What Contribution Can Pharmaceutical Companies Make to Cancer in Asia?

Cross-boundary Cancer Studies at the University of Tokyo: Astellas in Asia: Challenge for Cancer

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LECTURER PROFILE
Representative Director, Chairman of the Board, Astellas Pharma, Inc., a research and development oriented pharmaceutical company headquartered in Tokyo, Japan. At Astellas Pharma, Inc., Mr Masafumi Nogimori has served as President and CEO from 2006 to 2011, Executive Vice President from 2005 to 2006 and has been Representative Director since 2005. Prior to the April 2005 merger between Fujisawa Pharmaceutical Co., Ltd. and Yamanouchi Pharmaceutical Co., Ltd., which created Astellas, Mr Nogimori was Corporate Executive Vice President of Global Strategy at Fujisawa. Upon joining Fujisawa in 1970, Mr Nogimori engaged in Licensing, Business Development and various planning functions for about 30 years. He also led businesses at regional headquarters, in the USA, as Vice President, Business Development at Fujisawa USA, Inc. from 1993 to 1995, and in Germany, as President at Fujisawa GmbH from 1998 to 2001. Mr. Nogimori has a Bachelor of Pharmaceutical Sciences from the University of Tokyo.

ASTELLAS IN ASIA: CHALLENGE OF CANCER

Astellas’ OVERALL BUSINESS INCLUDING ASIA

Astellas Pharma, Inc. is currently in the global leading position in medicines for urology and transplantation and is trying to establish cancer business as a third strategic area in which we possess global strength. Astellas’ business comprised ‘Ethical drugs’ only, and it accounts for almost 100% of our revenue. In addition, Astellas focuses particularly on the research and development of novel drugs, and we are not engaged in the business of generic drugs in Japan.

I think there’s no doubt that Astellas is competitive globally in medicines for urology and transplantation, which are key R&D areas for Astellas. While Astellas is trying to establish cancer as the third key R&D area, we are also making efforts in other therapeutic areas, such as Alzheimer’s and schizophrenia in neuropsychiatric disorders, as well as complications from diabetes and kidney diseases. We are capable of a range of technologies in drug discovery, and currently, are also working on the development of technologies in antibodies and proteins, in addition to technologies in small molecular drug discovery which are one of our strengths.

Japan accounts for ~10% of the global ethical drug market. Compared with 40 years ago when Japan accounted for 20% of the global market, Japan’s relative market proportion is decreasing. The market in the USA, on the other hand, has grown significantly. While Astellas has a business presence in Japan, North America, Europe, Asia and Oceania, our major product lineups differ from region to region. Although our strengths in urology and transplantation are worldwide, we have particular strength in drugs for cardiovascular and gastroenterology in Japan. In North America, Astellas has its business presence in cardiovascular and infectious diseases, and in Europe, we have strength in products for dermatology and infectious diseases. In addition, we have a total of ~6000 medical representatives (MR) in >40 countries worldwide, thus ensuring well-balanced global business.

ATTRACTIVENESS OF ASIAN MARKET

I would now like to provide an overview of Asian pharmaceutical market. If we take a look at the correlation between the forecast of gross domestic product (GDP) per capita for 2016
and of the average annual growth rate of GDP per capita from 2011 to 2016, we can see that the countries in Asia, particularly China and India, are among the countries highest in the estimated average annual GDP per capita growth rate. Given the considerable growth potential in GDP per capita among the emerging countries in Asia, it is likely that the Asian pharmaceutical market will continue to grow steadily. Also, as economy develops in those countries, people’s standard of living will improve, and, at the same time, people will gain better access to healthcare as country’s health insurance systems develop. Asian countries are familiar with the basic trends of increasing economic burden of healthcare expenditures in North America and Europe, thus some countries are implementing cost containment measures in parallel to efforts to improve people’s access to health.

Next, if we take a look at the data that forecast the size of the pharmaceutical market in Asia and Australia in 2012 and 2016, we can see that the overall Asian market is forecasted to grow by >12% of the annual average. The growth drivers are China and India in particular (Fig. 1).

Astellas has established 100% owned local subsidiaries in a number of Asian countries. Since Astellas established a sales subsidiary in Taiwan in 1963, a direct sales subsidiary network has expanded to nine countries, including China, Korea, the Philippines, Thailand, Indonesia, India and Australia (as of June 2012). The main products in those subsidiaries are drugs for urology and transplantation.

Astellas has ~1700 employees in the Asian region, excluding Japan. Many of these employees are located in China, and the number of Chinese employees has been increased rapidly in recent years. Similar to the proportion of the number of the total employees in the Asian region, China has the largest number of MRs (currently ~530). The revenue in Asia was 33.7 billion yen in 2010, and Astellas is seeking to achieve further growth, mainly in its urology and transplantation business.

### Asia and Cancer: Focus on China

It is anticipated that even in 2015, the proportion of generic drugs in Chinese pharmaceutical market will remain at a high level (2). It is still the case that the generic business is given greater focus than the novel drug business and expanded use of generics is expected to drive greater market growth.

According to a market data, the most prevalent forms of cancer in China are gastric cancer, colorectal cancer, lung cancer, breast cancer and liver cancer (3). Although the prevalence of prostate cancer is low compared with industrialized countries, there is a possibility that this is due to the insufficient diagnostic practices in China.

One of the reasons for the high prevalence of liver cancer in China is thought to be the high number of cases of hepatitis B. High prevalence of lung cancer is largely due to the high number of smokers in China and it is likely that as westernization of lifestyles advances, cases of prostate and breast cancers will also increase.

In 2010, the size of the anticancer drug market in China was ~200 billion yen, which is one-tenth of the size of the markets in North America and Europe. The market size in

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**Figure 1.** Predictions for the drug markets of Asia and Australia.
Japan is also currently larger than that of China, but considering the difference in the population size, the growth potential in China is larger than that of Japan (4,5). Molecular-targeted drugs, which are often used in the USA, are not widely employed in China, and almost all of the 15 top-ranked anticancer drugs in China are inexpensive chemotherapeutic agents. In contrast, more than half of the top-ranked anticancer drugs are molecular-targeted drugs in the USA (Fig. 2).

In recent years, a number of the global pharmaceutical companies that had operated R&D bases in Japan have relocated most of these bases to China. The purpose for this relocation is believed to gain clinical data from Chinese population, which will facilitate earlier drug approval with faster clinical development and reduced development costs.

So what are the positive and negative factors when we observe the future trends in the Chinese market? On the positive side, we can see the moves toward reform of the medical health insurance system and the elimination of the drug lag in the development process. On the negative side, we face price reductions for drugs that are covered by the insurance system as part of government efforts to control healthcare expenditures, as well as the increased use of generic drugs and restrictions on prescriptions for antibiotic drugs. Notwithstanding these negative factors, it is believed that factors for overall market growth will outweigh negative factors.

In terms of anticancer drugs alone, while the annual growth rate of the markets of industrialized countries is expected to remain in single digits in medium term, that in China is expected to be double digits (6,7).

**Strategy of Astellas to Tackle Cancer**

I would now like to introduce strategy and some of the business activities for cancer at Astellas. One of the reasons that Astellas has decided to enter into the cancer market as the third strategic therapeutic area was the high degree of unmet medical needs, despite the introduction of new drugs for the treatment of cancers. Molecular-targeted drugs do not provide an universal solution for cancer treatment, which is becoming increasingly segmented. For example, drug A is effective for a certain type of cancer, but drug B is not for the same cancer. It was against such a backdrop of unmet medical needs that Astellas embarked on research and development.

From 2006, Astellas started its own research activities in cancer at the company’s Tsukuba Research Center in Ibaraki Prefecture. In 2007, technologies were introduced externally, including the Phage Antibody Library (MorphoSys) and the VelocImmune mouse (V-mouse, Regeneron), followed by the acquisition of Agensys, a cancer-focused antibody R&D company based in California. In 2009, Astellas has in-licensed two late-stage products in cancer. In 2010, Astellas has acquired the US firm, OSI Pharmaceuticals, with the aim of expanding the clinical stage oncology pipeline and gaining access to a small molecule discovery research platform. Of the products

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**Comparison of top-ranked anticancer pharmaceutical agents**

- Top 15 anticancer drugs in China are inexpensive chemotherapeutic drugs (sold by Chinese local companies).
- Almost half of top 15 drugs in the United States are molecular-targeted drugs, which account for more than 60% of the total market.
- New, expensive anticancer drugs have not been widely used in China.

**Proportion of top 15 anticancer drugs in sales**

- **China**
  - Molecular targeted drugs: 11%
  - Chemotherapeutic drugs: 89%

- **USA**
  - Molecular-targeted drugs: 64%
  - Chemotherapeutic drugs: 36%

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*Figure 2. Comparison of top-ranked pharmacological agents (China, USA).*
that were in-licensed in 2009, a new drug application for MDV3100 was submitted in the USA ‘for the treatment of castration-resistant prostate cancer in patients previously treated with docetaxel’ in May 2012 (it was subsequently launched in September 2012). We expect that Astellas’ anticancer products will continue to increase including antibody drugs.

With regard to our activities in Asia, we have the commercialization rights to Eligard, drug for advanced prostate cancer, which is already marketed by Astellas in Europe. By utilizing the drug application in Europe, we have submitted new drug applications of Eligard in Hong Kong, Thailand, the Philippines, Taiwan and Indonesia. An application in China is also expected in the near future. Since the review process of new drugs is relatively slow in China, it is unlikely that Eligard will be approved within 1 year, but we think that Eligard will become the first anticancer drug to be marketed by Astellas in China, followed by MDV3100 and other pipeline products.

One of the attractiveness of Chinese pharmaceutical market is the fact that the country has a massive population of ~1.3 billion. As its economy grows rapidly, the level of investment and the standard of living are improving considerably. Although anticancer drugs are generally expensive, their use is gradually expanding, from high-income households in China. Also, it is relatively easy to collect cases in clinical development and the quality of the development is also improving.

On the other hand, there are issues in clinical development, such as variability in the quality among medical facilities, long review period for new drug application and insufficient regulation of pharmaceutical drugs. In particular, although so-called ‘multinational clinical trials’ are a standard practice in the global pharmaceutical industry, it is still very difficult to include China in such international clinical trials. Therefore, it will be necessary for China to make efforts to develop an internationally compatible environment for clinical trials.

Since Astellas is already engaged in new clinical trials in Europe and North America, if China can improve its own environment for clinical trials, it is likely that Astellas’ introduction of new drugs would be accelerated in Asia. The gap between Asia and the West is still large; however, it will continue to decrease over time.

Discussion

Akaza: Among the anticancer drugs in Astellas’ development pipeline, I believe that MDV3100 is particularly exciting and could be a real breakthrough. Now, there are some issues that we need to address with regard to new drugs. The first of these is that in clinical trials, efficacy can be measured relatively in short term among patients at the late stages of cancer. However, if trials are performed in pre-metastatic patients, it would take longer time to evaluate efficacy. The time and capital investment by pharmaceutical companies are limited. The second issue relates to the effects of drugs on overall survival. The effect for extended survival period by MDV3100 is just 5–6 months, while an annual cost for the drug is >6 million yen. The question therefore is how many patients in Asian countries, where there are less developed economy and insufficient healthcare insurance system, can actually utilize such drugs, and does their use ultimately put a price on life? I would like you to consider such issues as you ask Mr Nogimori questions today.

Q: Anticancer drugs are designed for treatment not for prevention, but is there anything that pharmaceutical companies can do in the cause of cancer prevention?

Nogimori: First, people have to change their lifestyles that are deemed to lead to cancer, such as quitting tobacco to prevent lung cancer. In the case of infectious diseases, vaccines are effective for prophylaxis. On the other hand, there are many factors that are not yet fully understood about the pathogenesis of cancer. Although it is often said that cancer is caused by genetic abnormalities, this does not mean that cancer is caused by only a single gene mutation. The human body is far more complex than that and has many repair and regeneration systems. Other measures that are said to be effective for prophylaxis of cancer in nature are infrastructure development, including water supply, education, and the development of health insurance systems.

Akaza: From an academic perspective, there are a number of drug candidates that would appear to be effective for prevention, but under the existing regulatory system, the clinical testing of such preventive drugs requires considerable time and money. The success rate for such preventive drugs is rather low and this keeps pharmaceutical companies away from development of preventive drugs.

Nogimori: Furthermore, it is very difficult to gain regulatory approval for prophylaxis indications, since it would require long-term patient follow-up period, approximately 20 years, in order to obtain and evaluate hard endpoints. What is more, there are the cases to halt clinical trials if a testing drug given to a healthy person develops adverse effects. Side effects are inevitable in drug treatment, but when a prophylaxis drug develops adverse effects in healthy people, it will be considered difficult to continue clinical trials.

Q: Do you expect that the market of emerging economies such as BRICs will be dominated by emerging pharmaceutical companies in such countries?

Nogimori: Today, R&D for novel drugs is almost exclusively being conducted in industrialized countries. Although China and India may catch up with the industrialized countries in the future, they face considerable hurdles. Take the case of Japanese companies, for example, which started their own R&D activities in the 1960s. It has taken until the 2010s for these companies to catch up with companies in Europe and North America. Even if countries such as China and India could catch up in half the time, it would still take 20 years. However, it is imperative for every nation to overcome diseases and improve healthcare of people.

Q: Sales of anticancer drugs appear to be falling in the United States, so what is the prospect for sales in the U.S. and other industrialized countries?

Nogimori: Note that although revenue may be going down in monetary value, the actual volume of drugs is increasing. A drug with large sales of 200 billion yen may only generate 30 billion yen after the generic products are launched. Anticancer drugs are now reaching a point where generic drugs are entering to the market. In Japan, the market growth has always been small, but this is because the drug prices have consistently been reduced once every two years.

Q: Early detection of cancer and subsequent treatment means a high cost in terms of drugs used, but treatment following early detection is also highly effective. What are the challenges for pursuing early detection and early treatment?

Nogimori: Molecular-targeted drugs are now being widely used to treat cancer and diagnostic drugs are also being developed. In some cases, such drug may be effective for just 20 percent of patient population, and has no effect for the remaining 80 percent. In other words, this 80 percent patient group only experiences the adverse effects of the drug. If such 80 percent patient group is excluded from the treatment, it could not only avoid unnecessary adverse effects, but also precludes unnecessary drug treatment thereby results in a positive economic effect. This is what we refer to as precision medicine and it will become increasingly more important.

Q: I believe that the drug prices tend to be expensive due to economic factors of pharmaceutical companies, such as salaries for employees, but...
doctors see it pity if a drug cannot be prescribed for patient for price reason alone. Is there any possibility in the future that organizations such as the International Review Committees (IRC) could collect funds from mega pharmaceutical companies and redistribute these funds through a mechanism like public works or other means?

Nogimori: There is currently no such organization in existence. Private companies are run on the principle that they create profits and return these profits to shareholders. In order to pursue objectives for patient welfare and humanitarian, it will require a public body. However on the other hand, there are no incentive for competition in the public sector. Thus, I think there is a possibility that a creation of organizations would resolve the issue, which would serve as a buffer between the public and private sectors.

Akaza: Another reason why drugs are so expensive is regulatory systems. Conducting clinical trials takes time and money, including in China. While regulation itself cannot create new drugs, by forming global cooperatives and engaging in multinational trials from which data could be shared and approval sought, it may be possible to cut drug development costs by half. Another point is that pharmaceutical companies like Astellas could perhaps consider creating funds from surpluses that could be employed to provide global support for less developed countries.

Conflict of interest statement

None declared.

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