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Regulatory Assessment & FDI Review

Life Science Industry in Japan

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Innovation and surging demand

Several aspects of the Japanese market have made it a target for European outward foreign investments. It is the world's second-largest market for pharmaceutical products, medical devices and healthcare services. The combination of an ageing population and one of the world's most comprehensive public healthcare schemes make it particularly attractive for both exports and direct investment, but it is also a source for intensive and high-quality R&D.

In addition to these prospects, Japanese demand is picking up. Although stories of Japan's deflation and modest growth have been a fixture for western business reporting, GDP numbers show eight quarters of consecutive growth at the time of writing, with the longest stretch of positive growth in Japan for 28 years.[1] Similarly, IMF World Economic Outlook adjusted the real growth projections upwards for both 2018 and 2019.[2]

The policy package of Abenomics has succeeded in defeating deflation, boosted profits and dividends. It has depreciated the Japanese yen and stimulated growth. The promotion of life sciences under the Economic Revitalisation Strategy has resulted in series of reforms that facilitated the adoption of new medicines and medical technologies.

Foreign investments driven by trade and innovation

Although most of the bilateral trade in pharmaceuticals, medical devices and technologies are already traded duty-free, the EU-Japan Economic Partnership Agreement (EPA) also harmonises the regulatory environment of the two economies. This will, in turn, improve the business climate, reduce regulatory uncertainties and thereby corporate profit margins.

Some emerging markets may display an impressive GDP or sectoral growth compared to the EU or Japan. But not all of that growth is actually available to a foreign investor in life sciences: Local hospitals may be required to buy from domestic manufacturers. R&D incentives, reimbursement or pre-marketing authorisation procedures can be openly discriminatory. Inadequate enforcement of patents and trade secrets or coerced joint-ventures with local competitors may drain the competitiveness of foreign-invested firms.

Against this background, the EPA sends a clear signal that the life sciences industries in Europe and Japan are open for business at a time when global foreign direct investments (FDIs) are dropping. This report looks to the market prospects, which is primarily driven by demographics, regulatory reforms and the investment creation from R&D and Japan's trade agreements, including the EU-Japan EPA, which is expected to swiftly come into force.

[1] Bank of Japan, Quarterly Data October-December 2017, released February 14th, 2018

[2] IMF World Economic Outlook, January 2018

2. Market prospects

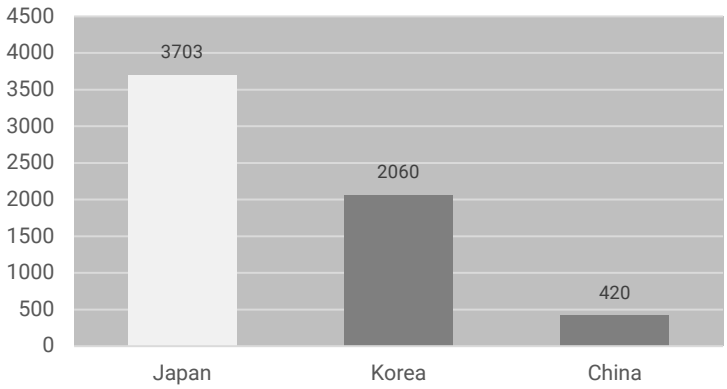
A stable and high-expenditure market

Japan is the world's second largest national market for pharmaceuticals, medical devices and other life sciences industries, with at least 10% of the global turnover.[3] The pharmaceutical sector in Japan alone is valued at more than €102 bn per year,[4] while medical devices account for another €22bn.[5]

In total there are 8,442 hospitals, 101,529 medical clinics and 68,940 dental clinics in the country, which is more than all of EU28 taken together. The comprehensive and publicly funded healthcare scheme accounts for 82% of the total healthcare spending,[6] making the public spending amongst the highest among the major economies.

Japan has an annual medical care expenditure of over €2,500 per capita in 2015 according to official statistics.[7] International comparisons from the WHO indicate an even higher number, while China's rapidly growing health expenditure is just 11% of Japan's.[8] As a result, the health markets (measured in expenditure) of China and Japan are roughly of same size.

Figure 1. Health expenditure per capita (current US$)



Source: WHO Global Health Expenditure database, 2014

In addition, approximately 20% of Japanese demand is already satisfied by foreign suppliers (which is similar to the US and other developed economies), making Japan the largest accessible market in Asia for foreign entities. In the medical devices sector, nearly half of the national consumption is derived from imports,[9] and it is already Europe's second

[3] JETRO, Life Sciences, 2016; Eucomed calculations, based on manufacturer prices, 2012f

[4] Based on IMS Health Market Prognosis, 2015; PwC, Pharma 2020 Report, 2011

[5] JETRO, 2016

[6] World Bank, World Development Index, 2013

[7] Ministry of Health, Labour and Welfare of Japan, Annual Health, Labour and Welfare Report, 2016

[8] World Health Organization Global Health Expenditure database, 2014

[9] JETRO, 2016

largest export destination for medical technology.[10] There is already considerable industrial cooperation, component trade and SME participation of specialised technology suppliers and SME participation.

Growth drivers – demographics, reforms, the economy

Japan's life sciences market has been stably growing for the past decade, and has retained its share of global healthcare spending.[11] Although Japan's population is forecasted to decline with an ageing society and low replacement rate, the evolution also spurs demand and investments in life sciences.

A quarter of the population is above retirement age, and this group accounts for about half of the country's healthcare costs already. The Japanese health market grows at least 1.2% per year from demographic effects alone,[12] while public healthcare cost is increasing in total by nearly 3% per year.

The population of Japan reached its peak in 2008 at 128 million inhabitants, and Japan became one of the first countries to encounter challenges from an ageing society. But it is not the last. Firms active in Japan are early adopters to the market opportunities of the phenomenon, which is currently taking place across Europe and will reach China within a decade.

But markets are not driven by demographics alone. Japan's overall GDP growth per capita in absolute terms (which in the end determines the spending power of consumers and businesses) is at $850 per year and capita – which is still growing and nearly twice the absolute growth of China.[13]

In addition, regulatory reforms are a second major driver of market growth. A new revised pharmaceutical law – the Pharmaceutical, Medical Devices (PMD) Act came into effect in 2014,[14] with the aim to ease regulatory burden, reduce development costs and speed up pre-marketing approval times. Such reforms were deemed necessary for effective commercialisation and to keep pace with the technological developments, especially due to digitalisation as well as regenerative and gene therapy.[15]

Prior to the PMD Act, reforms on drug price premiums, fast-track authorisation (so-called *Sakigake* package),[16] programs to promote drugs for unmet medical needs and other measures to address 'innovation lag' – the delay in the authorisation of new drugs and medical technologies – have been going on for more than a decade. The medical devices sector has seen a 5.3% growth per year following the reforms.[17]

But in response to the increasing healthcare costs, the premiums for innovative drugs are balanced by government programmes to diversify national supply with increased use of

[10] MedTech Europe, The European Medical Technology Industry in Figures, 2014

[11] The Global Use of Medicines: Outlook Through 2015 Report by the IMS Institute for Healthcare Informatics

[12] OECD, Public spending on health and long-term care: a new set of projections, June 2013

[13] Calculations based on IMF WEO, 2018

[14] The Act on Securing Quality, Efficacy, and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (PMD Act), November 25, 2014

[15] Ibid; see also Regulatory Information Task Force, Japan Pharmaceutical Manufacturers Association, Pharmaceutical Administration and Regulations in Japan, 2017

[16] Sakiage package announced by Ministry of Health, Labour and Welfare in June 2014

[17] Authors calculations based on Yano Research Institute data, 2009 to 2013.

generics. The market size for generics in 2015 is estimated about 789.7 billion JPY, or about 12% of the prescription drugs market as a whole. The generics market is expected to grow this year (2018) to around 1,117 billion JPY.[18] Similarly the biosimilar markets are expanding thanks to new guidelines.

[18] Research and Markets, The Overview of Japanese Generic Drug Market, 2016

3. FDIs in the sector

Internationalisation of Japanese industry

In contrast to the transatlantic M&As that reshaped the pharmaceutical industry in the past twenty years, Japan's internationalisation of the life sciences sector has been relatively limited until recent years. Thanks to a sizeable internal market, the Japanese market actors have traditionally focused on catering for local demand, with some emphasis on generics.

In recent years, however, a number of Japan's pharmaceutical firms have been internationalising their R&D and established research centres in, e.g. the UK and Singapore.[19]

R&Ds are also the main drivers of outward M&As, and often age-related diseases (e.g. oncology) are the major transactions primarily involve Japan's largest pharmaceutical corporation, Takeda, between 2011 and 2017:

- US$ 14 billion acquisition of Nycomed (Norway)
- US$ 9 billion acquisition of Millennium (US)
- US$ 5 billion acquisition of ARIAD (US)

In addition to Takeda's M&A transactions, Astellas Pharma has acquired OSI Pharmaceuticals for US$ 4bn in 2010. There are fewer acquisitions in the other direction, and only a few inward M&A transactions and licensing agreements have already been concluded

- AstraZeneca acquired the rights to Takeda's Parkinson drug in 2017.
- The dermatology business of Astellas was acquired by LEO Pharma of Denmark in 2015.
- The Japanese cancer drug manufacturer Carna Biosciences licensed its CDC7 drug to ProNAi Therapeutics in 2016

However, the most prominent feature of inward FDIs are not M&As, but greenfield investments for R&Ds. This is in part due to a national program to promote R&D spending. For the fiscal year of 2017 and onwards, up to 14% of R&D expenditure can be exempt from taxation, with additional deduction up to 10% if R&D costs have exceeded 10% of average sales.[20] R&D subsidies that are specifically for the life science sector were also established, which are managed through the National Institute of Biomedical Innovation (NIBIO). A specific tax exemption was created for rare diseases (so-called orphan drugs) already in 1993 for their societal benefit, and as they are also otherwise often unprofitable.

Japan's corporate tax environment is also overall advantageous to investors. At 23 to 30%, corporate income taxes have been lowered by ten percentage points in the past fifteen years, and now the lowest amongst the major Asian-Pacific economies with more than US$ 1 trillion in GDP.[21] Thanks to these measures to improve R&D returns and

[19] Chugai Pharmaceuticals has established research site in Singapore, while Eisai has a site in the UK

[20] Deloitte, Taxation and Investment in Japan, 2017

[21] Deloitte, 2018, accessed at: https://www2.deloitte.com/content/dam/Deloitte/global/Documents/Tax/dttl-tax-corporate-tax-rates.pdf

commercialisation, approximately twenty foreign-affiliated companies (including Pfizer, Novartis, GSK, Janssen, Boehringer, and Bayer) have established R&D in recent years.[22]

Business and investment environment

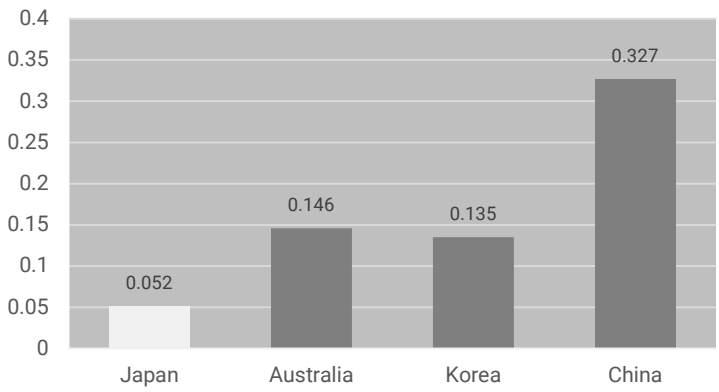
Japan's incentives for attracting FDIs are not for liquidity, but a more competitive and connected business environment, and for the structural reforms of the economy. FDIs benefit the host country through increased competition, new know-how and linkages to overseas markets. Despite investments being a major part of Japan's economy, oversea capital has consistently played a marginal role to date. At just 0.7% of GDP, the levels of inward FDI are disproportionately low compared to other developed economies.

However, the share of FDIs in the economy is not always a measurement on how open it is for foreign investments, but rather indicates the demand for capital. As Japan is world's most liquid capital market, it had few incentives to import investments from overseas, but rather exported its surplus capital as investments in other economies.

In general, Asian economies tend to be more restrictive to foreign investors. Foreign equity caps, investment screening and restrictions on key foreign personnel are imposed in China and much of south-east Asia. Governments remain in strict control of market entry to control capital flows or preserve monopolies and state-owned enterprises (SOEs).

As investments are restricted in much of Asia, Japan is the only country in the region with the level of openness as the European countries with no cases of expropriation, foreign equity caps, forced licensing or performance requirements imposed on foreign investors.

Figure 2. FDI regulatory restrictiveness index, 2016



Source: OECD, 2016

In addition to openness to FDIs, Japan's investor climate scores consistently above its competitors in the Far East. On indices for the rule of law,[23] non-discrimination and least-restrictiveness of product and market regulations,[24] and restrictiveness on business use

[22] JETRO, 2016

[23] World Justice Project, Rule of Law index, 2017

[24] OECD PMR, 2013

of data (which is relevant for R&D and clinical tests),[25] Japan perform distinctly above the emerging markets.

Although no sectoral specific data exists for EU investments, the return of investment of EU investments in Japan across all sectors is at 6.6%, which exceeds by far both intra-EU investments (3.4%) or the average returns from non-EU markets (3.9%).[26] In relation to these cross-sectoral numbers, the EU investments in life science industries should generate similar or higher returns thanks to the fiscal incentives and growing Japan's internal market with a predictable reference pricing scheme, which also pays an innovation premium. Moreover, the combination of yen appreciation and undervaluation of corporate assets in the past have lowered the cost of market entry, while boosting profit remittances back to Europe.

[25] ECIPE, Digital Trade Restrictiveness Index, 2018

[26] Eurostat, 2016

4. The impact of trade agreements on life sciences

Large-scale liberalisation

Liberalising for international trade and investment is a cornerstone in the 'third arrow' of the Abenomics policy package aiming at structural reforms. Japan aims to conclude two of the largest trade agreements ever undertaken: the EU-Japan EPA and the Comprehensive and Progressive Trans-Pacific Partnership (CPTPP) despite the US's withdrawal from the latter.

However, there are no incidences of expropriation, foreign equity caps, forced licensing or performance requirements imposed on foreign investors in Japan. Japan is also issuing guarantees in the EPA that it will not do so in the future against European investors.[27]

In addition, Japanese tariffs are already amongst the lowest in the industrialised world even before these trade agreements are implemented. Japan applies no tariffs on 55% of its tariff lines, which is the highest share of duty-free trade amongst the G20 economies.

Both Japan and the EU are signatories to the WTO agreement on Pharmaceuticals that eliminated all tariffs amongst its signatories on pharmaceuticals or related trade in substances and chemicals.

Medical devices are a diverse combination of products and services made out of 500,000 technologies, spanning from digital and complex equipment to simple consumables. These products are dispersed over several product categories – including pharmaceuticals, papers, textiles, machinery, software and scientific instruments. Some medical devices are difficult to distinguish from other industrial and consumer applications, and a simple average applied tariff of approximately 1% have been applied. All such remaining tariffs are effectively eliminated as the EU-Japan EPA comes into force.

In addition to the already low tariffs, the regulatory cooperation between the EU and Japan were already comprehensive prior to the EPA. Mutual recognition agreements acknowledge Good Manufacturing Practices (GMP) certificates of the parties for conformity assessments on pharmaceuticals, homoeopathic medicinal products, vitamins and herbal medicines.

Parties had also already established collaboration on Good Clinical Practice (GCP) ordinance and minimum requirements for biological products in accordance with international standards on specifications and testing of vaccines. In addition, EU and Japanese medical regulators had already signed confidentiality arrangement to allow exchange of non-public data.

Regulatory harmonisation

While the final text is not yet published by the signatories in all annexes, the general approach of EU and Japan is to ensure that their standards and technical regulations are based on international standards to the greatest possible extent.

The EPA expands the coverage of the existing mutual recognition agreement on Good Manufacturing Practice to new products, including active pharmaceutical ingredients and

[27] EU-Japan EPA, chapter 8 section B

biological pharmaceuticals, immunologicals and vaccines. Japan and EU also align their quality management systems (QMS) for medical devices, cutting the application times and costs for market approval.

In addition to the EPA, a number of unilateral reforms were undertaken by Japan that coincided with the trade negotiations with the EU and the TPP countries. One example is the 2014 PMD Act which aimed to reduce development costs and times on software, regenerative and gene therapy. The law expanded the scope of products eligible for third-party certification via private notifying bodies and allowed quality inspections to be conducted for a group of products rather than individual products one-by-one. Stand-alone software is also classified as Class II devices that benefit from less specified controls for authorisation.

In 2016, the Japanese government also abolished import notifications on cosmetics and "quasi-drugs", which is a special category of medicated cosmetic that used to require pre-marketing approval in Japan. Such products included vitamins, bath preparations, skin, hair and dental products,[28] most of which are over-the-counter products that do not require any authorisation in Europe.

A survey amongst European executives active in Japan shows how these regulatory divergences created an additional cost for European life sciences firms equivalent to a 22% tariff –[29] a cost saving which could be used for investments and further market expansion.

[28] JETRO, Quasi Drugs in Japan, 2011

[29] Copenhagen Economics, 2009, p.175.

5. Innovation

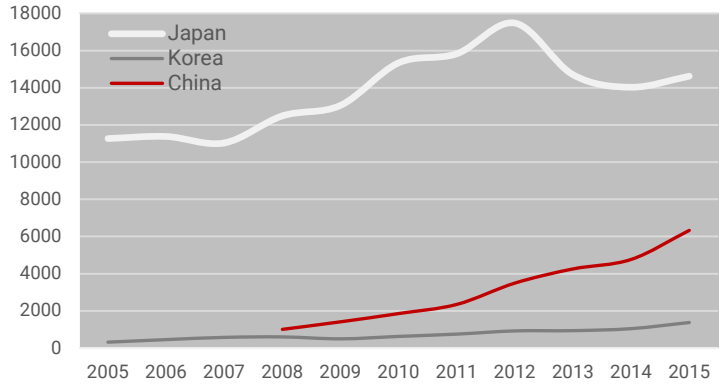
High-end R&D capabilities

An objective of foreign-invested firms entering the Japanese market is not solely for market access, but to benefit from the high-end R&D in life science which also enjoy a number of fiscal benefits. There is also a high degree of complementarity between European and Japanese R&D: For example, Japan has a unique specialisation on diagnostics and precision measuring technologies that are integrated as components by European firms and then exported to the rest of the world.

The competitiveness and capability of Japan's R&D capability are proven the fact that amongst the hundred top-selling pharmaceutical products 13 products were discovered and developed in Japan (compared to nine in the UK, five in France and four in Germany).[30] The know-how also extends to auxiliary technologies, e.g. packaging and quality assurance.

Statistics over business R&D spending on pharmaceuticals and medical instruments and supplies, which clearly shows that Japan still outspends other economies in Asia despite an impressive growth and technical upgrade in China.

Figure 3. R&D spending on pharmaceuticals and medical instruments, bn €, 2005-2015



Source: OECD, 2016

In the medical devices field, Japanese R&D is prominent in diagnostics, imaging or in seeking new synergies with fields, such robotics. For example, Japanese technology has propelled local and international firms to global market-leading positions in e-health, magnetic resonance imaging, tomography and endoscopy. Such R&D activities are not fully captured in the statistics.

As an indication of the parity of spending on imaging or new innovative technologies, Japan is currently outspending Korea on R&D in optical and photographic equipment

[30] IMS, IMS World Review, 2013

technologies (including also non-medical applications) by approximately hundred to one in current value and exchange rates.

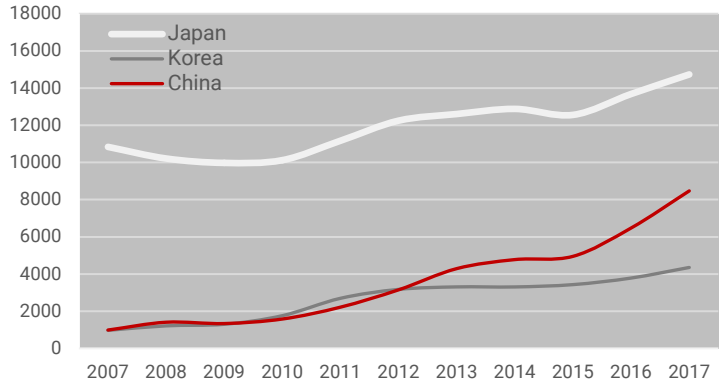
Patent applications

The resulting output from private sector R&D activities is evident in the international patent application according to the WIPO PCT treaty, which can be converted into individual foreign patent applications in multiple jurisdictions where patent protection is to be sought.

As the PCT system neither examine patent applications fully nor grant patents, some of the applications are 'junk patents' where low quality (and unexamined) patents are often filed to discourage market entry. In 2014, China's patent office (SIPO) received nearly 2.4 million patent applications, 93% filed by domestic applicants. China has also climbed to third place in terms of international applications, as applications costs (even for junk patents) are subsidised by the Chinese state.

Despite this distortion in the international patent statistics, the clear difference in the number of international applications gives an indication on the productivity and commercial viability in pharmaceuticals, biotechnology, medical technology, optics, diagnosis and healthcare informatics.

Figure 4. International patent registrations (PCT publications) in life sciences 2007-2017



Source: WIPO, 2018

6. Conclusion

Life sciences and healthcare play a pivotal role in Japan's societal transformation and economic reforms. The sector is central to coping with Japan's challenges with shifting demographics with high market capitalisation and innovativeness make it an interesting laboratory for policy-induced structural reforms. As the European countries, as well as China, are heading towards the same demographic developments, many pharmaceutical and medical device companies are establishing themselves in Japan to become early adopters to future technologies and market conditions. A subsidiary or R&D investment in Japan is a market presence in Europe's future – and indeed, Germany has already passed Japan to have world's lowest birth rate in 2015.[31]

Japanese life sciences industry remains the largest accessible market for foreign investors, with strong growth drivers from underlying increase in demand as well as market liberalisation. Continuous reforms have also got rid of the 'innovation lag' which used to delay innovations on the local market.

The high success rate amongst its innovations and successful commercialisation in combination with fiscal incentives and stable business environment have already attracted foreign R&D centres and other greenfield investments rather than M&As that have driven the transatlantic FDI.

The business environment will be further improved through the expanded mutual recognition and alignment of European and Japanese GMP and QMS systems under the EPAs, even further reducing regulatory compliance costs – which are the highest market entry costs in the life science industry.

[31] BBC News, Germany passes Japan to have world's lowest birth rate – study, May 29, 2015, accessed at: http://www.bbc.com/news/world-europe-32929962

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