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Globalisation and Regional Economies:
Can OECD Regions Complete in Global Industries?

PART II

Chapter 6

Regional Case Studies in the Biopharmaceuticals Sector[1]

This chapter looks at the evolution of the biopharmaceuticals industry and the impacts that changes in the structure of the industry are having on four regions specialised in drug production and/or biotechnology. In each case, the regions are struggling with the impact of restructuring of the global pharmaceuticals industry but also striving to build on the R&D strengths and innovative capacities that the regions have acquired over time as leaders in a dynamic technology-driven industry.

Global outlook

The pharmaceutical industry has enjoyed steady, and sometimes spectacular, growth since its modern form emerged in the early 20th century and is still one of the most profitable sectors of the world economy. Pharmaceuticals is one of the few branches of manufacturing that has seen growth in both output and employment within the OECD over the past ten years. Total global pharmaceutical sales grew 7% at constant exchange rates in 2005 to USD 602 billion according to the market intelligence company IMS. In the ten major markets, growth was 5.7% in 2005, compared with 7.2% the previous year. This group accounts for 81% of the total global pharmaceutical market, but emerging markets including China, Korea, Mexico, Russia and Turkey all experienced double-digit growth, outpacing global performance. This suggests that in the coming decade, these markets will receive increasing attention both as potential clients, but also, for some of them, as potential sources of competition (see the section on China and India below).

In 2003, total drug expenditure per person was highest in the United States (more than USD 700 per person), followed by France (just over USD 600), Canada and Italy (about USD 500); lowest in Mexico and Turkey (just over USD 100). Significant cross-country variations in spending levels exist also in terms of total health spending. In 2003, the United States spent USD 5 635 per person on health, more than twice the OECD average and around ten times more than Mexico and Turkey. The United States devoted 15% of its GDP to health spending, followed by Switzerland and Germany, at over 11%. At the other end of the scale, Korea and the Slovak Republic allocated a little less than 6% of their GDP to health. The OECD average in 2003 was 8.6%.

The industry is centred on a limited number of very large-selling drugs, so-called blockbuster products. The best-selling drug in 2005 as in 2004 was Pfizer's cholesterol-lowering drug Lipitor, worth over USD 11.36 billion. The number of blockbuster products (annual sales exceeding USD 1 billion) reached 94 in 2005 compared with 36 in 2000 and included 17 products reaching this level for the first time. While six blockbusters are expected to lose their patents in 2006, the launch of new products and continued growth of those already on the market will result in an increasing number of blockbusters over the next five years. Sales of generics in the top eight markets (United States, Canada, France, Germany, Italy, Spain, United Kingdom and Japan) exceeded USD 55 billion, and are expected to experience double-digit growth over the next five years.

Pharmaceuticals have helped to eradicate or render much less deadly an impressive series of diseases. But despite this continuing success, all is not well. Margins are being squeezed as major clients in both public and private health systems demand price reductions. The patents on many big money-earners are expiring, and the pipeline of new products is not being replenished as it once was. Public attitudes are increasingly negative, following well-publicised product withdrawals, price-fixing scandals and even accusations of "disease mongering", *i.e.*, the accusation that pharmaceutical companies exaggerate the

importance of certain conditions just to sell treatments (see, for example, the April 2006 issue of *PloS Medicine*: *http://collections.plos.org/diseasemongering-2006.php*).

The industry is reacting to these challenges in a number of ways, notably by rethinking business models and the innovation process.[2] Biotechnology is a key factor in this shift, both in itself and as part of the convergence with other innovative domains such as nanotechnology and informatics. However, its situation is paradoxical. Although biotechnology will gradually come to dominate the drug development process in the coming decades, the oft-predicted flood of new cures has not materialised, and many biotechnology firms are surviving only because they have sold important assets to bigger companies, while others will either disappear completely or lose their identity in mergers and acquisitions.

Innovation is at the heart of the pharmaceutical industry, and depends on carrying research through to profitable products. However, in recent years, the return on investment in pharmaceutical R&D has been falling due to a number of factors, including the increasing complexity of the molecules studied and the expense of complying with regulatory approval procedures. Estimates for bringing a new drug to the market range from USD 900 million to almost twice that. Biotechnologies can lower some of these costs and speed up processes, and are also changing relationships within the industry. Small firms can develop drug leads and then outlicense these leads to larger firms with the resources to take the drug through the following stages. The experience of large firms adds sufficient value to offset the costs of operating the alliance.

Many governments are seeking to encourage this process by supporting biotechnology clusters. As for the innovation process in general, no single model works across countries or regions, and the success of clusters varies both within and across countries. But the OECD does identify a number of factors that successful clusters share: a strong science base (universities, laboratories, and private firms), availability of finance (from private *and* public sectors), infrastructure, close physical proximity, networks, and an ability to attract a knowledgeable, skilled workforce.

Key drivers and trends

Consolidation and rationalisation of the pharmaceuticals industry

The structure of the pharmaceutical industry was fairly stable for most of the 20th century, seeing comparatively little of the concentration that characterised other major industrial sectors. However, by the late 1980s, overcapacity and the challenges posed by increasing globalisation put pressure on the industry to evolve towards a less fragmented structure and resulted in three waves of mergers. The first wave, in the late 1980s and early 1990s saw the emergence of Bristol-Myers Squibb and Smith-Kline Beecham. The second wave started in 1994 when American Home Products merged with Ayers and Wyeth, followed a year later by the creation of Glaxo Wellcome, Pharmacia and Upjohn, and Hoechst, while in 1996, Novartis was created from Ciba-Geigy and Sandoz. In 2000, Pfizer merged with Warner Lambert and then acquired Pharmacia in 2002.

According to Genetic Engineering News, the top ten pharmaceutical companies by market capitalisation are Pfizer (USD 193.57 billion), Johnson and Johnson (USD 171.53 billion), GlaxoSmithKline (USD 149.61 billion), Sanofi Aventis (USD 114.53 billion), Novartis (USD 111.37 billion), Merck (USD 76.44 billion), AstraZeneca (USD 73.36 billion), Abbott (USD 67.70 billion), Wyeth (USD 67.17 billion), and Eli Lilly

(USD 63.53 billion) (*Pharmalive.com*, 2006). Amgen heads the list of biotechnology firms (USD 93.09 billion) followed by Genentech (USD 89.53 billion), Gilead Sciences (USD 27.96 billion), Genzyme (USD 17.74 billion), and Biogen Idec (USD 15.94 billion). Amgen's market cap increased 28.4% from the previous year and Genentech's grew by 17%. It is worth noting that Amgen and Genentech have market capitalisations greater than five of the top ten traditional pharmaceutical companies. Despite the size of these companies, only Pfizer has a market share of over 10%, so pharmaceuticals still have some way to go to attain the levels of concentration seen in automobiles or computers, for instance.

One of the most significant deals in recent times was the February 2006 acquisition of Germany's fourth-largest generics manufacturer Betapharm by the Indian company Dr Reddy's. The sums quoted (EUR 480 million) are not huge compared with many deals in the pharmaceutical industry, but the other main bidder was also an Indian company, Ranbaxy, suggesting that in the generics market at least, new players are starting to challenge incumbents. The Indian and Chinese pharmaceutical industries are discussed in more detail below.

The number of large pharmaceutical firm-biotech alliances increased from 69 in 1993 to 502 in 2004, but the number of biotech-biotech alliances surpassed the number of pharmaceutical-biotechnology alliances according to figures released by Deloitte Touche, while for the top ten deals, most of the acquirers were other biotech companies (Deloitte, 2005). The type of technology involved in the alliances seems to be shifting away from genomics towards proteomics and bioinformatics.

The rationale behind all the alliances with and among biotech companies is clear. Biotech increases the range of drugs being developed and helps to make the development process itself more efficient. For large pharmaceutical companies, alliances with smaller biotech firms provide access to new products and specialist technologies (Arora, Fosfuri and Gambardella, 2001). Alliances among biotech firms enable specialist companies to achieve the synergies needed to develop new products and services; *i.e.*, to transfer technology or other resources across the value chain. This integration can also be geographic, helping to form clusters in innovation systems at local or national level. However, for some countries, participation in the international innovation system is more important than the national level, as shown by the number of alliances with US firms compared to national ones.

The impact that these alliances with and among biotech firms will have on future industry structure is not clear yet. At one extreme, the biotechnology firms could simply remain suppliers of specialist technologies, with the alliances providing the mechanism for technology transfer. At the other, alliances would only be a temporary phase, providing the funding and other resources the biotechnology firms need to become fully integrated pharmaceutical companies. Given the increasing share of drugs developed using biotechnologies in markets everywhere, it makes sense for biotech companies to strive towards the integrated company model. Counterbalancing this, many biotech companies lack the resources to develop an idea through the long, complicated and expensive process of getting a molecule to the market, so they may have to sacrifice autonomy to ensure longevity.

Biotechnology and the pharmaceuticals industry

The pharmaceutical industry is driven by innovation, and innovation depends on scientific research. In the years to come, this research will increasingly be based on the

biosciences, so the following sections outline some of the main fields expected to contribute the basic knowledge that may be transformed into new therapies at the outlet of the pipeline. (More details can be found in the annexes.) The anticipated benefits of biotechnology for the pharmaceutical industry can be summarised as follows (*Pharmacogenomics*, 2004).

- More powerful medicines. Pharmaceutical companies will be able to create drugs based on the proteins, enzymes, and RNA molecules associated with genes and diseases. This will facilitate drug discovery and allow drug makers to produce a therapy more targeted to specific diseases. This accuracy will maximise therapeutic effects and decrease damage to healthy cells.
- Better, safer drugs, the first time. Instead of the standard trial-and-error method of matching patients with the right drugs, doctors will be able to analyse a patient's genetic profile and prescribe the best available drug therapy from the beginning. This will take the guesswork out of finding the right drug and speed recovery time and increase safety as the likelihood of adverse reactions is eliminated.
- More accurate methods of determining appropriate drug dosages. Methods of basing dosages on weight and age will be replaced with dosages based on genetics, how well the body processes the medicine and the time it takes to metabolise it. This will maximise the therapy's value and decrease the likelihood of overdose.
- Advanced screening for disease. Knowing their genetic code will allow people to make adequate lifestyle and environmental changes at an early age to avoid or lessen the severity of a genetic disease. Likewise, advance knowledge of particular disease susceptibility will allow careful monitoring, and treatments can be introduced at the most appropriate stage.
- Better vaccines. Vaccines made of genetic material promise all the benefits of existing vaccines without all the risks; *i.e.*, activate the immune system but unable to cause infections. They will be inexpensive, stable, easy to store, and capable of being engineered to carry several strains of a pathogen at once.
- Improvements in the drug discovery and approval process. Pharmaceutical companies will be able to discover potential therapies more easily using genome targets. Previously failed drug candidates may be revived as they are matched with the niche population they serve. The drug approval process should be facilitated as trials are targeted for specific genetic population groups, providing greater degrees of success. The cost and risk of clinical trials will be reduced by targeting only those persons capable of responding to a drug.
- Decrease in the overall cost of healthcare. Decreases in the number of adverse drug reactions, the number of failed drug trials, the time it takes to get a drug approved, the length of time patients are on medication, the number of medications patients must take to find an effective therapy, the effects of a disease on the body (through early detection), and an increase in the range of possible drug targets could help cut the cost of healthcare. However, a certain number of barriers to progress will have to be overcome.

Biotech in the value chain: the links with large pharmaceutical firms

The pharmaceutical value chain comprises four large sections: basic research and candidate identification, clinical trials, regulatory approval, and manufacturing and commercialisation. Given the time scale, expense, and complexity of the entire chain, only

the large companies are involved at all stages. They are particularly strong in the last stages (Phase 3 trials, regulatory compliance, sales and marketing). Smaller companies, including almost all biotechnology firms, tend to focus on the early stages such as pure research or early phase trials.

Emerging trends in the collaboration between large pharmaceutical firms and smaller firms will reinforce this division of labour. The mid-2000s have witnessed an increase in deals targeting early stage compounds by large pharmaceutical firms seeking to fill pipelines, but conscious of the fact that the possibilities of acquiring late-stage products via collaboration and licensing deals is limited. The shift towards earlier-stage deals is reinforced by a reluctance to bear as much of the risk for later-stage deals as previously. A comparison of two deals, one from December 2005 and one from 2002 illustrates how things are changing (Anderegg, *et al.*, 2006). In the 2002 deal involving an insomnia compound, Pfizer paid Neurocrine USD 100 million upfront with an agreement to pay up to USD 300 million more in milestones[3] and royalties of 26% to 30%. Pfizer was also committed to funding any remaining development costs and was responsible for the remaining risk. In the 2005 deal involving an atherosclerosis compound, AstraZeneca paid only USD 50 million upfront, with USD 300 million in development milestones, USD 650 million in sales milestones and royalties of 15% to 35%. AtheroGenics has to fund the Phase 3 trials.

Although the division of labour mentioned above will continue, the coming decade is likely to see a drastic reduction in the number of "traditional" deals where large pharmaceutical firms buy and commercialises promising products in return for royalties and various other payments, while accepting most of the risk. The most likely development is that deals involving cost-sharing at all stages of the value chain become widespread, with profit-sharing based on the relative contributions of each partner. This could even extend to co-promotion; *i.e.*, the right to market the final product in a given country or territory. For smaller biotechnology firms, cost-sharing arrangements hold out the promise of much larger income than present licensing deals if the product is successful, and a chance to move up the value chain towards new activities. But it also implies much greater, and more speculative, investment in the early stages of product development; *i.e.*, at a time when a small company may not have the resources to maintain its part of the bargain. The risk is that the small biotech may have to sell valuable intellectual property or some other vital resource just to keep going.

There may be an argument for biotechnology firms to seek partners other than pharmaceutical companies, notably medical device companies. The idea would be to create synergies between the company producing a treatment and another one that develops an appropriate delivery technique. The practical benefits of such an approach seem clear, but investors are likely to remain wary of an alliance that seems to combine the worst of both worlds from their point of view: the long, uncertain development process of biopharmaceuticals plus the smaller returns associated with investments in medtech. For investors prepared to take risks, biotechnology firms specializing in discovery are likely to become more attractive in the coming years, especially given the increasing interest of large pharmaceutical firms in early stage compounds and discovery platforms.

The different segments in this industry can be viewed as independent sectors that share certain common features in that they are all linked to the healthcare sector to varying degrees. They can also be considered as a system in which values are created and

where new fields arise at the point of intersection. For example, there are links with agriculture, pulp and paper, and IT, which are perhaps best captured under the concept of bioeconomy.

Key challenges

Regulation

Pharmaceuticals is probably the most heavily-regulated industry in the world. Every stage of developing, manufacturing and marketing a drug has to obey strict rules; the doctors who prescribe the drug have to possess professional qualifications that take longer to obtain than any other; the pharmacist who supplies the product is subject to strict oversight; and even the patient who takes it has to obey certain rules to be reimbursed. Regulation has three main objectives: ensuring the safety of drugs, preserving the incentives for research and development and the flow of innovative drugs (mainly through protection of intellectual property rights – IPR), and controlling the quantity and quality of drug expenditures.

Safety and IPR regulations are unlikely to change significantly over the period considered here, but in the longer term, regulations for product approval will evolve. The one-off endorsement common at present may give a way to a continuous process where scientific advice is sought for successive stages of the authorisation process. If this approach proves successful, licensing authorities may implement the so-called "rolling dossier", whereby data are submitted on an ongoing basis during development, with the authority reserving the right to see all the data before issuing an approval. In a further stage, the current system of clinical trials may be replaced, or significantly modified, due to the impact of biotechnology-based development and drugs. For example, biotech may allow a number of safety questions to be answered sooner, or the extremely small target population may mean that practically every potential patient would have to take part in the trial to reach the numbers demanded in present-day protocols. In such cases, authorities may demand extensive post-approval testing.

In the short and medium term, price regulation by governments will influence the evolution of the pharmaceutical industry. The future of biotechnology-based pharmaceuticals will be affected by this too, of course, the more so since biotechnology is expected to change not only the type of treatment available, but also the role of health services in preventing disease rather than curing it.

Price regulation

When discussing price regulation, it is common to distinguish the market for non-reimbursed or over-the-counter medicines, for which the consumer pays the full price, the market for reimbursed, prescription, or "ethical" medicines, for which the demand is affected by health insurance and the market for pharmaceuticals purchased by hospitals. Mechanisms used to ensure cost-effective drug consumption include the use of co-payments, formularies, and controls on the prices paid for drugs, on prescribing physicians and on pharmacists (OECD, 2001).

1. Co-payments and reimbursement policies. The incentives for individuals to control their expenditure on drugs depend on the "co-payment"; *i.e.*, the percentage of the cost they pay themselves. This can depend on the drug, the individual (*e.g.*, the poor or chronically ill may pay less) or the level of the annual expenditure of that individual on

drugs or on healthcare (*i.e.*, the individual pays everything up to a certain threshold). When pharmaceutical purchases are covered by health insurance, the consumer is partially or fully insulated from the cost and therefore has a weakened incentive to trade-off cost and quality, to substitute other treatments or to forego treatment entirely.

2. Formularies. Nearly all health insurers maintain a list of drugs they will reimburse, the extent and conditions of that coverage, and any conditions on use or prescribing. This list is known as a formulary. Simple techniques, such as excluding from the formulary drugs that do not meet a cost-effectiveness threshold, can have a big impact on pharmaceutical consumption.
3. Price controls. Most health insurers also control the prices that they pay for drugs (or limit the price which will be reimbursed for a drug). These prices are set in different ways. Where the products in a therapeutic class are close substitutes, the prices of the drugs in that class are often set equal to the lowest price in that class. Where a drug has few close substitutes price-setting is more difficult. It is common to set prices based on international price comparisons of equivalent drugs. If almost all countries set prices on the basis of international comparisons, the importance of the price-setting policies in those countries which do not use international comparisons is magnified. A few countries fix prices on the basis of costs (also known as profit controls). These policies are also occasionally complemented with other industry-wide controls such as a limit on annual rate of increase, a broad freeze on prices or an enforced across-the-board price reduction. From a theoretical perspective, pharmaceutical prices should be set on the basis of cost-benefit analysis, also known as pharmaco-economic analysis. This analysis quantifies the beneficial effects of a drug (*e.g.*, fewer side-effects, fewer hospitalisations) and compares it with the cost. In principle, all those drugs (and other health inputs) with a benefit-to-price ratio above a given threshold should be accepted. Several countries have adopted a policy of using pharmaco-economic analysis to assess the quality of pharmaceutical and other healthcare spending. However, the price of a drug can vary considerably, even among OECD countries, leading to "parallel trade", where the drug is imported from a cheaper destination, rather than being bought in the country of use. This is discussed more fully below.
4. Controls on physicians and pharmacists. Most insurers control the prescribing practices of individual physicians, to ensure the most cost-effective treatment of patients. These controls typically take the form of prescribing guidelines or controls on who may prescribe certain medications. Some countries also impose nominal or explicit "budgets" on prescribing physicians or give a financial incentive to doctors who achieve a certain level of generic prescribing. In a few cases, the payment to the health care provider is fixed, giving strong incentives to economise on pharmaceutical use along with all other health inputs. The clearest example of this is the United Kingdom "GP Fundholder" programme under which the local doctor is given responsibility for purchasing healthcare services on behalf of a group of patients in return for a fixed per capita payment. Such schemes rely on competition between doctors to ensure incentives to maintain quality are retained. Many insurers also control the activities of pharmacists. Since pharmacists are typically compensated on the basis of a percentage margin on the products they sell, in the absence of explicit controls they have an incentive to increase rather than reduce the price of the medications they sell. Many countries allow, encourage or require substitution of cheaper bio-equivalent products. In some cases, pharmacists are allowed to keep some of the cost-savings from substituting cheaper

equivalent products. The costs of maintaining a retail distribution network are a substantial component of the total costs of pharmaceuticals. Where consumers are insured against the price of pharmaceuticals they have no incentive to shop for the cheapest pharmacy and competition between pharmacies cannot be relied upon to ensure efficient and effective delivery of pharmacy services. In these cases, it is necessary to regulate the margins of pharmacies.

Biogenerics

The patents on many leading therapeutic proteins (biologics) such as human growth hormone will expire over 2005-2010, theoretically opening up at least half of this USD 30 billion-a-year market to competition from biogenerics. Not all biologics would be replaced, but if experience with traditional compounds is repeated, biogenerics could take up to 15% of the market. (The nightmare scenario for patent-owning manufacturers would be a repeat of Prozac, where Eli Lilly lost almost 90% of its sales to a generic.)

The size of the market alone would seem to make it potentially attractive, the more so given the high cost of the patented products plus the fact that in the major market, the United States, recent changes in drug prescription rules for Medicare could lead to soaring demand for biologics, followed by political pressure to reduce the concomitant budgetary consequences. As of 1 January 2006, everyone with Medicare, regardless of income, health status, or prescription drug usage, will have access to prescription drug coverage, at an estimated cost to the federal government of around USD 700 billion over 2006-2015 (*Medical News Today*, 2006; see also *www.medicare.gov/medicarereform/drugbenefit.asp*).

A number of programmes to develop biogenerics have been reported over the past five years as the patent expiry date approaches. These often involve partnerships of North American and European companies with partners from other parts of the world (Polastro, 2001). The scientific and technical challenges are considerable, but the main obstacle may turn out to be regulatory. The European Medicines Agency EMEA published draft guidelines for four biogeneric products in the first quarter of 2006, with guidelines on quality and other issues to follow (EMEA, 2005), but in the United States, the FDA has made little progress in establishing an approval pathway. This may change over time due to financial pressures arising from the Medicare reform mentioned previously, but in the shorter term, the FDA may be forced to act as a result of a lawsuit brought by Sandoz regarding Omnitrope, a generic form of human growth hormone. Sandoz filed its application to the FDA in 2003, but the Agency said that although it could not identify any deficiencies in the application, it was unable to reach a decision because of scientific and legal uncertainties. Sandoz meanwhile launched Omnitrope in Australia (priced 25% below the non-generic form) and in January 2006 received a positive response from the EMEA (see *www.sandoz.com/site/en/company/media/news/detail/Omnitrope_20060127.shtml*).

Whatever the FDA decides regarding Omnitrope, the approval process for biogenerics will require much more data than traditional chemical generics because proving biosimilarity is more difficult and regulatory guidelines will have to be defined product by product, probably meaning also that abbreviated procedures similar to those used for conventional generics in the United States will not be developed (Ansell, 2006). Regulatory barriers will not be the only delay: companies marketing branded products will probably use legal means such as patent lawsuits to defend themselves from generics. These constraints lead some industry analysts to forecast that although biogenerics will start to

claim market share in the latter-half of the decade, they will not become fully established before the 2010s (*Datamonitor*, 2005).

The question also arises of who will actually produce the biogenerics. Generics manufacturers generally prefer low-risk strategies supplying dependable if unspectacular returns, and may in some cases even try to develop branded biologics given that the resources required are similar to those for a generic, but with better profit margins. Start-ups are unlikely to have the financial and other means to go far in this sector. Given the cost and complexity of developing and marketing biogenerics, established companies may prefer to concentrate on branded products, especially where the generics threat is distant. Where the threat is immediate, they are best-placed to take advantage of the new opportunities created. In the foreseeable future, therefore, generics are unlikely to threaten the profits of the major pharmaceutical companies, although they may have an impact on a certain number of products.

Cosmeceuticals and nutraceuticals

The pharmaceutical industry may suffer from a poor public image, but this has not prevented the expansion of the market for pharmaceutical products into non-medical applications, although it is probably more accurate to speak of products with implied pharmaceutical properties. Foremost among these are "cosmeceuticals", which, as their name implies, are cosmetics containing pharmaceutical-style components. Cosmeceuticals are applied like cosmetics, but claim to contain ingredients that act on the skin's biological functions. The US market alone was worth an estimated USD 12.4 billion in 2004, up 22% from 2000, and is projected to reach at least USD 16 billion by 2010 thanks to ageing baby boomers (Barrett, 2005).

Given this demographic influence, the most widely-used cosmeceuticals are "anti-ageing" products, notably retinoids, vitamin A (retinol) derivatives present in all living organisms, and hydroxy acids. Some studies claim that retinoids can partially reverse sun damage to skin, but the results quoted are generally from in vitro tests that can be criticised for being poorly constructed, so authorities such as the FDA generally find their utility in clinical situations marginal at best. Hydroxy acids are supposed to make the skin appear smoother through actions such as increasing the density of collagen, but once again, the scientific evidence is incomplete and controversial (Schwartz, *et al*., 2006). Some cosmeceuticals such as Botulinum A exotoxin (Botox) or the antimicrobials used in antidandruff shampoos do have demonstrable effects, but the vast majority of these products have so far failed to meet the standards of evidence-based scientific trials.

It is thus not surprising that licensing authorities do not recognise cosmeceuticals (or nutraceuticals) as a category, generally defining pharmaceuticals as non-food products that affect the structure of functions of the body for use in the prevention, diagnosis or treatment of disease, while cosmetics are considered simply as products for cleaning or beautifying the body. Some products correspond to both definitions so must meet the stricter requirements of drug approval, but many others are either in the grey area between the two or clearly have no pharmaceutical effect, although they may be manufactured by drug companies.

Nonetheless, pharmaceutical companies active in this sector can take advantage of existing know-how and resources to propose products and services without the costly risks associated with drug development. This trend is likely to be reinforced by mergers and

partnerships involving pharmaceutical companies and enterprises from other domains that exploit similar or complementary technologies; *e.g.*, plant biochemistry for the development of phytochemicals. Nutraceuticals, sometimes called "functional foods", fall into this category.

Counterfeiting

Most, if not all, types of drugs are susceptible to counterfeiting, and the counterfeiters are putting fakes on the market extremely rapidly. The US authorities have already intercepted so-called "generic Tamiflu" destined for China, following media reports of the outbreak of avian influenza (no such generic exists). The Internet contributes to the problem, the more so since many sites selling cheap drugs give the false impression that they are subject to strict control; but many sites require no prescription before sending drugs, and the customer has no real way of knowing where the drug came from and what it contains. The cases listed below give some idea of how widespread the problem is (Cockburn, *et al.*, 2005).

- One-third to one-half of packets of artesunate anti-malarial tablets bought in South-East Asia were fakes, containing no active ingredient at all.
- Almost 200 000 Chinese patients are reported to have died in 2001 from fake drugs, and in the same year Chinese authorities closed 1 300 factories while investigating 480 000 cases of counterfeit drugs worth USD 57 million.
- In North America, counterfeit atorvastatin, EPO, growth hormone, filgrastim, gemcitabine, and paclitaxel have been reported.
- Counterfeit Reductil, an obesity medication, has been found in Britain.
- The Colombian anti-drugs agency INVIMA confiscated 6 million doses of counterfeit Voltaren anti-inflammatory eye drops, representing more than the country's annual consumption.
- Nigeria threatened to ban the import of all drugs from India, a major supplier, because of the high prevalence of counterfeits amongst the imports.
- In Haiti, Nigeria, Bangladesh, India and Argentina, more than 500 patients, predominantly children, are known to have died from the use of the toxin diethylene glycol in the manufacture of fake paracetamol syrup.
- During the 1995 meningitis epidemic in Niger, the authorities received a donation of 88 000 Pasteur Merieux and SmithKline Beecham vaccines from neighbouring Nigeria. The drugs were found to be counterfeit, with no traces of active product. Some 60 000 people were inoculated with the fake vaccines.
- Counterfeit antiretrovirals used to combat AIDS were discovered in central Africa.

As mentioned in the introduction, it is hard to know the exact scale of the problem. Unofficial estimates quoted by the WHO for the percentage of the total pharmaceutical market represented by counterfeit drugs range from 1% to 50%, while the WHO's own estimate, like that of the FDA, is that 10% of all medicines sold world wide are counterfeit; *i.e.*, annual criminal sales worth over USD 35 billion (Forzely, 2006). This figure was challenged by Harvey Bale, president of the Pharmaceutical Security Institute, at a conference on intellectual property rights organised by the OECD (Bale, 2005). He argued that 85% of the world pharmaceutical market is in the developed world, where counterfeits are less than 0.2% of the market, so the incidence of counterfeiting in the remaining 15% would

have to be 66% to reach the 10% claim. However, the sources for some of the statistics he cites later include "some sampling", "guesstimates", "anecdotal" and "some survey work".

Whatever the actual sums involved, almost all stakeholders agree that the problem is growing, and that the market is being driven by many of the same trends affecting legitimate trade, such as globalisation of the supply chain and new technologies, in addition to specific causes such as weak regulation and enforcement. The damage to public health is direct and immediate if the drugs are ineffective or dangerous, and there are longer-term impacts too; *e.g.*, when diluted compounds facilitate the build-up of resistance. There is also the worry that the public will start to lose confidence in the pharmaceutical industry.

Parallel trade

Differences in national price control policies translate directly into price differences that can be substantial. A study by the US Department of Commerce's International Trade Administration estimates that aggregate pharmaceutical prices in 11 OECD countries are 18 to 67% less than US prices.[4] When extrapolated to a broader set of OECD countries, the loss to pharmaceutical companies on patented medicines is estimated at USD 18 to USD 27 billion annually. Given the share of R&D in company spending, this would mean an extra USD 5 to USD 8 billion a year for product development, on the simple assumption that the "extra" income would be distributed along the same lines as current budgets. The Department of Commerce argues that the additional cost of patented drugs could be offset by higher utilisation of generics, with savings estimated at USD 5 to USD 30 billion annually.[5]

The Internet and cheap communications, particularly mobile communications, have abolished the time and location constraints on many daily activities. Banking, shopping and entertainment, for example, are available to many OECD citizens, and an ever-increasing number elsewhere, when it suits them, rather than the traditional suppliers. Health services are one of the few domains where the client still has to adapt to the supplier, for obvious reasons. However, this too is bound to change, as a result of advances in technology and the spread of an attitude that might be summarised as "when I want it, where I want it, and at the best price possible if I have to pay". Drug sales are already carried out over the Internet, for example many US citizens take advantage of lower prices in Canada to order prescription drugs. Canada's Fraser Institute even claims that trade through Internet pharmacies has grown to such an extent that it is jeopardising Canadians' access to prescription drugs. The Institute quotes estimates that there are 278 cross-border Internet pharmacies in Canada whose annualised value of drug sales to the United States as of June 2005 was USD 507 million at manufacturer prices. This is down 18% from total sales of USD 618 million over the previous 12 months, but the final price charged to American consumers is probably higher than these figures and does not include cross-border sales through "brick-and-mortar" pharmacies (See the following link for a series of articles on the subject: *www.fraserinstitute.ca/pharmaceuticalpolicy/index.asp?snav=pa*).

Differences in policies regarding price controls lead to differences in the wholesale prices of pharmaceuticals across different countries. This, in turn, encourages international trade in pharmaceuticals, known as parallel trade, generally justified by one or more of the following hypotheses:

- Cross-country effect: Parallel trade leads to price equalisation across countries – "arbitrage" leading to more efficient market operation.

- Destination country effect: Increased price competition in destination countries reduces overall pharmaceutical prices, benefiting payers and patients.
- Aggregate welfare effects: If price competition is the result of parallel trade, then the resulting price convergence may lead to overall welfare improvements for payers.
- Patient benefits: Patient access to innovative medicines is improved, with lower direct and indirect costs.
- Industry impact: Parallel trade has minimal impact on the pharmaceutical industry as a whole, in terms of profitability and potential to innovate, and indeed, improves overall industry efficiency.

However, according to a study of parallel trade in the EU by the London School of Economics, no measurable direct benefits accrue to patients due to the structure of user charges, and patient access to medicines is unaffected (Kanavos, *et al.*, 2004). The vast majority of benefits from parallel trade accrue directly to parallel importers, where gross profits and revenues accrue over time in line with higher penetration rates. Taking the same sample of products across all study countries suggests that parallel imports for 2002 sales to the six major destination countries accounted for only 0.3 to 2% of national medicine budgets, representing a total saving of just EUR 44.7 million (or EUR 100 million if estimates for the clawback are included) over locally developed and manufactured products. The parallel importers who bought these same medicines from across the EU made profits of EUR 648 million. In the United Kingdom, for example, the NHS saved EUR 55.9 million (if the clawback is included), or 2.8% of the medicines budget from parallel imports in 2002, *versus* a mark-up of 49% and profits of EUR 469 million made by the parallel importers who sold these products.

Policy makers may be sensitive to arguments for restrictions on parallel trade, particularly in countries with an important research-based pharmaceutical industry. However, the savings to health systems, though small, are immediate and quantifiable, while the benefits of stopping the trade would be longer-term and uncertain.

Where the industry is going: from blockbusters to biotech

Before considering this, it is worth recalling the salient features of the model that dominates at present. The traditional business model for developing and marketing drugs features strong vertical integration from the laboratory to the point of sale in the hope of creating a blockbuster. In pharmaceuticals, only one compound in a thousand even makes it as far as the first stage of clinical trials; it takes over a decade for a new compound to reach the market as a drug; and an estimate based on data from 1983 to 2000 indicates that a typical new drug costs around USD 900 million to bring to market in a country such as the United States (Ki, 2003). Even this colossal sum may be an underestimate, with some analysts calculating a total almost twice as large (USD 1.7 billion) once indirect costs, costs of product launch, etc., are factored in (Gilbert, *et al.*, 2003). This analysis suggests that higher total cost, combined with lower average margins and shorter exclusivity periods, translates into returns on investment of only 5% for an average compound, which is significantly less than the risk-adjusted cost of capital for the industry, and that there is only a one-in-six chance of a new compound achieving a return on investment of 12% or more.

Increased costs and lower return on investment are due partly to the decline in R&D productivity in pharma. Pharmaceutical firms already invest a greater percentage of sales

in R&D than any other industry, but without a new model, costs will continue to rise. The high costs are due to three, interrelated factors (Danzon, *et al*., forthcoming):

1. High input costs for both drug discovery and drug development, including human clinical trials.
2. The various scientific and regulatory steps necessary are extremely time-consuming, taking 12 to 15 years.
3. High failure rates (for each new compound that is approved, roughly five enter human clinical trials and 250 enter preclinical testing).

Biotechnologies can lower some of these costs and speed up processes, and are also changing relationships within the industry. Small firms can develop drug leads and then outlicense these leads to larger firms with the resources to take the drug through the following stages. The experience of large firms adds sufficient value to offset the costs of operating the alliance (Nicholson, *et al*., forthcoming). The probability of success varies substantially across therapeutic categories but firms appear willing to undertake projects with lower probabilities of success in categories where the expected sales, if successful, are relatively large, consistent with a model of dynamic, competitive entry. Products developed in an alliance tend to have a higher probability of success, at least for the more complex Phase 2 and Phase 3 trials, particularly if the licensee is a large firm; *i.e*., there are economies of experience in these stages, but not for the simpler, Phase 1 trials.[6]

The overall cost of manufacturing and supply operations will grow further, owing to the increasing expense of regulatory compliance as well as the growing complexity of the molecules themselves. At the same time, health service providers are increasingly reluctant to pay the high prices demanded to recover investment costs, while patent challenges limit the total revenue potential of the average drug. The market data quoted above show that the blockbuster model is far from finished, with 94 blockbusters in 2005 compared with 36 in 2000 and 4 in 1992. Moreover, biotechnology is contributing blockbusters of its own: 17 according to one study of R&D productivity (CHA Reports, 2006). However, to remain viable in the long term, productivity will have to reverse the downward trend and improve to an extent that appears unlikely at present. Apart from supplying new drugs, biotech could provide a reprieve; *e.g*., improved preclinical toxicology screening could increase success rates and reduce expensive failures in the later stages of development, while automation of clinical trials could reduce time to market and total cost. Sales and marketing costs could probably be reduced too, but even if all the cost-saving measures prove successful, they are unlikely to assure the long-term viability of the blockbuster approach. None of the biotech-based drugs approved by the US FDA in 2005 were blockbusters (van Brunt, 2005).

High-tech high-cost industries such as computer manufacturing show that industries can change their business models successfully, and that the best source of inspiration is often small, relatively new firms. In pharmaceuticals, this essentially means biotech firms, and a number of pointers can be derived from their experience:

- Focus. Research in one area can sometimes produce results elsewhere, leading to unexpected and perhaps even spectacular success, as the case of Viagra shows. However, such windfalls are the exception, and the vast majority of drugs are created by companies with significant experience in the category concerned. Smaller companies have succeeded by focusing in a number of different ways; *e.g*., on specific biotechnologies or diseases. Moreover, generic drugs will increasingly compete with

today's blockbusters, so big companies may find that in the future it is more profitable to develop specialist treatments rather than "one size fits all" primary-care therapies. Marketing costs are also likely to be lower than those in the primaries markets, which require large sales forces and are likely to attract more competitors.

- Partnerships. Large pharmaceutical firms tend to do everything themselves, unlike Hollywood or the IT industry, whose successes are made by recruiting the best available talent, as and when needed, even if this means collaborating with companies who may be rivals elsewhere. For example, a company that makes a promising discovery in an area where it lacks experience could seek a partnership with a company with more experience in this area.
- Complete solutions. Once again, the computer industry provides a good example of how firms can grow by supplying various applications and services to exploit a core product. Although the actual drug itself will remain the biggest source of profit for some time to come, biotech offers the possibility to provide an integrated package of diagnostics and other complementary products and services to make the therapy more effective, so-called "personalised medicine".

Combining these different aspects into a business model that can exploit the potential of biotechnology will require a major reorganisation of company structures away from the traditional function-based approach (R&D, marketing, etc.) towards smaller units capable of moving flexibly to identify and exploit emerging opportunities.

Stockholm, Sweden

Introduction and basic data about the region

Stockholm is the capital of Sweden and located on its eastern coast. The city of Stockholm is part of the much larger Stockholm county. Together with five other counties, Uppsala, Södermanland, Västmanland and Örebro, Stockholm county forms the Mälardalen region, which is of principal importance to Sweden as its major economic engine. The region produced 39% of the GDP in 2002 and its growth is significantly higher than in the country as a whole. However, there are several ways of delimitating the region and for the purpose of this study data refers to the three counties of Uppsala, Stockholm and Södermanland. These data also correspond relatively well with a functional definition of the Stockholm region.

Stockholm county is, from a growth perspective, the strongest region in Sweden. Between 1995 and 2004 the average regional annual growth (GRP) was 5.5%. The accumulated growth for the same period was 63% compared to 44% on the national level. The rate for openly unemployed in the county of Stockholm was 4.2% at the end of 2005, compared to 5.6% for the whole country.

Several of Sweden's largest and most well-known universities, such as Karolinska Institute (KI), Stockholm University, Royal Institute of Technology (KTH), Uppsala University and Swedish University of Agricultural Sciences are situated in the Stockholm-Mälar region.

The region hosts a number of strong "clusters" in several sectors such as ICT, biopharma, financial services and logistics. These are dominated by a few firms, for example, Ericsson, Nokia and IBM in ICT, AstraZeneca, GE Healthcare and Pfizer in biopharma.

Formally, the County Administrative Board is the principal regional governing body representing the national government. Swedish municipalities are autonomous in relation to the national level and have their own elections every fourth year. The County is responsible for regional economic development while local government is providing public services and supporting local economic growth. Another separately-elected administrative body, the County Council, is responsible for healthcare, public transport and regional planning. Due to the allocation of public resources, the city of Stockholm is the most influential governing body in the county.

The biopharma sector in the Stockholm–Mälar region

The Swedish biotech industry is Europe's fourth-largest and the world's ninth-largest as regards the number of enterprises. In relation to the population, the pharmaceutical industry and medical technology industries are also very extensive. Sweden has great potential to continue to be one of the world's leading nations in applications and industries based on life science.

Sweden, and especially the Stockholm region, has a long tradition of internationally competitive life science research with effective collaboration between researchers at the universities, industry, authorities and the healthcare sector. The Swedish pharmaceutical and medical device industry has emerged as a result and has generated a number of globally competitive innovations such as the pacemaker, gastric ulcer drugs, diagnostic allergy tests and equipment for protein separation. Two major pharmaceutical companies have started in the region. One traditional strength in Sweden has been clinical testing. This comparative advantage has diminished over the last 15 years since the Swedish healthcare system has been decentralised.

In 2004, the sector employed approximately 45 000 people nationwide in 1 300 companies with an annual turnover of EUR 19 billion. The Stockholm region is the strongest region with an annual turnover of EUR 12 856 and 30 000 employees. This equals about 2.5% of the total number of employed in the Stockholm region in 2005. The region attracts several of the world's leading life science companies and there has been a significant increase in the number employed in the biotech sector, with an annual growth rate of 10% between 1995 and 2003 (Sweden Bio) and the annual turnover in the Stockholm region increased by approximately 8% between 2001 and 2004. The pharmaceutical industry is an important net exporter and has been the largest growth sector since the mid-1990s. The sector is small in absolute terms when it comes to number of employees but the sector is the fastest-growing as regards salaries and employment. Moreover, the sector is an important net exporter. Also in this context, the sector has, between 1997 and 2003 been one of the fastest-growing (in the region as well as in Sweden). Moreover, it should be noted that biotech is one of the only sectors within prioritised growth areas that has been growing.

The cluster contains all parts of the value chain and could be seen as coherent. To a large extent, the biotech companies in Uppsala focus on biotechnology-based tools for application in the pharmaceuticals industry or within diagnostics. Stockholm provides a strong group of companies across the drug development value chain and in early stage research, while Strängnäs, south of the region, puts more focus on drug manufacturing and production processes. On the other hand, the sector is dependent on a few large companies (AstraZeneca, Pfizer, GE Healthcare) which makes the sector vulnerable to changes in company strategy and localisation. Lack of financial resources and national priorities

concerning resources allocated for research might also be a problem, as well as the fact that the region may be too "research-driven" with too few production facilities. One result of this is that the demand for highly skilled human capital is strong. Companies both compete and co-operate in attracting skilled-personnel.

During the last decade, the life science sector has experienced several mergers and restructuring of major companies resulting in several spin-offs and new employment opportunities. In 1999, Sweden's largest pharma-company Astra merged with British Zeneca and formed AstraZeneca. The head office was moved to London, while the main R&D units remained in Sweden (Södertälje and Gothenburg). The new company expanded its operations in Sweden and the number of employees increased by nearly 40% between 1997 and 2003. Pharmacia went through a number of mergers and reorganisations during the 1990s which has contributed to the current dynamics of the sector. New companies have emerged and the total number of employees has increased by 19%. Pfizer are currently concentrating most of their Swedish operations, including applied research, in Strängnäs and decided in 2005 to further invest SEK 1.8 billion in the Strängnäs plant as it is to be given the status of a centre of excellence. An important decision both for the local economy and the life science sector nationwide since it was regarded as a proof of Sweden's high level of expertise in medicine and biotechnology research. As for the globalisation of R&D, the implications for the region will mean increasing pressure on the industry. AstraZeneca, for example, are outsourcing R&D as well as shutting down some production facilities. Moreover, young companies are bought by international firms and, thus, there is a risk – if the region does not provide the resources needed for developing the industries – that strategic activities would be relocated to other biotech hot beds. Therefore, it is immensely important that companies manage to keep strategic functions (HQs, R&D activities) in the region, since these activities make the firms more attached to the region.

Regional governance and strategies

The general business climate is important for cluster growth and development. These comprehensive conditions are to a great extent decided on the national level, for instance, tax policies and market regulation policies, but also issues such as investment in large infrastructure projects: motorways, railways or airports. Other policy areas on the national level relevant and important to clusters are of course industrial and regional policies.

Even more relevant for cluster development are national policies on education, research and development as well as innovation systems. In general, money is distributed via national programmes[7] and tender procedures in open competition.

The comprehensive regional planning of the facilities for economic development is the responsibility of the County Council and its expertise at the Office of Regional Planning and Urban Transportation. There is no single, unified economic development strategy for the entire Stockholm region. The fact that the region consist of several administrative units reflecting neither the Stockholm labour market area, covering two counties, nor the expanded Stockholm-Mälar region, covering five counties, leaves the governance structure somewhat complicated and fragmented and not well-adapted to the tasks and challenges it faces. The administrative borders do not match the functional borders with respect to, *e.g.*, labour markets and commuting; and the regional level does not have the authority to work with these issues since it lies within the jurisdiction of local municipalities, which have both the resources and capacity to implement strategies.

The County Council put together the Regional Growth Programmes (RTP) and the Regional Development Programmes (RUP) which aim broadly to sustain regional growth and better co-ordinate efforts of local actors, through collaboration for the development of overall strategic plans. However, these plans and programmes could not be described as comprehensive economic development strategies, since the resources and ability to implement the strategies rest with municipalities. Furthermore, the programmes are regarded as platforms for common understanding with no direct financial means allocated.

In terms of cluster policy, there are two national cluster programmes implemented at present, VINNVÄXT and Nutek's Regional Cluster Programme. Also to be mentioned is Visanu, which ended in December 2005. Visanu was a joint-initiative in which VINNOVA (the Swedish Governmental Agency for Innovation Systems), Nutek (Swedish Agency for Economic and Regional Growth) and ISA (Invest in Sweden Agency) supported a three-year cluster programme. As concerns regional strategies to support the life science sector, it is important to note that the sector is one of five prioritised growth areas by the national government and one of the key areas in all three RTP documents relevant to the Stockholm region. In the context of regional strategies, it is interesting to consider that a number of initiatives have been launched in the region. Several of these initiatives have been supported by national actors such (VINNVÄXT, Visanu and Nutek's regional cluster programme).

During the last six or seven years, a number of industrial cluster initiatives have emerged in the region, supported by the public sector. In their initial stages, many of these initiatives were often linked to the general regional development process (and in this context often supported by one or another national funding structure). Stockholm Bio Region aimed to co-ordinate the different initiatives in the life science sector in the region. STAND UP was a strategic group consisting of the three county council governors, CEOs, participants from academia and from the cluster initiatives formed in 2002. The aim was to support a more well-functioning system for regional governance. However, since the autumn of 2006, Stockholm Bio Region as well as the STAND UP group have been terminated and other actors are taking over their mission.

The main actors in this context are some of the cluster initiatives. Uppsala Bio is a collaboration between the local biotech industry, the two universities in Uppsala, and the regional development bodies. The initiative aims to contribute to long-term growth of the biotech sector in the Uppsala region. The initiative is one of five original pilot projects initiated in 2001 to fully develop a model for the coming VINNVÄXT programme. The Biotechvalley cluster initiative has the ambition of strengthening the biotech industry in the entire region and was important in the process of co-ordinating and facilitating Pfizer's site-selection, for example, by acting as an intermediary between the local and national policy level and in marketing the advantages of Strängnäs and Sweden (providing information, finding the right contacts, etc.). Biotechvalley also works as a virtual pharma company and can play a vital role as a help to SMEs in assisting them so that when a large company wants to buy a small company they can be assured that the company has gone through certain procedures and followed regulatory guidelines. Biotechvalley is supported by the Nutek's regional cluster programme. Uppsala Bio, on the other hand, has a more "local" perspective and focuses mainly on Uppsala. On a vertical level it can be said that these cluster initiatives, through their triple helix approach, actively work to bring actors

from different levels of the governance structure (local, regional and national) and from different sectors (public, private and university) together.

Biotechvalley, Uppsala Bio, Uppsala Innovation, Karolinska Holding and Stockholm Business Arena are, thus, actors/initiatives that little by little have emerged as embedded in the industry, mainly by providing different types of added values. Moreover, these actors are increasingly starting to co-operate. One such case in point is the co-operation between Biotechvalley and Karolinska Holding concerning support for young start-ups, etc. Stockholm Business Arena, Uppsala Bio and Biotechvalley (together with the municipalities in the region) are co-operating concerning branding and marketing of the region. Uppsala Bio and Biotechvalley have gradually started to work to upgrade competence in the region. Stockholm Bio Region and STAND UP are now defunct. The most prominent feature in this process is the strong bottom-up perspective.

What, then, are the roles of clusters and cluster policies in the region? The life science cluster initiatives presented in this report can be seen as working to link actors both on a vertical and a horizontal level. Horizontal by trying to bridge traditional geographical and administrative barriers between the counties and municipalities. Vertical by bringing actors from academia, industry and the public together in order to facilitate a more effective innovation and commercialisation process in the region. This is, to some extent, the main goal for regional policy makers in meeting the challenges of globalisation. Much of the work within clusters and in regional growth programmes also aims to secure a supply of qualified labour for local industry. One of the main future challenges is the lack of skilled workers, so the universities need to co-operate to develop the skills needed, not only with a focus on product development but technology development. The relationship between large firms and SMEs is quite weak and further collaboration mechanisms are needed in order to integrate SMEs with research institutions, the private sector and government. Cluster policies are also important in this context.

General conclusion

There is a strong common understanding concerning the importance of the sector for the regional economy. Different tendencies are emerging, with various actors trying to bridge traditional geographical and administrative barriers between the counties and municipalities; *e.g.*, the Stockholm Business Region initiative. It is also important to note that there is some flexibility at the local level. When Pfizer chose to invest in the Mälardalen region, factors influencing this decision included a critical mass of production competence and the fact that the local municipality was very flexible as regards infrastructure planning. In terms of cluster policy, the national cluster VINNVÄXT, Visanu and Nutek's regional cluster programme initiatives have benefited the life science clusters. Cluster initiatives in the region can be seen as working to link actors both on a vertical and a horizontal level. The success of Biotechvalley and Uppsala Bio is built upon the energy of such firms, with the support of the universities.

The different life science initiatives are embedded in an environment which in itself is strong and tradition-bound: old universities, international connections and ownership in the corporate sector and the other components of the triple helix, etc. Various points of inertia are built into this system, regardless of the existence of the cluster initiatives. The fragmented governance structure, divided into several administrative and political regions, is considered to obstruct co-ordination between the life science clusters in the region. No public actor has taken the role of "intraregional leader" but the cluster organisations are

important in this context. An overall-functioning triple helix constellation in the proper sense of the term does not yet exist in the region, for reasons related to both institutional and organisational aspects. Compared with other regional initiatives in Sweden, the Stockholm region would certainly seem fragmented and complex. At the same time, it could be questioned whether it is even possible to compare a region like the Stockholm region with other regional environments in Sweden, even though several of the environments described definitely have potential with respect to competitiveness and resources (firms, research, branding, etc.).

The region is also characterised by the existence of many different players which in themselves are strong enough to pursue their own agendas, but perhaps are not strong enough to fill any structural holes in the network. It is extremely difficult to navigate in the public support system with 30 different but overlapping organisations. Perhaps this is why the network structure and consequently the impediments to collaboration look different in such a region, in an urban innovation system of this type. Initiating interplay in Stockholm may require other types of initiatives and arenas. One such initiative may be to free up resources for players that can go between the different policy layers. In brief, what may at first appear to be fragmented and not interconnected may not necessarily be so; it might more accurately be described, simply, as a "big city problem".

Perhaps it is merely that the process exemplifies the problems and opportunities of doing "business as usual" in a big city reality. To some extent, we find this in the other regions as well. There are also differences as regards prioritisation in the regional growth programmes. Moreover, it should be noted that the public sector is the driver in many development, cluster and innovation system strategies. One of the major implications in this context is perhaps that policy measures have a tendency to be more supply-driven (focusing on research) rather than demand-driven (focusing on the market).

In terms of more sector-specific problems and challenges, which are not necessarily a result of the regional governance structure, is the fact that Sweden lacks appropriate and relevant tax incentives targeted at R&D-intensive companies. The lack of these incentives is probably an important factor working against the biopharma sector in Sweden. Secondly, there is a lack of capital in the region. Thirdly, the number of young R&D companies may be a problem since it is not self-evident that funds and financing will be available after companies have left their pre-seed phase. Last, but not least, it must be stressed that, albeit a national policy and high visibility in regional strategy documents, a more long-term vision concerning the role of biotech is lacking, support-wise and financially as well as regarding its role in the regional economy.

A number of new firms have emerged in the region. Some actors have argued that the region may even contain too many in relation to its size. Moreover, another challenge is the fact that the large pharmaceutical companies are downsizing in the region. AstraZeneca has been crucial for the growth of the sector.

Taking the above conclusions into consideration, what advice is appropriate? One of the more important policy implications in the Swedish context is that Swedish policy makers from the national to the regional level need to be more proactive. A strategy for life science now exists, but the sector is in need of more resources. Tax incentives might also be considered. This is by no means the only solution and/or a quick fix, but almost every other competitor nation-wise offers such measures, in one way or another.

Another challenge is, understood broadly, the financing aspect of biopharma (regardless whether it's public or private money). This has implications for young, R&D-driven DBFs in early stages as well as for AstraZeneca (health and social policies, reimbursements, providing a milieu for clinical trials, providing innovative financing, etc.) Regional funding could also improve different co-operative measures. Problems related to co-operation often exist within the public sector, while business and academia function somewhat better. Sweden should consider focusing on measures to support the industry, competence-wise. The educational system needs to be more closely-matched with firm needs in order to ensure future supply of qualified labour.

Despite high international ranking in research and education, low mobility between the sectors and few incentives for co-operation characterise the relationship between the educational establishments and trade and industry, as well as the fact that academic research is not valued in business and business experience is not a merit within academia. Instead of spreading the funds to several regional colleges, it is importance to allocate the means to the strong universities in the Stockholm region in order to maintain a critical mass and close connection to the international companies in the region. Moreover, there is no clear regional R&D strategy. The RTP and the life science clusters mentioned above promote and support R&D within their prioritised fields, but are not trying directly to influence the direction of the research conducted at universities and research institutions. Each university decides what fields to prioritise and how to allocate their means. In the long-term perspective, measures need to be taken in order to focus resources and specialise in different research fields. All in all, four challenges related to the R&D-environment in the Stockholm region concern biopharma. These are the connection between production and R&D, co-operation between educational establishments and trade and industry, the concentration on regional colleges and universities and the tendency towards a regional shift regarding companies' research efforts. The connection between research and production should not be undermined since removal of production will result in a subsequent removal of research. Generally, it is also an advantage to carry out R&D close to important customers, and since the larger markets are outside Sweden this tends to draw research activities away from the country. Therefore, it is extremely important to continue to provide policy measures that attract large pharmaceutical firms as well as new, innovative firms.

North-western Switzerland

Introduction and basic data about the region

In the centre of the trinational Upper Rhine Valley area of Switzerland, France and Germany, lies north western Switzerland (NWCH), with the core of the region found around the city of Basel. It is among the most populated areas in Switzerland, with a population of 557 000, and the city of Basel as an urban centre. Thirty per cent of the country's population – or approximately 2 300 000 people – lives in the extended region, comprising several cantons and covering 23% of the area of Switzerland.

Though the NWCH region is not a political entity in itself, it is part of the Swiss Confederation, the highest administrative level in the country and responsible for foreign and defense policy, customs and monetary policy, and other areas that are in the common interest of all Swiss citizens. Each of the 26 cantons has its own constitution, parliament, government and courts; *i.e.*, acts as a regional authority with a relatively high degree of

autonomy. A large proportion of fiscal jurisdiction is delegated to the cantons and the tax level varies between regions. Each canton is divided into municipalities or communes (at present 2 760) at the local level. Local authorities, in addition to the tasks entrusted to them by the Confederation and the canton – such as responsibility for the population register and civil defense – are also in charge of areas such as taxation, education, social welfare, energy supply, road building and local planning, among others.

NWCH's core area is not large; in fact it is the second-smallest economic area in Switzerland, covering 2.4% of the country's area and with only 7.4% of the population. The core region ranks relatively well when compared to other regions, both in terms of employment and Gross Value Added (GVA)/capita. It had 287 000 employed persons in 2000 – equal to 7.3% of the country's total workforce. The unemployment rate (3.8%) is in line with the national average and the GVA/capita (CHF 68 700, approximately 15% higher than the Swiss average of CHF 59 600) is higher than in most of the cantons. Companies in NWCH are mostly SMEs with less than 250 employees. A number of industrial branches, such as the health and public sector, the chemical industry, retail business and repair of consumer goods, services for enterprises and the building sector dominate the core area. The chemical industry is the most significant, accounting for 10.5% of total employment (*versus* 1.2% of national employment).

The biopharma sector in north western Switzerland

Accounting for 3.5% of the national GDP and 5.81% of the GDP of the Metrobasel area, an area covering the core area of north western Switzerland and the adjacent French and German regions, life sciences employed 27 800 in 2004. Regional GDP in other leading life science regions does not exceed 2%, so 5.8% of regional GDP is certainly significant. The significance of life sciences for the national economy is clearly evident in terms of GVA. The contribution of the life sciences becomes even more apparent when examining its impact on economic growth in the region,

As influential and important as it is to the trinational economic space of the Upper Rhine Valley, the life science industry is equally important to the regional industry. With more than 1.2 percentage points per year of overall economic growth in the Metrobasel region directly attributable to it, the life science industry's economic contribution is unique.

Over the past decade, life sciences have been the economic motor of NWCH, outpacing the aggregated Swiss economy (3%). Between 1995 and 2004, it grew at a steady pace in the trinational Metrobasel area: on average, by approximately 10% GVA per year. The pharmaceutical industry – of which the agrochemical industry makes up only a very small part – has experienced rapid growth in recent years; but the life science industry has grown even more.

One reason for the success of the north western Switzerland life science cluster was the general change of focus of the chemical/pharmaceutical industry towards more emphasis on its pharmaceutical segment and less focus on traditional chemical production. A great number of spin-offs were formed in the course of various mergers and restructurings among the major pharmaceutical companies. These spin offs were able to benefit from the skills and experience of their executives and scientists. The pharmaceutical industry in Metrobasel actually makes up more than 80% of the life science sector, whereas in regions such as Zurich, the medical devices sector accounts for more than 70% of value added in life sciences.

A significant number of new jobs were also created between 1995 and 2004, companies in the sector finding the region to be a dynamic centre. Large pharmaceutical companies were the major drivers in NWCH. The merger between the two Basel pharmaceutical MNEs Ciba-Geigy and Sandoz, which together became Novartis in 1996, was an important event in this context. Some business segments were sold to other firms or produced spin-offs as the merger triggered changes in the industry. To support these spin-offs and ensure they had firm foundations financially, the Novartis Venture Fund was founded. Among other consequences, the outplacement of qualified and experienced personnel created a regional stock of both business angels and consultants. More or less at the same time, Hoffmann-LaRoche began to concentrate its business activities on core competencies. The spin-offs this triggered have since developed into major players in the biopharmaceutical industry – such as Basilea and Arpida. This demonstrates the importance of: 1) the existence of MNEs, particularly large pharmaceutical firms; and 2) the importance of an environment that is supportive of entrepreneurship. The existence of different types of funding, capital, etc., is crucial in this context.

Regional governance and strategies

The regional political and administrative responsibilities are fragmented, with no unified economic development strategy. In addition, there are few institutions to co-ordinate regional policy activities, rarely covering the entire region, and with insufficient competence. A concise summary of the economic development strategies of the cantons in north western Switzerland is thus difficult to provide. Cross-cantonal initiatives are certainly rather weak and mainly oriented towards co-ordination and location marketing. The strong position of the cantons in the Swiss political system contributes to this. Still, some similarities are evident in the economic development policies of the NWCH cantons. A veritable industrial policy or micro-steering of the cantonal economy are non-existent. The emphasis is, rather, on reduction of governmental spending and taxes, liberalisation and deregulation, provision of infrastructure (especially in higher education and transport) and cross-cantonal co-operation activities related to location-marketing. As a result, a more integrated approach to economic policy in the future would be welcome.

No specific government programme covers the entire area, furthermore, either in the narrow or in the broader definition of "cluster policy". Targeted business development measures are not used in the NWCH region to support life sciences. The cantons limit their activities to creating a framework of laws and regulations that is conducive to innovative R&D, entrepreneurial initiative, firm creation and spin-offs. The MNEs located in NWCH, above all Novartis and Roche, are important assets in this strategy, but also other global players like Syngenta or Ciba Speciality Chemicals. A considerable amount of spin-off activity was sparked in 1996 by the merger of the two MNEs Sandoz and Ciba-Geigy (the result of the merger of Ciba and Geigy in 1970). SMEs in NWCH are robust because they are market-driven, not the end-product of public business development agencies.

A set of spatially restricted initiatives, as well as projects below the programme level, do exist, related to the idea of supporting cluster structures despite there being no integrated approach. Among others, these include: activities promoting life sciences by the Basel cantons and the Basel Chamber of Commerce, the BioValley project, the Metrobasel initiative conducted by the BAK Basel Economics consulting firm and the Bern Cluster Policy.

Basel and its surrounding area are home to a significant part of the life science activities in the region. With its origins in the chemical and pharmaceutical industries, this organic cluster has long been a pillar of the cantonal economies, and, to a greater or lesser extent, cantonal economic development policies have always taken this into account. The cantons and different partners, particularly the local chamber of commerce, but also the local universities, cantonal banks, business associations and other institutions, co-operatively work to support the development of the life sciences in the region, though there is no integrated cluster policy or programme to support the cluster. The following paragraphs must be seen in the light of the more specific descriptions mentioned in different sections of this report.

The Cantonal Council in Basel Town focuses its business-oriented support activities on measures that interfere as little as possible with market processes and that supplement private activities. The Life Sciences Strategy of the Cantonal Councils of Basel Town and Basel Country and the Chamber of Commerce of both cantons (Regierung Basel Stadt, Regierung Basel Land and Handelskammer beider Basel, 2004) is a recent new initiative. A joint strategy aimed at improving the locational conditions for the life sciences in the Basel area has resulted from ongoing discussions.

The Metrobasel initiative is another recent monitoring and co-ordination initiative, propelled by the Basel-based consultancy firm BAK Basel Economics and several regional stakeholders. Its principal function is a reporting one. In order to propagate the idea of a metropolitan area in the environs of Basel, all of the various projects aim to present statistical data to a wider audience. Due to political borders within the trinational area, consisting of parts of Switzerland, France and Germany, the region appears fragmented; the goal is to make the region surrounding Basel more unified, and to bring those various political entities closer together.

Georg H. Endress, a local businessman with a pronounced trinational orientation, and Hans Briner, the first president of REGIO BASILIENSIS, the Swiss organisation responsible for managing trinational co-operation at the cantonal level in the Upper Rhine Valley, conceived the BioValley initiative. Some years later, the BioValley project was established as an EU-funded, trinational (France, Germany, Switzerland) Interreg II project in the Upper Rhine Valley. It started to receive EU funding in 1997 and has since been twice extended. In terms of its spatial dimension and focus, the project is unique in north western Switzerland.

For approximately 10 years, the canton of Berne has been implementing its cluster policy. With the aim of making Berne more attractive as a location for companies within the selected clusters, Berne established four cluster organisations and two centres of competence (Berne Economic Development Agency BEDA, 2006). Two hundred and eleven thousand are employed as staff by member-companies involved in the cluster organisations; said companies being responsible for 40% of the cantonal GVA. The cantonal centre for technology and knowledge transfer, InnoBE (*www.innobe.ch*) manages the four cluster organisations, with budgets between CHF 100 and 170 000 per cluster and year. The canton of Berne financially supports each one to the extent of CHF 80 000, with all four "clusters" organised in the form of an association.

General conclusion

Of outmost importance for the positive development of the sector, the division of labour between the regional MNEs and SMEs seems to function well in the region.

Biopharmaceutical SMEs, for instance, can benefit from the MNEs in regard to the funding of clinical trial phases and the marketing of developed products through global sales networks. MNEs benefit at the same time from the innovativeness and flexibility of the SMEs. Cluster-related co-operation may even contribute to overcoming administrative borders; this is a positive aspect since many clusters in "small" regions (compared to some of the mega-centres in biotechnology) often need to be bigger in order to compete.

The BioValley project is an example of cluster-related business networking that has been established as a cross-cantonal and cross-national initiative; nevertheless, it has suffered from a lack of wholehearted co-operation.

One example of a successful cluster-oriented and cross-cantonal initiative that is active in the field of promoting biotechnology in Switzerland as a whole is the Swiss Biotech Association.

Because such approaches tend to be market-driven, their marketing has been successful (particularly the Metrobasel initiative). The importance of clusters (and cluster policies) that are bottom up is one general observation. Industry-driven clusters, rather than those driven by the public sector, tend to be preferred. But even those cluster initiatives need to have a critical mass of strategic companies as supporters, members, etc.

Due to the division of responsibilities of the federal system (central government – cantons – communities), the existence of six cantons on a rather small spatial perimeter with administrative borders and functional boundaries misaligned, and, last but not least, three countries and a trinational setting, north western Switzerland is politically and administratively fragmented. As such, the co-ordination of administrative procedures in different cantons needs to be improved. In addition, it is difficult to communicate the details of differing cantonal rules and the consequences for an investment decision in one canton *versus* another canton from the point of view of location-marketing and attracting investments. Tax competition and differing tax rates across Swiss cantons are also considerations. Lack of funding for carrying out influential economic policy strategies is another negative aspect of the territorial fragmentation. The result is a very limited perception of the cantons beyond the Swiss borders; only the major urban centres are known outside of the country. It is, moreover, a question of implementing health policies that are effective (both in terms of health economy as well as for supplying an effective structure for clinical testing). Many small regions in the global competition for talent (*i.e.*, competent researchers, managers, entrepreneurs) and capital face similar problems.

Political commitment and support for the life sciences is an additional factor that is not necessarily lacking, but needs to be improved by policy makers. Support of networking activities, innovation processes or even governmental funds are not the top priority of many firms, but rather a clear commitment of politicians to support the industry, measures that increase acceptance among the regional population and support of other policy sectors. The sector depends on it for its long-term development. Also helpful would be further PR measures aimed at the regional population and at a national and international level to show the importance of the cluster.

R&D results commercialisation should be speeded up and intensified. Universities, for example, could increase their openness to problems and research demands formulated in industry, providing the requests reach a certain standard of research interest. To increase the overall quality of regional R&D in the life sciences, more competencies and resources for universities to attract highly qualified scientists from abroad should be sought; there

seems to be an increasing shortage of engineers and qualified technicians in NWCH. A supply of highly skilled individuals across the whole value chain is a prerequisite for the long-term development of the sector.

Shanghai, China

Introduction and basic data about the region

Shanghai is the largest city in the People's Republic of China and the eighth-largest in the world. The 2000 census put the population at 17 million, including the non-official resident (floating) population of almost 4 million. Shanghai is now an international financial hub and a major destination for corporate headquarters. It is the third-busiest port in the world, following Singapore and Hong Kong, China. It recorded double-digit growth for 14 consecutive years since 1992. In 2005, Shanghai's nominal GDP experienced 11.1% growth to CNY 912.5 billion (approximately EUR 95 billion). The "pillar industries" which account for the majority of its gross regional product (GRP) include microelectronics, automotive, fine chemistry, high-quality steel, machinery and shipbuilding. It also includes prominent ICT, biotechnology and pharmaceutical and financial services sectors.

Administratively, Shanghai is a municipality that has province-level status. The municipality oversees 19 districts which are further subdivided into counties. Within the provincial government, the Shanghai Municipal Development and Reform Commission has a very broad mandate to lead economic and social development, in line with national-level goals. The Science and Technology Commission serves an important role in orienting science and technology policy as well as financing R&D and developing platforms to support the technology needs of different actors and sectors.

Shanghai possesses a number of important assets to support innovation. On many indicators, it is in fact the highest-performing region in the country. For example, public R&D investment in the region has grown quickly, from 1.78% in 2001 to 2.34% of GRP in 2005 (STCSM), albeit with a focus on basic and early stages. A number of the most prominent industrial parks, development zones and universities are located in or near Shanghai (Fudan University, Nanjing University, China Science and Technology University, Zhejiang University and Shanghai Jiaotong University). Central government policy has been a major driver behind the concentration of these resources in certain regions. It is expected that Shanghai and the rest of the Yangtze River Delta area, along with the two other major growth poles of the Pearl River Delta and the Bo Hai Rim, will drive China's high-tech industrialisation.

The biopharma sector in Shanghai

China's pharmaceutical companies are very much focused on the domestic market, and this is likely to remain so if they continue to concentrate on high-volume generics. The government is seeking to develop national champions, but they have nothing to compare with Indian companies such as Dr Reddy's. Some form of partnership with international firms could be one way to evolve, but many industry experts are cautious about recommending this to Western firms. Ernst &Young, for example, state that merger and acquisition risk in China "still may be too high for many multi-national companies to bear" (Ernst & Young, 2005). Boston Consulting Group echo this to some extent concerning biopharma, insisting that outsourcing R&D to China is a strategic choice that signals commitment to the country and can help strengthen relationships with key opinion

leaders and officials, but the report goes on to stress that this "*won't* achieve major cost-savings for global biopharma companies" (Wong, *et al.*, 2005). Despite these caveats, China does offer a number of attractive features for global pharmaceutical companies, particularly for R&D and many multi-nationals have already set up R&D facilities. The country has around 20 biotech clusters, with 500 to 1 000 biotech SMEs. Clinical trials can benefit from similar advantages to India concerning the number, variety and cost of subjects. It is also possible that if opposition to animal testing intensifies in the West, China will increasingly be seen as an attractive alternative.

Government efforts to promote healthcare insurance in urban areas and to improve health services as part of the fight against rural poverty will benefit the pharmaceutical sector, but a number of other programmes and measures will have to be implemented to assist the industry in domestic and international markets. The Chinese pharmaceutical industry suffers from a vicious circle formed by a dependence on generics, a lack of innovation, and falling prices for generics, which means less investment available for innovation (Chinese pharmaceutical companies spend less than 2% of total revenues on R&D compared with 15 to 20% for multi-nationals). This is hampering the government's initiatives to stimulate the emergence of national champions capable of competing internationally. Measures include the introduction of the policy on Good Manufacturing Practices (GMP) in 2004, based largely on WHO guidelines. The high cost of upgrading facilities to meet the new norms (around USD 3.5 million per manufacturer) is one of the main causes for the dramatic reduction in the number of companies mentioned above. Intellectual property rights were reformed in 2002 as part of China's accession to the WTO, and should help the pharmaceutical industry to attract foreign capital and stimulate innovation, and also reduce the risk that the assets of Chinese companies are seized as a result of patent violation litigation.

The life science sector in Shanghai is an important and growing sector in the city's economy. It is by employment standards quiet small though. Compared to some other sectors in the region's economy it is still relatively small when it comes to world export shares. One possible explanation is the fact that the domestic market in China probably is sufficient at present for the existing industry.

The region has over 140 foreign-controlled R&D laboratories. A rapid and continued expansion of higher education is ongoing. Shanghai now has 59 colleges and universities with a total enrollment of approximately 600 000 students. The city has 10 universities which are included in the Top-100 list, selected by the Ministry of Education; such universities receive special treatment and extra resources. Furthermore, a number of Chinese universities with expectations to become recognised as global research universities are located in Shanghai: Fudan University, Tongji University and Shanghai Jiaotong University.

The predominant part of the sector is located in the Zhin Yang science park in Pudong, established some 15 years ago. In 1993, the government decided to focus on high technology, particularly on two areas: ICT and pharmaceuticals. Since 1996, with comprehensive support from MOST (Ministry of Science and Technology) and Ministry of Health (equivalent to the FDA), among others, there has been a more formal delegation to support the growing life science cluster in the area. In the last six to seven years, a number of institutions and research institutes as well as foreign large pharmaceutical firms have located to the area (for example Eli Lily, Roche and Novartis). The Zhin Yang science park

today demonstrates every known feature of an emerging cluster. There are approximately 50 manufacturing companies located in the park, national as well as international.

Moreover, a number of organisations doing clinical research are present in the park. At present, approximately 200 start-ups, some listed on exchanges in China, United Kingdom and Singapore, are located in Zhin Yang. Finally, it should be noted that many R&D centres in sectors related to the pharmaceuticals industry are located in the cluster, for example DuPont and Estée Lauder.

Over the last 10 years, Shanghai – regardless of sector – has emerged as an important R&D hub in Asia, even globally. Moreover, some 20 government-funded R&D institutes (excluding ICT) are located in the park. ZZHTP aims to attract recognised pharmaceutical companies from overseas and from China, and to expand its R&D structure and improve its content by attracting talent. More than 120 small and medium-sized companies have already set up in the Park, which also hosts the Shuguang Hospital and the Shanghai University of Traditional Chinese Medicine.

Regional governance and strategies

Regional governance targeting innovation systems and competitive clusters in Shanghai is a somewhat complicated mix of national and regional measures.

As concerns policies to increase inputs, they can be divided into two subcategories. First, measures targeted at creating a better environment for funding, public as well as from VC companies. Second, to attract human resources. Attracting venture capital is no longer regarded as a big problem, since seed capital and venture capital are readily accessible in Shanghai. There are a lot of dynamic VC-firms and finance groups, with those funded by the government highlighted as the most important. The lack of truly private firms (particularly international) may be a problem in the long run. Moreover, another important aspect of the strategy is to develop closer interactions and to increase R&D over the next five to ten years. Biotechnology is listed in the central and municipal governments' medium- to long-term plans for support.

When it comes to measures targeted at creating a better environment for innovation, a number of strategies exist, many of them related to the role and function of government, regulations and the creation of competitive market conditions. One such example is to provide preferential policies and subsidies. Another is to invest in infrastructure and institutes and to promote high-tech parks and incubators. To attract major R&D to Shanghai, support facilities will be needed. In addition, government procurement to provide a market for the products is supported. To secure IP protection and encourage patents, associations to establish technology standards for that industry or encourage them to adopt international standards are promoted. Finally, measures aimed at developing the labour pool for innovation, from R&D-personnel to managers and entrepreneurs, are envisaged.

As concerns cluster strategies, it should be noted that the cluster concept is in the initial stage here as a proactive economic and regional development tool. With a number of industry parks, firms and other actors (related services, supporting organisations, academia, etc.) gradually realised that they could be more competitive if a formal cluster initiative was launched. On a general level, the municipality of Shanghai is more interested in technology than in attracting foreign direct investment. An important aspect of the

strategy is that the region not be just a location for manufacturing and sales, but also for cutting-edge R&D.

General conclusion

It is obvious that biotech in Shanghai is a growing sector, a sector that benefits immensely from: 1) the large Chinese market; and 2) the public systems, understood broadly, for support. Shanghai, thus, is a strong region when it comes to funding. One major reason behind this is of course related to the fact that there seems to be a fairly coherent policy concerning life sciences on the national and the regional level. Moreover, another feature which seems to have worked is the fact that competence-provision is supported. All in all, this has led to the Shanghai cluster taking a giant leap up the biopharmaceuticals value chain.

What has worked less well? Firstly, and this is a feature shared with other regions as well, is the level of academic entrepreneurship. Possibly, innovation policies are putting too much focus on input (*i.e.*, academia) and not enough on commercialisation. Secondly, it should be noted that a proper cluster strategy does not yet exist. Up to now, the model has been rather to promote science parks and technology transfer within the parks.

Concerning the implications of the development of pharmaceutical technology on Shanghai's policy making, it should be noted that the pharmaceutical industry, the biological pharmaceutical industry in particular, is a typical R&D-intensive industry. From the perspective of international experience, technological innovation activities of the pharmaceutical industry occur in the context of market-oriented competition among enterprises and are an important component of the country's state innovation system. When considering support from the government to the so-called state innovation system for the pharmaceutical industry, the major challenge involves how the government should co-ordinate co-operation among universities, research institutes and pharmaceutical companies, as well as developing technological resources, and how to tap the potential for development of biological pharmaceutical technology in Shanghai.

With regard to competition for technological resources in Shanghai's (and of course China's) domestic pharmaceutical market, the competition for technological resources is intensifying over time, especially competition from pharmaceutical powers such as the United States. In this context, one may argue that government organs and the enterprises involved should accelerate communication between basic research and technological innovation in Shanghai's biotech and pharmaceutical industry. Moreover emphasis must be given to the development of patent technology resources and control strategies, in response to efforts of foreign companies to control Shanghai's technological resources in the field of biotechnology, pharmaceuticals and medical devices.

Moreover, the Shanghai governments – on different levels – should facilitate the growth of a true cluster initiative in Shanghai, not by direct market intervention, but by supporting an efficient public sector and the quality of China's overall regulatory framework. Government should, thus, play the role of "enabler" of private business, and build on Shanghai's already-existing comparative advantages; *i.e.*, superiority of educational standards, position as a hub for cutting-edge research in China, attractiveness as a work location for knowledge-industry professionals, and position as a financial services hub.

One important implication for policy in this context is to support the creation of different types of institutions for collaboration that are a combination of efficient

government-sponsored and private-sector-led institutions focusing on serving industry needs. This should be done by promoting co-operation and networking throughout the biopharmaceutical innovation system, especially between actors in science and the business system. Thus, there needs to be a division of labour where private firms should improve their own individual competitiveness (and work together to improve the competitiveness of the overall cluster where co-ordination creates "win-win" outcomes) and the public sector which must continuously create the preconditions for an attractive environment and a growing business community by offering quality services and infrastructure at the right price, and a "business friendly" culture that encourages the creation of more companies or the establishment of offices in the region. Academia, finally, should strive for a combination of delivering globally-excellent research in combination with regionally embedded applied research supporting the firms located in the cluster.

Montreal, Canada

Introduction and basic data about the region

The Montreal region is usually defined as the Montreal Census Metropolitan Area (CMA), an area surrounding the urban core of the municipality of Montreal measuring over 4 000 km^2 with a population of 3.7 million people. In Canada, it is the second-largest urban centre; in North America it is the sixteenth-largest.

The Montreal Metropolitan Community (CMM) is a co-ordinating, planning and funding body covering (with some minor exceptions) the CMA area. Infrastructure, economic development, social housing, arts and culture promotion, the transit and arterial network, and environmental issues are among its responsibilities. A Council made up of 28 elected officials from member municipalities manages it. Eighty-two municipalities, responsible for a wide range of tasks such as urban development and zoning, urban transit, waste, water, police, and fire protection, make up the CMM. Fourteen Regional County Municipalities (RCMs), which are supra-municipal, grouping certain municipalities in a given area, are also included. The CMM contains eight of these entirely within its territory, with six partially included.

The benefits of economic restructuring have significantly benefited the Montreal area, and it is increasingly in the business of selling "knowledge". The shift from traditional industry towards high-tech industries such as aerospace, biopharmaceuticals, and communication and information technologies (CIT) characterises the industrial base with high-tech products as its primary exports. With an annual output of CAD 112 billion, Montreal CMA is the second-largest contributor to the Canadian GDP. The region's employment rate has climbed faster than that in the rest of the continent since 1997.

The biopharma sector in Montreal

A significant role in the Canadian life science sector is played by the Montreal area. In terms of the concentration of jobs in the North American biopharmaceutical sector, the area ranks sixth. Canada as a whole is ranked second world wide in the field of biotechnology, just behind the United States, in terms of the number of biotechnology companies. Canada ranks highest in terms of R&D expenditure per employee. With the Montreal metropolitan area hosting nearly half of the Canadian biopharmaceutical industry, all phases of pharmaceutical product development can be carried out locally in the region – from basic research to market launch, including all stages of pre-clinical and

clinical research. The bulk of basic and clinical research in Canada, as well as about 90% of Quebec's work in life sciences, is conducted in the Montreal area. The life science sector accounts for nearly 40 500 jobs in the region. The main fields include pharmaceuticals, with approximately 10 000 employed in drug manufacturing, and about 30 international pharmaceutical companies with their Canadian head offices in the Montreal metropolitan area (major players are Merck Frosst Canada [1 400 employed], Wyeth Canada [1 300] and Pfizer Canada [700]); biotechnology, with about 75 out of a total of 165 biotech firms in the area in the health sector and employing a total of approximately 2 100 workers; contract research organisations (CRO), with about 3 600 employed in the 16 CRO companies in the region (major players are Clintrials Bio [1 400], Recherches and Mds Pharma Services [1 100]); and medical devices, employing about 10 000 workers in the region.

Life science research is mainly conducted at the two universities, McGill and Université de Montreal, the exception being company-based R&D. With 25 institutes and research centres in the field of life science and six affiliated hospitals, McGill ranks second in Canada in health sciences. The Université de Montréal has a network consisting of 24 research centres and 10 affiliated hospitals. The fact that even though the province of Quebec represents only 23% of Canada's population, the region accounts for 68% of Canadian prescription drug patents, 42% of investments in pharmaceuticals R&D, 41% of investments in biotechnology R&D, and 32% of Canadian grants for peer-reviewed medical research, is another indicator of Montreal's importance to Canadian life science research.

The Montreal area accounts for approximately 90% of these activities in Quebec; the Quebec region receives nearly 50% of Canadian health research funding and most of the research activities are carried out in the Montreal area.

The Greater Montreal area hosts a number of major venture capital companies with experience in biotech; E&B Data lists 21, of which six are government-related and five are linked to unions. The remainder are private companies offering rounds of funding to products in various stages of development (validation, pre-clinical, early- or final-stage clinical trials).

Regional governance and strategies

Since 2002, the 27 surrounding municipalities on the Island of Montreal have merged (and some of them then demerged). The larger Montreal Metropolitan Community is in charge of planning, co-ordinating, and financing economic development, public transportation, garbage collection, etc., across the metropolitan area of Montreal. The City of Montreal is, thus, only one component of the CMM, but the president of the CMM is the mayor of Montreal.

The CMM Council, after holding public consultation sessions, adopted a new economic development plan in 2005. The plan forms the basis of the CMM's efforts to improve its international competitiveness and ranking among the world's major cities. The goal is for Montreal to become: 1) a learning metropolitan region that meets the challenge of improving training for its human capital and ensuring that the supply of skilled workers meets the demand; 2) a competitive and prosperous metropolitan region that fosters the development of metropolitan-wide industrial clusters and nourishes the dynamics of innovation; 3) an attractive metropolitan region with a modernised municipal infrastructure, consolidated urban and inter-city transportation systems and an improved

quality of life; and 4) a world-class metropolitan region with an established brand that helps promote Montreal on international markets and stimulates foreign direct investment.

The fact that innovation, productivity, competitiveness and prosperity are all interrelated is the point of departure for the biopharmaceuticals cluster strategies in Montreal. The strategies of big cities to ensure their competitiveness, as a result, increasingly rely on the development of innovative clusters, that is, a geographic concentration of firms and institutions working in a particular industry. Interaction and a free-flowing exchange of ideas and knowledge are fostered by the physical proximity of the actors.

The CMM is therefore facing the challenge of instituting a development strategy for its existing metropolitan clusters, which, for the most part, have not been able to take sufficient advantage of the business synergy among the various actors in the cluster. Finding clusters that are already active in the metropolitan area and activating them by supplying appropriate tools and opportunities is the CMM's role, not creating new clusters. In the regional strategy, the life science cluster is one of the most prominent and therefore highlighted.

Montreal International (MI), the agency in charge of contributing to the economic development of Metropolitan Montreal and increase the region's international status, was at the origin of adopting the cluster approach in the CMM with the creation, in 2001, of the 2002-2010 Action plan *Accelerating the development of the life sciences cluster in Metropolitan Montréal*. It was following this first exercise that the decision makers in the cluster's private sector signified their intention to remain mobilised in order to ensure the implementation of the plan, and the Canadian and Québec governments decided to finance the creation of a unit within MI dedicated to life sciences. Thanks to sustained efforts, both by cluster members and the MI team, definite progress was made. The cluster's actions were focused on priority transversal cases, such as access to venture capital or the improvement of market conditions for biopharmaceutical products, as well as other cases that arose, like the relaunch of activities at the Shire-Biochem laboratory or the location of the head office of Sanofi-Aventis' Canadian subsidiary.

Over the last three years, MI has worked on maintaining the mobilisation of cluster parties at a high level, ensuring follow-up on the action plan, adapting it based on changes that may arise in the environment – both local and international, energising exchanges within and outside the cluster through the *www.lifesciences-montreal.com* website, and contributing to meeting job creation objectives stipulated in the action plan. In addition to actions specifically designed to reinforce local capabilities, MI has supported the cluster's efforts to raise awareness at the two higher levels of government of the actions that are required and are essential to take full advantage of the wealth creation potential in this sector. Finally, in conjunction with all cluster partners, MI has continued efforts to reinforce the international positioning of Metropolitan Montréal's life sciences cluster, and therefore ensure expansion equal to the cluster's true strengths.

Furthermore, MI's life sciences unit has launched an initiative aimed at refining identification of world-class fields of expertise in the research environment established on the CMM's territory. During the course of the next three years, MI has leveraged the sectorial intelligence of the life sciences unit to reinforce its proactive targeted prospecting strategy in life sciences. Through this inclusive process that unites decision makers from all the links in a sector's value creation chain, MI hopes to contribute to reaching the full potential of the life sciences sector, in terms of both endogenous and exogenous growth.

Within a framework of decentralised governance involving all economic stakeholders, cluster-based action plans are being developed and implemented. The CMM does not act as a substitute for the actors and decision makers currently working in this field; it focuses instead primarily on its designated planning and co-ordination role in order to mobilise those involved and help organise all the clusters on a metropolitan scale. The task of co-ordinating a cluster's development plan – once a consensus has been reached on that plan – is assigned to what is known as a cluster initiative (or secretariat). The secretariat's role is to lead the cluster, safeguard the common vision, make good use of the competitive capital, make sure that the strategic plan is carried out and, in the process, help improve the economic growth of the metropolitan area. A competitiveness fund was created to support, in terms of financing, the development of any organised metropolitan cluster that has developed a growth strategy. Funding totalling CAD 18 million over a three-year period comes from quadripartite financing from the municipal, provincial and federal governments and the private sector.

Like Montreal InViVo, the branding name of the life sciences cluster, each cluster initiative could also develop its own website. Particularly in terms of branding Montreal as a biotech hot bed and supporting the regions' marketing efforts, Montreal InViVo was the first major cluster initiative in the region. Its bottom-up, firm-led approach is the most positive aspect of Montreal InViVo, since most of the major players are active and supporting this cluster initiative. Montreal probably also needs a more proactive cluster policy in the long run, targeted at more actively adjusting factors and structures that hinder positive development.

It should be noted, in this context, that a number of biotech hubs exist in the larger region, for example, the BioCity of Laval. The City of Laval, the National Institute for Scientific Research (INRS), and the Science and High Technology Park were conceived in 1987 by LAVAL TECHNOPOLE; as stated on the website, they were "developed to meet the needs of companies and institutions with a strong science and technology orientation and to promote inter-disciplinary dynamics in a campus-like environment". However, firms in life sciences are not predominant in the Park presently. In the greater Montreal region, the BioCity in Laval is one of the more important hubs making up the larger regional cluster (one of five poles identified by InViVo in its action plan).

General conclusion

To successfully support the biopharma industry Montreal has a critical mass of activities: four universities committed to fundamental research in life sciences, a fiscal environment conducive to such research, specialized service businesses (especially in clinical research) and the Canadian head offices of several major pharmaceutical companies distributing biotech products.

The region has, furthermore, managed to attract a number of large pharmaceutical firms R&D-centres. In order to secure a more R&D-driven regional sector, this is extremely important. All the more so, since it is evident today that large pharmaceutical firms rely more and more on buying innovations from small firms.

Montreal InViVo acts as a branding organisation for the cluster. The fact that it is a bottom-up organisation where the companies are the drivers is one of its positive aspects; another is that the Montreal strategy, or rather the Canadian strategy, seems to enjoy a coherence between national and regional policy measures. In addition, there seems to be a

recognition that it is extremely important to merge different policy fields, such as health policies and industrial policies.

One may highlight the fact, on the negative side, that one of the regional strengths is R&D in vaccines. In itself of course this is not a negative aspect; compared to other fields in biopharmaceuticals, though, vaccines could to some extent be regarded as fairly generic and easy to produce in many regions. Although at present no such signs are visible, the region could face a risk that some of the premises for R&D are relocated to other countries (China, etc.). Of course, one way to retain this competitive edge is to offer different types of tax incentives. For regions today competing in a global context, this is probably a necessary prerequisite, but it is not the only one that regions should rely on since many countries/regions offer similar incentives.

Another problem in this context is the level of salaries in the sector in Montreal. Compared to other regions, they are still lower, particularly neighboring regions in the United States. Another particular weakness in the cluster is the lack of large pharmaceutical firms headquartered in the region. The marked deterioration of the business climate in Canada for innovative pharmaceutical products is a common complaint of pharmaceutical companies, causing their head offices to be hesitant about reinvesting in Canada. Since one of the more crucial components in developing a long-term competitive cluster is the existence of a critical mass of large pharmaceutical firms and small R&D companies, this is extremely important to consider.

Several policy recommendations suggest themselves. It is important, first of all, that the region continue to work within the context of the larger region, fighting the tendency to be fragmented and muddled. It is important in this context that Montreal InViVo continues to work marketing the region and the cluster as a *regional* cluster comprised of several sub-regional technology parks/clusters, such as BioCity Laval.

R&D results commercialisation should be speeded up and intensified. Important in this context, of course, are both public funding, and different measures for attracting venture capital (as well as pre-seed capital). It should not be as difficult as it is for biotechnology companies to obtain the funding required for them to grow; the continued growth of biotechnology companies, despite a generally favourable context, is far from certain without greater availability of venture capital. The availability of sources of funds represents an ingredient that is key to the success of young firms, since such firms "consume" a lot of capital before being profitable. Although providing an attractive environment for international capital and foreign direct investment is important, it is not entirely an economic issue. The existence of managerial and entrepreneurial skills is equally important, since it is often management, not the 'research' part that is a problem in a young research-driven firm.

Attracting more skills and resources for universities to attract highly qualified scientists from abroad is another measure that could increase the overall quality of regional R&D in the life sciences. Support for measures that increase the inflow of relevant competencies (*i.e.*, providing for "the good life", etc.) is important in this regard. There is a need to continuously target issues such as housing, infrastructure, schooling, etc.

In terms of the budgets currently allocated to research, increases are to be desired. The cluster has significantly benefited over the last ten years from investments in public life science research and healthcare. The region seems to have a strong competitive edge in this area. As an anchorage point for the cluster's development, integration of teaching

hospitals is a crucial measure, as well as continuing to merge different policy areas, since health policies, etc., cannot be separated from innovation policies in the context of the life sciences.

Political commitment to support the life sciences by policy makers and other key stakeholders in the region is, in this context, an important factor. Although many firms are not in need of support for their core activities, a clear vision concerning the importance of supporting the sector from the public sector and from policy makers would be welcome. Such policy measure support is vital for the long-term development of the sector. It would also be helpful to show the importance of the cluster by further PR measures aimed at the regional population and at the national and international level. Montréal InViVo is a prime example.

Notes

1. The report draws on the study "Global Outlook for the Biotechnology Sector – Future Drivers, Trends and Barriers", prepared for OECD International Futures Programme by Patrick Love, background material provided by the case study regions and interviews with representatives from industry, academia and local and regional authorities. As preparation for the interviews, a questionnaire, focused on basic information and statistics, was completed by the region. The interviews were carried out by the sector expert in collaboration with representatives of the OECD/ Nutek Project Team. Sector experts were Peter Eklund, The County Administrative Board of Södermanlands län and Daniel Hallencreutz, Intersecta AB.

   The views expressed are those of the authors and not necessarily an official position of either Nutek or the OECD.

2. It is tackling its image deficit by spending heavily on public relations and advertising, and by funding various humanitarian projects. In 2004, Pfizer, for example, spent almost USD 3 billion on advertising in the United States, and Johnson and Johnson over USD 2 billion (see Glaeser, 2005).

3. A milestone payment is a lump sum payment that is paid by a licensee to the licensor upon certain milestone events taking place. A milestone event demonstrates that intellectual property is progressing through its development, clinical or regulatory phase, and is getting closer to a market-ready state. As the intellectual property progresses through these milestone events, the uncertainty and speculation of market entry diminishes, and the intellectual property correspondingly becomes more valuable. A milestone payment is in part designed to compensate the licensor for this increase in value. The achievement of some of the following milestones might be the trigger for the making of milestone payments: identification of a lead compound, commencement of animal studies, filing an Investigational New Drug application to the FDA or its equivalent elsewhere, commencement of Phase 1 clinical trials, commencement of Phase 2 clinical trials, commencement of Phase 3 clinical trials, product registration (see Mendes, 2006).

4. The study does not incorporate possible effects of the Medicare Modernization Act, which may reduce drug prices for seniors (see US Dept of Commerce, 2004).

5. The wide range depends on whether the calculation is based on dollars per kilogram of active ingredient or as dollars per standard dose. See page 23 of the report for fuller details.

6. Clinical trials in most countries follow a similar multi-phase protocol:

   Phase 1: A small group of people (20-30) all take the same drug but have different methods of delivery and/or different dosages to test the safety and dosage of the drug. Although usually conducted with healthy volunteers, Phase 1 trials are sometimes conducted with severely ill patients, for example those with cancer or AIDS.

   Phase 2: The new drug is compared with the current standard treatment or placebo on a larger group than Phase 1 studies (100-300 people) to test drug safety and efficacy. The people tested have the disease or condition to be treated, diagnosed or prevented, and are often hospital patients who can be closely monitored.

   Phase 3: These are large trials (1 000 to 3 000 people) that randomise patients to test the effects of the new treatment without bias from researchers. Phase 3 studies test the effectiveness of the drug as well as potential side-effects. Safety of the drug also is monitored.

Phase 4: These studies occur after the drug has been approved. Phase 4 studies may be used to evaluate formulations, dosages, durations of treatment, medicine interactions, and other factors. Patients from various demographic groups may be studied. Phase 4 studies are important in detecting and defining previously unknown or inadequately quantified adverse reactions and related risk factors. Phase 4 studies that are primarily observational or nonexperimental are frequently called post-marketing surveillance, and are sometimes known as Phase 5 studies.

7. The Swedish Agency for Innovation Systems (VINNOVA) and the Swedish Agency for Business and Regional Development (NUTEK) have been responsible for innovation systems programmes and cluster programmes, respectively.

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