



Biomedical Innovation and the Future of the Pharmaceutical Industry in Japan

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What is Innovation?

Innovation is an ill-defined term, but there are several useful ways to describe the concept which complement each other; much of what we call innovation relates to incremental progress but from time to time true breakthroughs occur which change the way we think or treat a condition.

Such paradigm-changing contributions to science and breakthrough innovations are often characterised by the fact that the thinking behind them crosses disciplinary and/or functional boundaries – at Catenion we call this “Recombinant Innovation”. It is often driven by individuals who can see beyond the confines of their specialty and collaborative approaches across scientific disciplines, organisations and geographies.

The origin of all innovation lies with individual creativity, which especially in the biomedical field is often reinforced by “serendipity” or lucky accidents. Individuals depend on their colleagues and the organisations in which they work to stimulate their full creative potential and to provide the resources to turn ideas into products or services and make them accessible to society.

These organisations need to be managed in one way or another and how best to do it is a subject of intense debate. Why? Because there is an inherent paradox of managing R&D in both academe and industry: Too much freedom leads to grand ideas, not innovation; too much constraint kills creativity.

The Pharmaceutical Industry and Biomedical Innovation

Based on the rapid progress of molecular biology and the advent of new technologies allowing a better understanding and measurement of human body functions and disease, the pharmaceutical industry began to industrialise its approach to R&D in the nineties. It was thought that eg.: Functional Genomics would deliver many new targets related to diseases, that the new screening technologies would allow to rapidly identify molecules binding to these targets and that the remaining task would be to simply develop these molecules fast and efficiently into new medicines.

Unfortunately, reality did not match these expectations: Most of the new targets turned out to be worthless and our understanding of how diseases develop and can best be fought in many cases is still very limited. Worse, the managerial approach to



R&D in industry killed creativity, the number of new molecules launched every year declined and a majority of those actually launched have been in-licensed from the emerging biotech industry.

As a result, large companies were forced to consolidate and as of today, only Eli Lilly and Boehringer Ingelheim have maintained a position among the global top-fifteen companies without a major merger. In addition, over the last few years many companies such as GSK, Pfizer and Sanofi-Aventis have begun to diversify into other businesses such as OTC, generics, as well as into new drug formats, for instance monoclonal antibodies and siRNA.

Pharmaceutical managers have also re-discovered the old truth that in creativity-related activities, “small is beautiful” and diversity drives breakthrough innovation. New R&D operating models are being put in place and novel forms of funding innovation, sharing risk and collaborating with academe, biotech and other large pharmaceutical companies are being experimented with. The latest example is ViiV, the joint venture between GSK and Pfizer in the field of HIV/Aids.

Finally, there is a growing realisation that new technologies are enablers, but not the primary drivers of innovation. Segmentation of diseases and populations is an emerging reality not only within Oncology; this segmentation is driven by biomarkers, phenotypic markers and Personalised Medicine approaches. Combinations of existing treatments plus novel-novel combinations can help companies innovate within existing target space. As a result, a stronger linkage between clinical research and Discovery is key. At a time when target space coverage and chemical space become more and more crowded, the fastest and smartest clinical strategy will win!

The Economics of Pharmaceutical Innovation and Cost Control

Pharmaceutical innovation is very risky, it demands high investments and it takes a long time. Biomedical innovation cycles last easily around 25 to 30 years from the first idea in academe to large scale application in patients and the pharmaceutical R&D part of this cycle makes up about half. So there need to be incentives in place to reward companies for taking on the huge risk of pharmaceutical innovation.

What this means in practice is that you have to provide a substantial reward for the few truly innovative medicines that make it through to the market. The incentive system for pharmaceutical innovation in developed economies consists of three key elements: Patent protection for a determined period, a guaranteed (reimbursed) price and access by patients to the new medicines.

The problem is this: Who pays? We all want access to medical innovation but we would like somebody else to pay for it. This is understandable at the level of the

patient, most of whom simply cannot afford hundreds of thousands of dollars if they get seriously ill - and this is why we have health insurance. But it becomes a problem at the global level when we notice that the US has borne a disproportionate share of the global cost of innovation for the last decades; although less pronounced than for small molecules, this continues to be the case for the newer biologics medicines.

Put differently, there is a policy conflict when it comes to biomedical innovation: On the one hand, governments would like industry to invest, develop new medicines and make them available to the population at large; on the other hand, they have a need to control healthcare cost.

How have governments approached this conflict? In a nutshell, the US has provided generous incentives for innovation; it leads the world in biomedical science and has the most competitive pharmaceutical industry, but has seen its healthcare cost rise to unsustainable levels; at the other end of the continuum, France and to a lesser extent Germany have succeeded in controlling healthcare cost but have seen their pharmaceutical industries lose competitiveness.

In Catenion's view, only England has partly succeeded to reconcile both policy objectives of having a flourishing biomedical industry and controlling healthcare cost. It has done so through the judicious mix of industrial policy and free market elements, providing generous incentives for true breakthroughs but denying them for what a specially set-up institute called NICE finds to be not cost-effective. It should be noted that this view is not widely shared by pharmaceutical executives...but by health policy makers in other countries, especially Germany and the US.

Biomedical Innovation, Government Policies and the Pharmaceutical Industry in Japan

Japan beyond doubt has built one of the best healthcare systems of the world and spends rather less on it than most other nations. In the pharmaceutical sector this has been achieved by rigorous periodic price cuts including the most innovative medicines, thus dis-incentivising investment in high-risk potential breakthrough medicines. As a result, the pharmaceutical industry in Japan has missed the biologics revolution, has not been able to continue to fill its proud track record of innovation and has lost competitiveness at the global level.

The latest pricing & reimbursement reform goes in the right direction: It provides better incentives for innovation (a higher and stable price during the patent-protected period) and at the same time controls cost by a more determined effort to push generics at a lower price after patent expiry.

At Catenion we consider that this reform will need to be followed rather sooner than later by a second step. The key issue is that the new policy incentivises novelty, not medical usefulness. It provides essentially the same incentive, regardless whether a new medicine offers an additional treatment option to physicians in an area such as blood pressure control, where a large arsenal of medicines is already available or whether it significantly prolongs lives in a cancer indication for which few treatments have been available.

But the future of biomedical innovation and the pharmaceutical industry in Japan depends on more than a further reform of pharmaceutical pricing & reimbursement. Japan with its legacy of very successful industrial policies in areas such as cars, electronics and ship-building has curiously missed the biologics revolution. In Catenion's view this is a case of "better late than never" and we recommend considering an integrated approach to a national biomedical innovation strategy and policy.

Here are some of the major issues to be addressed by such a policy:

- Insufficient priority and funding for biomedical science & technology as compared to US
- Structure, culture and funding in academe not optimal for breakthrough innovation: Working groups in universities are often too small, only a few larger, programme-driven research institutes exist, eg.: RIKEN; academic culture is not sufficiently open towards interacting with business and risk-taking nor is it sufficiently attractive to foreigners; block grants dominate at the expense of innovation-fostering project grants and personality-based funding
- No significant late-stage biotech industry exists, despite well-established IP rights and plenty of seed-stage biotechs
- Financial Markets don't support development of biotech, no tradition and culture for venture capital
- Insufficient incentives exist for international pharmaceutical companies to perform R&D in Japan despite its excellent science base

Finally, what about the future perspectives of the Japanese pharmaceutical industry?

At first sight, Japan's major pharmaceutical companies present a rather strong picture: Collectively, they have a proven track record of inventing blockbusters, among them pravastatin, donepezil, aripiprazole and levofloxacin – to name but a few; they present strong balance sheets and many are shielded from stock market volatility and pressure through the controlling interest of a conglomerate or a family. Management has a long-term horizon which is well-suited to the requirements of an



R&D-based pharmaceutical business and to the outside observer it appears that Japanese managers as a whole seem less addicted to the latest management fad than some of their Western colleagues.

However, despite their successes and recent moves to globalise, culture and R&D operating model in many of the large Japanese pharmaceutical companies have a flavour of Big Pharma in the West ten to fifteen years ago.

At Catenion we have developed some general hypotheses for change for Japanese companies to establish competitiveness at the global level – obviously, these need to be discussed and adapted to the reality of each individual company:

1. Continue globalisation and consolidation but be careful to pay not more than warranted value for acquisitions
2. Build institutional partnerships with academe
3. Continue to diversify technology platforms, but put more focus on clinical applied research by building capabilities, partnering with university hospitals and investing more in translational research
4. Whatever the future Pricing & Reimbursement system in Japan, develop the innovation mix in the R&D pipeline towards more targeted and “useful” approaches rather than emphasising me-too’s and novelty
5. Improve on risk management by
 - Reviewing/diversifying the business mix
 - Partnering individual assets or programmes with biotechs, other pharma companies or Private Equity
 - Improving portfolio management system, tools and processes
6. Develop culture, organisation structure and governance by delegating more authority to Therapeutic Area management and project teams

In a nutshell, we would argue that the leading companies in Japan should consider a change in strategy and culture by shifting emphasis from raw science and technology to applied clinical research, as well as from M&A and managerial control to partnering and delegation.

We are convinced that if the country improves the external conditions in which the industry operates through a well thought-through biomedical innovation policy and if companies move fast in redesigning their innovation strategies and operating models, the future will be bright.