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Pharmaceutical R&D -
Opportunities for Asia?*

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The Changing Nature of Pharmaceutical R&D – Opportunities for Asia?

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Abstract

During the 1990's, the pharmaceutical R&D process has witnessed tremendous technological changes. The emergence of new tools like 'combinatorial chemistry', 'high throughput screening' and the in-creasing use of computer-aided *in silico* experiments has led to significant improvements of research efficiency. This paper discusses the economic impact of this trend. It is argued that the resulting radical improvements in R&D productivity have lowered the minimum efficient scale in pharmaceutical research. As a consequence, the main bottleneck in pharmaceutical research has shifted from the mechanical act of synthesising and screening a sufficient number of active compounds to scientific excellence. Empirical findings indicate that the latter can more easily be achieved in smaller, highly focused firms. Accordingly, the most efficient way to currently conduct pharmaceutical R&D may be a new 'division of labour' in research between small, highly specialised firms conducting research and large firms focusing on the development, testing, and marketing of new drugs. This reopens a 'window of opportunity' for Asian pharmaceutical firms who had lost out in the previous race to ever increasing size.

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I. Introduction

Over the last 15 years, the world pharmaceutical industry has witnessed a merger and acquisition (M&A) wave that was unprecedented in history. The rationale for this hectic deal making is the inherent volatility of profits in the pharmaceutical industry. Costs of R&D are enormous (currently ~ USD 500 million per new drug) and rising, while the risk of innovative failure is equally high. Since firms typically introduce just 1-3 major new medicines per year of which only very few become commercial blockbusters, size is seen as a cushion to ensure a more regular profitability.

Over the same period, however, under what is sometimes referred to as the 'biotechnological revolution', there has also been a wave of new, small entrants into the pharmaceutical industry. In this paper, we will argue that this is no passing fad, but evidence of new 'division of scientific labour' made possible by recent technological advance and breakthroughs in scientific understanding which opens up a 'window of opportunity' for Asian firms.

II. Some stylised facts on the pharmaceutical industry

More than in any other industry, commercial success in the pharmaceutical industry is determined by successful research and development (R&D) and subsequent marketing¹. The 'search space' for this R&D is virtually unlimited; a simple combinatorial exercise shows that there are potentially as many as ~ 10^{180} possible drugs and ~ 10^{18} potential drugs (cf. Nightingale 2000, p. 337). Since it is impossible to investigate every single of these compounds, the difficult task is to filter out and focus on those compounds that have the biggest commercial potential. Few drugs do, as only one in three ever recoups its development costs and a handful of blockbuster drugs account for the lion share of all profits². For example, LOSEC™, currently the world's top-selling drug, accounts for 67% of total revenues of ASTRA, one of the world's biggest pharmaceutical firms that has recently merged with Zeneca to become ASTRA-ZENECA.

In an ideal world, firms would know which drugs would be most profitable in the market place. They would exactly understand the causes and mechanisms of the respective disease and would then be able to design a compound that would precisely target these without any unpleasant side-effects. Unfortunately, the reality of drug discovery and development is very remote from this ideal.

In the real world of modern pharmaceutical research, firms have at best a vague idea about the ultimate commercial success of a new drug. Similarly, the causes and mechanisms of most diseases and the chemical and biological properties of most compounds are largely unknown. Developing a new drug is therefore largely a probabilistic process governed by trial and error. The process starts with the synthesis of a large number of active compounds, which are then screened for pharmacological effects. Those molecules that show promising effects are optimised and subjected to extensive toxicological trials. Compounds clearing this hurdle then undergo clinical trials and are finally registered with the respective authorities in all markets where the new drug is to be sold.

¹ The pharmaceutical industry has both the highest R&D/sales and marketing/sales ratio. While the former lies in the 10% to 20% interval, the latter one is even higher and estimates range between 15% and 30%.

² This phenomenon is not confined to the pharmaceutical industry. In the most comprehensive study to date, Scherer *et al.* (2000) find rewards from innovation to be highly skewed across a large number of industries. In fact, something like a 20-80 rule also seem to apply in this case, where 20% of the innovations account for 80% of the profits.

In the absence of adequate knowledge on the underlying causes and effects, this process is extremely wasteful. Out of 10,000 compounds that display promising pharmacological properties at an early research stage, only 1 arrives on the market as a marketable drug. Even among active compounds that have passed all initial hurdles and advanced to the pre-clinical trial stage (i.e. toxicological trials), the odds for success are still a mere 6 out of 100. With every hurdle that is cleared, the likelihood of success rises, as displayed in Table 1, but the probability of failure remains considerable until the very last stage. Hence, even the biggest pharmaceutical firms do not manage to create more than 1 to 3 major new drugs per year.

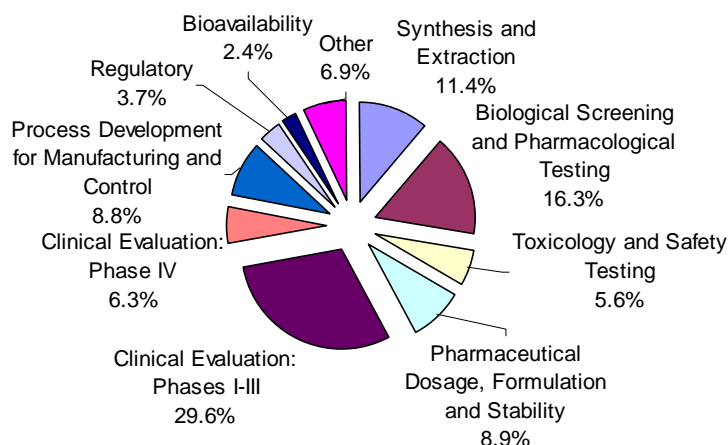
Table 1: Typical Survival Rate of Drugs Entering Trials

	Pre Clinical	Phase I (50-100 healthy volunteer)	Phase II (200-400 patients)	Phase III (3000+ patients)	Registration	Market
Survival Rate per 1000	1,000	480	220	71	61	60
Percentage to Market	6%	12.5%	27%	85%	97.5%	100%
Percentage to Next Phase	48%	46%	32%	87%	97.5%	

Source: Nightingale (2000).

While the probability of success rises with every stage of the R&D process, so do cumulative costs. Since development and testing costs the same for successful and unsuccessful drugs, resources spent on the latter are essentially wasted, but drive up the average costs of R&D per successful drug to a current USD 500 million. As can be seen from Figure 1, the lion share of these costs accrue in research, i.e. synthesis and screening (28%), and during clinical trials (36%).

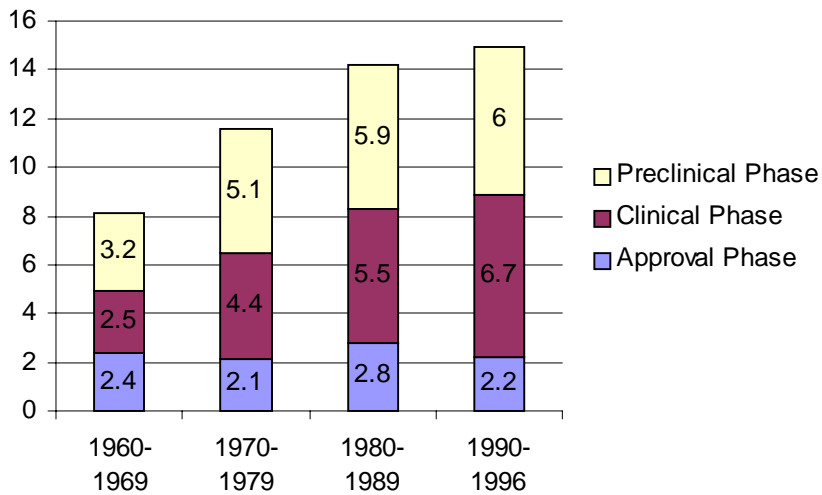
Figure 1: Breakdown of R&D Expenditures



Source: PhRMA (1998)

Average development costs have risen steeply over the past decades, as the average period required to discover and develop a new drug has almost doubled from around 8 to nearly 15 years between 1960 and 1996 (cf. Figure 2). Two reasons mainly account for this trend: First, pharmaceutical firms have to take on increasingly complex illnesses and drugs, as 'simpler' targets are largely exploited. Second, requirements on toxicological and clinical trials are rising since authorities are increasingly concerned about safety standards and minimizing side effects.

Figure 2: Average Period of R&D (1960-1996)



Source: PhRMA (1998)

Rising development periods are problematic for two reasons: Besides driving up R&D costs, which are mainly a function of time, they also reduce the time that a new drug is effectively protected by a patent. While the official patent term is 20 years from the filing of the patent application, lengthy development times reduce the effective patent protection to 11-12 years. Unlike other industries, patents are the predominant means to protect a new product from imitation in the pharmaceutical industry and have an enormous commercial value. For example, in the first year after the patent protection of ZANTAC™ – at that time the second best selling drug in world – expired in 1996, revenues plummeted by 26%. Since patents must be taken out at a fairly early stage of the R&D process, every additional day a new drug spends in the development is a day lost in terms of revenues under patent protection. The sums involved can be gigantic. For example, daily world-wide sales of BAYER'S best-selling anti-infective, CIPROFLORAXACIN, amount to around USD 2.5 million (cf. BAYER 1998, p. 61)!

Not all of the different stages of the pharmaceutical R&D process have evolved in the same manner, as Figure 2 also reveals. The clinical phase has almost tripled in length from the 1960s to the early 1990s, while the pre-clinical phase has grown nearly twice. Registration, however, was quicker in the early 1990s than during the 1960s. What are the factors responsible for these disparate dynamics?

III. Recent trends in pharmaceutical R&D

Success in the pharmaceutical industry depends on a firm's ability to reliably turn out new drugs, some of which may become multi-billion dollar block-busters. The more major new drugs a firm manages to bring on the market each year, the higher are its chances to score. Two complementary strategies lead to that aim: First, given the extremely low odds of finding a new major drug, a firm can increase the throughput of its R&D pipeline by raising the number of new compounds it can synthesise, screen, and test. Second, a firm can try to raise the odds by increasing the accuracy of its search. Technological advance and growth in scientific understanding has permitted breakthroughs along both lines over the last decade.

Research

Until quite recently, the search for new active compounds was a crafts-based, sequential process in which new molecules were either found in nature, i.e. plants, animals, or bacteria, or synthesised in the

laboratory. Since synthesis and screening were manual tasks, they were tedious, time-consuming, and inaccurate. Experiments could only be conducted on the 'beaker level' and were confined to the understanding of the bio-chemical properties of single molecules. Moreover, the outcome of experiments critically hinged on the manual aptitude and intuition of each individual researcher. Technological advance over the last decade has revolutionised this process by turning synthesis and screening into an automated, mass-production processes of parallel experimentation on populations complemented by computer simulations and *in silico* experiments:

Combinatorial chemistry allows to mass-produce countless, structurally related molecule variations through the parallel synthesis of combinations from any number of starting substances. With this new technology, it is possible to synthesise 50-75 new compounds *per day* instead of 20 to 25 new compounds *per year* with manual methods (BAYER 1998, p. 59).

High Throughput Screening (HTS) permits the parallel testing of a very large number of compounds in parallel at a micro scale by automated robots. This increased yearly throughput of a typical lead discovery group from about 75,000 samples tested on about 20 targets to over a million samples tested on over 100 targets (Houston/Banks 1997, pp. 734-35).

Rapid *improvements in computer technology* have turned computers into a crucial tool in pharmaceutical research. Innovations in database technology permit to store the vast amount of experimental data generated by population experiments. New statistical software enables researchers to analyse this wealth of information in more comprehensive ways. Finally, breakthroughs in visualisation technology along with gigantic increases in computing power help to accelerate the growth of scientific understanding.

The key to success in pharmaceutical research lies in the precise understanding of the relationship between chemical structure and biological activity. Over the past decades, theoretical progress in biochemistry and biomedicine has radically changed the way how these relationships can be explored. Advances in structural chemistry along with the aforementioned technological improvements in computer and visualisation technology allow to model and visualise in 3D the structure of molecules, proteins and genes, and simulate their interactions. This permits researchers to test and refine their implicit theories of why certain behaviour takes place. Moreover, if the simulations are accurate enough, they can be used to screen databases of compounds to pre-select promising compounds for further empirical testing.

Although initially hailed as cheaper substitutes for traditional 'wet' chemistry, *in silico* experiments have turned out rather to complement traditional methods. This is due to higher than expected computational cost and limited accuracy of such simulations as the complex quantum mechanical calculations overtax even the best available supercomputers and are prone to non-linear error growth.

Hence, despite a clear trend towards more fundamental science to increase the accuracy of the search for new drugs, current scientific understanding is still insufficient to produce new drugs in a completely 'rational' way. Although *computer aided molecular modelling* or *rational drug design* can help to narrow down the number of possible targets, it cannot completely eliminate all trial-and-error based experimentation. Indeed, after pursuing 'rational drug discovery' strategies, many pharmaceutical firms have returned to more 'random' methods as they realised that 'overly rational' approaches were in danger of producing very similar drugs with similar performance and hence limited commercial potential (Nightingale 2000, p. 334). Clearly, however, the more scientific understanding will advance, the more it will

shape drug development and scientific excellence will become ever more important in pharmaceutical research.

Development

The aim of pharmaceutical research is to discover as many compounds with promising pharmacological properties as possible. However, not all of these compounds can be turned into drugs, as there is rarely an effect without a side effect. Therefore, active compounds have to undergo extensive toxicological tests and clinical trials to determine whether they meet prevailing safety standards and whether they can be justified in a risk-benefit assessment of effects and side-effects.

Toxicology

Chemical compounds can produce scores of undesirable reactions in the human body that may range from outright poisoning to cell mutations and the deformation of embryos. Any of these must be avoided at any price by extensive toxicological testing. Toxicological tests fall into tests of acute toxicity, i.e. toxicity upon single administration, subacute toxicity, which is determined over a few-months period, chronic toxicity, i.e. carcinogenic and mutagenic effects, and reproductive toxicity.

Akin to the research stage, toxicological tests have also been massively affected by technological changes. Wherever possible, toxicological tests have been automated and many of the tests have become smaller in scale. Traditionally, toxicological tests invariably had to be carried out *in vivo*, i.e. on living animals. Thanks to innovations over the past decades, many of these can nowadays be conducted *in vitro*, i.e. in a test tube on cell cultures, bacteria, or isolated organs. For example, at BAYER, a German pharma giant, use of experimental animals has declined by over 70 percent over the past 25 years (BAYER 1998, p. 69).

Also, advances in scientific understanding help to increase the efficiency of toxicological tests, as certain toxicological properties can be determined *a priori* without extensive (and expensive) experiments. The earlier such disqualifying properties can be detected the better, since every additional day a drug spends in development raises cumulative costs.

However, cost-savings because of scientific progress in toxicology are only one side of the coin. As scientific knowledge in toxicology has increased over the years and more exact methods have been developed, so too have the obstacles that candidate drugs must overcome, especially with respect to carcinogenic, mutagenic and reproductive toxic properties. This and the growing international harmonisation of toxicological tests are driving up costs. For example, a study quoted in Schwarzer (1994) estimates that the introduction of 'Good Laboratory Practice' (GLP) guidelines has raised the costs of toxicological test series by 25% due to strict requirements on documentation and data handling. Overall, stricter regulatory requirements more than offset the cost-savings due to technological and scientific advance.

Clinical Trials

Active compounds that have cleared all toxicological hurdles move on to the clinical research stage, where they are tested for tolerance and efficacy on humans. Clinical trials are typically subdivided into four stages. In *phase I*, new active compounds are tested mainly for tolerance on 60-80 healthy volunteers. *Phase II* is devoted to efficacy assessment and tolerance testing on a limited number of patients (100 to 500), to determine whether the active compound takes effect as expected and whether it is also tolerated by patients. In *phase III*, the active compound is applied therapeutically on a larger groups of

patients (several hundreds to several thousands) under the same conditions as subsequent practical use to complete findings on efficacy, to answer special questions and to determine any rare side effects. Finally, during *phase IV*, after a new drug has been registered successfully, the drug continues to be supervised to collect and evaluate information on rare side effects, to quantify the therapeutical risk and to determine possible new areas of indication.

The costs of clinical trials are rising, which is illustrated by the following numbers (cf. Boston Consulting Group 1993, PhARMA 1998): Between 1980 and 1995, the number of trials required for registration rose from 30 to 68 trials per drug and the number of test people per trial climbed from 1,321 to 4,237 over the same period. Similarly, the number of medical procedures per test person rose from an average of 109 in 1992 to 161 in 1997. Three main reasons account for this trend: 1) Chronic diseases, which are increasingly targeted by pharmaceutical firms, necessarily require longer trials, 2) regulatory requirements grow, such as the request for demographic analyses of clinical data in the US, and 3) shrinking health budgets put pressure on pharmaceutical firms to demonstrate the cost-effectiveness of new drugs in an increasing number of countries.

Registration

Before a new drug can be marketed, it must be approved by the competent registration authority in each market. Registration is a costly and time consuming process, which requires considerable competence and know-how. This is partly due to the fact that registration procedures differ between different markets, although international harmonization is under way ('International Conference on Harmonization'). The other reason why the application process is very time consuming is the sheer size and complexity of such an application, as typically thousands of pages have to be filed to document the efficacy, contra-indication and side effects of the prospective drug. To successfully clear all administrative hurdles, a drug company not only has to meet all safety standards for its products, it also has to bring its manufacturing sites in line with certain regulations ('Good Manufacturing Practice'). Processing all this information takes more than two years on average (see Figure 2) which further adds to the costs of development. This is less because of the direct costs of registration, which are comparatively modest, but because every day lost in registration is a day lost of revenues under patent protection. And as has been mentioned above, in the case of a top-selling drug, these may amount to a few million dollars per day!

IV. Implications

The trends discussed in the preceding section have far-reaching consequences for the nature and organisation of the pharmaceutical R&D process. R&D in the pharmaceutical industry has always been an integrated process that could not be conducted profitably below a fairly high and rapidly rising minimum scale. Because of the inherent uncertainty of the R&D process, a large number of compounds had to be synthesised, screened, and so on. Since each of these steps had to be conducted by hand and output per researcher was more or less fixed, the only way to step up throughput was to increase the number of researchers which raised the minimum efficient scale.

Being big has a number of obvious advantages in the pharmaceutical industry, including the deep coffers required to shoulder the risk of R&D, the ability to reap economies of scale in distribution, and the market power that comes with size. With respect to research, however, size also carries a number of disadvantages. As stressed before, one key to successful innovation in pharmaceutical R&D is scientific excellence, which is more likely to thrive in smaller firms. Managing a larger number of employees requires more hierarchy and bureaucracy. However, a rising number of hierarchical tiers increases the distance between researchers working in the lab and R&D managers who decide about budgets and

general directions of R&D. This impedes communication between managers and researchers who may be better positioned to assess chances and risks (Mueller/Tilton 1969). As a consequence, large firms may be reluctant to develop radically new products.

It is a recurring pattern of empirical case studies on highly successful innovations that individual product champions had to struggle and fight for the necessary budget against massive resistance from management. Moreover, bigger firms are frequently plagued by the 'not invented here' syndrome, which impedes the adoption of external knowledge and inventions. Finally, large firms may quickly promote their most talented researchers to management and marketing positions, leaving the actual R&D work to less creative researchers (Scherer 1980). As a consequence, big firms may find it difficult to retain top talent that prefers to work in the less hierarchical and bureaucratic atmosphere of a small, research-oriented firm.

All of these reasons suggest that small firms may be more productive in pharmaceutical *research* than big firms. A study of 252 pharmaceutical firms worldwide, Mahlich (2001) supports this conjecture. He finds that small pharmaceutical firms with an average number of around 470 employees file five times more international patents and publish 12 times more scientific publications per year than their bigger rivals with an average size of approx. 7,400 employees.

The fact that sheer size is not necessarily beneficial in creative processes has been known for a while. However, given the limited output per researcher, pharmaceutical firms had not other choice but to opt for bigger laboratories to ensure an adequate output of new drugs. Because of the technological changes described above, however, this rationale no longer applies. By means of combinatorial chemistry and high throughput screening, a fairly small team of highly qualified researcher can produce a more than adequate number of active compounds. Hence, the main bottleneck in pharmaceutical research is no longer a sufficient input of new active compounds. Rather, the problem is to isolate and optimise these which have the biggest commercial potential, which critically hinges on superior scientific knowledge.

Scientific excellence, however, cannot be attained across the whole range of possible diseases and potential drugs. Rather, it requires specialisation on particular fields of expertise which appears to be organised most efficiently in fairly small, research oriented firms. This suggests that research and development no longer have to be organised in a fully integrated way. For example, in 1995, BAYER, one of the world's most admired pharmaceutical companies decided to split research and development into two separate, albeit collaborating organisational units. Accordingly, the most efficient way to currently conduct pharmaceutical R&D may be a new 'division of labour' in research between small, highly specialised firms conducting research and large firms focusing on the development, testing, and marketing of new drugs. This argument is developed in more detail in Arora/Gambardella (1994) who describe the changing nature of the knowledge base on which pharmaceutical companies draw. Recent scientific advances improve our understanding of how certain biological mechanisms work. Thus, the relevant knowledge base becomes more and more scientific, i.e. codified. This implies that knowledge can be 'assembled' piece by piece and is tradable via market transactions which in turn affects the market structure in that it will be no longer necessary for research intensive firms to possess and master all the downstream tasks necessary to bring a drug to the market. Instead, companies can make use of specialisation gains and economies of scope. Indeed, empirical evidence suggests that an increasing number of projects in the early research phase are contracted out by incumbent companies to young biotechnology start ups. Biotechnology firms succeed in supplying innovative activity, while the large enterprises, whose core competencies are in marketing and in coordination and organization of the R&D

networks, serve 'merely' as developer (Table 3). Again, the rationale for that trend lies in the new technological paradigm that makes the production process of new technologies more divisible. As Arora/Gambardella (1994, p. 528) put it: 'Boundaries between various sub-tasks can be more usefully drawn because the output from the different tasks can be represented in terms of abstract and universal categories, and hence be combined with each other.'

Table 3: Number of R&D agreements between incumbent and new biotechnology firms

		Originator		
		Big Pharma ¹⁾	Biotech ²⁾	Institutions ³⁾
Developer	Big Pharma	203	1761	32
	Biotech	51	509	666
	Institutions	1	19	8

¹⁾ **Big Pharma:** Firms founded before 1973, ²⁾ **Biotech:** Firms founded after 1973, ³⁾ **Institutions:** Research Centres and Universities.

Source: Orsenigo/Pammolli/Riccarboni (2000)

We can say that a 'window of opportunity' has opened for new, *small* firms to thrive in the pharmaceutical industry. Although a 'window of opportunity' is no guarantee for success, it at least reopens a door for Asian pharmaceutical firms which had more or less closed during the race to become ever bigger. In 1997, the biggest Asian pharmaceutical firm, Japan's Takeda, was only number 19 in the world. The relative small size of Asian pharmaceutical companies used to be a major obstacle to achieve success on the world markets since high fix costs were responsible for scale economies and market entry barriers. But the rules of the game have changed and size is no longer a prerequisite for an outstanding corporate performance. New players find access to the international markets and increasingly challenge established firms. This trend offers promising opportunities for Asian companies if they manage to plug into the international research network. Even if successful companies who come up with new discoveries are likely to be acquired by large multinational companies, the chances for Asian countries to upgrade in the pharmaceutical value chain have never been better than today.

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