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Patterns in Biotechnology Industry in the Netherlands: An Evolutionary Approach

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Biotechnology is widely attracting attention as a generic technology used in many different industry sectors. This paper deals with biotechnology in the pharmaceutical industry in the Netherlands, by focusing on the spatial pattern of firms and on business strategies of an important segment, namely independently established firms. The pharmaceutical industry is relevant because it is expected to become the leading sector in the application of biotechnology in the near future.

The paper first discusses the theoretical basis for the interpretation of the location pattern of firms and the latter's strategies, i.e. evolutionary approaches. Further, it pays attention to the selection environment by focusing on market and technology trends, and institutional factors. These trends and factors are then linked with opportunities and threats for the application of biotechnology by small firms. Against this background, various strategies for survival are analysed, such as connected with uncertainty in R&D, shortage of finance and expertise, and lack of access to global distribution networks. Particular attention is paid to collaborative agreements with larger firms. The empirical part of the study is based on statistics covering the sector, as well as in-depth interviews with on-site managers of small firms.

Keywords: biotechnology, pharmaceutical industry, location pattern, the Netherlands, survival strategies, evolutionary approaches.



1. Introduction

Biotechnology is a broad generic technology; it is the application of scientific and engineering principles to the processing of materials by biological agents. By using this broad definition, biotechnology encompasses processes based on fermentation, cell culture and bio-catalytic principles, and those areas of biomedicine and agriculture which involve the application of cellular or molecular biology. Accordingly, biotechnology includes old activities like brewing and microbial production of antibiotics, alongside new activities. In a narrow sense, biotechnology is confined to those technologies connected with recombinant DNA-techniques and cell fusion (OECD, 1989). More recent definitions include combinatorial chemistry as a technique, as well as genome analysis. In the context of health care, the latter aims to depict the genetic sequence variation in humans, as the basis for variation in risks among individuals for medically important diseases. A relatively new term is life sciences (Ernst & Young, 1997). This encompasses new application fields like renewable resources and environmental affairs, aside from health care and animal health, agriculture and food processing

One of the key discoveries has been recombinant DNA technology (1973) which allows direct manipulation of the genetic material of individual cells. The ability to determine which genes are used by cells enables more control over the production of biological molecules than ever before. Thus, recombinant DNA technology can be used to develop micro-organisms that produce new products, existing products more efficiently, or large quantities of otherwise scarce products. It can also be used to develop organisms that are useful themselves, e.g. micro-organisms that degrade toxic waste, or new strains of agriculturally important plants. It needs to be emphasised that the commercial success of specific applications of recombinant DNA and other techniques depends critically on advances in bio-process engineering. Bio-process technology allows the adaptation of biological methods of production (such as single batches) to large-scale industrial use.

Basic research in biotechnology occurs mainly in the publicly funded science base, although industrial partners may be involved. Small specialist firms have historically been most effective in converting scientific discoveries into product and service ideas with commercial potentials. These firms have the flexibility to transcend disciplinary boundaries which are basically structuring R&D



departments and activity of large pharmaceutical firms. In addition, many large firms moved back to their core competence since the mid 1970s, times in which it was difficult to allocate budgets to entirely new technologies with highly uncertain outcomes. Although certain large pharmaceutical firms have developed in-house biotechnology R&D, there is an important role for the small firms' segment.

Nowadays, biotechnology is an important integral part of many industry products and processes (Ballentine and Thomas, 1997). The above discussion on terminology indicates that researchers come up with different statistical data on the size of the biotechnology sector, dependent on the definitions used. By using a broad definition of life science industry and confining this to small and medium-sized enterprises (excluding chemical and pharmaceutical multinationals), it is estimated that the sector encompasses almost 1,200 firms in Europe and almost 46,000 jobs here (Ernst & Young, 1999) (Table 1). Revenues amount to 3,7 billion ECU and investments in R&D to 2,3 billion ECU.

Table 1 Entrepreneurial firms in Europe and United States of America (1998)

Indicator	Europe	US
Revenues (a)	3,709	15,777
R&D expense (a)	2,334	8,398
Number of firms	1,178	1,283
Employees	45,823	153,000

(a) Euro in millions.

Source: Ernst & Young's European Life Sciences 1999.

The US has been more successful than Europe in creating a new industry based on biotechnology. Europe has partly missed the first wave of new specialist firms in the early 1980s exemplified by American Genentech, Cetus and Centocor (Daly, 1985). The relatively late take-off in Europe has caused a much smaller size of the present biotechnology-based industry compared with the US, such as in terms of revenues (3,7 versus 15,8 billion ECU) and employment (46,000 versus 153,000 employees). Europe's position seems now improving, particularly in terms of number of firms (witness a growth in 1998 by 14% versus 1% in the US) (Ernst & Young, 1999).



The Dutch biotechnology sector is relatively small with around 65 firms in all size classes and fields. There are no global players as far as the pharmaceutical industry is concerned. Dutch firms have, however, good opportunities to take niche positions due to a well-developed science base in the Netherlands. The latter includes important publicly funded research institutes, as well as well as an internationally advanced infrastructure for clinical testing (Ministry of Economic Affairs/Booz, Allen & Hamilton, 1993). With regard to the future use of biotechnology, it is expected that the contribution to the pharmaceutical sector will be the largest of all sectors in 2010 (Table 2). In the Netherlands, experts estimate shares of 34% and 38%, with agriculture as the second largest sector (20% and 38%).

Table 2 Percent share of biotechnology in turnover in sectors in the Netherlands (a)

SECTOR	1996		2010	
	I	E	I	E
Pharmaceutical	9	10	34	38
Agriculture	2	9	20	38
Food	3	6	30	25
Chemicals	13	6	27	20
Environment	9	4	18	21

a. Estimates by experts, from the sector itself (I) and from the remaining sectors (E).

Source: Degenaaars and Janszen, 1996.

2. An Evolutionary Approach

In management and innovation studies there is now a growing attention for evolutionary approaches, particularly concerning the interaction between firms and their environment over time (Baaij and van den Bosch, 1999; Douma and Schreuder, 1998). In highly innovative environments firms have to adapt themselves continuously, not only because of risks from a fast changing technology but also institutional factors (regulation) that cannot keep pace with new technology. Given such dynamics, evolutionary approaches seem rather useful in the analysis of the establishment and survival of firms in connection with opportunities and threats in their



environment. Evolutionary approaches seek to explain the movement of an entity (or entities) over time and the causes of the state of an entity at a moment in time in terms of how this entity got there. In addition, it puts an emphasis on the different adaptation of entities to changes in the selection environment (Nelson and Winter, 1982; Silverberg et al., 1988; Dosi and Nelson, 1994).

While major steps have been taken by Nelson and Winter in the early 1980s, there is currently a new wave of evolutionary theorising (cf. Dosi and Nelson, 1994; Cimoli and Dosi, 1995). This is fostered by various converging factors, such as the recognition of the difficulties of equilibrium theory - and the concept of perfectly rational actors - in the interpretation of wide fields of economic behaviour, the providing of useful heuristics for applied research, and the contribution of applied research to inductive generalisations from which evolutionary theory can draw behavioural assumptions. Evolutionary economic approaches provide the following important notions, more or less in analogy with evolutionary biology (Nelson and Winter, 1982; Metcalfe and Gibbons 1986; Arthur 1994; Dosi and Nelson, 1994):

- Firms embody the units of selection (equivalent of genes), such as technologies, strategies, and inherent preferences. Accordingly, firms are subject to various types of selection with the market as the single most important *selection environment*. In addition, there are selection environments such as government regulation and patenting regimes (institutions). Competition is the major mechanism of selection; there is competition with regard to market share and with regard to access to scarce resources (Pfeffer and Salanchik, 1978). Threats emerge from suppliers, customers, and new entrants, as well as substitute products and new technologies. Competition may lead to closure of weak performing firms through failure (bankruptcy) or acquisition by stronger firms.
- Different from Darwinian theory, the survival of strong firms does not rest on mutation by chance but on a more or less *active adaptation* to the environment. Accordingly, firms are seen as entities displaying purposeful behaviour and adapting themselves to the environment, as well as changing the environment to their needs (Baaij and van den Bosch, 1999). *Fitness* is the extent to which firms interactively adapt themselves to the multiple selection environment. The adaptation process is mainly directed by *routines*, i.e. forms of



rule-guided behaviour that are largely invariant to fine changes in the environment. Routines are based upon the learning history of the firm and pre-existing knowledge, and are associated with incremental adjustments, i.e. close to pre-existing patterns. Accordingly, firms' behaviour is largely path-dependent. Path dependency is the situation in which it is difficult to abandon once selected directions (e.g. technologies, product-markets) due to an accumulation of experience, routines (and networks) and capital in the recent past (Arthur, 1994).

- According to particular theorising in regional economics, path dependency in a *spatial* form tends to influence the location of new technology and new technology-based firms. This process is caused by the principle of increasing returns on investments and manifests itself in *agglomeration economies*, such as from the availability of highly specialised labour, knowledge and research infrastructure, and the proximity of specialised suppliers and customers. Accordingly, new technologies preferably emerge where the local selection environment provides a number of positive external economies and this is often based on *existing* structures (Boschma and Lambooy, 1998). In addition, it is recognised that stochastic developments may take place leading to unexpected concentrations of new technology.
- In selection environments where market competition is strong and R&D expensive and full of risks, the best mode of co-existence of firms with different needs and capabilities is to develop *collaborative relationships*, such as based on complementarity. Sometimes, relationships based on interdependence tend to the development of complex forms of symbiosis, a state in which no single firm can be considered in isolation.
- Some evolutionary models emphasise that particular firms look forward to anticipate future developments, while other firms do not (Silverberg et al., 1988). Accordingly, there are *offensive* firms (breaking new grounds) and *defensive* firms. A similar typology is recognised in theories about innovative behaviour (Freeman, 1982), i.e. first innovators and followers, and non-innovators. First innovators aim to maintain a lead over innovative competitors. This strategy is costly in terms of research efforts and risky in that the technology can fail or can be overruled by a superior adapted technology, but profits may be high after some painful first years. The point here is the recognition of diversity between



firms in their preferences and capability for adaptation.

Against the above theoretical background, the study addresses the location pattern of bio-pharmaceutical firms in the Netherlands and their strategies for survival, given different opportunities and threats in the selection environment. The analysis of the location pattern is based on data including all relevant firms in the Netherlands (Note 1). As indicated previously, there is an important definition problem influencing statistics about the industry. Based on various sources, 34 bio-pharmaceutical firms can be identified in this study by excluding other types of biotechnology industry like food and agriculture, and environmental biotechnology. Mere trade firms are also excluded. Different from the category of entrepreneurial firms mentioned in the introduction, large and medium-sized multinationals are included in our database (such as Akzo Nobel Pharma and Solvay) because they are potential places where new technology emerges (Table 3). In the Netherlands, the share of these firms is relatively small (17.6%). A majority of the bio-pharmaceutical firms can be qualified as independently established (61.8%). These firms are often relatively young and small.

Table 3 Dutch bio-pharmaceutical industry according to firm type

Firm Type	Absolute number	Percentage share
Established multinational	6	17.6
Newly established (foreign) subsidiary	7	20.6
Independently established	21	61.8
Totals	34	100.0

The exploratory analysis of survival strategies in this study is based on various sector studies (e.g. Degenars and Janszen, 1996; Ernst & Young, 1997/99) and on five in-depth case studies of small bio-pharmaceutical firms. Desk research (company documents, branch journals) and interviews with corporate managers at two points in time (around 1990 and in 1998) have been the main information sources. The analysis here is largely confined to independently established firms.

3. Opportunities



In the pharmaceutical industry one can identify three major trends indicating an important role for new bio-pharmaceutical firms. First, there is an ongoing process of merging and acquisition between large pharmaceutical firms. This development leads to a concentration of R&D and an outflow of highly qualified researchers. A good example is the merger of Swiss Sandoz and Ciba-Geigy, with the establishment of various small firms by former employees as a logical consequence. Secondly, among large pharmaceutical firms there is an increased preference for co-operation with small biotechnology firms (strategic alliances). Large firms need new ideas and products that witness clear market potentials at the same time that they avoid to cover a large repertoire of different technologies in-depth (the strategy to remain mean and lean) (NEFARMA 1998). Accordingly, it is expected that the pharma industry will spend up to a maximum of 30 percent of its drug discovery budgets for external collaboration (Ernst & Young, 1999). Thirdly, there is an important application of biotechnology in the development of new drugs for disease for which no effective therapy is available thus far. This is connected with the coming depletion of traditional development paths and the coming expiring of patents for traditional drugs. Regarding the latter, various major firms will see a huge proportion of their drug sales hit by patent expires in the next coming years. For example, more than half of Lilly's sales comes from products which face patent expiry by 2003. For Merck & Co this is true for nearly half of its sales (Ernst & Young, 1999).

New biotechnology offers various opportunities regarding the wide range of different technologies as well as the new combinations derived from them. When considering the technologies used in Dutch bio-pharmaceutical firms it becomes apparent that there are many of them, sometimes very different from each other (Degenaars and Janszen, 1996):

- Recombinant DNA
- DNA amplification
- Genomics
- Gentransfer technology
- Transgenic animals
- Cloning
- Cell/tissue culture and engineering



- Cell fusion technology
- Monoclonal and polyclonal antibodies
- Labelling of DNA and antibodies
- Protein engineering

A further interesting development is the merging of formerly separated technologies, leading to a range of new products, processes and services. A good example is the diagnostic kit and its use, combining information technology, micro-electronics and biotechnology in diagnostics. A further example is genomics, combining gene research with a highly intensive use of information technology and mathematics.

Another favourable condition in the selection environment in the Netherlands is the production of excellent knowledge in relevant fields by universities. In a comparative study between European metropolitan areas, cities like Amsterdam, Leiden and Utrecht rank high in the quality of their academic research, such as in molecular biology, immunology, and biochemistry (Science, August 1998). Given this situation in knowledge supply, alongside the favourable conditions for clinical trials, the relatively small number of bio-pharmaceutical firms points to a shortage of entrepreneurs that can transform scientific ideas into marketable products or processes. This phenomenon can be ascribed to a great deal of risks, to be discussed in the next section.

In terms of institutional trends, there is an ongoing government pressure to reduce expenses in human healthcare (van Geenhuizen and van der Knaap, 1997). This pressure manifests itself in a growing prescription of (relatively cheap) generic drugs and in price-reductions of patented drugs, leading to smaller revenues for basically innovative firms. This may work in favour of biotechnology firms regarding their potential to contribute to the introduction of more efficient and cheaper production processes. The policy for cost saving in healthcare manifests itself also in a decrease of consulting medical specialists. This leads to an increased demand for 'near patient-tests', often based on biotechnology.

4. Threats from a small firm's perspective



This section identifies various threats in the application of biotechnology in the pharmaceutical and medical sector in the Netherlands by considering young start-ups (Degenaars and Janszen, 1996; Ernst & Young, 1999). The threats are all very basic and usually much stronger than in other high technology sectors:

- *The uncertain nature of research outcomes.* In some cases, there is the threat of an entire failure. This is quite risky, given the fact that the development of a modern biomedical drug takes on average 10 years, including approval by regulatory authorities. At the same time, attention for particular technologies may be subject to swift change. For example, nowadays genomics and combinatorial chemistry increase in importance in the development of new therapeutic drugs, being almost unknown a few years ago.
- *Uncertainty from the time of emergence of the marketable product (process).* It often happens that the novel product or process emerges too early compared with market demand. This may be due to negative public opinion or a lack of context in which the discovery would fit.
- *A shortage of equity capital in particular development stages.* This refers mainly to basic research firms for which the period without profits is often longer than expected. It is also true for the stage in which small firms move to manufacturing and need capital for a production plant. At early stages of development, there is usually no shortage of investment capital in the Netherlands. Investments stem from individuals (founders, business angels), venture capitalists or strategic corporate partners. In later stages, public offering may be a solution but access to the Official Market of Amsterdam Exchange (AEX) is difficult due to various limitations. It is only very recently that two newly established exchange markets take account of the particular conditions of young fast growing firms (NMAX and EASDAQ) (Note 2).
- *A shortage of specific expertise and experience.* The application of biotechnology is a critical combination of different disciplines, like genetics, biochemistry, manufacturing under pharmaceutical rules, and entrepreneurial management. A shortage of the latter is often the key problem. Managing a bio-pharmaceutical firm means managing a number of paradoxes that may change in the course of time. For example, the entrepreneurial drive to launch a firm does not necessarily match with the ability to negotiate the financing by venture capitalists and securing interest from large pharmaceutical firms. The former aims at a safe use of their investments,



whereas the latter aims at innovation and creativity.

- *A shortage of qualified personnel* in the local (regional) labour market. This becomes apparent when a facility for manufacturing is planned and holds particularly for qualified laboratory analysts.
- *Difficulties in finding access to global distribution outlets.* Marketing and sales in the pharmaceutical industry are dominated by large firms that can afford the huge expenses for these activities on a global scale. Bio-pharmaceutical firms usually decide not to become an integrated firm, meaning that for marketing and sales they have to rely on other parties, often large pharmaceutical firms.
- *Uncertainty in intellectual property protection.* Small firms struggle with the dilemma whether to invest large amounts of time and capital in patent protection and potentially benefit from revenues from licensing, or do nothing and save time and money. A further danger is the small evidence about what can and what cannot be protected by patents, including the lack of European patent regulation. Since May 1998, the situation has improved significantly when the European Parliament passed legislation that makes human gene sequences and transgenic plants patentable under particular conditions. However, the EU directive on patents will be postponed in the Netherlands due to procedural mistakes (Ernst & Young, 1999).
- *Legal barriers to the use of transgenic animals for research.* Transgenic animals are seen as helpful and (in the future) cheap devices to produce certain compounds for human drugs. There are, however, ethical objections against such use of transgenic animals. A new law on the health and well-being of animals may cause important barriers in this particular field. The current Dutch policy can best be described as: “no, unless specifically approved by a committee”(Ernst & Young, 1999).

The above overall picture indicates various serious uncertainty in the early years and some later development stages of bio-pharmaceutical firms. When such situations of uncertainty coincide or accumulate, survival becomes questionable. As discussed in Section 2, evolutionary reasoning indicates that various uncertainty costs may be reduced by benefiting from external economies in existing clusters of (dis)similar firms and institutes.



5. Location Pattern

The main characteristics of the location of new bio-pharmaceutical technology in the Netherlands can be summarised as follows (Table 4):

- In terms of shares, the new technology has emerged in an almost even pattern in cities of different size. Only small medium-sized towns account for a relatively large part of the firms (38.2%). With regard to the regional distribution, the metropolitan region of the Randstad accounts for a small majority (58,8%).
- In terms of concentration, larger medium-sized towns are most important with large cities in second place (concentration quotients of 29.4 and 22.0 respectively).
- The most important larger medium-sized town is Groningen located at a distance from the metropolitan region of the Randstad; the most important large city is Amsterdam located in the Randstad.

The above pattern partly follows the existing spatial distribution of pharmaceutical industry (van Geenhuizen and van der Knaap, 1997) with concentrations both in the Randstad (medium-sized towns and large cities) and the adjacent zone. This confirms the reasoning in evolutionary approaches in that new technologies preferably emerge on the basis of existing patterns. However, at the same time, the spatial distribution points to an “unexpected” cluster of bio-pharmaceutical firms in the Northern part of the country.

Table 4 Spatial distribution of bio-pharmaceutical firms (a)

City-size (x 1.000 inhabitants)	Percentage of cities (1)	Percentage of firms (2) (b)	(2) : (1)
< 50	91.1	14.7 (5.9)	0.2
50 – 100	5.3	14.7 (8.8)	2.8
101 – 150	2.4	38.2 (26.5)	15.9
151 – 200	0.5	14.7 (0.0)	29.4
201 – 800	0.8	17.6 (17.6)	22.0
Totals	100.0	100.0 (58.8)	-

a. N = 34.

b. Within brackets is the percentage of firms per size-class located in the metropolitan area of the Randstad.



The following factors can be forwarded as favourable in Groningen and different from the Randstad. First, Groningen is located in a region that benefits from subsidies in the context of European regional policy and Dutch national regional policy. Subsidies may help to establish incubator buildings and provide relatively cheap premises. Secondly, actors in the academic world together with financiers and consultants in Groningen seem particularly active in identifying marketable innovative ideas (products) and providing opportunities to bridge the gap between such ideas and market introduction (van Geenhuizen, 1996). It may be that such an “entrepreneurial elan” can relatively easily flower at a university in an area without competing initiatives from other universities.

6. Survival Strategies

The results of the case study analysis indicate a large differentiation between firms regarding the level of innovativeness and risk taking, both at one point in time and in the course of time. The findings point to the following types of firm (Table 5):

- Firms engaged in basically innovative R&D over a long time period. They take large risks, including a considerable period without profits (such as firm A).
- Firms that manufacture an established product almost from their start. The present development activity aims at minor product improvement (new product types), and hence these firms are less innovative and take smaller risks (such as firm C).
- Firms that have been highly innovative in their first 5 to 10 years. Nowadays, they are engaged in development activity and manufacturing by contract from other companies and institutes. They reduce risks from the market by working by contract and on customer specification (such as firm B and E).
- Firms engaged in the development and manufacturing of innovative products, while contracting out basic research as well as manufacturing (such as firm D around 1990). These firms are like virtual firms.

It is quite clear that only the first type bears large risks in terms of highly uncertain outcomes of



R&D over a long time. Furthermore, it is interesting to see that small firms create various options to avoid risks in the initial stages, such as to undertake research exclusively by contract from other parties, to refrain from the most risky activities by contracting them to others, or to conduct risky activities by themselves but making use of laboratory equipment at universities. A further option is to add 'safe' activities in such a way that the innovative R&D can be financed internally. Accordingly, sales of accepted products from other manufacturers or relatively simple contract research may be added (Walsh, 1993; Feldman, 1998).

Aside from internal financing, capital in the initial stages is usually available from venture capital banks or informal investors. However, problems may arise when the R&D stage needs to be extended because of lack of results or when the firm needs to move to manufacturing activity under pharmaceutical rules. In these situations, there are three ways to attract capital while remaining independent, namely from investment banks, from a flotation on exchange markets, and from a large partner. In all cases, *trust* in the firm's fortune is of crucial importance. Accordingly, the best time for attracting equity capital is shortly after a major success has been achieved in the R&D. Thus, firm A has communicated its success in breeding transgenic animals in the press in Spring 1998 while planning flotation on the AEX later in the year. This illustrates the need for a creative interplay between R&D planning, financial planning, and public relations aimed at gaining credibility. Firm A also exemplifies a strategy in response to potential barriers from laws on the well-being of animals. The firm operates laboratories in various countries, which enables a move of the activity to a country without such barriers.

Regarding the need for specific expertise and experience, a good strategy is to establish a firm with a minimum of two founders, each with different crucial knowledge. Survival may be enhanced when the managing director has both experience in the technology and in entrepreneurial management of a pharmaceutical firm. Firm D exemplifies a situation in which the latter experience was absent among the founders. As a result, the investment banks involved in the through-start forced the firm to find a managing director offering such a combination of experience. Firm D also illustrates the need for in-house expertise in financial management.



It is almost crucial that small firms hold strategic positions in knowledge networks. This touches upon the following point. As indicated before, developments in biotechnology are risky in terms of uncertain outcomes and unforeseen changes. Path-dependency as a natural tendency of firms, therefore, needs to be avoided by a high alertness and easy access to the newest information. In addition, investments that 'fix' the direction in research of a firm for many years need to be avoided. Firm D exemplifies this avoidance by contracting research requiring a highly expensive infrastructure to other parties (public laboratory). There is, however, a need for a *balance* between core-activity and activity contracted to others. Firm D may have broken this balance and lost core-competence, a situation that probably contributed to its bankruptcy. The issue of path dependency is also relevant from another perspective. It seems that firms that were low innovative in their initial stages, tend to extend their activities later-on with low innovative products. The danger seems to be similar to the previously mentioned one, namely a loss of core-competence.

When there is a marketable product, small firms face difficulties in finding global sales and distribution outlets. A 'creative' strategy to overcome these difficulties may be to acquire the sales department of an established firm including established products in the same field. This is exemplified by firm C that uses the acquired sales organisation for selling and distributing its own products. In this particular case, lack of capital has been overcome by paying royalties to the previous owners of the sales department during a number of years. Furthermore, with regard to the above mentioned problems in finding qualified personnel, the case studies have brought to light the strategy of exchange and pooling of personnel between similar firms and research institutes in the region. This strategy of course, supposes that the start-up is located in a region with a concentration of bio-medical and pharmaceutical firms, and research institutes.

7. A Focus on Strategic Alliances

An option that may prevent most of the above threats is to enter cooperative alliances with large pharmaceutical firms (Ernst & Young, 1999; Senker and Sharp, 1997). The evidence in this study shows various forms of collaboration agreements aimed at improving the financial position of small firms and their access to marketing and global distribution channels, as well as an expansion of their R&D activity. One can observe a trend to start collaboration with a Dutch pharmaceutical firm and



then to add contracts with foreign firms. This points to a cautious learning approach, in which the small firm first gains experience with the national regulatory environment (such as registration).

Most collaborative agreements are based on complementarity in assets between the two partners. Thus, in the situation of a small innovative firm seeking finance a large firm often supplies this finance in return for new product ideas. Although such exchange is the essence of the agreements, the latter usually includes important side-effects for small firms. Evidence from the United Kingdom suggests that collaboration with established large firms gives small firms the credibility to raise further finance (e.g. through the Stock Market) and to develop further collaborations (Senker and Sharp, 1997). Furthermore, collaboration may have a tremendous impact on learning processes, such as concerning the way to conduct various stages of clinical trials and understanding of the market. In addition, the many informal interactions in the large firm's laboratory may lead to additional learning experiences, for example, in process scale up.

Collaboration with a large pharmaceutical firm is, however, not a bed of roses (Senker and Sharp, 1997). First of all, it is difficult and time-consuming to find the right partner that accepts the specific terms, unless there is a strong time pressure. Small biotechnology firms increasingly prefer the deals to be more of a partnership than a supplier-client contract (where payments are merely a fee for services), thus retaining more rights than previously. Secondly, there is always the question of the right time to enter an agreement. In some cases, it may be wise to hand over a discovery quite early in the process, namely before pre-clinical R&D. However, there is a growing belief that the best stage to leave activities to a big pharmaceutical firm is just before Phase III in clinical trials (a stage including comprehensive studies required by regulators) (Ernst & Young, 1999). Thirdly, the agreement may end in an unhappy way, such as in the case of large firms forced to sell most of their subsidiaries and shares (including those in small firms), due to huge losses from broad diversification in the past. Another unhappy situation that may be a reason for ending the agreement is a decreasing commitment of the big firm because the latter has so many other promising projects in active development.

A final strategy that needs to be mentioned here is full acquisition by the larger firm, while the small



firm remains relatively independent. This often happens when small firms need huge amounts of capital in order to establish a manufacturing plant. At the same time, it must be emphasized that a full acquisition may also lead to the dissolution of small firms, particularly when they are forced to integrate activities.

It can be concluded that under particular conditions collaborative agreements satisfy certain basic needs of small firms, and add to survival by important credibility effects and various learning results. These findings hold, however, for the short term. It remains unknown under which conditions collaboration with a large partner leads to a full acquisition and integration on the long run. In addition, it remains unclear whether the ending of a collaboration brings small firms back into a weak position.

Table 5 **Events and strategies connected with survival (case study evidence)**

Firm A

Establishment: in 1989, as a subsidiary; independent since 1994

Activities: basic R&D on transgenic animals and human drugs produced from their milk (a major success in breeding transgenic animals in 1998)

Successful Strategies

- Fine tuning of financial planning, R&D planning and public relations
- Good position in network of research institutes, enabling joint projects and investment by others in the firm
- Avoidance of legal barriers by using laboratories in different countries.

Firm B

Establishment: in 1986, independent (with founders experienced in pharmaceutical industry and process engineering)

Activities (around 1990): mainly R&D, additional manufacturing of monoclonal antibodies, both on a contract basis

Present Activities: mainly manufacturing of monoclonal antibodies, vaccines and proteins by contract; additional research on process development by contract.

Strategic Events:



- 1994, collaboration with large firm (minority share)
- 1996, joining of this firm in order to finance a production facility (remains a stand alone firm)
- 1997, opening of production facility (GMP)

Successful Strategies (present situation):

- Joining of a large firm
- Focus on core competence.
- Operation of a production facility close to the market (abroad).

Firm C

Establishment: in 1984, independent

Activities (around 1990): R&D (product improvement), manufacturing and sales of therapeutic drugs against allergy

Present Activities: manufacturing and sales of diagnostics and drugs against allergic disease; design and sales of bedroom clothing against allergy

Successful Strategies (around 1990):

- Research collaboration (1987/1988) with larger Dutch firms (enabling independent growth)
- Equity capital from flotation on the (non-official) Parallelmarket (since 1986), followed by an official flotation (1991)

Successful Strategies (present situation):

- Acquisition of sales activity of large company in order to sell own products (in 1991/1992)
- Opening of new production facility (to meet requirements for pharmaceutical registration).

Table 5 Continued

Firm D

Establishment: in 1982, independent (lack of scientific and management background)

Strategic Events:

- 1985/86, through-start, externally financed (various investment companies)
- 1985/86, appointment of managing director (combining biochemical expertise and management in pharmaceutical industry)
- 1994, bankruptcy

Activities (around 1990): development, manufacturing and (partly) sales of diagnostics

Successful Strategies (around 1990):

- Co-operation with large research laboratories (contracts capital-intensive research to others)
- Collaboration with larger Dutch firms in sales and distribution (since 1986)

Barriers to Survival (early 1990s):

- Weak financial management (connected with different investors)
- Lack of focus on core competence
- (Hypothetical) too much contracting to others and no solid internal basis.

Firm E

Establishment: in 1986, independent (two founders with scientific expertise)

Strategic Events:

- 1988, collaboration with larger Dutch firm (as majority share holder), mainly for marketing and



investment reasons (broken in 1990)

- 1992, joining of a larger American firm in the same field (as an independent business unit)

Activities (around 1990): development and manufacturing of ceramic implants

Present Activities: research by contract; manufacturing of ceramic implants and coating of metal components on customer specification

Successful Strategy (present situation):

- Synergy with American mother company.
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8. Concluding Remarks

Based on the previous analysis, a number of research paths can be identified. First, the results give rise to various hypotheses concerning the propensity of small bio-pharmaceutical firms to survive. These hypotheses address the role of particular strategies in survival, such as team entrepreneurship (combining expertise), collaborative agreements, and focusing on core-competence. It is necessary to test hypotheses by using a population of bio-pharmaceutical firms, thus enabling quantitative modelling. Such research needs also a focus on exploration and testing of the concept of path-dependency, by identifying the way in which early routines in innovativeness and risk taking behaviour, etc., have an impact on later performance and survival. A second interesting research avenue is concerned with the spatial distribution of the sector, particularly the concentration of firms in Amsterdam and Groningen. In this context, spatial differentiation in the background to new firm formation and the nature of survival strategies call for attention. The research preferably includes an analysis of external economies.

It is now widely accepted that the role of biotechnology in the medical and pharmaceutical sector will increase in importance and that small firms are a significant element. However, more than any other type of small high technology firms, bio-pharmaceutical firms are exposed to high risks. It is therefore, important to further improve the support from the business environment in the Netherlands. This is the subject of a third research pathway. It includes various recommendations for policy studies addressed to the national government and branch organisations. A major point of attention is the *science base* in the medical-pharmaceutical sector. The swift and unexpected shifts in emphasis require an extension of the science base in

different fields, in order to react efficiently on new developments. This calls for a continuous monitoring and interpretation of early warning signals in order to adapt the science base in the best direction, given a relatively small size of the country and limited budgets. A further important point is the critical availability of *management experience*. For bio-pharmaceutical firms without such experience, easy access to management knowledge would be supportive. A potential way is to establish a pool of experienced managers which advice start-ups on a regular basis. Another way is training. Quite recently branch organisation NIABA (Netherlands Biotech Industry Association) has organised a course for researchers seeking an entrepreneurial career and business people interested in entering biotechnology markets (van der Meer, 1999). There are a number of other important and broader initiatives in the field, mainly action lines from the national government aimed at the “protection” of gradual and solid development paths running from innovative ideas to marketable products. These action lines include the advancement of applied research, and the stimulation of high value added investments and university incubators. In addition, there are older (generic) stimulation instruments available in the system of public loans and subsidies, like a loan that bridges the stage between start-up and manufacturing firm with a focus on stages close to market introduction (Technology Development Credit). It is worth monitoring what type of firms emerge from projects under these supporting policies, what type of existing firms benefit most, and how survival rates change. A final point that calls for attention is the potential benefits from *collaboration* with a larger firm. It would be interesting to identify and test various models of successful collaboration, for example, regarding timing, precise terms, type of partner, costs and benefits, etc. This requires to identify the dimensions along which success needs to be measured and the conditions under which success may arise. Such models serve a better underpinning of collaborative agreements and accordingly, may contribute to survival of small firms.



Note 1.

A database could be established by using various sources, i.e. a guide for the biotechnology industry (Two Rivers, 1999), member lists of branch organisations (pharmaceutical and biotechnology industry), newspaper coverage, and inquiry by telephone.

Note 2.

NMAX is the New Market of Amsterdam Exchanges (established in 1997). This is an easily accessible market aimed at young, fast growing companies. It forms part of a network of similar markets in Europe.

EASDAQ is a screen based EU regulated stock market (established in Brussels). It also aims at young, fast growing companies.

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