

PMDA Consultation for Clinical Drug Development in Japan

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Function of the PMDA

The PMDA (Pharmaceuticals and Medical Devices Agency) is the Japanese regulatory agency that conducts scientific reviews of pharmaceuticals and medical devices for marketing authorization. While it is registered as an "Independent Administrative Institution" and not organizationally part of the Ministry of Health, Labor, and Welfare (MHLW), it describes itself as "working together with MHLW", and many of the PMDA staff are sent from the MHLW, and naturally they have mutual missions and objectives regarding pharmaceutical approval and use. This commentary will describe these missions and objectives and the flexibilities and inflexibilities inherent in the system.

The Japanese health system is national so that the same groups who pay for medical care are closely related to the ones that also determine what types of treatments should be available and at what pricing. Recent articles in PHARMA JAPAN have clearly described the new pricing system and how the rewards and punishments for premium pricing now tied into requirements to develop specific drugs are a way the government is able to exert control and motivate the pharmaceutical industry's business practices. This may or may not be negative, depending on the angle the system is viewed from.

Why would the government want to control the pharmaceutical industry? The government wants to get as many safe and helpful drugs as possible on the market at a reasonable cost to society, and for these drugs to reach only the specific patient population in need of each drug. It also does not want the economic value the pharmaceutical industry provides to society in terms of jobs and services it purchases to crash. This seems to be the actual mission of the PMDA as guided by the health policies of the MHLW and the budget policies of the Ministry of Finance, although not all of these missions may be clearly stated. The government also states it wants to foster innovation in R&D from pharmaceutical companies, but it is not clear from the recent pricing system changes if this is actually the case as the savings from the cut in price of long-listed drugs has been transferred to the health insurance programs (see the Feb 8th 2010 edition of PHARMA JAPAN for details on pricing reforms).

Containing Medical Costs

How is the PMDA connected to cost? Isn't the price of a drug determined by the MHLW and its associated bodies? While the price may not be determined by the PMDA, the PMDA would want to limit drugs that might not be medically necessary, or drugs that might have explosive markets (like antidepressants, drugs that promote wakefulness, drugs for attention deficit disorder, etc.), and the PMDA or MHLW may make restrictions or put hurdles to their development and/or sales, essentially restricting market size. Restrictions can consist of requiring full clinical development in Japan despite a million-patient use history abroad (i.e., SSRI antidepressants), age limitations on their use (i.e., Concerta), requiring physicians to have special certification or prescribing approval and requiring an all-case post-marketing study (PMS) for a term such as one year (i.e., Modafinil).

With this background, we can begin to understand the approach the PMDA would want to take toward drug development and approval. Medical needs, cost, and political opinion among the stakeholders (patients, industry, physicians, taxpayers, and government) will guide the type of development and post-marketing restrictions.

The importance of the opinions of physicians, patients, and taxpayers to the government's policies is obvious. Regarding the importance of industry, Japanese pharmaceutical companies have provided a stable source of employment for many educated persons for many years and are an important economic driver for Japan. Small foreign pharma are still in need of partnering or licensing with domestic companies. Large foreign pharmaceutical firms are a double-edged sword to the government; they provide valuable drugs, jobs, and service needs to Japan (and tax revenue on all of these), but they also have the potential to take the profits (government money from reimbursements) out of Japan. In recent years these foreign firms have overcome the obstacles in development and marketing of their drugs in Japan so that they depend less on domestic partnerships and licensing than they did a mere 20 years ago, but they still provide significant benefit to the Japanese economy and medical care. Thus, the government has some incentive to ensure that the pharmaceutical industry continues to stay economically healthy, but at the same

time, it does not want it to be a burden on the health system.

Many non-Japanese firms are surprised and frustrated at the hurdles the PMDA poses for the approval of their compounds in Japan despite large amounts of clinical trial and use data generated abroad. If you are a foreign firm and your compound has a local partner, do not be surprised if your partner does not want to challenge the PMDA on issues you may think are illogical. Remember, your partner has other compounds in development and in discussion with the PMDA and their relationship needs to be stable for the long term.

Development Planning

With this background in mind then, depending on the indication, the clinical and pre-clinical properties of the drug, and presumed cost and market size, we might be able to predict the type of requirements the PMDA might ask for the approval of a particular compound. It will be easier to bridge global data for indications that have a high socio-medical need, i.e., certain malignancies, Alzheimer's disease, influenza, etc., especially if the drug has shown particular efficacy abroad.

With the proper development strategy, it may be possible to reduce the number of dosing arms, to omit a placebo control, or reduce the number of safety subjects in a clinical trial (i.e., drugs with a significant history of overseas use), or Phase III in its entirety (i.e., novel influenza or Alzheimer drugs), or just submit overseas data (i.e., HIV drugs). There is even the rare approval initiated by a physician key opinion leader's lobbying of the PMDA with no official approval process (i.e., a drug for a rare form of leukemia). Long-term safety study data can also be added to the data package after NDA, but before approval.

The PMDA likes to see dose-response in Japanese, and will like the development in Japan to find the lowest effective dose. The proposed design of the clinical trials and development as a whole should take these factors into consideration as repeat-trials have been required if the dosing in Japanese is missed. Japanese to non-Japanese direct PK comparisons in Phase I are often a way to be able to bridge dosing arms, placebo controls, etc. later in the development if there is global data to bridge into Japan, but study of dosing in Japanese is still a critical factor.

Special Considerations

Finally, we would like to mention special considerations with the PMDA and MHLW including post-marketing restrictions, safety, special CMC specifications, and other items that may cause concern to the authorities in Japan.

Post-marketing restrictions may have more of a negative commercial impact on the drug than R&D requirements so that these considerations need to be carefully discussed with the authorities during the early planning phases of the clinical development. Post-marketing restrictions can include all-subject PMS, restrictions on the number of weeks allowed to be prescribed, or restrictions on the physician specialties allowed to do the prescribing etc. While these restrictions may seem illogical or superfluous for compounds that have been widely used abroad, they need to be seen in light of the social, economic, and political needs of Japanese society.

Regarding safety, various incidents over the years (sorivudine reaction with 5-FU, HIV and Hepatitis-C tainted blood products, jumping incidents suspected to be due to Tamiflu etc.) have made the Japanese health authorities extremely averse to any safety problems with the drugs they approve. Once safety warnings are on the label it is virtually impossible to remove them no matter how much new data there are due to an extreme adversity of the authority to re-crimination (i.e., suicide risk in antidepressants; dimer contrast media and anaphylaxis), and the development of otherwise helpful drugs may get held up for years (Clozapine, an innovative drug for schizophrenia for example was finally approved in Japan in 2009 after being on the market for over 20 years in Western countries because of agranulocytosis concerns that were handled by a patient registry abroad and finally in Japan).

Other concerns include special CMC issues. Compounds that use viral vectors or bovine materials will need to have significant CMC and overseas clinical data submitted as "Pre-NDA" materials available even before entry into humans at Phase I. These CMC issues may actually be a full no-go for the authorities and the potential for failure of development of these compounds should be assessed carefully before funding any development activities. A pre-IND PMDA consultation is a good way to hear the concerns of the authorities before significant investment is made.

Summary

This article has reviewed how the objectives of the PMDA need to be seen as part of the larger whole of the government and the society which it serves. The expectations and strategy plans for PMDA consultation should be made with these objectives in mind. Especially for foreign firms, clinical development professionals who understand the limitations of the system in Japan need to be able to articulate the system to their commercial counterparts throughout the development process in order to put the medical and commercial success in Japan in the proper perspective for the company.