

THE JAPANESE GENERIC DRUG MARKET: OPPORTUNITIES AND STRATEGIES FOR SUCCESS



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Japan is the world's second largest pharmaceutical market, commanding annual sales of approximately 6.45 trillion yen (US\$64.5 billion)¹. However, only 6.6% of its prescription drug sales are contributed by generics². A combination of major drug patent expiries before 2012, a rapidly aging demographic, wide-ranging government initiatives to reduce health care spending, and comparatively high reimbursement prices are making the generic drug sector in Japan increasingly attractive to foreign manufacturers looking for a large, relatively untapped and receptive market.

In this white paper, Thomson Reuters draws on the unique intelligence of *Newport Premium*[™] and *Thomson Pharma*[®] to reveal exactly what's happening in the Japanese generic drug market, predicts how it may change under the incoming DPJ administration, and details the strategies that companies must follow if they are to succeed.

1. THE OPPORTUNITY

The prospects are attractive for foreign incursion into the Japanese generic drugs market. 40% of pharmaceutical products available in Japan are currently off-patent and so open to generic penetration. Many more will come off-patent before 2012 (see figure 1).

FIGURE 1 BLOCKBUSTERS EXPECTED TO COME OFF-PATENT IN JAPAN BETWEEN 2010 AND 2012³

Year	Active ingredient	Sponsor in Japan
2010	insulin aspart	Novo Nordisk
	risedronate sodium	Ajinomoto
	salmeterol xinofoate	GlaxoSmithKline
	tacrolimus	Astellas Pharma
2011	atorvastatin calcium	Astellas Pharma
	pioglitazone hydrochloride	Takeda
	pramipexole dihydrochloride	Nippon Boehringer Ingelheim
2012	anastrozole	AstraZeneca
	losartan potassium	Banyu Pharmaceutical
	quetiapine fumarate	Astellas Pharma, AstraZeneca
	rabeprazole sodium	Eisai Co Ltd
	raloxifene hydrochloride	Chugai Pharmaceutical Co Ltd, Eli Lilly Japan KK
	telmisartan	Nippon Boehringer Ingelheim, Astellas Pharma
	zoledronic acid	Novartis

For long held down by the country's generous public health insurance system, the generic sector is finally now burgeoning thanks to successive Japanese administrations eager to reduce costs in the face of an aging population⁴.

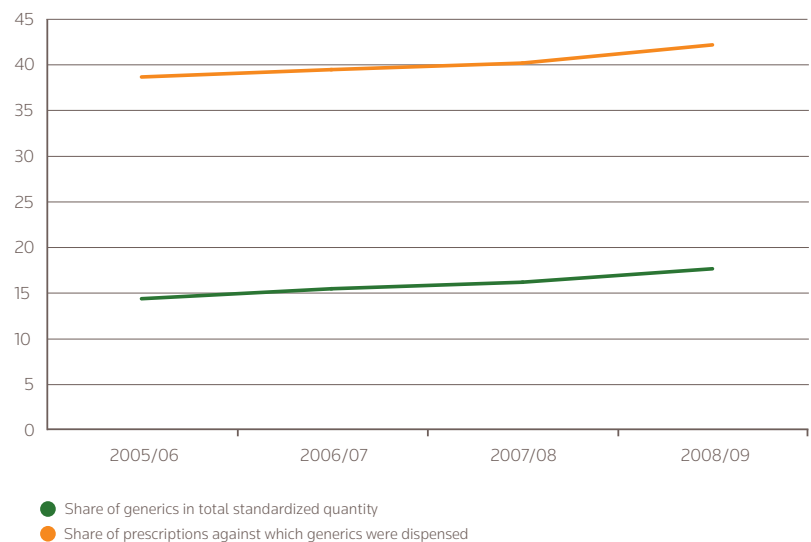
In June 2002 the Ministry of Health, Labor and Welfare (MHLW) notified hospitals that they should use generic drugs where possible. The driving factor is the fixed-fee reimbursement program called the "comprehensive evaluation based on Diagnosis Procedure Combination", similar to the diagnosis-related groups (DRGs) and prospective payment systems (PPSs) in the US, which encourages cost-cutting. Under this program, large regional hospitals and teaching hospitals are paid a fixed fee, inclusive of drug cost, instead of fees for each provided service. Because cost savings are automatically added to the hospitals' income, many of those selected for the program (known as "DPC hospitals") have begun to use generics more widely⁵.

In 2007 the MHLW announced the “Action Program for the Promotion of the Safe Use of Generics”, setting a target of achieving a 30% market share (by volume) for generic drugs by 2012, up from 18.7% in September 2007. The Government at the time predicted that achieving the target would save it 500 billion yen (US\$5 billion) over those five years⁶.

The incoming Democratic Party of Japan (DPJ) Government has signaled that it intends to continue to support the promotion of generic pharmaceuticals⁷. According to industry newspaper *Nikkan Yakugyo*, in 2006 the DPJ set a target of 50% market share (by volume) by 2025⁸, though this has not been confirmed elsewhere.

Whether it is true, it suggests that the Government remains highly receptive to generic substitution. Physicians, pharmacies and patients are all being incentivized to adopt generic drugs and are gradually becoming receptive, while the market itself is growing and still under-represented (see figure 2).

FIGURE 2 GENERIC PENETRATION RATES IN JAPAN (% OF TOTAL PHARMACEUTICAL INDUSTRY)⁹



If the target is true, domestic suppliers will face serious difficulties matching it. This is the case even if the DPJ adopts the proposed increase to 30% by 2012 outlined by the previous administration. Currently most of the generic drugs sold in Japan are manufactured by domestic companies¹⁰. This does not necessarily make them large companies—the benchmark for a ‘large’ generic company in Japan is a 30 billion yen (US\$300 million) turnover¹¹, and a 2008 survey by the Japan Generic Medicines Association (JGA)¹² shows that only four member companies¹³ were of that scale.

Unsurprisingly then, Japan is seen as a largely untapped market by foreign generic manufacturers, one that until recently was all but closed to them.

2. JAPAN AND THE GLOBAL PHARMACEUTICAL INDUSTRY

Neither the Japanese Government nor its physicians, pharmacies and patients are hostile to foreign drugs and active pharmaceutical ingredients (APIs) in principle. In practice, however, there is significant resistance to foreign generics, as we will explore in the following section.

Japan has long been the target of foreign innovators, who therefore undoubtedly have better knowledge of the local market than those foreign generic companies that have not previously entered the country, and hence may be better placed to succeed in the generic space. AstraZeneca, Abbott, Pfizer, Roche, Merck, Novartis and Boehringer Ingelheim are all building up a presence in the country.

Some foreign generic companies have been present in the Japanese market for many years. The most prominent of these are western, including US-based Hospira Inc (originally an Abbott subsidiary), Mylan Inc (which bought Merck's generics operations in 2007), and Novartis's subsidiary Sandoz. The latter acquired German generics company Hexal AG in 2005, which included its Japanese arm Nihon Hexal, originally Kyoritsu Yakuhin¹⁴.

Iceland-based Actavis has announced plans to enter Japan in 2009 through a joint venture with ASKA Pharmaceuticals. Israel's Teva opened a Japanese subsidiary in November 2005 and applied for approval to sell drugs in Japan the following March, though none had reached market at the writing of this report. Teva is however rapidly building up staff numbers in Japan¹⁵, and has entered into a strategic alliance with domestic OTC and generics manufacturer Kowa Co.

But the shift is now toward Asian entrants. China is not yet a significant player in Japan, though that is likely to change. *Newport Premium* notes that between 2005 and 2008, 130 Japanese DMFs have been filed by Chinese companies. At the moment, the country targeting the Japanese generics market most vigorously is India.

The first Indian generics company to make in-roads into Japan was Ranbaxy Laboratories Ltd (now wholly owned by domestic innovator Daiichi Sankyo). In 2002, Ranbaxy acquired a 50% stake in Nihon Pharmaceutical Industry, a generic subsidiary of Japanese innovator Nippon Chemiphar.

The relationship has been troubled. To date, Ranbaxy has successfully launched just a handful of products in the Japanese market, though these do include amlodipine (see 'Amlodipine' box below). Although none of Ranbaxy's approvals in Japan have been suspended or terminated, Nippon Chemiphar has been damaged by Ranbaxy's troubles with the US FDA¹⁶. In January 2009, the two companies announced that they will terminate their relationship, Nippon Chemiphar noting two months later that it will take steps to assure the quality and continuous supply of the products manufactured by Ranbaxy.

Hyderabad-based Dr Reddy's is currently considering enlarging its opportunities in Japan, with the possible establishment of a local office in Tokyo or Osaka. It is also seeking a Japanese partner. Zydus Cadila, based in Ahmedabad, opened a fully-owned subsidiary called Zydus Pharma in Tokyo in August 2006, and acquired the small Japanese generic company Nippon Universal Pharmaceutical the following April. The first product of this venture has already been completed, in-licensing the hypertension treatment methyldopa (brand name Aldomet) from Japanese innovator Banyu, a subsidiary of Merck & Co¹⁷.

Torrent Pharmaceuticals, also based in Ahmedabad, opened a fully-owned subsidiary in Yokohama in April 2006, only to exit from the Japanese market two years later. In contrast, Mumbai-based Lupin Ltd has had a positive experience in Japan. Its subsidiary Kyowa Pharmaceutical Industry achieved a revenue of 9.47 billion yen (US\$ 94.7 million) for fiscal year 2008–9¹⁸. This revenue has been achieved mainly through its generic versions of risperidone and amlodipine (see below)¹⁹.

AMLODIPINE

Pfizer's anti-hypertensive treatment amlodipine (Norvasc®) came off patent in Japan in 2007. The first generic formulations were approved in Japan in July 2008.

At that time, the number of listed sponsor firms was 34. While the majority are Japanese generic companies, there are also two innovator companies (Tanabe Mitsubishi and Meiji Seika), and two foreign firms—Sandoz and Ranbaxy—manufacturing the drug in Turkey and India respectively among the sponsor firms. Another, Kyowa Pharmaceutical Industry, a subsidiary of Lupin Ltd, markets the drug under its own brand name and supplies it to other finished formulation manufacturers.

Analysis by *Japan Generics Journal* in January 2009²⁰ found that the 34 approvals consist of only 18 distinct products, meaning that some products were associated with multiple marketing authorizations.

While imported finished formulations are nothing new in Japan, the Ranbaxy approval is the first of its kind in that the sponsor is located outside Japan. In all previous cases of generic approval of an imported formulation, the sponsor was either a Japanese partner firm or a local subsidiary of a foreign firm.

Ranbaxy decided to market the drug not through the 50% stake it had in Nihon Pharmaceutical Industry at the time, but through another Japanese company, I'rom Pharmaceuticals. In March 2009, I'rom issued a statement regarding the quality of its amlodipine, similar to the one put out by Nippon Chemiphar.

According to a separate article in *Japan Generics Journal*²¹, the quantity-based market share of generics in amlodipine, which had a total Japanese market value of 63.6 billion yen (US\$636 million) in 2007–08, was estimated to be around 20% in early 2009. This is disappointing, given that over 30 generic formulations had been approved by that time. Aside from reasons we explore in this white paper, the same article mentions that historically generic uptake has been low in the anti-hypertensive segment. An unspecified industry source²² suggests that the reason for this is higher effort by originator companies to protect their market share, as hypertension drugs tend to have higher sales. These claims are yet to be verified with data.

3. THE PUBLIC PERCEPTION OF GENERIC DRUGS IN JAPAN

The Japanese pharmaceutical market may be large, but it comes with many challenges for generic companies. The country's belief in itself as wealthy means it is able to choose quality over price, a mindset that remains ingrained in Japanese consumers and sits at the heart of its designer-brand led culture. Cheapness is therefore associated with lower quality, and means that generic drugs are generally regarded as inferior to the brand equivalent²³.

Compounding this, health scares over imported food²⁴ exacerbate a condition in which Japanese consumers only trust the brands they know (specifically, *Japanese* brands they know) and are skeptical about the efficacy and safety of plain packet drugs, particularly if there is the chance that they may have been manufactured in China, India or elsewhere. The country's generic drug manufacturers have therefore suffered from low public esteem and recognition in comparison with innovators.

In 2007 the Central Social Insurance Medical Council (CSIMC), an advisory body to the MHLW, carried out a survey called *The Status of Generic Medicine Usage*²⁵. The survey elicited responses from a nationally representative random sample of 583 pharmacies, 688 clinics, and 408 hospitals²⁶. It found that in 9.2% of cases where generic substitution was authorized by the physician²⁷, the patient nevertheless elected to take the branded product.

The most common reason the sampled pharmacists gave (31.7%) was that the patient decided the reduction in out-of-pocket expenses was not sufficiently high to justify switching away from the brand. According to the survey, the total prescription cost, including drug cost, was reduced by only 27.6% on average when the patient switched to a generic equivalent.

The second most common reason (30%) was concern over the quality of generic products. This implies that if patients still believe that generics are a lower quality alternative, it will take more than a relatively modest decrease in cost to persuade them to switch.

The CSIMC asked physicians how many prescriptions they had authorized for generic substitution²⁸. 60.5% of hospital-based physicians and 66.4% of clinic-based physicians said that they had authorized generic substitution at least once. They were then asked what proportion of these generic-authorized prescriptions had been instigated by the patient. Part of the findings are tabulated in figure 3.

FIGURE 3 PERCENTAGE OF PRESCRIPTIONS AUTHORIZED FOR GENERIC SUBSTITUTION IN 2007

	Hospital-based physicians	Clinic-based physicians
Less than 10% patient instigated	58.9%	62.1%
More than 90% patient instigated	17.0%	22.4%

In other words, though many doctors claimed that they themselves instigated the bulk of the generic-authorized prescriptions, a significant amount relied largely on the patient to ask for the substitution.

The MHLW has worked hard to educate the public on the benefits of generic substitution, intended as much to encourage doctors and pharmacists to trust generics as to reassure patients of their quality and efficacy. A nationwide advertising campaign consisting of point-of-sale posters such as the one reproduced below²⁹ and a detailed leaflet³⁰ explain the cost benefits of switching to a generic equivalent and pointedly compare the situation in Japan with that in other countries such as the US and UK.

This awareness campaign is, of course, a huge boon to Japanese generic manufacturers. Many of them—as well as generic industry associations such as the JGA—have run awareness campaigns of their own. In 2004, for example, Sawai Pharmaceutical Co promoted itself with a series of high-profile television advertisements starring TV personality Hideki Takahashi, chosen expressly to appeal to the 60-year-old actor’s demographic.

However, education might not be the only problem. Though there appears to be a far greater awareness of generic drugs among patients, and a greater willingness to use them³¹, only 14% have actually asked their physician to prescribe them. If patients don’t approach their doctor to ask for the generic alternative, relying on patients to drive the penetration of generic drugs into the Japanese marketplace can only have a limited success.

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WHAT DO YOU KNOW ABOUT GENERIC DRUGS?

Generic drugs are pharmaceutical products that are marketed after patents on the originator products have expired. Generics contain **the same active ingredient, and have the same indications and effects** as originator products.

Point 1 They are cheaper and more economical than originator products.

The use of generics leads to less out-of-pocket expenditures for patients, and contributes to improvement of the finances of our health insurance system.

Note: Prices may vary among different generic products. In some cases, the price of the generic is less than half that of the originator product.

Point 2 Their safety and efficacy are equivalent to that of originator products.

Japanese government agencies employ the same standards as those of their counterparts in North America and Europe to examine whether the generic products have the same level of quality, efficacy, and safety as the originator products.

Note: In some cases, the shape, color, or taste of the generic drug may differ from the originator product.

Point 3 They are widely used in North America and Europe.

In the USA, UK, and Germany, approximately half of the prescription drugs used are generics.

By comparison, the share of generics in Japan today is less than 20 percent.

If you wish to use generic drugs, please consult your physician and pharmacist.

The Ministry of Health, Labor and Welfare

4. ACCEPTANCE OF GENERIC DRUGS BY JAPANESE PHYSICIANS

If there is legitimacy for Japanese patients to distrust generic drugs, it is because Japanese physicians largely share the same view. Some dismiss the drugs as cheap copies provided by small companies with inadequate quality control, and hence are unlikely to prescribe them. Others, though not opposed to generic drugs outright, believe it is up to them, not the pharmacist, to decide what treatment the patient receives.

The situation is sustained by the Japanese belief in conformity and an unwillingness to question either seniority or implied authority. The honorific term for a doctor, *sensei*, is the same as that used for a teacher, and presumes that as a trained expert, the doctor knows best. A patient is extremely unlikely to dare to question the treatment their doctor has decided upon. In many cases, similarly, the doctor feels under no obligation to explain even the basics of the treatment or regime they are prescribing, and may not discuss possible side effects. Until recently, Japan had no practice of obtaining informed consent—this is still only slowly beginning to change.

Moreover, Japanese physicians may not even know the names of generic equivalents. Medical schools taught students to recognize the brand names of the drugs only, meaning that generic equivalents are unfamiliar at best. Again, the situation is slowly changing, partly driven by a better educated, gradually more assertive (and cost-conscious) patient population, but also as a result of a greater number of new doctors spending part of their training abroad.

Manufacturers are targeting doctors by distributing products and supporting literature and volunteering limited clinical studies to prove that their products are as safe and effective as those of the originator. Until recently only innovators are known to have employed medical representatives to sell direct to clinicians. The JGA reports that two of its members now employ more than 300 medical representatives each, and six more have more than 100 each.

Initial survey results from September 2008, sponsored by the Japan Pharmaceutical Association (JPA), a trade body of pharmacists, suggests that the number of prescriptions containing generic substitution authorization has increased markedly. The JPA reported that the share of prescriptions that did *not* prohibit generic substitution was 59.8%—a huge increase from the 17.5% permitting substitution the previous year³².

The DPJ, eager to gain the support of physicians' body, the Japan Medical Association (JMA), in the run-up to the August 2009 election, may have attempted to appease doctors on their 'right to prescribe' in its July 2009 manifesto: "When generic

substitution is carried out by pharmacies with the agreement of patients, we will make sure that information regarding the particular generic product dispensed by the pharmacy will be sent to the prescribing physician, and maintained for a sufficient amount of time.”³³

It is not yet certain to what extent this will signify a change in policy from the previous administration. However, it signals that the Government’s relationship with the JMA will be one of the key factors in deciding the country’s acceptance of generic substitution in the near future at least.

5. THE IMPORTANCE OF QUALITY AND BRAND EQUIVALENCE

It is clear that cost savings are not the only driver of generic uptake in Japan—quality is just as important.

We already noted the dangers of lapses in quality control when discussing Ranbaxy in section 2. Even where the Japanese authorities have not taken action, as in the case of Ranbaxy, the company’s reputation has suffered, making it much harder to build up trust and hence sales from Japanese physicians and acceptance from the Japanese public. Indeed, as we just saw, a perception that there is a quality issue with drugs imported from India and China is one of the greatest challenges facing generic companies based in those countries, regardless of where they actually manufacture their products.

The issue, damaging though it is, may well be merely a *perception*. Both generic drugs and active ingredients are subject to rigorous quality control in Japan, roughly in line with that in the US and Europe, driven by the strict standards demanded by both the Pharmaceuticals and Medical Devices Agency (PMDA) and finished formulation manufacturers.

In order to make generic substitution as easy as possible, and just like in other countries, the MHLW requires generic drug manufacturers to supply strengths of the same dosage form as those of branded drugs. However, Japan goes further, demanding that the generic manufacturer supplies *all* the strengths and *all* the dosage forms of the branded version, even if a given strength or dosage form has negligible market share.

Moreover, some foreign companies complain that Japanese regulators insist their generic versions must match the branded drug precisely—rejecting an active ingredient powder, for example, that has a trace of brown when the branded drug specified it to be pure white. Since these specifications are likely to be unique to the Japanese market, for many foreign manufacturers it is only now that the small generic market in Japan is picking up that supplying to this market is even considered economically viable.

In its July 2009 manifesto, the DPJ addresses the worry among physicians that generics may have different bioavailability profiles to the brand versions, or may cause new side effects in some patients: “Even though generics are judged to be equivalent to the brand-name drug, the current tests for equivalence are insufficient, and we will promote the collection of additional information to be used in further evaluation of generics.”³⁴

We don't yet know what this ‘additional information’ and ‘further evaluation’ involves, but it may mean that generic regulation in Japan is about to become tighter still.

6. CONCERNS WITH DRUG REIMBURSEMENT

The Japanese enjoy universal health insurance, provided through employer-administered insurance schemes, occupation-based programs, and National Health Insurance (*kokumin kenkōhoken*) which covers dependents, the self-employed, and everyone else³⁵. Prices are agreed by negotiations between manufacturers and the MHLW, resulting in a standardized Drug Price List (*Yakka Kijun*). The health insurance system will contribute only to drugs that are listed in the *Yakka Kijun*³⁶.

Expressed as a proportion of the price of the branded, innovator drug, the price of the generic equivalent is comparatively high in Japan. In the first year of listing in the *Yakka Kijun*, generic prices are set at 70% of the innovator price. The price of generic drugs does decline faster than for innovator products, but not as fast as in other countries such as the US.

A large proportion of the drugs prescribed in Japan are dispensed at the clinic or hospital where the diagnosis was made³⁷. However, most patients choose to take their prescription to one of thousands of independent pharmacies countrywide. These pharmacies make profits both through dispensation fees and from the difference between the cost of the drug supplied by the wholesaler or manufacturer and the reimbursement price (*yakka*) paid to them by the health insurance system on dispensation, as detailed in the *Yakka Kijun*. This commercial margin is known as *yakka saeki*.

Since generic drugs have a lower *yakka* than branded drugs, the suspicion is that they must therefore offer a lower *yakka saeki*³⁸. We do not presently have supporting data to say if this is really the case. Toshiaki Iizuka notes that Japanese generic manufacturers sometimes provided a higher *yakka saeki* than their originator counterparts³⁹.

lizuka mentions the finding, based on data from August 2003 to December 2005, that generic manufacturers offered higher margins than originators at the time of generic entry. However, since the *yakka saeki* for generics falls rapidly over time, in a few years it is lower than that of brand medicines. While lizuka finds this pattern to hold over the entire market, because his estimates are made at the economy-wide level it is not possible to tell whether the higher margins are offered to pharmacies as well as dispensing physicians.

7. GENERIC DRUGS AND THE PHARMACIES

Aside from the reimbursement issues, pharmacies may also be reluctant to swap to a generic version due to the need to hold an even greater inventory than presently, consisting, at worse, of the innovator's branded version and a complete range of generic branded versions for *each* drug on their shelves, all of them in danger of expiry before being dispensed.

It is worth noting that many of the pharmacies approached in the 2007 CSIMC survey expressed a hope for a mandatory generic name prescription policy that would mean they need to stock only one generic brand for each drug. A fair proportion of physicians oppose such a change—the survey found that during the week of 23–29 July 2007, the physician specified a particular brand of generic product in 22.1% of generic prescriptions, and did not authorize substitution by another brand—and it hardly needs mention that so do the generic manufacturers. Moving away from the branded generic model has contributed to dramatic price erosion in many generic markets.

In some regions, local pharmacists' associations have begun to coordinate their inventory management in order to increase their collective ability to satisfy generic substitution opportunities. However, such initiatives will also incur a cost that is not being compensated under the current policy environment⁴⁰.

The 2007 CSIMC survey found that of all the generic prescriptions that came to the pharmacies, and where the patient had not refused to take a generic drug, only 10.2% were actually substituted to a generic by the pharmacist. This means that the overwhelming bulk of generic prescriptions, even though both the physician and the patient were happy to switch to a generic, were not fulfilled in the pharmacy and the patient went away with the brand version. In fact, out of all the pharmacies where a generic prescription was presented⁴¹, 34.7% conducted *no generic substitution whatsoever*.

Why? After all, pharmacies can charge a number of bonus fees if they provide generic drugs, including a “generic dispensation preparedness increment” of 40 yen (US\$0.40) for every prescription they dispense, provided that 30% of those prescriptions include a generic equivalent.

One problem may be the pharmacy’s obligation to provide information on the benefits of switching to generics, which requires time and effort. In April 2008 the MHLW ruled that all customers whose physicians have authorized generic substitution *must* receive information on the benefits of making the change. In return, pharmacies are entitled to an information provision increment fee of 100 yen (US\$1) per generic prescription⁴².

Pharmacies must also explain why they have chosen the generic product of a certain manufacturer. The reasons might be, for example, the price of the drug, or the manufacturer’s ability to provide accurate information on drug quality. This policy signifies a desire by the MHLW to promote responsible drug selection by pharmacies—indeed, it is of great importance to the MHLW that pharmacies are able to select generic product responsibly.

However, according to the 2007 CSIMC survey, it takes an average of an extra six minutes per patient to provide all this information—at the end of which the patient may still choose to go with the brand. This may be considered more trouble than it is worth in a busy pharmacy with patients queuing to be seen. Quality of service, and hence returning customers, is more important than the relatively modest incentive fee.

Similarly, the fees themselves may be seen as an impediment. They have to be paid partly by the patient. Pharmacies may therefore be unwilling to dispense generics in case customers choose to shop elsewhere—at a pharmacy down the road that doesn’t charge the higher fees⁴³.

8. APPROVAL AND EXCLUSIVITY ISSUES

The comparatively huge Japanese innovators wield a proportionate degree of power in the domestic market, enabling them to retain significant market share even after losing patent protection. Their resistance to the MHLW’s actions in promoting generics has understandably been strong.

Traditionally Japanese innovators had little to fear and as little reason to move into generic manufacture or distribution for themselves, though they are swift to protect their interests against those generic companies that dare to challenge them. This is demonstrated by Sankyo Pharma Inc’s action against generic versions of its cholesterol-lowering treatment Mevalotin® (pravastatin), the patents of which expired in 2002⁴⁴.

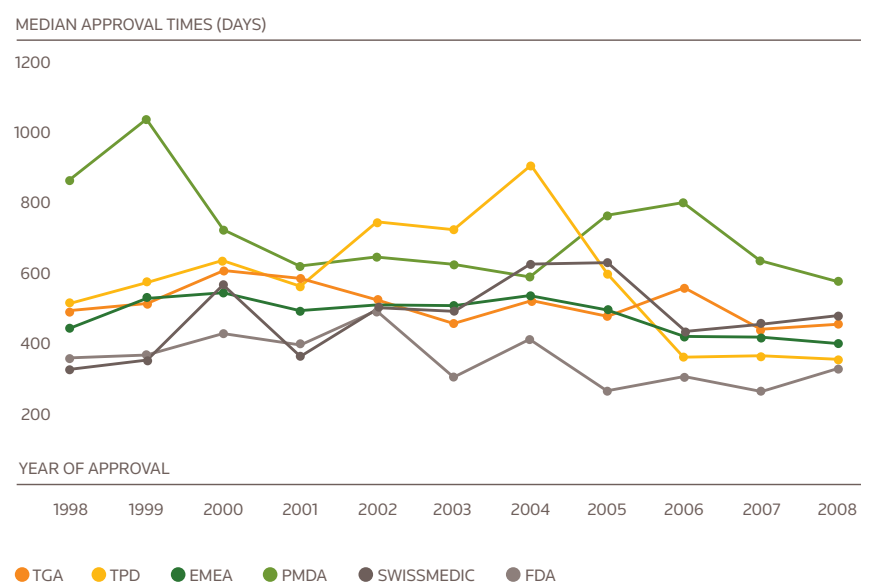
Generic products are reviewed for equivalence by the PMDA, which reports its findings to the MHLW. There is no clear regulatory provision in the Japanese Pharmaceutical Affairs Law (PAL) and other regulations for the patent of branded products. As in the US and Canada, the MHLW refuses to approve generics when the branded product patent has not expired. Disputes are treated by the Patent Office, or in court. It is up to the applicant to show that manufacture or import of the active ingredient is possible without delay after its approval⁴⁵. Unlike in the US and Canada, the MHLW holds but does not publish the list of the originator patents to which it refers in making its decision.

The MHLW does not grant marketing exclusivity to the generic company that is first to file a patent challenge. There is therefore little incentive for generic companies to challenge originator patents, and it is not possible to make the high profits associated with patent challenges in the US.

Generic companies also face slow review times for their applications. The problem appears to be limited resources in the PDMA, a situation it acknowledges—it intends to increase manpower. A committee of the Health Ministry has pledged to reduce the review time for new drugs to 18 months by 1 April 2011. It is hoped that this initiative will also reduce the review time for generic drug applications.

Figure 4 compares median innovator drug approval times in six major regulatory agencies from 1998. Since 2005, the PMDA has had the longest median approval times of all those listed, totaling almost 600 days (about 20 months) in 2008.

FIGURE 4 INNOVATOR DRUG APPROVAL TIMES 1998 TO 2008⁴⁶



Whereas new medicines are listed in the *Yakka Kijun* four times a year, before 2006 generic drugs were listed only once a year, meaning that it took significantly longer for a generic to reach the *Yakka Kijun* than a new medicine. In 2006 the MHLW changed this to twice a year, shortening the timescale for listing generics if not actually bringing it to parity with new medicines.

9. THE JAPANESE DISTRIBUTION SYSTEM

Japan's distribution system is complex, multilayered, and hence costly to foreign companies. Until recently, innovators enjoyed close reciprocal relationships with the country's large, independent drug wholesalers (*oroshi*), which in some cases meant that these wholesalers refused to handle generic equivalents, starving doctors and pharmacies of generic drugs even if they wished to prescribe them. Generic manufacturers were forced to rely on their own affiliated wholesale companies (*hansha*), devoted entirely to generic products and each serving a particular geographical region.

That situation is changing. Industry associations such as the JGA are encouraging generic companies to form relationships with *oroshi*. In their 2008 survey, the JGA found that 32% of its member companies deal mainly with *hansha* while 27% deal mainly with *oroshi*⁴⁷. This may reflect simple economic necessity: because many of their larger customers, especially DPC hospitals, are increasing their use of generics, *oroshi* can no longer afford not to handle them.

10. THE KEY TO SUCCESS

Given everything we have discussed so far, there is one clear recommendation we can make to foreign companies intending to enter the Japanese generic market: don't go it alone.

The in-country experience and brand reputation offered by partnering with a domestic company, plus access to their relationships with Japanese partners, are vital to success. The Japanese business community—indeed, the country as a whole—is driven by personal recommendation, personal introduction and close, personal contact. Without these things, it is extremely difficult to open the door to physicians, hospitals, pharmacies and the public.

This is the route we see being taken by entrants such as Teva, Lupin, Hospira, Ranbaxy and Actavis, whose deals with Kowa Co, Kyowa Pharmaceutical, Taiyo Yakuin, Nihon Pharmaceutical Industry and ASKA Pharmaceutical respectively we mentioned in section 2. Those who attempt to do it on their own—such as Torrent Pharmaceuticals, whom we also mentioned in section 2—are likely to have a harder time and, like Torrent, may be doomed to failure in this market.

It's an approach that tallies exactly with the Japanese generic industry's own overseas ambitions, particularly regarding deals that give them a route into the uncertain markets of China, India and Eastern Europe—the benefits work both ways. In just a few years, Japan's traditional independence has corroded, making mergers and alliances easier than ever.

It is certain that this activity will continue. More Japanese innovators will launch generic products, and more generic drugs will be introduced by overseas manufacturers. There will be many more mergers and acquisitions, both domestically and with foreign companies. Even if the generic drug market does not grow as fast as the Government hopes, it *will* grow, and those who succeed most will do so because they have best understood the unique challenges of this market.

NOTES AND SOURCES

- ¹ Source: Japanese Ministry of Health, Labor and Welfare (MHLW), 2007. Prescription drugs account for 5.83 trillion yen (US\$58.3 billion). The conversions in this report are based on an approximate August 2009 rate of 1 yen = US\$0.01.
- ² Source: MHLW, September 2007.
- ³ Sources: *Newport Premium*, *Thomson Pharma*
- ⁴ Japanese life expectancy was 78.6 years for males and 85.5 years for females in 2005. According to the Japanese Cabinet Office, this is due to reach 83.7 and 90.3 years respectively in 2055. It is estimated that by 2050 as much as 40% of the population will be over the age of 65.
- ⁵ Source: *Understanding Recent Developments in the Japanese Generic Pharmaceutical Market*, Kensuke Kubo, Institute of Developing Economies, Japan External Trade Organization 2009. The first teaching hospital to use only generic drug names in its prescriptions (rather than brand names) was St Mariana University School of Medicine Hospital, Kawasaki. Source: "Generic Name Prescribing Begins at Teaching Hospitals: Generic Drugs Likely to Get Unexpected Boost." *Nikkei BP*, June 25, 2004. According to the Hospital's pharmacy director Keiso Masuhara, the move saved it 150 million yen (US\$1.5 million). Source: "Despite roadblocks, generic drugs gaining traction." *Japan Times*, June 17, 2004.
- ⁶ Source: Council on Economic and Fiscal Policy, May 2007. <http://www.keizai-shimon.go.jp/minutes/2007/0515/item3.pdf>
- ⁷ *Seisakushu 2009*, DPJ policy document. <http://www.dpj.or.jp/policy/koseirodou/pdf/090731medic.pdf>
- ⁸ Source: *Nikkan Yakugyo*, July 2009. <http://nk.jiho.jp/servlet/nk/gyosei/article/1226551609108.html?pageKind=outline>
- ⁹ Source: MHLW. 2005–6 values are estimated from October 2005 to March 2006. 2008–9 values are estimated for April to July 2008.

- ¹⁰ It is estimated that in 2007 the top six domestic manufacturers alone accounted for 56% of the market.
- ¹¹ Kubo 2009. This has increased from 20 billion yen.
- ¹² Until 2009 this body was known as the Japan Generic Pharmaceutical Manufacturers Association (JGPMA).
- ¹³ Almost all domestic generic manufacturers of any size are members of the JGA. Their average size is 10.1 billion yen. This is again an increase—it was 7.4 billion yen in 2003.
- ¹⁴ Kyoritsu Yakuhin was acquired by Rohrer in 1979, and sold to Hoechst in 1995. Hexal acquired it in 1998.
- ¹⁵ In January 2007, it was reported that Teva planned to increase its Japanese staff from 7 to as many as 200.
- ¹⁶ Ranbaxy is banned from bringing products into the US due to good manufacturing practice violations at two of its Indian plants. The FDA has stopped reviewing applications submitted from one of these plants due to evidence of falsified data.
- ¹⁷ In-licensing innovator pharmaceuticals (a business known as *shokei*) is expected to be one of Zydus Pharma's main activities in Japan.
- ¹⁸ Up from 7.7 billion yen in 2007–8, making it the 10th largest generic company in Japan in sales terms. Source: Kyowa Pharmaceutical Industry website.
- ¹⁹ Launched in 2007 and 2008 respectively.
- ²⁰ "The Era of 30% Generics Share Starts from These Areas." *Japan Generics Journal* No.70, January 2009 pp 10–22.
- ²¹ "Antihypertensives: Dividing the Largest Market between Brands and Generics." *Japan Generics Journal* No.71, February 2009 pp 8–13.
- ²² The article quotes "a sales executive at a generics manufacturer".
- ²³ This is not a phenomenon unique to Japan. Singapore, equally designer-brand obsessed, also shows a marked preference for brand drugs. 56% of consumers in Singapore prefer the brand version, according to the BMI report *Health Is The New Wealth*.
http://www.ddb.com/ddb_health/pdf/yellowpapers/DDB_YP_Health_April09.pdf.
- ²⁴ For example, a high profile pesticide scare over Chinese *gyōza* dumplings in 2008, which led to more than 1,000 reports of food poisoning according to the Japan Times.
- ²⁵ *Report on the Survey Regarding the Status of Generic Medicine Usage*, CSIMC 2008.
<http://www.mhlw.go.jp/shingi/2008/07/dl/s0709-7i.pdf>
- ²⁶ Questionnaires were sent to 1,000 pharmacies, 2,000 clinics, and 1,000 hospitals. The response rates were 58.3%, 34.4% and 40.8% respectively.
- ²⁷ In April 2008 prescription forms were changed so that the physician had to authorize *not* to have generic substitution.
- ²⁸ Again, this was before the April 2008 change to prescription forms.
- ²⁹ This poster, published in March 2009, is available for viewing online at <http://www.mhlw.go.jp/bunya/iryuu/dl/jene-poster.pdf>. We reproduce it with kind permission of the MHLW. Translation by Kensuke Kubo.
- ³⁰ Published in March 2008, the leaflet (in Japanese) is available for download at <http://www.mhlw.go.jp/bunya/iryuu/dl/jene-qa.pdf>.
- ³¹ A survey sponsored by the National Federation of Health Insurance Societies in September 2007—before the current awareness campaign—found that

74.4% of those interviewed already knew about generic pharmaceuticals.

- ³² Source: a 2008 survey by the JGA of its members.
http://www.jga.gr.jp/pdf/19_keiei.pdf
- ³³ *Seisakushu 2009*, DPJ policy document.
<http://www.dpj.or.jp/policy/koseirodou/pdf/090731medic.pdf>
Translation by Kensuke Kubo.
- ³⁴ *Seisakushu 2009*, DPJ policy document.
<http://www.dpj.or.jp/policy/koseirodou/pdf/090731medic.pdf>
Translation by Kensuke Kubo.
- ³⁵ Source and breakdown: MHLW.
http://www.mhlw.go.jp/english/wp/wp-hw2/part2/p3_0001.pdf.
- ³⁶ Since 1992, the price of these drugs has been reduced every two years according to a fixed parameter. The latest review in December 2007 proposed an overall cut of 5.2%. Some classes of drugs, particularly those that had performed better than expected, were hit hardest. High blood pressure drugs such as angiotensin II receptor blockers, SSRIs and some cancer treatments were targeted most.
- ³⁷ Source: *The Economics of Pharmaceutical Pricing and Physician Prescribing in Japan*, Toshiaki Iizuka, July 2008. Iizuka suggests that the high incidence of doctors both prescribing and dispensing drugs in Japan (45% of all prescriptions) may be due to traditions in Oriental medicine.
- ³⁸ Source: "Will This Year Be a New Beginning for Generic Drugs?" Tsutomu Wada *Kenko Hoken* 62(2) 2008. This argument assumes that wholesalers and other intermediaries set margins as a fixed percentage of the *yakka* (Kubo 2009).
- ³⁹ Source: *The Economics of Pharmaceutical Pricing and Physician Prescribing in Japan*, Toshiaki Iizuka, July 2008.
- ⁴⁰ This includes the cost of maintaining stock at prefecture level or city-level "pharmaceutical stocking centers" (*bichiku* centers) run by local pharmacists' bodies (*yakuzaishi-kai*).
- ⁴¹ 83.9% of all the pharmacies surveyed.
- ⁴² This fee does not apply when the prescription specifies a particular generic brand.
- ⁴³ Pharmacies that dispense generics do not abstain from claiming the fees. A survey by the JPA in September 2008 found that 85.3% of sampled pharmacies were eligible for the increment and 83.6% charged it.
- ⁴⁴ However, this is changing. For example, generic famotidine was found not to infringe on Gideon Richter's polymorph patent (on Astellas' product), Daiichi Sankyo's patent term restoration on levofloxacin was found to be invalid, Otsuka's new use patent on rebamipide was found to be invalid, and a generic version of acabose was found not to infringe Bayer's process patent.
- ⁴⁵ PAB/PCD Notification No. 762, dated October 1994.
- ⁴⁶ Source: *The CMR International Pharmaceutical R&D Factbook*.
CMR International, 2009.
- ⁴⁷ Out of 41 companies that responded, 13 deal mainly with *hansha* and 11 with *oroshi*.

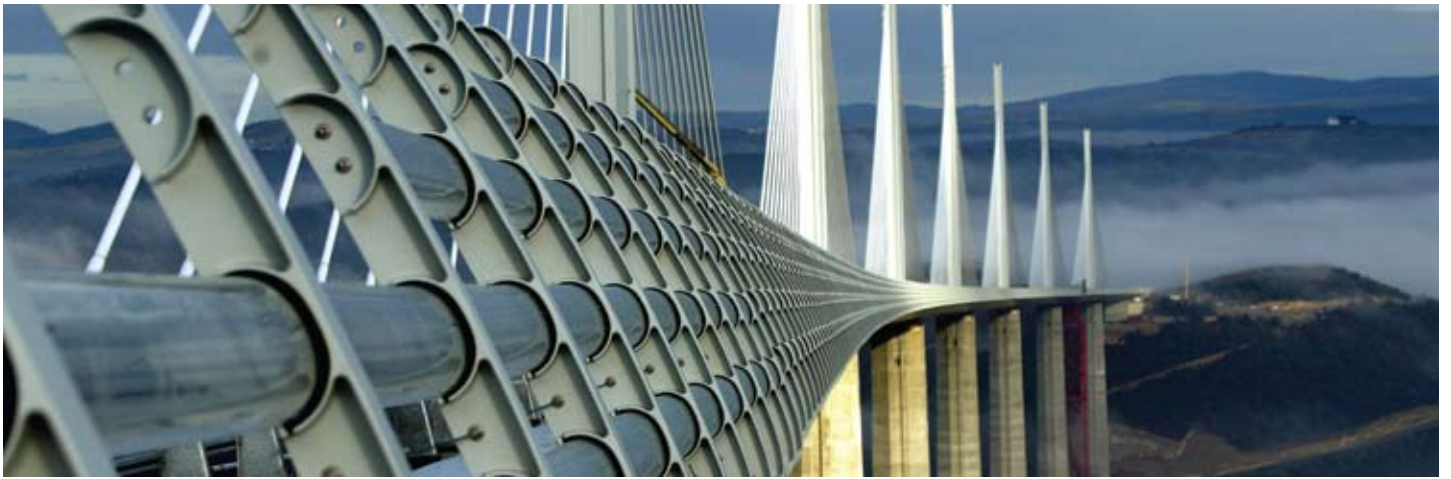


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Sue Besaw

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