

Biopharmaceutical innovation and industrial developments in South Korea, Singapore and Taiwan

Chee-Ruey Hsieh and Hans Löfgren

Abstract

South Korea, Singapore and Taiwan are well known as export-oriented developmental states which for decades employed industrial policy to target particular industries for government support. In the past fifteen years, these three countries all identified the biopharmaceutical industry as a strategic sector. This article explores, through economic analysis, the rationale for this decision and the strategies chosen for linking into the global bio-economy with the objective of catching up in biopharmaceuticals. The paper identifies three comparative advantages enjoyed by these countries in the biopharma sector: (1) public investments in basic research; (2) private investments in phase 1 clinical trials; and (3) a potentially significant contract research industry managing latter-stage clinical trials. Governments employ a range of industrial policies, consistent with these comparative advantages, to promote the biopharmaceutical industry, including public investment in biomedical hubs, research funding and research and development (R&D) tax credits. We argue that the most important feature of the biopharmaceutical industry in these countries is the dominant role of the public sector. That these countries have made progress in innovative capabilities is illustrated by input measures such as R&D expenditure as share of gross domestic product, number of patents granted and clinical trials, and volume of foreign direct investment. In contrast, output indicators such as approval of new chemical entities suggest that the process of catching up has only just commenced. Pharmaceutical innovation is at the stage of mainly generating inputs to integrated processes controlled by the globally incumbent firms.

Aust Health Rev 2009; 33(2): 245–257

What is known about the topic?

Many recent studies have shown that Asian countries, particularly China and India, but also other Asian nations such as South Korea, Singapore and Taiwan, are rapidly becoming important centres for biopharmaceutical research and manufacturing.

What does this paper add?

This paper provides an analysis of developments in the biopharmaceutical sector in South Korea, Singapore and Taiwan, including comparative advantages, industrial policy, current performance and future challenges. These countries are in the process of building substantial capabilities in innovation and production, but will not in the foreseeable future emerge as fully integrated competitors with established global companies.

What are the implications for practitioners?

Policy debates in developed economies on growth in the biopharmaceutical sector need to consider the dynamics and structure of the global industry. From an Australian perspective, South Korea, Singapore and Taiwan loom large as examples of countries which, in some respects, seem to have overtaken Australia in biopharmaceuticals. This article qualifies that impression while identifying opportunities and limitations of different strategies of linking into the global bio-economy.

SOUTH KOREA (henceforth Korea), Singapore and Taiwan — the “East Asian Tigers” — have achieved remarkable results in economic and social development. Real gross domestic product

Chee-Ruey Hsieh, PhD, Research Fellow
Institute of Economics, Academia Sinica, Taipei, Taiwan.

Hans Löfgren, PhD, Senior Lecturer, Politics and Policy Studies
School of International and Political Studies, Deakin University, Burwood, VIC.

Correspondence: Dr Hans Löfgren, School of International and Political Studies, Deakin University, 221 Burwood Highway, Burwood, VIC 3125.
hans.lofgren@deakin.edu.au

(GDP) per capita in Korea increased from US\$1110 in 1960 to US\$13 209 in 2005 (in 2000 US dollars). Life expectancy at birth in Korea increased from 54.2 to 77.6 years in the same period, and the economic and social trends in Singapore and Taiwan are similar.¹ Governments in these countries, from the 1960s, employed industrial policy to drive a continuous shift into more technologically sophisticated and higher value-added economic activities, and private firms were impelled to look to export markets. This story is described and theorised in the large volume of literature on the “developmental state”. Key elements of the developmental state model include public investments in education and infrastructure, targeted tax incentives and other forms of direct support for sectors identified as having high growth potential, state steering of credit allocations, land reform and relative social equality, and a business-friendly regulatory environment, combined with political authoritarianism enabling planning agencies to exercise a high degree of autonomy.²⁻⁶

More recently, governments in these three Asian countries (hereafter referred to as A3) identified the biopharmaceutical industry as a priority sector. The major players in this globalised industry are large companies supplying mainly chemistry-based drugs, but biotechnology, where smaller R&D-intensive firms are important, is its fastest growing segment.⁷ In recognition of fundamental changes in the science and technology which sustains the industry, we therefore use the term biopharmaceutical (or biopharma) in a broad sense (not to narrowly designate biotechnology-based drugs). There are also a range of other types of firms in the biopharma sector, many of which are linked as suppliers to the global companies. The dual role of this industry presents governments with exceptional challenges and dilemmas. First, the biopharma sector contributes directly to GDP and is often seen as critical to economic competitiveness in the 21st century, potentially sustaining another long wave of economic growth.⁸ Second, new drugs, vaccines and diagnostics are essential inputs to the production of good health. Economic policy tar-

geting the biopharma industry is therefore intertwined inextricably with health, social and ethical considerations.

Of course, governments in many countries, including Australia, have assigned a high priority to the life sciences as driver of industrial renewal.⁹ But we find in A3 a more explicit and ambitious focus on the biopharmaceutical sector than was ever the case in North America and Europe, where the potential of the life sciences became apparent more gradually in the 1980s and 1990s. Consistent with the developmental state experience, the emphasis in Korea, Singapore and Taiwan is determinedly on the economic dimension of developments in biopharmaceuticals. Limited attention has been paid to the safety hazards and ethical dilemmas, which in the most industrially developed countries have generated pervasive popular apprehensions.¹⁰ In the aftermath of the 2006 suspension of a high-profile Korean stem cell scientist, along with six other researchers, for fabricating data in studies published in *Science*, claimed as ground-breaking, a taskforce of scientists and public officials called for “a heightened awareness of ethical issues”. But it also committed “to spend \$454 million over the next 10 years in the hope of having Korea emerge as one of the top three global leaders in stem cell research”.¹¹

Mytelka and others have shown that the developmental state model, which sustained rapid growth in traditional and electronics-based manufacturing, is not well attuned to “new wave technologies”.¹² Yet aspects of the developmental state model seem to provide a good fit with the requirements of biopharma innovation and production. In particular, there is continuity in the pervasiveness of technocratic and de-politicised public policy; government agencies are deeply implicated in the life sciences and associated private sector entrepreneurialism. Indeed, this sector is everywhere characterised by a tendential fusion between science and technology, capital, and the state, and such linkages appear particularly strong in A3.⁹ Policies to foster biopharma innovation and other science-based technologies cannot however be effectively centralised to the emblematic nodal agencies of the developmental

states, such as Korea's Economic Planning Board or Singapore's Economic Development Board. Through such agencies, governments in the East Asian countries from the 1960s to the 1990s coordinated a process of incremental industrial upgrading through means such as the acquisition of technologies from abroad, which were then allocated or licensed to domestic firms.¹³ But it is well recognised that innovation and growth in biopharmaceuticals cannot be centrally coordinated through the tools of conventional industrial policy. Science-based sectors are characterised by a fragmentation of policy across a range of government agencies which interact with firms, universities and research establishments within horizontal and internationalised policy and innovation networks.^{12,14} (The focus here is on biopharma strategies and performance; we are not addressing the vexed question of whether the developmental state can be said more broadly to have been superseded in these countries.)

The priority assigned by government in A3 to biopharmaceuticals was given a boost by the exogenous shock of the SARS epidemic in 2003 and the avian influenza virus. Under the threat of new viruses, the development of drugs and vaccines becomes a matter of economic stability and national security.¹⁵ Countries without biopharmaceutical innovation and manufacturing capabilities risk not being able to access vaccines in case of a major pandemic. All in all, there is a strong set of economic, social and security imperatives for governments in the A3 countries, as elsewhere, to assign a high priority to the biopharmaceutical sector.

The purpose of this paper is to delineate key policy aspects of the development of innovative and industrial capacities in biopharmaceuticals in Korea, Singapore and Taiwan. We provide a basic economic analysis of the R&D process, and then proceed to identify the position and comparative advantages of firms in these countries within global production and innovation networks. The final sections compare industrial policies in the A3 countries and summarise performance and future challenges. We argue that Korea, Singapore and Taiwan pursue varieties of a strategy of

catching up in biopharmaceuticals through linking in with incumbent global leaders. It is a strategy based on state steering which draws on aspects of the model of the developmental state.

Catching up in science-based industries

Korea, Singapore and Taiwan relied, from the 1960s, on the export of manufactured goods, such as textiles and clothing, and later more complex components and products, as an engine of growth. In Korea and Taiwan, exports came to be underpinned increasingly by capabilities in electronics and information technology. The Korean *chaebol* conglomerates Samsung, Hyundai and LG are today global brands for products ranging from ships and cars to mobile phones and consumer electronics. Taiwan, a country with few natural resources, where small and medium-sized firms play a larger role than in Korea, is a leading exporter of products such as LCD panels and laptops. Industrial advancement in this country entailed a shift from exports of electronic components, so-called original equipment manufacturing (OEM), to products embodying original design and manufacturing (ODM) capabilities.¹⁶ The government of Singapore, an independent city-state since 1965 with very limited labour supply and no cheap land, has employed consistently interventionist measures to promote industrial upgrading and knowledge-intensive activities. In this pursuit, Singapore has promoted investments by foreign multinationals more strongly than Korea and Taiwan, where local markets and domestic firms play a greater role.³

These developments show that firms in some developing countries, notwithstanding initially low technological skills, were able to enter international markets in sophisticated manufactured goods. Upgrading and catching-up was achieved through the incremental accumulation of capabilities by way of borrowing and technology transfer, reverse engineering and learning-by-doing.¹² There are few examples of this trajectory outside East Asia, though in the 1980s and 1990s Indian firms built competitive capabilities in pharmaceu-

ticals manufacturing through reverse engineering.¹⁷

Governments in the A3 countries recognised early that manufacturing of textiles and mechanically-based goods, or even electronic products, would not sustain long-term growth in the face of wage competition from less developed economies and a new wave of science-based technologies. This provided the impetus for policies to drive a shift “from the industrial learning paradigm to the creativity paradigm”¹³ (p. 493) or, in a different turn of phrase, a focus on the building of a “system of innovation” rather than a “system of production”.¹² Catching up in science-based sectors is not “cumulative and path-dependent”, but requires a capacity to absorb and combine scientific and industrial knowledge from many domains. In response to these challenges, the A3 governments have decentralised industrial policies and now focus strongly on science and innovation, a shift captured in concepts such as the “techno-scientific state” or “competition state”.^{9,18}

The biopharma sector presents obstacles as well as opportunities in this context.^{19,20} Skeptics argue that the high costs and complex requirements of innovation in science-based industries mitigate against a policy focus on biopharmaceuticals.²¹ Indeed, few new drugs, and none of major commercial or therapeutic significance, have as yet emerged from developing or emerging economies.²² On the other hand, the fragmentation of pharmaceutical R&D across many firms and public sector organisations has opened up opportunities for firms in some emerging economies to link into global innovation networks.²³ The traditional model of the large vertically integrated big pharma company is weakening, not least as a consequence of falling R&D productivity — business investments in R&D have increased year by year but launches of new drugs have slowed to a trickle.²⁴ The response by incumbent firms has been to link in with small biotechnology and other science-intensive firms spun off from universities and public research institutes. In recent years, a high proportion of drug innovations have emerged from this sector.^{23,25} A few new biotechnology companies have

grown into fully integrated competitors (Amgen is a major case in point) but most have either been acquired by established firms (for example, Genentech is now fully owned by Roche) or operate as specialist suppliers. The global industry has become a web of alliances, strategic partnerships, joint ventures, and other forms of collaborative arrangements, between different types of firms, with big pharma companies as nodal points.²⁶ According to a Merck executive, this company in 2007 entered into 55 “partnerships” and more than 65% of revenue in that year was attributable to alliance products and patents.²⁷

The shift from vertically integrated firms to a more fragmented innovation and production process opens up outsourcing and other opportunities for firms outside the established industry centres of North America and Europe. This process is generally facilitated by the attributes of medicinal products. When drugs are under patent, they tend to have high value relative to weight, and transport costs are typically lower than in industries manufacturing bulkier products (though they may require temperature stability and other complex logistical arrangements). With distance to market not a major consideration in decisions on the location of R&D and manufacturing, firms in some developing and emerging economies may have growing opportunities in this industry.²¹

Competitive advantages in biopharmaceuticals

The R&D process for pharmaceuticals is lengthy and expensive. New entrants focus initially on particular stages of this process where they are competitively positioned to link in with incumbent global multinationals through collaborations and outsourcing. Many recent studies have shown that R&D and manufacturing activities are shifting from Europe and the United States to Asia, particularly China and India (now two of the world’s three largest producers of active pharmaceutical ingredients [APIs]) but also the A3 countries.²⁸⁻³⁰ The key issue for biopharma

industry policy in Korea, Singapore and Taiwan is the nature of the comparative advantages that firms in these countries enjoy, and what the prospects may be for moving beyond outsourcing to more autonomous growth. In this section, we explore these issues through an analysis of the economics and institutional features of R&D in this sector.

The R&D process can be broken up into two stages: upstream discovery research and downstream development. The discovery phase encompasses basic science research, and the application of research tools for the identification of new compounds with potential for development into new drugs. The development phase entails directly market-driven activities, including preclinical testing and clinical tests in three stages, to demonstrate the safety and efficacy of new compounds.³¹ Private firms lack incentives to invest in basic research because of its public-good nature; like other public goods, such as national defense, public funding is required for its provision. Compared with other industries, public investments thus account for a large proportion of R&D in the pharmaceutical industry.^{32,33}

Notwithstanding its public nature, basic research is not free, from the firm's perspective; dissemination of knowledge to the private sector can be costly and time consuming. Firms must invest in capabilities to access and absorb basic research findings through some in-house basic research and collaborative linkages with publicly funded researchers aimed at joint publishing of scientific papers. Cockburn and Henderson report that co-authorships of scientific papers are positively related to the firm's research productivity, as measured by number of important patents (those granted in at least two of the three major markets: the United States, Japan and the European Community).³⁴

Cockburn and Henderson argue that public and private investments are complementary, not substitutes, since private research is predominantly market oriented. Based on detailed case histories for 21 important drugs introduced between 1965 and 1992, they find that 14 were developed with input from the public sector. This

suggests that public research investments play a critical role in drug discovery and development, something which has long been recognised by policy makers in every country where pharmaceutical companies are headquartered. In the United States, public funding channeled through the National Institutes of Health, with an annual budget of around US\$30 billion, sustains a significant proportion of global basic biopharmaceutical research.³³

It follows from this reasoning that public basic research investments decrease the cost for private firms of acquiring knowledge for biopharma innovation. Such investments serve to expand the stock of knowledge used by applied researchers, and provide an incentive for private firms to increase spending on downstream product development. The A3 countries have a history of public investments in industrial infrastructure, and an established pattern of the public sector acting as leader in the creation of new industries, an experience which suggests a comparative advantage of Korea, Singapore and Taiwan in drug discovery research.

At the development stage, the comparative advantages possessed by firms in these countries depend partly on the relative productivity of small and large firms. Based on data obtained from over 900 firms in the United States for the period 1988–2000, Danzon et al find only a weak relationship between experience, measured by the number of compounds with which the firm was involved as an originator or licensee, and the prospects of success in phase 1 trials. Experience however did have a significantly positive effect on success in phase 2 and phase 3 trials.²⁵ In addition, they find that the number of alliances between small startup firms and large pharmaceutical companies has a significantly positive impact on R&D productivity. Products developed through an alliance have a higher probability of success in latter-stage trials. This suggests, perhaps unsurprisingly, that new firms, such as those in A3, have a comparative advantage in performing small and relatively simple phase 1 trials, but not in carrying out larger and more complex latter-stage clinical trials.

Although local firms are not well positioned to perform phase 2 and 3 trials, the A3 countries, which form part of a region with “very fast growth in global drug development activities”, are increasingly chosen for such trials by specialised international contract research organisations (CROs).³⁵ (p. 37) In a sample of more than 17 000 trials conducted by or for global pharmaceutical firms, the proportion outsourced to CROs increased from 7.7% in 1995 to 22.9% in 1999.³⁶ In general, large companies outsource more data- and labour-intensive functions, while keeping knowledge-intensive projects in-house.²³ Other things being equal, A3 could be expected to have a comparative advantage in CRO-operated clinical trials. In the following analysis, we explore the consistency of empirical biopharma developments in these countries with this conceptual schema.

Industrial policies

Private firms make R&D investments for the purpose of profits. Optimally, firms invest in R&D to the point at which marginal returns from the investment equal the marginal cost of capital. In general, marginal returns from R&D investments depend, in part, on market size, that is, population numbers with particular diseases and income levels. Countries with a large market could be expected to have advantages in inducing sufficient private downstream R&D in the biopharma sector without resorting to some form of government intervention.

In contrast, other things being equal, economic logic suggests that in countries with small markets, domestic demand will be an inadequate driver of private outlays on R&D, and such countries can be expected to be less attractive to foreign investors. Small countries are also more vulnerable to shortages in the event of emergencies such as pandemics, and for these reasons government intervention will be required to overcome the disadvantages of small market size. Following this reasoning, and consistent with empirical evidence, the major characteristic of biopharma innovation in A3 is the dominant role

of the public sector. Economists classify government initiatives to stimulate R&D into two categories: pull and push policies. Pull policies have an effect on demand for the final products, which in turn affects marginal return on investment. Push policies affect the marginal cost of funds to the firm of investments in R&D. Governments in these countries mainly rely on three types of push policies.

First, as we discuss below, there are substantial government investments in biomedical hubs and industry parks. The central components of Singapore’s National Biomedical Science Strategy, operated by the Agency for Science Technology and Research (A*STAR), are the Biopolis and the Tuas Biomedical Park. The Biopolis is a biomedical cluster encompassing seven large buildings, two dedicated to private firms and five to biomedical research institutes. Around 2000 scientists and other staff are located on this site and further expansion is planned over the next 15 years. Foreigners make up around 75% of PhD-level researchers at the Biopolis, a proportion expected to decrease as top local students, funded by the government to gain doctorates overseas, return to Singapore. In a different location, the Tuas Biomedical Park has attracted API and final formulation manufacturing by foreign multinationals such as Merck, GlaxoSmithKline, and Pfizer.¹⁰

Public investments in cluster developments of this type offer incentives for private firms such as reduced cost of land and knowledge acquisition through scale economies. In Singapore, investments in physical infrastructure are complemented by a determined effort to support R&D directly and provision of a supportive regulatory environment.³⁷ For example, in Singapore stem cells can be cultured from embryos for up to 14 days (though human cloning is not permitted). As the momentum for embryonic stem cell research in the United States partially stalled during the Bush administration, Singapore’s liberal regulation made the city–state an attractive location for research teams specialising in stem cells. Intellectual property legislation is consistent with United States and European standards and is enforced strongly.^{38,39}

I Global innovation in the biopharmaceutical industry: time trends

	Share of global pharmaceutical R&D		Share of US pharmaceutical patents		Share of Industry-sponsored global trials		Share of new chemical entities	
	1990	2004	1990	2002	2000	2006	1982–1992	1993–2003
USA	37.3%	36.5%	55.1%	57.2%	51.4%	45.2%	24.9%	34.9%
EU-15	39.8%	39.0%	24.6%	22.8%	32.2%	26.8%	47.7%	42.0%
Japan	16.2%	14.8%	15.3%	9.5%	0.0	2.7%	25.9%	20.2%
Other developed countries*	6.7%	8.0%	2.8%	6.5%	7.5%	7.2%	1.5%	2.9%
New Europe†	–	1.2%	–	–	–	–	–	–
Other emerging economies‡	–	0.6%	–	–	–	–	–	–
India and China	–	–	0.1%	1.5%	0.0	2.0%	–	–

Sources: Data in columns 2–7 are from Tables 1, 3 and 5 of Cockburn.⁴³ Data in columns 8–9 are from Exhibition 4 of Grabowski and Wang.²² * Australia, Canada, Iceland, Korea, Norway, Singapore and Switzerland. † Czech Republic, Hungary, Poland, Slovenia. ‡ Taiwan, Mexico and Turkey.

Following the same strategy, Taiwan and Korea have invested in several science and industry parks for the biopharmaceutical industry. Taiwan established a dedicated biotechnology “plaza” within the Nankang Software Park, which is close to institutes such as Academia Sinica and seven major medical centres in northern Taiwan. By the end of 2008, this site had attracted more than 50 mainly R&D-focused firms. At the same location, there are two incubation centres set up by the Genomics Research Center of Academia Sinica and the Ministry of Economic Affairs, which have contributed to the establishment of more than 20 small start-up firms specialising in biopharmaceuticals and medical devices.⁴⁰

Second, the governments in these countries subsidise the cost of capital through tax credits for R&D. In Taiwan, the government in 2007 enacted a law which provides a tax credit for up to 50% of the costs of R&D and personnel training. In Singapore, tax credits are provided not only for R&D investment but also for foreign direct investment (FDI). The city-state provides full corporate tax exemptions on qualifying profits for 5 to 10 years, depending on volume of investment and degree of technological sophisti-

cation. Foreign investments are central to its growth model; there is a strong focus on the provision of specialised infrastructure to attract foreign companies and the government generously funds public research institutes to recruit foreign star researchers.⁴¹ In Korea, a tax credit policy applies to FDI in several high-tech industries, including biopharmaceuticals.

Third, governments offer research grants to reduce private R&D costs and training grants to help biopharma firms access skilled labour. In Taiwan, the government offers several types of subsidies and grants for the development of new drugs as well as direct public investments in new start-up firms. Between 1995 and 2007, public funds contributed to the set-up of 36 private biopharmaceutical firms with the share of public funds ranging from 1% to 40%.⁴⁰

Current performance

In this section, we use five indicators to assess trends in biopharma innovation in the A3 countries. Four of these capture inputs to the innovation process: (1) R&D expenditure; (2) patents; (3) clinical trials, and (4) foreign direct invest-

2 Basic indicator of R&D investment and productivity in A3 countries

	Singapore	South Korea	Taiwan
GDP Share of R&D Expenditure in 2004 (%) ⁴⁴	2.25	2.85	2.52
Accumulated Number of US Patent in Bio-Medical Field, 1980–2001 ⁴⁵	63	757	810
Number of Clinical Trial Registrations, 2000–2008 ⁴⁶	502	1068	1295

ment. Patents are here considered inputs since most patents are not linked to new drug applications and rarely to products which receive marketing approval. For example, in the United States, only 8% of drugs for which an Investigational New Drug application is filed ultimately receive approval from the Food and Drug Administration (FDA).⁴² The fifth indicator captures outputs from the innovation process measured by new chemical entities (NCEs) approved by the regulatory agency.

The indicators of innovation shown in Box 1 demonstrate continuing concentration to the United States, the European Union and Japan. In the years around 2000, these regions accounted for more than 93% of global R&D expenditure, 95% of US pharmaceutical patents, and 97% of NCEs launched globally. However, this concentration declined slightly over time. Their low share in overall global innovation should also not distract from a trend for clinical trials to be increasingly located in the A3 countries. Between 2000 and 2008, 1295 drug trials were registered in Taiwan; Korea registered 1068 and Singapore 502 (Box 2). In 2007, Korea ranked third after Australia and Japan (excluding the US) in newly listed industry-funded drug trials conducted in the Asia–Pacific region.³⁵

Box 2 shows that the A3 countries spend around 2.5% of GDP on R&D, above the OECD (Organisation for Economic Co-operation and Development) average, and close to the level of many high income countries, such as the United States and Germany. This also compares favorably with Australia where R&D expenditure in 2006–2007 was 2.01% of GDP.⁴⁷ Although this aggregate figure does not provide information on R&D in particular sectors, it is an indicator of the commitment of A3 governments to capability

building in innovation, including the biopharma sector.

Patents are an important indicator of R&D success in the biomedical field. According to United States Patent and Trademark Office data, Taiwan obtained 810 US biomedical patents between 1980 and 2001, and Korea 757 in the same period. In contrast, Singapore obtained only 63 patents while spending roughly the same share of GDP on R&D as Taiwan and Korea. This does not necessarily suggest low R&D productivity, but that strategies for developing the biopharma sector in the A3 countries have different emphases. A plausible explanation is that Singapore’s reliance on FDI may not be as effective in strengthening domestic capabilities as, for example, Taiwan’s focus on investments in basic research and local infrastructure for research training. Singapore appears to pursue the traditional developmental state model in a way which may not be fully conducive to a culture of biopharma innovation. Finegold et al note that “the government appears to exercise strong, centralized control over most aspects of Singapore’s biomedical industry development”, which may cause a “stifling [of] alternative approaches and marginalizing [of] non-conforming groups”.⁴⁸ (p. 921) The entrepreneurial, risk-taking culture is said to be weak among researchers and managers in Singapore, home-grown biotechnology firms are rare, and very limited private sector venture capital is available for biomedical start-ups. A small number of big pharma companies, with predominantly manufacturing activities in Singapore, dominate the sector. In late 2006, the government’s biomedical strategy triggered a rare public conflict within the ruling elite. Lee Wei Ling, the head of the National Neuroscience Institute and the daughter of Singapore’s founding leader, Lee

Kuan Yew, openly criticised A*STAR and its head, Philip Yeo, for a lack of coherent focus and excessive dependence on imported star researchers. In early 2007 the government confirmed however that the National Biomedical Science Strategy will proceed as planned and approved funding for phase two of the Biopolis.^{10,39}

As noted, the A3 countries adopted similar strategies of building biomedical hubs to attract foreign investments, but comparable data are lacking. However, Singapore appears as the most attractive FDI location among the A3 countries. More than 10 global drug manufacturers have set up clinical trials coordination centres in Singapore, in addition to substantial manufacturing facilities, and several CROs have established facilities to conduct clinical trials management and central laboratory testing of patient tissue samples.⁴⁹

Only Korea of these three countries has reached the stage of achieving a new drug approval from the US FDA. In 2003, a Korean company, LG Life Sciences, received approval for FACTIVE (gemifloxacin), a novel quinolone antibacterial agent providing improved activity against gram-positive organisms, while retaining the gram-negative activity of ciprofloxacin.⁵⁰ This suggests that some firms in Korea are no longer engaged narrowly in the early stages of the drug discovery and development process, and this case has encouraged the Korean government to set as an objective the registration of one NCE per year. This would be a very good result for an emerging economy, but is well below outcomes in countries with established innovative capabilities. Grabowski and Wang show that France, Germany, Italy, Japan, Switzerland, the UK, and the United States introduced 848 NCEs between 1982 and 2003, on average 5.6 per country per year.²²

Future challenges

The A3 countries have made progress in the biopharmaceutical industries, but their contribution accounts for only a small share of global innovation. As new entrants, A3 firms still have a

long way to catch up with the global leaders. One of the challenges is managing tensions between health and industrial policy.

As emphasised, the biopharma industry depends on public support such as “push” policies to reduce the cost of capital for R&D. In contrast, governments in Korea, Singapore and Taiwan pay less attention to “pull” incentives affecting demand for final products.³³ A common argument against pull incentives is that pharmaceutical R&D is global and hence relatively unaffected by demand conditions in particular markets; policies aimed at increasing domestic demand are hence not likely to be effective as incentives for innovation. This argument may be valid to Singapore, but may have less applicability to Korea and Taiwan, where domestic demand accounts for a larger share of the potential market for new products.

Conceptually, pull incentives affect R&D investment in two ways. First, pull policies, such as high prices for patented drug products, can be expected to increase returns on R&D, which in turn increases the firm’s optimal level of investment in R&D. Pharmaceutical firms based in the United States on average spend 13–14% of sales revenue on R&D.²⁸ This suggests that a 10% increase in revenue should lead to an increase in R&D investment by about 1.3%. Second, an increase in expected return on R&D in turn increases profit margins, thereby positively affecting availability of internal funds for investment, as reflected in the marginal cost of capital to the firm. The cost of capital from internal funds may be lower than that of external funds, such as debt and equity. Of course, many real-life factors, such as R&D productivity issues, are not taken account of in this type of abstract economic reasoning. But the proposition is plausible (and much emphasised by the industry) that, other things being equal, there is a positive association between revenue and profitability conditions and the volume of private R&D undertaken. (Whether the resulting type of private R&D is also optimal from a health policy and broader social perspective is beyond the scope of this paper.)

Both Korea and Taiwan have introduced national health insurance (NHI) systems which include prescription drugs, and spending on pharmaceutical benefits (public insurance) account for more than one quarter of NHI expenditure.^{51,52} Singapore has a system of universal health care which differs from Korea and Taiwan in that public funding is relatively minor. (A system of medical saving accounts was established in 1984 with a public funding component, but more than two thirds of health costs are paid from private sources.) Pharmaceutical benefits expand the size of the market and hence provide positive pull incentives for pharmaceutical innovation, but public insurance also entails regulation of drug prices, which can generate negative incentives for innovation, as argued by the drug industry.³³ Whether the negative incentives resulting from price regulation dominate positive pull incentives from pharmaceutical benefits is an empirical question (often discussed in Australia over the years but never resolved satisfactorily). However, price regulation may discourage investments by global companies, even if the effect (in a small market) on profitability is marginal. This is because of direct and indirect linkages between drug prices in different countries; lower prices can have flow-on effects elsewhere. Thus governments in Korea and Taiwan face a policy dilemma in simultaneously pursuing health policy to achieve value-for-money outcomes and industrial policy to promote industrial development.

A feasible way of resolving the tension between health and industrial policy is to apply economic evaluation in the process of assessing products for inclusion in NHI systems. Since Australia pioneered mandatory cost-effectiveness analyses in 1993, economic evaluation has been adopted in more than ten countries as a tool for resource allocation in health care.⁵³ One of the benefits of economic evaluation is a shift from cost containment to assessments of the health outcomes of funding drugs, potentially achieving a balance between cost containment and innovation. Korea has announced a reform plan to formally adopt an economic evaluation to establish prices for

new drugs, while Taiwan remains at the stage of planning for economic evaluation.⁵¹

Conclusion

Korea and Taiwan, and Singapore to a lesser extent, have reformed traditional mechanisms of government steering of economic development to achieve a less centralised and more flexible response to the requirements of biopharmaceutical innovation. Yet the most important feature of this industry in the A3 countries is the dominant role of the public sector. This is a pattern which appears to conform to aspects of the developmental state model. The government acts as a leader in investments in infrastructure and upstream basic research while private firms operate as followers in downstream drug development.

Based on a conceptual analysis and empirical evidence, we suggest that these countries enjoy several comparative advantages in biopharmaceuticals: (1) public investments in basic research; (2) private investment in phase 1 clinical trials; and (3) favourable conditions for the CRO industry which manages latter-stage clinical trials. The government employs a range of industrial policies to promote industry growth, including investment in biomedical hubs, research grants and R&D tax credits, resulting in significant progress in innovative capabilities as indicated by input measures such as GDP share of R&D expenditure, patents, clinical trials, and the volume of FDI. By contrast, output indicators, notably NCE approvals, suggest uneven and limited progress. Clearly the A3 countries still have a long way to go before catching up with North America and Europe. Among the challenges is the tension between health policy that imposes price regulation and industrial policy promoting the biopharma industry as an engine of growth.

These findings have important policy implications. Biopharma innovation in developing and emerging economies has a different orientation than in the advanced countries where incumbent global firms are headquartered. As far as the latter are concerned, the launch of new drug (and vaccine and diagnostic) products is the key out-

come of the innovation process. In contrast, in the developing and emerging economies biopharma R&D and innovation serve as input to globally integrated processes, controlled by incumbent firms. This suggests that learning-by-doing, through alliances and outsourcing relations, in conjunction with public investments in R&D, to build innovative capabilities, must be the key strategy, at least in the circumstances prevailing in A3. It remains to be determined whether this strategy has the potential of enabling some firms in the A3 countries to actually catch up, or whether the structural features of the global industry mean that they are likely to essentially remain sub-contractors. The experiences of technologically and commercially advanced Indian drug companies are in this respect not encouraging,⁵⁴ though the overall higher level of industrial and social development in the A3 countries provides more favourable conditions.

Korea, Singapore and Taiwan all rely on the public sector as the driver of biopharma innovation but there are significant differences in strategies and R&D performance. Singapore emphasises a favourable business environment to attract FDI in R&D and manufacturing. Taiwan focuses on public investments in basic science for drug discovery and infrastructure for research training. Rather than focusing on selected stages of the drug discovery and development, public policy in Korea has sought a balance between the various stages of the innovation process. It will take more rigorous analysis to determine which strategies are more effective in terms of innovation, growth, economic competitiveness, and indeed, public health outcomes.

Competing interests

The authors declare that they have no competing interests.

References

- 1 World Bank. World development indicators, 2007. Available at: <http://www.worldbank.org/>

- 2 Weiss L. The myth of the powerless state: governing the economy in a global era. Cambridge: Polity Press, 1998.
- 3 Tsui-Auch LS. Bureaucratic rationality and nodal agency in a developmental state: the case of state-led biotechnology development in Singapore. *International Sociology* 2004; 19 (4): 451-77.
- 4 Radice H. The developmental state under global neoliberalism. *Third World Quarterly* 2008; 29 (6): 1153-74.
- 5 Amsden AH. Asia's next giant: South Korea and late industrialization. New York: Oxford University Press, 1989.
- 6 Wade R. Governing the market: economic theory and the role of government in East Asian industrialization. Princeton, NJ: Princeton University Press, 1990.
- 7 Ernst & Young. Beyond borders: global biotechnology report, 2007. Available at: [http://www.ey.com/Global/assets.nsf/International/Industry_Biotechnology_Beyond_Borders_2007_Full/\\$file/BeyondBorders2007.pdf](http://www.ey.com/Global/assets.nsf/International/Industry_Biotechnology_Beyond_Borders_2007_Full/$file/BeyondBorders2007.pdf)
- 8 Organisation for Economic Co-operation and Development. Biotechnology for sustainable growth and development. Paris: OECD, 2004.
- 9 Benner M, Löfgren H. The bio-economy and the competition state: transcending the dichotomy between coordinated and liberal market economies. *New Political Science* 2007; 29 (1): 77-95.
- 10 Löfgren H. Building the bio-economy: state steering and deliberation in biotechnology in Asia and Australia. In: Stranger M, editor. Human biotechnology and public trust: trends, perceptions and regulation. Hobart: Centre for Law and Genetics, 2007: 10-23.
- 11 Normile D. South Korea picks up the pieces. *Science* 2006; 312: 1298-9.
- 12 Mytelka LK. Divides and rules: the impact of new wave technologies on learning and innovation in the South. *Journal of International Development* 2006; 18: 861-76.
- 13 Wong J. From learning to creating: biotechnology and the postindustrial developmental state in Korea. *Journal of East Asian Studies* 2004; 4 (3): 491(27).
- 14 Wong J. Re-making the developmental state in Taiwan: the challenges of biotechnology. *International Political Science Review* 2005; 26 (2): 169-91.
- 15 Feldbaum H, Patel P, Sondorp E, Lee K. Global health and national security: the need for critical engagement. *Medicine, Conflict & Survival* 2006; 22 (3): 192-8.
- 16 Hobday M. East versus Southeast Asian innovation systems: comparing OEM- and TNC-led growth in

- electronics. In: Kim L, Nelson R, editors. *Technology, learning and innovation: experiences of newly industrializing economies*. New York: Cambridge University Press, 2000: 129-69.
- 17 Chaudhuri S. *The WTO and India's pharmaceuticals industry: patent protection, TRIPS, and developing countries*. New Delhi: Oxford University Press, 2005.
- 18 Uttam J. Korea's new techno-scientific state: mapping a strategic change in the 'developmental state'. *China Report* 2006; 42 (3): 257-68.
- 19 Cooke P. *Growth cultures: the global bioeconomy and its bioregions*. London: Routledge, 2007.
- 20 Dickins A. Vital issues and theoretical challenges: international political economy and the global bioeconomy. *GBRG Working Papers No 7*. Norwich: Global Biopolitics Research Group, University of East Anglia, 2006.
- 21 Sloan FA, Hsieh C-R. Conclusion and policy implications. In: Sloan FA, Hsieh C-R, editors. *Pharmaceutical innovation: incentives, competition, and cost-benefit analysis in international perspective*. New York: Cambridge University Press, 2007: 262-77.
- 22 Grabowski HG, Wang YR. The quantity and quality of worldwide new drug introductions, 1982-2003. *Health Affairs (Millwood)* 2006; 25 (2): 452-60.
- 23 Comanor WS. The economics of research and development in the pharmaceutical industry. In: Sloan FA, Hsieh C-R, editors. *Pharmaceutical innovation: incentives, competition, and cost-benefit analysis in international perspective*. Cambridge: Cambridge University Press, 2007: 54-72.
- 24 Garnier J-P. Rebuilding the R&D engine in big pharma. *Harvard Business Review* 2008; 86 (5): 68-76.
- 25 Danzon PM, Nicholson S, Pereira NS. Productivity in pharmaceutical-biotechnology R&D: the role of experience and alliances. *Journal of Health Economics* 2005; 24: 317-39.
- 26 Mitra J. Life Science Innovation and the restructuring of the pharmaceutical industry: mergers, acquisitions and strategic alliance behaviour of large firms. *Technology Analysis & Strategic Management* 2007; 19(3): 279-301.
- 27 Anonymous. Pharma firms for collaborations. *The Hindu* 2009; 3 February: 4.
- 28 Reinhardt UE. The pharmaceutical sector in health care. In: Sloan FA, Hsieh C-R, editors. *Pharmaceutical innovation: incentives, competition, and cost-benefit analysis in international perspective*. New York: Cambridge University Press, 2007: 25-53.
- 29 Frew SE, Kettler HE, Singer PA. The Indian and Chinese health biotechnology industries: potential champions of global health? *Health Affairs (Millwood)* 2008; 27 (4): 1029-41.
- 30 Roumeliotis G. India set to overtake Italy in API production: DrugResearcher.com 2006; 10 May. Available at: <http://www.drugresearcher.com/news/ng.asp?id=67610>
- 31 Congressional Budget Office. *Research and development in the pharmaceutical industry*. Washington, DC: 2006.
- 32 Murphy KM, Topel RH. The economic value of medical research. In: Murphy KM, Topel RH, editors. *Measuring the gains from medical research: an economic approach*. Chicago: University of Chicago Press, 2003: 41-73.
- 33 Sloan FA, Hsieh C-R. Effects of incentives on pharmaceutical innovation. In: Sloan FA, Kasper H, editors. *Incentives and choice in health care*. Cambridge, Mass: MIT Press, 2008: 227-62.
- 34 Cockburn IM, Henderson RM. Absorptive capacity, coauthoring behavior, and the organization of research in drug discovery. *Journal of Industrial Economics* 1998; 46 (2): 157-82.
- 35 Tsuei SE. The role of the Asia-Pacific region in global drug development strategy. *Drug Information Journal* 2009; 43 (1): 35-40.
- 36 Azoulay P. Capturing knowledge within and across firm boundaries: evidence from clinical development. *American Economics Review* 2004; 94 (5): 1591-612.
- 37 Agency for Science Technology and Research. *A*STAR Yearbook 2007/08*. Singapore, 2008. Available at: http://www.a-star.edu.sg/a_star/412-A-STAR-YEARBOOK-2007-2008
- 38 Yeoh K-C. Singapore's biomedical sciences landscape. *J Commer Biotechnol* 2007; 14 (2): 141-8.
- 39 Normile D. Biomedical research: an Asian Tiger's bold experiment. *Science* 2007; 316: 38-41.
- 40 Ministry of Economic Affairs. *Biotechnology industry in Taiwan [Chinese]*. Taipei: MOEA, 2008.
- 41 Walsh G. Biopharmaceutical benchmarks 2006. *Nature Biotechnology* 2006; 24: 769-76.
- 42 Philipson TJ, Sun E. Is the Food and Drug Administration safe and effective? *Journal of Economic Perspectives* 2008; 22 (1): 85-102.
- 43 Cockburn IM. Pharmaceuticals. In: Macher JT, Mowery DC, editors. *Innovation in global industries: US firms competing in a new world* Washington, DC: National Academies Press, 2008: 207-30.
- 44 National Science Council (Taiwan). *Indicators of science and technology*. Taipei: NSC, 2004.

- 45 Sun C-L. Innovation strategies of Taiwan's biotechnology industry [Chinese]. *Review of Taiwan Economics* 2003; 9 (2): 1-22.
- 46 US National Institutes of Health ClinicalTrials.gov, 2009. Available at: <http://clinicaltrials.gov>
- 47 Australian Bureau of Statistics. Research and experimental development, all sector summary, Australia, 2006-07. Canberra: ABS, 2008. (ABS Cat. No. 8112.0.)
- 48 Finegold D, Wong P-K, Cheah T-C. Adapting a foreign direct investment strategy to the knowledge economy: the case of Singapore's emerging biotechnology cluster. *European Planning Studies* 2004; 12 (7): 921-41.
- 49 Gin BS. A global biomedical sciences hub. *Drug Discovery Today* 2005; 10 (17): 1134-7.
- 50 Food and Drug Administration. Approval letter for NDA 21-158. Rockville, MD: FDA, 2003.
- 51 Yang BM, Bae EY, Kim J. Economic evaluation and pharmaceutical reimbursement reform in South Korea's national health insurance. *Health Affairs* 2008; 27 (1): 179-87.
- 52 Hsieh C-R. Pharmaceutical policy in Taiwan. In: Eggleston K, editor. Prescribing cultures and pharmaceutical policy in the Asia-Pacific. Brookings Institution Press, (forthcoming) 2009.
- 53 Drummond MF. Using economic evaluation in reimbursement decisions for health technologies: lessons from international experience. In: Sloan FA, Hsieh C-R, editors. Pharmaceutical innovation: incentives, competition, and cost-benefit analysis in international perspective. New York: Cambridge University Press, 2008: 215-25.
- 54 Löfgren H. India's drug multinationals: growth strategies and global industry dynamics. In: Löfgren H, Sarangi P, editors. The politics and culture of globalisation: India and Australia. New Delhi: Social Science Press, 2009: 181-98.

(Received 8/03/09, revised 19/03/09, accepted 19/03/09) □