Charting the future for new drug development in an age of globalization

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How can the lessons of consumer electronics be applied to new drug development?

Japan's manufacturing sector has lost its former prosperity and now faces a crisis, prompting heated debate over the path that electronics makers and other manufacturers should take in the future. In the past, Japanese companies focused their business activities in markets of the developed world, relying on the twin weapons of advanced technology and high quality, and reaping considerable rewards. Not so long ago the world could be neatly divided into the United States, Europe, Japan, and the rest of the world, with globalization being thought of as business expansion within the developed world. But recently, and particularly in the wake of the Lehman Brothers crisis, stagnation in developed economies has led to a rise in the importance of emerging markets. Japan also faces difficult times. Whereas the business model utilized by Japanese companies leveraged advanced technology and high quality to conquer developed-world markets, the business model in emerging markets is qualitatively different, and presents a major challenge for companies that are unable to adopt new values and new perspectives. An argument can be made that Japanese companies have won on science and technology, but are losing out because of their business model. Perhaps there are lessons from the consumer electronics industry that can be applied to new drug development.

Emerging countries and the new globalization

Emerging countries are having an ever greater impact on politics and economics. China and India in particular—both of which have strong ties with Japan—form the kernel of the BRIC group of rapidly developing nations (Brazil, Russia, India, and China). In terms of scale, the BRICs include the world's largest nations, and account for about 40% of the global population and 30% of the world's land. The international community was formerly dominated by a cluster of European
nations with populations on the order of 50 million people, but with the assimilation of countries having over a billion people, the international community is taking on a very different complexion.

This affects not only politics and economics but also science. For example, the International Society of Nephrology (ISN), of which I am a member of its Executive Committee, is illustrative of this new influence on the international scientific community within Asia-Pacific countries, including Japan. Since its inception 50 years ago, this international scientific organization has seen its membership expand to include scholars from 127 countries. Until 1990, Japan and Australia were the only Asia-Pacific countries to be represented on the governing council, with Japan holding an honorary seat as Asian representative, but at present, 10 of the 32 council members—more than from any other region—represent Asia-Pacific countries, namely Japan, Taiwan, China, South Korea, Australia (2), India (2), and Thailand, and 4 of the 10 elected Executive Committee members are also from Asia-Pacific countries. This example illustrates how many Asian nations now have a voice in the international community and a direct line to the rest of the world, giving the world a window into the activities of its many countries. As a result, Japan's position, vision, and actions are also under the spotlight.

**Huge pharmaceutical markets and new medical needs**

Until now, large pharmaceutical companies have mainly targeted the developed-world markets of the United States, Japan, and Europe. Success in these countries was largely due to high levels of pharmaceutical use against the background of comprehensive healthcare systems and advanced medical technologies. With their high levels of economic growth, the emerging countries have also recently seen a growing need for more advanced healthcare and medicines, and this need, coupled with improvements in medical technology and the expansion of healthcare systems, has led to a rapid expansion in the scale of the pharmaceuticals market.

In 2011, the pharmaceuticals market in emerging countries was estimated to be worth between $170 billion and $180 billion, completely eclipsing the Japanese market. According to information published by IMS Health, a healthcare information service, the pharmaceuticals market in 2009 was worth $90.3 billion in Japan, $31.7 billion in China, and $10.3 billion in India, but by
2011 the market had rapidly increased in the BRICs to $66.7 billion in China and $14.3 billion in India, compared to $111.2 billion in Japan. The estimates for 2016 are $120 billion in Japan, $160 billion in China, and $30 billion in India. The BRICs market has seen a growth rate of 10% to 20%, compared with just single-figure growth in the United States and Japan, currently the world's largest markets. China's growth rate is particularly impressive.

The rise of the emerging countries is also giving rise to new, unmet medical needs. Take dialysis treatment for example. Dialysis in emerging countries is certain to develop along a path different from dialysis in the developed world, where, for instance, hemodialysis is the main form of renal replacement therapy used to support patients with end-stage renal failure (this is true of about 90% of Japanese dialysis patients and about 70% worldwide). The emerging countries are also facing a sudden burgeoning of problems seen in the developed world such as aging societies and changes in disease patterns. Aging societies and lifestyle diseases such as diabetes mean that the emerging countries have a huge number of future end-stage renal failure patients, and that the medical costs of treating these patients is already an important policy issue in a number of these countries. However, unlike the developed countries, which have seen a gradual increase in patients, the existence of untreated patients in emerging countries has become an issue overnight. But the cost of hemodialysis-centered healthcare for renal failure is too high to be adequately met by the BRICs. It would not be possible to simply introduce into these countries the full suite of cutting-edge medical technologies developed by the advanced nations, and it could be argued that the most advanced levels are not what is needed in emerging countries. To meet these large-scale medical needs that have suddenly emerged, the priority must be to deliver healthcare to a much larger number of people at an economically feasible level. It seems that there may be points of commonality between this situation and the failure to penetrate emerging markets with hi-tech, high-quality consumer electronics so successfully sold to the developed world.

Some emerging countries are, in fact, already exploring a different framework for renal replacement therapy. For example, in June of 2011, China's Health Ministry announced that it would be promoting peritoneal dialysis, which costs less than hemodialysis. It also announced the creation of 30 centers in China to promote broad adoption of this method. These policies were supported by the Chinese Society of Nephrology. The ISN itself has launched a program focusing
on education and awareness of peritoneal dialysis to help kidney disease patients in Africa and other emerging countries. Though peritoneal dialysis is received by only 5% of all end-stage renal failure patients in Japan, it is likely to become the de facto standard in emerging countries, and this will necessitate the development of, for example, therapeutic drugs to deal with issues such as complications associated with long-term peritoneal dialysis. As these examples illustrate, this new phase of globalization involving emerging countries will continue to give rise to new medical needs, and if we are to seize the opportunities found in the pharmaceuticals markets in these countries, it is essential to understand their new medical needs and respond to them as quickly as possible.

**New perspectives in drug development**

A serious discussion is needed between industry, government, and academia about ways to ensure that new drugs developed in Japan can expand into the new global community characterized above. Without such discussion, the Japanese pharmaceutical industry will repeat the same mistakes as the consumer electronics industry. I believe that an academic perspective can contribute much to the debate. A key element for future success will be to strengthen relationships with government agencies and medical institutes in emerging countries, and full use should be made of science and technology diplomacy and international academic networks to achieve this. A range of medical and pharmaceutical policies are being implemented in various emerging countries with the goal of eradicating diseases of particular importance in those countries. Even if only a limited amount of budget in emerging countries is allocated to support such policies (because there was no short-term profit), the results of such a contribution will raise awareness of Japan within the recipient country’s government and among medical workers, and if the policy is a success, building firm and strong government relations will be important in securing the place of Japanese pharmaceuticals within the emerging markets, and I believe that business expansion in emerging countries can be achieved more effectively through cooperation between industry, government, and academia.

Japan has around 1200 pharmaceutical companies, but only 9 of them have an overseas sales rate accounting for more than 10% of consolidated net sales (calculated for the financial year ending March 2010). To date, Japanese
pharmaceutical companies have been successful in foreign expansion within
developed-world markets. There have also been some active advances into the
emerging economies, but it is uncertain whether the same business model will
yield future successes in these new territories.

Because of the variety of systems and structures related to healthcare and
drugs in emerging countries, a long-term, multiperspectival approach is
necessary, taking full account of the differences in each country's market
structure, laws, and regulations (patents, pharmaceutical affairs), current state
of drug prescription practices, medical context (insurance system, drug
reimbursement mechanism, etc.), and so forth. In many cases, the values,
thought patterns, and mentality are qualitatively different by each country. The
best approach will be to think and act from the same standpoint as the
government organizations and medical institutions in the target country. To build
relationships of trust, and for both sides to gain more practical experience, it may
be necessary to deliberately yield in some matters.

In Japan, a drug discovery support mechanism based around the Medical
Innovation Promotion Office — an office established within the Cabinet
Secretariat—has been proposed in order to promote new drug development. In
the flow of events from drug discovery to clinical development, a large number of
researchers, often pursuing diverging research targets, are employed in basic
research (identifying target molecules, searching for hit compounds) and clinical
trials, and since this overall process is too multifaceted for a single agency to
oversee, it is important that there is a network among several agencies involved
in the process. On the other hand, flow is important for the efficient progress of
non-clinical studies (pharmacokinetics, toxicity studies), structural optimization
of hit compounds (the joint work of pharmacokinetics and toxicity studies), good
manufacturing process (GMP) synthesis and formulation, non-clinical good
laboratory practice (GLP) studies, and other studies, and what is essential for
this is a research structure that is horizontal rather than vertical. Structures like
the drug discovery support mechanism are also significant in terms of
concentrating funding from the public and private sector and controlling rights
relationships.

For emerging countries in particular, new drug development is a major
enterprise of potentially great significance to the national interest. Emerging
countries will also be unable to introduce new drugs if they are unable to
continue paying the high license costs to the large U.S. and European
pharmaceutical companies. For these reasons, most countries are considering mechanisms for introducing new drugs which should also help to stop patent infringement, illegal copying, and the like.

China is currently establishing structures for accelerating drug discovery and clinical development, based around, for example, the Institute of Materia Medica, Chinese Academy of Medical Sciences, which is under the control of the Ministry of Health. Until now, the focus in China has been on introducing drugs approved in the developed world which could easily enter the Chinese market (economically manageable generic drugs), but we are now starting to see new drugs developed in China and exported globally. Similarly, the Egyptian government is engaged in bolstering the foundations of government-led drug discovery and development, primarily through drug research institutes established as part of the SRTA-City (City of Scientific Research and Technological Applications) mechanism. Japan has some new drug seeds owing to the government's policy of providing funding commensurate with the fruits of basic research, and if Japan's seeds can be developed in a way that ties in with the medical and pharmaceutical policies of these emerging countries, we will be making an international contribution at the same time as paving the way for participation in pharmaceutical business in these countries. Rapid entry into markets for new drugs in the Middle East and Africa may be difficult, but by establishing gateways in Saudi Arabia, Egypt, and Turkey, the Middle East and Africa could come within our sights. Using advanced science and technology in developed countries as a leverage point, new ideas, models, and networks will be required so that new drugs developed in developed countries can be taken up throughout the global community including the emerging countries.

International academic institutions also have an important role to play. The mission of such institutions has changed in recent years: their main goal is no longer the furtherance of science and technology in academia. Instead, for many of these institutions the key concepts are now humanitarianism and philanthropy toward emerging countries. The ISN has also adopted these ideals as its mission, and its main activities are now being planned and operated for that. In the current financial year, the ISN has set up the Advisory Committee for Clinical Trials and Studies to support and raise standards in investigator-driven clinical trials in emerging countries, and has launched a number of horizontally organized, international investigator-driven clinical research projects to solve the medical problems likely to emerge in these countries in the future. One such
scheduled project is an international project involving China, India, Egypt, and Japan to evaluate whether unapproved drugs developed in Japan could be used to treat complications that hinder continuation of long-term peritoneal dialysis. Although a successful model has yet to emerge, this project is significant in its attempt to tie science and technology to health policy in emerging countries through international academic networks.

The important elements for expansion within emerging countries are not only business, but also international academic networks and a perspective aligned with the health policies of each country. This use of the international expansion of science and technology as a pivot to involvement in the health policy of these countries and to the expansion of business could be classed as science and technology diplomacy.

The role and challenges of academia in new drug development

High levels of science, technology, and basic research are not limited to consumer electronics. In the field of new drug development, basic research has yielded many fruits, and we have an abundance of information on drug discovery target molecules, together with the infrastructure needed for drug discovery. Researchers in universities are now able to use high-throughput screening using large-scale compound libraries thanks to an initiative by the Ministry of Education, Culture, Sports, Science and Technology in Japan. They also have access to various in silico technologies which use computers for compound design. This means that with the right effort, using the latest science and technology and working smartly in cooperation with contracting research organizations, it is possible even for universities to start from in silico searching for hit compounds, move through GMP synthesis and formulation as well as non-clinical GLP studies, and reach phase 2a clinical trials in humans. Japanese universities now have a solid infrastructure for drug discovery, but the question for the future is to what extent we can build cost-effective mechanisms for obtaining high-quality materials and data in the context of limited budgets, labor, and time.

The main benefits of drug development initiated in academia are the many research networks formed through joint research between domestic and foreign academics and international investigator-driven clinical trials. If high-quality material (GMP synthesis/formulation) and GLP safety data are available, it
should be possible, in principle, to conduct clinical trials through such international networkings. This would be facilitated by making materials and data available as open resources. At present, we are developing an oral low-molecular inhibitor targeting plasminogen activator inhibitor (PAI-1), but in addition to its bone marrow regeneration action, this drug also has antithrombotic and anti-inflammatory effects. The drug is a new, unapproved compound originating from a hit compound discovered through in silico techniques based on the structure of the human PAI-1 protein. After structural optimization of the hit compound, involving synthesis of about 540 new lead compounds, a compound was selected for clinical development. We have completed GMP synthesis/formulation and a panel of GLP toxicological studies. In spring of 2013, the compound will enter phase 1 development in an investigator-driven clinical trial (single and repeat doses). An investigator-driven phase 2a trial is then planned with the goal of evaluating the drug's bone marrow proliferation effect, but after safety and efficacy have been demonstrated in humans, we wish to offer up the drug for clinical evaluation in a number of diseases, using a large number of domestic and foreign academic networks. Clinical development of the same drug is also underway in the United States in collaboration with Northwestern University, and we have had a kickoff meeting (pre-pre-investigational new drug meeting) with the U.S. Food and Drug Administration so that the Japanese GLP data and GMP materials can be tied into the U.S. trials.

Unlike products such as cars and computers, which consist of combinations of numerous components, pharmaceutical products must in themselves embody a range of technologies. They must also satisfy various legal and regulatory standards such as GLP safety certification based on animal tests, GMP assurance of materials, and good clinical practice assurance of safety and efficacy.

There is much debate on the question of what is the key to cooperation between industry and academia in new drug development. Researchers tend to overvalue their own research, and thus debate based solely on the scientific aspects of the research is unlikely to lead to licensing-out to industry. Academia, too, must consider the question of what assets it can develop in a global context.

What are the keys that will allow new drugs developed in universities to reach the international community, including the emerging countries? I think there are three main keys: (1) globally recognized intellectual property rights (substance patents, including novel pharmaceutical compounds), (2) high-quality data and
materials, and (3) mechanisms for building connections through global expansion of (1) and (2). Furthermore, rather than applying for only domestic intellectual property rights as soon as hit and lead compounds have been discovered by high-throughput screening and in silico analysis, we should wait until after sufficient structural optimization, and then file substance patents for new compounds encompassing a broader range of analogues, not only in developed countries, but also in emerging countries. A support mechanism to make this possible will also be required.

A further key is the provision of internationally acceptable high-quality non-clinical data packages and bulk drug for clinical trials. These are already perfectly feasible. Cooperation with the regulatory authorities of each country will also become important, and this cooperation must be achieved through provision of model seeds and the build-up of experience and results. If we regard global intellectual property, non-clinical GLP data, and GMP-synthesized trial drugs as a single new drug development package from academia, and if we can provide a mechanism for clinical development with a global perspective from phase 2a trials onward, so that development can advance through international investigator-driven clinical research networks, it should be possible for new drug development from academia to extend globally beyond its current reach. The large pharmaceutical companies will probably continue to be at the center of drug discovery in the developed world, but in the emerging countries academia should be able to drive development in conjunction with the health policy of each country.

New drug development has become a challenge even for the large pharmaceutical companies. In particular, first-in-human (first testing of an unapproved drug in human subjects) and proof-of-concept studies (clinical trials to prove a drug's efficacy in humans) are crucial milestones in the development of new drugs, but in reality it is unfeasible to target all diseases in this way. While the importance of new drug development for orphan diseases is recognized, in practice such diseases cannot be tackled by large pharmaceutical companies alone, targeting the Japanese market only. University-led drug discovery and international, investigator-driven clinical research networks surely have an important role to play.

The graying of societies and changes in disease patterns are not only issues for the developed world, but are also a rapidly growing problem in emerging countries. In addition to communicable disease, the World Health Organization...
has recently begun focusing efforts on non-communicable diseases (NCDs) in emerging countries, and currently recognizes cancer, cardiovascular disease, diabetes, and chronic respiratory disease as key NCDs. These four diseases account for 60% of deaths worldwide, and 80% of those deaths are in low- and middle-income countries. If the quality of clinical trials in emerging countries can be raised, in some cases it may prove more economically efficient to push clinical development in those countries in order to meet the medical needs common to both emerging and developed countries.

Conclusions

We have entered a new phase of globalization, which includes emerging countries with massive populations of over 1 billion people. To deal with this new reality, we need new values and perspectives. Rather than structure and organization, there needs to be greater emphasis on fostering individuals and ideas that can prosper in a borderless world. It is probably unnecessary to be overly concerned with emphasizing “brand Japan” in emerging countries. Instead, efforts must focus on securing important matters such as intellectual property and high-quality materials and data, but ideally these should be introduced in a flexible manner according to the social and economic situation of each country. Superficial differences should not matter as long as the underlying content is of our origin. With this approach there is high probability that science and technology in developed countries will be actively utilized in the new global community.