BIOTECH CLUSTER PROJECT
BIOPHARMACEUTICAL NETWORK DYNAMICS IN FLANDERS AND SECTOR COMPETITIVENESS

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Executive Summary

- The total pure biotech industry in Flanders is relatively young and counts some 30 to 35 companies. In the medical biotech sector, expertise has been developed mainly in the fields of diagnostics and platform technologies, and to a much lesser extent in therapeutics. Most of the Flemish medical biotech companies have been founded after 1995. Innogenetics, founded in 1985, is the only mature biotech company in Flanders from the first European Biotech wave. Genzyme Belgium, Thromb-X and Tibotec-Virco (Johnson&Johnson) are other important players with a business history of some 10 years.

- The strength of a industrial cluster has multiple dimensions. A cluster can be an entry attractor, meaning that economic actors outside the cluster are attracted to the cluster. A cluster can also be a growth promotor, meaning that the companies in the cluster can grow just because they belong to the cluster. Both positive phenomena are conditional. Clusters firstly need to grow or take-off. Growth is only possible once a sector-specific critical mass of the cluster is reached.

- An industrial cluster can grow and develop by either an increase of newly founded companies or by attracting important leading foreign companies. In Flanders, the perspective on cluster dynamics was mainly oriented at setting up new companies. However, the presence of leading companies creates numerous incentives for new companies and international case studies show that most intense network dynamics result from the presence of several large and mature companies next to a majority of smaller companies. In principle, Janssen Pharmaceutica is one of the few companies in Flanders able to act as a leading cluster company (although Janssen does not really focus on medical biotechnology).

- The small Flemish biotech cluster employed around 1600 people in 2002. Employment in medical biotech companies is much lower and Innogenetics alone employs close to 600 people. In the last years, the number of new companies founded each year is rather low and no major foreign biotech company located its activities in Flanders. In a region of equal population size like Denmark, more than 20 new medical biotech companies were founded in 2001 while several leading global companies entered the region with significant investments. The modest level of entrepreneurial dynamism in medical biotechnology in Flanders partly confirms a general problem for the Belgian economy.

- Several Flemish biotechnology companies are founded with a very modest starting capital. BioMARIC is a privately founded biotechnology company with a capital of only 500 000 Euro. For many other young companies, equity ranges from 1 to 3 million Euro. These low figures not necessarily point to a problematic weakness for these companies but risk to limit growth potential.

- The gap between Flanders and the leading biotech regions in Europe is growing. Denmark created with Medicon Valley in Hilleroed the fastest growing biotech cluster measured by products in development. In Medicon Valley, founded in 1992, a couple

of industry giants like Novo Nordisk and Lundbeck together with more than 100 medical biotech companies and 6 six science parks employ 40 000 people and generate annual exports of $ 4 billion. In 2001, Medicon Valley could attract a $ 357 million investment from Biogen, one to the global leaders in medical biotechnology. The location decision of a big player in the industry has enormous symbolic value for a region. To choose the region among many others is a validation of the superior local business environment. The location decision of one important company can influence the future location decisions of many other company, also from other industries.

- In the last years, Genzyme strongly increased its activities and presence in Flanders. Genzyme took over the Pharming Plant in Geel, which specialises in the development of a therapy for Pompe's disease. Genzyme started to build a completely new plant in Geel. With this €130 million investment over two years, Genzyme will focus on the production of new drugs based on recombinant enzymes and monoclonal antibodies to treat rare diseases. In 2005, this new plant of Genzyme Flanders should be operational.

- Among the recent biotech starters in Flanders, we can distinguish university spin-off companies (Methexis Genomics, reMYND,…) from starters founded by existing companies. To the latter category belong companies like DiaMed EuroGen, Galapagos Genomics and XCELLentis. Generally, the activities currently pursued in starters founded by private companies already existed inside the founding company. So two different business models should be considered : the model of a spin-off commercializing knowledge from universities, next to the model of an existing company concentrating specific corporate knowledge into a separate business entity. Another possibility consists of joint-venture companies, set up by consortia of companies and universities. It is possible that the latter business models are partly a rational reaction to existing funding opportunities for basic research (e.g. small and medium enterprises are favoured by the IWT-Vlaanderen).

- Most biotech starters that are founded by existing biotech companies develop in short time a comprehensive network for research and production. This network mainly consists of the founding companies in addition to clients that initially bought the services of the new company at the level of the parent company. Universities play a minor role in these networks. The access to existing customers and financial resources creates good conditions for these young companies to further develop their activities.

- The 'classical' therapeutical spin-off companies in Flanders are still some years away from commercialisation. With almost all their activities in the research phase, the network or cluster around these companies is therefore mainly and sometimes exclusively composed of universities and research organisations. Most Flemish biotech starters can easily position themselves in leading research networks. The quality of research at Belgian universities is unanimously praised.

- The pioneering biotech company - Innogenetics – is illustrative for the logical transformation that can be expected for most young biotech start-ups. Innogenetics transformed itself from a typical research company into a market-driven research company. Research at Innogenetics is of the highest quality. A publication analysis – based on ISI Web of Science- showed that the company could establish a global research network that provides at this moment quick access to global knowledge and problem-solving capabilities. The publication-intensity of Innogenetics' recent

research is now lower because the company is coming nearer to possible market introduction (especially for the hepatitis C vaccine).

- Innogenetics first developed diagnostic activities and products. With these revenues the company could finance therapeutic research in a later phase. This strategy was necessary given the limited availability of risk capital in Belgium in the second part of the 1980s. In the latest years, Innogenetics could set up collaborations with important companies like Bayer Health Care, Roche Diagnostics and Abbott Laboratories. The collaboration with a 'Big Pharma' firm like Bayer helped to reduce strongly the regulatory costs of bringing a product – here an in vitro diagnostic medical device- to the market. Especially for launching a product on the US market, the regulatory costs are that high that the decision to register a product depends on a cost-benefit analysis.

- For Innogenetics, the quality of collaboration not only depends on the scientific quality of the researchers involved. For a company with products on the market and promising therapeutics in clinical tests, the time needed to achieve results or to solve problems is crucial. Therefore, collaboration is preferred with flexible and open organisations that have the means to achieve results under time pressure.

- The therapeutic pipeline of Innogenetics looks attractive. Trials for therapeutic hepatitis C vaccines are in Phase II. The preliminary indications are promising but Innogenetics cannot finance itself a complete Phase III. This is not a surprise. DiMasi e.a. (2003) estimate in a recent survey the average out-of-pocket pre-approval costs of a new drug at $ 802 million. For the Phase III of the HCV vaccine, Innogenetics will establish a collaboration with a leading pharmaceutical company.

- Several other biotech companies in Flanders, especially those close to commercialisation, confirm that bringing a product to the market depends on collaboration with 'Big Pharma'. With respect to therapeutics, Belgian young companies simply cannot finance a standard Phase III of clinical trials. Also for diagnostics and technology platform services, the regulatory costs before a product can be brought on the market can be overwhelming. Next to the regulations for marketing a product, product process regulation is of equal complication in specific areas.

- Many biotech companies in Flanders are pure research companies, providing state-of-the-art technologies, services and tools to mature pharmaceutical, biotech or industrial companies. Research at these companies rarely leads, or will lead, to product development. Once Thromb-X entered Phase I/II of applied research, ThromboGenics in Ireland has been founded to manage further product development. Thromb-X remains a research department in Flanders. Remaining a research company brings inherent risks because only products on market can generate cash incomes over longer periods. New technological developments can outdate existing platforms and strongly reduce the market value of pure high-tech companies. Furthermore, major companies outsource part of their research or technological services to focus on their core business of bringing products to the market. Under though economic conditions, major corporations will cut back outsourced research and limit their scarce resources to internal research programs. Sudden business fluctuations can harm pure technology companies.

- All the visited companies are pleased with the role of the IWT-Vlaanderen. This is not so surprising since they all receive money from the IWT-Vlaanderen. It is also considered as a very professional organisation. In the recent years, the Flemish government strongly increased R&D expenditures. This resulted in more research projects that could be financed but not necessarily in new companies. Research funding alone does not suffice to bring a product to the market and to create jobs in non-research activities like production, logistics and marketing. For some companies, research funding became just an alternative for other financial means like commercial loans. By launching new research projects, new research money is attracted but this money is not necessarily used to complete the research project. In some cases, the money of the grant is used to finance the commercialisation of earlier projects. One CEO stated he had in his desk 10 possible research projects. He had other priorities than launching new research projects but *'once more research money would become available'*, he would submit some projects to finance ongoing operational expenses.

- Several companies complained that the Flemish Government only developed a research policy but not an industrial policy. But the latter is essential in a highly regulated market environment. Companies receive grants for research but that's it. There is no close follow-up of the research results, there is no support for the commercialising of the research results, there is no service point to help companies with practical problems during the regulatory and (pre-)production process, etc… In general, a proactive industrial policy for biotechnology is lacking in Flanders. The inevitable result is that young medical biotech companies depend on collaboration with leading corporations for their survival. As large corporations are perfectly aware of this dependency, they can almost unilaterally determine the conditions for further collaboration.

- In the highly regulated health care market and drug development industry, bringing a product to the market is a business on itself. This market should not be approached with the same philosophy as for instance the IT-market. The existing diagnostic as well as therapeutic markets are dominated by Big Pharma. Small companies depend on collaboration with larger firms. This dependency brings the risk that Big Pharma can set the price (for assets, royalties, milestone payments,…). Ultimately, many small biotech companies act as price-takers during negotiations with Big Pharma or endanger their existence. The question whether or not Big Pharma pays a fair price for an acquisition (e.g. Johnson & Johnson paid $ 320 million for Tibotec-Virco) is very difficult to answer.

- From an industrial perspective, the ultimate question is whether or not governments sees its role limited to funding research in small companies that will be later sold to dominant firms. When the answer is negative, a more active industrial policy is a necessity.

- Policymakers seem to confuse industrial policy with the availability of capital. In many publications it is stressed that the availability of financial resources for knowledge-intensive new industries in Flanders is excellent. This can be the case but venture capital funds focus on opportunities that can be consolidated after a couple of years, typically when interest from larger companies grows. When the venture capitalist then exits the biotech company, there is still no product on the market. This is simply not the task of a venture capitalist.

- Industrial policy for medical biotechnology can have many aspects. Medicon Valley is so successful because Denmark developed an excellent international reputation for quality clinical trials at low costs and detailed public registration. This is an essential condition for every region with the ambition to develop a medical biotech cluster. Therefore countries with a strong pharmaceutical tradition have the highest chances to become the leading medical biotech countries.

- Several companies explicitly demanded for coupling an industrial perspective to research policy goals. This should start with an assessment of current problems and bottlenecks for young and small biotech companies. Once the nature of the mentioned problems becomes clear, the government could channel a minor part of research funds to a prototype of a general service organisation for young companies with the unique task to collect and distribute specific information on regulatory affairs, production technologies, available external consultants that can be hired, etc…

- Furthermore, the investment decisions of non-European companies in Europe but outside Flanders should be closely investigated. Small biotech companies depend on large biotech and pharmaceutical companies and preferential relations with these companies are only possible when all parties operate in the same geographical region. Despite the similarities between European regions, why are other regions preferred above Belgium? Once this question is answered, realistic ambitions for the future development of a biotech cluster in Flanders can be set.

- In network dynamics, the quality of the network stands or falls with the quality of each point in the network. We found that the collaboration between companies and universities is of crucial importance, especially for young companies. Several people at Flemish biotech companies complained about the problematic relations with Technology Transfer Centres (TTC) at Belgian universities. It often takes too much time simply to make up a contract. In some cases, it took 9 full months just to make up a contract while the best centres can manage this in 2 months. Time is a very important variable, especially for companies close to market introduction. Another finding is that some TTCs have no understanding of what really happens in industry and set unrealistic royalty rates that fully erode the profit margin of the company. Most of these problems probably result from understaffing at TTCs in Belgium.

- Flanders has certainly the capabilities to develop a medical biotech cluster. Past efforts need to be consolidated in an effective operational structure that dares to make choices and provide leadership. There is no '*guaranteed success formula'* for a proactive policy but the start can be the selection of sets of niches to target. Conditions that can complement the niche strategies should then become part of the strategy (e.g. investing in specific courses to guarantee the supply of enough specialists). A share of frontier scientific research can then be allocated to these niches and pre-market applied research in these niches can be financed with significant input from industry. Finally, a biotech service point provides low-cost access to advice for young companies and an experienced organisation tries to attract foreign investments.

Introduction and motivation

This short-term research project had two goals:

1. to gather information on the networks used by biopharmaceutical companies in Flanders, and:
2. to link this information to a basic assessment of competitiveness of the industry

The findings should then be used for policy recommendations.
Given the focus on **medical** biotechnology, not all findings and recommendations are relevant for other biotechnology sectors (agricultural & industrial biotechnology). In the report, general terms like biotech cluster or biotech industry always relate to medical biotechnology.

Collecting network information was conceived as a complementary data gathering effort next to the frequently used statistics on the number of firms, total sales, total R&D expenditures, number of employees and number of patents. Network information belongs to *soft* or *tacit* company information. Only the most important collaborations and deals are mentioned in sources such as annual reports.

For companies with a relatively long business history, networks change frequently in composition, size and importance. Given the informal nature of most of the collaborations, it is hardly impossible to present a detailed overview of all actual and past networks for larger companies. For smaller or younger companies, the network is mostly limited to a research network with academic partners. The industrial network will be developed at later stages.

We depended on the willingness of biotech companies to participate in this project. We do not present a complete sector overview but hope that our selection of companies is representative for the industry. Thanks again to all companies that provided us with relevant information.

1. Biotechnology and human capital in Flanders

Since the discoveries by Cohen and Boyer in 1973, biotechnology has been gradually transformed from emerging scientific fields into sets of recombinant DNA technologies, leading to marketable products. The growing biotechnology industry is a recent phenomenon. The first biotech IPO – Genentech- dates back from October 1980. The industry is strongly concentrated in a limited number of countries or even country regions. Zucker, Darby and Brewer (1998) found that the presence of 'star scientists' – based on the number of registered sequences in the GenBank- is the most important explanation for the geographical emergence of the biotechnology industry in specific regions in the US in the 1980s. Human capital appears to be the strongest predictor of clustered industrial capital in biotechnology.

Flanders is one of the European regions that have always been at the forefront of biotechnology research and its various applications. The quality of the scientific research at Flemish universities is outstanding and recent figures even indicate strong progress. The Flanders Interuniversity Institute for Biotechnology or VIB unites the research forces of different universities and employs around 750 scientists and technicians. In 2002, VIB scientists published 147 articles in high-rank journals (Impact Factor > 5) with 51 publications in top journals (Impact Factor > 10) like *Nature Genetics, Cell, Nature Medecine, Plant Cell, Nature Cell Biology, Neuron, Immunity* and others. In 1996, there were 'only' 63 high-rank publications and 14 publications in top journals. The scientific output of biotechnology researchers in Flanders increased spectacularly. This is a strong indication of the high quality of the scientific human capital but some industry insiders remarked that current publication policies at Flemish universities seem to neglect that published breakthroughs cannot be patented anymore.

In 2003, VIB launched its 'VIB New Project Program' to attract top scientists in emerging biotechnology fields with strategic importance like tissue and stem cell biology, compound library technologies and interface research between biology, microelectronics and computational biology. More than 50 applications were submitted after the international call, almost half of them coming from the US. A striking feature was the great interest of Flemish scientists currently working in the US to return to Belgium and work at VIB. The reputation of some of these scientist is exceptional. Patrick Callaerts, one of the examples of this 'reversed brain drain', has been awarded the Newcomb Cleveland Prize from the American Association for the Advancement of Science for the best 1995 'Science' Paper. Thanks to

consistent increases in government funding for R&D, a world-class biotechnology research community developed in Flanders. Scientific research is rarely a goal by itself. At some point in time, public investments are expected to generate a return for society; useful products, problem-solving capacities, employment and socio-economic welfare. The latter goal requires the development of a dynamic and competitive biotechnology industry. In the next section, recent evolutions in the industrial community are discussed.

2. An emerging industry

The *pure* biotech industry in Flanders is relatively young and counts some 30 to 35 companies. The number of biotechnology companies varies according to the source and the used definition. In some publications, every firm that has some link with biotechnology is counted as a biotechnology firm (e.g. Algist Bruggeman and Interbrew). With respect to medical biotechnology, expertise has been developed mainly in the fields of diagnostics and platform technologies, and to a much lesser extent in therapeutics. This is not really surprising since in this young industry, there are only a few large biotechnology companies successfully bringing therapeutics to the market. Most of these companies are based in the US (Amgen, Biogen, Chiron, Genentech,…). Of the major pharmaceutical companies present in Belgium (Janssen Pharmaceutica, UCB Pharma, Baxter Healthcare, Pharmacia & Upjohn, AstraZeneca, Schering-Plough…), GlaxoSmithKline Beecham is the purest biotechnology company with its human vaccine production. From a broader perspective, many small companies provide services to these large therapeutic companies. When these small companies are also considered as therapeutic companies, over the last decade on average 40 percent of all US biotech firms operate in the therapeutics sector while in Europe as a whole less than 20 percent are engaged in therapeutics.

Next to pharmaceuticals, Flanders has also a strong tradition in related fields such as medical devices (with Contrel, Cyberonics and Guidant) and medical imaging (with Agfa).

Although the label *emerging* is still used for the biotech industry, the number of medical biotech products on the market is strongly growing and the pipeline with future products is really impressive. In recent biotech reports for Europe and the US, the product pipeline over the pre-clinical, Phase I, Phase II and Phase III is presented for the most important biotech countries. Although pipeline information should always be treated with some precaution, Table I shows that other small European countries clearly outperform Belgium in terms of (future) pharmaceutical product development. There are probably many diverse explanations

for this situation but the more important question is how this disappointing situation can be improved. The most obvious answer to the latter question is get active involvement from government. A partnership between industry, research centres and government is found in every successful country. Only with a well established industrial policy, new highly-knowledge intensive sectors can emerge, grow and flourish. In extremely complex regulatory environments – such as life sciences-, sector development can't be left to the market. This aspect will be further elaborated in the next sections but it is striking that in the UK- the leading European biotech country- the national bioscience industry together with several government departments recently published a report to safeguard a successful national bioscience industry. Simply too much is currently at stake. The biggest fear of the UK industry is that part of the industry will relocate to the US, attracted by the world's largest end-market, the critical mass of established profitable companies, the deep talent pool, and the generous funding (from the $ 27 billion annual budget of the National Institutes of Health through the most developed public capital markets for technology in the world in NASDAQ).

Table I – Product pipeline of public bioscience companies worldwide (2002)

	Pre-clinical	Phase I	Phase II	Phase III	Total
US	584	96	148	44	872
UK	65	50	56	23	196
Switzerland	45	12	11	11	79
Sweden	14	8	10	-	32
France	16	8	6	1	31
Denmark	14	5	5	4	28
Italy	9	-	4	3	16
Israel	2	3	6	4	15
Germany	7	4	3	1	15
Norway	8	2	2	3	15
Netherlands	9	1	1	-	11
Finland	9	1	-	-	10
Ireland	2	-	2	3	7
Belgium	2	-	1	-	3

Source : Pharma Projects for the US; Ernst & Young for Europe

Most of the Flemish medical biotech companies have been founded after 1995. Innogenetics, founded in 1985, is the only mature medical biotech company in Flanders from the first

European Biotech wave. Genzyme Belgium and Tibotec-Virco are two other important players with a business history of some 10 years.

The small Flemish biotech cluster employed some 1600 people in 2002. Employment in medical biotech companies is much lower and Innogenetics alone employs close to 600 people. Despite the spectacular increase of top publications by VIB and other Belgian scientists, the number of new companies founded each year is rather low over the last years. Innovative scientific breakthroughs mostly need further research before the market potential of derived products can be assessed. A research policy with most incentives dedicated to generate top publications risks to neglect less innovative research that is necessary to transform knowledge into economic value. A closer collaboration between industry and research institutes could lead to the selection of research fields in which more applied pre-market research will be concentrated. This type of collaboration or biotech niche-creation has multiple benefits. New firms can be created when the time-to-market is shortened thanks to more applied research. The reduction of market risks will improve the access to venture capital for the new companies. It is also conceivable that several new firms provide complementary services in the new niche. The collaboration with industry can also include important inputs from industry (equipment, regulatory support, logistics).

This collaboration should not be confused with a research policy that allocates most resources to applied research. Most research will be directed at the creation of frontier knowledge since applied research is traditionally the field where private industry takes the lead, often in collaboration with universities. However, when the goal of research investments is to stimulate the industry in Flanders, research priorities should be in line with this goal. Furthermore, the closer basic research moves to applied research, the stronger the negotiation position of universities.

3. New companies and cluster dynamics

New companies can be founded by existing private companies, can be a spin-off of universities or are the result of a joint-venture between private companies as well as universities. In Flanders, all types of new biotechnology firms can be found. Typical university spin-off companies are Methexis Genomics, reMYND, Vivactiss and Beta-Cell. New companies can also be a spin-off of several universities. PharmaDM was established in 2000 as a spin-off from the universities of Leuven, Aberystwyth (UK) and Oxford (UK).

DiaMed EuroGen, Galapagos Genomics and Xcellentis are examples of companies founded by private companies. Generally, the activities currently pursued in starters founded by existing companies already existed or were prepared inside the founding company. The activities developed in university spin-offs already existed or were conceived inside universities. So two different business models should be considered : the model of a spin-off commercializing knowledge from universities, next to the model of an existing company bringing specific corporate knowledge into a separate business entity. The network in which the new companies operate strongly depends on the origin of the company. University spin-offs conduct research as part of academic networks while company spin-offs generally work close together with industry partners from the beginning. This general observation will be illustrated in the next section.

New companies are founded because either private companies or universities consider the new knowledge as marketable : expected benefits exceed expected costs. This type of investment decisions include a high degree of uncertainty. Existing companies have some advantages compared to university scientists without entrepreneurial experience. In principle, existing companies should be able to set more realistic targets. Should the new company try to develop new therapeutics or should it develop specific knowledge that can be sold to the leading therapeutic companies? However, in industries with very specific knowledge dynamics like biotechnology, the best business model today can become outdated next week.

Next to the conventional investment decisions, it is quite possible that some companies are founded as a rational reaction to the limited funding opportunities for basic research. In Flanders, small and medium enterprises are targeted by the IWT. Furthermore, most large companies have multiple research goals but the chance of finding funding for each research trajectory is limited. Bringing a specific research trajectory into a separate business entity can make it much more easy to attract new research money.

4. Equity : size matters

Given the close connection of new firms to existing firms and universities, the initial operational costs for new companies can often be reduced by agreements to hire equipment and buildings, to share administrative personnel etc. This makes it possible to start a company with a limited starting capital. And indeed some recent Flemish biotechnology companies are founded with a very modest starting capital. BioMARIC is a privately founded biotechnology company with a capital of only 500 000 Euro. For many other young companies, equity

ranges from 1 to 3 million Euro. PharmaDM raised 2.6 million Euro of seed and venture finance to date. Equity of PharmaDM in 2001 was only 488 887 Euro. In 2001, equity of Beta-Cell totalled 1.2 million Euro and raised venture capital was 1.5 million. Total R&D expenses in the same year however totalled 918 788 Euro. The starting capital of RNA-TEC, a small company founded in 2000, was 900 000 Euro. Equity of AlgoNomics in 2001 was 3 million Euro and the company also raised 3 million Euro venture capital. These low figures not necessarily point to a problematic weakness for these companies. It is quite possible that a starting company with 5 scientists simply hires equipment from universities or other companies and realises a breakthrough that attracts abundant venture finance. After all Rudi Pauwels, the founder of Tibotec, developed in his own garage a robot that made it possible to later attract money from Janssen Pharmaceutica. However, when there is no spectacular progress in the first years, companies with a low working capital become extremely vulnerable.

A limited starting capital for a university spin-off can follow from limited resources for further research inside universities. Typically, universities do not invest in pre-market research although this would strengthen the negotiation position of universities in later phases of product/company development. In that case, leaving the university can be the condition to attract venture capital. In some other cases, privately founded companies with a very low starting capital could be a rational response to available funding opportunities.

Due to the enormous heterogeneity of the sector, it is impossible to define a starting capital benchmark that guarantees a stable corporate climate for 3 to 5 five years. However, even in non high-tech sectors empirical analysis confirms the risks of a small starting capital. Undercapitalised companies face the risk of remaining small. In sharp contrast, a recently founded company like Galapagos Genomics has raised 30 million Euro since its incorporation in 1999. The initial capital was provided by Tibotec-Virco and Crucell Holland, both private companies.

5. Clusters : size matters

International comparisons on biotechnology activities traditionally focus on the quantitative items like number of companies, employees, patents, venture capital raised, sales and R&D expenditures. Belgium and especially Flanders perform very well in these comparisons. These comparisons are however very relative. As already indicated, multiple definitions of a biotechnology company are used. Furthermore, competitiveness is a dynamic concept that can

be influenced by government choices. Some European regions can currently lag behind but they can host the leading companies of the next platform technologies. Furthermore, the characteristics of the existing companies are much more important than the number of companies. The future market potential of ten young companies that are strongly supported by existing companies and leading research institutes can hardly be compared with the impact of hundred small undercapitalized companies. Starting from this perspective, the dynamic competitiveness of a biotechnology region like Flanders depends mainly on the interactions between different companies and to a lesser extent on the number of companies. An interactive network of companies or a cluster has in effect a life cycle, conceptually distinct from but related to the life cycle of the technologies produced at the cluster. The forces that influence the growth and entry of firms in clusters are not simply related to the stage of each technology: they depend also on the stage of the cluster in its own life cycle. The strength of a cluster has multiple dimensions. A cluster can be an entry attractor, meaning that economic actors outside the cluster are attracted to the cluster. A cluster can also be a growth promotor, meaning that the companies in the cluster can grow just because they belong to the cluster. Both positive phenomena are conditional. Clusters need to grow or take-off. Growth is only possible once a sector-specific critical mass of the cluster is reached. Cluster growth is limited since mature clusters can be transformed in newer clusters with own dynamics. Empirical work on the US computing industry in the 1980s found that the critical mass for software development clusters was close to 9000 employees (Swann, 2002). As long as the software sector was smaller, growth remained modest. For peripherals and hardware, the critical mass was slightly higher (over 10000 employees) but the sector of chips development had a much lower critical mass (4000 employees). Given the growth of new applications and technologies, comparable *critical mass* indicators are hardly conceivable for most biotechnology industries. For the therapeutical biotechnology sectors that develop final products, the cluster concept is probably less relevant. The existing market situation is dominated by relatively few global pharmaceutical companies of which some employ more than 100 000 employees. Every pharmaceutical giant is composed of many clusters. With respect to therapeutics, only specific supporting niches can develop internal cluster dynamics.

The concept of critical mass has strong theoretical underpinnings but its policy implications are unclear. When the critical mass of a specific bioinformatics cluster should be *x* employees, which strategy can then be followed? One could think of sector-specific funds that provide equity to possible starters. This is however a strategy leading to an uncertain return far away

in the future. The most pragmatic strategy to reach critical mass is to attract large foreign companies, especially biotechnology firms with various activities such as diagnostics next to therapeutics and bioinformatics. These companies are not only important since they inject experience into a region. Most benefits from the presence of large companies are only measurable over time. Leading companies will outsource specific activities to small companies to limit up-front investment costs and risks. As such, a contract market for young companies is created. Young companies will locate into the region for other reasons too. They know that the leading companies employ many specialists and very experienced people. Some young companies will come to the region to profit from the available human capital potential. Especially experienced product managers in leading companies receive many attractive job offers from small companies.

The location decision of a big player in the industry has enormous symbolic value for the region. To choose a specific region among many others is a validation of the superior local business environment. The location decision of one important company can influence the future location decision of many other companies, also from other industries.

A competitive cluster policy should not only aim at providing incentives to start new companies. It should also ensure that critical mass is created in a relatively short period of time. Once other regions or companies could gain leadership in a specific industry and effectively protect their position with licensing agreements and patent policies, it is very difficult to overtake leadership. New industries therefore should be developed before potential competitors are strong enough to compete. Attracting leading companies is essential to increase critical mass in short time.

6. Flanders versus Denmark

Flanders hosts several important pharmaceutical companies but their activities in Flanders do not focus on medical biotechnology. So the described positive cluster effects on small biotechnology companies are limited. The Flemish biotech cluster grows but at a slow pace. Other regions in Europe seem to perform better. Denmark with a population of 5.3 million inhabitants is an excellent point of reference for Flanders. Denmark created with Medicon Valley in Hilleroed – 40 kilometres north of Copenhagen- the fastest growing biotech cluster measured by products in development. In Medicon Valley, founded in 1992, a couple of industry giants like Novo Nordisk and Lundbeck together with more than 100 medical biotech companies and 6 science parks employ 40 000 people and generate annual exports of $ 4

billion. Medicon Valley's seeds were sown in 1992 during discussions between researchers from the University of Copenhagen and the University of Lund in Sweden. These scientists discovered they had more collaborations with partners in the US and in Japan than with each other. Their willingness to increase collaboration among neighbouring countries has been enforced by the Oresund Bridge that connects the two nations. This bridge created many economic opportunities and strongly increased mobility of Scandinavian researchers.
As of 2003, 60 percent of the Scandinavian pharmaceutical and medical industry is located in Medicon Valley what makes it the 3rd largest Life Science Cluster in Europe. Around 50 venture funds are currently active in biotechnology. Danish universities received resources to invest actively in new domains like bioinformatics. The Center for Biological Sequence Analysis at the Technical University of Denmark was formed in 1993 and is now the largest bioinformatics centre in Europe. Already in 2002, Denmark counted more than 300 students with a MA or PhD in bioinformatics. No other region in Europe has this asset.

In 2001 alone, more than 20 new medical biotech companies were founded in Denmark. This is more than the number of new companies founded in Flanders over the last five years. A comparison is however difficult because the number of new companies in Flanders counts only pure biotechnology firms. Furthermore, small undercapitalized companies with a few employees cannot be compared with larger new companies. What matters, is the future development of these new firms. In Germany, 150 biotechnology companies have been created since 1999. There are currently some 370 biotech companies in Germany but the number of products in the pipeline from these companies is very low. The aggressive programme of venture capital funding in Germany is frequently criticized for leading to the hasty creation of too many companies that lack viable business plans. The strongest indication of the Danish success in medical biotechnology deals with the ability to attract leading biotechnology companies. In 2001, Medicon Valley could attract a $ 357 million investment from Biogen, one of the global leaders in medical biotechnology. The investment in Denmark will lead to the first non-US Biogen manufacturing facility and is part of Biogen's strategy to consolidate world leadership in biotechnology. The European headquarter of Biogen is in Paris but the company did not yet produce in Europe. Biogen will employ 400 people at the 24 hectare facility, of which half will be recruited in Sweden. The decision of Biogen was made after 14 months of thorough research and evaluation of many potential sites. It is not know whether Flanders was among the other sites. The importance of Biogen coming to Denmark cannot be underestimated. *Fortune* ranks Biogen among the '100

fastest growing companies' and in 2001 the income position of the company made it possible to pay cash for the new facility without requesting location incentives. As a result of the decision to invest strongly in new production capacity, many other biotech companies already contacted Biogen to consider joint ventures or technology licensing. So before Biogen arrived in Denmark, its expected arrival already created market potential for small production and engineering companies.

Danish officials correctly understood the importance of getting Biogen to Denmark and presented the case of Medicon Valley already in early 2000 at the US headquarter. The director of Copenhagen Capacity became Biogen's permanent contact point in Denmark. Ultimately, Biogen choose Medicon Valley because of the existing biotechnology and pharmaceutical cluster, the outstanding service from Copenhagen Capacity and other Danish officials, and finally because of the liberal business climate in Denmark that is comparable to the US business culture. The latter aspect is confirmed by the World Competitiveness Yearbook 2003 that ranked Denmark as the country in which bureaucracy hinders activity least. The second country in this list is Sweden, the US is on third place.

Biogen is not the only success story for the Danish biotechnology cluster. Genmab is also in the process of constructing production facilities in the valley. Medicon Valley could also attract Bayer to locate its Nordic headquarter in the biotechnology cluster, as well as Yamanouchi Pharmaceuticals, the leading Japanese pharmaceutical company with annual sales exceeding $ 3.5 billion.

In rapidly changing technological environments, predictions are hard to make but the chances of achieving *critical biotech cluster mass* and subsequent strong growth obviously look better in Denmark than in Flanders.

It would not be a luxury for Flanders and Belgium to closely investigate the recent investment decisions of non-European biotechnological and pharmaceutical companies in Europe. This analysis can eventually result in some basic recommendations that need not require large investments. The permanent availability of experienced local contact persons who really understand the sector and the specific needs of the investing company is probably the most important condition to attract leading companies. Does Flanders provide this type of service adequately?

7. Supporting biotech entrepreneurship and attracting foreign investments

New companies are strongly supported by the VIB. Since 2000, the VIB provides a bio-incubator to life science companies. The bio-incubator is a 40 000 square feet up-to-date building located in the heart of a hot-spot for biotech activity and is available for R&D oriented life science companies. Currently, the bio-incubator houses the following biotechnology companies; Ablynx, AlgoNomics, BioMARIC, Devgen and Methexis Genomics. VIB also established several core facilities focused on advanced technologies (with high through-flows, miniaturisation,…). These core facilities – a Micro Array Facility, a Proteomic Facility and a Genetic Facility- operate in a fee-for-service mode and are available for both academic groups and companies.

A broader and not just technology-oriented initiative is that of spin-off support by K.U.Leuven Research & Development. This unit promotes and supports the transfer of knowledge and technology between the university and the business world. The multidisciplinary team consists of legal counsellors, patent experts, economists and engineers/scientists. Next to supporting the development of business plans and helping to attract venture capital, Leuven R & D also provides management, intellectual property and infrastructure support.

In Ghent and Leuven, new biotechnology companies are adequately supported. In one of the next sections, one of the conclusions at the end of the company overview is that young companies seem to experience problems in the first growth phase. While there is in Flanders enough support to start a research intensive company, it is often heard that there is hardly support for R&D-intensive companies once they enter into the production phase.

In addition to supporting new companies, Flanders recently increased its efforts to attract foreign investments. The Flanders Foreign Investment Office (FFIO) provides free advice to companies that are interested to invest in Flanders. The FFIO has offices in Brussels, Dallas, Chicago, San Francisco, Tokyo and Singapore. In the Brussels office, some 5 general staff members work together with 7 project managers. According to the website of FFIO, most of the Brussels-based project managers started to work at FFIO in 2002 and 2003. Some 10 people work for FFIO in the US, of which only one person has a background in the life science industry. Less than 10 people work for FFIO in Asia.

An organisation like FFIO is indispensable for the further development of the Flemish biotech cluster. Flanders should offer to foreign companies the same services as offered in other

European countries. Given the very specific nature of the biotechnology industry, it would be advisable that FFIO has the means to invest in access to relevant biopharmaceutical knowledge. A foreign biotechnology company is not only interested in the central location of Flanders but often needs very specific information on for instance the organisation and characteristics of clinical trial structures in Belgium, on biopharmaceutical and related regulation in Belgium as well as in the European Union, on the speed of the regulatory process (not only biopharmaceutical), on the availability of specific scientists and professionals, etc…

8. The Flemish Biotech Cluster : company profiles

In this section, the network in which several Flemish medical biotechnology companies develop their activities is presented. In the small Flemish biotechnology cluster, it is difficult to find many comparable companies. As a result, very different companies have been analysed. This overview does not contain very detailed financial information on each company. This is not always relevant and it turned out to be rather difficult to obtain detailed financial information from young companies. Many promised to send annual reports or financial summaries but very few have been received.

This overview is based on research networks that can be expected for different phases of economic activities. Given the R&D-intensive character of the industry, we always try to start with the basic and applied research network and then continue with production, logistics and marketing networks. The latter networks are of course only relevant for companies beyond the research phase.

In general terms, the number of interactions between different companies depends on rather evident variables like the number of companies in the industry, the total number of employees, the type of activities in the companies and the history of the company. Typically, university spin-offs operate in a mainly academic network while starters founding by private companies seem to focus on industrial partners.

8.1 Innogenetics

Innogenetics, a Belgium-based international biotechnology company founded in 1985, is pursuing a challenging twofold growth strategy. The company is committed to becoming a world leader in high-value added diagnostics (especially 'theranostics') focusing on infectious diseases, neurodegeneration, and genetic testing. The theranostic approach can be defined as the clinical targeted integration of therapeutics and diagnostics. Tests are created that can identify which patients are most suited to a particular therapy. The new tests also provide feedback on how well a drug is working what makes these tests very valuable from a pharmacoeconomic perspective[1]. The theranostic approach is probably the most effective strategy to establish a niche reputation in the mature diagnostic market, valued at $ 20 billion and strongly dominated by seven companies[2]. Innogenetics established strategic partnerships with leading in vitro diagnostic players such as Bayer, Roche and Abbott.

Innogenetics has 9 subsidiaries, mostly to ensure marketing and sales of Innogenetics' products abroad. There are three special subsidiaries. XCELLentis has been incorporated to further develop wound care products while Delft Diagnostic Laboratory (the Netherlands) and Instituto Em Diagnostico Molecular Theranostica (Rio de Janeiro, Brazil) are subsidiaries that participate in research projects or provide input for research.

The principal technologies of Innogenetics are INNOTEST, LIA ans LiPA. The INNOTEST is based on ELISA technology and is used for testing large numbers of samples at low costs. The INNOTEST product line represents around 15% of total sales. LIA or the line immunoassay system technology exhibits excellent sensitivity, specificity and reproducibility for multiple disease parameters. The LIA product line accounts for some 25% of total sales. Half of diagnostic revenues comes from the LiPA products. LiPA is a multi-parameter detection system for nucleic acids, based on the reverse hybridization principle. This molecular product line addresses the theranostics market and the profit margin ranges between 50 and 80%.

In 2002, total revenues of Innogenetics were 55.4 million Euro, of which more than 86% resulted from selling over 20 diagnostic products. The profitable diagnostics business finances the development of new therapeutics. Operating income from diagnostics was 993 000 Euro in 2002 while operating loss from therapeutics was 17.4 million Euro. In 2002, total R&D

[1] The use of resistance tests to monitor HIV patients response to treatment can lead to annual cost-savings in drug expenditure of thousands of Euros per patient.

[2] Roche Diagnostics, J&J-Ortho Clinical Diagnostics, Abbott Diagnostics, Bayer Diagnostics, Beckman-Coulter, Becton Dickinson and Dade Behring

expenditures were 28.6 million Euro of which over 57% was for therapeutic purposes. In the same year, consolidated R&D income was 6.9 million Euro.

At present, Innogenetics's therapeutic portfolio consists of innovative candidates in the fields of hepatitis C, immune disorders and wound care (the latter through its wholly owned subsidiary XCELLentis). The clinical development program for a hepatitis C therapeutic vaccine is currently in Phase II. This therapeutic vaccine candidate contains a strain of proprietary purified viral E1 protein of HCV (E1). This candidate has been selected since a broad research program at Innogenetics suggested that the humoral and cellular immune responses to the HCV E1 envelope protein are largely impaired in patients with chronic active hepatitis C and may be important for clearance of HCV.

Preclinical programs are underway for the treatment of pulmonary edema and sepsis as well as for a prophylactic vaccine against hepatitis C.

Since 1996, Innogenetics has been listed on NASDAQ Europe. Currently, the company is listed on the first market of Euronext Brussels and is planning to engage in a public offering of new shares for a maximum amount of 11% of the current issued share capital. Innogenetics currently employs around 600 people.

Research network

Innogenetics organises collaborative research with universities and academic research organisations as follows :

1. Joint research projects between Innogenetics and universities. Innogenetics finances a significant part of total expenditures and makes use of IWT subsidies;
2. Innogenetics participates in academic research projects and pays one or two scientists at the university. The goal of this collaboration is to realize a Proof of Principle. Further research will then take place at Innogenetics.
3. Informal collaboration for testing and validation. This is more service-oriented research.
4. Ad hoc exchanges of materials with a material transfer agreement.

The latter two options are mostly used for collaboration with other private companies.

The focus of collaborative research is currently less on basic research but on validation although the company receives proposals for scientific collaboration from everywhere. This indicates the excellent scientific reputation of the company.

For Innogenetics, the quality of collaboration not only depends on the scientific quality of the researchers involved. For a company with products on the market and promising therapeutics in clinical tests, the time to achieve results or to solve problems is crucial. Therefore, collaboration is preferred with flexible and open organisations that have the means to achieve results under time pressure.

A quantitative assessment of research networks can be based on patent information or on publications. Publication information offers the advantages that annual changes in the number of publications, the number of co-authors or the geographical location of co-authors can be easily detected. Innogenetics developed over time a complex research network in which universities play a dominant role. An analysis of publications by researchers from Innogenetics can reveal structural characteristics of this network. In Table II, we present the evolution of joint publications over time. Only publications cited in the Web Of Science (ISI Science Citation Index – Expanded, 1972-2003) were used for the analysis. As of August 2003, researchers from Innogenetics co-authored in total 527 publications in ISI. Most of the publications relate to work on hepatitis C and hepatitis B with respectively 103 and 47 publications. Some 90 publications on hepatitis C deal with E1. Innogenetics furthermore has 57 publications on Alzheimer's disease, 43 publications on AIDS/HIV and 8 publications on the Creutzfeldt-Jakob disease.

For a company with three diagnostic product sets, many publications on HCV or HIV refer to LIA or LiPA. So the research networks for a specific disease in practise also conducted research to develop the most appropriate diagnostic products. Especially with recent and very complex diseases, a better understanding of the disease can be facilitated by precise diagnostic technologies. Diagnostic expertise is for the later development of therapeutics.

In Table I, the number of publications on five diseases as well as the number of geographical network point is mentioned for each year. A geographical network point is a city in which universities or hospitals are located that collaborated to research projects and joint publications. Often more than one hospital in a city collaborated to a project and publication but then only one geographical point is counted.

Table II – Network analysis based on publications by researchers from Innogenetics (number of publications – geographical network points)

Topic	'88	'89	'90	'91	'92	'93	'94	'95	'96	'97	'98	'99	'00	'01	'02	'03
HCV					2-4	4-5	15-32	24-28	10-20	5-8	8-12	5-7	4-8	8-11	12-20	3-7
HBV						4-6	1-2	1-4	2-4		5-9	7-8	9-12	6-6	8-11	4-5
Aids/HIV	1-3			3-2	2-5	2-5	3-6	4-5	4-10	6-17	5-16	1-6	6-18	3-27	2-7	1-3
Alzheimer	3-4	1-3	1-2	3-3	3-5	1-4	8-10	5-8			4-7	6-17	5-10	9-10	3-7	5-10
Cr-Jakob											1-1			4-6	2-7	1-3
TOTAL	4-7	1-3	1-2	6-5	7-14	11-20	27-50	34-45	16-34	11-25	23-45	19-38	24-48	30-60	27-52	14-28

Most geographical network points are located in Europe but there are large differences depending on the research subject. Joint publications on HCV started with a limited number of authors from Brazil and Niger in 1992. In 1994, authors from 32 locations collaborated with researchers from Innogenetics. Most of these authors worked in Europe but there were also researchers from Brazil, the United States, Japan, Argentina and Taiwan involved. In the same year, there were joint publications with researchers from Chiron, Roche and Abbott. After 1995, the number of geographical points has been strongly reduced but the collaboration with researchers from Brazil (Rio de Janeiro, Goiana and Sao Paulo) remained sustainable. Only in 1998, there were joint publications with researchers from China (Shangai) and Benin and Burkina Faso.

The publication network for HBV contains less publications and geographical points. In 1993 there were publications with mainly European researchers and with a team from Rio de Janeiro. Only in 1998, the publication network included authors from the United States (Seattle and Atlanta), as well as authors from India (New Dehli) and Venezuela (Caracas). Since 2001, there are publications with authors from Hong Kong and China (Macau). In 2000 and 2002, there are joint publications with researchers from Glaxo Wellcome.

The network for joint publications on AIDS/HIV started with collaborations with authors from Antwerp and Amsterdam. In 1992 and 1993, several joint publications were written together with African researchers (Gabon, Cameroon, Cote Ivoire). Between 1996 and 1998, the contributions from African researchers did increase. There are joint publications with researchers working in Senegal, Zambia, Nigeria, Congo, Cameroon, Gabon and Niger. The collaboration with authors from Dakar and Congo persisted until 2001. After 2001, the number of publication decreased and the network contained mainly European cities, next to Miami and Rio de Janeiro.

Joint publications on Alzheimer's disease started in 1988 with co-authors from Antwerp, Cleveland and Los Angeles. The collaboration -leading to publications- with researchers located in Antwerp continued until 2000. From 1992 until 1995, there were joint publications with researchers from Cambridge (UK). In 1995 a fruitful collaboration with researchers from Gothenburg (Sweden) started and yielded every year several publications. Other Swedish co-authors can be found in Stockholm, Malmo, Huddinge and Pitea. In 1996 and 1997, there were no publications on Alzheimer's disease co-authored by researchers form Innogenetics. Another fruitful collaboration, namely with researchers located in Munich started in 1996. It is striking that on Alzheimer's disease joint publications with authors outside Europe is rare. In 1996 and 2000, there are joint publications with researchers from New York and Toronto and in 2003 there are joint publications with scientists in Australia (Melbourne and Clayton).

The limited number of publications on Creutzfeldt-Jakob's disease does not reveal specific trends. Most publications in 2001 were co-authored by researchers in Sweden while in 2002 most publications resulted from collaboration with German research units.

This information on joint publications can be compared with a short overview for Chiron (Emeryville, California), one of the most important competitors of Innogenetics. Chiron was founded in 1982 and the focus of its activities during the 1980s was on HIV and hepatitis. After 1990, the company developed products against other diseases like kidney cancer and multiple sclerosis. In 1995, a partnership with Novartis AG was formed. In 2002, Chiron employed 4044 people of which 1819 outside the US. In the same year, total revenues were $ 1.276 billion with a gross profit margin of 63 percent of net product sales. In Chiron's actual vaccine pipeline, research on a HCV vaccine is going on in collaboration with CSL Ltd, St.Louis University and the NIH. The collaboration with CSL Ltd did lead to successful Phase I results.

Researchers from Chiron co-authored in total 2117 publications, more than 4 times the number of publications by researchers from Innogenetics. Since Chiron is more than six times bigger than Innogenetics in term of employees, the effectiveness of research at Innogenetics seems to be excellent. 436 publications by researchers at Chiron relate to hepatitis C. Around half of these publications (218) was published after 1994. In total, 311 of the publications on hepatitis C relate to E1. This is more than three times the number of publications on E1 by researchers working at Innogenetics. Researchers from Chiron also co-authored 295 publications on AIDS/HIV, and 68 publications on hepatitis B. In contrast to Innogenetics, researchers from Chiron have no publications on Creutzfeldt-Jakob's disease and only one publication on Alzheimer's disease.

Since the late 1990s, more strategic alliances with leading companies shape the future research at Innogenetics. Solvay Pharmaceutical became the first strategic partner of Innogenetics. Both companies started a research collaboration in November 1997. Solvay took a stake in Innogenetics' capital, today amounting to approximately 8%. This deal has been renewed in January 2003 for a period of three years. Both parties will complete the work-up of previous targets for drug development as well as explore new ons. Collaboration with other companies is presented in the next section.

Production and marketing networks

Innogenetics primarily uses three channels for marketing and distribution. First of all, there are own subsidiaries covering Germany, Italy, France, Spain, the US, Benelux, Switzerland, Austria and Eastern Europe. Secondly, a network of independent distributors is used and finally there are several strategic marketing and distribution partners such as Bayer Diagnostics and Abbott Laboratories. Marketing and production agreements with other companies typically contain research collaboration. This is the case with the agreements with Rhein Biotech, Bayer Diagnostics and Cepheid.

Rhein Biotech (acquired by Berna Biotech in July 2002)

In March 1999, Innogenetics concluded a strategic collaboration with Rhein Biotech in the field of biotechnological production. Both companies established a research program to develop *Hansenula polymorpha* strains for the production of specific proteins.

Bayer Diagnostics

In March 2001, Bayer acquired the exclusive worldwide sales and marketing rights to Innogenetics LiPA HIV drug resistance and LiPA HCV genotyping testing products. These products are now sold by Bayer under its own VERSANT® label. In return, Bayer made an up-front payment of 10.4 million Euro and an equity investment of 10 million Euro. In June 2002, Bayer paid a 2 million Euro milestone payment for the successful completion of the study on the clinical utility of HIV-1 resistance arrays (LiPA). This agreement includes further R&D funding and a transfer price for the purchased tests.

Roche Diagnostics

In May 2001, Roche Diagnostics and Innogenetics entered into an exclusive licensing and collaboration agreement to develop and market a new range of rapid molecular microbiology tests. Roche aquired a worldwide exclusive license from Innogenetics for the exploitation of these patents in the field of bacteriology. Roche paid Innogenetics an up-front amount of 10 million Euro but the deal includes also full R&D funding, milestone payments as well as royalty payments on sales. For Innogenetics, this deal provides a better valorization of its intellectual property through access to Roche's worldwide sales and marketing network.

Abbott Laboratories

In 1999, Innogenetics concluded a distribution agreement with Abbott Laboratories. According to the new distribution agreement of July 2002, the Innogenetics' LiPA HLA tissue typing products are now marketed worldwide by both Innogenetics and Abbott Laboratories.

Cepheid

In November 1998, Innogenetics entered into a research collaboration and supply agreement with Cepheid, a leading California-based micro-diagnostic technology company. Cepheid is providing its technology and system integration expertise (microelectronics and micro-fluidics) while Innogenetics' contribution will involve expertise in the development and processing of DNA-based test systems. Cepheid will produce the microsystems and Innogenetics will be the exclusive distributor of the resulting diagnostic products.

Innogenetics and the necessity to collaborate?

The network in which Innogenetics develops its activities is extended and complex. As long as the main goal of the company was research, academic partners dominated. However, those products with highest value added – the LiPA products- are distributed and further developed in close collaboration with dominant firms like Bayer Diagnostics. This will also be the case once the therapeutic vaccine against hepatitis C proves to be successful. Innogenetics is too small to finance a complete Phase III of clinical trails and possible partnerships are currently

discussed. Every possible partnership implies the sharing of profits but also of risks. A successful Phase III outcome does not lead by definition to a product on the market. There can be later complications or competitors can be earlier on the market with a similar product. A partnership for therapeutic products is therefore for Innogenetics the best strategy to limit the business risks and strongly increases total income by some up-front payments. Given the market value of an effective HCV vaccine, these payments will significantly change Innogenetics' balance sheet.

Collaboration with the largest companies not only offers access to their capital, technologies and scientific expertise. Large companies are best equipped to bring a new product to the market and this is a challenging task in the highly regulated markets of diagnostics and therapeutics. Every step during manufacturing and marketing of therapeutic and diagnostic products is subject to very strict regulatory controls that can be different in each country. The processes to obtain these approvals and the subsequent compliance with appropriate statutes and regulations are often complex, time-consuming, and require substantial resources.

For small companies, these regulatory costs can lead to a barrier that effectively closes the market. But even for a large company like Innogenetics, shifting the regulatory costs to strategic partners like Bayer offers enormous cost savings. In the 2001 letter to the shareholders it was mentioned that sales and marketing expenses have been reduced from 19.9 million Euro in 2000 to 16.8 million Euro in 2001. This reduction resulted from the transfer of the LiPA HCV and HIV marketing business to Bayer, mainly reducing sales and marketing expenses in the US. This cost reduction of 3.1 million Euro represents 7.5% of total revenues from product sales in 2001 (41.1 million Euro).

Competitors

Many companies work on hepatitis C vaccines but is difficult to compare the efforts and progress of all the potential competitors for Innogenetics. Furthermore, therapeutic vaccines should be clearly distinguished from prophylactic vaccines. Depending on the stage of development, very few companies have a therapeutic vaccine in Phase II of a clinical trial. The Austrian company Intercell AG (Vienna) announced in November 2002 the start of a Phase II with patients who exhibit no response to interferon-ribavirin combination therapy. The vaccine of Intercell combines a pool of five peptides and Poly-L-Arginine which is known to stimulate the immune system. When the study is successful – results are expected by the end of 2003- Intercell will go ahead immediately to enable international regulatory

filing of the product to start in 2007. In the past, Innogenetics worked together with Intercell what again illustrates that this industry is based on intense knowledge-networking.

Other companies working on therapeutic vaccines are Genencor/Phogen, Merix, Tripep, GenPhar. The vaccines of these companies are still in the development phase.

8.2 AlgoNomics

AlgoNomics was founded on the 30th of June 1999 as a spin-out of KULAK (Kortrijk-based division of KULeuven). AlgoNomics is operating from the Technologiepark in Ghent. The company is active in the drug discovery field and has its roots in structural bioinformatics. It owns a rich, proprietary platform for structure-based drug design. AlgoNomics' technology platform contains biologically validated, innovative tools, which have been developed in-house. These tools add great value in drug target characterization and lead discovery and optimization. AlgoNomics is a private company that raised over 3 million Euro in venture capital to date. The main shareholders are Gemma Frisius Fund (K.U. Leuven), Fortis Private Equity, KBC Investco and TrustCapital Technology. AlgoNomics' research is supported by government grants from the Flemish Government (IWT-Vlaanderen) for the implementation of its core research program, totaling 1.5 million Euro to date. The founders of the company are Dr. Johan Desmet, who was a post-doc researcher of the FWO-Vlaanderen at the IRC, and Dr. Ingnace Lasters.

In 1990, Algonomic's founders discovered at KULAK the "Dead-End Elimination" theorem. This theorem enables to predict more accurate structure predictions and was published in *Nature* (1992). The main engine of the technology platforms -the proprietary FASTER algorithm- is based on the Dead-End Elimination (DEE) algorithm. The discovery of FASTER in 1999 gave rise to the founding of AlgoNomics. This algorithm has the accurateness of the DEE-method, but is about 1000 times faster. Suddenly, a number of advanced applications were possible on a personal computer. Examples of these applications are flexible docking, analysis of structural flexibility, drug prediction and so on. Based on DEE, FASTER and other technologies, AlgoNomics developed the powerful technology platform Tripole™. It is a proprietary technology platform for target characterization and lead optimization used in the pharmaceutical industry.

A second platform is AlgoNomics' Epibase™, a product platform that is used to discover and select specific epitopes. This epitope discovery is applied to vaccine development for infectious diseases, for cancer treatments as well as to protein de-immunization.

AlgoNomics aims to become a leader in the discovery process of novel therapies for the treatment of human infectious diseases and cancer. To this end, it applies its proprietary technology mainly in the field of peptides and antibodies, and in the development of prophylactic and therapeutic vaccines. In order to realize its goals AlgoNomics intends to use

its technology platform to identify and improve potential therapeutic products. Additionally, AlgoNomics offers services and contract rights to other companies for the use of its drug discovery technology against payments and future royalties. Currently, AlgoNomics holds 7 patents. Finally, the company wants to bring products from research to early stage human clinical trials.

Network

AlgoNomics is a young company but collaborations with other biopharmaceutical firms and academic organisations are a central component of the business strategy. There are different types of collaborations:

- collaborations where AlgoNomics offers technology platform services to enhance drug discovery process of biopharmaceutical companies;
- academic collaborations in research projects to characterize drug targets (AlgoNomics brings in its lead discovery and optimization expertise) ;
- specific types of collaboration like outsourcing pilot production, biological validation, or (pre)clinical studies before seeking licensing partners.

Most collaborations with biopharmaceutical companies will take the form of a partner-funded study program of three to eight months in duration (Stage I). At the conclusion of this stage, the objective is to demonstrate that their lead discovery and optimization technology improves the drug discovery process substantially. At that time, the partner has the option to enter into a research collaboration program (Stage II), including negotiations for a licensing agreement pertaining to the specific compounds studied. AlgoNomics believes that this partnering approach allows more intense and frequent collaboration with other companies. Important ongoing collaborations involve Innogenetics, Pepscan Systems and Ablynx. Since February 2001, Innogenetics uses the Tripole™ and Epibase™ technology platforms of AlgoNomics for vaccine development. Pepscan Systems BV is a Dutch biotech company offering peptide-based discovery technologies for studying protein-protein interactions and identification of lead peptides. These tools are internally used for a strong pipeline of synthetic peptide vaccines that target humoral mediators of oncology.

AlgoNomics argues that collaboration on their technology platforms Tripole™ or Epibase™ gives a partner the advantage of acceleration and cost reduction of the drug target characterization and lead discovery and optimization. Also, the partner gains a better understanding of protein and peptide molecular structures and binding properties, reducing surprises and lowering the probability that drugs with adverse effects will survive early stage discovery screens and enter clinical trials. Next, all theoretical binding properties of a drug target and their potential leads can be mapped, thereby improving the intellectual property. Finally, collaboration allows predicting and improving binding possibilities on drug targets that are hard to find in a laboratory environment.

The most important academic collaborations were initiated with:

- Laboratory for Retroviral Research (LU)
- Medical Research Council (Cambridge, UK)
- Institute of Tropical Medicine (Antwerp, BE)
- Academic Medical Center (Amsterdam, NL)
- Rega Institute (Leuven, BE)
- Université de Liége (Liége, BE)

8.3 XCELLentis

XCELLentis was established in February 2001 as a spin-off of Innogenetics. The rationale for this wholly-owned subsidiary of Innogenetics was twofold. First of all, the new company would increase the focus on Innogenetics' wound care activities and build on in-house competencies. Secondly, separating wound care from other activities would increase the visibility of XCELLentis in the marketplace and thereby facilitating the build-up of market recognition. XCELLentis' products are geared to treat difficult to heal wounds such as burns and chronic ulcers. Additional target areas may include reconstructive, plastic and cosmetic surgery as well as otological wounds. In 2002, 19 people were employed by XCELLentis in Merelbeke.

By the end of the 1980s, Innogenetics was already active in the field of autologous wound healing (AutoDerm), i.e. with patients' own cells, and allogeneic wound healing (TransDerm), i.e. with donor derived cells. By 1994, Innogenetics tried to make a marketable product on the basis of their in-house knowledge. Grants were given by IWT-Vlaanderen and VLAB (Vlaams Actie Programma Biotechnologie; this programme was also coordinated by IWT-Vlaanderen). Innogenetics collaborated with VUB (Vrije Universiteit Brussel) and the Brussels Military Hospital Burn Centre. Innogenetics had its production centre and its warehouse on the domain of the Military Hospital. The products AutoDerm and TransDerm are already reimbursed in Belgium and registration is ongoing elsewhere.

Beside these two products, Innogenetics also developed a donor-derived deep frozen tissue (CryoCeal) with a 6-month shelf life. The production of this product takes place in the infrastructure of Innogenetics. It is also reimbursed in Belgium and registration is ongoing elsewhere. To control expenses for this expensive product, reimbursement is only allowed when a hospital or burn centre provide this service.

The fourth product is LyphoDerm. It consists of freeze-dried keratinocytes, which contain the key factors that can stimulate and speed up the wound healing process. Because of the 'non-living' characteristic of this product, it is categorized by the American an European agencies as a medicinal product. Innogenetics started in 1995 with this project and collaborated with VUB. The pre-clinical phase was performed by an English company that has built up the necessary know-how during the past two decades. Grants were awarded by IWT-Vlaanderen for a part of production. Concerning clinical research, Innogenetics collaborates with Clinical Research Organisations (CRO). These CROs screen the medical centres that could participate, contact them, start up and conduct the clinical trials, and report the results. Concerning

LyphoDerm, study centers in the United Kingdom, Poland, Germany and Belgium are participating in the Phase II trial.
Finally, XCELLentis developed in close collaboration with Polymer Chemistry (Ghent University) a new self-supporting hydrogel wound dressing, named UlcoDress Plus. XCELLentis is planning to license out this technology for its commercialization.

XCELLentis regrouped Innogenetics' wound care activities. When XCELLentis was founded in 2001, the first products and networks of companies, university hospitals and dermatologists were already present. For basic research, XCELLentis collaborated with universities and support was given by government through IWT-Vlaanderen and VLAB. Concerning applied research, cooperation with a CRO is appropriate. Setting up their own production and distribution network is too expensive and XCELLentis has to rely on other bigger market players. For the production phase, XCELLentis is supported by its parent company. Finally, XCELLentis has given an exclusive distribution right for its wound healing products to Fagron, a subsidiary of Omega Pharma.
As mentioned before, AutoDerm, TransDerm and CryoCeal are already available. But the revenues from these products are too small to make the company self-supporting. These products are rather necessary to give the company its reputation. XCELLentis has made clear in which study field they are specialised and with the new LyphoDerm and UlcoDress Plus products they hope to become an auto-financing company. Nowadays, XCELLentis is almost completely financed by Innogenetics. In the future, the company wants to create its own financing sources.
Like most young biotech companies, XCELLentis faces some specific problems. One of these problems is that federal government regulations for wound healing products are unclear. Are these products transplants or medical devices? This is very important since it has implications on reimbursement. A company absolutely needs to know which rules are applicable on its product before bringing it to the market. The Ministry of Health should make the regulations more clear and transparent. Another regulatory problem is that Europe is not yet a market as unified as the US market.. The regulatory status of pharmaceutical products varies from country to country. This does not simplify the situation for biotech companies who wish to bring their products to the market. Another issue is that the reimbursement of clinical tests is highly regulated in Belgium and could be organised more efficiently. Currently, reimbursement is restricted to tests performed by academic institutions. But when private companies perform these tests more efficient, why can their tests not be reimbursed? It is

possible that the reasons can be found in the political and protectionist attitude of decision makers.

8.4 Devgen

Devgen is a privately held company set up in 1997. Devgen is also operating from the Technologiepark in Ghent and employs around 100 people. The company focuses on the rapid discovery of novel, validated targets and active compounds for the pharmaceutical and agrochemical industries. Its technology is based on the industrialization of the model organism *Caenorhabditis elegans*. Large-scale target identification experiments of human diseases are conducted with this organism. This allows the rapid selection of targets that restore the disease physiology to normal in this organism. Next, Devgen's proprietary comparative genomics tool rapidly identifies human homologues of the selected target. Assays using the human targets are then configured to perform target specific high throughput screening and to initiate drug discovery programs.

Devgen is active in the fields of human health and crop protection. The agro activities are booming. Whereas the activity balance agro/pharma was about 30/70 last year and 40/60 this year, it will probably be about 50/50 next year and possibly move further in the agro direction. The road to be taken will, of course, largely depend on the outcome of the different research programs and business opportunities. This turnabout is mainly caused by the fact that Devgen's technology is easily applicable to agricultural biotechnology research and it has become a profitable business. Due to the complexity of human diseases, the pharma side is more laborious and brings higher risks. It just takes more effort and time to develop a new pharmaceutical drug than a pesticide. However, Devgen continues its pharmaceutical activities since these have a larger long-term value potential. The profitability of the agrochemical activities is positive for the pharmaceutical activities. In the first place these revenues fund pharmaceutical research. Secondly, this positive financial situation strengthens the company's negotiation position and offers more time to find good partners.

Up till now, there were no problems to combine the agrochemical and pharmaceutical activities. For research purposes, the same technology is applied and from an administrative and accounting perspective scale effects are present. However, in the long run it is quite possible that the two branches will split up to create a distinct profile for themselves.

Financial

Institutional and venture capitalists were responsible for the short-term financial input. In 1997 and1998 Abingworth and GIMV invested 7.6 million Euro. In 1999, ING (BBL and De

Vaderlandsche), KBC, Life Science Partners, Sofindex, Rendex and Mercator raised another 23 million Euro. Another 6.3 million Euro was gathered in the year 2000 by Polytechnos and Capricorn. This resulted in a total raise of 37 million Euro since inception.

Devgen collaborates with pharmaceutical and agrochemical companies to further develop its technology and to pursue the development and commercialization of products. These partners provide Devgen with committed research funds, milestone payments for assays and royalty payments for products that might emerge from the collaboration. In 1998, Devgen entered in a two-year term collaboration with Janssen Pharmaceutica in the field of target discovery. In 1999 and 2000 a collaboration agreement was signed with FMC for the discovery of novel insecticides, which was continued for another five years in 2001. Other partners after 2001 were Sumitomo (agro), Genentech, Syngenta, Dupont (agro) and Merck. All together, these partnerships increased research revenues up to 23 million Euro. The revenues of external partnerships are responsible for the medium-term funding.

Besides the private input, funds were also granted to Devgen. In comparison with the private investors, these contributions were rather small. First of all, the European Community sponsored international projects. Next, the Flemish Government supported investments. Finally, support was also given by the IWT-Vlaanderen. In total, these grants amount to 6.3 million Euro over the period 1997-2003, with the largest part provided by the IWT-Vlaanderen. In the period 1997-2001, 3 million Euro was granted by IWT-Vlaanderen. This was about 9 per cent of Devgen's expenses for the same period, i.e. 32.7 million Euro. For the period 2002-2005, total IWT support will increase to about 4.3 million Euro or about 7 per cent of estimated expenses. Devgen's experience with IWT-Vlaanderen is that it is a professional organisation. This is reflected in its support to submit projects and the pace in which conclusions are taken and funds are received.

According to Devgen, the decisions of the Flemish Government with respect to economic support - other than through the IWT-Vlaanderen- take much longer. In general, it also takes a long time before the funds from the Flemish Governments for e.g. investments support are actually received and more explication has to be given to justify certain expenses.

Collaboration

In the beginning Devgen paid salaries of researchers at universities. This kind of academic cooperation is now reduced. Now Devgen prefers to pay fee for service or to swap services, which is not the daily routine in academic institutions. Devgen prefers to collaborate with

consultants and other private companies. The company also tries to internalize essential know-how by recruiting specialists.

Devgen's activities with private partners are concentrated on delivering validated targets that are drugable, in vivo and in vitro high throughput screening assays and lead compounds and identifying the molecular mechanism of compounds. As mentioned before, these external partnerships are very important for the medium term funding. Devgen's technology has also been validated through these collaborations.

Besides providing other companies with information, Devgen uses its technology platform in its own programs to discover and develop drugs. These programs are focused on metabolic diseases including diabetes, obesity and dyslipidemia, and several central nervous system related disorders. Devgen selected these areas since the market opportunities are obvious. Devgen will proceed independently up to the stage where lead compounds with in vivo therapeutic effects in mammals have been developed. Thereafter, further work will take place in partnerships with pharmaceutical or biotech companies. In other words, Devgen purely performs basic research. After research on mice, rats and higher forms of primates, Devgen will out license lead compounds for its clinical trials. Due to the high costs and risks, the company prefers not to invest in the following phases. Since the agrochemical branch is profitable, Devgen does not feel obliged to link its business to other companies immediately or license out its knowledge. Partnerships will result in milestone payments and royalties. These revenues may make the company self supporting for its research activities.

8.5 Vivactiss

Vivactiss is a Leuven-based biotech company that has been founded in 2001. The research activities that lead to the creation of Vivactiss were started early 1995 at IMEC, the Interuniversity MicroElectronics Centre of KULeuven. Vivactiss is IMEC's first spin-off in the emerging fields of microelectronics and biotechnology, known within IMEC as the Human++ program. Most of the early research was performed during the PhD of Katarina Verhaegen, one of the founders of Vivactiss. During her PhD work, a prototype sensor was fabricated in 1998. Biological tests proved that the device could sense the activation of living cells by addition of an agonist. A system was built (calorimeter) that allows the measurement of minimal temperature differences. The work resulted in the creation of Vivactiss, first incubating in IMEC (July 2001), and starting its activities in February 2002. Vivactiss' technology is situated on the cross borders of MicroSystem technology and biology. It is a biotechnology platform company primarily serving the life science industry, but also the food and chemical industry seem to be promising markets.

Vivactiss' activities require a dynamic combination of several scientific disciplines: biochemistry, biology, drug discovery, electronics, MEMS engineering and computer science. Vivactiss has as double mission statement to bring screening and assay development of any target at the fingertips of any scientist, and secondly to give the scientist information of the complete activity spectrum of any compound.

Vivactiss' in-house synergy between microsystem technology and biology enables the company to bring its proprietary microcalorimetry technology as a general and universally applicable assay technology to the drug discovery market. The microcalorimetry technology and a number of strategic applications are protected by patents.

Core business

Vivactiss' business is not geared towards consumer products and is inherently oriented towards the research activities of pharmaceutical industries. Vivactiss develops tools that facilitate the research process in the pharmaceutical and biotech industries. A clear cut distinction between academic research and industrial R&D is rather artificial but in the drug development industry the research is both more innovative and more applied than in university laboratories. Thus, contacts and contracts in both settings are equally important to

push the business forward. Obviously, a direct collaboration with an industrial partner generates revenues more directly.

Partnerships / Networking

Vivactiss has an ongoing collaboration with IMEC, which allows access to integrated sensor fabrication facilities. Vivactiss' partnerships are geared towards the pharmaceutical and biotech industry for drug discovery and development, and towards the food and (bio)chemical industry for enzyme/catalyst discovery and optimization, and physicochemical characterization. In the drug discovery as well as in the food industry segment, Vivactiss signed a collaboration deal with two multinational companies. The names of these companies are not made public. These collaborations were set up after thorough screening. Vivactiss wanted to get deals with large, well established and well known multinationals. They succeeded in contacting the right people via telephone conversations and internet searches. It is still very much of their strategy to seek for the 'right' partners in such a way.

In the area of the chemical catalysts Vivactiss acquired a 387 000 Euro subsidy from the IWT-Vlaanderen for an Industrial Research Project in collaboration with a department from the Katholieke Universiteit Leuven (Prof. Jacobs, Agricultural Sciences). This research collaboration is important since Prof. Jacobs brings in a wide network of contacts with multinational companies (Bayer, BASF, …).

For the drug discovery and development process, Vivactiss' technology allows testing of all kinds of targets, even the so-called 'tough targets'. It is their aim to revive orphan drugs, to expand the field of lead profiling and eventually to develop a proteome-wide screening, all this with only one technology and using only microliters of precious samples. For the food and (bio)chemical industry, Vivactiss' technology revolutionizes high-throughput screening of enzymes and catalysts because it can be done in harsh environments, without the constraints associated with conventional labels. It can visualize the effect of physical, biological and chemical additives in real-time, and this is a function of a large set of parameters, like temperature, pH, concentration, pressure, etc…

Vivactiss explicitly chooses to keep the basic knowledge in house and to outsource as much as possible other activities. The idea to build a huge lab was abandoned although the firm still aims at developing new drugs. In order to do so, they can purchase a chemical library or license in molecules. For the IWT-Vlaanderen project, all activities that are related to the Calorimeter, are kept internal.

Vivactiss's competitors consist of those firms that are also offering tools for steering the drug discovery/development process. No company has similar technology as Vivactiss has. Since the drug development process easily takes 15 years, a 'final' judgment about which technology is most appropriate will only be possible in a couple of years time. In the meanwhile, the different players are trying to convince the pharmaceutical industry of the superiority of their technology.

At the time of founding, Vivactiss had 2 pure technical patents and 3 applications. As of November 2003, a total of 7 patents are filed in the US as well as in Europe (of which 1 is granted). The management team needs to invest a lot of time and energy to follow up these procedures, to enhance their likelihood of being granted. Also, they need to screen the patent situation in their market continuously.

8.6 Tibotec-Virco

In February 1994, Tibotec was founded in Mechelen by Rudi Pauwels, an expert on HIV. Rudi Pauwels studied pharmaceutical sciences at the KULeuven and obtained a PhD in 1990 on the development of new anti-HIV agents. Around that time, Rudi Pauwels had the idea to automate the drug discovery process for HIV. This is a very labor-intensive activity especially since there are many HIV-strains which are resistant to different kind of compounds. For this purpose, existing robots needed to be adapted to the features of the 'laminar flow' workbench for the drug screening conditions for HIV. Rudi Pauwels started to work on his own and in 1994 he contacted Janssen Pharmaceutica in Beerse with his proof of concept (this was not a working prototype yet). Based on his proof of concept, Janssen Pharmaceutica was willing to pay the development costs in the form of contract research during the following months until the new company Tibotec was founded and venture capital was attracted.

During the first months Tibotec employed about 4 or 5 people and was established in the incubator of the University of Antwerp. It was very difficult to find a good location for Tibotec. The company needed expensive and safe laboratories (lots of regulations for HIV-research).

The automated screening process (the robot) for HIV offers two different applications, drug screening and diagnostics. Firstly, the automated process could be used for drug screening. More specifically, the robot offered the possibility to screen large numbers of compounds on their anti-HIV activities at a much higher speed than is possible with 'normal' screening tools. The main mission for Tibotec was therefore the discovery of new drug candidates in the fields of infectious diseases, including HIV/AIDS, and oncology. During the first years, Tibotec used the automated screening technology also to find drugs for other diseases such as Leishmania. However, these 'product lines' were stopped in order to focus completely on HIV drugs discovery.

Since 1994, Tibotec started to build its own database of compounds. Now the database includes about 250 000 compounds. Tibotec also set up a small team of researchers that went to Asia and Africa to study local 'medicinal' plants. The researchers extract different compounds from those plants that are tested to see if they have anti-HIV properties. Currently, the company has two drug candidates in Phase IIb of a clinical trial.

The second application of the automated HIV-screening process was for diagnostic purposes. The automated screening tool could be used to screen blood samples of HIV-patients to determine the type of HIV that infected them and to give advice on which drug cocktail would

be most effective for that patient. The end result of such a screening service is a medical report that is send to the doctor. This report contains valuable advice on possible treatments. This application is commercialized by Virco founded in 1995 as a spin-off from TIBOTEC. Virco does not sell the technology or method, but conducts the screening procedure.

The market for this service consists of pharmaceutical companies which use this service during their clinical trials of potential HIV drugs and of course HIV-patients. The latter market is however difficult to enter since insurance companies must pay back the costs of the screening and doctors must be willing to use it and follow the advice.

In March 2001**,** Tibotec and Virco merged because the complementarity of two companies turned out to be higher than initially thought. Virco has large databases of HIV wild types and mutants and the capabilities of screening growth rate of viruses. Tibotec has a broad knowledge on potential drug candidates and the capability of automated high speed screening of those compounds. Tibotec needs the knowledge of Virco about the different HIV-strains and the most violent viruses. Tibotec uses for its drug screening those HIV-strains for which all known drugs fail. So the first reason for the merger is the leverage of technological knowledge. There is also a financial reason. Tibotec is a drug development companies and is therefore confronted with large development types, high up-front investments and no cash inflow during the development time (except for contract research). Virco is a diagnostic company with a product on the market. After the merger, the cash flow of Virco could be used to finance part of the development cost of Tibotec. The merger did lead to some specific concerns. Virco delivered services to a lot of companies that were direct competitors to Tibotec. Performing diagnostic services for several large pharmaceutical companies in the industry gives Virco access to a lot of confidential information. However, Virco succeeded in building a firewall of confidentiality.

The acquisition of Tibotec-Virco by J&J in March 2002

On March 22, 2002, Johnson & Johnson (New Brunswick, NJ) announced that it has signed an agreement to acquire all of the assets of Tibotec-Virco. For this transaction Johnson & Johnson paid approximately $ 320 million in cash and debt. Johnson & Johnson did incur a one-time charge of approximately $ 145 million to write-off in-process research and development costs. As a matter of comparison, total R&D expenses by Tibotec-Virco in 2001 were 46.6 million Euro.

The initial dream of Tibotec was to become an independent therapeutic company but this goal turned out to be not realistic. The development cost for a new HIV-drug amounts to a minimum of $ 100 million. It is almost impossible to raise this amount with venture capital consortia. Given the bad economic climate, it is also not possible to raise enough money on the stock market. Next, the company needs at least another $ 100 million for the marketing and sales and for the subsequent clinical trials (Phase IV of trials for other applications). Additional investments relate to distribution and sales canals approximately three years before the drug is 'ready' to market, i.e. when the drugs go into Phase IIa.
The only possible way for Tibotec to get access to such large amounts of money and to distribution and sales canals was an acquisition by a large pharmaceutical company. In 2002, there were 4 potential candidates, which all conducted a due diligence. Eventually, Johnssen & Johnssen seemed the best choice for Tibotec-Virco because J&J is not in the HIV market and has no expertise in this disease. Thus, J&J is depending on Tibotec for its HIV-expertise and Tibotec can continue as a relative independent R&D unit within J&J. Further, J&J has the financial strengths to make the necessary R&D investments to get the new HIV drugs through the clinical trials and through the sales pipe.

The acquisition did not really change the business strategy of Tibotec-Virco. The company wants to become a meaningful independent R&D and service company in a billion market.

Networks

In order to fill in their business strategy, Tibotec and Virco built out a complete different network in which they operate.
Tibotec, as from 1994 until today focusing on product development and clinical research, has 'partnerships' at three different levels.

1. **Social Partnerships, World Health Organization, WHO**

   Tibotec cooperates in a cost recovery distribution program as a response to the dilemma that over 70% of the world's current 42 million people infected with HIV live in sub-Saharan Africa. The annual expenditure for global health needs in most of these sub-Saharan countries is approximately 5 US$ per capita per year. The small and fragmented pharmaceutical market in developing countries is characterized by weak health care systems, distinct disease environments, and general pharmaceutical

misuse. While pharmaceuticals are meant to improve health, these benefits can only be realized if existing pharmaceuticals are correctly used and are integrated into overall cost-effective public health measures.

The objectives of the programme are two-folded:

- ensure availability and affordability of Tibozole™(miconazole nitrate 10 mg muco-adhesive buccal tablet [MAT]) as a first line treatment for oropharyngeal candidiasis in people living with HIV/AIDS;
- gain experience in accessibility issues for resource-poor settings.

Actions undertaken by Tibotec are:

- Basic Drug kit initiatives: through collaborations with the Belgian government, WHO, and the World Bank, Tibotec has delivered more than 400,000 patient treatments of miconazole MAT as a component of Basic Drug Kits in Africa.
- Donations: Tibotec has donated more than 100,000 patient treatments of miconazole MAT through a variety of other programs in Africa.

2. **Research Partnerships**

   These partnerships are pure contract research partnerships. They support the research activities within the overall product development and clinical research performed by Tibotec. Tibotec has several academic partners performing support research activities within Europe and the US.

3. **Strategic Partnerships**

   Tibotec has one very important partnership with the Institute for Tropical Medicine, Antwerp Genesis, ITG. Common research is performed to get a better understanding of the different types of existing HIV-viruses. The ITG gets a lot of information out of this research regarding to the development of vaccines. Tibotec acquires knowledge to further develop their products. The research itself is subsidized by the IWT-Vlaanderen.

Problems related to these partnerships

Typically when partnerships need to share risks, negotiations often do not run smoothly. It becomes even more complex when academic partners are involved. The latter do not have a

tradition of investing themselves resources other than personnel in collaborative research projects. Tibotec often solved this problem by writing a proposal in order to get subsidies for the partnership. The fact that Tibotec made this effort distinguishes the company from a lot of other biotech companies. 80% of the obtained subsidies are of Flemish origin. Submitting to e.g. the 6th European framework program is a much more time consuming effort for young companies.

8.7 Galapagos Genomics

Galapagos Genomics nv (Mechelen, Belgium) was established in 1999 as a joint-venture between Crucell Holland BV (The Netherlands) and Tibotec-Virco nv (Belgium). Its other shareholders are Abingworth Management (UK), Apax Partners (France), Burrill & Company (US) and NIB Capital (The Netherlands). Galapagos' technology is based on Crucell's proprietary PER.C6^{TM} human cell line expression platform, for which it has an exclusive license for functional genomics applications. Tibotec has contributed with its mega HTS method by which quick automated research can be performed. This expertise of the two parents resulted in a unique functional genomics platform for the discovery and validation of drug targets and therapeutic genes. This platform consist of the construction and screening of adenoviral human cDNA expression libraries in a broad range of cell-based functional assays to identify genes of interest. Galapagos Genomics employed 81 people in 2002.

Technology

Understanding which genes are involved in biological processes and diseases is the start of the development of a therapeutic product. A gene product that is responsible for the initiation of a specific disease process is a potential drug target. In the beginning, Galapagos Genomics used phenotype selection libraries (PhenoSelect^{TM}) to discover therapeutic targets at genome scale, i.e. to identify those genes that have therapeutic relevance. It's mission was to offer the fastest gene to function technology enabling expedited target gene discovery and validation.
Beside PhenoSelect, Galapagos Genomics built two other human gene collections in adenovirus. FleXSelect is a human drugable gene over-expression collection and SilenceSelect is a human drugable gene knock-down collection. They differ from the PhenoSelect collection in the way that they are pre-selected based on membership of drugable gene families.

Funding and network

Tibotec-Virco nv and Crucell Holland BV provided the initial capital. In March 2002, Galapagos Genomics raised 21.4 million Euro in private placement with Venture Capital Investors and Crucell Holland BV. Since inception, Galapagos has raised 32 million Euro.

In the beginning, the company offered pharmaceutical and biotechnology companies access to its discovery platform (PhenoSelect) through partnering agreements. Galapagos developed customised functional assays for a partner to meet the desired discovery need. Alternatively, proprietary assays of the partner could be adapted for screening of the libraries. These assays were based on introducing the viruses into specific cell types and subsequent screening for the occurrence of a desired phenotypic change. Identified targets are further validated by the partner or by Galapagos.

In the year 2000, Galapagos had collaborations with Incyte Genomics and The Netherlands Cancer Institute, a non-profit organisation. In 2001, new contract services were concluded with UCB, Bayer, Vertex Pharmaceuticals, VIB, Incyte Genomics, Procter & Gamble Pharmaceuticals, Pharmacia Corporation and Euroscreen. In 2002, Galapagos collaborated with Exelixis and expanded collaboration with Bayer and Procter & Gamble. This year, further contracts were concluded with Degussa and Inpharmatica and collaboration with Procter & Gamble was expanded.

In the short term, these contract services were a good financing source and indicate Galapagos' ability to identify and validate drug targets with their powerful technology platform. But in the long run, a compromise between technology service incomes and further self development of the company had to be found.

Nowadays, Galapagos is applying its functional screening platform to both internal target discovery programs and external collaborations. Partnerships with leading pharmaceutical, nutraceutical and biotech companies remain but research activities are focused on internal programs in Alzheimer's disease, osteoporosis, rheumatoid arthritis and osteoarthritis. To increase the probability of success in drug discovery, specialisation was necessary. In addition to the projects in the core disease programs, Galapagos Genomics has validated cellular assays for asthma and type II diabetes. SilenceSelect and FlexSelect are screened in all these assays to identify drugable targets. Proprietary targets resulting from these internal programs will be used for the development of drugs in their core disease areas. This downstream development of drug targets discovered in their own internal research programs should happen both in house as well as through selective out-sourcing and licensing.

In other words, Galapagos Genomics used to be a service company in genomics and offered their technology platform to companies to use it for various fields of study. In the future Galapagos would like to be a drug discovery/pharmaceutical company. Within one year Galapagos would like to start with preparing the development of medicines. The company

could perform its activities on its own as long as it only concerns Phase I and maybe phase II of the clinical trials.

Academic cooperation is an appropriate way to gain know-how and to progress rapidly. Once knowledge was built up and the company focussed on its internal programs, collaborations with Big Pharma for cooperation in their niche became the focus over academic collaborations .

With respect to relationships with government, Galapagos Genomics was full of praise for IWT-Vlaanderen. In May 2000, the company was awarded a 2.7 million Euro grant, or 60 per cent of the total project cost, to construct and screen adenoviral expression cDNA libraries for the discovery and validation of new therapeutic targets. This project allowed Galapagos to further develop their functional genomics platform. This was necessary to be able to enter into valuable partnerships with pharmaceutical and biotechnology companies active in the drug discovery area.

In June 2002, another 2.6 million Euro grant was awarded by the IWT-Vlaanderen to Galapagos for a project aimed at building libraries of specific human gene classes for the discovery of novel therapeutic targets, which will form the basis for the development of new pharmaceuticals. This and another grant (1.4 million Euro by Senter, the Netherlands Institute for the Stimulation of Technological Development and Collaboration) allowed Galapagos to further broaden their functional genomics platform and support their own drug target development programs.

In November 2002, a 1.2 million Euro technology development grant was awarded to Galapagos for bone disease research. The project aimed at identification and validation of drug targets in related bone diseases, focusing on rheumatoid arthritis, osteo-arthritis and osteoporosis. This enabled the company to apply their technology in an important disease area and to move from a technology provider into a disease focused drug discovery entity.

The IWT-Vlaanderen gave a lot of financial support to Galapagos during its first years. This supported their growth and helped them to create their own niche. This was necessary to create a distinct profile for the company and become well-known. As a result, research collaboration with Big Pharma will be stimulated.

In the beginning, as mentioned before, the company started as a service company. Through contract services, Big Pharma could use their technology platform or Galapagos Genomics performed the research themselves and passed on the results to pharmaceutical companies. Now, the company focuses on the rapid discovery of novel drug targets and protein therapeutics for pharmaceutical development.

8.8 Thromb-X

Thromb-X (Leuven) is a biotechnological company which activities are focused on the development of thrombolytic and antithrombotic drugs and on the development of improved technologies for transgenesis in mammalian species. In 1991, Thromb-X emerged as a spin-off company from the University of Leuven and in 2002, Thromb-X employed 23 persons. The company was founded by Prof. Désiré Collen and KULeuven Research and Development. Prof.Désiré Collen directs the Molecular and Cardiavascular Medecine Group at KUL. This lab initially developed t-PA which is one of the most effective thrombolytic drugs on the market. The proprietary molecule is licensed to Genentech in return for royalties on worldwide sales. The activities of Thromb-X were initially dedicated to the research and development of a compound to dissolve blood clots.

In addition, Thromb-X started in 1996 with the development of improved embryonic stem (ES) cell technologies for transgenesis. Gene-targeted mice created at Thromb-X, have led to the identification of novel drug targets, validating the use of this technology for the development of pharmaceuticals. Thromb-x focuses on the R&D of transgenic animals. The purpose of this activity is to develop biotechnological reagents, animal models of human diseases and the use of stem cells for therapeutic applications. At this time, Thromb-X concluded an exclusive collaboration and licensing agreement with Leuven R&D and the Flanders Interuniversity Institute for Biotechnology. In 1999, Thromb-X started to function as the Research and Development division of the company ThromboGenics Ltd. ThromboGenics Ltd, located in Dublin, is a biopharmaceutical company focusing on innovative pharmaceuticals for the prevention and treatment of cardiovascular diseases, including Acute Myocardial Infarction (AMI), Central Venous Catheter (CVC) Occlusion, Peripheral Arterial Occlusive Disease (PAOD), Ischemic Stroke (IS), Venous Thromboembolism and Unstable Angina Pectoris (UAP). ThromboGenics Ltd currently has 2 compounds in phase II clinical trials for 3 indications, 1 compound for phase I and 5 additional compounds in preclinical development.

ThromboGenics has been founded in 1998 by Prof.Désiré Collen who also founded Thromb-X. On the website of ThromboGenics, Thromb-X is called the ‘development arm’ of ThromboGenics, respectively subsidiary or simply research lab. Thromb-X has recently reached a strategic alliance with Thrombogenics for the clinical development of thrombolytic and antithrombotic drugs. The R&D team of Thromb-X consists of 17 scientific, and

technical staff. ThromboGenics recently opened its US headquarters in New York City. According to Prof.Collen there is a great potential for research collaborations in the US pharmaceutical and biotechnology community that will help the advancement of the clinical programs. For the US headquarter, ThromboGenics could attract chief business officers with more than 20 years of global experience in the commercialisation of novel life science technologies. It is not so clear why ThromboGenics has been incorporated next to Thromb-X. Managing two companies brings additional transaction costs. However, this strategy seems to suggest that specific skills or resources where less available in Flanders than in Ireland.

Network

At present , there exists a strategic alliance between Thromb-X, ThromboGenics, Leuven R&D, CTG and CMVB for the development of thrombolytic and antithrombotic drugs. Thromb-X and ThromoGenics maintain relationships with leading contract manufacturers and contract research organisations such as 4C, Seneffe (Belgium), Covance Biotechnological Services (US), Quintiles (UK), Medisearch International (Mechelen, Belgium), Eurogentec (Belgium) and Shearwaters Biopolymers (US). In addition, Thromb-X markets its innovative embryonic stem (ES) cell technologies in Europe through its corporate partner Eurogentec. Thromb-X has currently 21 patents. Some of these patents are shared with other Centers, institutions, in accordance of an existing collaboration.

The Molecular Cardiovescular Medicine (MCM) Group is a basic research and R&D consortium comprising the Center for Molecular and Vascular Biology (CMVB) of the University of Leuven (KUL), the Center for Transgene Technology and Gene Therapy (CTG) of the Flanders Interuniversity Institute for Biotechnology and Thromb-X. These entities share 3600 m² of space, which was build with the support of the D. Collen Research Foundation and consists of fully equipped research laboratories, a 600 m² animalium for SPF mice, a 120 m² animalium for SPF rabbits and 4 biohazard safety suites. Both Centers work in close proximity, sharing laboratory space and equipment, but are identified and defined by their respective research projects and personnel. So, Thromb-X, operates alongside but separate from the Center for Molecular and Vascular Biology (CMVB) and the Center for Transgene Technology and Gene Therapy (CTG) of the Flanders Interuniversity Institute for Biotechnology (VIB). The personnel of Thromb-X is housed in rented laboratory space provided by the D. Collen Research Foundation.

CTG focuses on gene manipulation, gene transfer and drug design studies. The team comprises 69 scientific, undergraduate and technical staff. CMVB focuses on fibrinolysis, extracelaar proteolysis, hemostasis, astherosclerosis, and immunotherapy. Within the MCM Group a significant effort is invested in the operation of core facilities that are shared by all investigators, and are also available for external collaborators. Dissemination of gene targeting/gene transfer technology is canalised via collaborations or via scientific alliances. Studies performed as 'collaborations' are part of the research projects described. Studies performed as 'scientific alliances' are performed within the framework of 'technology transfer to third parties'. In gene targeting alliances, the embryonic stem cell culture and the generation of chimeric and transgenic mice is provided by the Center, whereas initial DNA work on the targeted gene and phenotyping of the transgenic mice is primeraly performed by allied research group.

Competitors

Thromb-X operates in a biopharmaceutical sector with a focus on cardiovascular diseases. In this sector it has to compete with players like UCB and Janssen Pharmaceutica. Because Thromb-X has still a strong link with the KUL, it can respond very quickly to new technologies. Furthermore, the established research network should make it possible to convert innovative research findings into attractive industrial products.

8.9 Janssen Pharmaceutica

Janssen Pharmaceutica is part of the world's largest healthcare company Johnson & Johnson. In Belgium the company has sites in Beerse, Geel and Olen. These employ 4 234 people and another 250 people work at Janssen-Cilag in Berchem. The company developed more than 80 drugs and is active in a wide variety of areas: mental illness, neurological disorders, anaesthesia and analgesia, gastrointestinal disorders, fungal infections, allergies, cancer, and biotechnology.

EPREX™

EPREX™ is a biotechnological product which brought a breakthrough in the treatment of the most common blood disorder, i.e. anaemia. Anaemia is a reduction in the number of erythrocytes in the blood. One of the most important causes of anaemia is a deficiency of erythropoietin, a protein secreted chiefly by the kidneys that promotes the production of red cells. Until recently, the only available treatment for chronic renal failure was blood transfusion. Epoetin alfa, marketed as EPREX™, PROCRIT™ or ERYPO™, is developed to treat various types of anaemia. It is currently the most widely used biotechnology drug in the world which already achieved sales of more than $ 3 billion. It is applied in the treatment of patient populations suffering from anaemia associated with chronic renal failure, HIV infection and cancer. Recently, it has also demonstrated to reduce the need for blood transfusions during surgery, without letting the patient participate in an autologous blood donation programme.

We had contact with MD J. Van der Veken, Senior Director Drug Evaluation – Clinical Operations of Janssen-Cilag. We asked if it was possible to receive further network information about EPREX™, especially about the research and clinical trial phases. After consideration, they did not comply with our request. As a result, we could only gather general information.

Johnson & Johnson Pharmaceutical Research & Development (PRD), the worldwide research organisation of Johnson & Johnson works together with Janssen Research Foundation (JRF). To enhance its growing reservoir of knowledge, Janssen Pharmaceutica also interacts with academic and other outside research organizations. As mentioned before, we could not further specify the partners Janssen-Cilag collaborated with for its research and clinical trials.

Janssen-Cilag has chemical production plants in Belgium, Ireland, Switzerland and the USA. The pharmaceutical production plants are located in Belgium, France, Italy, Switzerland, Portugal and Puerto Rico. The production unit for EPREX™ is located in Schaffhausen, Switzerland. A transport company brings the products to the warehouse of Janssen Pharmaceutica in Beerse.

Janssen Pharmaceutica and Cilag had established separate marketing and sales operations in various countries to support the medicines discovered in their laboratories. In the early nineties, these marketing affiliates were joined to form Janssen-Cilag, in countries where both had a presence. This unified structure allowed increased flexibility and customer responsiveness, and ensures the optimal use of resources. In Europe, Janssen Pharmaceutica's products are distributed by Janssen-Cilag. Janssen-Cilag in Berchem is responsible for the Benelux markets.

8.10 Genzyme Belgium nv

Genzyme Corporation is a global biotechnology company. The company was set up in 1981. It is dedicated to developing products and services specifically designed to meet unmet medical needs. It employs about 5,500 people worldwide and serves patients in over 80 countries.

Genzyme has three major divisions. '*Genzyme General*' develops and markets novel therapeutic products for well-defined patient populations. The focus is on the treatment of genetic disorders and other chronically debilitating diseases. Secondly, there is '*Genzyme Biosurgery*'. This division consists of Genzyme Surgical Products, Genzyme Tissue Repair and Biomatrix, Inc. *Genzyme Biosurgery* is a leader in the emerging market for biotechnology products to improve or replace surgery. The activities focus on orthopaedics and cardiothoracic surgery. Products are created to enable surgeons to reduce the time and complications of surgery, shorten recovery periods and improve patient outcomes. Finally, there is the '*Genzyme Molecular Oncology*' division, which develops a new generation of cancer products, focusing on cancer vaccines and angiogenesis inhibitors.

Financial

In 1986, Genzyme raised $27.4 million through a public offering. In this period, 75% of Genzyme's revenues were generated by product sales. Beside product sales and a public offering, money was also raised through R&D partnerships to fund the development of certain products. Up till 2003, the three divisions of Genzyme Corporation had their own series of common stocks quoted on NASDAQ: Genzyme General; GENZ, Genzyme Biosurgery; GZBX and Genzyme Molecular Oncology; GZMO. These tracking stocks provided the investors the ability to evaluate each division's individual performance. Genzyme eliminated this tracking stock structure on July 1, 2003. Now the company is listed as one on the NASDAQ stock exchange; GENZ. In 2001, Genzyme General ended the year with a market capitalization of $13 billion and over $1 billion in cash.

The most important product for Genzyme is Cerezyme®. This product was filed with the FDA in 1993. In 2002, this product raised about $619 million in revenues of which more than half came from outside the United States. This was about 52% of total product revenues. Patents protect the production method of the Cerezyme enzyme until 2010 and the composition of the Cerezyme enzyme until 2013. To compare with the more recent launched products, sales of

Thyrogen hormone were about $28.3 million and sales of Fabrazyme were about $26.1 million in 2002. Total Genzyme General's product revenues were about $1,199 in 2002. Taking into account service and R&D revenues, Genzyme Corporation's total corporate revenues were about $1,329 billion in 2002. Corporate R&D spending increased from $169 million in 2000 to $264 million in 2001 and $308 million in 2002, or about 23% of total corporate revenue.

Collaboration

In 1986, Genzyme had four facilities located in Boston and Cambridge, Massachusetts, and Maidstone and Haverhill, U.K.. In 1987, a new facility was constructed in Cambridge, MA. In 1988, manufacturing capacity in Haverhill was doubled. In the same year, an R&D facility was opened in Framingham, MA and one year later, a DNA laboratory was established over there. In 1992, a R&D center was opened in West Malling, Kent, to expand research capabilities. During the same year, the construction of a biopharmaceutical manufacturing plant began in Allston, MA, and plans were announced to add R&D and manufacturing facilities in Framingham. Genzyme also acquired Vivigen (Santa Fe), until then the cancer lab of Integrated Genetics. In 1994, another manufacturing facility located in Liestal, Switzerland, and BioSurface Technologies, Cambridge, MA, were acquired. The pharmaceutical facility in Liestal was upgraded in 1996. During the same year, Genzyme acquired Genetrix and added genetic testing labs in Tampa, Florida, and Yonkers, New York. In 1998, the pharmaceutical plant in Haverhill, U.K. was converted to a bulk Renagel® manufacturing facility, which was expanded in 2000. One year later, a plant in Waterford, Ireland was purchased to produce Renagel tablets and other products. In 2001, there was a major expansion of the Liestal pharmaceutical plant. Genzyme also acquired a protein manufacturing facility in Geel, Belgium. Beside the manufacturing and R&D facilities, Genzyme also has a lot of office space in Geel.

Each of Genzyme's divisions shares the combined resources of the Corporation, such as research an development, technology, manufacturing , intellectual property, and clinical and regulatory structures.

With respect to production, Genzyme works independently. For research and development Genzyme cooperates with external companies or buys the needed technologies. The companies affiliated to Genzyme in 2002 were ABIOMED, BioMarin Pharmaceutical, Cambridge Antibody Technology Group, Dyax Corporation, GTC, Healthcare Ventures,

Oxford Bioscience Partners, MPM BioVentures III, Myosix, Peptimmune, Pharming Group, ProQuest Investments II, Targeted Genetics Corporation, ViaCell and Wyeth Laboratories.

Genzyme in Belgium

The European headquarters of Genzyme were opened in 1992 in Naarden, the Netherlands. In Belgium, there are several subsidiaries of Genzyme Corporation (Cambridge, MA, USA). It has its 'Corporate Affairs Europe' office in Leuven and its 'Commercial' office for therapeutics and biosurgery in Ghent. Genzyme took over the Pharming Plant in Geel, which specialises in the development of a therapy for Pompe's disease. In the short term, this allowed Genzyme to assume control over the production of the transgenic enzyme and secure its access to nine patients with Pompe's disease that were participating in a clinical trial. Genzyme also started building a completely new plant in Geel. It will take a €130 million investment over two years and will focus on the production of new drugs based on recombinant enzymes and monoclonal antibodies to treat rare diseases. In 2005, this new plant of Genzyme Flanders should be operational. In the longer term, the acquisition of the Pharming Plant and the new plant will broaden Genzyme's manufacturing infrastructure by providing the company with a biopharmaceutical production facility located in continental Europe. This supports the strong growth of existing products and the launch of new products that are still in the development pipeline.

In September 2002, a Belgian sales office was opened in Zaventem. Within Genzyme General the Therapeutics business unit has products on the market in the areas of renal disease, thyroid cancer and lysosomal storage disorders (LSD). The sales office in Zaventem concentrates on the LSD products. Since the products are categorised as orphan drugs, Genzyme can make use of specific programs that support orphan drug research. The production of these products happens in Boston and Haverhill.

Cerezyme® (imiglucerase) is a recombinant enzyme replacement therapy to treat Gaucher's disease. This disease results from a deficiency in the enzyme glucocerebrosidase that is necessary to break down the fatty substance glucocerebroside. This genetic disorder affects less than one in 100,000 people. About 3,500 patients with Gaucher's disease in 75 countries are now on enzyme replacement therapy with Cerezyme®. Genzyme expects strong growth for this product line.

Fabrazyme® (agalsidase beta) is also a recombinant human enzyme to treat another rare inherited disorder, named Fabry's disease. This lysosomal storage disorder affects on average

one in every 40,000 males. Genzyme launched this product in the European Union in 2001. In 2003, the Allston manufacturing facility was expanded to include bioreactors for this product.
Thyrogen® (thyrotropin alfa) is the recombinant human thyroid stimulating hormone (rhTSH), developed to maintain quality of life for patients who have had their thyroid gland removed due to well-differentiated thyroid cancer. Thyrogen® was approved for use in the 15 member states of the European Union in 1999 and is marketed from 2001. In 2003, Genzyme received an extended European label for Thyrogen®.
Renagel® (sevelamer) is the first calcium-free, aluminium-free binder for reducing dialysis patients' phosphorus to normal target levels. Genzyme granted marketing approval of Renagel® capsules in the European Union in 2000. All patients who depend on dialysis to replace kidney function, about 225,000 in Europe, can experience high blood phosphorus levels. The primary active ingredient in Renagel® is manufactured in the United Kingdom. As mentioned before, the pharmaceutical plant in Haverhill, U.K. was converted in 1998 to a bulk Renagel® manufacturing facility. This production plant is going to be expanded and Genzyme bought a manufacturing facility in Ireland for the production of the tablet formulation of Renagel®, which will be operational in 2003. Future earnings growth will depend on Genzyme's ability to increase sales of Renagel phosphate binder.

Genzyme also has a strong commitment to develop *new products* to treat patients suffering from lysosomal storage disorders. It is currently developing enzyme replacement therapies for MPS1, Pompe's and Niemann-Pick B disease. For MPS1, the phase III study of Aldurazyme™ was successfully completed. Furthermore, Genzyme is also developing a substrate inhibition approach with small molecules for oral therapy of several lysosomal storage disorders. Additional treatment options in Gaucher's disease are also investigated. These therapies are either developed through Genzyme's own research and development programmes or through collaborations with a partner company.

Specific remarks

Staff members at Genzyme Belgium argued that the reimbursement procedure in Belgium has improved recently. A file has to be judged within 180 days. The problem is however the order only becomes valid after it has been published in the Bulletin of Acts. The file concerning Fabrazyme® was submitted in August 2001 and approved before the Summer of 2003 when the 180-days-rule was not operative yet. But up till now, the decree has not been published yet

due to the change of government. Fortunately, there is a special solidarity fund which intervenes financially when the medication is not reimbursed yet and the disease is life-threatening. The publication of decisions should however be accelerated.

Another problem is caused by the limited appearance of some diseases. Genzyme tries to make general practitioners become aware of the fact these diseases exist and can be treated. Information about diagnosis and treatment are given through e.g. direct contact, symposia, mailings and physician papers. Once patients are recognised, they can be treated with the expensive medications by their own general practitioner. However, it would be better to centralise these patients, not so much for treatment, but especially for follow-up. There are for example CEMA's which are assembly points for information and aid to persons with metabolism disease, which can be found in Antwerp, Brussels, Edegem, Diepenbeek, Leuven, Ghent, Liège, Gerpinnes-Loverval and Montignee. It would be interesting to have one place to follow-up patients with a certain metabolism disease.

9. Overview, conclusions and policy recommendations

Biotechnological research in Flanders is of very high quality and did lead to a number promising companies. The pharmaceutical industry and especially the medical biotechnological industry is characterized by long and expensive research and development phases. Surviving in this industry requires access to financial resources over long periods. In contrast to the US, Belgium lacks a tradition of a flourishing stock market with many biotech IPOs (Initial Public Offering). At this moment there are hardly any Belgian biotechnological companies on Euronext or other stock exchanges. As the economic situation seems to improve, there is a good chance that in the coming years some biotech IPOs will be possible. While successful IPOs can generate many millions of cash, the alternative of venture capital is less attractive. Venture capital funds prefer to invest modest amounts in many companies. This is a matter of diversification and risk management. In Flanders, it is striking that many new companies start with very modest cash resources. Although next rounds of financial inputs can follow after the limited initial investments, venture capitalists are by definition not interested in the long-term development of the company. The goal of a venture capitalist is to realise a profitable exit after some years. Venture capital can help to start up a biotech company but will always be insufficient to finance the complete development and market introduction of therapeutic products.

In many publications, it is stressed that the availability of financial resources for knowledge-intensive new industries in Flanders is excellent. This can be true but when the venture capitalist exits the biotech company after a couple of years, there is still no product on the market. Similarly, Belgian investment banks play an important role in several venture capital funds but are not eager to finance very risky biotech product development products.

The availability of capital for biotech start-ups in Flanders strongly improved when compared to the middle 1980s when a company like Innogenetics was founded. There are probably enough funds for small start-ups but sufficient funds for further company development are hard to attract. This problematic situation has important consequences for corporate strategies. Several Flemish biotech companies developed a twofold strategy in which one product category is financing another product category. Positive cash-flows from diagnostics (Innogenetics, Virco) or agricultural biotechnology (Devgen) finance therapeutic research. This is of course not an option for every start-up company. Coordinating two different business goals brings additional complications but once a product category yields operational

profits, the overall business risk of the company is reduced in comparison with single-product companies.

The company overview showed that most – but not all - biotech companies in Flanders are pure research companies, providing state-of-the-art technologies, services and tools to mature pharmaceutical, biotech or industrial companies. Research at these companies rarely leads, or will lead, to product development. Once Thromb-X entered Phase I/II of applied research, ThromboGenics in Ireland has been founded to manage further product development. Thromb-X remains a research department in Flanders. Remaining a research company brings inherent risks because only products on the market can generate cash incomes over longer periods. New technological developments can outdate existing platforms and strongly reduce the market value of pure high-tech companies. Furthermore, major companies outsource part of their research or technological services to focus on their core business of bringing products to the market. Under tough economic conditions, major corporations will cut back outsourced research and limit their scarce resources to internal research programs. Sudden business fluctuations can harm pure technology companies.

The ultimate goal of many biotech companies is to bring a new therapeutic product to the market. This goal proves to be very difficult to attain. Several biotech companies in Flanders, especially those close to commercialisation, confirm that bringing a product to the market depends on collaboration with 'Big Pharma'. With respect to therapeutics, Belgian young companies simply cannot finance a standard Phase III of clinical trials. Also for diagnostics and technology platform services, the regulatory costs before a product can be brought on the market can be overwhelming. Next to the regulations for marketing a product, product process regulation is of equal complication in specific areas. In addition, production technologies for biotechnology can be that unique that a lot of time passes before production can start. Young companies can have the best engineers but typically lack experienced product and regulatory affairs managers. Leading pharmaceutical companies have complete departments to manage product introduction and regulatory requirements. Furthermore, drug development regulation is constantly changing. In most countries, consultation with the most important industry representatives typically takes place before regulatory changes are adopted. Obviously, only large companies have access to the regulatory process and will try to shape the process to consolidate their position. Small companies are forced to hold on a passive stance and can never develop the same ability to launch a product without delays. A further complication for European companies is that the European market is still not really unified.

In the highly regulated health care market and drug development industry, bringing a product to the market is a business on itself. This market should not be approached with the same philosophy as for instance the IT-market. The existing diagnostic as well as therapeutic markets are dominated by Big Pharma. Small companies depend on collaboration with larger firms. This dependency brings the risk that Big Pharma can set the price (for assets, royalties, milestone payments,…). Ultimately, many small biotech companies act as price-takers during negotiations with Big Pharma or endanger their existence. The question whether or not Big Pharma pays a fair price for an acquisition (e.g. Johnson & Johnson paid $ 320 million for Tibotec-Virco) is very difficult to answer. From an industrial perspective, the ultimate question is whether or not government sees its role limited to funding research in small companies that will be later sold by dominant firms? When the answer is negative, a more active industrial policy is a necessity.

Several companies complained that the Flemish Government only developed a research policy but not an industrial policy. But the latter is essential in a highly regulated market environment that complicates spontaneous growth. In the literature on cluster dynamics, achieving critical mass is an essential condition before growth takes off. It is almost impossible to set specific critical mass benchmarks for biotech sectors but a strong initial growth of a cluster should be promoted by all means. Once several biotech clusters strongly grow and reach critical cluster mass, their competitive position will improve at the expense of those clusters that remained small. Furthermore, Europe will probably not host more than a few strong medical biotech clusters in the coming decades. The most obvious candidates for Europe's *general* medical biotech clusters are the UK, Switzerland and Sweden-Denmark. For the other countries, a targeted niche strategy can be most rewarding.

Currently, academic biotech research is heavily supported and companies in Flanders receive grants for industrial biotech research. That's it. Although informal contacts clearly exist, there is no structural collaboration between research centres, industry and government. There exist several positive local initiatives in Flanders but an industrial niche strategy is not elaborated. There is neither a close follow-up of the academic research results or a systematic screening of scientific results in terms of marketability. Also lacking is sufficient support for the commercialising of the research results and a service point to help companies with practical problems during the regulatory and (pre-) production process, etc… In general, a proactive industrial policy for biotechnology is lacking in Flanders. The inevitable result is that young medical biotech companies with therapeutic ambitions face growth problems and depend on collaboration with leading corporations for their survival. As large corporations are perfectly

aware of this dependency, they can almost unilaterally determine the conditions for further collaboration.

In Flanders, most research funds for biotechnology are managed by the VIB while IWT-Vlaanderen is the most important player for funding industrial research. We found that all the visited companies are very pleased with the role of the IWT-Vlaanderen. This is not so surprising since all these companies receive money from the IWT-Vlaanderen. In the recent years, the Flemish government strongly increased R&D expenditures. This was partly an effort to bring Belgian R&D efforts to the European average of R&D investments as share of GDP. Belgium still invest less than most other European nations. The recent increase mainly resulted in more research projects that could be financed. Some new companies have been founded but the impact of research funds on company development is unclear. Maybe Flanders is investing too many resources in frontier research that will only lead to products in the next decades. VIB is actively seeking for research proposals in newly emerging biotech fields. This is of course the appropriate role of an academic organisation but a fixed investment in pre-market research – not necessarily by VIB- could reduce future product development time and enforce the relationship with industry.

From a general perspective, research funding alone does not suffice to bring a product to the market and to create jobs in non-research activities like production, logistics and marketing. Only for specific service companies that offer screening tools, research funding can lead to sales incomes within a couple of years. For other companies, research funding became just an alternative for other financial resources like commercial loans. By launching new research projects, new research money is attracted but this money is not necessarily used to complete the research project. In some cases, the money of the grant is used to finance the commercialisation of earlier projects. One CEO stated he had in his desk 10 possible research projects. He had other priorities than launching new research projects but *'once more research money would become available'*, he would submit some projects to finance ongoing operational expenses.

Industrial policy for medical biotechnology can have many aspects. Medicon Valley is so successful because Denmark developed an excellent international reputation for quality clinical trials at low costs and detailed public registration. This is an essential condition for every region with the ambition to develop a medical biotech cluster. The UK will also invest in improving its attractiveness for setting up clinical trials. Denmark was also one of the first countries that invested strongly in bioinformatics. This was a modest investment in terms of

resources but with an important human capital return. Therefore countries with a strong pharmaceutical tradition have the highest chances to become the leading medical biotech countries. The investment decisions of non-European companies in Europe but outside Flanders should be closely investigated. Small biotech companies depend on large biotech and pharmaceutical companies so preferential relations with these companies are possible when all parties operate in the same geographical region. Despite the similarities between European regions, why are other regions preferred above Belgium? Once this question is answered, realistic ambitions for the future development of a biotech cluster in Flanders can be set. In network dynamics, the quality of the network stands or falls with the quality of each point in the network. We found that the collaboration between companies and universities is of crucial importance, especially for young companies. Several people at Flemish biotech companies complained about the problematic relations with Technology Transfer Centres (TTC) at Belgian universities. It often takes too much time simply to make up a contract. In some cases, it took 9 full months just to make up a contract while the best centres can manage this in 2 months. Time is a very important variable, especially for companies close to market introduction. Another finding is that some TTCs have no understanding of what really happens in industry and set unrealistic royalty rates that fully erode the profit margin of the company. Most of these problems probably result from understaffing at TTCs in Belgium.

Several companies explicitly demanded for coupling an industrial perspective to research policy goals. This is not a luxury leading countries such as the UK clearly plans to enforce its existing bioscience industry. Although there is already a rather close collaboration between industry and government departments in the UK, a Bioscience Leadership Council (BLC) will be established to further improve the collaboration between the involved stakeholders. Flanders should not try to copy the structures that exist in other countries but it is obvious that very complex and highly regulated industries depend on a close and targeted collaboration between research centres, industry and government. This collaboration can be successful when :

1. a niche - or a set of niches – is targeted and is the starting point of an adaptive and evolving strategy;
2. conditions that can complement the niche strategies become part of the strategy (e.g. investing in specific courses to guarantee the supply of enough specialists)

3. a share of frontier scientific research is allocated to these niches;
4. pre-market applied research in these niches is financed with significant input from industry;
5. a biotech service point provides low-cost access to advice for young companies;
6. an experienced organisation attracts foreign investments.

Flanders has certainly the capabilities to develop a medical biotech cluster. Past efforts need to be consolidated in an effective operational structure that dares to make choices and provide leadership.

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Appendix 1 : Publications by scientists from AlgoNomics

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Appendix 2 : Why DiaMed EuroGen is not in the company profiles

In a first conversation over the phone we had contact with Ir. Mondelaers of DiaMed EuroGen. We explained the purpose of our project and talked about the cooperation network. The first reaction was that everybody was very busy and that it was difficult to make time for things like this. Giving further explanation about the needed information and asking who could help us Mr Mondelaers noted their company did not cooperate with other companies. This was however not the case. We found e.g. information on the website of the Hellenic Pasteur Institute (Department of biochemistry, laboratory of molecular neurobiology and immunobiology) that they cooperate with DiaMed EuroGen. In the project "Innovative therapeutics for the prototype autoimmune disease, myasthenia gravis", Mr Mondelaers was even mentioned as one of the members of the principal research personnel (weblink: http://www.pasteur.gr/eng/research/molneuro_immunology_proj2e.htm)

We asked Mr Mondelaers whether he knew somebody else who could help us further with this subject. Mr Mondelaers preferred not to redirect us to one of his colleagues. Instead, he would see himself who could help us and contact us again. Since we did not receive any reaction we tried to contact Mr Mondelaers again. Since no direct or personal numbers were given we called to the general number of DiaMed EuroGen and asked for Mr Mondelaers. We were not put through with him and only received the message that Mr Mondelaers had informed his colleagues about the needed information but that the end of the year was always a very busy period and that nobody had time for this. Explaining the purpose of the project to the person of the general number and asking whether it was possible to be put through with somebody else did not help.