

Japan's Drug Lag and National Agenda

By Eriko Tsukamoto, MBA and Satish Tripathi, PhD

Since 1999, a drug called Doxil has been used in 75 countries as the standard treatment for recurrent ovarian cancer. In Japan, however, patients waited nearly 10 years before Doxil received approval and became listed in April 2009. This case is merely one example of how Japan's drug approval lag is adversely affecting its patients, who do not have access to medicines that are marketed in the rest of the world. Japanese patients sometimes must wait for a marketed drug to be approved for a new indication, and at other times they must wait for a drug to become available at all. Drug lag impacts drugs developed in Japan and those developed in other countries and marketed in Japan.

The Drug Lag Problem

Despite the fact that Japan is the world's second-largest pharmaceutical and medical device market and a center for cutting-edge life-science research, it has a deplorably slow approval process for new drugs (Figure 1). This otherwise advanced nation has become known for its "drug lag"—a term that generally refers to both the elapsed time between approval of a drug of foreign origin in other countries and in Japan, and to the period from discovery of an active ingredient in Japan to availability of the resulting drug to the general public.

Based on 2004 data regarding new molecular entity (NME) product launches, it took an average of 3.8 years for a drug to be launched in Japan—2.5 years longer than it took in the US.

The Japanese government and concerned parties have been struggling with drug lag for years. Most recently, the Japanese Cabinet released a decision on 31 December 2009 entitled, "The Basic Policy of Japan's New Strategy for Economic Growth: 'For a Shining Japan.'" The importance of addressing the drug lag issue was specifically mentioned in this stimulus plan for the healthcare industry; it stated that Japan needs to improve the infrastructure surrounding the drug development and approval processes to expedite patient access to potentially lifesaving drugs. The initiative echoed the five-year plan entitled, "New Drug Industry Vision" launched in 2007 by the Ministry of Health, Labour, and Welfare (MHLW), in which Japan was described as critically behind other developed and

technologically advanced countries in the area of drug innovation. MHLW aims to eliminate the lag by 2011 so that the average time for a drug launch in Japan will be comparable to what it is in the US.

Drug Innovation and Drug Lag

The drug lag problem in Japan can be attributed to two major causes: sluggish drug innovation and the suboptimal environment surrounding the clinical trial and drug approval processes.

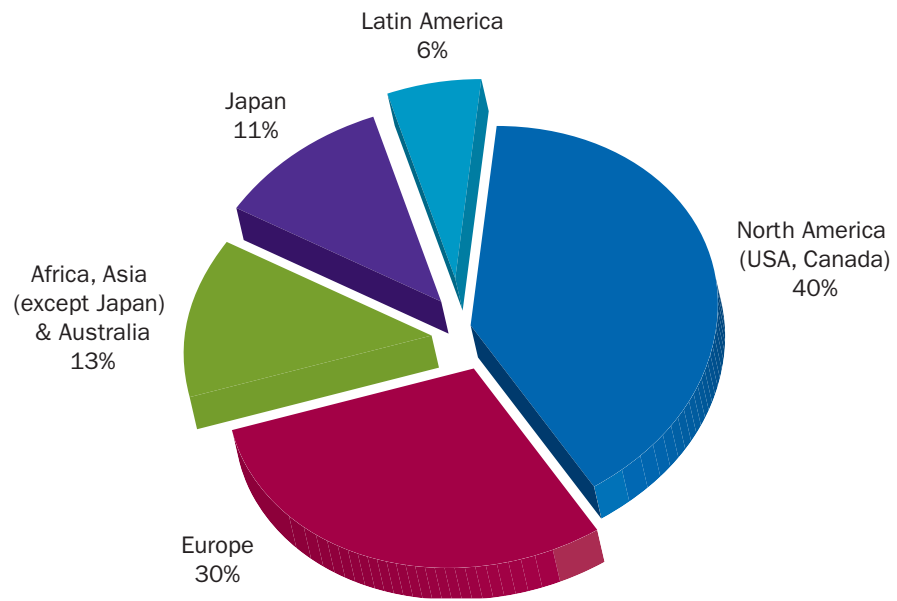
The number of molecular entities originated in Japan that make it to market has been declining in recent years, despite the fact that Japan is a technologically advanced nation. Figure 2 shows the extent to which Japan is lagging behind the US and Europe in pharmaceutical R&D expenditures, and Figure 3 illustrates how Japanese companies produce significantly fewer new molecular and biological entities than their American and European competitors.

There are several reasons for this lack of innovation. First, new drug development is strongly influenced by the current resource allocation structure, particularly Japan's highly controlled drug pricing system. Because the Japanese health insurance system reimburses 70% of all drug costs, drugs go through a highly selective review to qualify for reimbursement. Also, until April 2010, Japan employed a drug reimbursement system that lowered all prices biennially across the board. This drug pricing system offered pharmaceutical companies little incentive to focus on innovator products; they tended to develop low-risk drugs that would reap the most profit with the least upfront investment.

In addition, compared to the US, the entrepreneurial climate in Japan is still developing. The majority of Japanese bio-ventures, or biotechnology start-ups, are founded by academic researchers who tend to have difficulty acquiring funding because they are usually not professional entrepreneurs. These bio-ventures, borne out of university research labs, often lack the strong relationships with the industry needed to access funding, and it is widely believed that the current business environment does not support IPOs well enough. However, the government has addressed this issue by expanding local biotech clusters and helping commercialize translational research. A program called "Coordination, Support and

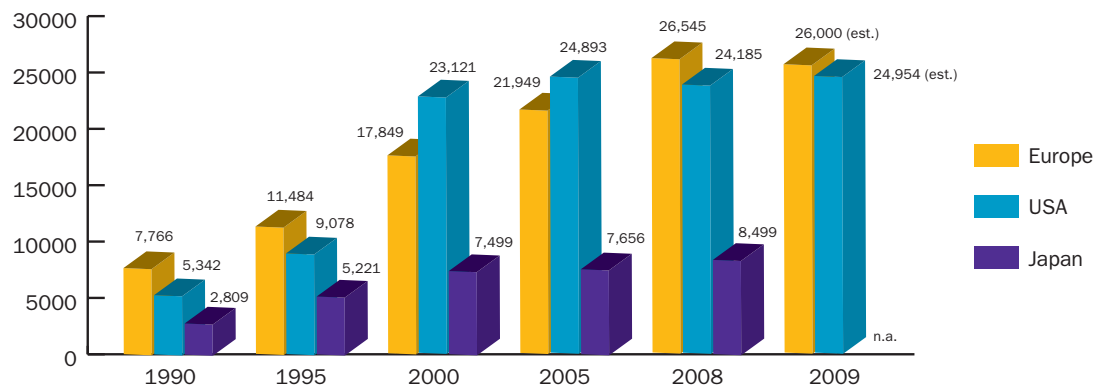


Figure 1. Breakdown of the World Pharmaceutical Market—2009 Sales



Source: EFPIA The Pharmaceutical Industry in Figures

Figure 2. Pharmaceutical R&D Expenditure (¥ Million, Exchange Rates 2010)



Source: EFPIA member associations, PhRMA, JPMA

Training Program for Translational Research” was launched in 2007 by the Ministry of Education, Culture, Sports, Science and Technology (MEXT)¹ to help biotech companies obtain funding and commercialize their products.

The second main cause of drug lag is the clinical research environment, which is yet to mature. In Japan, clinical trial costs are significantly higher than in comparable countries, and there are not enough adequately equipped clinical trial institutions or qualified doctors (investigators) to handle the trials. Therefore, Japan’s clinical trial landscape is far less active than that of the US and Europe.

The lack of clinical investigators can be attributed to few incentives or rewards for doctors to participate in clinical trials, as well as a dearth of available training in clinical trial management. Presently, participation in clinical trials is not regarded as a significant achievement by academic conferences and does not add much to physicians’ professional growth and development. In addition, grant money from pharmaceutical companies is sometimes allocated in such a formulaic manner that doctors are not satisfactorily compensated for their clinical studies.

According to MHLW conference minutes, a clinical trial can cost ¥ 2.7 million per patient in Japan, compared to ¥ 0.6 million in EU.² In fact, the concept of clinical trials is still a novelty in Japan and the infrastructure needed to conduct them is still under development in many parts of the country. All of these factors contribute to the difficulties surrounding the process of enrolling patients in clinical studies.³ This environment is one of the reasons that Japan is often not chosen as a primary site for new drug launch for global pharmaceutical companies.

Bringing Foreign Drugs to Japan

A major reason for the delay in bringing foreign drugs to Japan is the required additional round of testing on the Japanese population, adding time to the drug adoption process. This extra step is mandated because of concerns that ethnic differences might cause patients to react differently to the same compound. The International Conference on Harmonisation (ICH) was established to promote global trials and simultaneous launches in the US, EU and Japan by synchronizing standards, but this has not eliminated the requirement to perform additional bridging studies in Japan. However, increasing numbers of Phase 3 studies are being conducted with Japanese participants simultaneously with studies in other countries in an effort to close the gap.

There has been a growing movement by patient groups to persuade pharmaceutical companies and government entities to bring in drugs marketed in other countries. As one of the efforts to bring drugs to Japanese patients more quickly, in February 2010, MHLW launched an initiative, “Review Session for Highly Needed Unlisted

Drugs/Non-Indication Use,”⁶ comprised of medical and pharmaceutical experts to evaluate 372 yet-to-be-approved drugs (including new indications) for which academic conferences and patient groups have been pleading. Since many are widely used in foreign countries, the possibility of allowing preliminary introduction of drugs based on wide experience is under discussion.

Navigating the Drug Approval Process

In Japan, all manufacturing and marketing applications for drugs and medical devices are reviewed by the Pharmaceutical and Medical Devices Agency (PMDA), which was established in 2004. The agency serves three major functions: reviewing and screening new drug and medical device applications before they are submitted to MHLW for approval; ensuring postmarketing safety; and providing relief services for major damage caused to patients by adverse health effects.

Foreign companies often find it difficult to navigate Japanese clinical trial/drug approval processes, due in part to language and cultural differences. A non-Japanese pharmaceutical company without a local subsidiary must first receive accreditation as a foreign manufacturer before manufacturing and selling medicinal products in Japan. In addition, it requires a marketing approval under Japan’s *Pharmaceutical Affairs Law (PAL)*, a national decree, or the equivalent via the drug marketing authorization holder in Japan. Then, all the highly specialized forms related to product approval must be submitted in Japanese language.⁸ It is not easy to find a bilingual intermediary who possesses sufficient knowledge of scientific and regulatory details. The establishment of a RAPS Japan office in 2008⁷ was a positive step in addressing this issue; however, additional training efforts are needed.

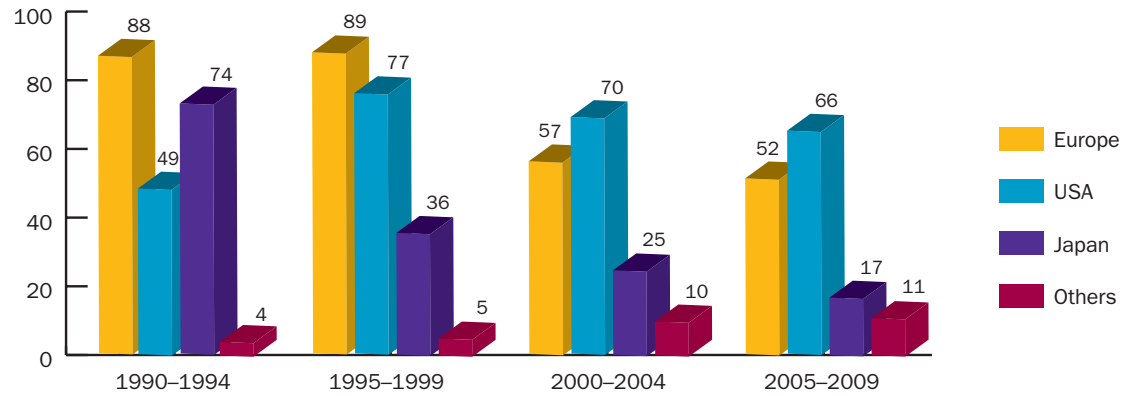
Internal PMDA Issues

Review and evaluation of drug applications by PMDA (for both Japanese and foreign manufacturers) is a lengthy process and a commonly cited reason for drug lag in Japan.

Employment issues are an underlying factor in chronic understaffing at PMDA. At its inception, the agency had 256 full-time employees, of which 154 were in the review department and 29 in the safety department. By 2009, those numbers had grown to 430 full-time employees, with 279 in the review department and 66 in the safety. Despite this increase, PMDA remains woefully understaffed in comparison to its US and European counterparts. There is still a significant wait for preapplication consultation or actual review (a priority review path does exist for drugs meeting an urgent need). As the US Food and Drug Administration (FDA) successfully resolved a similar staffing problem with the introduction of the *Prescription Drug User Fee Act (PDUFA)* in 1992,^{10,11} allocation of more resources has proven to be an effective measure. In fact, PMDA charges fees for

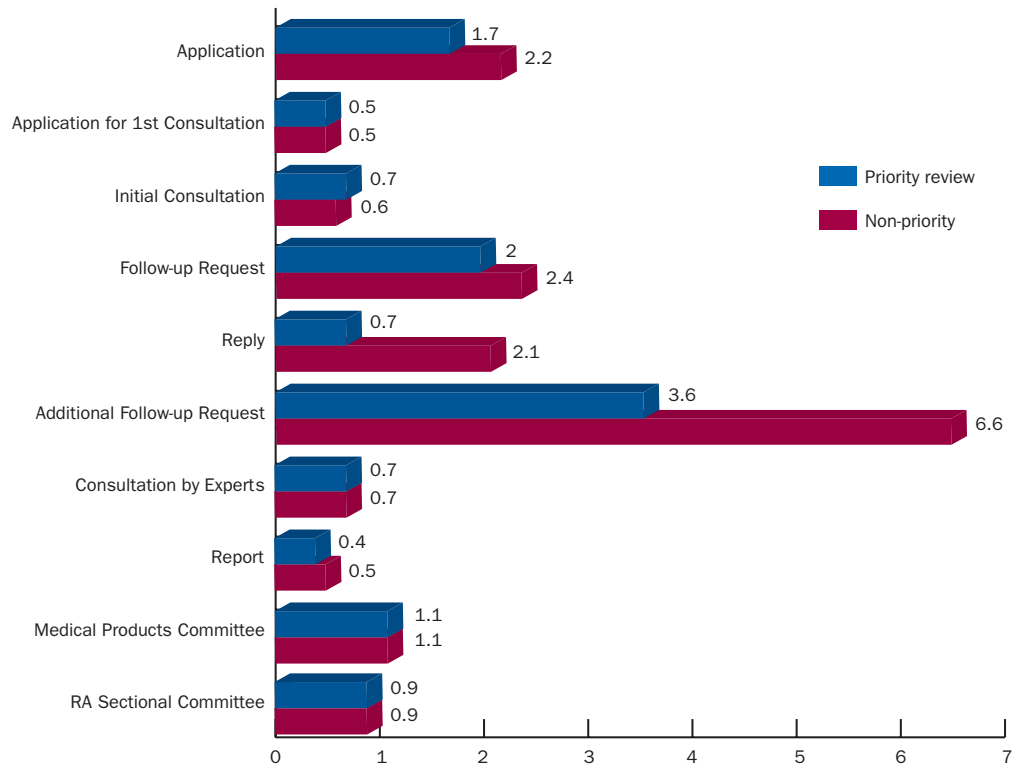


Figure 3. Number of New Chemical or Biological Entities



Source: SCRIP, EFPIA (Calculations according to company country of origin)

Figure 4. Review Process Breakdown (unit: month)



Source: Research Paper 47 (2009), Office of Pharmaceutical Industry Research

most application review procedures, which are a major source of revenue for the agency.

PMDA is becoming more open to hiring experienced specialists (usually regulatory specialists from the pharmaceutical industry) earlier in the review process.

A related issue is PMDA's difficulty in finding skilled reviewers. Like FDA and the European Medicines Agency (EMA), PMDA holds its reviewers to high standards: they are expected to not only have extensive knowledge of regulatory affairs but also an understanding of the nuances in evaluating drug risks and benefits for patients.

Further, there is a scarcity of reviewers; PMDA has to compete with pharmaceutical companies offering much more lucrative compensation. Moreover, once they join the agency, it takes five years or more to acquire sufficient expertise. Additionally, students with a master's degree in pharmacy can only be trained to work as Project Managers. PMDA needs more reviewers with advanced degrees and, although not explicitly mentioned, adequate knowledge of foreign language(s), especially English.

Dossier Quality Improvements

Another factor contributing to delays in PMDA review is the uneven quality of dossiers that it receives from industry. If a dossier is not of high quality, it can take longer for PMDA's review staff to evaluate, including requesting additional information from the applicant. As shown in **Figure 4**, lengthy delays caused by follow-up inquiries result in additional time needed for review and evaluation of drug applications.

To help PMDA reduce review times, industry needs to provide better data presentation and explanations in the dossier. Consequently, seasoned regulatory affairs experts are needed to support clinical study design, data packaging and dossier creation. They are also instrumental in the preparation of effective responses to inquiries by PMDA.

PMDA is becoming more open in hiring experienced specialists externally and using these specialists (usually regulatory specialists from pharmaceutical industry) earlier in the review process.

PMDA's New Initiatives

PMDA stated in its 2009 mid-range plan (covering 2009-2013) that it aims to shorten the drug review time by 2.5 years by 2011. More specifically, it plans to reduce the time from drug development to New Drug Application by 1.5 years by adding 236 PMDA reviewers and consultants, as well as by streamlining the review standards and guidelines. Then, it plans to cut another year of review time by upgrading the preapplication consultation process, implementing a project management system and training the reviewers and consultants more extensively.⁹

Dr. Tatsuya Kondo, appointed as the chief executive of PMDA in 2009, strongly advocates the concept of regulatory science and strives to turn reviewers into subject specialists. He also espouses training staff to handle international regulatory needs. Dr. Kondo supports the active promotion of global clinical trials (GCTs)¹⁸ and interchange with foreign regulatory bodies, such as FDA and EMA, in order to facilitate international regulatory standardization and contribute to ICH initiatives.¹⁹ In 2009, the international operations department was created and managers are being assigned to the US and EU.

Conclusion

The drug innovation landscape in Japan is beginning to change. In April 2010, after years of debate, a drastic change to Japan's drug pricing system was implemented, allowing certain drugs still under patent to be exempt from the mandated biennial drug price reduction. Because the new system will allow these drugs to maintain a price premium, it should protect pharmaceutical companies from their utmost concern, loss of exclusivity, as well as help them afford to invest more in R&D.

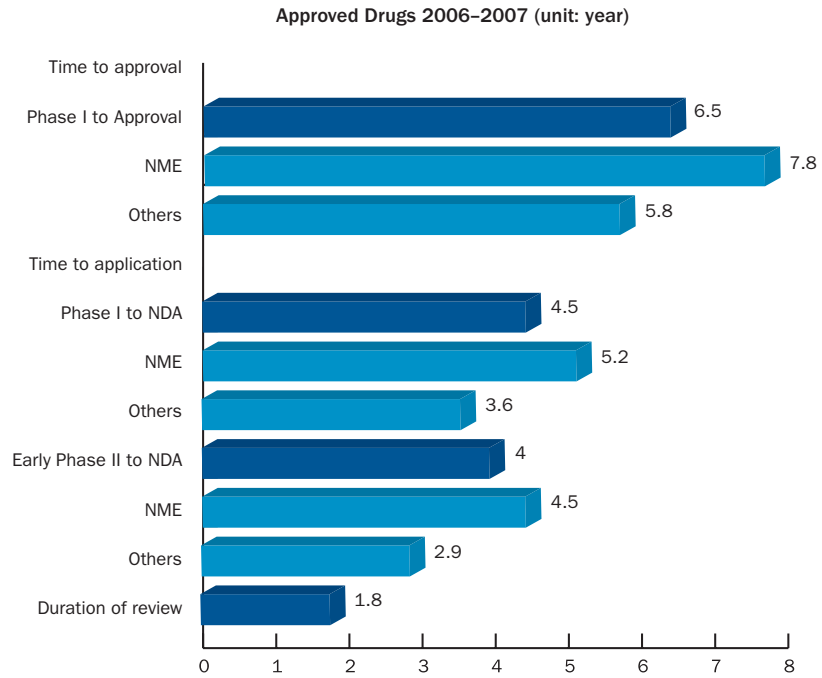
In early 2010, MHLW selected 109 prescription drugs to receive prompt approval for reimbursement and requested pharmaceutical companies to expedite the development and marketing of 91 products. In June 2010, the Japanese government officially stated its plan to resolve the drug lag, announcing the establishment of a new system by 2012, in which approximately 200 medical institutions will be selected to exclusively prescribe unlisted drugs/devices to meet the dire needs of high-risk patients. Moreover, MHLW announced in late August 2010 that selected drugs that are widely used in foreign countries will be reimbursed nine months prior to official listing for reimbursement. These events seem to indicate that a wave of increased activity is expected in Japanese drug development.

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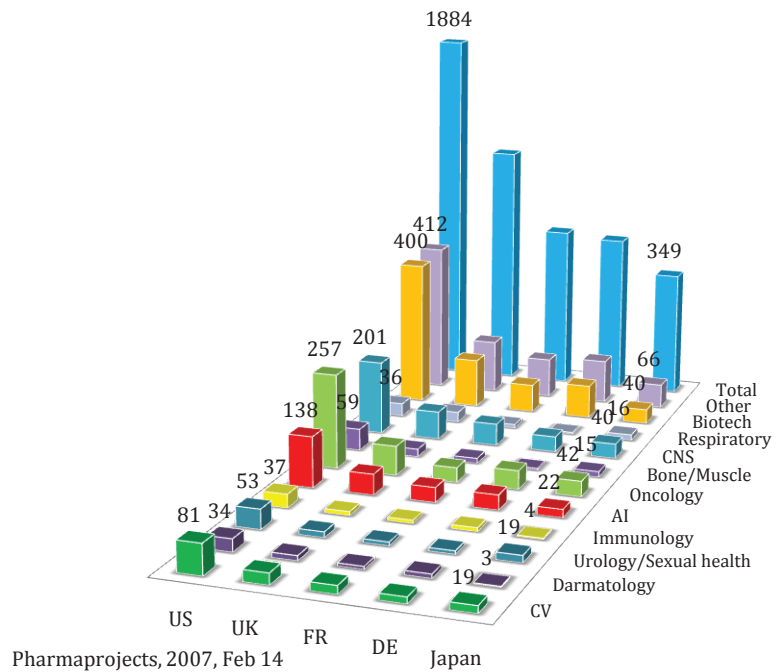
Appendix 1



Source: JPMA News Letter No. 127 (2008/09)

Appendix 2

R&D Projects by Therapeutic Area



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