Interview: Osamu Nagayama – President, Japan BioIndustry Association (JBA)



"Bio is something that Japan has not always been on the frontline of"

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Osamu Nagayama, president of the Japan BioIndustry Association (JBA) and chairman and CEO of Chugai Pharmaceutical, discusses Japan's footprint in biologics and how mergers between Japanese pharma companies, thereby creating larger R&D funding pools, could hold the key to future success in the biotechnology field.

Can you begin by introducing JBA?

JBA's history dates back to 1942 and the foundation of the Fermentation Industry Association, bringing together the producers of fermented food and drink products such as sake, soy sauce and miso. The association was renamed JBA in 1987 and still addresses fermented foods, as well as pharmaceuticals and energy.

We have 168 member companies from across these sectors. Furthermore, we have 79 small businesses as members and 116 institutions from the public sector, including embassies and domestic and foreign local governments. We also have bio-clusters and universities as members. It is a very broad membership.

How is Japan performing in terms of biologics?

Bio is something that Japan has not always been on the frontline of. In pharmaceuticals, of the top ten best-selling compounds in the world, seven are bio and only three are small molecules. The

Japanese ethical pharmaceutical market is worth ten trillion yen, and biotech products account for two trillion within that, around 20 percent. The pace of biologics development however is faster and products are penetrating the market faster, particularly as the current pharmaceutical market is focusing on oncology. The oncology sector is growing very quickly and many oncology products are biologics.

Historically, Japanese companies lagged behind in biologics and did not fully managed to embrace the trend when big pharma jumped onto the wagon, why?

In Japan, there are still not many pharma companies which have the platform to do research, develop and manufacture biologics. Japan has traditionally been very strong in chemistry and most Japanese pharma companies made successes out of small molecules up until 2000. Even most Western companies, until the mid-1990s, were making small molecule drugs such as H2 receptor antagonists, statins, anti-diabetes products and anti-hypertension products. Japanese companies are now realizing the commercial potential of biologic products. The first generation products were erythropoietin and G-CSF. These two drugs made a fortune and were a great success in the world market.

Eventually, the antibody pharma came and in the year 2000, there was an announcement made by President Clinton and Prime Minister Blair about decoding the human genome. Three or four years later, they completely decoded it. That was the beginning of the biologics revolution, but many Japanese companies stayed with the small molecules in which they had more confidence, the manufacturing facilities already in place, and therefore lower production costs. The benefit of small molecules is that patients can take the drugs orally rather than through injection.

There are two exceptional companies which entered the biologics market. The first is my company, Chugai Pharmaceutical and the second is Kyowa Kirin. Kirin, a brewery, and Kyowa, a company with expertise in fermentation, merged in 2008. They wanted to enter the pharmaceutical market and their first products were erythropoietin and GCSF in a joint venture with Amgen. Kirin launched these products into the Japanese and Chinese markets.

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Has it been a lack of capital or a risk-averse culture that has stunted the growth of Japanese biologics companies?

Conservatism is to blame, along with the fact that entering biologics requires a lot of large capital expenditure without visible targets. Even in the USA, Genentech and Amgen were start-up

companies: most large pharmaceutical companies such as Pfizer and MSD only began developing biologics later on when they acquired other companies. In Japan, the culture is still not to merge, every company likes to be independent or ‘international’ rather than ‘global.’

Also, if the CEO of a company asks the head of research what path they should follow, the answer that comes back is often, “we have skills in chemistry and small molecules; why should we flirt with emerging technologies like biologics?” This could be a very good decision, but meanwhile, if you look back 20 years, we now understand that most strong small molecule medicines have already been developed and that there are not so many more opportunities remaining in this field. Nobody wants to spend two billion dollars to develop a product only slightly better than the existing statin or H2 blocker.

Amgen, for example, was founded by venture capital money. How is the biotech industry funded in Japan, who are the actors behind biotech’s ventures?

Major companies here are self-financing. Most companies have no borrowing from the banks and actually lend money to the banks as they are cash-rich. Nowadays, many products are running out of patent life and being replaced by generics, but until fairly recently, companies could still do good business from old drugs that were out of patent as doctors still wanted to deal with leading companies rather than small generic makers. Some drugs introduced by generics companies were not as effective as the originators and doctors had no incentives to use generics. They bought old drugs from leading companies with a discount; the discount then became income for the hospitals.

Now, the government is facing fiscal problems on a national level and social security costs are building up, the population is declining and the society is aging, placing enormous pressure on the government to contain medical expenditure. There is now a push for 80 percent generics penetration, up from the current levels of 67 percent. The government has been frustrated by the fact that the prices of drugs did not drop as they wanted. Therefore, they introduced a price cut to these old drugs; cutting into pharma companies’ income and therefore their ability to invest in R&D.

Do many large Japanese firms therefore feel that the biotech R&D train has already left the station? How will their R&D structure look moving forward?

Some leading Japanese companies have taken action by acquiring businesses in the US. But to be frank, very few Japanese companies have succeeded in this area. They have bought projects or companies with significant numbers of projects that have not worked out. Unless you already do research on biologics, you cannot judge what should be bought; creating a dilemma. It is not only

cash accumulation that can solve a problem. The likes of Roche, Novartis and Pfizer are standing by, watching attractive mid-sized venture businesses, and are able to spend several billion dollars overnight to acquire them. Japanese companies are finding it difficult to compete on this level.

This is why a couple of years ago, the Japanese government produced a paper on the prospectiveness of the future pharma industry, concluding that more companies should merge, consolidate and create a much larger base for global R&D spending. The dilemma here is that if two large companies have to merge, they have to do it for the sake of developing biologics R&D. It does not make sense for two companies only developing small molecules to merge in this way. Japan is approximately 20 years behind the West in this regard but this is probably the only way forward. And also Japan does not have a workable ecosystem for creating innovative treatments which we can see in the US and fostering bio-ventures in Japan is an urgent issue.

A lot of faith is being placed in regenerative medicine in Japan, what is JBA's position on this exciting new field?

Regenerative medicine is extremely intriguing, but it must be noted that it is totally different to the pill business, in that it provides one single cure for the patient, forever. Therefore, the business model of major pharma companies does not really fit. It will take a long time for these companies to rebuild and reach the point where they can expect the same levels of revenue and profit with regenerative medicine as they currently have with a pill-based business model. The difficulty is that companies have to keep the traditional pill business vibrant until they reach the point where it can be replaced by regenerative medicine. Even cash-rich global companies have not announced that they are shutting down their pill business and focusing on regenerative medicine, this does not look as a reality.

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Pharma companies now have to find a way to make an assurance of success. We have to get technologies of various treatment modalities to approach target molecules. That requires being in biologics or mid-size molecules rather than only small molecules. Furthermore, there are future generation technologies such as nucleic acids, gene therapy and cell therapy. Beyond the pill, there are a lot of things that companies have to do such as digital medicine, Artificial Intelligence (AI) and the Internet of Things (IoT). This is a conversion of electronic technology and biochemistry. We think that AI can solve many problems for the pharma industry: finding new drugs much faster, manufacturing more accurately and with higher quality, and as a result, lowering R&D costs for example. This could work but we are right on the threshold.

Do you have the sense that Japanese pharma can leverage on the country's strong IT and digital companies?

One has to give careful consideration to the fact that unless a platform of appropriate technologies exists, just partnering with IT companies in itself will not be successful as these companies have limited expertise in terms of creating new medicines.

A critical matter for us is to get more targeted molecules. The number of targeted molecules available for us to develop any drug is getting narrower and narrower. We talk about antibody pharmaceuticals, but there are about 400 projects on antibody pharmaceuticals including those already on the market. However, only 34 potential antigens exist. A similar phenomenon occurred in the 1970s and 80s when almost every leading company rushed to develop H2 receptor antagonists, beta-blocker, ACE inhibitor, Proton pomp inhibitor, Angiotensin II receptor blocker, etc. What is important is identifying new targets or antigens, which often come from academia, in hospitals, and research science on immunology.

In your experience, what kind of leaders does the pharmaceutical industry need to meet these new challenges, as visible the weight of science and business outside the traditional route are taking more and more relevance?

The current leader of a large pharmaceutical company needs to know how to do the traditional pill business well. If a general manager only thinks about 'beyond the pill,' the company will go bankrupt! There is not just one kind of manager that can navigate a company though this ever-changing environment. There is a need to keep good scientists and developers who can see the trends of technologies and also the targets. That requires frequent communication with academic institutions engaged in pill and beyond the pill development. The leaders of today needs to visit the innovation centers and discuss directly with scientist, it is a very fundamental point.

Agility is also very important. Academic institutions and clusters are often where the next great idea for the future comes from. You cannot afford to do everything and need to find which areas need to be shut down and move to that. In order to do that, you need people within the organization who really understand the science.

What can the Japanese pharmaceutical industry at large learn from the actions of your company, Chugai Pharmaceutical that as you mentioned is one of the few actors in biologics in Japan?

My company did something extraordinary in allowing Roche to gain a controlling share in 2002. Our actions surprised the industry and government. There was no precedent and remains no precedent. Roche acquired the majority of our shareholding but we remained a publicly listed company with full autonomy. At the beginning, people thought it was a crazy idea but, 15 years later, we have probably been the most successful Japanese company in terms of creating breakthrough therapies. Roche is number one worldwide in terms of breakthrough therapies granted by the FDA with 17, five of which are from Chugai's research.

At the time, Chugai's size meant that we could not afford to capitalize on all of the opportunities present in biologics. Even Roche has found that it cannot afford to do everything. Roche, Genentech and Chugai are now doing research with autonomy. This allows us to secure diversity for creating innovation as well as establish robust research infrastructures for rapidly advancing technologies through mutual use of research resources and information exchanges. As a result, this autonomous system can maximize research efficiency of the group totally.

How optimistic are you that the Japanese industry will embrace this way of operating?

The media has predicted that several companies will follow the example set by Chugai and Roche, but so far this has not been the case, perhaps due to cultural issues. There is still an antagonism towards mergers from Japanese companies, both with other Japanese companies and especially with foreign entities.

After us, several companies merged: Fujisawa and Yamanouchi into Astellas, Daiichi and Sankyo, DaiNippon and Sumitomo, and Tanabe and Mitsubishi. But there it stopped and since then, nothing has happened. As previously mentioned, the government produced a paper implying that more mergers would be preferable because the size of the R&D budget in Japanese companies is much smaller than that of Roche, Pfizer and Novartis. The biggest budget is that of Takeda with three billion USD, but Roche spent ten billion USD last year.

The top ten pharma companies globally spend on average between five and ten billion on R&D annually and have established more than 150 country operations, despite operational costs being so high. Despite this, they are making profits of 10-15 billion USD per year. They pay 20-30 percent tax and net profit and half is paid in dividend to the shareholders. The rest is free cash, standing by to capitalize on any new opportunities, either in terms of technology or products. If you look at the balance sheets, Pfizer receives 50 percent of its total revenue from ten products, Roche around 70 percent, meaning that the revenue from each of these products is around 2.5 to three billion dollars. Usually patent life validity is ten years, meaning that, of these ten big products, one

disappears every year and you have to refresh. That is how Big Pharma is playing the game.

Do you think that Japanese companies should be partnering or even merging more with Western companies?

Culturally it is difficult to overcome and deal with foreign companies. Probably, it is more feasible that they merge among themselves, thereby creating a larger budget for biologics R&D, slashing the budget for small molecules, and being ready for around the pill and beyond the pill. These companies do not have 100-150 operations worldwide as the Big Pharma players do. To deliver their products to the rest of the world, they would somehow cooperate with large foreign companies. Securing a certain level of R&D budget for creating innovation is crucial to surviving in future. Then these companies have to consider how to develop their global sales channels.

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