OUTSOURCING RESEARCH IN THE PHARMACEUTICAL INDUSTRY

by

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ABSTRACT

Pharmaceutical companies tend to enter in more R&D partnering because of the pressure to deliver innovative drugs, the pressure to control R&D costs, and the rapid pace of biologic delivery. This represents a major shift for the biggest firms which are accustomed to retain research activities in-house. Pharmaceutical companies in the ethical segment of the business will have to manage some outsourcing of this core competence. They tend to collaborate more with biotech companies and to acquire the firms with the most complementary portfolio of potential products, or with new technology for drug discovery.

Recent disappointments regarding the financial performance of most biotech firms have reduced the funding available to aspiring biotech companies. Some new start-ups organize themselves as a virtual company with very little fixed costs. Virtual organizations reduce the amount of money required at the time of the company's creation. Alternatively, companies with a very attractive technology platform are able to fund their development through early licensing of their technologies. The collaboration with established pharmaceutical companies offer access to complementary capabilities to progress research stage compounds through the development process.

Academia is also facing financial constraints and is more willing to collaborate with the biomedical industry. Biotech companies, because of their origin and culture, represent a direct link between academia and the pharmaceutical industry. Academic centers are enrolled in network organizations that some companies create to develop innovative and difficult projects.

The challenges facing the biomedical industry, i.e., control of heath care costs, rapid biology discoveries, and the need for more innovative products are transforming its organization. Increased collaboration in research and increased consolidation in development are the new credo of the late 1990s in the pharmaceutical industry.

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INTRODUCTION

This thesis analyses the increase in the tendency for innovative biotechnology and pharmaceutical companies to collaborate with others to acquire or exploit research know-how. I will review the changes that are affecting pharmaceutical research and development, and how these changes are driving the outsourcing of research activities (chapter 1). I will discuss how companies can collaborate and maintain control on outsourced research activity (chapter 2). The data from the literature are compared to those obtained from field studies from companies of varying size, to illustrate the following situations:

- The development at Rhone-Poulenc of a relatively large research organization in the pharmaceutical industry (chapter 3).
- The creation of the Gencell network organization, within Rhone Poulenc (chapter 3)
- The creation of Apollo Genetics, a virtual biotech company (chapter 4).
- The creation of Millenium, a biotech company funded on large contract research and licensing agreements (chapter 5).
- A collaboration between industry and academia, based on the Amgen-MIT agreement
  (chapter 6)
- The acquisition by Genzyme of research capacities through small biotech company acquisitions (chapter 7).

Because it was difficult to design a unique questionnaire for these different situations, the data collected may seem heterogeneous. However, they illustrate specific situations that pertain to the changes in the biotechnology industry. We cannot draw formal conclusions from these case studies, but we will compare them to other surveys,

or studies on the same topic. This will be done in the discussion (chapter 8), that contains data obtained at two recent meetings on the relationships between academia and industry, and pharmaceutical and biotech companies.

CHAPTER ONE

CHANGES IN PHARMACEUTICAL RESEARCH AND DEVELOPMENT

In this chapter, we will review the recent changes affecting the pharmaceutical research and development. We assume that the reader has a good knowledge of this matter. A good review of pharmaceutical R&D is provided by the Office of Technology Assessment report (1993).

THE WORLDWIDE STRUCTURAL CHANGE OF THE PHARMACEUTICAL INDUSTRY

In the 1970s and 1980s, the pharmaceutical industry blossomed. Sales for the industry increased 10% annually in the 1980s, resulting in an exceptional compound annual earning growth of 18%. The early 1980s was a golden era for the industry: drugs representing 26% of the world pharmaceutical market were launched between 1981 and 1986 (Lehman Brothers).

As we entered the 1990s, managed health care organizations became the dominant force in controlling health care costs in the US and abroad. This force has created a shift of power from drug manufacturers to drug purchasers and payers.

In the US

Managed care organizations control pharmaceutical utilization and costs through formulary management, generic substitution and utilization review. Sixty percent of the American market will be controlled by managed care organizations in 1995. Employers,

with or without an HMO option for healthcare, may offer a separate drug benefit for employees by contracting with Pharmacy Benefit Managers (PBM), such as Medco. PBM contracts are increasingly capitated whereby the PBM will guarantee a corporation pharmaceutical coverage at a fixed premium per employee. As a result of these changes, the key to success of a drug in the 1990s is to be listed on most formularies as possible at reasonable prices.

With pharmaceutical prices declining without a matching offset in drug industry expenses, the return on pharmaceutical research investments is falling. A precipitous fall in R&D returns suggests pharmaceutical research budgets should be slashed and, in fact, several US-based drug companies have budgeted for flat to declining research spending in 1994 compared to 1993.

Drug companies must rationalize and refocus R&D activities. Marginal and me-too projects should be eliminated. Drugs unable to prove cost-effective in comparison to existing therapies should also be discarded.

In Europe and in Japan

Governments in Europe have been exercising their regulatory powers (delisting of drugs from reimbursement, mandatory price cuts) to slow down the rate of pharmaceutical growth and obtain better value for taxpayer money. In 1993, the German and the Italian market shrank by 12 and 5%, respectively.

In Japan, the government mandated limitations on hospital reimbursement, drug prices, and physician services.

In conclusion, Lehman brothers expect that margins and returns on R&D will fall. The requirement to reduce internal R&D and manufacturing capacity will prompt a write-down of asset values. The reduction in R&D staff is already reflected in an

increased use of contract resources. To maintain return on capital at current levels the industry would have to increase its average operating margins to 30% from 24% (Lehman Brothers, 1994).

Three things have changed to unsettle the favorable relationship which has existed between R&D spending and the profits which can derive from it:

First, whereas R&D spend as a proportion of sales was only around 5-7% for a typical company in the first half of the 1980s, this has now more than doubled to around 15%;

Second, price increases on existing drugs are no longer routinely achievable for drugs which are readily substitutable;

Third, the prices for new products, even with innovative characteristics, are not guaranteed to be premium. Companies will have to negotiate the prices based on cost-benefit analysis with managed care organizations (or social security systems in Europe).

Only *blockbuster drugs* with sales of at least $500 million per annum can make a meaningful difference to the sales growth of a major company. The new managed care environment will stimulate more price competition earlier than usual and result in the shortening of the normal product life cycle (through increased generic substitution). Lehman Brother has calculated that to get a return on investment at year 10 after launch (sales decrease after year 8) and totaling over $115 millions, companies should be looking to develop products with peak sales of over $400 millions.

According to Lehman Brothers, the industry will probably not be able to achieve a 10% return on its R&D in the future. The predicted level of sales in the Lehman study suggests a return on investment of only 3% on the aggregate spending of the industry today. Consolidation must be the answer.

This situation is spurring *mergers and acquisitions* in the industry:

Exhibit 1.1
Major pharmaceutical industry acquisitions in 1994 (SCRIP)

Acquiring Company	Acquired Operations	Value ($million)	Vendor/notes
AHP	Cyanamid	9,700	take over bid
Roche	Syntex	5,300	agreed offer
Lilly	PCS	4,000	McKesson
SB	DPS	2,300	United Healthcare
Sanofi	Sterling Rx	1,000	Kodak
SB	Sterling OTC	2,925	Kodak
Ciba	Chiron(49%)	2,000	strategic alliance
Bayer	Sterling N Am OTC	1,000	SB (inc rights to Bayer name in US)
BASF	Boots Pharma	1,350	Boots
Astra	Astra Merck	820	50% of JV
Ivax	Zenith	595	stock merger
RP	Cooper (95%)	520	agreed offer
Pharmacia	FICE	465	495 to 100%
Nycomed	Sterling imaging ops	450	Sanofi (after Kodak deal)
Ivax	McGraw	440	agreed offer
Bayer	Schein(28%)	310	inc strategic alliance
Ciba	Iolab	300	J&J
Amgen	Synergen	240	agreed offer
Astra	Fujisawa-Astra	230	51% to 90%
Beaufour-Ipsen	Porton	100	agreed offer
Amersham	NMP	85	Sumitomo
Lilly	Sphinx	72	agreed offer
BMS	UPSA	n/a	45% to 100%

Source: SCRIP Magazine

Some pharmaceutical companies look for regaining market power through downward integration. Merck was the first firm to buy a PBM Medco for a premium price. Others look for horizontal integration. They hope to increase their market share in the most significant markets and to achieve significant cost cutting through the development of synergy. Merger also increase portfolio diversity. Portfolio diversity is according to R. Henderson the key to success. (The average number of compounds in development per company was 26 (range: 5-67) in the Center for Medicine Research (CMR) study on 45 firms. The top ten companies had an average of 32 compounds).

These mergers are accelerating the lay-off of employees. More than 30.000 jobs were lost in 1993 (before the merger wave).

INNOVATION IS NECESSARY FOR COMMERCIAL SUCCESS

Management will have to aggressively cut all me-too projects in development, and target all discovery efforts at novel modes of therapies. They must seek out and gain right to new ideas irrespective of their origin. *In-licenses* from the emerging bioscience companies, should increase their chances of achieving a return on R&D although it may increase the risk of failure. Alliances increase access to related research outside the company and increase the chance of success. Spill-over boosts productivity (Henderson, 1994). Furthermore, risk in the portfolio may be reduced by licensing in products to supplement the self-originated pipeline. This enables companies to exert some control over the balance of their portfolio eg to fill gaps as compounds are lost during development, or to facilitate entry into unfamiliar therapeutic areas. The number of collaborative R&D agreements increased in 1994. A table of selected alliances is described below (SCRIP, 1995).

The *cost of bringing a new pharmaceutical to the market*, including the cost of the failures has been estimated at $360 millions, with less than half that amount

representing money actually spent (the majority represents the "opportunity cost of capital") (OTA, 1993). Salaries and other staff-related costs represented on average 50% of a company's R&D expenditure and $87.000 per R&D employee in 1992 (CMR Report). The R&D process from discovery to registration takes 12 years on average. The cost of bringing a new drug to market is very sensitive to changes in science and technology, shifts in the kinds of drugs under development and changes in the regulatory environment. We should be aware of the fact that predicting the cost of bringing a new drug to market today, from estimated costs for drugs whose development began more than a decade ago, is difficult.

Portfolio concentration will be an inevitable consequence of the requirement for outcome data and a concomitant raising of clinical barriers to success by managed care formularies and social security systems. The therapeutic areas most likely to yield blockbuster drugs are those which address high potential populations and where there is a high requirement for new drugs. The profit per patient will rise with the value of the product relative to the outcome and versus alternative therapies.

Biotech drugs may be successful in niche markets if they achieve good pricing, because these drugs address unmet but substantial medical needs. Furthermore some groups have argued that biotechnology drugs, especially rDNA products, have much higher clinical success rates than conventional drugs (Bienz-Tadmor, 1992).

It is notable that five of the seventeen drugs projected to have sales in excess of $1 billion in the year 2000 are biotechnology products in the portfolio analysis of Lehman. This list includes erythropoietin, G-CSF, Growth Hormone, interferon and Human Insulin.

Companies will have to increase efficiency by cutting R&D spending, and by speeding development sufficiently to increase the effective life cycle of a product. A survey conducted by Roche suggests that the industry is indeed moving towards more

innovative drugs, with a much higher number of new drugs launched representing novel therapies now.

R&D COLLABORATION

Even the pharmaceutical giants can hope to discover, with their own in-house research, only a small proportion of the potential blockbusters. It is likely that an increasing proportion of new drugs will come from the rapidly expanding of smaller *research-only companies*. The winners on a ten to fifteen year time frame could be those companies which are aggressively constructing a collaborative development portfolio. Emerging bioscience companies have nearly one third of R&D staff as the pharmaceutical companies. They will supply an increasing proportion of the technology for new drugs. In a survey of R&D spending, the first 6 biggest biotech companies in the world were the 6 world leaders in term of R&D expenses as percent of sales (Business Week, 6/27/94). They will enter in development collaborations with the big companies in order to reduce expense and risk, while potentially gaining a faster route to market and an attractive royalty stream for innovative products. As biotech companies live with very long product development cycles, their need for cash resources is urgent. Pharmaceutical company will have to get better at looking for valuable projects outside of the firm and at evaluating them. Sophisticated financial analysis such as option pricing may help to analyze the strategic value of these projects. (Nichols, 1994).

The *number of deals* between pharmaceutical, biotech companies and universities is increasing. Windhover collected in its database 200 (1991), 210 (1992), 371 (1993), and 383 (1994) deals. Biotech companies were involved in 131 (1991), 189 (1992), 206 (1993), and 383 (1994) of these deals (Longman, 1994). The main research alliances for 1994 were as follows:

Exhibit 1-2

Selected Research Alliances of 1994

CORPORATE PARTNER	TECHNOLOGY PROVIDER	THERAPEUTIC FOCUS/DISEASE
AHP	Cygnus	transdermal HRT products
Merck	Tularik	viral transcription inhibitors
Yamamouchi	Tularik	inflammation/sepsis
Kabi	Arris	structure-based drug design
Japan Tobacco	Agouron	antivirals
Novo-Norsdisk	Karo-Bio	osteoporosis
Genentech	Cytotherapeutics	neurodegenerative disease
Roche	Millenium	obesity/type2 diabetes
Glaxo	Megabios	cystic fibrosis gene therapy
Syntex	GeneMedecine	inflammatory disease
Chiron	Cytomed	complement protein inhibit.
Medtronic	Neurex	pain
Bayer	Onyx	ras gene inhibitors
Ciba	CoCensys	ACEA for stroke/trauma
Hybridon	Medtronic	implanted oligonucleotides
Cephalon	Takeda/Abbott	RTK inhibitors for prostate cancer/BPH
Amgen	Medtronic	implantable BDNF
Pfizer	Neurogen	sleep disorders
Lilly	Somatogen	rHb
Ciba	LT	joint PDT development
Glaxo	Spectra	migraine therapeutics
Genzyme	Celtrix	TGF beta-2 tissue repair
Abbott	Ligand	TF inflammatory diseases
Merck	Celltech	PDE VI inhib.
Genetic Institute	AHP	IL12 for cancer and HIV
Sankyo	Glycomed	cell adhesion inhibitors
BMS	Cadus	screening
Glaxo	Sequana	type2 diabetes
Fournier	Allelix	atherosclerosis
Ciba	Synaptic	neuropeptide Y
Chiron	Ribozyme	cancer, inflammation
Human Genome	GTI	gene therapy
RPR	Darwin	gene therapy
BASF	Vertex	beta thalassaemia
Schering-Plough	Canji	gene therapy
Chiron	Procept	immunomodulator
RPR	introgen	gene therapy
Zynasis	Supragen	autoimmune
Hoechst	Biopharm	BMPs for osteoporosis
Lilly	Autoimmune	oral tolerance/diabetes

Source: SCRIP, 1994

Both partners will have to manage the relationship right from the start, by defining goals, managing expectations, and maintaining strong communications throughout in order to succeed in their relation (KPMG, 1993).

In 1992, the *Centre for Medicine Research* conducted a survey representing 45 of the top 50 pharmaceutical companies worldwide. This surveys documents the extent to which these top companies have pursued biotechnology and licensing as strategies to supplement their development pipelines.

Thirty-four of these companies are developing a "biotech" product. Nearly all respondents(41/45) used biotechnology in discovery. Eight percent (8000 people) of the R&D staff was engaged in biotechnology research in 1992. Most companies were involved with biotechnology companies for the purposes of research and the majority (34/43) had licensing agreements with biotechnology companies. Companies use more often biotechnology as an enabling technology than as a way to manufacture drugs. All the top companies have been involved in research and licensing agreements with a biotechnology company. Most of the top companies held equity in biotechnology companies.

The *location of collaborative partners and number of agreements* for biotechnology research are as follows:

Exhibit 1-3

Location	Universities	Other institutions	Totals
Europe	201	109	310
Japan	53	14	67
USA	385	338	723
Elsewhere	26	10	36
Totals	665	471	1136

Source: CMR

For companies with agreements, the average number per company was 23 (excluding one company that had 253 agreements). Of 1,136 agreements, more than half were made by American companies. The agreements were more often for directed research than undirected (74:26). The American companies had a greater proportion of agreements for directed research (84%) than the other companies.

We have to consider that the *relationships between academic and industry* entities can be quite diverse (Blumenthal, 1994).

- Research relationships, in which industries support university-based research through grants or contracts;
- Consulting relationships, in which industries compensate universities or members of their community in exchange for advice or information;
- Patenting or licensing relationships, in which industries obtain the rights to commercialize intellectual properties owned by universities;
- Equity relationships, in which members of the university community or academic institutions themselves own substantial equity positions in new companies;
- Training relationships, in which industries support the research of doctoral students, or contract with universities to provide training to industry employees.

In 1992, *licensed-in products* represented about 20% of products in development. On average this was 15% for the European and top companies, and more than 25% for Japanese and American companies. Two-thirds of compounds first marketed by the companies between 1986 and 1992 were self-originated. Compounds originating from other sources were most frequently licensed in from other companies (25%; universities: 4%; collaborative research/joint venture: 6%).

THE IMPACT OF BIOLOGICAL DISCOVERY ON PHARMACEUTICAL R&D

As stated earlier, a reason for increase collaboration from big pharmaceutical companies is the breathtaking progresses that take place in biology. Most of the pharmaceutical companies were traditionally "good" at chemistry and random screening in various disease models. Even after the huge investment in biotechnology described earlier, they have lagged behind in most of the major discoveries with commercial applications of the last 10 years (the biotechnology industry started in 1975 with the creation of Genentech). Even if we consider that basic research is outside the scope of industrial research, industrial research needs to catch-up at some point in time to maintain its drug discovery ability.

Some of these *major innovations or discoveries of the past 10 years include*:

polymerase chain reaction
gene therapy
receptor based drug and molecular design
large-scale human gene discovery
cell separation/amplification procedures
antisense technology
human monoclonal antibodies
new drug delivery systems
combinatorial chemistry...

These discoveries offer huge opportunities for the development of new drugs or of new diagnostic procedures.

In conclusion, pharmaceutical companies tend to enter in more R&D partnering because of the pressure to deliver innovative drugs, the pressure to control R&D costs and the rapid pace of biologic delivery. This represents a major shift for the biggest firms which were used to keep research in-house. Pharmaceutical companies in the prescription business will have to manage some outsourcing of this core competence. We will see, in the next chapter, how they can move R&D organization boundaries of their firms.

CHAPTER TWO

THE R&D BOUNDARIES OF THE FIRM

There is evidence that the past decade has witnessed an increase in the tendency for innovating companies to collaborate with others to acquire or exploit technology know-how (see Windhover data, Chapter 1). Some have argued that the innovative performance of firms is hindered by an over-reliance on larger, vertically integrated structures which are often slow to respond to rapid changes in technology. These writers have highlighted the merits of industrial structures organized around smaller, functionally specialized entities, tied together in loose coalitions or networks. Such networks are characterized as more flexible and dynamic than the bureaucratic control structures of the corporate enterprise.

According to a survey of 1200 companies ("outsourcing institute"), companies outsource for ten reasons:

- Improve company focus. (Managers maximize returns on internal resources by concentrating investments and energies on what the enterprise does best.)
- Gain access to world-class capabilities. (Outsourcing allows the full utilization of external suppliers' investment, innovations, and specialized professional capabilities that would be prohibitively expensive or even impossible to duplicate internally.)
- Accelerate the benefits of reengineering and create better responsiveness to customer needs
- Share risks
- Free non-capital resources

- Make capital funds available
- Reduce operating costs and shorten cycle time
- Looking for cash infusion
- Resources not available internally
- Function difficult to manage.

Unfortunately, many companies assume that because they have performed an activity internally, or because it seems integral to their business, the activity should be insourced. However, on closer investigation and with careful benchmarking, a firm's internal capabilities may turn out to be significantly below those of the best-in-world suppliers. (Quinn, 1994)

On the other hand, hollow corporations, may seem more dynamic in the short term but may have limited prospects for long-term survival. Joint venturing and other forms of collaboration are viewed as potentially dangerous in that they may transfer critical know-how to competitors or prevent a company from building up its own stock of capabilities. Quinn has described three risks that management is concerned about:

- Loss of critical skills or developing the wrong skills;
- Loss of cross-functional skills;
- Loss of control over suppliers.

Firms that successfully outsource find it absolutely essential to have both close personal contact and rapport at the floor level and political clout and understanding with the supplier's top management. Successful outsourcers upgrade both their top management talent and their information systems for this purpose. When they move aggressively, many companies have found that they actually improve their knowledge through strategic outsourcing.

This may be particularly true for pharmaceutical R&D because of its need to gain a competitive edge and to protect from strategic vulnerability.

THE ECONOMIC ORGANIZATION OF INNOVATION

The dominant paradigm of innovation over the past fifty years has been vertical integration. Teece (1988) explains this by arguing that vertical integration among R&D, manufacturing, and marketing facilitates critical cross-functional coordination and avoids the difficulties associated with writing, executing, and enforcing R&D contracts. Integration facilitates communication because secrecy is not jeopardized, and a common internal language can be employed. The existence of a common coding system facilitates both technology transfer and the formulation of appropriate research objectives. Furthermore vertical integration allows economies of scale and of specialization. However, innovation in other industries, such as computer hardware and software relies heavily on outside contractors (Quinn, 1994). Knowing when and where to vertically integrate and how to structure relations with outside partners has become a critical skill in managing innovation.

TECHNICAL CHANGE, VERTICAL INTEGRATION, AND COLLABORATION

Economic theories suggest that a firm should draw its boundaries in order to minimize the sum of production costs and transaction costs. It predicts that a firm would tend to undertake those activities where it has a distinctive competence or, lacking such an advantage where the transaction costs of using the market are relatively high. However technological changes complicate this scheme. Such changes can alter the relative production costs of different firms, and it can stimulate either vertical integration or disintegration. Technical changes and competence are cumulative, vertical integration decisions taken at one point in time may have consequences for the firm's strategies in the future. A firm which fails to build certain technical competencies at one point in time may be unable to vertically integrate in the future. Technical changes can alter the specialization of the assets.

Teece describes four factors which pertain to the decision to integrate a new activity which is outside the core business of the firm.

- whether the technology can be transferred at lower cost to an unaffiliated entity than it can be transferred to an affiliated entity;
- the degree of intellectual property protection afforded to the technology;
- whether a contract can be crafted which will regulate the sale of technology with greater efficiency than division-to-division sales can be regulated by internal administrative procedures;
- whether the set of complementary competencies possessed by the potential licensee can be assessed by the licensor at a cost lower than alternatives.

The Locus of Competence

Frameworks that predict how technical change affects competition normally indicate that when a given episode of technical change destroys existing competencies, incumbent firms are likely to be overtaken by a swarm of new entrants who possess the new skills needed to compete. However, when technical changes leads to asymmetries in complementary competencies between entrants and incumbents, it can create opportunities for collaboration. Revolutionary and niche creating episodes of technological change can alter a firm's existing boundaries because they create opportunities for entrants to occupy specialized segments along the value chain.

Biotechnology is an example of technological change for the pharmaceutical industry, where the new specialists became suppliers to the incumbent manufacturers. Although revolutionary in technical terms, biotechnology has left largely intact the downstream capabilities needed for clinical evaluation, regulatory approval, and distribution and marketing of drugs. Furthermore biotechnology and traditional drug discovery represent fundamentally complementary and different approaches to the

problem of finding therapeutically attractive molecules. Biotechnology firms do not initially compete head to head with incumbents.

During the 1980s, a market for know-how emerged in biotechnology with the start-up firms positioned as upstream suppliers of technology and R&D services and established pharmaceutical companies positioned as downstream buyers who offered capital as well as access to complementary assets. By such arrangements, it can be anticipated that the licensor/biotech will not, in general, receive the full monopoly rent available from the application of the firm's technology. Not surprisingly, the result is that technology holders prefer to exploit the technology themselves when deemed possible (niche market and sufficient in-house resources). Only one biotech company, Amgen, has been able to transform itself into a fully integrated, independent, pharmaceutical company. The other successful companies have thrived on strategic alliances (e.g., Chiron, Genentech...).

If technical competence builds in a cumulative and firm-specific manner, we would expect significant first mover advantages to accrue to entrants into the R&D field. After a revolutionary technological change, new entrepreneurial entrants become a source of R&D skills and technological change for incumbent firms holding complementary assets. Over time, it will become increasingly difficult for the incumbent to match the R&D competence of the entrants especially if know-how and skills accumulate within the entrant firms. This will particularly be the case if the firm requires a set of basic internal capabilities or absorptive capacity in order to acquire technology from the outside.

On the other hand technical change does not favor first movers when competence diffuses easily. This is mostly the case in technologies driven by basic science (biotechnology...) which become available relatively quickly through publications, meetings and other mechanisms. Over time, few biotechnology entrants have be able to successfully integrate forward into some selected markets while all established

pharmaceuticals have built in-house biotechnology R&D programs. Rather than exclusively using biotechnology to develop protein-based drugs, most pharmaceutical firms are using biotechnology as a methodology to enhance their ability to rationally design small molecules via organic chemistry (CMR study, chapter 1).

Furthermore, they do more research projects internally in order to build absorptive capacity needed to acquire know-how through development stage agreements. We could argue that it is more easy to outsource part of the biotechnology projects than in the past, because the ability to make judgments and the information available to a pharmaceutical executive has increased.

The Impact of Transaction Costs

Transaction cost includes engineering intensity, design specialization, technology uncertainty and the co-localization of specialized assets. "Small number bargaining" hazards stemming from specialized R&D capabilities is the most relevant to biotechnology. Transaction-cost theory posits that the cost of contractual governance increases in case of uncertainty or investment in transaction-specific assets. Contracts made under uncertainty are necessarily incomplete and may require renegotiation when unexpected contingencies occur. Renegotiation may be hazardous when a firm has invested in transaction specific assets that are costly to transfer. It could make the firm vulnerable to opportunistic reconstructing. Transaction cost theory predicts that pharmaceutical firms might not credibly threaten to change partners. R&D funding provided to the original biotech contractor is a transaction-specific investment. It has much less value if the project is not completed by the original contractor. On the other hand, it makes sense for a pharmaceutical company to terminate a collaboration that does not deliver potential product or know-how. The cost of pharmaceutical R&D is increasing regularly along the R&D chain.

By creating a potential barrier to using the market for know-how, transaction costs can provide a strong incentive for firms to develop certain competencies internally. Pharmaceuticals were more likely to undertake R&D programs in-house instead of through collaborative relationships in fields where there were significant risks of "small numbers bargaining" hazards.

Furthermore, uncertainty also affect the delineation of property rights. Even if parties can agree to a distribution of property rights, problems enforcing the allocation may arise. Technical knowledge may accumulate asymmetrically when one party has responsibility for the R&D project. The problems are compounded in biotechnology because of the scope and enforceability of patent claims.

Pisano (1990) has suggested a few rules pertaining to this situation:

- Pharmaceutical companies will be more likely to internalize R&D in those biotechnology products areas in which R&D capabilities are concentrated in fewer R&D suppliers.
- Pharmaceutical companies will be more likely to internalize R&D in those biotechnology product markets in which it faces greater competition from established pharmaceuticals.
- Pharmaceuticals companies that tend to use in-house R&D for its traditional products will have a greater propensity to internalize R&D for biotech-based products because firms may be expected to behave in the future according to routines they have used in the past. Firms lacking experience with R&D contracting are likely to be less able to search for and select R&D partners and to absorb technologies from external sources. R&D experience reduces the cost of internalizing new R&D projects as long as the new project does not create a significant break with past methods.

- Pharmaceuticals will be more likely to undertake a biotechnology R&D project in-house when it has accumulated more in-house R&D experience in the relevant area of biotechnology.
- Corporate management will be more likely to approve internalization when it views the emerging technology as strategically important to the corporation.
- Large firms have more resources to invest in the development of internal capabilities. Large firms may have scale economy advantages when expanding R&D capabilities involve fixed costs. On the other hand, because increasing size adds complexity to the administrative process, size can have a negative effect on R&D performance.

Nevertheless, the cost of internal organization may be quite high. Managers often tend to overlook back-up costs, as well as the losses from laggard innovation and non-responsiveness of internal groups that know they have a guaranteed market. Headquarters and support costs of managing the insourced activity have to be added. Time of the executives may be consumed for managing peripheral activities. Japanese assemblers are able to reduce the internal complexities of managing product development projects by moving some component engineering work to suppliers.

Partial Equity Ownership

A second factor is that vertical integration is not the only alternative to arm's length contracting. Full integration can distort the incentives of manager of the acquired firm. The difficulty of replicating the incentive structures of the entrepreneurial firms represents a critical barrier to the acquisition of such firm by large organization (such as the failures of the acquisitions of Alza and Hybritech by, respectively, Ciba and Lilly). There is evidence that firms attempt to mitigate transaction costs through long-term contracts, joint ventures, partial ownership. Pisano argues that partial ownership is

preferred to pure contractual governance when a relationship involves uncertainty, transaction-specific capital and other transactional difficulties.

Equity participation also reduces the possibility of opportunistic behavior by aligning the incentives of the partners. Their mutual interest in the success of the collaboration reduces problem hazards associated with cost plus contracting schemes. Restrictions on either partner's rights to buy out the other or to sell off their position can be used to prevent premature termination of a relationship. The board of directors help each partner to enforce its rights as an owner. Participation on the board also provides the collaborators an arena for resolving conflicts, exchanging strategic information, and adjusting collaborative activities as contingencies arise. Ownership conveys rights to control decisions that have not already been set by a contractual agreement.

Collaboration is a learning process. To collaborate effectively, partners must learn certain idiosyncrasies of each other's organizations. Knowledge about a partner procedure and technical skills may be important in coordinating joint projects. Knowledge about a particular partner and how to collaborate with that partner represents important relationship-specific capital. Such organization know-how is a function of the collaborative experience partners share with each other. Relationship-specific know-how becomes deeper for collaborative agreements encompassing multiple projects. Both partners risk the loss of this relationship-specific capital in the event of termination.

The results of a study by Pisano on biotechnology suggest that some of the governance properties of internal organization may be attainable through partial equity ownership.

THE NATURE OF COLLABORATIVE ARRANGEMENTS IN BIOTECHNOLOGY

Research Relationship

Marsh, in "University-industry research partnerships" (Reams, 1986), establishes seven philosophical points for lawyers and corporate officials to consider in creating a research relationship:

1. A successful licensing relationship is a long-term one.
2. Analyze the technology in great detail before going into it.
3. Apply the same analysis to your partner. Can he provide what you lack?
4. Negotiate fairly. Don't screw (sic) your proposed partner for short-term gain. Don't destroy the trust. Do ensure that has been verbally agreed gets put on paper accurately.
5. Seek an agreement that has positive incentives to achieve the desired results.
6. Take care with the implementation and ensure your licensee continues to value your license throughout its life.
7. Last, but not least, structure the license so that if it does fail the parties may disengage cleanly.

Elements of Collaboration

The typical "corporate partner" for a biotechnology firm provides more than just capital; it almost always agrees to perform at least some of the critical activities needed to commercialize the fruits of the firm's R&D. The new biotech firm carries out upstream R&D activities while the established partner undertakes downstream activities. They exploit mutually beneficial gains from trading know-how.

Biotech typically receives an up-front cash payment, R&D service fees on a cost plus basis and fixed milestone payments. Finally, in virtually every contract, the biotech firm receives a royalty as a percentage of future net sales if and when the drug reaches the market. In 55% of agreements studied by Pisano, exclusive manufacturing rights are retained by the established partner, who also carries out marketing.

Dealing With Complexity and Uncertainty

In the framework of outsourcing, there is a constant trade-off between flexibility and control. Form high to low flexibility come, in order, short term contracts, call option, long-term contract, joint development, partial ownership. The firm has the ability to exploit strong outside parties'specialized capabilities through temporary consortia. RPR (see Chapter 3) has created a pool of biotech firms callable on options. The company may end up with large numbers of subcontractors, which may be more costly to manage than in-house operations that are individually less efficient.

The high degrees of contact with the parties assists in the communication of non-codified information from the biotechnology firm to the collaborative partner. *Trust* appears to play a critical role. Contracts are full of provisions for negotiating critical issues at some future point in time, the only stipulation being that such critical issues being carried in good faith. *Contracts* may specify only a lower bound and upper bound for such item as royalties (6%-10%). The royalty rate for biotechnology products has been studied extensively and can be used as a benchmark for negotiations.

Exhibit 2-1

Royalty Rate Comparisons

Technology classification	Exclusive License	Non-exclusive License	Up-front Payments
Reagents or production method	2-4%	0.25-1%	recapture patent costs
Drug delivery component	2-3%	0.5-2%	recapture patent costs
Diagnostic product	3-4%	1-2%	$5-20,000
Therapeutic product	5-10%	3-5%	$20-200,000
DNA Drug, early stage	7-10%	3-5%	$20-200,000
DNA drug approved	10-15%	5-10%	$50,000+

NOTE: Licensors can negotiate minimum annual royalties. Milestone payment should be added. The rule of thumb is that the revenues from licensing a ready to market product are equal to 25% of the sales.

Source: M. Lytton, Palmer & Dodge, 1995

Parties agree on a specific governance mechanism or process for making necessary adaptations or resolving conflicts. Joint steering committee composed of representatives of both companies are required to convene monthly or quarterly. One purpose of the steering committee is to serve as a mechanism to exchange technical information and coordinate critical technical and operating decisions on the project. These joint committee also serve a governance purpose; they provide a forum for raising and resolving disputes and for making any necessary adaptations in the project plan.

Early stage collaborations may be more complex and difficult to negotiate and manage because of the inherent uncertainties and complexities of the research project itself. At the same time, by agreeing to fund biotechnology firm's project early in the development cycle, the established pharmaceutical company can preempt competitors. Firms can lessen investment risks through a combination of licensing and development.

The difficulties in coordinating early stage collaboration may translate in higher transaction costs for foreign contractual arrangements with foreign pharmaceutical firms compared to US firms. Transfer of information across organizational boundaries are dependent on similarity of experiences and shared context between parties (Teece, 1988). The closed personal interaction required for collaborating on R&D projects may be more difficult between an American biotech and a foreign partner than with two US partners. Foreign pharmaceutical firms may favor development agreements which require relatively less coordination and communication. At that stage, it may be possible to rely on contractual mechanisms to achieve efficient supply. When specifications define in detail the product to be procured, the buyer has a better chance of assuming that the contractor delivers what was promised, and the contractor can in turn ensure that it will be asked to deliver no more than was promised.

CHAPTER THREE

RHONE POULENC SANTE

A pharmaceutical R&D based on biological research
From French government partially supported research
to an international network of research centers

It is very difficult to rapidly expand drug discovery capabilities and to start new research programs in the pharmaceutical industry. Pharmaceutical companies with this major objective have to hire good scientists, plan research programs in new domains, and acquire the requested instrumentation and facility. From these initial investment, a long time usually elapses before the company obtains its first, significant, positive results. Collaboration with universities or biotech companies is a good way to accelerate the process of entering new research domains. It allows the company to progressively acquire the internal capacities and to minimize the up-front costs.

Rhone Poulenc has significantly increased its health care business over the last several years. The company is betting on innovative research to discover the products that will fueled its new marketing channels. We have studied this company because of:

- its partnering with public sector research in France (Bioavenir Project);
- its involvement in vaccine research which requires significant investment in biotechnology (PMC); and
- its bet on gene and cellular therapy. RP has created an original network (Gencell) of companies which together should develop the different pieces required for these new therapies. This network organization has not been applied so far to pharmaceutical research.

These three strategies offer good opportunities to study how research can be outsourced by a pharmaceutical company, and how the company tries to maintain control in a very flexible environment.

RHONE POULENC (RP)

Rhone Poulenc is a French chemical group with a major part of its business in the human health care sector. Forty percent (FF.33,720 million) of its total sales (FF.80,564 million in 1993) are in this sector. Rhone Poulenc has two primary subsidiaries in the Health division:

- Rhone-Poulenc Rorer, based in Pennsylvania, is 68% owned by Rhone-Poulenc. It sales represent 67% of the RP health care segment
- Pasteur Merieux Connaught, a world leader in the manufacturing and research of vaccines is fully owned by RP. It sales represent 13% of the RP health segment net sales. It is the world's leading producer of vaccine products for human use.

Both companies were formed through the acquisition of North American firms. The RP strategy for these acquisitions was to increase the worldwide presence of Rhone Poulenc in the health sector. Previously RP direct sales had been restricted to Europe and Third World countries.

Presently RP has nearly 25% of its consolidated net sales in North America as compared with 8% in 1986. (French sales now represent 21%). From 1986 to 1990 RP made acquisition totaling approximately FF.41 billion, which were paid for in cash and securities. It acquired in the health care sector:

- Connaught Biosciences, Inc., a Canadian health care company for CDN$959 million in 1989

- Rorer Group, a US pharmaceutical company in 1990. It combined is human pharmaceutical business with Rorer resulting in the company owning approximately 68% of the new entity called Rhone Poulenc Rorer.

These acquisitions were targeted to increase the presence of RP in the sectors like fine chemicals or heath care that offer the highest growth potential. RP is, according to the company, one of the ten largest pharmaceutical companies in the world. The health segment contributed to 41.8% of the sales but to 96.3% of the operating income in 1993.

These acquisitions were encouraged by the French government. The company was nationalized in 1982 by the socialist government and privatized in December 1993.

RP's R&D activities are generally carried out within each business segment. Biological research accounts for two-thirds of RP total R&D expenditures. The R&D expenditures (3,992 million) represent 11.8% of the sales in the heath care segment. In this sector RP has concentrated its R&D efforts in France, United States and the United Kingdom. The research strategy of RP has been strongly influenced by its strong position in biomedical industry in France and the traditional attitude of the French government to support the major players in critical sectors of the economy.

The French government encourages links between French companies like RP and the public sector research. The rationale for this relationship is that government supported research has traditionally focused on basic research with little application for commercial use. On the other hand, scientists in the pharmaceutical industry were not involved in fundamental research until recently. Since, academic scientists are mainly biologist, industry scientists are mainly chemists and developers, it is anticipated that combining these two groups will foster the development of innovative drugs.

This links explain the funding of major French laboratories by RP and the licensing-in of drugs like Taxotere which comes from the Centre National de la Recherche Scientifique (CNRS).

3.1 RP AND THE BIOAVENIR PROJECT

RP realized a few years ago that it would need to have access to the cutting edge of biological research to develop innovative drugs.. The research was considered by some in the industry as insufficiently focused and open on the external world. As stated earlier, RP was encouraged by the French government to gain access to innovation through the collaboration with public laboratories.

The BioAvenir project, launched at the end of 1991, brings together the French government, the French public research centers and RP in an effort to:

- foster the technology transfer from basic research to applications in life sciences.
- develop a long-term research program to bring innovative products to the commercial partner.
- finance basic research.

The program is followed by four scientific committees, one for each technical part of the collaboration agreement. The domains, chosen by RP, encompass:

<u>methodologies required to</u>:

identify new biologic targets (gene identification...)

design selective products (protein structure, molecular design...)

evaluate the efficacy and safety of products (transgenic animals, models of human diseases...)

reach target (membrane crossing)

human health

gene therapy for:

-certain cancers

-neuro-degenerative diseases

-atherosclerosis

agriculture

identification of new molecular targets

relation of the plant with its environment

biochemistry

Two additional boards review the scientific results and the administration of the project. The administration oversees the budget and assures that the commitments of each partner in the venture and the development of industrial applications are respected.

The overall budget of the project is FF.1.8 billions (1 $ = 5 FF.). RP's portion is FF.1 billion. Six hundred million are provided by the French government budget. Two hundred million is funded by the research agencies (Centre National de la Recherche Scientifique, Institut National de la Recherche Agronomique (INRA), Institut National de la Recherche Medicale (INSERM), Commissariat a l'Energie Atomique (CEA)) out of their own budgets.

Fifty percent of the FF.1.8 billion amount is ear-marked for the health care project.

The programs are chosen by RP, which can also cherry-pick the laboratories involved in the venture. It is, to my knowledge, the first time in France that public researchers accepted that the program could be determined by a commercial partner.

This innovation and the selection of the funded laboratories on undisclosed criteria have been the object of criticisms in France.

The research is limited to basic research. This was a condition for the acceptance of the funding by the European Commission. Funding of applied research which could produce potential products on the market in the next 10 years would have been considered as unfair competition by the European Union and other drug manufacturers in France. Because of this limitation, the head of research of a major competitor is skeptical that there will be on the real benefits in terms of commercially viable products from this basic biological research. This observation was based on experience with major funding of first-class American academic centers, which failed to produce any new products in the past. Good examples are the Scripps Clinic-AHP research agreement and the Hoechst-MGH contract. In these agreements the scientists of both parties were not mixed. The industry scientists did not benefit fully from the development of academic knowledge during the contract period. There is little spill-over to sponsor's other projects. Furthermore, the academic scientists are not focused on the firm's project but on the most interesting research for them (in terms of publications, career...). In the Bioavenir project RP scientists work in the academic laboratory funded and equipped by RP.

A good example is CNRS laboratory of Pr Pericaudet in the Gustave Roussy Institute (IGR) in Paris. This laboratory is a world leader in gene therapy with adenovirus vectors. Clinical trials using vectors developed in this laboratory will start for the treatment of lung cancer and cystic fibrosis this year (Genzyme pursues the same target with a similar technology). The alliance with RP has increased the size of the laboratory from 15 to 30 people due to the arrival of RP scientists and "post-doc" funded by RP. RP scientists concentrate on improvement of adenovirus for clinical applications and have learned a great deal from this collaboration. CNRS scientists are working on their own projects with a much more flexible agenda. The relationship between the two groups is excellent. All the patents coming from the laboratory are

written by RP on behalf of CNRS-IGR-RP. The present arrangement seems to avoid the lost of independence for the academic researchers, which is the risk of a tight collaboration.

It is too early to appreciate the results of the Bioavenir project. The project has just reached the mid-point of its five-year duration and to date half the committed funds have been used. Five laboratories with RP and CNRS/INRA/CEA have been created or expanded and more than 500 scientists are working on this project. One hundred forty are trained through Ph.D. or post-doctoral programs. RP will have the opportunity to hire the best people. The teams have filed 100 patents and published 110 papers. This Bioavenir program has fostered the modernization of the RP research organization. It has helped to change the culture inside the research group in France. It is our understanding, that this change is resented by some members of the "old generation". They consider that the new biology oriented projects are favored by management over more traditional projects and that these latter projects have a higher chance of success. Collaboration with universities can help to change the culture inside R&D organizations.

We are not aware of the desire from any other pharmaceutical company in France to structure a similar deal with public laboratories. In fact, the head of research at Sanofi does not believe that this type of basic, unfocused research should be supported by a pharmaceutical company. He gives the examples of the Hoechst/MGH agreements, the Roche Institute in New Jersey or the Immunology center in Basel as proof of fine industry supported research that failed to result in any tangible products.

RP may benefit in term of public image from this deal. The commitment to innovative research may be appreciated by financial analysts. RP has organized a major conference to share the interim results with journalists. All pharmaceutical companies negotiate a deal with the French government to set the prices and to control the volume of the drugs sold on the French market. This system takes into account the research effort. The influence of these types of deals in countries where the government controls

the prices of drugs or the profits of the companies may provide the companies with leverage in the negotiation with the government.

The Bioavenir contract was favored by the French system where coexist a very potent government, a few major industrial (here pharmaceutical) companies and very few small high-tech (here biotechnology) companies. (The Paris stock exchange will open in 1996 a new market, equivalent to the American NASDAQ, to foster the listing of "high-tech, small cap" companies. The financing by venture capitalists of French high-tech ventures was limited by the impossibility to exit on the French stock market through Initial Public Offerings.)

In the US, the projects and the patent rights are usually transferred from the academic institutions to the private sector through biotechnology companies. In France, the limited entrepreneur mentality in the high technology sector and the absence of venture capitalism (at the seed or start-up stage) has not allowed so far this route of technology transfer. Furthermore the public academic system does not allow the professors to move back and forth from the private to the public sector. A Chinese wall exists between the two sectors of the economy. A few indicators such as "the NASDAQ initiative", or the creation of companies by academic scientists suggest that the situation is changing under the influence of the American system.

3.2 PASTEUR-MERIEUX-CONNAUGHT (PMC)

PMC is a subsidiary of RP in charge of developing and marketing vaccines. Pasteur has always marketed vaccines and diagnostic tests. The quality of manufacturing in this prestigious research institution was not at the level expected of a modern manufacturing company. For this reason, Pasteur first sold its commercial division Institut Pasteur Production to Sanofi (Sanofi is the pharmaceutical division of ELF, the leading French oil company. Sanofi recently acquired the prescription Business of Sterling to increase its market presence in the US.). Sanofi kept the diagnostic part (which sells tests like the HIV tests...) and sold the vaccine division to Merieux. Pasteur still offers the rights for all its discoveries with diagnostic applications to Sanofi and for its discoveries with vaccines applications to PMC.

The relationship with Pasteur increases PMC access to scientific information in the immunology domain. The head of the Research at PMC is the head of one of the best laboratories at Pasteur and the co-founder of Transgene, the leading biotechnology firm in France. Merieux bought Transgene a few years ago. These relationships have allowed PMC to develop a first-class research division that was fairly small 10 years ago. PMC has invested heavily in biotechnology. The vaccine sector is one of the only pharmaceutical sectors which has dramatically changed by the emergence of biotechnology. This PMC activity represents a good example of how a pharmaceutical company can have access to key technologies and people through the acquisition of a biotechnology firm.

Merieux bought Connaught to increase its size in a very competitive market and particularly its presence in North America. Connaught, based in Toronto, has a special relationship with major Canadian academic centers. The funding of academic projects by PMC gives it the commercial rights for all discoveries. The support (a few million dollars) was requested by the Canadian government when Pasteur-Merieux bought Connaught.

Recently PMC bought Viral genetics and signed a deal with Vical (for five diseases). This company is a leader in the field of vaccination with naked DNA. This technology published in 1989 was overlooked by the major players in the field. Merck and PMC subsequently acquired the rights to this technology. This illustrates the role of biotechnology companies as a channel of technology transfer. They add value to the patents coming from the universities but do not have the financial resources to develop a vaccine. This is also exemplified by the Chiron-Ciba deal. Pharmaceuticals on the other hand do not always have people inside their organizations qualified or informed enough to understand the value of new university ideas and patents. Furthermore, "The quality of the patents filed by universities has regularly increased over the last years, which facilitates the use of these patents by pharmaceutical and biotechnology firms," says PMC's head of research.

PMC does not outsource a lot of its applied research. The head of research believes that it is difficult to control the quality of the experiments and thus to use them for the registration dossier. The academic laboratories do not work under the Good Laboratory Practices that contract research organizations (CRO) respect. They do not have any quality insurance.

PMC offers a good example of the development of an important research organization (800 people employed) based on the collaboration with biotech companies (Transgene) and a research institution (Pasteur). Both Transgene and Pasteur have very good basic research programs. The French government played an indirect role in these types of alliances through its control of public research funding and its control of the previously nationalized pharmaceutical companies.

(NB: PMC has an agreement with Merck to develop combination immunotherapeutic vaccines and to co-promote several vaccines. A number of vaccine collaborations have occurred recently as companies attempt to develop combined vaccines, particularly for routine childhood immunization, since no single company has all the critical antigens. These deals are at the outer limits of research agreements).

3.3 THE GENCELL ORGANIZATION INSIDE RHONE POULENC RORER (RPR)

Rhone Poulenc Rorer is a pharmaceutical company with $4 billion of sales. Gencell is a new division of RPR devoted to the development and commercialization of cellular and gene therapy. The Franco-American consortium was created at the end of 1994. The first step in this formation was the acquisition of Applied Immune Sciences (AIS) in 1993 by RPR. RPR acquired 38% of AIS for $113 million and established with AIS a joint venture to start cell therapy centers to market and distribute cell therapy products and services. RPR could build on the Bioavenir project and the relationship with its cousin company PMC to leverage its important investment on AIS. RPR looked for other investment or collaboration opportunities to establish itself as a major player in gene and cellular therapy.

Several key points emerged from this exercise:

- Most biotech companies were based on strength in one key technology. T. Soursac, the general manager of Gencell, sees those companies as manufacturing parts for automobile rather than building the car itself.
- There are a huge number of underlying techniques, each of which must come together to create a single successful gene therapy.
- The main biotech companies in the field would be very expensive to acquire (and some of them may be overvalued).
- It is very difficult to sort out the winners (and the value of some of the patents) in this early and rapidly evolving technology.

RPR has decided to create a consortium that would bring together groups with key technologies in this domain. RPR did not need exclusive access to everything because it is counting on the unique combination of resources to create a winning product. The competitive advantage will come from the building of complementary assets.

The companies and academic institutions in the consortium were screened using a special framework. They had to bring complementary technologies or products for the treatment of cancer (or cardiovascular and central nervous system diseases) by gene and cellular therapy. The scientists at Rhone-Poulenc were instrumental in selecting the companies. They knew the scientists in these companies. They had started to collaborate with some of them on specific projects. They would have to work together if the deals come through. Furthermore the due diligence is mainly based on scientific achievements for early stage biotech companies. Scientists within the company are the main people than can appreciate the value of the collaboration.

The members in the present Gencell network are as follows.

Exhibit 3-1

Applied Immune Science	California	Cellector technology, which isolates specific immune cells, allowing for ex-vivo processing of cells and cell therapy
CNRS	France	French researchers inside the Bioavenir project. Includes J. Mallet for CNS disorders and D.Scherman for lipid-based vectors
Darwin Molecular Corp.	Seattle	Large scale DNA sequencing. ($16.5 millions over 4 years)
Genethon	Paris	Research organization specializing in gene mapping and sequencing
Genetix Pharmaceuticals	New York	Exclusive licensee of AM12 retroviral cell packaging line. Transport of MDR gene (to protect cells from chemotherapy) into cells
Genopoietic	Paris	Herpes simplex virus thymidine kinase anti-tumor program
Institut Gustave Roussy	Paris	Adenovirus vector developed by M.Pericaudet. Clinical center
Institut Pasteur. Lille	Lille France	High density lipoprotein cholesterol
Introngen Therapeutics	Houston	Treatment of cancer with p53 and K-ras gene therapy. Linked to MD Anderson Cancer center. (up to $50 millions, minority stake for RPR)
The Lawrence Berkeley Human Genome Center	California	Part of the US Genome Program. Large scale sequencing of the genome. Animal models
PMC	Lyon	Vaccine technology
Transgene	Strasbourg France	Minority owned RP company that uses adenovirus vectors for gene therapy
Louis Pasteur University	Strasbourg	Lipid -based molecules for gene transfer
Virogenics	New York	Majority owned by PMC. Rights to canary pox virus to antigen presentation for cancer therapy

The alliance was secured with a relatively limited amount of money (with the exception of AIS). By the end of the year RPR will have invested about $300 million in setting up the network, of which roughly $150 million was invested in AIS. Upfront payment and equity position have been minimized. Milestone payments will be linked to the delivery of promised results. RPR will invest more in the winners inside its organization. The option of delaying major investment decreases the financial risk for RPR. Nevertheless, the cost of financing the network is quite expensive around $100 million in 1994 (for the first year, this corresponds to less than $5 million up-front component per member, a first year running budget and an equity investment for Gencell). RPR could spend up to $1 billion by year 2000.

A deal (for example, with Introngen) typically involves for the worldwide commercial rights (two projects: P53 and Ras), the first right of refusal of what the company is doing in the field of interest (here cancer), an equity participation, the funding of development and clinical trials, milestone payments on preclinical and clinical achievements and royalties for the licensed products.

Two hundred employees of RPR are working in Gencell, including 150 researchers. Eight hundred people are working in the network. RPR is planning to spend roughly $100 million per year in the venture, or nearly 20% of its R&D budget on the venture.

The network is used for basic research. Clinical trials, strategic marketing and business development, project management are under the RPR jurisdiction. The RPR organization is also setting the cellular therapy centers in the US, Europe, and Japan. T. Soursac has the vision that clinical development and regulatory affairs should be centralized. He believes that huge centralized research organization may suffer more from bureaucracy and political games than they gain from the centralization of resources. "Critical mass is more important for development than for research".

The network provides all the tools for gene therapy, e.g., vectors, genes, packaging cells, and the therapy centers. The diseases which will be targeted are cancer (i.e., p53 and Ras genes), cardiovascular diseases (i.e., lipoprotein disorders (apolipoprotein A)) and neuromuscular diseases (i.e., muscular dystrophies).

Members in the group should take advantage of the exchange of ideas inside and outside the direct consortia business. D. Nance, Introngen's CEO, says that,

> *Introngen can call to Darwin for rapid sequencing and that a partner can go to Introngen for preclinical models and clinical perspectives in Oncology. The exchange should move the science faster towards the market place. Members of the group also benefit from the clinical and regulatory structure of Rhone Poulenc and of a worldwide network of GMP validated cell-processing centers.* (Bioworld, 11/14/94)

Scientists on the network are regularly corresponding with each other through the Internet, Lotus Notes, teleconference systems, and e-mail. Gencell is bringing to its partners a coherent information system to foster information exchanges within the network organization.

Two annual meetings with the network scientists are planned, at which scientists will discuss the state of the art of Gene therapy and present the status of the different projects. The decisions on the project choices and the discovery strategy are made twice a year by a team where the scientists of all the network members are represented.

The network of competencies inside RPR and its alliance should give RPR the ability to change direction quickly, without having to go through the painstaking process of agreeing with a new partner with the desired delivery method. Gene therapy efforts need access to broad based technology to have the flexibility to reconfigure. "In this alliance, RPR did not fear to enter any kind of arrangement without setting all the terms out ahead of time. They are not having lawyers draft 2 feet worth of documents before they get started. They put all this together in six months," says R. Leheny of Hambrecht

& Quist. The portfolio may evolve and new partners, possibly Japanese, may join. The Japanese government encourages the collaboration of Gencell with Japanese universities. Gencell has more difficulties to find Japanese partners in the private sector.

T. Soursac, the President of Gencell, is planning to work on all aspects of gene therapy for cancer. "When there is a good idea, a specific agreement between the partners will be done, from day one, to determine the (up-front, milestone and royalty) flow back to each partner. Nothing today is put in concrete," he said, "but a royalty structure has been discussed in which those providing the gene for a successful product may get 6 to 10 percent, the successful vector company about 5 percent and the packaging cell line company 2 percent." (Bioworld) T.Soursac is looking for flexibility. "Furthermore RPR network does not work to stifle the entrepreneurial spirit of research institutions and small companies," he adds. Partners are keen to keep their independence.

This heterogeneous consortium may be difficult to manage for different reasons:

- The groups are very distant from each other. They belong to two different countries with different mentalities. Most of the French groups belong to non-profit organizations, while most of the American groups belong to biotech companies. American companies have an incentive to maximize short-term returns through public offerings or the sale of part or whole of their company. RPR has obviously a long-term plan, since it will not make any money in gene therapy for a long time. Although groups inside and outside this alliance have started clinical trials, they have not mastered the technology. The registered products will probably be different from those presently tested in clinical trials.
- Some members of the Gencell organization have products which are very closed to each other, like the herpes virus vector. Gencell will have to decide which product it wants to develop on a large-scale basis. In this collaborative effort, it is going to be the originators of the successful

technology that benefit at the end of the day. This situation can create a challenging competition between the members while also causes a lot of conflict of interest which will be very costly in arbitration and management time.

- One member of the group, AIS has a special position because of the RPR investment size. On the other hand, Genopoietic is a very small start-up company which sold all the rights for oncological applications of its products to RPR in order to finance its research and some manufacturing facilities. Genopoietic will start two clinical gene therapy trials in 1995. The link of Genopoietic with the Pitie hospital, whose founders are professor of medicine there has decreased significantly the cost of the clinical trials for this virtual organization. Genopoietic is now raising capital to improve its manufacturing facilities and hire coworkers. Partners, however may not be equal in this alliance.
- RPR has decided to build a proprietary position through the acquisition of complementary assets, since it did not acquire the major player in gene therapy. Some critics allege that RPR is acquiring the young companies desperate for cash. Medium-size companies are unwilling to settle for $5 million upfront. (Butler, 1994) RPR may not be the first company to have products on the market for that reason. Furthermore the technologies and patent positions of several of the members are not widely known. Patent litigation in gene therapy with retroviral vectors is possible. Nevertheless RPR will be in a good position for cross licensing agreements because of its size and its complementary assets.
- The alliance is very loose. RPR has held back from the big cash outlay to buy equity stakes or obtain exclusive deals. (Butler, 1994) "Companies such as Darwin retain their full independence while getting the opportunity to form collaborations on specific projects in a particular facile way," says the CEO of Darwin. (quoted in Bioworld Today, 10/28/94) "We do not have any obligation (except on suicide gene

project) to do anything except to negotiate in good faith with RPR and the other members." There is a risk of a permanent negotiation and "small number bargaining" which consume the management's time that should rather be devoted to the development and marketing of the products.

- This type of loose alliance is very unusual in the pharmaceutical/biotech industry. It is reminiscent of the microcomputer/software industry. Companies put together their resources and their information to reduce the use of capital and to get a competitive edge in the development of new products. This collaboration is very important when different parts have to be used together, and the parts are designed by different specialized companies. Furthermore a consortium may have the possibility to try to set a standard when the consortium is allied to a major company with some market power. This is very important in the absence of dominant design. The safety of gene therapy is really unknown. It is suggested that only a few techniques that could be applied to a set of genes will be registered. The cost of other techniques' validation and the aversion to risk of regulatory agencies will foster the emergence of a dominant design.
- As previously stated, the network organization has demonstrated its efficiency in the software industry. It is interesting to note that one of the backer of Darwin is Bill Gates, the founder of Microsoft. The success of this organization was built on the very close relationship of its member in a west coast, relaxed atmosphere. It will be a major challenge to manage a network of people from different company and country cultures and living far away from each other. Will regular meetings, Internet, and teleconference be sufficient to create the social links that compensate for the absence of formal legal links?

The Gencell alliance is a major commitment for RPR. Gencell has been organized as a separate division inside RPR. Gencell is controlling the whole value chain from research to marketing. This company inside the company may allow RPR to spin-off its biotech division.

The core of the alliance is the AIS acquisition. The joint venture with AIS will allow RPR to start cell therapy centers. These GMP centers involve both autograft (e.g., cellular amplification and purging for bone marrow or peripheral blood transplantation, cellular immunotherapy) and allograft transplantation, and will be the initial source of revenues for RPR. There is a potential synergy between these centers and some of the RPR existing drugs, such as G-CSF in Europe, and the RPR anticancer drugs in France. Gene therapy is a longer term commitment and a much larger project than pure autotransplantation. It is very difficult to predict when the products will arrive on the market. The size of the investment may put RPR at risk if the project does not succeed. Many of the best people and of the budget in the R&D domain in RPR are devoted to this project and are not any more involved in classic small molecule R&D. Timing is key. If RPR gets involved too early and on a large scale in this venture, it may give-up a promising technology in the long term, if, after a while, it does not see any clear, promising, profitable product in the pipe line.

The network organization is a new organization in the pharmaceutical industry. It both reduces acquisition costs for RPR and provides a lot of flexibility in a very unsettled field. It builds on the acquisition of complementary assets to put together a product which needs a lot of different, highly specialized technologies. This lose network containing many members working across the world may be difficult to manage. The disparity of the partners and potential hidden agendas may add to the difficulty.

This Gencell "toolbox" strategy can be compared to that of other major pharmaceutical companies interested by gene therapy. They have decided to make major,

focused, acquisition in larger biotechnology firms in 1994. Some of these gene therapy companies such as Viagene, Vical, Somatix, or GeneticTherapy have progressed much further on the road towards commercialization :

Exhibit 3-2

Roche	Milenium GeneMedicine Targeted Genetics	diabetes obesity inflammatory diseases therapies for HIV and HMV
Glaxo	Megabios Sequana therapeutics	cystic fibrosis diabetes
Shering-plough	Canji	cancer
Pfizer	Incyte pharmaceuticals	cancer
Sandoz	Genetic therapy	cancer (extension of a 1991 agreement)
Baxter	Somatix	cancer
Merck	Vical	cancer

Source: KPMG

The ability of RPR to leap ahead of the leading gene therapy firms will depend on (1) its ability to manage the network, (2) the success of its new partners, (3) management's ability to choose and combine technologies for specific indications, and (4) the ability of RPR to bring in new collaborators in the future.

In conclusion, Rhone Poulenc, a leading chemical company, has decided to become a major player in human health. The acquisition of Rorer and Connaught to increase the size of its business in this field was a first and major step in this direction. RP subsidiaries should now discover new therapies and launch them on all the major markets. RP has to boost its research capacities to meet this challenge. RP has realized that the discovery of innovative treatments will be based on excellent biologic research. RP was traditionally strong in chemicals and traditional pharmacy. It had to build a new research environment to succeed in its new goal. RP is building these capabilities through a lot of external collaborations with academic centers and biotech companies in France and in the US. This allows RP to change the culture inside its organization,

to access key technologies at a reasonable cost, to improve the quality of its research teams, and to internationalize its research base. RP has launched two original structures the Bioavenir project and Gencell. The first one is based on a strong collaboration with French public institutions, and it is supported by the French government. The second realizes an alliance of biotechnology companies and universities. The informal link between the participants and the risk of a research non focused on product development on the mid-term represents a major management challenge. Furthermore, these new technologies may not bring any significant product in the next ten years on the marketplace. Thus, it is too early to evaluate the success of this original approach largely based on research outsourcing.

CHAPTER FOUR

APOLLO GENETICS, A VIRTUAL COMPANY

To Wall Street, most of the biotechnology industry is a batch of long-shot, underfinanced wannabe drug makers and it is no place to put your hard-earned money.

--Wall Street Journal, 4/11/95

This type of feeling on Wall Street, and as a consequence in the venture capital community, has reduced the funding available to biotechnology start-up. Some new start-ups organize themselves as a virtual company with very little fixed costs. Virtual organizations reduce the amount of money required at the time of the company's inception. These virtual firms outsource their R&D.

This chapter will present the challenges facing virtual biotech companies. Can they maintain flexibility and perform high quality research at the same time? How do they select their partners? The field study of Apollo Genetics, a virtual company located in Massachusetts, can be instrumental in answering those questions.

THE STORY OF APOLLO GENETICS

How Did the Company Start?

Apollo genetics is a biopharmaceutical company founded in 1992 by Katie Gordon. Apollo is basically a one-person company. Gordon started this company after a study on the scientific and business opportunities offered by recent discoveries on the

aging process. Gordon became very much interested by the neuro-endocrinology of aging. She decided in 1991 to start her company on this concept and not on a particular technology.

Apollo Genetics is focused on the largest health care problem in the developing world, the degenerative diseases in the aging population. This domain represents a huge and untapped market as very few products can claim efficacy on the aging process. The only products with clear efficacy are hormones particularly estrogen in women. Addressing such a large market may be very attractive to investors although the cost of developing products for that market is tremendous.

The Organization

Gordon decided to work only with academic centers and to license the technology from these centers. She selected three centers through scientific meetings, literature search, contacts at the National Institute of Health and a dozen of laboratory visits. Gordon studied more than 100 university departments in this process.

This licensing strategy will allow her to save money. She will not have to build any research facilities or offices. The limited cash outlay will not require venture capital financing at the start-up stage. Gordon will be able to keep a better control on her company although she may not benefit from the management experience in start-up and biotech companies that a Venture Capitalist firm can offer. Apollo Genetics was financed through Angel Financing. Gordon has known the investors through her past career in the biotechnology industry. Apollo got $1 million altogether. Apollo had to look for early technology in order to limit its research expenditures. License options from universities may not require a lot cash in the beginning. Apollo can obtain the right to the technology with limited up-front payment and research financing.

Apollo needs more money at a time when one of its product enters clinical development. At that stage the management become more time consuming. At the present time 4 people, either part-time employees or special consultants, are helping Gordon; one as a CFO, one for business development, two for the research as head of projects. The scientists are members of the universities with which Apollo Genetics has licensing agreements. These four people have an equity position in the company. They all work off-site. This requires a fair amount of travel for Gordon.

Clinical trials and regulatory affairs require a lot of paper work. Increased burn rate needs particular management attention in a poorly capitalized company. Cash burn rate is presently $600,000 annually for the sponsored research and the clinical trial. The clinical development will need some kind of partnership that the joint venture with Endocon will provide. Finding the potential partners and negotiating the deals needs a lot of experience and requires a lot of time and attention. Apollo is relying heavily on consultants and contract research organizations for pharmaceutical development, clinical trials and regulatory affairs. Apollo has a preferred consultant for the regulatory strategy and for the paper work needed for IND submission. The contracts are written with the help of external lawyers. This use of external resources is not as expensive as developing the same activities internally from scratch.

The Projects

Apollo started with the endocrinology/geriatric departments of three universities. These centers have identified and developed products which intervene in the cellular processes that cause the death of brain cells. By keeping essential brain cells alive, Apollo claims that its core products will prevent and treat chronic degenerative diseases of the brain.

Two lead products have been identified which can intervene on the cell death process. Furthermore the team of one of the university has discovered that estrogen can

also prevent death of nerve cells and can increase learning performance and memory in animal models. The university has a medical use patent for estrogen in this indication. Clinical trials have started with the Neurestrol where the estrogen is embedded in a control release system. The study is performed in the university center that started the research. This will further reduce the cash requirements. The scientist involved in Apollo's management does not take part in the clinical trial to avoid any conflict of interest.

This estrogen compound is already on the market. The use of this estrogen for other indications will reduce the registration requirements for this potential indication and thus the cost of development dramatically.

The sustained release formulation was developed by Endocon.

THE JOINT VENTURE WITH ENDOCON

Apollo has created a joint venture with Endocon, called AG/E. AG/E will focus initially on controlled release of estrogen compounds for the treatment of Alzheimer's disease.

Apollo contacted Endocon through scientists of the NIH, specialized in geriatry. These scientists are collaborating with Endocon. Furthermore, the CEO of Endocon, R. Leonard is serving on the board of a company with investors in Apollo.

Apollo is a company specialized in drug delivery. It has a strong program in sustained release delivery of steroids. The steroids are embedded in a bioerodable, removable rode. Endocon has licensed its technology for its use as a contraceptive agent and as a treatment of menopause to American Home Product. AHP got the world wide marketing rights but Endocon kept the manufacturing rights. Endocon and Apollo were

interested in locking up a new patented clinical claim. Endocon and Apollo both believe that a sustained delivery system represents a distinctive advantage for the treatment of elderly.

Apollo was, a the beginning of the negotiation, looking for a straight licensing agreement. Endocon explained to Gordon that Apollo could not afford such an agreement that would require an initial cash outlay and the commitment to fulfill some development milestones. Endocon thought that a joint-venture will save money for Apollo. Apollo will also benefit of the experience of Endocon in manufacturing, regulatory affairs and clinical development. Apollo saw wisdom in these arguments and agreed to sign a joint venture that will allow Endocon to enter the neurodegenerative disease market. The partners believe that this deal provide a lot of flexibility. R. Leonard has the experience of negotiating deals with big pharmaceutical partners. He thinks that the combined technology, offered by AG/E, has a better chance to speak to the needs of a major pharmaceutical company that a single technology.

The clinical trial sponsored by AG/E is monitored by a contract research organization.

AG/E is currently seeking to form an alliance with a major pharmaceutical company to participate in clinical development and worldwide commercialization of these products.

APOLLO GENETICS AS A VIRTUAL COMPANY

Apollo will have to raise further capital through private placement. It is more difficult to raise money for a virtual company. The virtual model is not well understood or appreciated by the financial community. Investors have more difficulties to appreciate the value of the company and are missing the stability provided by a management team.

They may also consider that a very small management team limits tremendously the opportunity for the company. For these reasons virtual companies usually command lower than average valuations in their early stages.

The step-by-step approach of the virtual company is very efficient in term of cash management. Apollo has been able to bring a product to a clinical trial stage with very limited resources and a joint venture. Apollo took advantage of the consultants, and contract research organizations that are largely available to the biotechnology industry. The main risk is that of suboptimal strategy. Apollo does not benefit from the experience of seasoned pharmacy or biotechnology executives or venture capitalists. Apollo has no experience of drug or business development. This knowledge can be hired to some extent through contracting-out. Nevertheless contracting out requires some monitoring. An extensive experience in dealing with external companies is considered critical when those CROs are in charge of products which are strategic for the development of the company. Apollo will hire a part time medical director. Can Apollo get good people and sufficient attention from external suppliers with very small contracts?

It is difficult to control the work done outside the organizations when the contracts cannot be easily written or are difficult to enforce. Agreements with the university are good examples of the latter situation. It is our understanding that Apollo had encountered some difficulties with academic collaborators. These researchers have different conflicting agendas. They can work with other companies outside the field of research defined in the contract with Apollo. Apollo can try to foster the interest of the key scientists by giving them some type of financial interest in its venture. The distribution of equity cannot be general enough to control all the stakeholders. Furthermore an objective appraisal of the project may suffer from the vested interests of collaborative scientists.

It is too early to know whether Apollo will remain a virtual company if Apollo is successful in raising additional capital and moving its product further into development. Virtual organization may represent a growth stage when raising start-up capital is difficult. The organization can be scaled-up when the concept of the main products or processes of the biotechnology company are proven. Some biotech executives believe that most of the value in biotech companies is created not in the early laboratory work but in clinical trials and that it is wiser to save the money for the clinical trials. On the other hand, Apollo may develop some type of network organization. Even in this setting Apollo may benefit from a beef-up management team. Gordon believes that virtual company represents a development stage in a biotechnology company with little capital endowment.

VIRTUAL COMPANIES MAY COME OF AGE FOR DIFFERENT REASONS

An increase in quality laboratory services and the broad availability of intellectual capital is allowing more biotech companies to enhance their values with less financial capital. Contract labs, usually started by early biotech alumni, now specialize in different biotechnology techniques formerly conducted within the early biotechnology companies attempting large scale vertical integration. Contract resources are widely available nowadays. Though executives insist that the quality of outsourced work is much higher in the 1990s, all of them stress that selection of the contract lab and design of the trial are the two most crucial decisions a virtual company must make.

Some former biotech executives are using their experience to add value to companies with science that far along on the technology curve. Burill & Craves (San Francisco) have worked with new biotech companies and received most of their compensations for this work through equity options and warrants. Their network of experienced industry executives may bring the right scientist, regulatory executive or management plan that the company needs to increase its value.

Such virtual growth requires companies to do a better job at selecting the right drug targets, finding the right marketing partner, and responding quickly when opportunity knocks.

Driven to some degree by investor reluctance to part with financial capital, virtual integration strategies allow to institute variable costs whenever possible. Many biotech companies are revising capital intensive business strategies and instead are seeking to enhance their value through out-sourcing of services that used to be conducted internally. Some companies are embracing the virtual corporation concept at every possible stage of the value chain. The large availability of information through biotechnology forum, specialized journals, Internet services is very helpful to make this decision.

Public market are becoming very difficult for biotech companies. Even when the traditional financing sources can provide cash, the terms are hardly favorable. Those times favor step by step investments and the replacement of fixed costs by variable cost.

In conclusion, different financial and technical reasons have accelerated the development of virtual companies. More and more biotech companies are started as virtual companies. Venture capitalists encouraged their founders to start with very few fixed costs (S. Lazarus, ARCH Venture Partners). Will these companies remain virtual if they are successful at developing products and raising capital? Can they build a core competence in managing outsourced project? Have virtual start-up companies a competitive advantage over integrated biotechnology start-ups? It is too early to appreciate if virtual companies represent a new model of organization in the biotech industry.

CHAPTER FIVE

MILLENNIUM

A basic research company funded on collaborative relationships with major pharmaceutical companies

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New discovery technologies are attractive because innovative drugs are in short supply. Drug companies need to bet on novel therapies these days. They are looking for biotechnology companies which have new products or new platform technologies for drug discovery. Some biotechnology firms have been recently created to commercialize gene-based analysis and computerization. These biotech companies need a lot of money to conduct expensive genomics research. In their formative years, they need pharmaceutical partners with deep pocket. We have studied Millennium, a Massachusetts firm, to answer the following questions:

- How do biotechnology firms that form early alliances with pharmaceutical firms benefit from their funding and drug discovery expertise and still retain their independence?
- How do pharmaceutical companies outsource basic research? How do they try to benefit from the knowledge spill-over of these contracted programs? How much are they willing to pay for a window on new drug discovery technologies?

THE COMPANY

Millennium is a biotech company that will utilize genetics and proprietary automated genomic technologies to develop targeted therapeutics for human health disorders. The pharmaceuticals will be based on the identification of disease-causing and

disease-related genes and their cellular functions. This knowledge will lead to a new generation of diagnostic and therapeutic products capable of addressing major diseases at their roots rather than simply identifying and treating symptoms. The disease targets of the company include Obesity, type II Diabetes, Asthma and Immunologic disorders, Cardiovascular diseases, Central Nervous System disorders and Cancer.

The company was founded in early 1993. The founding scientific advisors are academic researchers that have major positions in prestigious institutions such as the Massachusetts Institute of Technology, Le Centre d'Etude du Polymorphisme Humain, Rockfeller University, Albert Einstein College of Medicine.

The company has a very prestigious board of directors, advisors and collaborators. It is backed by a pool of renowned venture capitalists. The company raised initially $8.45 million in its seed financing from venture capitalists.

> *Millennium has spread its technological risk by undertaking development programs in multiple disease areas. Financial risk will be reduced and product development accelerated through the formation of a number of collaborative relationships with major pharmaceutical companies, focusing on specific diseases* (company communication).

"Millennium is looking for more than $50 million in a major collaboration," says Mark. Lewin, CEO.

Millennium relies on these external members to be in a unique position to apply the genome technologies to develop therapies for complex but common genetic conditions.

The recent licensing-in of the "fat gene" discovered by one of the founders, J. Friedman, by Rockfeller University to Amgen demonstrates the limitation of this approach. As a consequence, Friedman will provide some consulting to Amgen. The French government restricted the commercial use of the databank (and thus by Millennium) on Diabetes families collected by D. Cohen, another founding scientist on

the basis that the research was funded with money from the public. Scientists cannot go against the policy of their universities, which may wish to auction their discoveries to get the best possible deals, or make the discoveries available to everyone.

THE SCIENCE AND TECHNOLOGY PLATFORM

> *It has long been known that many rare diseases, like cystic fibrosis, are genetically based-caused by a defect or mutation in a single gene. Until recently, it was less evident that susceptibility to common major diseases is also genetically determined. With the advent of the Human Genome Project, it is now feasible to identify the genetic bases of such complex diseases. The Human Genome Project provides a publicly available genomics infrastructure that Millennium uses in its proprietary drug discovery program.* (company communication).

The reliance on some academic research provides the risk of severe competition, because of a potential bidding war.

Millennium's core technologies lie in several basic areas. The first is in the direct isolation of disease genes including an exclusive license from Stanford University to develop a new genetic mapping technique, Genomic Mismatch Screening. GMS is expected to accelerate mapping of multigenic traits by reducing the need for conventional genetic mapping. The second area is a proprietary system for the large-scale automated identification of genes that are candidates to be key components of disease physiology. Lastly, Millennium is developing resources to elucidate gene function and design disease-specific therapeutics. The company's humans genetics programs involves a series of collaborations with leading clinical researchers throughout the world to study family members with inherited diseases and to identify the responsible genes.

The genomics-based approach identify the role of genes that cause or increase susceptibility to a disease. Drug candidates can then be selected and drugs designed

based on their ability to intervene at this fundamental level of disease initiation and progression.

THE DEAL WITH HOFFMANN-LA ROCHE

In March 1994, less than one year after its creation, Millennium entered into an agreement with Roche to collaborate on the discovery of novel therapeutics based on genomics technologies. The agreement, valued at more than $70 million, covers two disease targets; Obesity and Type II Diabetes.

Looking for corporate partners with deep pockets has been the strategy of Millennium since its inception. Millennium calculated that it needed more than $200 million over 10 years with 3 to 6 partners in order to succeed. The amount of money that Millennium raised with venture capitalists was not sufficient to finance genomic research. Millennium needs long-term corporate partners because its research is fundamental. Millennium will not be able to get money on the public financial market without any products in the pipeline. Millennium is not expecting to be in this situation for a long time. (At that time, the backing from major companies will be seen as a proof of quality and sustainability of the business by the potential investors.) The reputation of the scientific founders, and their connections inside the Research and Development organizations of major pharmaceutical companies are instrumental in seeking partners.

One of the founders of Millennium knew J. Andreas, President of Roche who was precommited to the technology. Roche had made major investments in Biotech with the acquisition of Genentech, the licensing or co-development of major recombinant drugs (Interferon, G-CSF), and the construction of a research center devoted to biotechnology in the US. Roche is now shutting down its Nutley Institute and is planning to invest more outside of its organization.

It took eight months to sign the Millennium-Roche deal. Millennium worked with experienced business development consultants and lawyers. Negotiating these deals requires a lot of experience. Start-up companies have to rely on outside specialists to achieve maximum efficacy in the negotiation. It requires a lot of negotiating skills to obtain a sizable amount of money when no clear product is foreseen in the near future. We believe that there is a learning curve in business development and that the experience of the Roche negotiation will be very useful for other Millennium negotiations.

Under the terms of the agreement, Hoffmann-La Roche receives exclusive worldwide rights to small molecule therapeutic applications of data gathered utilizing Millennium's proprietary genomics technologies for obesity and type II diabetes, and outside North America, exclusive rights to antisense, protein and gene therapy applications. Millennium retains exclusive rights in North America to antisense, protein and gene therapy applications subject to Hoffmann-La Roche having an option to co-promote these types of drugs. Hoffmann-La Roche also has a worldwide option on all diagnostic applications.

In return, Hoffmann-La Roche will take an equity position in Millennium and will provide substantial research funding. Millennium will receive a royalty on all product sales by Hoffmann-La Roche. On products co-promoted in North America, the companies will share profits on sales. The majority of the $70 million is in research support committed over a five-year period. In addition, Millennium will receive preclinical and clinical milestones payments.

Also of critical importance to Roche was obtaining the right to apply Millennium's technologies to areas of interest that are outside the scope of the deal. "We can use the technology in house to study other diseases," says Roche. "This was very important to us."

Millennium retains all the rights to use the information and technologies developed through the sponsored collaboration for the development of diagnostics and therapeutics for disease indications other than Obesity and Type II Diabetes.

It was not possible to have access to the Roche team that negotiated the deal. The head of Roche R&D, Juergen Drews, President of Roche International Research and Development, made the following comment: "

> *We are very excited to be working with Millennium. The company has strong core technologies, a first class team of scientists and significant depth in their approach to multifactorial genetic diseases. We believe these factors are key in attaining our goal of not only identifying the genes that cause obesity and type II diabetes, but developing therapeutics products as well.*

Roche is taking a very long-term view on the collaboration. If the partners are lucky and identify a gene that codes for a protein that can be used as a drug, there is a good chance they could move a drug into clinical trials within 5 years. Small molecules could enter clinical trials in a 5 to 10 year time frame.

THE CONSEQUENCES OF THE ROCHE DEAL FOR MILLENNIUM

The funding had allowed Millennium to hire key research scientists in July 1994. At the end of 1994, Millennium has assembled a group of 95 scientists and business executives. The team collectively has experience in more than 12 academic institutions and 5 biotech companies.

Millennium's human genetics program involves a series of collaborations with leading clinical researchers throughout the world from which to collect DNA samples, and clinically characterize human family members in whom the disease under study is inherited.

All together Millennium has collaborations with more than 25 academic groups.

Millennium will continue to work on projects outside type II diabetes such as immunologic disorders-asthma, cardiovascular disease and cancer. Millennium is looking for partners to develop these activities, which presently represent minor research domains for Millennium. Millennium is seeking the formation of multiple long-term funded collaborative partnerships with major pharmaceutical companies, most often focused on a specific disease. Millennium also anticipates entering into additional alliances with biotechnology companies possessing complementary resources to develop proprietary products. These partnership may be more restricted and involve specific product applications of Millennium technologies.

The potential spill-over in genome research is important. This may be a major issue in the case of multiple partnerships. We do not know how Millennium plans to share its time between different research domains and partnerships.

GENOMICS BIOTECH COMPANIES

The deal with Millennium is one of several that were organized in 1994 on Genome data. The biotech companies working on this platform technology were created in 1993. In 1992-1993 different scientific groups working together inside the Human Genome Project had made major contributions towards the realization of a physical map of the genome. The news struck the scientific community that was not expecting such breathtaking pace in Genomic Research. The potential applications of these discoveries as a platform for drug research became evident for the scientists involved in this new domain. At that time no pharmaceutical companies were involved in this very basic research, which the pay-off in terms of drug development, is very remote in the future.

Most of the research in this domain has been financed through government money. Groups have collaborated together to tackle this very difficult scientific task. Each group concentrates on specific parts of the genome or on different techniques to obtain maps. The pioneer discoveries of 1992 has fostered an unprecedented effort in the biological sciences. The goal of the Human Genome Project is to identify all the approximately 100,000 genes in the human genome and to assign or map these genes to their chromosomal locations. This information, and the advanced technologies, reagents and databases developed through the Human Genome Project constitute a resource publicly available. Genomics infrastructure is of potentially enormous value to the biopharmaceutical industry. Pharmaceutical companies will have the opportunity to access this technology through internal research, biotechnology firm deals and in-licensing from universities. Universities, as stated above, are the major player in this fundamental research.

The controversy regarding the patentability of genes whose functions are unknown, the free availability of information which is key for the discovery of new genes, and widespread scientific collaboration have questioned the development of companies in genomic research.

Genomic companies will have to work with academic centers on the discovery of new genes which may have some major health care implications. This has two implications:

- The universities can bypass the biotech companies if the basic discovery is valued as such by the pharmaceutical companies with deep pockets. Amgen has agreed to pay $20 million to Rockfeller University to obtain access to the "fat gene" that appears to be successful in treating obesity, so far only in mice.
- The biotechnology companies will have to make some of their databanks available to the universities. The president of HGS insists that the company's material transfer agreements with academics are not different

from the NIH's. Recently a gene involved in hereditary colon cancer was jointly discovered by Johns Hopkins and HGS scientists. Johns Hopkins asked HGS if it had DNA repair genes in its collection. HGS scientists were then brought into the Hopkins effort. These biotechnology companies may have access to genomic banks or technologies (some of them proprietary) that are not available to academic researchers in non specialized centers. Incyte wants its database to be open on a contract basis. Incyte is structuring different partnership agreements with academic researchers and drug companies. The academic relationships will typically involve joint ownership of discoveries that result from the collaborations, while the drug company deals will involve licensing of genomic data to the big company (according to Incyte).

On the other hand, the Human Genome Project's publicly available genomics infrastructure provides the starting point for Millennium's proprietary, genomics based drug discovery. Millennium currently utilizes its genomic capabilities in synergistic technical approaches. Millennium will have to collaborate with other companies or academic centers in biological screening and protein and small molecule. Because of the interplay with major discoveries made inside the human genome project, the difficulty of gene research for complex trait genetic disease and the need for parallel biological research to identify the functions of the genes, genomic research inside and outside biotech firms will require an incredible *network of scientists*. Pharmaceutical companies will have a major role in financing the downstream research (the upstream being financed by government programs) and in providing their screening capabilities. Research may be quite expensive as companies look for the treatment of multigenic diseases.

These degenerative diseases will not be approached by a single therapeutic modality. *Companies will have to collaborate* in a very complex patent environment and look for an entire range of therapeutic alternatives-including small molecule, gene

therapy, recombinant protein and antisens approaches. Roche, with its experience in small molecules and recombinant protein therapies (that can be beneficial if the non functioning gene encodes a protein), will be able to contribute significantly to Millennium research efforts (outside research funding).

New diagnostics will be developed that are capable of distinguishing between genetically distinct types of disease. These diagnostics will be used to detect a disease disposition even prior to the presentation of symptoms. Clinical responsiveness to therapies might be correlated to more precise characterization of the patients. Diagnostic applications may be expected earlier than therapeutic applications.

The first products to hit the market place are expected to be research reagents (according to the president of HGS).

The value of genomic research has been perceived by other pharmaceutical companies than Roche. The transactions in gene sequencing in 1994 were as follows:

Exhibit 5-1

Darwin Molecular Corp.	Research Collaboration	RPR gains rights to some of Darwin's gene therapy targets in exchange for $16.5 million over four years, including a $5 million equity investment.
HGS-Smithkline	Milestone	Milestone SB paid $12.5 million for achievement of first milestones to install 35 automated DNA sequencers for SB's use at HGS. Part of *$125 million agreement* finalized in 5/93
HGS-Smithkline	Milestone	HGS received another $12.5 million for achieving second milestone, the transfer of 45,000 unique expressed sequenced tags
HGS-Genentech	Option	Genentech signed an option to license the heart-lung specific DNAse gene for possible therapeutic use in cystic fibrosis
Incyte-Layton	Technology licensing	Incyte obtain exclusive rights to Layton Bioscience's non PCR RNA amplification technology
Incyte Pfizer	Technology licensing	Pfizer pays 15.75 million for 3-year access to sequencing and analysis technology; additional payments contingent on products discovered
Glaxo- Spectra Biomedical	Research collaboration	3-year collaboration to discover migraine-associated genes; Glaxo to make yearly research payments
Glaxo-Sequana	Research collaboration	5-year collaboration to discover Type II diabetes genes; Glaxo to make initial and yearly research payments plus milestones

These gene sequencing deals of 1994 illustrate the vast and immediate commercial value of the technology, thereby differentiating these start-ups from previous biotech platform technologies. Sequencing companies will become profitable via R&D dollars much earlier than traditional biotech companies. Instead of having to achieve clinical milestones, gene sequencing companies are more likely to be judged on the usefulness of the information they provide. They will be in direct competition with universities for that reason.

Some big companies now perceive they will gain quick and clear results from gene sequencing research and will pay the going rate to obtain the information. This came out as a surprise as:

- the Human Genome Project was spending billions to map the human genome and make the information publicly available;
- some companies (Merck) or agencies (NIH) abandoned their efforts to seek patents for gene sequences and made their database publicly available. One of the challenges each company will face is securing a strong patent position for its discoveries. The precise biological function of sequenced genes may not be known and utility could be the deciding factor in decisions rendered by the patent offices.

Big companies believe that they can reap quick value from DNA sequences. Genentech signed an option to license the heart-lung specific DNAse; Amgen recently acquires the rights for an obesity gene cloned by Rockfeller University for up to $20 million. The competition between Amgen, Bristol-Meyers Squibb and Eli Lilly drove the price up in the Rockfeller auction (Business Week). The fact that Amgen will commit such an amount of money for a single gene, as may be 10 genes can cause obesity, is for Incyte R&D head, "mind-boggling."

In conclusion, biotech companies based on genome data will be at the center of corporate and academic relationships. They will gather invaluable information for the

understanding of disease and drug discovery. The role of these companies related to the university or research center laboratories sponsored by the Human Genome Project is not clear. Major pharmaceutical companies are already willing to pay a premium to get access to new technologies and information on genomic research. Millennium is basing its business plan on that willingness. It is presently looking for partners other than Roche to address new research domains. Gene-based analysis will be at the origin of a large information exchange between universities, biotech companies and pharmaceutical companies. Collaborations will be fostered by the patent positions of the different players and the number of different and expensive technologies required to develop a drug from basic, genomic research.

CHAPTER SIX

MIT-AMGEN

We will present the agreement between the leading biotech company in the world, Amgen and one of the leading scientific universities in the world, MIT. This case will illustrate the interest of pharmaceutical companies for a long term collaboration with a university with strong biology departments. What is the industry expecting from this type of collaboration? How this partnership can complement the product focused research done inside the industry or through specific contracts with outside parties?

AMGEN

Amgen is the largest and most profitable biotech company in the world. Amgen is the only biotech company that has managed to integrate itself into a pharmaceutical company with worldwide operations and to remain independent. There are regular rumors of Amgen take-over by companies such as Bristol-Myers Squibb.

The company manufactures and markets Neupogen (G-CSF), a product that selectively stimulates the production of neutrophils. It is used to decrease the incidence of infections in patients receiving chemotherapy for cancer. The company also manufacture Epogen (Erythropoietin, EPO), a product that stimulates red blood production, and markets it in some countries including US for use by dialysis patients.

Amgen as stated above was able to keep the rights for its products in significant territories. Amgen started marketing its first product through license and joint-venture.

It was able to use the proceed of these alliances and of the sales of erythropoietin to market or co-market G-csf in most countries (with the exception of Japan). In 1985, the company granted Johnson & Johnson an exclusive license to sell erythropoietin throughout the US for all human uses except dialysis. This agreement generated conflicts between the parties on the appropriate marketing of the respective indications. Amgen licensed this product for all foreign territories. In 1988, Roche and Amgen entered a co-promotion agreement for the sales of Neupogen in the EU. Amgen has a joint venture with Kirin that manufactures and markets erythropoietin in Japan and US.

Amgen has entered recently into agreements with biotech companies such as Regeneron for neurotrophic factors and Arris for cytokine mimetics.

The sales of Amgen in 1993 were $1,306 million, which generate net income $383 million. The research and development expenses were $255 million in 1993. Amgen is richly endowed and has the resources to buy R&D through the acquisition of other biotech companies (Synergen was acquired in 1994 for $262 million, mainly for its neurobiology pipeline), or the licensing and support of universities projects and products.

The company focuses its research and development on consensus interferon (that could be launched next year for the treatment of hepatitis C), hematopoietic growth factor (Stem cell factor, Megakaryocyte growth factor. Megakaryocyte growth factor appears to play the same role on platelets that Amgen's EPO and G-CSF play on red and white blood cells) neurobiology (with Brain derived neurotrophic factor and Glial cell line derived neurotrophic factor), inflammation and autoimmune diseases, soft tissue repair and regeneration, and hepatitis B vaccine.

"Amgen has gotten a bad rap because there's been a perception that there's not much behind EPO and Neupogen," (editor of Bioventure World, quoted in *The Wall*

Street Journal). But Amgen has recently done a good job at increasing its pipeline of new products. It has 11 potential drugs in clinical trials or about to enter them.

It is clear that Amgen would like to boost its development pipeline with a strong research. The MIT agreement (as well as the acquisition of the "fat gene" from Rockfeller University) is an opportunity to meet that goal.

THE BIOLOGY DEPARTMENT AT MIT

The Biology Department has 55 faculty members, located in the main facilities or in the Whitehead Institute, the Center for Cancer Research, the Brain and Cognitive Sciences Department. The department has four Nobel laureates, 20 members of the National Academy of Sciences and 10 investigators of the Howard Hughes Medical Institute. The department has a very strong international reputation in research and teaching and has been a leading contributor to the development and application of molecular biology.

THE MIT-AMGEN AGREEMENT

The MIT-Amgen biological research agreement was signed in March 1994. The terms of the agreement have not been published but their broad lines are as follows:

- Amgen will have the exclusive rights to developments and technologies resulting from the research collaboration in exchange for funding of up to $3 million a year for as many as ten years.
- Amgen scientists (up to 4 at a time) may serve as visiting scientists at MIT.
- The research and projects will be proposed by MIT to Amgen. A joint Amgen-MIT will approve the projects based on their relevant interests.

- MIT will recruit new staff as appropriate. These projects can be conducted in any of the Biology Department of MIT and are not restricted to any specialty (i.e., cancer research, neurobiology). The agreement provides that up to $500,000 a year of the research may be done by MIT professors working at the Whitehead Institute. The $3 million annual budget should allow the support of 5 to 10 projects.
- Amgen will have the rights to terminate the agreement in the unlikely event that the program is not proceeding as envisioned.
- The patents will belong to MIT. Research results are owned by MIT, in accordance with MIT rules. Amgen will read and comment on the patents. Amgen has the right of first refusal for the commercialization rights of the patents resulting from the funded projects. The levels of the licensing royalties to MIT have been determined. Co-invention occurs in the only case where the research has been conducted by an Amgen scientist at MIT.
- MIT researchers will have the rights to publish on their research funded by Amgen. The publications will be reviewed by the company to make sure that no confidential information is disclosed.

The Dean of Science will chair the MIT research committee on the collaboration. This committee will include the head of the Biology Department, Prof. P. Sharp, the head of Brain and Cognitive Sciences, the Director of the Whitehead Institute, the Director of the Cancer Research Center, and the head of Chemistry. It is our understanding that this committee will select the projects that will be presented to Amgen.

Furthermore Amgen is planning to build its East Coast research facility in Cambridge close to the MIT campus. They have already bought the land.

The origin of this partnership lays on the close relationship that exist between MIT Faculty and the senior management of Amgen. The industrial liaison office (ILO) initiated contacts with Amgen in 1991. ILO asks MIT Professor Emeritus Raymond Baddour, co-founder and director of Amgen to explore relationship possibilities between Amgen and MIT. The negotiation took three years and involved Amgen CEO, T. Binder, MIT President C. Vest, and their staffs. The Industrial Liaison Office (with R. Malster) initiated the negotiation, the Office of Sponsored Programs conducted it, and the Technology Development Office helped for the part of the contract related to intellectual property (L. Nelson). The most famous biology scientists at MIT, such as Nobel laureates D. Baltimore and P. Sharp, were instrumental in this agreement on the MIT side. The senior scientists (P.Sharp and Dan Vapner) in both organizations were at the center of the negotiation. They were in charge of defining the program. On the Amgen side, Dan Vapner the senior vice president for Research was the main negotiator. He is presently in charge of following the implementation of the agreement.

The negotiation was fairly easy. Amgen has a long experience with university agreement (e.g., University of Toronto), and Dan Vapner is a former university professor. The expectations of MIT and Amgen were not far apart from the inception of the negotiation. Furthermore the involvement of Amgen's CEO, Binder has certainly facilitated the process. "It also generally is the case that discussions with industry leaders at the highest ranks within corporations seem to be much more flexible than with those at the operating level who are involved with making project level discussions." (C. Vest, MIT report).

WHAT ARE THE BENEFITS OF THE COLLABORATION FOR THE PARTIES?

Amgen can leverage its funding with the money coming from the government to support the research at MIT. Amgen is getting an early window on the future through

the relationship with one of the best biology department in the world. The close relationships between scientists of Amgen and MIT will allow Amgen to think further ahead in term of research strategy. Amgen may also get the commercial use of some interesting patents.

Amgen can have access to the MIT students to recruit them in its nearby research center. Amgen can stimulate its own research with the MIT scientific environment through the joint meetings, the presence of Amgen researcher at MIT. The MIT network and the Boston medical environment should benefit Amgen as well. Amgen can also benefit from the MIT image. Amgen get a limited control over the research because it can identify the subjects of interest for the company.

According to Binder, Amgen's CEO, "

> *Amgen is looking for the opportunity of having its own researchers work closely with the MIT scientists. Amgen is not expecting to get any product directly from this collaboration. This collaboration may pave the way for specific agreements that will be more focused on product discovery. Amgen was looking for the opportunity to test a new concept in Industry-Academy partnerships. MIT came as a good candidate for this type of deals, because it has both the will to collaborate with the industry and the capacity to make significant scientific contributions. MIT's Department of Biology offers a broad scope of research domains.*

Mr. Binder adds that this agreement is very unusual for Amgen. All the other Amgen's research agreements (about 200) have been signed on specific projects.

Pharmaceutical or biotech firms may be quite candid when asked directly why they explore out-sourcing opportunities with academic institutions. It is interesting to compare Amgen's motivations with those of other firms that out-source research (at least in part). One third of the companies partneed with universities to demonstrate "community" activity, while only about one tenth of the firms in this same survey claimed to have out-sourced to solve a specific technical problem. These survey responses are summarized in the table below.

Exhibit 6-1

Reasons cited by companies for sponsoring academic research

gain access to manpower	75%
window on science and technology	52%
general support of technical excellence	38%
gain access to university facilities	36%
obtain prestige / enhance company's image	32%
act as a good citizen / foster community relations	29%
make use of an economical resource	14%
solve a problem / had to get specific information	11%

Source: National Science Board; 1981 survey of 56 firms

MIT benefits from a significant grant ($30 million over 10 years, adjusted for inflation?). Five to 10 projects will be funded annually with $200,000 to $500,000. This grant should be compared with the $40 million 1993 Biology Department operation costs (and the MIT overheads) (MIT Report). The Amgen funding is not big enough to influence the Biology Department strategy. The department is mainly funded by the NIH and the Howard Hughes Institute. This deal cannot be compared to the megadeals of Scripps with Sandoz ($200 million after the renegotiation) or MGH (Harvard) with Hoechst, Shisheido and Bristol Meyrs Squibb. These deals generated a great deal of visibility and often became targets for crusading politicians, particularly when they involved foreign companies.

The MIT-Amgen agreement has little to no effect on the ability of the MIT Biology Department to work on long-term research in the domain of its choice, or to initiate collaborations with other companies. Amgen does not have the first right to pick-up projects. Projects are proposed to Amgen by MIT. Investigators in the Biology Department can pick up the collaboration of their choice. They can work with other companies if they wish so. The Amgen support is based on projects. The property rights do not spread beyond the projects.

The MIT/Amgen contract can be compared to a common sponsored research agreement. The main elements in those contracts, according to A. Stevens, are:

- right to publish, discuss and collaborate protected
- established, administered and directed by institution's staff in accordance with institution's policy
- payment of full indirect costs
- principal investigators select projects
- intellectual and tangible research property owned by institution
- option for exclusive, worldwide, royalty-bearing license
- objective time-limited due diligence milestones to be established
- institution held harmless and indemnified against product liability

The MIT/Amgen agreement offers a lot of flexibility to MIT.

MIT is permanently looking for corporate partners at a time when government money is more restricted. The Biology Department at MIT has other contract with biotech/pharmaceutical companies and will continue to have them in specific domains or research which do not conflict with those presently picked by Amgen. Most of contracts with the Biology Department are around $1 million and other significant deal such as Amgen's would be appreciated. MIT has a lot of contracts with smaller companies than Amgen. Small companies are more accessible and more flexible than large companies. Universities funded by the government have to make a fair share of their deals with small businesses, in compliance with the Bayh Dole act.

In conclusion, this deal seems to offer a window on the future of biology for the corporate sponsor and funding and independence for the university. It is too early to see if it will deliver its promises to the two institutions and if it will pave the way for more specific agreements.

CHAPTER SEVEN

GENZYME

Genzyme is a biotech company developed through the building of a large product portfolio, original financing and the acquisition of small biotech firms. This strategy gives a good opportunity to study:

- the role of cultural similarities in the management of partnerships or acquisitions of other biotech firms;
- the balance between internal research and the acquisition of new platform technologies or undeveloped products;
- the origin of the products in a very diversified pipeline with non conventional products.

Genzyme is located in Cambridge, Massachusetts. It was founded in 1981 to produce enzyme for diagnostic applications. The company has been very successful at bringing products on the market. The sales in 1993 were $233 million. The total revenues including research contracts were $270 million. The company is rapidly growing (revenues are up 23% in 1993 compared to 1992) and expanding its international implantation. Its regular and sustained increase has allow Genzyme to remain independent from any major pharmaceutical company. Genzyme did not need to license-out its products because of the low launch costs of its highly specialized products.

The success of Genzyme is based in part on the development and marketing of glucocerebrosidase for Gaucher's disease. In 1983, the company entered into a 10-year agreement with BioInformation Associates, a corporation owned by eight scientists on

the faculties of Harvard University and the Massachusetts Institute of Technology. BIA identified with Mr. Termer, the CEO of Genzyme, an opportunity to use Genzyme's technology in the treatment of Gaucher's disease. Patients with Gaucher's disease suffer from the lack of an enzyme, the glucocerebrosidase. This treatment is very efficient in reversing the severe symptoms of that disease. This enzyme is presently the main source of revenues of Genzyme. Genzyme was able to get a premium price for that treatment and to market it worldwide.

Genzyme has mastered the niche strategy in biotechnology. It has decided to enter different specialized markets in fine chemicals, diagnostic products, and diagnostic services. The development of these activities is less costly and faster than that of pharmaceuticals. These activities have provided Genzyme with a regular stream of cash-flows to finance its research.

Genzyme has used a very original approach to finance its R&D efforts. Most of the R&D in the therapeutic division, the most costly and the longer to deliver products, has been financed "off balance sheet" through limited partnerships and spun-off companies.

Genzyme considers itself as a product development oriented company in the biotechnology industry. Genzyme has acquired a lot of its core technologies mainly through acquisitions of smaller biotech companies but also through contracts with universities. Genzyme has been very successful at integrating these small companies inside its organization.

Genzyme may have different *distinct advantages* compared to pharmaceutical companies for biotech alliances:

- Genzyme is located in Cambridge, Massachusetts, in the heart of the biotech cradle and in the middle of a network of excellent universities. A significant number of the deals were done with local entities. The

acquisition of local entities facilitates the integration of those companies into Genzyme.

- Genzyme is a small company or at least it was up to recently. It can understand better the needs, wishes and fears of its partners. Partners are expecting to receive more attention, more priority from a smaller company. Decisions are also taken more rapidly. R.H Douglas, Genzyme's VP for development describes the collaboration in this context as a "win-win approach."
- The people in Genzyme belong to the biotech community and have the same culture as that of their partners. They are able to integrate easily the executives of these companies in case of acquisition. They are not as afraid of losing some of their operational independence with Genzyme as they might have been with a huge multinational.
- Genzyme has cultivated a very decentralized approach with fairly independent small units. This approach has been facilitated by the heterogeneity of its activities and the fairly distinct market and regulation needs. Genzyme has used a very original approach for financing development in new domains. It has started separate companies whose missions are to address very specific technologies or markets. Decentralization may foster creativity and entrepreneur mentality. Distinct companies allow to link senior executives' compensation to the performance of Genzyme and to the performance of their own divisions. We believe that this relatively hands-off approach may help to integrate entrepreneur created firms inside its organization. In fact, some of these entrepreneur have become senior executives of Genzyme. An example is G. Phels, Genzyme's senior VP, and former CEO of two biotech firms.

We will describe **the different divisions of Genzyme** to highlight the diversification of Genzyme. This diversification reduces the financial risk that be may be incurred by any regulation or market changes affecting a particular product.

Furthermore the R&D has been funded by "spinning-off" distinct companies to conduct research on different projects.

This model is coming from General Motors which created different entities to enter new businesses (acquisition of EDS and Hughes). Each of these new entities will be valued differently from the core activity. It has not been extensively applied to small companies setting up a different business.

The potential advantages of these tracking or target stocks are:

- management incentives: the shares are linked to the cash-flows of the specific division.
- tax advantages: target stocks are a tax-free distribution.
- appropriate risk and biotech valuation
- fund-raising through the division
- increased R&D spending does not affect Genzyme's bottom line.

The principal disadvantages are that during a time of low interest for biotech stocks, there is a liquidity problem and a low valuation problem. Furthermore shareholders are not enthused by target stocks because the shareholders don't actually own the assets of the unit, as they do in a spin-off. The parent company has the power to seize assets or divert earnings without shareholders approval.

Therapeutic Division

***On the market*:**

Cerezyme (recombinant glucocerebrosidase) and Ceredase (purified protein) for the treatment of Gaucher's disease.

In development (research funded through the formation of Neozyme I and II, formed in 1990 and 1992 respectively

- Gene therapy for Gaucher's disease
- Treatment of cystic fibrosis
- gene therapy with the CFTR gene, through Neozyme II (adenovirus vectors, cytofectin technology (Vical))
- polyclonal antibodies foe pseudomonas infections (HyperGAM + CF)
- protein replacement therapy

Thyrogen (recombinant TSH) for the monitoring and treatment of thyroid cancer

- Alpha galactosidase for *Fabry disease*

Cancer Research

- retinoids in liposomes (Tretinoin)

Would Care or Tissue Repair

Debridement for use in treatment of chronic wounds and burn injuries (Vianain) The tissue repair has been spun-off as a new class of shares (target stocks). The Tissue repair division has a new cell therapy product for the treatment of cartilage injury.

Surgical Products, initially funded through Genzyme Development Partners, started in 1989

Hyaluronic acid products (HAL). HAL has been registered in !994 and 1995 in several European countries as a mean to decrease peritoneal adherence after abdominal surgery. These new *devices* (that look like wax films) represent significant business opportunities for Genzyme. They will be sold by the surgical division with a specific sales force.

Diagnostic Products

- fetal cell separation for genetic analysis
- LDL Cholesterol test

Immunobiologicals

- Medix (diagnostic immunochemistry)
- Virotech (ELISA test kits) (Germany)

Pharmaceutical and fine chemical

- phospholipids
- chiral intermediates...

Diagnostic services

- Integrated Genetics, acquired in 1989 (manufacturing, genetic testing), 70% owned by Genzyme that plans to acquire the rest of the company.
- Genetic Associates, acquired by IG Labs in 1990 (fetal cell analysis)
- Genetic Design, acquired by IG labs in 1992 (paternity testing, bone marrow typing)
- Vivigen, acquired by Genzyme in 1992 (prenatal testing)
- Genzyme Transgenics, (70% owned by Genzyme) produces proteins in the milk of transgenic animals

This unique structure means that no one program or product has the power to make or break the company (Annual Report) in the mid-term although the company presently depends a lot on the sales of its cerebrosidase products.

The distribution of roles between the subsidiaries and divisions, and the corporate center is as follows:

- The manufacturing and the development/registration of new products is controlled at the corporate levels. Genzyme sees its manufacturing abilities as a core competence that it could trade against new products with small biotech companies. Small companies do not have the expensive, FDA approved centers to produce the products coming from their research.
- The research and the marketing are decentralized at the division level.
- The scientists at the division level. are the origin of most external collaborations. The negotiations take place at the corporate level.

So far there have been no conflicts between the different divisions/subsidiaries on budget allocation. The budget process is under the direct supervision of Genzyme's CEO.

This decentralization may create some redundancies. They have not been a problem so far because of the rapid growth of Genzyme.

The most recent deals of Genzyme show how, through alliances and acquisitions, Genzyme is building its product line.

Exhibit 7-1

4/92	Xenova	R&D collaboration	Inflammation
4/92	Neozyme II (Spinoff)	development and license agreement	gene therapy for cystic fibrosis
6/92	Genetic design	Acquisition	diagnostic services
10/92	Vivigen	Acquisition	Diagnostic services
11/92	Medix Biotech	Acquisition	diagnostic (immunochemistry)
4/93	Virotech	Acquisition	Elisa test kits (Germany)
5/93	Catalica	R&D collaboration	catalytic technologies
8/93	Univax	License and stock purchase	cystic fibrosis Univax's HyperGAM+CF
9/93	Argus	worldwide licensed equity purchase, R&D, Milestone, royalties	lipid based formulation of tretinoin for the treatment of leukemia
10/93	Neozyme I (spinoff)	purchase of the rights and technology from its research affiliates	burn treatment enzyme fetal cell separation
10/93	Vical	license option	lipid -based gene delivery for cystic fibrosis therapy
7/94	Celtrix	worldwide rights Stock + R&D funding + milestones	TGF-beta-2 for wound healing
11/94	Pittsburgh University	license	retroviral gene delivery therapy for Gaucher's disease
12/94	Biosurface	acquisition	exchange of tissue repair stock against Biosurface stock.

To date, Genzyme has favored a strategy of small biotech acquisitions to enter new domains that are complementary to its present businesses. It is taking advantage of the present low valuation of some of these companies that are running short of cash. Acquisitions give Genzyme access to platform technologies, a portfolio of products, and experienced scientists. Good examples are Biosurface and the diagnostic companies. When Genzyme wants to get a specific product, it restrict the equity deal to a minority interest (Univax, Argus, Vical).

In its acquisition of Biosurface, Genzyme has tried to balance the conflicting necessities of cost-effective management and a biotech firm's desire for independence and a financial return tied to performance through its Genzyme Tissue Repair (GTR) division. Genzyme gave Biosurface the two aspects of wound care technology that its

CEO felt it needed and the ability to raise more cash. GTR packages together all of Biosurface along with Genzyme's two wound-care programs: Vianin for severe burns and TGF b, which it had licensed from Celtrix Pharmaceuticals Inc. In July 1994 GTR is a wholly owned division of Genzyme with its own tracking stock. GTR makes its own SEC filings. Genzyme consolidates GTR's expenses for tax purposes (thus getting a tax write-off and improving its cash-flow) but files an income statement with the SEC that does not include GTR's losses-those go on GTR's statement. Biosurface shareholders own 50% of the GTR tracking stock-values, at the current Biosurface to GTR conversion rate at about $30 million, which is also Biosurface's market cap. Biosurface's employees thus all get shares in GTR which should perform more or less as GTR does. The stock should do better than Biosurface's had done because it will have the attention of the security analysts that follow Genzyme. These analysts will be following a stronger company with a broader, and therefore lower-risk portfolio of wound care products. The deal looks like a win for Genzyme, for Biosurface's employees, all of whom with the exception of the CEO were offered contracts.

The quality of the Genzyme-Biosurface deal follows the relatively disappointing results from the IG labs. IG labs was tough to manage. IG labs executives asked; are we independent or part of the parent? The Biosurface original acquisition may be a way to accommodate intact incentives with an acquisition without cash disbursement.

In conclusion, the development of therapeutic drugs by biotech companies is usually funded through private equity placement, public offering, and licensing out. Genzyme had had a different way to finance its growth. The company, rapidly after its inception, made money from the sales of specialized products (fine chemicals, diagnostic tests, diagnostic services) that can be developed rapidly. The proceeds were used to build manufacturing capacities, marketing departments, and to acquire small biotech companies. The targeted acquisition of small biotech firms has given Genzyme the access to platform technologies and products. The development of some of these products was financed through Research and Development Limited Partnerships and

Target stocks that has reduced the risk of developing new products to Genzyme. Genzyme has applied this financing, portfolio, and investment strategy instead of costly, equity financed, in-house Research and Development.

CHAPTER EIGHT

DISCUSSION AND REVIEW OF THE LITERATURE

I would like to conclude this thesis with a discussion of a few of the key issues raised during the analysis of the different firms' strategies. We gathered data through the Association of University Technology Manager (L. Nelsen, MIT and A. Stevens, Harvard) and two recent meetings on biomedical partnering were also used for the purposes of this analysis. The meetings, held in Boston, are "Pharmaceutical Biotech Companies Partnering," Mass Biotech Council (1995) and "Commercializing Biomedical Technologies," Harvard School of Public Health (1994).

BIOTECHNOLOGY FIRMS LINK PHARMACEUTICAL FIRMS TO UNIVERSITIES

Biotechnology companies play a key role in the technology transfer chain linking university and hospital research centers with fully integrated pharmaceutical companies. Although biotechnology firms and pharmaceutical firms have equal access to universities, information transfer is often exchanged from "science" (university) to "early development" (biotech firms) and then to "late development, product manufacturing and marketing" (pharmaceutical firms) organizations.

Size has been proposed to create trade-off which preferentially effect biotechnology firms, many of whom equate small, decentralized operations with their successful entrepreneurial cultures. Past attempts to integrate relatively small research-based biotechnology firms into large, fully integrated pharmaceutical firms resulted in systemic difficulties (e.g., Ciba and Alza, Lilly and Hybritech, Bristol-Meyers and

Genetic Systems Corp.). This can be contrasted with the apparent success of Genzyme's acquisitions. "Intrabiotech acquisitions" are at a record number in 1994 (Longman, 1994). The assertion has been made that entrepreneurial biotechnology firms inherently need the independence which comes from small-scale, decentralized operations. Ad hoc evidence in support of this conclusion might be drawn from the fact that, in some operations, the same egos needed to drive the entrepreneurial enterprise creates barriers for shared control. Hybritech scientists left their newly acquired company to start or join newly hatched biotech firms. Biotech firms need independence.

Pharmaceutical industries clearly do not lack the ability to adsorb and use university-derived technology. However, trans-cultural transactions might display an impedance mismatch. The proximity to universities through clustering around San Francisco, Boston, and the cultural link favors the biotech company, as much as the rapid decision procedures in small organization. This advantage may not be sustainable if the universities really auction out their discoveries (see the licensing out of the "fat gene" by Rockefeller University) and if the pharmaceutical companies are looking for more innovative research at a point in time when "me-too drugs" are becoming less profitable. The biotechnology industry may lose its middle man role if university transfer offices look for big money agreements and if pharmaceutical companies pursue a vertical integration through biotech acquisition.

A GROWING INTEREST FOR ACADEMY ENTERPRISE PARTNERSHIP

The reasons why firms partner with academia are (Stevens, 1995) the following:

- Technical driving force in basic biomedical research;
- Productive source of proprietary information;
- Cost effective?: $70-80,000 per year for a fully loaded post-doc;
- Non competitive: no manufacturing or marketing, no quid pro quos.

The survey conducted annually by the Association of University Technology Managers (provided by L. Nelsen, past president AUTM, MIT) shows a regular increase over the years in the total of gross royalties received by US universities and teaching hospitals. In 1992 the gross royalties was $259,305,404 for the responders which represent more than 85% of the 80 largest institutions. It is interesting to look at the following table to appreciate the role of the industry in the financing of US universities.

Exhibit 8-1

(dollars)

	US Universities	Total (with hospitals)
Industry Support	1,157,550,334	1,343,413,879
Federal Govt. Support	9,335,308,358	10,139,780,608
Total Sponsored Funding	12,979,022,384	14,378,388,084
Licenses/Options Executed	1,387	1,731
Total Licenses with Equity	321	371
Royalties Received	172,681,192	298,305,404
Licenses/Options Generating Royalties	2,632	3,177
Invention Disclosures	5,645	7,604
Total Patent Filings	2,329	3,251
New Patent Filings	1,734	2,238

Some general features found in biomedical research contracts are summarized in the following table:

Exhibit 8-2

Contract Trends (375) monitored by NIH

project specific agreements	**88%**
broad scope agreements	**12%**
$150,000 or less	**50%**
$1,000,000 or less	**95%**
$5,000,000 or more	**2%**
3 years or less	**70%**
3 to 5 years	**15%**
over 5 years	**15%**
agreements with "small businesses"	**45%**
agreements with domestic companies	**85%**
publication holdup of more than 60 days	**22%**

Source: Dr. Stevens (AUTM)

THE RELATIONSHIP BETWEEN THE BIOTECHNOLOGY AND THE PHARMACEUTICAL COMPANIES

In today's environment, pharmaceutical companies look for partners more than they did in the past. They no longer believe that they should own all the assets required for their activities. Pharmaceutical firms do not have the resources to do that anymore (D. Thompson, VP, Business development, Eli Lilly). Lilly increased its number of external transactions to 29 in 1994, half of them with biotechnology firms. Merck (E. Wyatt, VP, corporate licensing) has always been more conservative in terms of partnering. Merck looks for deals with a high probability of success. Merck selects the funded projects on the data presented by the biotech companies and the mechanisms of action of the potential drugs offered in license.

The concept of disease management where a company offers a bundle of goods and services to serve the needs of patient with a specific disease (diabetes...) may influence the licensing policy of firms (J.News, Director, Licensing and development, Pfizer). Merck did a deal with Celltech on phosphodiesterase inhibitors for the treatment of asthma. Merck was looking for other anti-asthma drugs to complement its program in leucotriene antagonists. Pharmaceutical companies may look for opportunities in the diagnostic of diseases that can be treated by their own drugs.

Companies increasingly favor co-development, because of the development cost of a drug, the risk associated with certain projects and the poor financial return on the "me-too"drugs. An example is offered by the Pfizer/ Esai deal. Pfizer co-develops an Esai drug for the treatment of Alzheimer disease. Pfizer, which had spent roughly $10 million on a similar drug was 18 to 24 months behind, agreed to retract its own compound as part of the agreement.

More and more deals are on platform technologies. The Gencell, and the Millennium Roche deals are good examples. They allow the pharmaceutical companies to get access to cutting edge technology (gene therapy, genomics...). They allow the

biotech companies to keep the rights to commercialize some of their products for other indications or particular molecules. The pharmaceutical company may be interested by developing biotech molecules (Gencell, Roche...) and/or by developing small molecules discovered through the new technology (SKB with Human Genome Science). Companies wants an equity position for "platform deals" to have some control. They may ask for a board representation commensurate with their investment. Furthermore equity sends a message of commitment that is appreciated by financial analysts.

A very interesting study was conducted by recombinant capital on partnership valuations. This study suggests that near-term financial benefit is increased for a biotech company by partnering because average NPV in the early years of an alliance is larger than for the independent project case. On the other hand, long term upside (year 8 and beyond) is reduced in alliances because of the profit sharing inherent in corporate alliances. These data may explain why biotech companies like Genentech, Chiron, Biogen, Genetic Institute, firms that have heavily relied on partnering in their earlier days, have been very successful.

At Merck, the amount of money devoted to deals is set annually by the senior management, but any significant deal should be approved by the senior management (and the board). The involvement of the senior management allows shift from the precommited budget if the deals are worth it. Capital expenditure may be easier to get for significant deals and favor equity position (D Thompson, Lilly). The dollar amount for the scientific collaborations is in competition with the internal budget. Scientists at Merck have to sacrifice only a small part of their own budget when they enter a new collaboration. The idea is to foster collaborations with external parties for which the company's scientists are really committed (Rosenblatt, personal communication). The first year of any significant research collaboration is funded on the business development budget. Then the project is financed by the research division.

Companies are looking more and more for flexibility and opportunities outside their own boundaries. This means competition between inside and outside ventures at a time when budgets are tighter than they were in the past. Market plays a more important role. Companies like Glaxo have decided to increase the share of the research done outside of the firm. Glaxo has a 30% target, which should be compare to the 10% figure in the CMR databank.

There is no guideline for the negotiations of these deals. Both partners have to understand what they do well, and negotiate on the basis of their core competencies. Pharmaceutical companies are usually looking for world wide rights for a product or the main indications of a product and the control on registration and clinical trials. They are looking to some control on the biotech company and some accountability. Control and accountability, as discussed in Chapter Two, can be secured by minority equity position and milestone payments. The figures for licensing royalties are given further in this chapter. Merck is using some financial models to appreciate the return on the investment. Merck, Roche (with Millennium) are also looking to have access to the technology spill-over of the funded project.

Successful deals are based on trust (see below). Both sides should be represented equally in the management teams independently of the asset contribution. A real involvement of the company's scientists in the original negotiation is a plus. Some of collaborative work in the Gencell network was initiated by the scientists before the negotiation of the general agreement.

Most pharmaceutical companies are independently working with their different biotech partners. They make relatively small investments for product rights or large investments for acquisition of market leaders (Roche with Genentech, Ciba with Chiron). RPR/Gencell has had a very different strategy. It has entered into partnerships with second tier companies and is expecting to extract value from the synergy between the partners. As a consequence, Gencell has to manage the collaboration/competition

between the different partners. This network organization represents a management challenge and require a genuine trust among the partners.

CONTRACTING ON TRUST

It is rumored that the late industrialist, J.P. Getty, was once closing a business agreement of some small consequence with a new business partner who, as the tale goes, turned the concluding discussion toward the subject of signing the contract. Getty is supposed to have used this occasion to say sharply "Why are you now looking for a contract? I've agreed to our deal, and having given my word you have a deal that no man can undo. If you had a contract, my lawyers could tear it apart in no time at all."

The story has its appeal because it reflects back to a glorified era when all important deals were based upon a mutual trust. With the emergence of corporate institutions, personal trust has become codified into institutional contracts. Organizations attempt to prevent contractual lapses by creating elaborate structures for regulating contracting processes. However, it is important to recognize that trust does not always fail when a contract has collapsed. Trust, therefore, is not always linked to the contract itself. Moreover, there is a strong disparity between trust and contracts: trust can repair a damaged contract, but a contract in itself can do little to repair damaged trust.

The role that trust plays in business operations is an area of emerging academic concern. Charles handy was recently quoted in fortune magazine as saying "organizations today have to be based on trust. How many people can you know well enough to trust? Probably 50 people at most. So, increasingly, organizations will be made up of groups of 50 that will bond together for different projects or needs." How will this prophetic vision translate into corporate interactions of the future ? Network organizations, such as gencell, may allow us to study this model.

THE ROLE OF CONTRACTS REMAINS

Nevertheless, contracts between firms and universities should be clearly written to decrease concerns and conflicts about academic freedom, stability of funding, potential for conflicts between different companies, and commercial rights. Fifteen categories of *legal issues* recur generally in drafting research agreements:

1. the scope of the research project
2. nature and extent of the sponsor's commitment to the project
3. nature and extent of the university's undertaking pursuant to agreement
4. control over the conduct of the funded research program
5. exclusive right of the industrial sponsor to fund research in the area involved in the agreement
6. the extent and terms of actual technical or scientific collaboration by the industry participants
7. reporting requirements
8. funding
9. competing interests in the use of research results
10. receipt of proprietary information from industrial sponsor
11. patent rights
12. the licensing of know-how
13. indemnification and hold harmless agreements
14. use of university's name
15. potential conflicts of interest on the part of the university researchers

The following sections will identify issues which impinge upon information transfer transactions.

STRATEGIC INTENT OF OUT-SOURCING

In biotechnology firms and pharmaceutical firms, as with many technology-based innovating firms, sharing research resources can provide both strategic and economic benefits. Strategic benefits represent advantages which these firms might gain only by out-sourcing. A catalog of benefits is presented in the table below, and specific benefits are subsequently considered in greater detail.

Exhibit 8-3

Strategic Benefits	*Economic Benefits*
economies of scope	economy of scale
program & portfolio flexibility	avoid specific assets sunk costs
new technology and ideas	new products and markets
serendipitous discovery spillover	capital
speed in first mover races	manufacturing networks
unpredictable competitive threat	distribution channels
future options for business growth	supplier access
entrepreneurial spirit vs. experience	specialized assets
continuous improvement	production process know how
prestige & technological validation	brand name recognition

Shan has studied the relationship between *interfirm cooperation and start-up innovation* in the biotechnology industry. He suggests that start-up innovation output does not attract large firm relationships but rather depends on them. Although start-up size affects level of innovation output measured by issued patents, size has no effect on commercial ties. This indicates that large start-up firms do not attract more established firm partners than small start-up. His finding also suggests that an established firm looks for *confirmation of a start-up's potential in the capital market* before entering into an

agreement with it. The distribution of social capital available to start-up determines the extent to which they form relationships. In this study, collaboration is dependent on public investment and on the structure of the network of interfirm cooperative agreements. Innovation in biotech firms seems to be better explained by agreements than the reverse. This study suggests that biotech companies benefit from partnering.

A. Scope

Win-win outsourcing partnerships will be characterized by: program complementarity (e.g., cross-licensing of product lines), operating or competency complementarity (e.g., research skills versus product development skills) or asset complementarity (e.g., geographic distribution channels). These economic factors will play a key role in selecting whom to out-source with, once strategic factors have established the corporate need to out-source. Complimentarities which have drawn both biotechnology and pharmaceutical firms to university and hospital research partners are provided in the table below. Complimentarities which lead pharmaceutical and biotechnology firms to share research operations typically involve capital and resources matched with entrepreneurial energy and new technology.

Complementary of practices between academia and industry

Exhibit 8-4

INDUSTRY	ACADEMIA
Strong Developmental Programs	Strong Basic Programs
high R&D overheads	low research overhead
government constraining profits	government constraining funds
discovers 60 - 80% new drugs	discovers 20 - 40% new drugs
decreasing lead in rational drugs	increasing lead in rational drugs
learning to work with alliances	tradition of cooperative research

B. Program and Portfolio Flexibility

Medium-size firms which practice out-sourcing stand to gain considerably through diversifying their product portfolio at low cost (see chapter 2). For example, one new product to a firm which has only 5 products in the market means a 20% growth in portfolio scope. Flexibility comes from minimizing costs sunk into specific assets, specifically when these assets have very large exit costs (e.g. substantial turnover of highly trained research staff with changes in therapeutic programs). Programs which are not anchored to specific assets with high exit costs are not constrained by switching barriers and can respond rapidly to seize new market opportunities. In this fashion, out-sourcing provides a means of facilitating cycles of rational resource allocation because program continuation becomes more of an option and less of an obligation. If it is difficult to kill a therapeutic product, it is much more difficult to kill a therapeutic area. Partnering is also an opportunity to enter a new technology domain (Gencell, Roche).

C. Continuous Improvement

Outsourcing also provides a mechanism for continuously improving technical quality of research operations. For every research program, firms will want to hire the "best of class" scientific minds. However, for these individuals there always exists a trade off between control imposed by corporate programs and full freedom for innovative research. Over time, one can expect conflicts of egos in negotiation trade off. Out-sourcing allows a means of both capturing willing talent and also releasing it when the dynamics change. The use of out-sourcing in a comparatively low-overhead environment allows the firm to draw on qualitatively superior talent (which is consistently matched to specialized program needs) at reduced labor cost.

D. Serendipitous Discovery

Strategic advantages in scale derive principally from the belief that, all other things being equal, research programs which are embedded into larger research

operations will out perform comparable free-standing programs. Spillover effects are a likely cause of such benefits. Two factors contribute to being able to appropriate benefits from spillovers position along the technology transfer path, and adsorptive capacity. Roche with Millennium, RPR with Gencell get access to spillover knowledge. Merck insists on the importance of that matter in its contractual agreements.

E. Speed and Competitive Threat

When a firm has acquired the core competencies for out-sourcing, it is then able to increase its virtual size rapidly and with comparatively low cost. Such a firm's competitive research strength is difficult to gauge. Like research programs themselves, if a firm does not get involved in out-sourcing activities specifically to create business opportunity (Amgen with MIT), it ultimately must become involved just to protect its business opportunities.

HOW TO FIND PARTNERS FOR OUT-SOURCING VENTURES

Searching for a partner is equivalent to marketing one's needs; as such it carries all costs of a marketing program (i.e., product definition, market research, advertising, and channel management). The first lead on the market is through highly visible research community networks and affinity groups. When using affinity group connections, the challenge will be to identify technologists who do or will have the need but not the in-house capacity and who are likely to seek external services. This could represent a significant intelligence gathering effort.

Exhibit 8-4

Locating Partners for Out-Sourced Research Programs

• consultants with personal contacts in the industry
• trade publications and scientific journals
• contacts with key scientific leaders
• exchanges among internal and extramural technical staff
referrals from university technology transfer offices
• research circles established by scientific staff
• corporate participants in reciprocal licensing / marketing efforts

Complementarity matches will shorten the list, however it would be inappropriate to presume a mismatch with a desirable partner simply because their needs are not obvious (Millennium). Approaching such firms will be facilitated if they, too, have made a commitment to compete through research outsourcing (Roche). If they have, they are likely to have in-house teams who will understand and appreciate your intentions. Firms which have established a tradition of out-sourcing will be known by industry analysts and by venture capitalists and their track records will periodically appear in industry newsletters and trade journals.

Representative data for *industry-university partnership* is as follows:

Averages in funding Per Alliance Suggests Differences in Investment Strategies

Company	Number of Alliances	Total Funding ($million)	Average $/program
Sandoz	4	309	77
Monsanto	5	176	35
Bristol-Myers Squibb	10	176	18
Hoechst	2	145	73
Amgen	3	132	44
Johnson and Johnson	2	125	63
Eisai	1	121	121
FIDIA	1	94	94
Shiseido	1	85	85
Glaxo	5	61	12

Source: Dr. A. Stevens, Dana-Farber Cancer Institute

A recent discussion at the "1995 Mass Biotech Council" shed a different light on the firms' motives. Biotech executives have the impression that most of the deals with pharmaceutical companies originate from the biotech companies. They must have a very proactive attitude to convince a priori reluctant pharmaceutical companies.

This pro-active approach is exemplified by Millennium. Pharmaceutical companies say that both entities are equally responsible for the initial steps. Pharmaceutical companies have both an opportunistic approach (reactive) and a strategic approach (screening). RPR had clearly a proactive approach to constitute the Gencell network. A "disease management" or a "platform technology" approach (Roche with Millennium, SB with HGS for genomics, Merck with Tulara on transcription factors, RPR or Sandoz in gene therapy) involve a corporate strategy based on marketing or science, a proactive search, and the screening of the available products or companies. Merck tracks 130 journals (and the patent database, meeting abstracts) and looks for opportunities in the therapeutic domains of interest to Merck. Scientists have regular meetings to review the databank and to pass the information to corporate business development if necessary.

Scientists are very often at the origin of the deals (see Millennium, Gencell). Business development has to screen an incredible number of potential deals. Lilly received or initiated 1000 propositions in 1994. Three hundred of them were of some interest for the company. Lilly signed 170 confidentiality agreements, and conducted due diligence for 100. Out of these 100, 29 deals came out in 1994. Eighty percent of these 29 were channeled through Lilly scientists.

Most companies will agree that scientists are very much involved in the transactions. Due diligence with biotech companies is mainly scientific. The scientists of the pharmaceutical companies will be involved in future collaboration with the biotech company. If the scientists want the deal, the deal has a greater chance of success. This is due to the fact that 60% of the deals concern products at a pre-IND

stage. Pharmaceutical companies are requiring "demonstration of principle" in preclinical models (E. Wyatt, Merck). More advanced products are not available anymore for licensing. One of the reason for early licensing (outside the decrease in cash reserves)' may be found in the startling results of a Recombinant Capital study. This study shows that ,on average, there is no appreciable increase in value associated with a project that is partnered at the IND stage compared to a discovery deal. Even Phase II drugs do not command a significant NPV premium to reward the greater cost and risks incurred by the biotech company prior to alliance formation.

BARRIERS TO OUT-SOURCING

The benefits of out-sourcing carry trade off decisions. The primary problem in letting someone else perform a task on your behalf is that you forfeit the opportunity to *develop your skills* in doing that task. For this reason, firms build a fence around skills which they feel they have built (and will continue to build) their business upon. Typical trade-offs are shown below.

Trade-offs in electing to contract research beyond the firm

Exhibit 8-6

STRATEGIC ADVANTAGES	STRATEGIC DISADVANTAGES
reduce in-house costs	loose contact with leaders
cover shortfalls (20 - 40%)	loose contact with future market
expand expertise	possible lack of commitment
work with growing technology	inaccessible database
get an industry standard output	don't build in-house skills
freeze on new hires	risk high turn-over of staff

Source: Scrips, March 1994

Broader issues of tradeoffs include negotiating a complete package of exchanged benefits, privileges, options, rights, goods, funds, etc. While significant attention is devoted to upfront *contract activity*, contractual negotiation should never be believed to become a closed process. It is probably most appropriate simply to contractually agree how disputes will be resolved in the future, and how channels for re-negotiation will be re-opened. A complex package of incentives and operating expectations are specified in an effort to encourage mutual investment in and commitment to an out-sourcing program. The more individuals involved in this process, the longer it takes to build consensus; and because some individuals will have incentives to contribute only by preventing exposure to risk, the bias is for large group review to favor inactivity. Examples of operating issues which arise between corporate and academic groups are illustrated below.

Sources of concern which can increase early stage transfer costs

Exhibit 8-7

COMPANY CONCERNS	ACADEMIC CONCERNS
Intellectual Property	**Academic Freedom**
30 day review until published	choice & direction of research
30 days patent preparation	timely publication
transfer collaborators' rights	free discussions with colleagues
	open collaboration opportunities
Funding Package	protection for post-doctoral staff
Leverage public funds	
Exclusive corporate funder	**Stability and Continuity**
Right to first refusal	fully fund launched projects
	define renewal points
Commitment to the Contract	phase down with academic cycles
clear milestones	
ability to monitor progress	**Conflicts of Interest**
	specify field of competition
Spillover Appropriations	voluntary participation
build firm's core competency	
claim unexpected inventions	**Financial Package**
right to require patent action	full direct costs
protect firm's confidential data	protect tax-exempt bond status

During the *implementation* phase, research projects will advance through a project life cycle. At different stages, different managerial issues will arise and changes in practices will occur. There is a natural desire to reduce uncertainty through specification; but there is an inherent dishonesty is giving in to this temptation. Uncertain processes cannot be fully specified. Specification must turn toward the manner with which uncertainty, itself, will be managed. Discussions at this level presuppose a continuity between the management philosophy of the launching team and the management philosophy of the subsequent implementation team. Scientists who participate to both steps of the collaboration are instrumental in making that collaboration work. The governing philosophy is mutual respect and personal commitment to fairness. The agreement is reached through the mechanism of "trust," and the sustaining implementation is every person-to-person contact. The value that the firm places in its reputation offers an insurance policy for this trust and may allow the firm to convey trust more readily.

The federal government is a fickle friend of the biomedical research community. The Bayh-Dole Act of 1980, for example, has been appreciated as stimulus for transfer of technology from universities into the commercial sector. The act gave universities and small businesses the rights to inventions and intellectual properties developed under research funded by federal contracts and grants and insures incentive payments to inventing university professors. The act has also mandated the use of domestic manufacturers to commercialize products generated with domestic tax dollars. Similarly, the Biotechnology Patent Protection Act of 1993 (S.298) benefits biotechnology by securing novel life forms protection as inventions. These actions served to build public support for joint academic-commercial interactions. Furthermore, in 1986 and 1989, congress authorized federal agencies and national laboratories to enter into cooperative research and development agreements (CRADAs) with private firms and other entities for the purpose of commercializing federal research.

Nevertheless, the philosophy of some politicians is that those financial interactions which government agencies are monitoring should be orchestrated from afar. This defeats local accountability and local trust relations. The CRADA agreements which have contained a clause on pharmaceutical pricing (since the public uproar over the launch price of AZT) have penalized relationship between firms and the NIH (this clause has been recently dropped). The pressure from the NIH on Taxol (Bristol-Myers) price is another example of this attitude. Furthermore, Michael Astrue, VP of legal affairs at Biogen, specifically points out that federal research laboratories have gained a poor reputation for attacking the Burroughs Wellcome patent claim to AZT.

A different issue is the Sandoz Scripps agreement that has to be rewritten at the request of congress and NIH to be less favorable to the foreign pharmaceutical company.

The extent to which negotiating under *conditions of uncertainty* presents a practical problem depends on the experience of the negotiating parties. Both experienced parties may share a common perspective and they may be able to negotiate a working contract with minimal transaction costs. A learning curve benefit is expected to exist for players who commit to become experienced out-source contractors

A lack of standard processes contributes to the *expenses of transacting out-sourcing agreements*. Judy Lewett, Chief Financial Officer for Merck, discusses a process for prioritizing research projects based on a financial option pricing model. Establishing parity between the processes of in-house research project planning and inter-firm out-source planning may codify and standardize out-source research planning transactions. To the extent that standards exist in the processes by which research projects are prioritized, one can hope to build complementary transactional standards for out-source work. An important question will be how evolution of such standards might be driven and research support firms continue to learn, in aggregate, through work with research sponsor firms. Martin L. Wolf, a partner at Deloitte & Touche, argues that firms should commit to creating clear and strong policies which limit the necessity for

negotiating over agreement type diversities, and thereby "package" the firm for low cost marketing

Spillover benefits deserve special mention. They represent a residual value, but unlike information derived directly from the intended results of the program, spillover benefits can accumulate to one party without any immediately measurable consequence to the party (which may be unable to appropriate those benefits). For example, one party may gain leads on a field of research which only it has the core competencies to pursue. If this unilateral benefit is consistent with the spirit of the agreement, it may represent no problem. Potential appropriation of spillover benefits is an expressed strategic incentive for participating in out-sourced ventures. Parties should recognize that equal access to spillover benefits does not mean equal access to appropriating those benefits. In most cases, partners which are significantly smaller then their co-participants will be at a disadvantage due to limited absorptive capabilities. Firms which are small and would like to capture these benefits must develop specific internal absorptive capacity (Cohen and Levinthal; 1992). The Silicon Valley evidence suggests that small firms might be able to make use of external absorptive capacity carried within their entrepreneurial community.

In conclusion, we have reviewed in this chapter data on R&D partnerships gathered from surveys and meetings. These data fit with our study of individual companies.

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