

Japan Report

2018 – a big year for Japanese pharma



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Japan at a Glance

Population: **126,702,133** Capital: **Tokyo** Chief of State: **Emperor Akihito** (since 7 January 1989)
Head of Government: **Prime Minister Shinzo Abe** (since 26 December 2012)

GDP:

\$4.73

Trillion

GDP growth rate: 0.5%

GDP per capita:

\$38.9

Thousand

Exports:

\$641.4

Billion – motor vehicles, iron and steel products, semiconductors, auto parts, power generating machinery and plastic materials

Imports:

\$629.8

Billion – petroleum, liquid natural gas, clothing, semiconductors, coal, audio and visual apparatus

Introduction

Japan has the world's third largest pharma industry. Yet, for many international companies the market has not proved easy to access. Very high barriers to entry have combined with a historically insular domestic market to limit opportunities. This is now changing. Japan's domestic market is looking increasingly at exports, and international companies are seeking opportunities to invest in and access the large, well-funded healthcare system.

Japan is enjoying its longest sustained period of growth in over a decade. The pharmaceutical sector is forecast to reach \$72 billion by 2021¹, representing 17% growth between 2011–2020. An aging population and broad access to healthcare are the driving factors. With over 100 domestic pharma companies, such a fragmented market is likely to develop into an acquisitional environment, particularly with internationals looking to enter.

Demographics are shaping the Japanese pharma industry. The population has declined and aged over the last few decades due to low birth and migration rates. Life expectancy is now 85 years². The result is a rising dependency ratio coupled with a shrinking tax base placing ever-greater financial strain on the system. Without change, insurance premiums and healthcare spending will inevitably increase.

There are a number of challenges ahead as many patents expire and annual price cuts and generics take hold. Another problem is a growing funding gap, which, if unchecked, will rise to around \$160 billion by 2020 and \$370 billion by 2035³. Simply increasing the country's insurance premiums is a sub-optimal response as it will damage sectors beyond pharma by increasing labour costs and reducing competitiveness. Also, co-payment rates are already high at around 30%; there is little scope for further expansion. An alternative strategy is needed and increasing generics consumption is an obvious option.

Total annual pharmaceutical spend is \$93 billion. Government is central, accounting for around 40% of health spending via the national insurance scheme. It now reviews prices annually for all therapies and quarterly for the newest and most expensive⁴. Industry commentators speculate that this could see revenues fall some 30% by 2025. Recent cuts to Opdivo from Ono Pharmaceutical and Gilead's Sovaldi,

along with a voluntary reduction in Merck's cancer therapy, Keytruda, are just a few of recent examples of the impact of these changes.

As pharma firms, large and small, begin to reposition themselves in response they will face key challenges. In particular, branded products have seen a gradual reduction in use; they are less resilient to brand erosion and government is targeting 80% generic penetration by 2020. The Japanese government has gone as far as to identify growth of the nation's generic drug market as "imperative to Japan's long-term economic health".

Japan has long been a bastion of patented drug consumption, with a strong innovative pharma industry, but as an impending patent cliff has loomed, many companies are now forced to reconsider their long- and medium- term strategies.

Main issues – domestic response:

Increased competition from the USA in Generics and patented environment, and China in terms of API

In spite of the challenges, a number of opportunities are present. Through diverging strategies there is clearly room for innovative big pharma to invest in its pipeline and grow exports. Opportunities for both Japanese and international generic companies are clear, especially with public attitudes shifting away from cultural scepticism of generic medicines. Active Pharmaceutical Ingredient (API) and generic finished dosage suppliers who recognise this potential and understand the unique needs and challenges of the Japanese market are well set for significant growth over the coming years.

Japan has already made many attempts to transform its pharmaceutical landscape from an internally-facing market to a global one. For example, Ole Moelskov Bech, chairman of EFPIA Japan, recently spoke in favour for the current pro-innovation policy as it has been a significant driver for foreign investments since its pilot introduction in 2010. Critically, Japanese pharmaceutical companies are now seeking professionals that have diverse experiences

and global outlooks. There is a move away from long-held inward attitudes as companies look to take the next steps internationally. Even Japan's generics market is growing and changing with transfers of generic drugs from big

pharma to local generic companies – for instance, the off-patent migraine treatment Zomig (zolmitriptan) moving from AstraZeneca Japan to Japanese generic major Sawai Pharmaceutical.

This report

This report builds upon primary research collected via in-depth surveys carried out by both domestic and international companies operating in Japan. It aims to present a holistic picture of recent trends, challenges and, most crucially, future opportunities for the pharma sector in Japan. Nearly 100 pharma companies that attended CPhI

Japan 2017 are included in the analysis from across the supply chain, including big pharma, biotechs, CRO/CDMO, generics, API manufacturers and pharmaceutical machinery and packaging.

Growth opportunities

Domestic and international companies we surveyed are bullish over their near-term prospects. Domestic companies are surprisingly optimistic with average growth of 17% forecast for 2017. This contrasts sharply with recent performance. International respondents were even more positive in outlook with expected average growth of 38%. Such a startling statistic reflects them starting from a far lower market base; several respondents are relatively new entrants. Joining the Pharmaceutical Inspection Convention and the Pharmaceutical Inspection Cooperation Scheme

(PIC/S) three years ago accelerated market entry for several international companies, particularly as the synchronisation of standards harmonises procedures.

Main issues – domestic responsee:

The domestic market has been slow to adapt to decreased R&D productivity, we are now playing catch-up

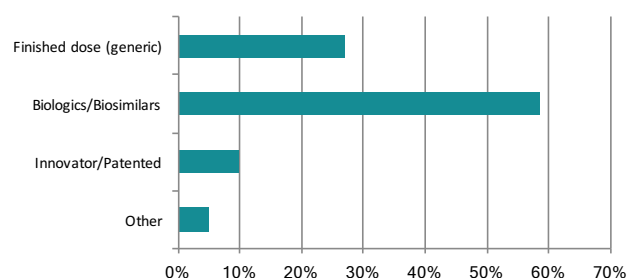
Fastest growing sectors – changing times with generics and biologics

The Japanese pharma industry has long been a sizable presence in the innovative part of the global market. Anticancer drugs have been at the forefront of Japanese development of biopharmaceutical products, as well as enhanced immune class drugs, including cutting edge technologies such as checkpoint inhibitors (e.g. PD1), chimeric antigen receptor (CAR)-T-cell therapies, antibody-drug conjugates (ADCs) and monoclonal antibodies (mAbs). However, focus on generics and biosimilars is increasing.

An analysis by sector of both domestic and international responses showed finished dose/generics and biologics/biosimilars are experiencing the fastest growth in the Japanese pharma industry. Domestic respondents believe the segments that will grow fastest are biologics (59%),

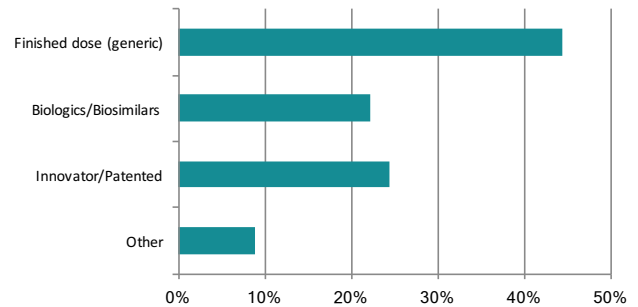
finished dose (27%) and patented (10%). International respondents placed a different emphasis on the segments – finished dose (44%), patented (24%), and biologics (22%) – but the trend is clear (see also Charts 1 and 2).

Chart 1: Domestic response on which segment of the Japanese pharma industry will grow fastest



Newer markets for lower cost and branded generics, therefore, coupled with advance biological products, offer the greatest returns over the traditionally successful innovative solid dose formulations, where the majority of domestic pharma companies have expertise.

Chart 2: International response on which segment of the Japanese pharma industry will grow fastest



Domestic response summary

As the population ages and healthcare costs rise, the Japanese government has committed to increasing market penetration of generics to 60% by the end of 2017. The majority of those surveyed believed domestic manufacturers will be able to meet the country's generic pharmaceutical demands. However, they also acknowledged potential opportunities for Indian manufacturers and branded generics from the United States and Europe. Overall, the rising generic usage was forecast as the biggest opportunity for domestic manufacturers (60%) and, surprisingly, Indian manufacturers (24%). Both US and European manufacturers were chosen by less than 10% of respondents suggesting that price will remain the primary factor when choosing imported generics medicines. Another limiting factor on the overall adoption of generic medicines remains the population's brand loyalty with nearly 40% of respondents believing it was still hindering efforts to increase generic usage.

Main issues – domestic responsee:

PMDA approval is still slow and acting as a break on the market

Interestingly, Japanese companies were much more open to sourcing foreign APIs (as opposed to finished products); from China (60%), India (48%) and Europe (67%: excluding Italy). A further 33% were happy to consider Italy and 18% the United states as potential sourcing options. Unusually for such a protective market, the preference for Japanese sourced APIs was only marginally ahead of other countries (63%). Greater tolerance of foreign sourced products is likely due to lesser overall importance placed on actives versus finished forms and the inevitable influence of cost considerations in a market environment driven by government policy aimed at making savings on healthcare expenditure.

Working at home or abroad?

Domestic respondents overwhelmingly preferred the domestic environment; only 18% Japanese pharma business is undertaken in foreign markets. This suggests a significant potential growth area as evidenced by nearly 75% of domestic respondents saying they intend to work with foreign partners in the next year. Companies are looking to increase their knowledge bases as well as to sell Japanese-made products abroad. Responses also showed that over two thirds of the companies surveyed look to target

Main opportunities – domestic responsee:

The Increased partnerships with international companies are bringing new innovations, development deal and opportunities.

Main issues – international respondee:

Lack of faith and compliance levels in Chinese and Indian manufacturers

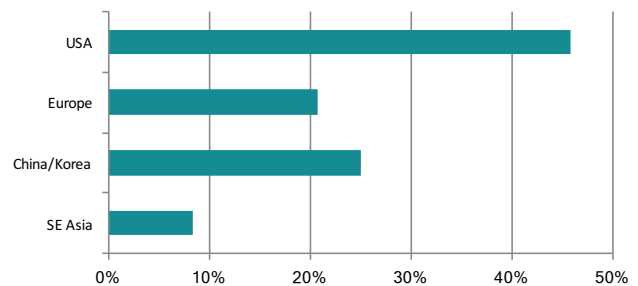
international markets; around half are targeting the US and 27% China and Korea. This may be due to the favourable reimbursement system within the US and the proximity of high-growth economies such as China and Korea.

Similarly, partnerships between Japanese pharma and the generic companies are expected to increase. 78% agreed that “the success of the Takeda-Teva collaboration has provided a model that companies can replicate” when looking for potential future partnerships.

Notwithstanding the growing horizons of the Japanese industry, almost a third (not included in Chart 3 above) said

they were not targeting international markets. Furthermore, a majority of companies suggested they had “no plans for acquisitions” (70%). Domestic acquisitions were by far the most likely (21%) with just 12% considering acquisitions in Europe and/or the USA, and only 9% in the Rest of the world.

Chart 3: International markets Japanese companies are targeting



Challenges ahead?

There were also areas of weakness identified by domestic respondents. Three quarters agreed that the Japanese regulator – the Product Development and Management Association – “was not yet doing enough to tackle the approvals backlog in the country”. Another area of concern was how to encourage a new wave of innovations across biotechs and medical devices.

The Pharmaceutical and Medical Devices Agency (PMDA) has undertaken several policy initiatives to tackle this problem. Nevertheless, the market players remain ambivalent;

- a quarter agreed that “we should see more innovations come to market”;
- another quarter disagreed believing that “alone would not be enough”; and
- around half agreed the “result won’t be known for several years, and it’s too early to judge the policy”.

The national health service price revisions moving to an annualised review period (rather than biannual) is another area of concern. Only 16% of domestic respondents felt this would be a positive step agreeing it would “increase competition amongst generic manufacturers”. However,

more than 70% expressed significant concern; the policy is likely to “quickly reduce margins and drive down prices”.

Main issues – international pharma respondee:

Competition for large pharma from generics manufacturers

Finally, for small and medium sized companies the introduction of pricing controls for “higher selling drugs” was also identified by more than 75% of respondents as “anti-innovative” and damaging the sector’s growth prospects.

Main issues – international pharma respondee:

the public still prefers to buy from established local brands – which means we have to tailor our strategy with partners

Domestic investments

Over the next 3 years a surprising number of domestic respondents (32%) said they “did not plan any investments in R&D, manufacturing technologies or capacity increases”. However, 42% planned to invest between \$1-10 million, with just under 10% projecting investment of \$10-20 million and further 10% investing \$20 million or more. The most prevalent technologies for investments – each being cited by around 30% of respondents – are:

- scale-up/commercial;
- biologics;

- continuous processing; and
- aseptic/sterile.

Surprisingly, for what is widely regarded as the next global growth area, just 25% of those survey suggested they were planning new biomanufacturing facilities in the next 3 years. Biopharmaceutical product classes currently being researched in Japan mirror trends globally, with “anti-cancer drugs” (71%) and “enhanced immune class” (48%) proving by far the most prevalent.

Chart 4: Technologies that Japanese companies are currently investing in

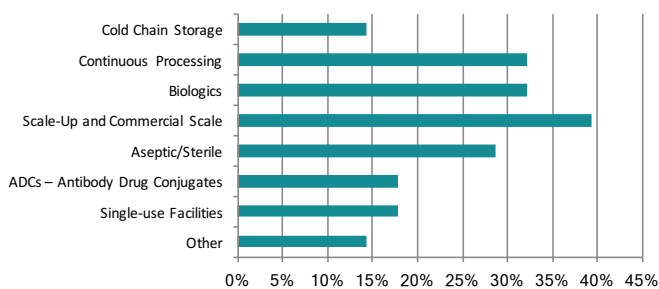
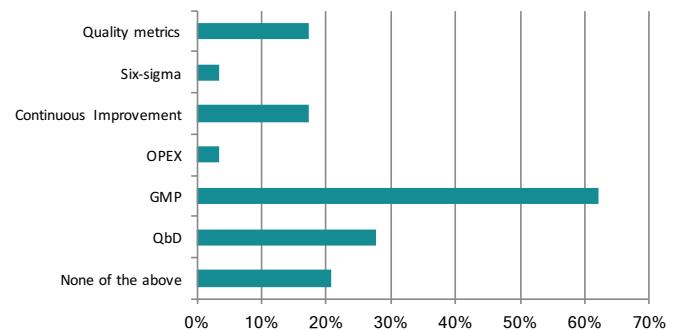


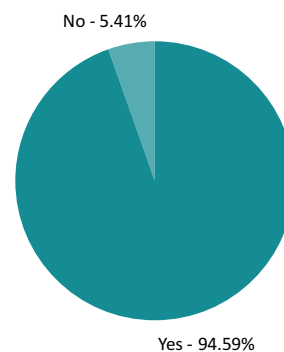
Chart 5: Quality systems that Japanese companies use



International response summary

The aging population and growing generics market has made Japan an attractive proposition. Japan joined the PIC/S in 2014. It has also synchronized manufacturing and quality control standards between overseas suppliers and domestic manufacturers. This has accelerated market entry of international companies. International respondents were overwhelmingly positive (95%) when asked if they intended to work with Japanese partners (See Chart 6).

Chart 6: International response if they plan to work with any Japanese partners within the next year



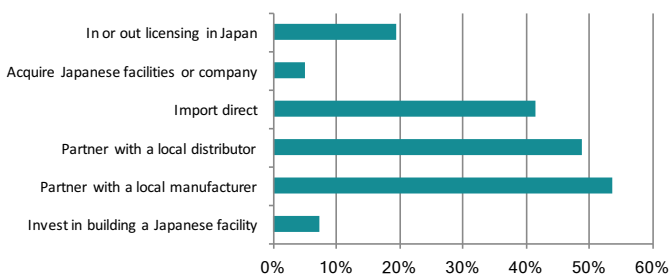
Main opportunity for growth – international pharma responsee:

international collaboration on innovative technologies

However, 62% responded that they “were not planning to invest in biomanufacturing capabilities for Japan”. Again, similar to domestic respondents, there is reluctance to commit to more expensive product classes in a market that is often hard to break.

Looking more closely at international companies’ strategies for operating in Japan, it becomes apparent that local knowledge and supply chain are seen as essential ingredients for growth.

Chart 7: International response to what their growth strategy is in the next 1-3 years in Japan



Main opportunity for growth – international generic company:

There is a huge opportunity for companies like us as the generics market will grow considerably

Some 54% of international companies said they planned to “partner with a local manufacturer” in the next 1-3 years, with 49% planning to “partner with a local distributor”. Unlike other markets, only a very limited number of companies planned to invest in facilities directly (7%) or make acquisitions (less than 5%). However, 42% of companies were “importing direct” and around 20% planning to either “in or out license” technology or products.

Global firms therefore are either working with local distributors and manufacturers or importing directly; very few are looking to establish a direct presence. It is likely that barriers to market entry, along with local employment laws and general production costs, are prohibitive.

Main issues – international respondent:

The inability to work with foreign companies effectively

One successful strategy that has been widely adopted for market entry in Japan is reverse co-promotion. Distributors obtain exclusivity (and through that higher sales), while the company selling the product receives a higher margin. The distributor agrees a lower ‘transfer price’ in exchange for a monopoly on country-wide sales. To use Astellas, one of the most prominent deal makers, as an example, they have agreed reverse co-promotion arrangements with AstraZeneca, for Symbicort, NBI for Micardis, and Pfizer for both Lipitor and Caduet.

The majority of international companies agreed; 53% believed reverse co-promotion deals are still “mutually beneficial to both partners”. The remainder split equally between those who feel such arrangements favour either distributors or the selling company.

International companies remain hesitant over opportunities presented by Japan’s generics usage even though significant growth is now a key government aim. Over 60% believe brand loyalty hinders uptake, in particular, for Indian-made products. Despite this, the international market had a strong view that Indian companies (47%) had the biggest opportunities for generics growth. This compares well with those citing domestic manufacturers (52%), while confidence in European (35%) and USA manufacturers (25%) was some way behind.

Positivity around the potential for increased collaborations between big international generic companies and Japanese pharma firms is a notable view from international respondents. An overwhelming 90% agreed that partnerships “like the one between Takeda and Teva would proliferate over the next few years”. Interestingly, this was notably higher than amongst domestic respondents.

In API sourcing, however, international companies see the big producers – China (44%) and India (48%) – and, unsurprisingly, domestic manufacturers (58%) as market leaders. There is extremely limited access for both European and US companies and we would expect this to continue

– Japanese manufacturers supplying the higher margin products and India and China the low cost generic APIs.

On a positive note for innovation, international respondents argued that the PMDA policy towards biotech and pricing premiums were driving a resurgence in new medical devices and product classes underway. Nearly 65% believed that impact of the new premium pricing system will boost innovations, with only 12% stating they did not believe this alone was a solution. This perhaps reflects gains already observed as foreign pharma companies look to bring their pipelines to Japan more quickly. As consequence, the number of drugs developed in Japan is likely to increase significantly over the next few years.

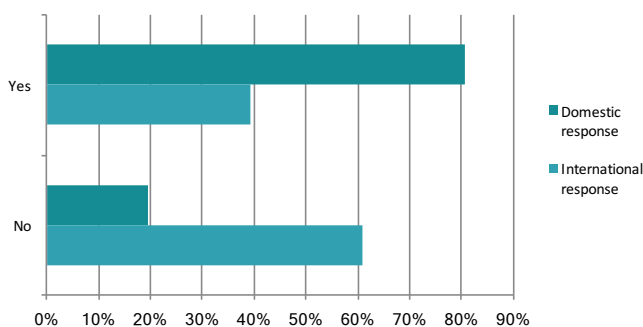
Global drug development partnership

A more recent trend that is the big pharma in Japan increasingly looking to partner with international terms for co-development of novel therapies, perhaps best exemplified by the recent deal between Takeda and Samsung biopsis. Under the partnership agreed in August 2017 they have agreed to ‘jointly fund and co-develop multiple novel biologic therapies in unmet disease areas’. The two companies will immediately begin working on the program’s first therapeutic candidate, TAK-671, which is intended to treat severe acute pancreatitis⁵.

Interaction between domestic and global markets

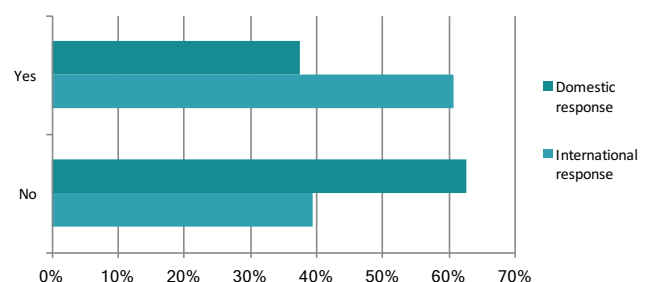
Although there was considerable overlap between international and domestic responses, there were also contrasting views in some areas. For example, many companies face an impending patent cliff edge. When asked if this caused them to rethink their strategy, domestic respondents overwhelmingly (80%) said it was, while a strong majority internationally (60%) held the opposite view (see Chart 8 below). This could suggest low awareness internationally of the fundamental structural changes occurring in Japan at the present.

Chart 8: Is the impending patent cliff causing Japan’s companies to rethink their strategy?



There were also disparities on the question of how much brand loyalty was hampering generics uptake. Domestic respondents downplayed its role (see Chart 9).

Chart 9: Is brand loyalty and the Japanese consumer still hindering efforts to increase generics consumption?



The drugs backlog

Respondents were asked if the PMDA has made enough progress in tackling the drug approval backlog. Again, responses differed starkly. International firms agreed strongly (79%) with many considering that it is much easier now to enter the market with so many new products forecast. However, domestically the opposite view prevailed (74%) amid concern that the approval backlog is holding back the market (see Chart 10).

With the Japanese pharma market expanding and new technologies being utilized, more biopharmaceutical products are being developed in Japan. Technologies, such as “scale-up and commercial scale”, “continuous processing”

and “aseptic”, are extending market versatility and the biopharma production capabilities.

All respondents agreed anticancer and enhancement to immune class drugs were the most prominent. However, there were also differences over other biopharma products. For example, diabetes drugs were considered the main type of product being worked on by only 13% of domestic

respondents but 70% internationally. Nervous system disorders were subject to a similar domestic (0%) versus international (37%) disparity. It is interesting that the research showed such stark differences for certain biopharma products, which poses the question of whether this is due to poor communication between domestic and international sectors or just inaccurate presumptions (see Charts 11 and 12).

Chart 10: Do you think the PMDA has made enough strides in tackling the drug approval backlog?

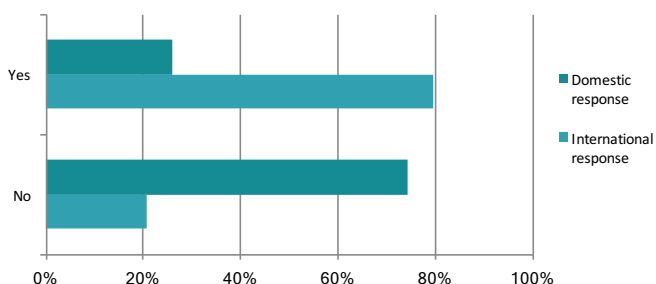


Chart 11: Domestic response on the main types of biopharmaceutical product classes being worked on in Japan

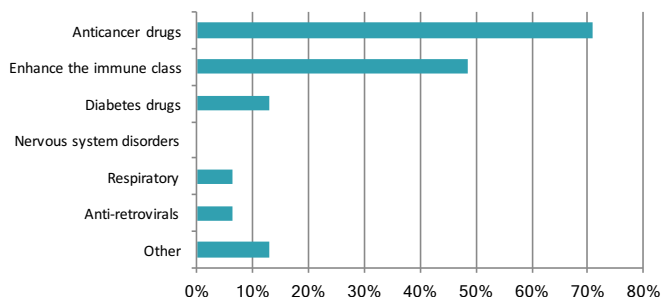
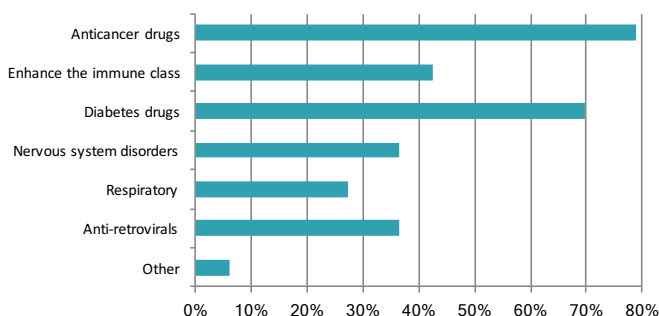


Chart 12: International response on the main types of biopharmaceutical product classes being worked on in Japan



Conclusion

Japan remains an elusive market for internationals. Significant barriers to market entry – economic, cultural and political – cannot be ignored. However, this report provides key insights on the changes taking place that suggest strongly that industry experts detect openings and opportunities.

Demographic pressures on healthcare costs are clearly driving a political agenda that benefits market players who can offer lower costs solutions. Generics are an obvious route, but Japan’s status as a highly developed economy with a pharma industry that leads in innovation opens other possibilities, particularly the biologics/biosimilars segment.

Crucially, as Japanese pharma markets are in a state of transition towards greater openness; potential rewards for early international movers cannot be ignored. However, an appropriate strategy is essential to overcome factors such as domestic brand loyalty – a local partner or local knowledge is a prerequisite of successful market entry. The report also hints at potential information asymmetries with international respondents having markedly different perspectives on certain issues to domestics, particularly on regulatory stances taken by Japanese government.

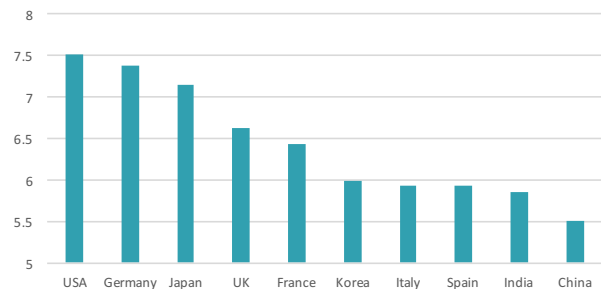
Partnership with domestic firms – taking advantage of local knowledge as well as technical expertise – would appear to be the name of the game, for now. However, respondents have a general air of confidence over prospects in Japan. The potential for direct entry and even acquisitions cannot be discounted in the medium term.

Addendum – Inaugural CPhI Pharma Reputation Survey
 Reputation matters in a rapidly changing global market. This is the first ever international study amongst pharmaceutical companies on the perception of the relative strength of each country’s industry. Investment decisions and supply-side arrangements can often hinge on this unspoken influence, particularly when working with new partners. Discover the reputational strengths and perceived weaknesses of the ten main pharma economies based on the insight of 500 international pharmaceutical companies from over 40 countries.

Japan Specific Results

Analysis of the inaugural CPhI Pharma Reputation League Tables, recently published in the CPhI Annual Industry Report 2017, indicates that Japan is perceived as part of the top three countries globally. As seen in Chart 13, Japan’s overall reputation rank closely follows USA and Germany (first and second place, respectively). The USA, Germany and Japan represent a clear tier one of nations in the pharmaceutical industry.

Chart 13: Overall reputation scores



Overall competitiveness scores. This takes the cumulative average of tax environment, quality of employees, infrastructure, research potential, labour costs, accessibility, and access to funds.

Categories that Japan excelled in include API manufacturing, innovativeness, finished product formulations, transparency, and knowledge of pharmaceutical professionals. Japan’s high rankings in quality and transparency attests to its particularly stringent quality control and assurance requirements, while placing second for innovativeness likely reflects Japan’s renowned emphasis on patented drugs.

Japan deviates from the top three in the predicted pharma growth and overall competitiveness rankings (see Chart 14 and 15), although it was still rated to have a significantly higher growth potential than the most of the Western European countries in the league – with the notable exception of Germany.

While Germany is akin to Japan in having a mature and innovative market, historically centred on domestic growth opportunities, unlike Japan it has benefitted from European Union membership trade links which significantly boosted its international market growth. Even so, Japan is only one ranking behind Germany in growth, demonstrating how recent efforts by the Japanese pharma industry to internationalise and increase global exports is seemingly paying off. Further highlighting this globalisation, 24% of companies surveyed said they were currently exporting to Japan. What is unclear, however, are the long-term implications of the impending Trans-Pacific Partnership (TPP) trade pact between Japan and 10 other countries in Asia and the Pacific.

It is also notable that Japan's overall competitiveness score is catching up to China and India – both of which have seen substantial market size increases in recent years – despite a stark contrast between their pharma business models. For instance, the Indian and Chinese markets are focussed on mass production generics, whilst Japan is widely known for quality and innovativeness (though it is growing its generics market).

Overall, our research indicates that Japan has generally performed very well as a tier one pharma nation, and even better than expected in growth and competitiveness compared to some of the other mature pharmaceutical markets (such as France and the UK), and likely because of Japan's recent efforts to globalise and diversify its market offerings (e.g. pro-generics policies).

Chart 14. Pharma market growth potential scores

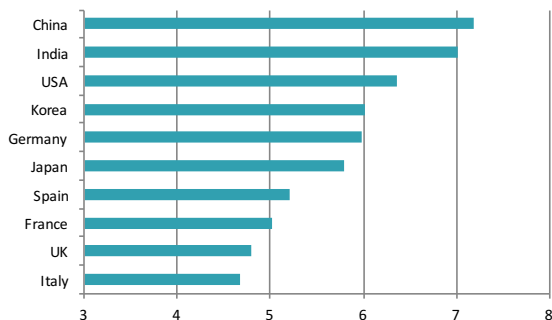
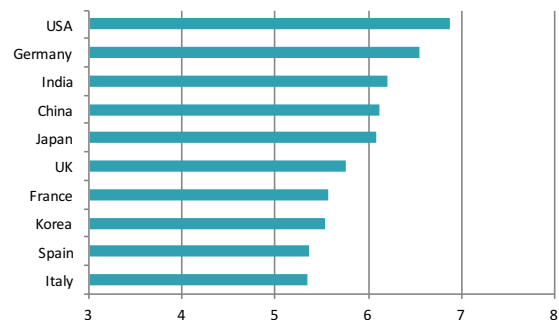


Chart 15. Overall competitiveness scores



This takes the cumulative average of tax environment, quality of employees, infrastructure, research potential, labour costs, accessibility, and access to funds.

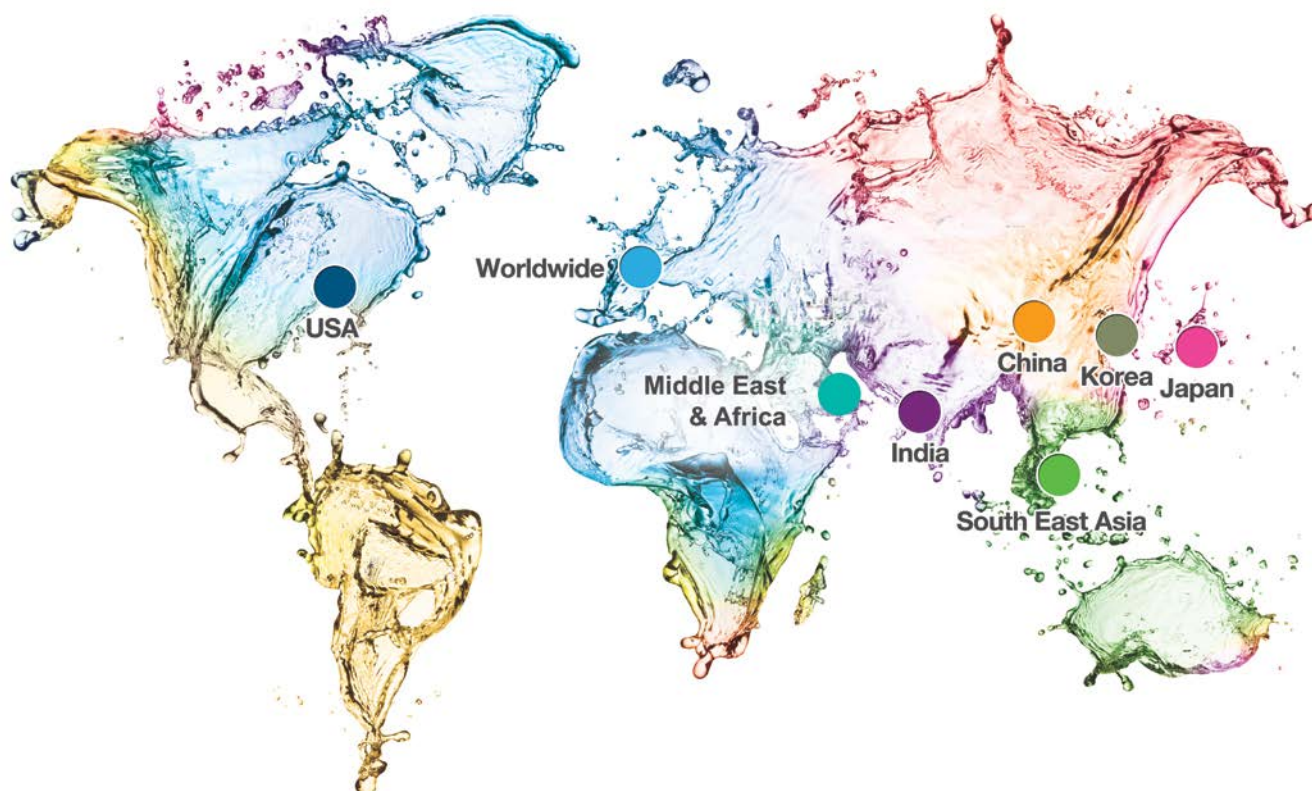
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CPhI Korea:	28-30 August 2018
CPhI Middle East & Africa	03-05 September 2018
CPhI Worldwide:	9-11 October 2018
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CPhI Conferences	year round