Challenges within the Life Sciences i Japan

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Förord

Denna rapport utgör en bilaga till rapporten "Vad händer inom life Sciences internationellt? -Nuläge och trender i utvalda länder" (Svar Direkt 2012:05) som Tillväxtanalys utfört på uppdrag av Utbildningsdepartementet.

I projektet studerades situationen för life sciences i sju olika länder och materialet är presenterat i varsin landbilaga samt i en övergripande och sammanfattande rapport. Speciellt stor vikt har bland annat lagts vid beskrivningar av strategiska forskningssatsningar, samverkansinitiativ, infrastruktursatsningar, klinisk forskning och translation.

Rapporten om Japan skrevs av Tillväxtanalys medarbetare Setsuko Hashimoto och Anders Karlsson. Martin Wikström var projektledare.

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Innehåll

1 Executive Summary – Life Science in Japan

The purpose of the chapter on Japan is to describe recent developments in the policies of life sciences, with special interest towards clinical trials. Like in many other countries the overall challenge in Japan is how to accelerate the translation from basic research in academia to clinical applications and to shorten the drug lag, i.e. the time before a newly discovered drug can be commercially available. Various initiatives described in the report depict the overall strategy and research and innovation policies to overcome the gaps between academic research and commercialization in the Life Sciences in Japan. Examples, non-exhaustive, are given on funding programs and specific research projects.

The main results can be listed as follows:

- Japan focuses the national strategy for innovation and growth on three major strategic areas of which one of them has been termed "Life Innovation". This includes major investments in the medical sciences and in healthcare. The country has over a long period of time invested quite heavily in basic and applied Life Science research. The focused efforts on the Life Sciences have created world-class research milieus of interest for Swedish collaborations. The challenge for Japan lies in moving beyond pure research.
- A stringent drug- and medical device approval system, with a conservative approach of the responsible Ministry for Health, Labour and Welfare (MHLW) has led to a substantial drug- and device lag compared to competing countries. This acts as hindrance to translation (taking research to practice), and has led to that many of the Japanese pharmaceuticals companies seek to start clinical trials abroad instead of in Japan.
- The innovation system to bridge academic research and industry/hospital interests is not well functioning in Japan. Stringent approval procedures are one reason. However, a more fundamental reason is a lack of human resources who can bridge academic research and business development such as product development, application development, sales and marketing. A further reason is a less favorable venture climate compared to for instance the United States.

Gradually the Japanese government is addressing these problems, i.e. creating focused research, "user driven" programs, targeted programs to support start-ups, and seeking to coordinate efforts between ministries. The progress, however, is not fast and issues such as the entrepreneurship climate will also require a change in mentality both of companies and individuals.

2 Japan – great science but problems with drug lag

In the first chapter an overview of the two overall strategies for growth and Science and Technology (S&T) respectively will be given, as well as a description on how the overall area of Life Sciences relates to these. We will only discuss the public funding and not the funding made by private companies. The chapter also contains an overview of the relevant ministries and organizations relevant for Life Sciences in Japan.

2.1 National Strategies for Growth and the 4th Basic S&T plan

Even if Japan has seen its relative global competiveness gradually decline, it still remains the third largest economy in the world with some of the worlds' most innovative companies including Toyota, Toshiba, Sony, Softbank and Takeda, to mention only a few. However some of the companies today struggle to remain competitive. From a governmental policy level, there have been a number of initiatives and growth strategies put into place to increase competiveness, however often by individual ministries and with a lack of coordination. Following the historic change of government in 2009[1], the new government set out to develop a comprehensive growth strategy. In June 2010, the 10 Year perspective "New Growth Strategy: Blueprint for Revitalizing Japan"[2] was released and "Green Innovation" and "Life Innovation" were introduced as the two main pillars for growth.

Following the Earthquake in 2011, the government urged efforts to reinforce growth capacity to overcome the challenges. The concept of "open reconstruction" was added as a third pillar to the strategy for growth. The delayed 4th Basic Science and Technology (S&T) Plan[3], with a five year perspective, was released in August 2011, is positioned to be in line with the Growth Strategy and aims to let S&T promote the three above mentioned pillars and in an addition a fourth generic one for S&T : "Promotion of Basic Research and Research Personnel". A basic shift of stance in the 4th Basic Plan compared to earlier plans is a shift from discipline-oriented funding to issue-driven science and innovation - that is to identify clearer societal areas where S&T could accelerate progress and to design cross-disciplinary programs.

These overall changes in strategy will also affect policies and instruments for funding in the "Life Innovation" programs. The targets for "Life Innovation" in the Growth Strategy are to foster industry growth to meet the demands for medical care, nursing care and other health-related services, as well to create jobs. This, according to the strategy, would involve roughly 50 trillion Japanese Yen (4.5 trillion SEK)[4] in new businesses, and with the goal to create 2.84 million new jobs. The backdrop of the focus on "Life Innovation" is of course the rapidly ageing and in population numbers decreasing society in Japan, leading

[1] With the exception of two short time periods, in 1993 – 1994, the Liberal Democratic Party of Japan was in power for 54 years, until in 2009 the Democratic Party of Japan took power. In this respect, the change of government can be referenced to as historic.

[2] "New Growth Strategy: Blueprint for Revitalizing Japan", available at: http://www.kantei.go.jp/foreign/kan/topics/sinseichou01_e.pdf

[3] 4th Basic Science and Technology (S&T) Plan. According to the 1995 Basic S&T law, the Japanese government should present a Basic S&T plan every five year, which should outline strategies and goals for funding.

[4] Throughout the material we have used the conversion: 1 Japanese Yen (JAPANESE YEN) = 0.09SEK

to a decreased work force and increased costs for health care. However, with Japan being the first country in modern days to enter this stage of a rapidly aging society, it also poses an opportunity for the development of new manufacturing and service industries through "Life Innovation" (innovation in the medical and nursing care sectors). Should the Japanese innovation system get the "first mover" advantage of an industrial sector adapted to the aging society, then this could also assist this sectors business expansion abroad[5].

To tackle the challenges, the government has set out to further promote research and development of highly safe, superior, and innovative pharmaceuticals as well as medical and nursing care technologies. A unified approach among industry, government and academia will be encouraged to foster drug development ventures and to promote research and development in a number of fields. This would include new drugs, regenerative medicines and state-of-the-art medical technologies, remote medical treatment systems making full use of information and communications technologies, the use of manufacturing technologies to improve personal mobility for the elderly, and medical and nursing care robotics.

Although the growth strategy and the 4th Basic Plan declare a unified approach of industry, academia and government, this has according to the relevant ministries and our analysis, so far only been a wish at best. It has as of yet not been found to work well to generate new business in the life science-sector. In spite of heavy investments both by the government and industry, commercialization is lagging behind that of the United States and Europe. This is well illustrated by a report building on a survey of bio-industries.[6] The report shows that there was no increase in revenue of biotechnology-based companies between 2000 and 2009, which was around 1,220 billion Japanese Yen (110 billion SEK)[7]. A further example is that MEXT in the fiscal year of 2001 set up a target to establish 1,000 spin-off companies from academia by 2004, and organized supporting grants. The number of newly started companies reached the target in 2004 with about 35 percent of them in life sciences[8]. However, only a couple of new products had reached the market and most of the companies were in red figures.

Major reasons for this gap include the strict regulations and complex drug approval procedures in Japan compared to those in competing countries. The approving authority of new drugs and medical devices, MHLW, takes a conservative approach especially when it comes to innovative drugs or new therapies such as regenerative medicines (see further below for more details). When the drug discovery companies spun out from academia and reached the clinical development phase, they had to face disapprovals by MHLW and their business development halted. Hence, although MEXT invested heavily to support start-up companies from academia, the "exits" were closed by MHLW. MEXT and MHLW seem to have operated with their own agendas which has not created a good start-up climate.

The government has realized these problems and in 2011 opened the Medical Innovation Promotion Office, which reports directly to the Cabinet and invites officers from MEXT,

[5] *For a discussion on the ageing market, see "Tillväxtmöjligheter för Sverige på den japanska åldrande "silvermarknaden", WP/PM 2011:05 (In Swedish).*
[6] *The report is issued by Ministry of Education, Culture, Sports Science and Technology (MEXT), MHLW, Ministry of Economy, Trade and Industry (METI) and Ministry of Agriculture, Forestry and Fisheries (MAFF).*
[7] *Compilation by one of the authors (Hashimoto) on the survey of bio-industry by MEXT, MHLW, METI and MAFF 2000,2009 (available only in Japanese)*
[8] *"Academic Start-ups Survey 2011", National Institute of Science and Technology Policy (NISTEP), MEXT, March 2012 (available only in Japanese)*

METI and MHLW.[9] However the office did not get to a good start. In December 2011, the appointed chairman Prof. Yusuke Nakamura, a leading genomics researcher, in frustration over the lack of speed for clinical trial approvals in Japan, decided to move his research base to the University of Chicago. After incidences such as this, the Japanese government is considering further changes to the strategy to support clinical development in Japan. In February 2012 the government announced a five-year strategy for medical innovation [10]. The plan includes development of innovative drugs and medical devices applying state-of-the-art science as well as establishment of infrastructure in medical care systems across the borders of existing organizations and regulations. This is one example of what has become known as an "All Japan" operation. Interestingly, both the vice-chairman, Prof. Teruo Okano (who is already collaborating with Karolinska Institutet), and the new chairman Prof. Yoichiro Matsumoto, who also is vice president at the University of Tokyo, has expressed a direct interest to collaborate with Sweden[11].

2.2 Japans Fiscal Year 2012 research budget

The Japanese governments S&T budget for FY2012 is 3,669 billion Japanese yen (330 billion SEK)[12]. This represents an increase of 0.6 percent or 21.3 billion Japanese yen (1.92 billion SEK) over the 2011 budget and is the country's largest public S&T budget ever. To be noted is that supplemental budgets often are added, the size of which for this year is not yet determined. In the budget process for 2012, what is new is that the Council for Science and Technology Policy (CSTP), in line with the 4th Basic S&T plan, has grouped projects along prioritized policies. The three following areas are of relevance for the life sciences:

1. **"Action Plan":** Aims to advance strategic S&T missions to benefit the nation with clear target dates for commercialization of the results of research. Consistent with the 4th S&T Basic Plan (JFY2011-2015), the Action Plan established priorities in disaster recovery, green innovation, ***Life Innovation***, and promotion of basic research and research personnel. Under the theme of "Life Innovation", priority is given to five areas: "early diagnosis", "cancer, lifestyle-related diseases", "regenerative therapies", "excellent medical technologies" and "care and support" (for elderly). The total budget for the priority area of "Life Innovation" 2012 is 38. 9 billion Japanese yen (3.67 billion SEK).

2. **"Policy Package":** Programs identified by each ministry or agency as highly prioritized in advancing its mission. Among these, Ministry of Economy, Trade and Industry (METI), has a small program, "Translational Research from Basic to Clinical", of 400 million Japanese yen (36 million SEK).

3. **"National Base Programs":** "Core" S&T funding. A part of this consists of the so called "Grant-in-Aid for Scientific Research" (Kaken-hi in Japanese), which constitutes the curiosity-driven basic research funding. The funding amounts to 256,836 million Japanese yen (23 115 million SEK). Many of the grants will go to life science research.

[9] *Medical Innovation Promotion Office; (in Japanese) http://www.kantei.go.jp/jp/singi/iryou/secchi/index.html*
[10] *Meeting minutes of Medical Innovation Meeting, Feb. 15, 2012 (available only in Japanese)*
[11] *Growth Analysis was invited for a meeting with Prof. Matsumoto at the Medical Innovation Promotion Office in June, and a very fruitful exchange was had concerning exchange of knowledge on translational research, as well as discussions on concrete R&D exchange between Sweden and Japan.*
[12] *"Japanese Government S&T Budget Proposal for JFY2012", Tokyo Regional Office, National Science Foundation (March 8, 2012)*

2.3 Special Supplementary Budgets for the Reconstruction of the Tohoku Area

The economy in the Tohoku area was heavily damaged by the Earthquake in March, 2011 and the nuclear power plant accidents in Fukushima. The infrastructure of the region has still not recovered, the population keeps decreasing and many people are living in temporary apartments and they are unemployed. In order to help recovery of the region, the Japanese government has decided to give extensive special supplementary funding to support reconstruction and recovery programs. A few of the programs will be spent for Life Innovation by different ministries. METI invested 39 billion Japanese yen (3.5 billion SEK) to establish a new research center for drugs and medical devices by appointing Fukushima Medical University as a core unit. The plan is to invite industry to test their pharmaceutical products, medical devices and robots in the center. MEXT will fund research on assessment methods/technologies of long-term radioactive effects with the objective to commercialize some of the outputs of the research in two years. Details will be given in paragraph 3.5.

2.4 Ministries, Agencies and Organizations involved in Life Science Policies and Operations

In this subsection we list the relevant councils and ministries that are affecting the funding for life sciences.

2.4.1 Council for Science and Technology Policy (CSTP)

The Council for Science and Technology Policy - CSTP was established within the Cabinet Office in 2001 and aims to integrate efforts to advance science and technology. It is basically a "control tower" to coordinate activities and policies between ministries and agencies. CSTP is responsible for the formulation and execution of the S&T Basic Plan. From August 2012, the 4th S&T Basic Plan will start and major points in the new plan include (1) promoting health technology assessment and (2) regulatory science. We can expect more target-driven initiatives and funding programs to be implemented in the 4th Basic Plan. Actually, already in the third plan, a number of special initiatives were implemented to promote strategic basic research with the participation of industry (providing matching funds). Instruments of this kind will be implemented as part of the 4th Basic Plan. At present, there are far reaching discussions within the government on a reform of CSTP into a new control tower with even more robust functions and greater authority. The establishment of a stronger control tower is expected to assist with correcting the bureaucratic compartmentalization of individual ministries.[13]

2.4.2 Ministry of Education, Culture, Sports Science and Technology (MEXT)

MEXT plays a central role in the funding of basic and applied research in life sciences. Despite an overall severe economic situation in Japan, the total amount of research funding has increased during the last 10 years, with funding for basic research as a priority. This has paid off well and we now see many life science publications by Japanese researchers in top scientific journals. However, innovation from basic research is far from what was ex-

[13] *Advisory Council on Science, Technology and Innovation Policy Promotion, Cabinet Office, Report December 19, 2011.*

pected. MEXT has realized the problems and has, some years ago, started to fund programs that include industry partners, largely through its funding agency, the Japan Science and Technology Agency (JST). For Sweden-Japan collaborations in the area of the life sciences, JST has been running the "Multi-disciplinary bio"-project in collaboration with VINNOVA and The Swedish Foundation for Strategic Research (SSF). This project and the "Sweden-Japan Bio-Nano workshop", initially funded by MEXT, are perhaps the two life science-related projects in the last ten years that has best served to create a Swedish-Japanese research community in the area of life sciences.

2.4.3 Ministry of Health, Labour and Welfare (MHLW)

MHLW is responsible for the approval of drugs and medical devices as well as the health care reimbursement system. The ministry has been taking a conservative approach for the approval of new drugs. There is an average of four to five year time lag for the approval of drugs, and much longer for medical devices, compared to their first approval in major competing countries. The problems of drug and device lag have been highlighted by stakeholders such as patient groups. The current approval system is criticized as being a hindrance for innovation[14]. The total number of newly approved drugs and clinical trials in Japan has been declining over the years. The move of many foreign pharmaceutical companies from Japan to China has furthermore been a big shock to the Japanese government. Some changes have been implemented such as an increase in the number of reviewers at the Pharmaceuticals and Medical Devices Agency (PMDA), the implementation of a pre-consultation system and a fast track system in the drug approval procedures. A five year project to activate clinical trials in Japan has been initiated, which will be described in detail in chapter 4.2. However, it is still very difficult to get an approval to start clinical trials in Japan, especially for novel therapies. Therefore, start-up biotechnology companies and pharmaceutical companies start clinical studies outside of Japan in order to get the drugs or medical devices approved faster in the US or EU and then return to Japan. The government has slowly realized this problem and will start some programs to facilitate early clinical introduction of novel drugs/therapies to Japanese patients.

2.4.4 Ministry of Economy, Trade and Industry (METI)

The objective of the Ministry of Economy, Trade and Industry (METI) is basically to support the Japanese industrial competiveness. METI's funding agency, the New Energy and Industrial Technology Development Organization (NEDO), funds projects combining industry, government and academia in all industrially relevant areas. Approximately eight percent of the funds are invested in the life science area. Generally seen, the life sciences and health care areas are primarily covered by MHLW. However, METI, via NEDO, takes a proactive role in trying to bring research closer to industrialization in the areas of human genomics, regenerative medicine, micro-dose clinical trials (Phase 0) and medical devices. Most of the NEDO projects are organized with academic researchers as project leaders and invited industry members and governmental institutes, such as the Advanced Institute of Science and Technology (AIST), as participants. AIST has a life-science laboratory. The projects are fully funded by NEDO and industry will be funded for the project activities. However, whilst NEDO takes pride in their project management, industry representatives often mention time-consuming administrative procedures and unfavorable IP-policies, which reduce the attractiveness of the projects for industry.

[14] *Strategic Initiative "The way how the approval system of drugs and medical devices to be" CRDS, JST CRDS−FY2007-SP-15 (available only in Japanese)*

3 The Drug and Medical Device Approval System in Japan

In this section the drug and medical approval system in Japan will be described. Understanding the special situation in Japan concerning drug and medical device approvals is needed for a complete understanding of the problems and challenges of the innovation system for life sciences in Japan. Some aspects of the clinical research in Japan have also been treated in an earlier report.[15].

3.1 Drug Approval in Japan and its problems

MHLW is responsible for pharmaceutical regulatory affairs in Japan and has appointed PMDA to conduct consultations and review work from the preclinical stage to approvals and post-marketing surveillance. A pharmaceutical company, which wants to sell drugs in Japan, has to obtain both a marketing business license as well as a manufacturing business license besides the approval of the drugs.[16] The requirements for approval are much more stringent than those in the US (FDA) or EU (EMA). For example, PMDA requires that clinical studies are made with Japanese patients. Japan is a member country of International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Still, specific Japanese rules and requirements constitute invisible barriers for fast approval and introduction of new products. According to a report from the Japanese Pharmaceutical Manufacturers Association (JPMA) [17], among 121 new drugs approved between 2002 and 2007 in Japan, 90 had been approved earlier in the US and 92 in the EU. Between 2002 and 2007, the number of new drugs in pipeline increased by 38 percent in the US, 26 percent in France, 24 percent in Germany and 22 per cent in the UK. During the same period the corresponding figure was -1 percent in Japan The report concludes that the introduction of a dynamic market structure is necessary to facilitate new drug development and thus improve the access to new drugs.

3.2 Drug price and the list of drugs approved for reimbursement

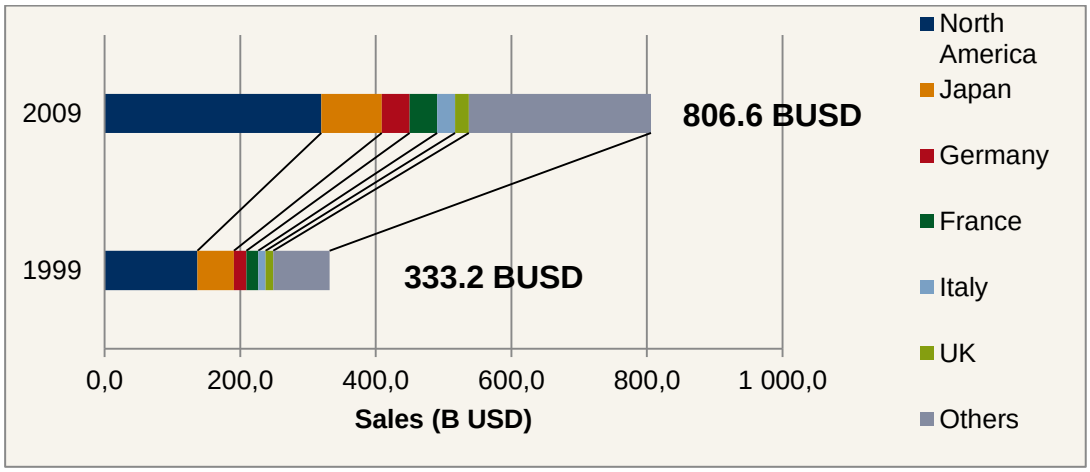
MHLW also decides the price of drugs after approval. The National Health Insurance (NHI) Drug Price List is a list of drugs for which medical providers can be reimbursed under the health insurance programs as specified in the regulations for hospitals and nursing homes covered by health insurances. The rules used to calculate treatment fees in accordance with the Health Insurance Law states that the reimbursement price of drugs for medical institutions is to be determined separately by the Minister of MHLW. As the Japanese society is ageing very rapidly and elderly require more medicines, the total medicare cost is increasing every year. MHLW revises the NHI drug prices every two year and in 2012, the drug prices will be cut by an average of 6 percent. Some companies are heavily affected by these cuts. While the global pharmaceutical market has increased from 333.2 billion US dollar in 1999 to 806.6 billion US dollar in 2009, the Japanese share of

[15] "*Testbeds in Health Care in the United States, Canada and Japan - Some examples", Svar direkt 2011:10, Growth Analysis Report.*

[16] *"Pharmaceutical Administration and Regulations in Japan" English Regulatory Information Task Force, JPMA (2009)*

[17] *"Access to new drugs and market dynamism" Research Paper Series No. 43, Office of Pharmaceutical Industry Research, Japan Pharmaceutical Manufacturing Association 2008 (available only in Japanese)*

the market has decreased from 16.11 to 11.1 percent. This may mean that Japan is losing its importance in the global market and that large pharmaceutical companies shift their focus to new emerging markets.



Fig, 1 Global Pharmaceutical Market Growth[18]

3.3 Double Standards in Clinical Research

Drug approval procedures must follow the requirements defined in the Pharmaceutical Affairs Law (PAL). If a new drug will be tested in humans, an approval for clinical studies must be obtained according to the regulation of the law. However, physicians are under the regulation of the "Medical Doctors Law", which allows the use of "unapproved drugs" under PAL within the hospitals if it is labeled as "clinical research". Therefore, novel drugs with new mechanisms or new technologies are often tested under the term "clinical research" in the university hospitals. However, this type of "clinical research" is said to have some problems. It does not require Good Clinical Practice - GCP. Without GCP, test protocols are not well reviewed and the quality of the results is not always satisfactory. The data will not be recognized as those of a real clinical study and the clinical study according to GCP will have to be repeated when an approval by PAL is sought.

The government has identified the problems in this double standard of clinical research, which is also a serious cause for the drug lag, i.e. requiring studies to be repeated. They have urged the change of Japanese GCP to be compliant with international standards ICH-GCP. Changes in the process of clinical studies are regarded as one of the most urgent issues in Life Innovation. In 2007, MEXT started a project called "Coordination, Support and Training Program for Translational Research" as a five-year program. The project will be expanded in the coming five years. This will be discussed further in chapter 4.3.2.

3.4 Medical Devices from abroad in high-tech Japan

The lag of the approval of medical devices is even longer than for pharmaceuticals. Though Japan is well-known for its electronics and high quality manufacturing, there are not many large Japanese companies in the medical device markets. In fact, Japan has a surplus in the imports of medical devices. Due to the tedious approval procedures, large Japanese companies have hesitated to enter the high-risk and time consuming domestic market of medical devices. In order to encourage Japanese companies, METI has intro-

[18] *modified from http://www.jpma.or.jp/about/issue/gratis/guide/guide11/11guide_07.html*

duced funding programs aiming to generate new industries around medical devices, elderly care and health care and to make them drivers for future growth. The plan includes (1) support for translational research in drug development and regenerative medicine and (2) development of medical devices. For the support of translational research, METI funds programs for technology development and commercialization of stem cell research. The programs help to develop advanced systems for large scale cell culture, quality control and cryopreservation of cells. METI will encourage the collaboration of medical experts and small and medium sized engineering companies that have expertise in manufacturing. METI also invests in the development of early diagnostic devices and treatment devices for cancer. METI's strategy is to establish clear guidelines for medical devices and to apply Product Liability (PL) but not PAL to minimize risks and costs of development.

4 New Governmental Strategies to Improve Translational Research and examples of Targeted Research Programs

The Japanese government has recognized the problems concerning the slow development of new drugs and medical devices. It has therefore introduced several supporting programs with the clear objective to bring the "products" to the market faster in order to stimulate industry and create new jobs. Below, several examples of programs related to the life sciences will be given, from basic research to clinical development of regenerative medicine funded by MEXT, METI and MHLW. At the end of the section, various life science-related projects are presented that are part of a special program to support reconstruction of the Tohoku area following the natural disaster in 2011.

4.1 Large-scale funding programs to basic research

4.1.1 World premier Research Initiative (WPI)

The Japan Society for the Promotion of Science (JSPS), a funding agency under MEXT, launched a program called World Premier International Research Center Initiative (WPI) in 2007 in a drive to build Japanese "globally visible" research centers to attract leading international researchers.[19] Six centers have to date been established. The centers are each given around 100-120 MSEK/year over a period of ten years. They are given a high degree of autonomy allowing them to virtually revolutionize conventional modes of research operation and administration in Japan. Two centers are in the field of the life sciences: The Institute for Integrated Cell- Material Science (iCeMS), Kyoto University and the Immunology Frontier Research Center (IFReC) at Osaka University. iCeMS contributes to the applications of stem cells (ES/iPS cells) in medicine and drug discovery as well as to next-generation innovations in environmental technology and industry. IFReC presently perform innovative research to unveil dynamic networks of immunity through interdisciplinary international collaborations. All of them have strong ambitions to bring their research forward to clinical and practical levels.

4.1.2 Funding Program for World-Leading Innovative R&D on Science and Technology (FIRST)

Following the allocation of a substantial supplementary budget in 2009, a large-scale research grant was launched directly under and awardees selected by CSTP. The grant was to be administrated by JSPS and the Japan Science and Technology Agency (JST). The grant was named "Funding Program for World-Leading Innovative R&D on Science and Technology" (FIRST)[20]. The aim of the FIRST program was "to advance leading-edge research and development that will strengthen Japan's international competitiveness while contributing to society and people's welfare through the application of its results". Initially the idea was to provide the 30 best researchers in Japan, all whom should be world-class or world-leading in their areas, with an overall grant of 270 billion Japanese yen (24.3 billion SEK) over 5 years. The original thought was that the researchers should

[19] *The JSPS WPI homepage (English) http://www.jsps.go.jp/english/e-toplevel/index.html*
[20] *The JSPS FIRST homepage (English) http://www.jsps.go.jp/english/e-first/index.html*

give up their other grants and fully focus on the themes provided through the FIRST-program. After long discussions concerning whether it was appropriate with such a huge top-down grant, the program was decreased to 150 billion Japanese yen (13.5 billion SEK), of which 60 billion Japanese yen (5.4 billion SEK) was to be used for young researchers, and 90 billion Japanese yen (8.1 billion SEK) for the top-level scientists. Finally, 30 top-leading scientists were awarded 3 billion Japanese yen (270 million SEK) each over a period 5 years. FIRST is in many ways a quite unique "winner-takes-it-all" program, giving already highly successful researchers substantial funding to allow them to excel further.[21].

Case study: A FIRST on Japanese Cell-sheet technology goes to Sweden

An excellent example from the FIRST program, which also illustrates the problems for clinical trials in Japan is that of Prof. Teruo Okano, Tokyo Women's Medical University (TWMU). Prof. Okano has developed a unique cell sheet technology for regenerative therapies. Since he could not start clinical trials in Japan with the cell sheets, he has instead chosen to collaborate with Karolinska Institutet to start clinical trials for the post-surgery treatment of esophageal cancer, as well as with the University Hospital in Lyon for other therapies. This is a typical case that illustrates that also advanced therapies of clear direct patient use, face serious difficulties in starting clinical studies in Japan. Interestingly, Prof. Okano is also the vice chair of the Cabinet Office Medical Innovation Office, which as mentioned above was launched in 2011 to better coordinate medical research and to improve the conditions for translational research in Japan.

4.2 Bridging between academia and industry

4.2.1 Creating a Japanese Model for the Regeneration of Japan by Science and Technology Innovation

MEXT will start a new program from FY 2012 to support seed technologies in academia with high risk, and high potential for commercialization, by providing funds as well as know-how from industry.[22] It is common in Japan that there is a lack of experienced professionals to bridge the gap between academia and industry. MEXT selects business "promoters" who have experience of starting businesses and have networks with venture capital and industry. Then MEXT invites applications from academia with seeds technologies. The "promoters" will act as mentors for research management and business development to the academic groups. MEXT has secured a budget of 1.3 billion Japanese yen (117 million SEK) for the first fiscal year to fund both business "promoters" and academic groups. This new program is based on lessons learned from past experiences of failures of start-up companies from academia. These usually cannot survive the "valley of death" without hands-on support by experienced business personnel. Approximately 30 percent of the companies spun-out from academic research are in the life science business

[21] Among the FIRST awardees, ten groups were life science related projects, which include, Prof. Yamanaka, Kyoto University, Prof. Okano, Tokyo Women's Medical University, Prof. Kataoka , University of Tokyo, Prof. Okano, Keio University, Prof. Nagai, Tokyo University, Dr. Tanaka, Shimadzu Corporation, Nobel Laureate 2002 in chemistry, Prof. Shirato, Hokkaido University, Prof. Kodama, Tokyo University, Prof. Kawai, Osaka University, Prof. Akira, Osaka University. Interestingly, among the 30 selected FIRST researchers, there are several who have had some research collaborations with Sweden.

[22] MEXT homepage (in Japanese): http://www.mext.go.jp/a_menu/kagaku/chiiki/daigaku/index.htm

sector. A large portion of the grants from the program is expected to go to life science projects.

4.2.2 Adaptable and Seamless Technology Transfer Program through Target-driven R&D (A-STEP)

JST has earlier had seven programs to support academic seeds technologies for commercialization. JST has recently reorganized the programs and in 2009 started a new, more comprehensive program, to streamline support technology transfer from academia to industry and product development. The new, interesting program is named A-STEP[23] and is often highlighted by JST. There are ten types of A-STEP supports depending on the development phase of the technologies. A-STEP consists of two stages, a feasibility study stage and a research and development stage. Researchers in academia and industry or innovation support organizations have to apply together for funding. The duration of the programs differ from two to seven years. In 2009, for the feasibility study stage, 14 percent of projects were related to drug development, and 23 percent were in medical technologies. One example of a project is the development of a disposable centrifugal blood pump. A new company has started to license out the patent that was obtained as a result of the project. As the global market of blood pumps is increasing, the project was evaluated positively.

4.2.3 Development of Systems and Technology for Advanced Measurement and Analysis

JST has furthermore a small, but interesting, program to promote the development of systems and technology for advanced measurements and analysis in order to meet frontier research needs.[24] The following three life science-related programs have been defined. Some of the programs include projects to develop medical devices and diagnostic devices.

1. *Technology Development Program for Advanced Measurement and Analysis (Program-T)*
   Development of a user-friendly four-tip scanning tunneling microscope with functionalized carbon-nanotube tips by Dr. Hasegawa, Tokyo University
   This project's objective is to provide a new tool for nanoscience and nanotechnology.

2. *System Development Program for Advanced Measurement and Analysis (Program-S)*
   Developing a new mass microscope system based on a ion-trap-time-of-flight, by Dr. Setou, Hamamatsu University. This instrument with high mass-resolution and accuracy will help to identify major components in tissue samples, which will lead to the discovery of new biomarkers.

3. *Prototype Validation/Practical Realization Program for Advanced Measurement and Analysis (Program-P)*
   High-speed three-dimensional tomography of the anterior eye, Dr. Kato, TOMEY Corporation. This tomography system provides a full 3-D numerical model for the eye

[23] *JST homepage for A-STEP (English): http://www.jst.go.jp/tt/EN/univ-ip/a-step.html*
[24] *JST homepage for projects for development of systems and technology for advanced measurements and analysis (English) http://www.jst.go.jp/sentan/en/*

that can be used for many kinds of clinical examination and intervention.

4.3 Support program for translational research

4.3.1 Coordination, Support and Training Program for Translational Research by MEXT

MEXT has been running an interesting project to support translational research on seed technologies in academia to bring them to clinical practice.[25] The first round of the project started in 2007 with a budget of 25 billion Japanese yen (2.25 billion SEK). MEXT selected seven organizations including the University of Tokyo, Kyoto University, Osaka University and started a supporting organization called the Foundation for Biomedical Research and Innovation (IBRI).[26] IBRI works as a project manager of this program with strong leadership to support and manage the seven organizations. IBRI is located in the city of Kobe. The first round of the project lasted for five years ending in March 2012.

The goal of the original program was to establish an academic platform to develop seed research to start two clinical studies. In the program, it was clearly stated that all clinical studies should be conducted according to GCP so that the results could be used for approval by PMDA. No "clinical research" was therefore allowed. IBRI played a role in educating the academic researchers on the requirements for clinical studies. IBRI also helped to manage the projects and in establishing an infrastructure to support intellectual properties, data management, regulatory requirements and networking, among the seven organizations.

With the success of the first round of the program, MEXT has decided to extend the program for another five years starting in 2012. The objective of the second round is to accelerate clinical development by adding one more center and to focus on cancer, Alzheimer disease, and metabolic diseases.

Case study: Osaka University Medical Center for Translational Research

Osaka University has developed a Medical Center for Translational Research in the Osaka University Hospital[27]. In the center, non-clinical studies under Good Laboratory Practice (GLP) and cell preparation compliant with Good Manufacturing Practice (GMP) can be performed. An organization to conduct clinical trials and to train the hospital staff was established. Researchers with potential technologies from Osaka University and the industry were invited to join the project. During the five-year period, two clinical trials sponsored by the industry have been run. Prof. Yoshiki Sawa, Cardiovascular Surgery, Graduate School of Medicine, has been working on a regenerative therapy to treat severe heart failure patients with the cell sheets of autologous cardiomyocites. 10 patients were treated and all have survived to date. Prof. Yoshiki Sawa will transfer the technology to a medical device company to start a clinical study in 2012. So far Osaka University has achieved 17 seeds developments, of which four were licensed to industry, two clinical studies and expanded the network to other universities.

[25] *MEXT home page (in Japanese) for project to support translational research on seed technologies* http://www.tr.mext.go.jp/

[26] *Foundation for Biomedical Research and Innovation home page (English)* http://www.ibri-kobe.org/english/index.html

[27] *Medical Center for Translational Research, English brochure: http://www.med.osaka-u.ac.jp/pub/hp-mctr/english/english.pdf*

4.3.2 5 year project to activate clinical trials

MHLW has also facilitated clinical trials since 2003 - starting with a four year program (2003-2006) followed by a five year program (2007- 2011). The project aimed to speed up the processes of clinical trials and reduce involved costs.

MHLW plans to start a new organization to support drug development in FY 2012. The organization will help screening academic seeds to hand them over to pharmaceutical companies. MHLW supports the establishment of databases on safety assessments of drug candidates. MHLW also helps developing adjuvants for vaccines, bio-banks that are the collection of cells and genes of rare diseases, through the National Institute of Biomedical Innovation (NIBIO). Hospitals that can conduct internationally compliant clinical studies will also be established.

4.4 A National Strategy for Regenerative Medicine

Since Prof. Shinya Yamanaka, Kyoto University published a paper that showed how to reprogram cell differentiation in 2006, the government has heavily supported research on induced Pluripotent Stem cells (iPS) and organized a number of funding programs to develop the research area of regenerative medicine focusing on such cells. Application of iPS cells have no ethical arguments while that of human embryonic stem (ES) cells have been suspended due to ethical problems in Japan.[28] As a part of the national strategy for growth, and as a show-case, the government will invest in a focused way on iPS cell research and have started a so-called "Highway Program to Realize Regenerative Medicine" from fiscal year 2012.

Case Study: Highway Program to Realize Regenerative Medicine

Three ministries, MEXT, METI and MHLW will collaborate to speed up the implementation of regenerative medicine and to support the creation of new industries. The collaboration consists of six projects. Project A (MHLW) seeks to screen research seeds that can go into clinical research in the next fiscal year. Project B (MEXT) will fund research on stem cells that can reach clinical research within 3 years. Project C (MEXT) is for research on iPS/ES cells that can reach clinical research in five to seven years. Project D and E (METI) is for the development of instruments necessary for the commercialization of regenerative medicine (cell evaluation, cell culture etc.). Project F (METI) supports the development of regenerative devices that enhance autologous cell regeneration *in vivo* based on the basic research on regeneration.

As an example, MEXT will invest 4.5 billion Japanese yen (405 million SEK) on research on iPS cells under the "ALL Japan" operation to streamline activities from basic research to clinical applications. Four centers will be supported: Prof. Yamanaka, Kyoto University, Prof. Okano, Keio University, Prof, Nakauchi, Tokyo University and Dr. Sasai, RIKEN. The theme of year 2012 is to study mechanisms using disease-specific iPS cells.

[28] *"Comments on handling human embryos" by CSTP 2004 (in Japanese) http://www8.cao.go.jp/cstp/tyousakai/life/haihu39/siryo5-1-1.pdf*

4.5 Reconstruction support to the Tohoku area

As mentioned in the introduction, following the natural disaster 2011 in the north-east Tohoku region of Japan, the Japanese government is currently investing heavily in reconstruction programs. Overall 90 trillion yen has been allocated for the reconstruction. Of this support, some will go into supporting existing or new research and industry in the Tohoku region

4.5.1 Tohoku Medical Mega Bank Plan

MEXT will invest 5.6 billion Japanese yen (504 million SEK) for "Innovation Creation in Science and Technology" in the Tohoku Area through collaborations between academia, industry and government**.** The ministry will start a project on epidemiology over three generations for healthy and disease populations. They will also analyze clinical samples with the consent of volunteers along with medical records. Tohoku University, one of the leading Japanese universities with many contacts to Sweden, will be a center of the study and collaborate with local hospitals. The plan includes the education of clinical research coordinators and bio-informaticians.

4.5.2 Development of Clusters in Fukushima for the Development of Medical Devices and Drugs

METI has budgeted 39 billion Japanese yen (3.51 billion SEK) as part of the Fukushima Reconstruction Supplement Budget. The ministry plans to create new biomedical clusters in the Fukushima prefecture, which has been suffering from both the tsunami and the accidents in the nuclear power plants. Setting Fukushima Medical University as a center, METI will start a cluster of drug development, collecting clinical samples and medical records. A new cancer treatment center will be started to develop and evaluate Boron Neutron Capture Therapy (BNCT). A new technology development center will be generated by developing robots to support surgery. Local engineering companies will be invited to participate. With these plans, the government wants to invite pharmaceutical companies, medical device companies, clinicians, and other industry to the Fukushima Prefecture and to reconstruct Fukushima to become a development center for novel drugs and devices.

5 Discussion

In order to increase Japan's competiveness and long-term economic growth, the government has devised a national strategy where one of the strategic pillars is "Life Innovation". Among other things this involves the fostering of industry growth to meet the demands for medicine, nursing care and other health-related services and job creation. Basically, Japan has had a number of strategies for growth. However, many of them have been just pertaining to one ministry or one business sector. What is new is the promotion of a comprehensive growth strategy. Furthermore, the external pressure based on Japan's loss in relative competiveness, as well as having a declining domestic market, has created a sense of urgency.

As has been described, three major ministries, MEXT, MHLW and METI are funding many projects aiming to bring academia, industry and government together to develop a new life science industry. Most of the programs are traditional in the sense of supporting industry academia collaborative research per se. However, some programs, such as the A-Step, are specifically trying to address the issue of "the Valley of Death", i.e. the period when a research idea shall be transferred to a viable and growing company. Each program, however, is organized independently by each ministry. Furthermore, as we have discussed, good potential seed technologies and results are often struggling to move forward to commercialization and there is a lack of coordination between ministries. The Center for Research and Development Strategy (CRDS) of JST issued a report already in 2008 arguing that a Headquarter of Life Innovation with a strong power to coordinate across the ministries is one component missing in the Japanese system[29]. Albeit this was indeed inaugurated in 2011, there are in our and others opinion, still many problems ahead before the Japanese life science innovation system will become effective in turning seeds from research into products.

Further challenges of the Japanese ecosystem for turning research into products within the life science-sector, apart from the compartmentalization of ministries and approval procedures, can be summarized in three points (see also Kneller[30]):

1) A lack of strong incentives in the academic system to bring ideas into products for the market.
2) A lack of human resources that can bridge academic research and business development (e.g. product development, application development, sales and marketing).
3) With some exceptions, there is, overall, no strong intention to be present on the global arena. This is even true for parts of the industrial life science sector.

Furthermore, when examining research programs, each program is well funded and looks very promising. However, during the implementation of programs, problems often seem to occur. In particular this is so when it comes to interfaces with industry and when projects move towards clinical trials.

[29] *Strategic Initiative "The way how the approval system of drugs and medical devices to be" CRDS, JST CRDS−FY2007-SP-15 (available only in Japanese*

[30] *Kneller, RW. 2007. "Bridging Islands: Venture Companies and the Future of Japanese and American Industry". Oxford U. Press. Prof. Kneller in particular analyzes life science innovation. Growth Analysis have also for other reports interviewed Kneller as well as invited Kneller as speaker to a EU-meeting under our coordination.*

The Japanese government has realized these problems and is gradually shifting the structure of the projects so that ministries collaborate in order to speed up the processes to bring the seed technologies to the market and the patients. This trend is clearly seen in the various funding programs presented in chapter three. The government has furthermore announced a five-year strategy for medical innovation. The objectives of the strategy are to increase the medicare business segment and to provide high quality healthcare to the Japanese people.

To achieve the objectives, the government intends to support the pharmaceutical and medical device industry to become world-competitive players and to establish infrastructure for the next generation of medicare including regenerative medicine and novel medical devices (present funding level of 152 billion Japanese Yen, 13.7 billion SEK). However, to be successful, drastic changes will most likely be required in academia, hospital, industry and regulatory systems across the borders of the ministries to create a new supporting organization to facilitate fast drug development from academia to hospitals. METI is trying some new initiatives in commercializing novel pharmaceuticals and medical devices. This however is currently within the main responsibilities of MHLW. At the same time, the ministries have recognized a lack of experienced human resources who can coordinate translational research projects. As mentioned, MEXT started a funding program to support "promotors" (described in 4.2.1) and to match them with academic research projects. This initiative could be of interest for Swedish actor as it is essential not only to fund research projects but also to educate "promotors" for taking ideas into commercial practice.

In our opinion, this study overall shows that the Japanese life science innovation system is less efficient than it appears on paper, i.e. in terms of actual outputs, number of products approved and the revenue generated from the projects. On the input side, basic research overall is reasonably well funded and there are several funding programs for top level research, e.g. the WPI-programs and FIRST to mention only two. These, and some other programs are clearly well focused and well-funded programs that will contribute both to basic research as well as to the generation and translation of results. If not in Japan, the results will be put to use elsewhere. Sweden can offer good environments for clinical development to Japanese top-level basic research.

As for Japan, the innovation system to bridge the academic research and the industry/hospital sectors (see also ref. 30) is not well functioning. Thus excellent Japanese life-science research often gets "lost in translation". As illustrated, a lack of experienced coordinators with industry background slows down the development processes. A conservative approval system discourages commitment of industry to join the translational research projects. We have seen many cases when the clinical trials had to be conducted outside Japan due to difficulties in getting approvals for trials in the country. Japan seems to have been trapped in "self-inflicted" regulations. For Sweden, a policy learning may be the importance of well-balanced policies and that the covering from upstream to downstream of development, is essential for medical innovation.