



# An Overview of Pharmaceutical and Medical Device Regulation in Japan

*With some of the strongest vital statistics in the world, Japan's large and affluent population forms an increasingly important marketplace for pharmaceutical companies and medical device makers. Lawyers from Morgan Lewis –TMI discuss the regulatory efforts made by the Japanese government to dispel the perception that the life sciences marketplace in Japan is a difficult one within which to do business.*

With a large and affluent population, Japan is one of the world's most important markets for pharmaceutical companies and medical device makers. As of 2005, the size of the Japanese pharmaceutical market was nearly 8 trillion yen, of which imports accounted for 1.4 trillion yen, and the medical device market was more than 2.5 trillion yen, of which imports accounted for 1.0 trillion yen, making Japan the second largest medical market in the world, after the United States.

Japan has some of the most impressive vital statistics as well, including the lowest infant mortality rates and highest adult life expectancies, and its health care system is often judged as one of the best internationally. Moreover, as the population of Japan ages, more patients are requiring both short and long-term medical attention.

Despite the great opportunities afforded by the Japanese market, Japan has had a reputation as a difficult mar-

ketplace in which to operate, especially for foreign firms. Reflecting this perception, some pharmaceutical companies had begun bypassing Japan to set up development bases in India and China, where costs are much lower.

## GLOBAL RETAIL DRUG SALES

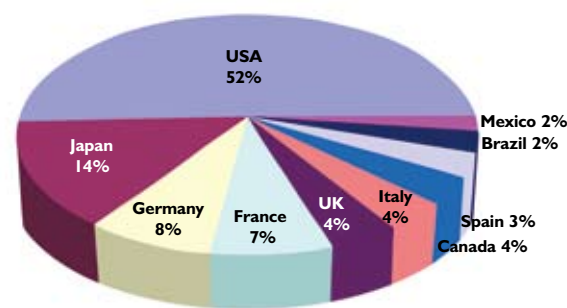


Illustration: Johnnie Au

Copyright 2008 IMS Health.  
Source: IMS Retail Drug Monitor, Nov.2007 Reprinted with permission

Concern that Japan's reputation as a difficult market might cause it to fall behind led the Japanese government to make significant revisions to the Pharmaceutical Affairs Law (PAL) in 2002. These revisions included a new risk-based classification system for products, adoption of internationally consistent pre-market submission documents, a third-party certification system for low-risk medical devices, and prioritizing governmental review of high-risk medical devices. In addition, medical devices were divided into three categories: general medical devices (Class I), controlled medical devices (Class II), and highly controlled medical devices (Classes III and IV).

At the same time, the government combined the Pharmaceuticals and Medical Devices Evaluation Center, the Organization of Pharmaceutical Safety and Research and the Japan Association for the Advancement of Medical Equipment into a new independent regulatory agency overseeing both medical devices and pharmaceutical products in Japan. The result was the Pharmaceutical and Medical Devices Agency (PMDA) which now has primary responsibility for administering the approval of new pharmaceutical products and medical devices in Japan, although final authority to issue approvals still rests with the Ministry of Health, Labour and Welfare (MHLW).

After thoroughly investigating a new drug or medical device, the PMDA will make an approval recommendation to the MHLW. Generally, the MHLW will follow the PMDA's recommendation, but for particularly difficult and technical reviews, the MHLW may seek the opinion of an outside advisory board before making a final decision.

## Getting to Market

In principle, bringing a new drug or medical device to market in Japan requires (i) an approval, or *shonin*, specific to the device or drug and (ii) a manufacturing

license, or *kyoka*, specific to the manufacturing facility where the device or drug is produced. The approval must be held by a Market Authorization Holder, or MAH--the entity that will actually bring the product to market.

## Market Authorization Holder

One of the most important revisions to the PAL enacted in 2002 was the introduction of the MAH concept. In the past, manufacturers would hold both the approval and the manufacturing license for a new drug or device in their own name. Foreign companies with no presence in Japan were required to appoint an in-country caretaker, or ICC, that acted as an agent for the foreign company, filing necessary documents and ensuring product safety, but the foreign companies, like their domestic counterparts, were otherwise permitted to hold both the approval and the manufacturing license in their own name.

In general, MAHs are responsible for guaranteeing the safety, quality and efficacy of the product.

The MAH system was instituted in part to move the focus of the regulatory system from the manufacturing facility to the point of sale, and separate the manufacturing and marketing responsibilities accordingly. In part, this

recognises the fact that production is being increasingly outsourced to third parties and that very often the 'owner' of the new drug or device may not be manufacturing it at all. Under this new regime, the product approval can only be held by the company placing the product into the market, a company that must be authorised as a MAH.

For example, if an Australian pharmaceutical company wishes to export its new Alzheimer's drug to Japan, it must either appoint a pre-existing MAH in Japan or create a Japanese subsidiary and have it certified as a MAH and then appoint its subsidiary as the

**"As in most countries, drug approval is extremely costly and time-consuming."**  
Satoru Nagasaka,  
Morgan Lewis-TMI



MAH. The appointed MAH will then apply for approval of the drug in Japan, while the Australian company applies for a manufacturing license for its production facility in Australia.

MAHs are authorised by product segment (such as pharmaceutical products or highly controlled medical devices), and can hold authorizations for multiple product segments if so desired.

MAHs must comply with numerous restrictions. In particular, they must be Japanese entities and are required to employ the following individuals in Japan on a full-time basis: a general manager, a quality assurance officer and a safety management officer. The quality assurance officer oversees compliance with good quality practices (GQPs), which includes compliance with good manufacturing practices (GMPs) for all manufacturing sites where the product is produced. The safety management officer, on the other hand, oversees compliance with good vigilance practices (GVPs) that monitors product safety after the product has entered the market.

For general medical devices and controlled medical devices, the MAH may combine the three roles outlined above due to the decreased risk of these devices to the public. For a general device authorization, the MAH can assign all three roles to one employee.

For controlled devices, the MAH may allocate the three roles among two employees, so long as the same employee is not both the quality assurance officer and safety management officer.

MAHs are authorised by the governor of the prefecture where the general manager is employed. Final authorization is still a matter for the MHLW, but the application is submitted to, and the approval is issued by, the governor.

A MAH may entrust import services to a non-MAH third party, so long as the first purchaser of the drug or device in Japan is a MAH. Schemes in which the party

entrusted with the import services initially purchases the product and then sells it on to a MAH are not permissible. In addition, the import service provider may not make substantive modifications to the product's packaging or labeling or temporarily store the product.

Labeling and advertising of the product in Japan is also the responsibility of the appointed MAH. The PAL stipulates that certain information (such as the manufacturer or seller's name and address, name of the product, product number, indication, ingredients, expiration, etc.) must be printed directly on the container or packaging of the drug or device. Advertising must not exceed the scope of the pharmaceutical's indications or the medical device's prescribed use. Both false and exaggerated advertising is prohibited.

In the event that a MAH fails to comply with the law, it may be subject to criminal liability and have its authorization revoked.

#### **Approval (Shonin)**

##### **Pharmaceuticals**

As in most countries, drug approval is extremely costly and time-consuming. A company

wishing to import a pharmaceutical product into Japan or manufacture and sell a pharmaceutical in Japan must conduct clinical trials in Japan and apply for approval from the PMDA. This applies even if the drug has already been authorised and is being sold in one or more foreign countries. In some cases, the PMDA permits applicants to submit clinical data from overseas, but this depends on the specific drug at issue, its class



**“The MAH system was instituted in part to move the focus of the regulatory system from the manufacturing facility to the point of sale, and separate the manufacturing and marketing responsibilities accordingly”**

*Benjamin Lang,  
Morgan Lewis-TMI*

(whether the drug is new or generic), and the perceived reliability of the foreign data. The PMDA may also determine that overseas clinical data may only be submitted as secondary reference material rather than actual evidence of the product's efficacy.

While clinical studies can vary greatly in length, the average duration of a clinical trial in Japan is approximately four years. This compares with just 18 months in the U.S. and the U.K. and 30 months in France—a phenomenon known locally as ‘drug lag.’ The government has been facing growing criticism for the length of the clinical trial stage in Japan, and the MHLW has recently released several new policies to address these concerns and accelerate the process, including the hiring of additional staff.

Following completion of the clinical trial process, the MAH must then apply for approval from the MHLW. The current administrative target is to complete this final approval process in about one year from the time the application is submitted. However, statistics show that the median processing time for 70 pharmaceutical products approved in 2006 was 23.4 months, so the MHLW still has considerable ground to cover. Processing time was significantly shorter, however, for those applicants who participated in non-mandatory, clinical study consultations with the PDMA prior to making the final application.

##### **Medical Devices**

Any highly controlled medical device that is manufactured in or sold into Japan must be approved by the MHLW. In addition, any controlled medical device for which the MHLW has not created a certification standard must also be approved on an individual basis. Those devices for which a certification standard has been created must be certified by a third-party registration institution such as

Underwriters Laboratories. General medical devices do not require approval for manufacture or sale, but the PMDA must be notified of manufacture and sale after the company has completed a self-certification.

Over 90 percent of medical devices are approved in one year (the government's target for approval time),

but, in limited cases, the process can take considerably longer, with three years not being unheard of.

To facilitate the approval review process, companies are encouraged to submit materials concerning the approval process and the status of use in foreign countries, as well as the occurrence of deficiencies and countermeasures taken to address such deficiencies.

As with pharmaceuticals products, the approval by the MHLW may be revoked in the event of subsequent problems with the efficacy or safety of a medical device.



**“Although approval times continue to lag behind those of other developed countries, the government has set ambitious goals...”**

*Mihoko Shintani,  
Morgan Lewis-TMI*

#### **Manufacturing License (Kyoka)**

Companies that manufacture drugs or medical devices in Japan or at foreign facilities for import into Japan are required to obtain a manufacturing license for each such manufacturing location (termed an ‘accreditation’ for foreign facilities). For manufactur-

ing facilities located in Japan, the manufacturing license is generally issued by the governor of the prefecture in which the manufacturing facility is located. However, in cases requiring particularly high levels of expertise, the MHLW may issue the license directly. For overseas manufacturing facilities, applications are made directly to the MHLW.

Licensed manufacturing facilities are required to satisfy criteria established by the MHLW.

Pharmaceutical manufacturers must employ a full-time pharmacologist to serve as the managing pharmacist in each licensed manufacturing location.





**“Concern that Japan’s reputation as a difficult market might cause it to fall behind led the Japanese government to make significant revisions to the Pharmaceutical Affairs Law (PAL) in 2002”**

Sayaka Ueno,  
Morgan Lewis-TMI

manufacturing license holder violates the law, the holder may be subject to criminal liability and have its license revoked.

#### Conclusion

Japan has made significant progress in reforming and modernizing its drug and medical device approval process in recent years. Although approval times continue to lag behind those of other developed countries, the government has set ambitious goals and the PMDA and MHLW have made marked improvements. These gains, along with Japan’s position as the world’s second largest medical market, continue to make Japan a desirable place for foreign pharmaceutical companies and medical devices makers to do business.

Medical device manufacturers are licensed according to the type of medical device produced, namely: sterilised medical devices; non-sterilised medical devices; medical devices that are only packaged, labeled or stored; and a fourth category, including biologically-derived medical devices, radioactive medical devices and other devices designated by the MHLW.

As with MAH authorizations, in the event that a

Satoru\_Nagasaka@tmi.gr.jp  
blang@morganlewis.com  
Mihoko\_Shintani@tmi.gr.jp  
Sayaka\_Ueno@tmi.gr.jp  
www.morganlewis-tmi.jp

Morgan Lewis-TMI is a joint venture between Morgan, Lewis & Bockius LLP and TMI Associates

## Promote your practice with professional reprints

Asian-Counsel offers a tailor-made reprint service designed to transform your article into an attractive and effective promotional tool. Reprints can be custom designed according to your specifications to include brand elements such as company logo, advertisement and contact details. We also offer advice on cover options, production specifications and can even deliver the finished product to your clients on your behalf.

For more information please contact

**Ricky Chu**  
tel: 852 2542 1225  
fax: 852 2575 0004  
ricky.chu@pbpress.com

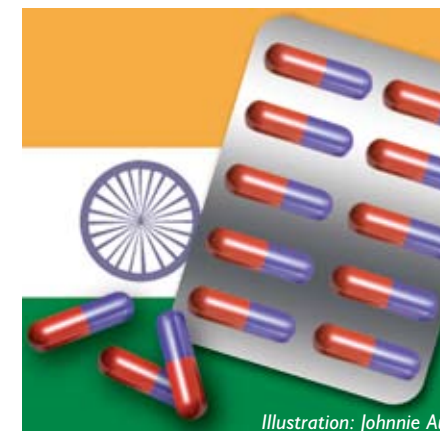
# The Glivec Patent Case

## Innovation hurdle or fair protection against ever greening?

*The Swiss pharmaceutical company Novartis’ recent challenge to the Indian intellectual property system has raised questions about India’s role as the ‘pharmacist of the developing world’. Bijesh Thakker, of Thakker & Thakker keeps us up to date on the latest developments in this landmark IP litigation.*

Recently, the Supreme Court of India stayed the proceedings before the Intellectual Property Appellate Board (IPAB) regarding the hearing on the rejected patent application of Novartis’ cancer drug Glivec®.

Glivec® is a cancer drug crucial in prolonging the life of patients suffering from Chronic Myeloid Leukemia (Blood Cancer). The active ingredient, Imatinib Mesylate, controls the cellular action that allows the cancer to grow but does not cure the disease. This means that patients must take it for the rest of their lives, unless another type of treatment or cure is made available. Glivec® is produced and marketed internationally by the Swiss pharmaceutical company Novartis and various Indian generic producers like Cipla, Ranbaxy, Natco and Hetro. Novartis sells Glivec® at Rs.1.44 million (US\$26,000) per patient per year. Generic version of drugs Glivec® in the Indian market are priced at about Rs.96,000 (US\$2100) per patient year. This price is well above financial capacity of the majority of patients in India.



#### Exclusive marketing rights

The patent dispute centres around the beta crystalline form of imatinib mesylate which is a particular polymorphic form of the methanesulfonic acid addition salt of the substance, imatinib. To date, 40 patents covering this polymorph have been granted to Novartis in various countries. However, owing to the unavailability of drug patents in India until January 1, 2005, Novartis needed to apply for protection of this polymorph in a mailbox application that was to be opened on January 1, 2005 and examined. This mailbox application, filed on July 17, 1998 covered the ‘beta crystalline form of imatinib mesylate’. Novartis was granted an exclusive marketing right (EMR) in November 2003.

The EMR operated like a patent. It forced Indian companies to discontinue production and sale of the generic versions of the drug-for the domestic market and export to developing countries. Consequently, the Cancer Patients Aid Association and other NGOs, who



provided the affordable generic versions of the drug to the patient, had to withdraw their support to cancer patients as Novartis' product was 10-times more expensive.

## India, while complying with the TRIPS agreement, introduced a product patent regime for new drugs that were invented, and coupled its law with a safeguard ... to prevent ever greening

### Rejection of patent application:

Patients in developing countries dependent on imports from India were also seriously affected by the unavailability of the affordable versions. This situation continued till 2006 when several pre-grant oppositions contested Novartis' patent and the EMR stood automatically terminated.<sup>1</sup> The application was rejected on the following grounds,

- lack of novelty/anticipation;
- the claimed polymorph did not demonstrate any added 'efficacy' under Section 3(d),
- obviousness and
- wrongful priority

### Appeal by Novartis

Aggrieved by this rejection, Novartis AG, along with its Indian subsidiary, Novartis India, filed two writ petitions in the Madras High Court. These petitions not only sought a reversal of the Assistant Controller's order, that the new crystalline form does in fact have an enhanced efficacy as it has a 30 percent increased bio-availability; but also a declaration that Section 3(d) was unconstitutional and violative of the Article 14 of the Constitution (right to equality).

Novartis subsequently challenged the order in the Madras High Court, rejecting its patent as well as the constitutional validity of Section 3(d) of the Patents Act, and claimed that the section is not in compliance with the TRIPS Agreement and hence should be declared unconstitutional.

### Section 3(d) – Constitutional validity

Section 3(d) in the Indian Patents Act acts as a safeguard

against the misuse of the product patent regime and provides a blanket ban from patentability of all new uses of known substances. In addition, Section 3(d) encourages the sequential development of existing products or technologies to help bring in improved products that address unmet public health needs.

Its enactment stems from events in the 1990s, when pharmaceutical companies obtained additional patents on cancer drugs like Zidovudine for new use (for example use of the anticancer medicine Zidovudine for the treatment of HIV/AIDS). The patent granted on Zidovudine prolonged the market monopoly of Glaxo and contributed to depriving millions in the developing world from accessing AIDS treatment until Indian manufacturing produced a generic version in the absence of product patent in India.

Therefore, India, while complying with the TRIPS agreement, introduced a product patent regime for new drugs that were invented, and coupled its law with a safeguard under section 3(d) to prevent ever greening by providing that only those pharmaceutical derivatives that demonstrate significantly enhanced 'efficacy' are patentable.<sup>2</sup>

Novartis claims that the active ingredient in Glivec (beta crystalline form of imatinib mesylate) is more effective than the Imatinib free base, since it displays better bio-availability properties i.e. it is absorbed more easily into the blood. To this effect, it submitted evidence before the Assistant Controller demonstrating an increase in bio-availability of up to 30 percent, but it was disagreed that this was sufficient to constitute 'increased efficacy'.

The Madras High Court ruled that section 3(d) was constitutional. More importantly, it also stated that it did not have jurisdiction to rule on the TRIPS issue. Rather, the proper forum to bring this before would be the Dispute Settlement Body (DSB), a body under the WTO Agreement.<sup>3</sup> A treaty provision that conflicts with domestic law is not enforceable. Therefore, even assuming that Section 3(d) of the Patents Act, 2005 violates TRIPS, the Courts cannot strike down this impugned provision.

### TRIPS compatibility

The Madras High Court ruling does not settle the TRIPS issue but only shifts the jurisdictional venue. Article 27 of TRIPS stipulates that 'patents shall be available for any inventions...provided that they are new, involve an inventive step and are capable of industrial application.' However, none of the terms used in this Article have been

defined. This leaves some flexibility in the hands of member states to define patentability criteria in a manner that suits their specific national interests. Since patentability criteria has not been defined under TRIPS, a deeming provision such as section 3(d) can be made and sustained, provided it is not entirely arbitrary.

Novartis argued that even if the court could not invalidate a domestic law (section 3(d)) as being non-compliant with an international obligation (TRIPS), it could still issue a declaration to this effect. The court however disagreed, stating that it would do so, only if such declaration served a 'useful purpose'. In the case at hand, the court could not have invalidated section 3(d) as contravening TRIPS. Therefore the court held that even if it declared section 3(d) to be violative of TRIPS, such declaration could never help Novartis, as the law would have continued to remain on the statute book.

### Defining 'efficacy'

The Madras High Court also clarified the meaning of the term 'efficacy'<sup>4</sup> and equated the meaning of efficacy with a therapeutic effect on the body. While doing so, the court also accepted the argument of the respondents that the '*... petitioner is not a novice to the pharmacology field but it being pharmaceutical giant ... cannot plead that they don't know what is meant by enhancement of a known efficacy and they cannot show the derivatives differ significantly in properties with regard to efficacy*'. Hence it was held that a patent applicant has to show enhanced therapeutic effect in order to obtain a patent for a new form of a known substance or for its derivatives. Therefore the court held that Section 3 (d) is not violative of Article 14 of the Constitution of India.

Hence, the burden of proof is on the applicant to show the enhanced efficacy. However, the application of therapeutic effect as a benchmark for efficacy does not entirely shut out the possibility of ever greening of patents. For instance, a combination of two drugs may offer substantial improvement in therapeutic effect and may be held patentable.

The Central government has strongly defended the validity of section 3(d) of the Patents Act 1970 (in its present form) and held that;

- an invention with a mere change of form without any enhanced efficacy could not be granted patent and if patent was granted, it would be arbitrary and;
- the amended provision along with the explanation fully complied with Articles 7 and 8 of TRIPS.

With the Supreme Court having stayed the proceedings, all the parties to the case, including Novartis, the Centre, generic companies like Ranbaxy and Cipla and the Cancer Patients Aid Association will now have to respond to the latest development within four weeks.<sup>5</sup>

### Remedial measures for Novartis:

Novartis would be required to plead to the IPAB that:

- in relation to the Section 3(d) that the 30 percent increase in bioavailability is an enhanced efficacy and so the beta crystalline form is patentable;
- the beta crystalline form of the mesylate salt is not obvious in light of the free base form.<sup>6</sup>

The appeal is pending for hearing in the High Court, along with the appeal against decision of patent office rejecting the patent for Glivec. The IPAB is scheduled to look into the rejection of the patent application.

If the IPAB decides to follow the dictum of the Madras High Court (as to whether the IPAB is bound to do so is uncertain), then Novartis effectively loses the case at the IPAB.

As to whether the IPAB is bound by this ruling of the Madras High Court is a moot issue. This will depend on whether and to what extent, the Court's finding that section 3(d) was not vague depended upon its definitive 'characterisation' of efficacy as something limited to 'therapeutic efficacy'. Therefore it may be 'obiter dicta' at best.

### ENDNOTES

1. Pitfalls of giving patents for ordinary inventions by Mr. D. G. Shah, CEO, Vision Consulting Group, published in The Economic Times of India, Mumbai edition dated May 08, 2007
2. As appearing on <http://www.evb.ch/en/p25012749.html> visited on February 09, 2008
3. The Novartis Case, K M Gopakumar, Research Officer, Centad
4. According to the court '*...the meaning of the word efficacy and therapeutic effect... what the patent applicant is expected to show is, how effective the new discovery made would be in healing a disease/ having a good effect on the body*'.
5. A draft paper on Section 3(D) Of The Indian Patents Act: Crude, Yet Constitutional by Shamnad Basheer (Research Associate, Oxford IP Research Center) and T.Prashant Reddy (National Law School of India University)
6. Worldwide: Novartis' Glivec Battle With India - Patentability Of Pharmaceutical Extension Patents, by Duncan Bucknell dated 08 August 2007.

[bjt@ttindia.com](mailto:bjt@ttindia.com)  
[www.ttindia.net](http://www.ttindia.net)