yen (FY2014)
	Humira (adalimumab) Eisai/Abbvie	Fujifilm Kyowa Kirin Biologics, Pfizer, Mochida Pharmaceutical	29.9 billion yen (FY2014)
	Remicade (infliximab) Tanabe Pharma	Nichi-Iko, Pfizer	70.6 billion yen (FY2014)
Cancer	Herceptin (trastuzumab) Chugai Pharmaceutical	Nippon Kayaku, Pfizer, Meiji Seika Pharma	32.7 billion yen (2015)
	Rituxan (rituximab) Chugai Pharmaceutical	Pfizer, Sandoz, Daiichi Sankyo, Nichi-Iko	29 billion yen (2015)
	Avastin (bevacizumab) Chugai Pharmaceutical	Pfizer, Fujifilm Kyowa Kirin Biologics	93.8 billion yen (2015)
Renal anemia	Nesp (darbepoetin alfa) Kyowa Hakko Kirin	JCR Pharma/Kissei Pharmaceutical, Nichi-Iko Fuji Pharma, Sanwa Kagaku Kenkyusho	57.5 billion yen (2015)
Insulin	Lantus (insulin glargine) Sanofi	Fujifilm	—

*1 Source: Fuji Keizai press release, <https://www.fuji-keizai.co.jp/market/17029.html>

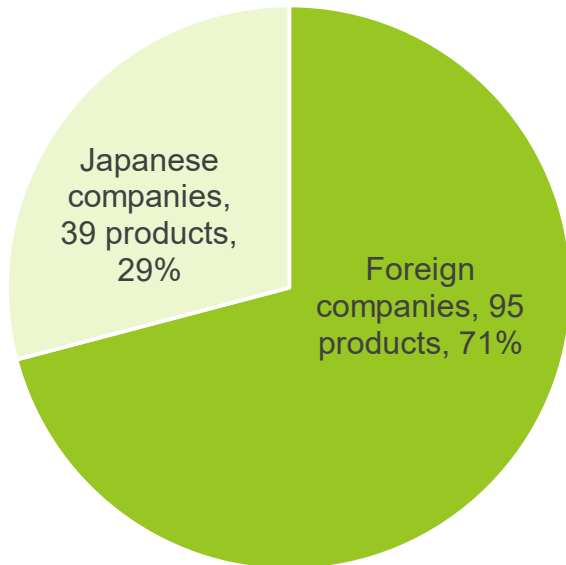
*2 Source: AnswersNews article (news website for the pharmaceutical industry), <http://answers.ten-navi.com/pharmanews/6344/>

2. Market Entry Opportunities for Foreign Companies

(1) Major Players in the Biopharmaceutical Market

Over 70% of approved biopharmaceuticals in Japan are provided by foreign companies, indicating their status as major players in the domestic market.

Breakdown of Approved Biopharmaceuticals in Japan
(total number of products as of Dec. 30, 2016)



	<u>Main Players</u>	<u>Major Approved Biopharmaceuticals</u> (number in brackets)
Foreign Companies	Novo Nordisk	• Turoctocog alfa, liraglutide, etc. (13)
	Sanofi	• Rasburicase, insulin glargine, etc. (10)
	Roche (Chugai Pharma)	• Epoetin beta, lenograstim, trastuzumab, etc. (10)
	Eli Lilly Japan	• Insulin lispro, teriparatide, ixekizumab, insulin glargine, etc. (8)
	MSD	• Follitropin beta, pembrolizumab, etc. (6)
Japanese Companies	Pfizer	• Gemtuzumab, nonacog alfa, etc. (5)
	Kyowa Hakko Kirin	• Mogamulizumab, epoetin alfa, etc. (8)
	Takeda Pharma	• Brentuximab, celmoleukin, etc. (4)
	Shionogi & Co., Ltd.	• Interferon gamma-1a, teceleukin, metreleptin, etc. (4)

2. Market Entry Opportunities for Foreign Companies

(2) Major Players in the Biosimilars Market

From among the 10 biosimilars approved in Japan by July 7, 2017, four are products developed by foreign companies.

Foreign/ Japanese	Name of Biosimilar Product	Developer	Generic Name	Reference Product	Year Approved
Foreign Company	Somatropin BS S.C. Injection (Sandoz)	Sandoz	Somatropin	Genotropin	2009
	Filgrastim BS Injection (Teva)	Teva	Filgrastim (Filgrastim biosimilar 2)	Gran	2013
	Filgrastim BS Injection (Sandoz)	Sandoz	Filgrastim (Filgrastim biosimilar 3)	Gran	2014
	Insulin Glargine BS Injection (Lilly)	Lilly	Insulin glargine (Insulin glargine biosimilar 1)	Lantus	2014
Japanese Company	Epoetin Alfa BS Injection (JCR)	JCR Pharma	Epoetin kappa (Epoetin alfa biosimilar 1)	Espo	2010
	Filgrastim BS Injection (Mochida)	Mochida Pharmaceutical	Filgrastim (Filgrastim biosimilar 1)	Gran	2012
	Filgrastim BS Injection (F)	Fuji Pharma	Filgrastim (Filgrastim biosimilar 1)	Gran	2012
	Filgrastim BS Injection (NK)	Nippon Kayaku	Filgrastim (Filgrastim biosimilar 2)	Gran	2013
	Infliximab BS for IV Infusion (NK)	Nippon Kayaku	Infliximab (Infliximab biosimilar 1)	Remicade	2014
	Insulin glargine BS injection (FFP)	Fujifilm Pharma	Insulin glargine (Insulin glargine biosimilar 2)	Lantus	2016

2. Market Entry Opportunities for Foreign Companies

(3) Potential Partners for Market Entry

Foreign pharmaceutical companies entering the market could form development or manufacturing partnerships with domestic drug companies and research institutions.

Types of Partnerships and Advantages	Potential Partners	Examples
<div data-bbox="87 411 323 691" style="background-color: #e1f5fe; padding: 10px; text-align: center; width: 100px; height: 100px; display: flex; align-items: center; justify-content: center;"> <p>Technical partnership</p> </div> <ul data-bbox="333 425 893 682" style="list-style-type: none"> • Licensing agreements and joint development contracts between multiple companies, and centering on intellectual property rights (technical patents, know-how, etc.). 	<ul data-bbox="955 425 1263 682" style="list-style-type: none"> • Pharmaceutical companies • Chemical producers • Research institutions 	<ul data-bbox="1313 396 1947 711" style="list-style-type: none"> • Novartis is conducting joint development with Japanese biotechnology company, PeptiDream. • AstraZeneca is participating in National Cancer Center Japan's (NCC) project. • Boehringer Ingelheim is conducting joint development with Kyoto University's Center for iPS Cell Research and Application.
<div data-bbox="87 751 323 959" style="background-color: #e1f5fe; padding: 10px; text-align: center; width: 100px; height: 100px; display: flex; align-items: center; justify-content: center;"> <p>Production partnership</p> </div> <ul data-bbox="333 772 893 943" style="list-style-type: none"> • Supplementation of production capacity by outsourcing a portion of production or the manufacturing process. 	<ul data-bbox="955 751 1263 959" style="list-style-type: none"> • Pharmaceutical companies • Chemical producers • CMOs 	<ul data-bbox="1313 779 1947 929" style="list-style-type: none"> • Kaneka has been contracted by European and US pharmaceutical companies for production of biopharmaceutical raw materials.
<div data-bbox="87 1019 323 1330" style="background-color: #e1f5fe; padding: 10px; text-align: center; width: 100px; height: 100px; display: flex; align-items: center; justify-content: center;"> <p>Sales partnership</p> </div> <ul data-bbox="333 1012 893 1375" style="list-style-type: none"> • 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. 	<ul data-bbox="955 1119 1263 1240" style="list-style-type: none"> • Pharmaceutical companies • CSOs 	<ul data-bbox="1313 1090 1947 1276" style="list-style-type: none"> • Teva and Takeda partnered up to establish Teva Takeda Yakuhin Ltd., aiming to combine Teva's developmental capabilities and Takeda's strong distribution network to develop business in Japan.

2. Market Entry Opportunities for Foreign Companies

(3) Potential Partners for Market Entry –Utilizing CROs/SMOs

There are over 70 CRO/SMOs in Japan supporting new foreign players in carrying out the necessary clinical trials and approval procedures.

	Activities	Main Companies
CRO (Contract Research Organization)	<p>Clinical trial support</p> <ul style="list-style-type: none"> • Clinical trial planning • Registration of medical cases • Monitoring • Data management (DM) / statistical analysis <p>Support with Regulatory Affairs</p> <ul style="list-style-type: none"> • Marketing Authorization Holder (MAH) application for drugs, and preparation of relevant documents • Marketing approval application for medical devices and in vitro diagnostics, and preparation of relevant documents • Applications for MAH, manufacturing, foreign manufacturer accreditation, and so on for new drugs • Support in preparing GQP/GVP-related documents • Support in preparing GMP/QMS-related documents, CTD preparation, etc. 	<p>Experience in supporting foreign companies</p> <ul style="list-style-type: none"> • Mediscience Planning • DOT World • AcroNet • CMIC • LSI Medience, etc. <p>Foreign Companies</p> <ul style="list-style-type: none"> • Quintiles Transnational • Charles River Laboratories • Parexel International • Icon, etc. <p style="text-align: center;">Over 30 CROs</p>
SMO (Site Management Organization)	<p>Clinical trial support</p> <ul style="list-style-type: none"> • Support with starting clinical trials at medical institutions • Support with implementing clinical trials at medical institutions • Support in setting up and running an IRB • CRC education and dispatching 	<p>Experience in supporting foreign companies</p> <ul style="list-style-type: none"> • CRC Japan • EP-Sogo • Progress • InCrom, etc. <p style="text-align: center;">Over 40 SMOs</p>




2. Market Entry Opportunities for Foreign Companies

(4) Issues with Market Entry and Resolutions

Foreign companies can achieve smooth entry into the Japanese market in several ways, including shortening clinical trial periods by joining global clinical trials, using CROs to lessen the burden of drug approval procedures, and developing high value-added drugs which are not subject to Japan's biennial pricing revisions.

Market Entry Issues Generally Faced by Foreign Companies

Resolutions

<p>Clinical trial period</p>	<ul style="list-style-type: none"> Clinical trial periods tend to be prolonged due to small number of patients in each facility 		<ul style="list-style-type: none"> Shortening the clinical trial period by participating in international joint clinical trials^{*1} <ul style="list-style-type: none"> No. of notifications submitted from int'l joint clinical trials: 3 in 2007 → 41 in 2015^{*2}
<p>New Drug Application process</p>	<ul style="list-style-type: none"> Know-how required to deal with the various new drug approval procedures stipulated by Japan's Pharmaceuticals and Medical Devices Law 		<ul style="list-style-type: none"> Employing the services of a CRO with knowledge of Japan's approval processes can alleviate the burden of paperwork and procedures
<p>Pharmaceutical pricing</p>	<ul style="list-style-type: none"> Pharmaceutical prices are revised every 2 years in Japan, resulting in a tendency toward lower prices (even during effective patent periods) compared with foreign countries 		<ul style="list-style-type: none"> Possible to maintain pricing and recover costs quickly by developing high value-added drugs (those targeting unmet medical needs, etc.), as price reductions for these products are postponed

*1 Source: Japan Pharmaceutical Manufacturers Association, *Utilization of Foreign Clinical Data in Clinical Data Packages* (2013)

*2 Source: Ministry of Health, Labour and Welfare, *Trends in Evaluations and Clinical Trials of Pharmaceuticals, etc.* (2016)

3. Business Environment in the Biopharmaceutical and Biosimilars Market

(1) Main Incentives

Financial support for orphan drugs, tax breaks, and subsidies are available to new entrants in the market.

Pharmaceuticals-related

Grant Program for Orphan Drug, Medical Devices, and Regenerative Medicine Product Testing and Research*¹ (NIBIOHN)

- Grant for experiment and research expenses offered to companies developing drugs for rare diseases (11 companies selected for FY2017).
- Used by foreign companies such as GlaxoSmithKline and numerous others.

Measures against Intractable Diseases*² (MHLW)

- Program that provides support to patients financially burdened with the costs of long-term treatment for an intractable disease, undertaken while waiting for further research into cures and for effective treatments to be established.
- In April 2017, twenty-four new diseases were added to the list of designated diseases, bringing the total number to 330.

 : Incentives for companies

 : Aid for patients/R&D

Special Zones

Kobe Biomedical Innovation Cluster*³ (Kobe City)

- Tax breaks
 - Reduced fixed asset tax, city planning tax, business office tax, real estate acquisition tax, etc.
- Subsidies
 - Capital investment subsidy offered for R&D firms, etc.

“Life Innovation in Keihin Coastal Areas” Comprehensive Special Zones for International Competitiveness*⁴

- Deregulation
 - Easing of land use regulations, restrictions on disposition of property, green space regulations concerning factory sites, etc.
- Tax breaks
 - Special depreciation, investment tax credits, etc.
- Financing support
 - Subsidies covering interest payments on loans, etc.

*1 Source: National Institutes of Biomedical Innovation, Health and Nutrition (NIBIOHN) website, <http://www.nibiohn.go.jp/information/nibio/2017/07/005219.html>

*2 Source: Ministry of Health, Labour and Welfare (MHLW) website, http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryau/kenkou/nanbyou/index.html

*3 Source: Kobe Biomedical Innovation Cluster (KBIC) website, <http://www.kobe-lsc.jp/develop>

*4 Source: “Life Innovation in Keihin Coastal Areas” Comprehensive Special Zones for International Competitiveness website, <https://www.keihin-tokku.jp/>

3. Business Environment in the Biopharmaceutical and Biosimilars Market

(2) Bio Clusters in Japan

The strong potential for drug discovery in Japan has seen the formation of numerous bio clusters that include world-class universities with cutting-edge technologies and know-how.

Bio Clusters in Japan

Kansai Innovation International Strategic Comprehensive Special Zone*1

➤ **Companies**

59 development and manufacturing bases set up by domestic/int'l pharmaceutical companies

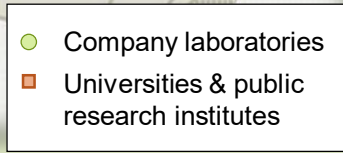
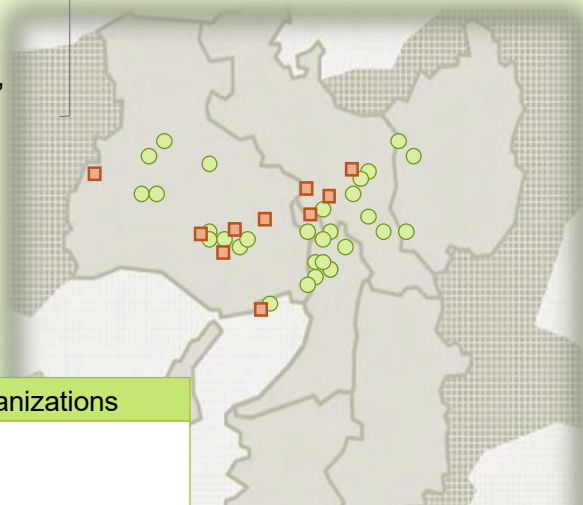
Astellas Pharma, Shionogi, Kyowa Hakko Kirin, Sumitomo Dainippon Pharma, Nihon Medi-Physics, Boehringer Ingelheim, Novartis, AstraZeneca, etc.

➤ **Universities & Public Research Institutes**

Osaka Univ., Kyoto Univ., Kobe Univ., Kindai Univ., Riken, Institute of Biomedical Research and Innovation, K computer, National Cerebral and Cardiovascular Center, etc.

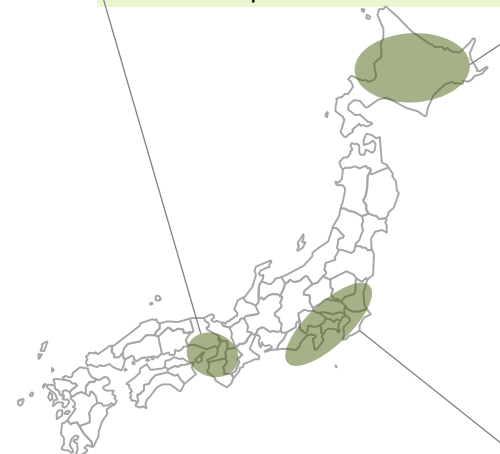
Main Drug Discovery-related Initiatives

Initiative	Organizations
Establishment of new branch by the PMDA (organization that conducts reviews, etc., under the Pharmaceuticals and Medical Devices Act)	PMDA
Establishment of a clinical trial center	Kyoto Univ./Osaka Univ., National Cerebral and Cardiovascular Center
Further application for Japan's first antibody drug (intractable diseases)	Osaka Univ., Chugai Pharmaceutical, Shionogi
Development of CNS depressants	Kyoto Univ., Takeda
Development of next-generation vaccine	Osaka Univ., NIBIOHN*4
Supporting innovative drug discovery that uses cutting-edge research equipment and facilities	Osaka Univ., NIBIOHN



Hokkaido Bio Technology Industrial Cluster*2

- No. of companies: approx. 132
 - No. of universities/public research institutes: 21
- Holds business meetings to match cutting-edge technologies with the needs of biopharmaceutical firms.



Metropolitan Bio Network*3

- No. of companies: 450+
- In partnership with the Japan Science and Technology Agency, supports development of new businesses.

*1 Source: Kansai Innovation International Strategic Comprehensive Special Zone, <http://kansai-tokku.jp/>

*2 Source: Hokkaido Bio Technology Industrial Cluster Forum, <http://www.noastec.jp/biocluster/>

*3 Source: Metropolitan Bio Network website, <http://www.jba.or.jp/syutokenbio/>

*4 NIBIOHN = National Institutes of Biomedical Innovation, Health and Nutrition

3. Business Environment in the Biopharmaceutical and Biosimilars Market

(3) Trade Fairs and Trade Associations

Biopharmaceutical and biosimilar-related events are held throughout the year, providing chances to find out about trends in the Japanese market and meet with potential partners. Related trade associations are also working to further develop the biopharmaceuticals industry.

Biopharmaceutical-related Events

Overview	Venue/Date
<p>BIO JAPAN</p> <ul style="list-style-type: none"> Main objective is business match-ups, with a focus on bio clusters and startups. Over 800 exhibitors. 	<ul style="list-style-type: none"> Yokohama/ Annual
<p>BIO tech</p> <ul style="list-style-type: none"> Gathers together laboratory equipment, reagents, analytical instruments, contract services, and other advanced biotechnologies under the one roof. 	<ul style="list-style-type: none"> Tokyo/ Annual (next event from Jun. 27 – 29, 2018)

Trade Associations

Japan Bio-industry Assoc.

- Japan's largest trade association with members including 190 major firms and approx. 90 organizations (public agencies, universities, public research institutes, etc.). With a focus on biopharmaceutical companies, activities range from discovering new technological "seeds" to dev't of cutting-edge technologies for industrialization and production infrastructure.
- 18 members are foreign companies.
- Gathers information on technologies, researches latest development trends, works to find new technologies with potential to form a new industry, and shares information through lectures and seminars, etc.

Japan Biological Informatics Consortium

- Founded by four ministries: Ministry of Education, Culture, Sports, Science and Technology (MEXT), Ministry of Health, Labour and Welfare (MHLW), Ministry of Agriculture, Forestry and Fisheries (MAFF), and the Ministry of Economy, Trade and Industry (METI).
- Conducts research and planning on latest domestic and int'l technological trends, and for implementing new industry-academia-gov't initiatives/projects.
- Over 60 member companies, with many biopharmaceutical firms.

Japan Pharmaceutical Manufacturers Association (JPMA)

- Private organization for R&D-oriented pharmaceutical companies. As of Jan. 1, 2017, has 72 members.

Pharmaceutical Research and Manufacturers of America (PhRMA)

- Leading organization for major R&D-oriented pharmaceutical companies and biotechnology companies in the U.S.
- Involved in a diverse range of activities, including promoting preventive medicine (with focus on chronic diseases, driving innovation, and shortening clinical trial periods), offering proposals to the government for reforming healthcare systems, and more.