ELSEVIER

Journal of Economic Behavior & Organization
Vol. 31 (1996) 381–399

JOURNAL OF
Economic Behavior
& Organization

The optimal organization of research: evidence from eight case studies of pharmaceutical firms

Francis Tapon[1], Charles Bram Cadsby[2]

Department of Economics, University of Guelph, Guelph, Ontario, NIG 2W1, Canada

Received 23 February 1994

Abstract

In this paper we examine the results of interviews of scientists and executives in eight pharmaceutical companies on the issue of how best to organize the R&D function. We find that vertical integration of R&D is still the solution of choice for pharmaceutical firms. Given this result, firms must combat organizational failures in the R&D function by paying special attention to the concepts of focus, openness and incentives. We also discuss exceptions to the vertical integration rule for R&D. This occurs when transaction costs associated with contracting out portions of the R&D project are low; when the firm is playing catch up in an area of science where it is weak; and when governmental policies force firms to carry out R&D in particular locations.

JEL classification: O32; L22; L89

Keywords: Pharmaceutical; R&D; Organization; Transaction costs

1. Introduction

Success for the top research-based firms in the pharmaceutical industry comes with the discovery of new, safe and effective drugs. Why are some pharmaceutical firms successful year after year, while others falter and are forced to merge with other firms in their industry? All these firms are able to hire the best scientists, equip their labs with state-of-the-art equipment and have access to the best advice. Yet, with all these advantages some firms enter periods of decline and are unable to recover, while others appear to be reborn.

[1]Internet: Francis@css.uoguelph.ca.
[2]Internet: Bram@css.uoguelph.ca.

PII S0167-2681(96)00881-5

In 1989, one of us (Tapon, 1989) argued that research-based pharmaceutical companies which in the 1980s were starting to open up their R&D activities to other institutions, would continue to do so and that the 1990s would see the vertical disintegration of their R&D from the rest of their operations. The links to outside organizations that were studied in that paper were long-term R&D joint ventures with university laboratories. The article foresaw the growth of these unconventional corporate-university arrangements.

These hybrid organizations owed their existence to three trends in the pharmaceutical industry. First, rational drug design (or discovery by design) as a method for discovering new successful compounds was rising in importance. Rational drug design requires a very strong foundation of basic research which most often thrives in university or certain independent laboratories, as well as in national research institutes. Pharmaceutical firms which linked up with university laboratories would likely be more successful than those which did not. Second, as new drugs became harder and harder to discover, firms increased spending on R&D and assembled ever larger groups of scientists in bigger laboratories. This led to bureaucratic sclerosis which could only be counteracted by dramatic reorganization of the way R&D was carried out. Joint ventures with university laboratories appeared to be a promising strategy. Third, the rise of biotechnology forced established pharmaceutical firms and new entrants from the chemical industry to learn new areas of research, as the focus of research shifted partly from chemistry, used in the old trial and error approach, to biology, used in the new rational drug design approach. Specialists in biological research were to be found mostly in universities; hence a link-up with a university laboratory enabled firms to tap this new kind of expertise.

Tapon's 1989 article used transaction costs analysis to hypothesize that new hybrid R&D organizations linking privately-owned firms and publicly-owned institutions like university laboratories would become a solution of choice to the R&D governance problem in the pharmaceutical industry.[3] Between 1989 and 1992 we conducted a series of interviews of eight pharmaceutical firms to investigate this vertical disintegration hypothesis. The hypothesis itself was rejected by the evidence, but the transaction costs analysis approach was corroborated.

Much has been written on these questions. Comanor (1986) and Scherer (1993) survey and discuss the issues currently facing the pharmaceutical industry. Grabowski (1989) analyzes the competitiveness of firms in the pharmaceutical industry from the perspective of firm ownership and country of origin. McGahan (1994) considers the impact of the acquisition of prescription-benefits-management companies on research-oriented pharmaceutical firms. Grabowski and Vernon (1990) and Hill and Hansen (1991) study the risks and profitability of drug discovery, while DiMasi et al. (1991) consider its cost and risk. Scherer and Ross (1990, pp.613–660) discuss the R&D process in different industries including pharmaceuticals. Schneiderman (1991) considers the difficulties in managing an R&D laboratory. Graves and Langowitz (1993) examine the relationship between R&D productivity and R&D budgets. Pisano (1990) studies the R&D governance problem in the pharmaceutical industry, while Pisano (1991) analyzes and

[3]Williamson has recently argued that, "vertical integration is the organization form not of first but of last resort – to be adopted when all else fails. Try markets, try long-term contracts and other hybrid modes, and revert to hierarchy only for compelling reasons." (1991, p.75).

compares the various governance structures used in developing and commercializing new biotechnologies during the last fifteen years. Henderson (1994) explains why pharmaceutical companies, in contrast to firms in other industries have been able to evolve, survive and thrive. She argues that pharmaceutical firms' success is based on a unique core competency: "the ability to foster a high level of specialized knowledge..., while preventing that information from becoming embedded in such a way that it permanently fixes the organization in the past, unable to respond to an ever changing competitive environment" (1994, p.100). The situation of pharmaceutical firms may be contrasted to that of firms in other industries such as the semiconductor photolithographic alignment equipment industry (Henderson and Clark, 1990).

In Section 2, we review our sample design and technique of analysis. In Section 3.1, we discuss the vertical disintegration hypothesis and explain why we found no support for it. In fact, we discovered that the costs of using research done by outsiders and of dealing with these outside suppliers are very high and often lead to significant market failures. In Section 3.2, we discuss the ways R&D is organized within the firms in our sample to minimize organizational failures. Section 3.3 discusses the conditions under which firms allow outsiders to carry out research for them. Section 4 concludes the paper.

2. Sample design and technique of analysis

2.1. Sampling plan

To gather data needed for this study, we carried our in-depth interviews lasting from one hour to two days with medical directors, scientists, and CEOs of Canadian subsidiaries of five U.S. multinational pharmaceutical firms (Merck, SmithKline,[4] Squibb,[5] Upjohn, and Monsanto/Searle) two Canadian research-based firms (Allelix, and Connaught) and a Canadian generic producer (Novopharm). We also interviewed the Director of University and Scientific Affairs of the Pharmaceutical Manufacturers Association of Canada. At the bottom of Table 1 we describe our sample as fully as our confidentiality constraints allow.

The "transaction" studied in this paper is defined as "a research program leading to the delivery of a new active compound for applied research or a new chemical entity for development." Williamson has argued (1985, p.1) that, "A transaction occurs when a good or service is transferred across a technologically separate interface. One stage of activity terminates [e.g. basic research] and another begins [e.g. applied research or development]." The firms which responded to our letters and phone calls (10 were contacted, 8 responded positively) agreed to talk to us on condition that they and issues of strategic significance would not be identified. As a result, in our "focused interview" approach (see Section 2.2), we asked each interviewee to consider a "typical" but unidentified research project with which he was involved and to describe in detail how it was carried out from his perspective. We were not able to compare projects for which

[4]Before the takeover by Beecham.

[5]Before the merger with Bristol Myers.

Table 1
Variables to combat organizational failures

	MNC1 (most R&D in-house)	MNC3 (some joint ventures)	MNC4 (some joint ventures)	MNC5 (some joint ventures)	Canadian Firm 1 (some joint ventures)	Canadian Firm 2 (some joint ventures)	MNC2 (joint ventures very important)	Canadian Generic Firm
Focus	*	○	○	*	○	○	○	○
Openness								
Project teams	*	○	○	○	○	○	○	○
Off-the-wall ideas	*	*	*	*	*	*	*	○
Incentives								
Stock options	*	○	○	○	○	○	○	○
Research stream	*	*	○	○	○	○	○	○
Publications	*	*	*	*	*	*	*	○
Survivor test	Independent	Taken over	Takeover Target	Merged	Taken over	Independent	Takeover Target	Privately owned

* Means that the interviewees specifically mentioned this variable in their description of their firm's R&D process.
○ Means that this concept was not mentioned.
Sample:

1.	MNC1	–	Director, Research Administration and Planning
		–	Director, Regulatory Affairs
		–	Senior Director, Medicinal Chemistry
		–	Senior Director, Pharmacology
		–	Director, Biochemistry
		–	Director, Pharmaceutical R&D
		–	Executive Director, Medical Research
		–	Researcher, Pharmacology
		–	Researcher, Biochemistry
		–	Researcher, Pharmacology
		–	Researcher, Medicinal Chemistry
2.	MNC2	–	Director, Research and Business Development
		–	Former Director, Corporate Research and Development Staff U.S.
		–	Medical Director, Canadian Clinical Research and Medical Affairs
3.	MNC3	–	Associate Director, Clinical Development Canada, Clinical R&D North America
4.	MNC4	–	Director, Medical and Scientific Affairs
5.	MNC5	–	Chairman and CEO
6.	Canadian Firm 1	–	Assistant V.P., Regulatory and Technical Affairs
7.	Canadian Firm 2	–	CEO
8.	Canadian Generic Firm	–	CEO

steps were sourced outside the firm with projects whose steps were all performed in-house.

The questions we discussed were geared to elicit information on the details of the R&D process to corroborate or refute the vertical disintegration hypothesis, and thus to measure indirectly the *market failures* associated with large scale contracts with outside

institutions. We also focused on *organizational failures* of in-house R&D and on the strategic architecture firms have designed to combat their effects. Transaction costs analysis[6] tells us that the decision to integrate vertically or to seek other governance structures for R&D depends on which of these two types of failures is most important (Williamson (1975, 1985)). If organizational failures outweigh market failures, the firm has an incentive to open up its R&D process through strategic alliances, long-term R&D joint ventures and equity stakes in independent laboratories. If market failures outweigh organizational failures, the firm has an incentive to keep the R&D process in-house, and although it may strike some strategic alliances with independent laboratories, these alliances will not form the centerpiece of that firm's R&D strategy.

The five multinationals (MNCs: Merck, Monsanto/Searle, SmithKline, Squibb, Upjohn) investigated, all have large R&D efforts. In order to obtain a variety of perspectives, we sought to have one firm which conducts most of its R&D in-house (MNC1) and another which is engaged in significant and numerous long-term R&D contracts with university laboratories (MNC2). MNC2 makes these joint ventures the centerpiece of its R&D strategy. The three remaining MNCs (MNC3, MNC4, MNC5) are also involved in R&D outsourcing contracts with university and independent laboratories, but at the time of the interviews, had signed fewer contracts with considerably less money involved than those signed by MNC2. The dollars involved for R&D outsourcing by MNC3, MNC4, and MNC5 were roughly comparable. Two of the three Canadian firms (Canadian Firm 1, Canadian Firm 2) are much smaller but spend significant amounts on R&D, and they too are outsourcing some R&D activities with university laboratories. Apart from different scales, they are rather similar to MNC3, MNC4, and MNC5. The Canadian generic producer is beginning to set up its own R&D operations and does not yet outsource research activities with independent and/or university laboratories.

Calculating and interpreting the profitability of R&D in the pharmaceutical industry is difficult because R&D programs leading to new products are so long (10–12 years) and so many new chemical entities never make it to market. To relate the variables discussed in this paper that promote effective R&D to performance, would require us to evaluate the profitability of the firms in our sample well into the next century. Instead we use a crude "survivor test" (Stigler, 1958) of which sample firms are surviving as independent entities and hence are successful, and which ones are taken over by, or merge with, stronger rivals and are hence less successful. Table 2, discussed in detail later, outlines the results of the survivor test for each of the firms in our sample.

MNC1 has been the most successful of the multinationals by this criterion. Canadian Firm 2 has also maintained its independence. However, it is a tiny firm with virtually no revenue surviving on the basis of funding from a few large investors. Canadian Generic Firm is not really comparable to the others because it does not do basic research.

2.2. *Interview method*

We used a "focused interview" approach (Merton and Kendall, 1956, Merton, 1957). We asked each person being interviewed to describe in detail the R&D process

[6] A review of transaction costs analysis as it applies to pharmaceutical R&D can be found in Tapon (1989). The general transaction costs framework is outlined in Williamson (1975, 1985 and Williamson, 1991).

Table 2
Pharmaceutical R&D process for the development of a new drug as described by MNC1

Basic Research	1. Basic Research	
		——→ A novel hypothesis is developed
	2. Drug Discovery	
	Medicinal Chemistry	
	Synthesis	
	Biological Research	
	3. Pharmacology	
	Pharmacological and Biochemical Screening	
		——→ An active compound is obtained
Applied Research	4. Biological Evaluation-Toxicology	——→ The compound is tested for safety
	Short Term Toxicology	
	Chronic Toxicology	
	Detailed Pharmacology	
	Biochemistry	
	Metabolism	
	Bioavailability	
Development	5. Chemical Process Development	
	Synthesis for Large Scale	
	Production Process	
	6. Pharmacy Research and Development	——→ The compound is tested for efficacy
	Formulation and Dosage Form	
	7. Medical Research	
	Clinical Testing	
	8. Regulatory Sequence	
	9. Marketing	
		——→ New Product Starts Earning Income

including the steps followed, problems encountered, measures taken to counter these problems and future evolution of the R&D process. Thus, we did not ask for information on specific pieces of research, but rather on a "typical" research project at each firm in the sample. We remained mostly passive throughout, except to ensure that the interviewee's comments stayed focused on the R&D process or to obtain additional clarifications when needed. We referred to a short list of questions during the interviews and if the various points had not been covered spontaneously, we asked the questions before the interview ended. Interviews were scheduled to last one hour, but often ran overtime. We recorded each interview with the permission of each interviewee. The transcript of these interviews came to about 1000 pages. These transcripts are analyzed in this paper.

2.3. *Method of analysis*

The theory we use to analyze the interview transcripts is transaction costs analysis. According to this theory, firms will seek to minimize the transaction costs associated with R&D by matching the governance structure of R&D to the attributes of the R&D transaction. This may result in firms which carry R&D in-house, or firms which

consistently and deliberately open up their R&D to outside institutions. The procedures we follow are adapted from the grounded theory method described in Gibbins et al. (1989) as follows:

1. Select the interview of MNC1 as the first case to analyze because we were permitted to conduct an in-depth investigation.
2. The interviewees of MNC1 describe in detail the R&D process based on their experience in a typical R&D project. They distinguish the various levels of R&D, these are highlighted in Table 1 discussed in detail below. The interviewees also describe measures taken to keep the R&D process creative and productive.
3. We relate the transactions between the various R&D levels obtained in step 2 to the notions of frequency, uncertainty and asset specificity discussed in the transaction costs literature (Williamson, 1985). Under frequency, we consider whether contacts between basic and applied researchers are common or rare and explore the same question for applied and development researchers. Under uncertainty, we ask whether the properties of active compounds delivered to applied research or development are well understood or not. Finally, under asset specificity, we consider whether the assets, particularly the intellectual assets, created in basic research, applied research and development are protected by exclusive property rights or intangible and hence unprotected. This enables us to evaluate the extent of market failure in an average pharmaceutical R&D transaction should market contracting be used to transfer a new active compound to applied research, or a new chemical entity to development.
4. Consider other characteristics of the R&D transaction which concern policies in place to keep R&D productive, and hence to combat organizational failures.
5. Identify from published sources other policies missing from the interview of MNC1 used by other firms to keep their R&D operations creative and productive. Add these policies to our list of measures used to combat organizational failures.
6. MNC1 does most of its R&D in-house. This allows us to calibrate the variables we categorized in steps 3–5 and to understand the conditions needed for market failures to outweigh organizational failures.
7. Ensure that the categories we developed make sense and fit the theory.
8. Repeat steps 1 through 7 for MNC2 by fitting the details from interviews of MNC2 into the categories constructed from the interviews at MNC1, as well as those from miscellaneous sources. Make sure that all information is classified sensibly.
9. MNC2 has opened much of its R&D to outside laboratories through long-term joint venture R&D contracts. Verify that the variables we have classified in step 8 predict that in the case of this firm, market failures are outweighed by organizational failures.
10. Repeat steps 1–7 for each of the remaining firms.
11. Ensure that no fact from these cases is left out. Verify in each case that our theory predicts whether R&D is done in-house, or through external R&D joint ventures, strategic alliances, or equity stakes, or whether a mix of both solutions is chosen.
12. Steps 1–11 are carried out by the first author of this paper. The categories and classification are then audited by the second author to ensure that details are correctly classified and interpreted.

13. An early draft of this analysis is circulated to each of the participating firms to check on the validity of the categories used and the explanations provided.

3. The detailed sequence of the R&D process and implications for the organization of R&D

Our findings indicate that the preferred solution is the vertically integrated in-house R&D laboratory.[7] The significant exception in our sample (MNC2) broke new ground by linking with a university laboratory. As explained in Tapon (1989), in this instance the research transaction was not subject to opportunism; hence market failures were outweighed by organizational failures.

Currently, pharmaceutical firms are pursuing a two-pronged strategy in their search for new successful products. The first is to invest more in basic research as the foundation of a discovery-by-design approach to come up with new drugs. The second is to link, through equity stakes, and/or long-term joint ventures, with biotechnology startups or university and government laboratories. Using transaction costs arguments, we argue that the second avenue for pharmaceutical R&D is unlikely to grow to such an extent as to become the dominant form of R&D architecture. R&D is likely to remain an in-house activity and this rebuts the vertical disintegration hypothesis.

3.1. The vertical integration of R&D: Dealing with failures in the market for external R&D contracts through internal R&D

Table 1 summarizes the pharmaceutical R&D process. It shows the three main steps in bringing a drug to market: basic research, applied research and development. We use this classification to organize the material from the interviews.

Fifteen years ago drugs were discovered almost solely by trial and error screening. A compound would be found to work in a particular animal model. Researchers would not be sure if it worked because it was blocking a mediator or because it had blocked some other pathway. In fact, the compound may not have worked through the mechanism researchers thought. Trial and error is still widely used, but is now supplemented with a more fundamental molecular discovery process called "rational drug design" or "discovery-by-design" that tries to hone in as precisely as possible on the therapeutic target and develop a compound that hits it accurately.

This approach became prominent in the 1980s as biological theory progressed by leaps and bounds. With rational drug design, scientists search for a molecule that causes certain biological processes in the body to go wrong and try to understand the mechanisms used by this molecule to create disease. The goal is to design another molecule that will interfere precisely and exclusively with these mechanisms and so cure the disease with no side effects. Designing such a "silver bullet" requires a precise understanding of the biological processes involved and this means having an accurate three-dimensional picture of the molecule causing the trouble and the one designed to interfere with the action of the first. If drugs could be designed this way with little uncertainty or risk of

[7]See also Schwartzman, 1976, for a discussion of the organization of pharmaceutical laboratories.

failure, the drug R&D process could be carried out sequentially in the manner described by Table 1. It would be possible for a pharmaceutical firm to contract out the first four steps in the R&D process to the best outside R&D laboratory, confident that the active compound delivered by this laboratory would act exactly in the desired way. Contracts could be written to outline the responsibility of the outside laboratory with little uncertainty attached to the outcome. Thus, market contracts could be used to govern the first three or four steps in the R&D process and firms would not necessarily have to integrate vertically from basic research to marketing.

However, the market failures due to the frequency of the transactions with outside suppliers of R&D, the uncertainty attached to its outcome and the specificity of the assets used and created by it are often too serious to allow a pharmaceutical firm to contract out these steps in the R&D process. Thus, it is usually optimal for pharmaceutical firms to keep most of the steps of the R&D process in-house and use a hierarchical arrangement to govern the R&D transaction.

There are two main reasons why it is too simplistic to believe that drugs can be discovered and developed sequentially, using a rational drug design approach. First, the discovery of a new active compound which is nontoxic requires the close multi-disciplinary collaboration of chemists, biologists, pharmacologists, biochemists and clinicians in constant communication with one another. As one scientist puts it: "It is crucial to continue the development and exploitation of the idea and the two way communications between the field and the basic science facility or the originator of the original idea, if the drug is going to be allowed to develop its full potential... It's very important for the man who invented the molecule to retain an open mind, to listen to scientists in the field... who come up with an idea that may be completely off-the-mark but which may also give a second, third, and a fourth draft to the original molecule." (Scientist at MNC1, p.133 of our transcript). Another scientist at MNC1 involved in pharmaceutical R&D (stage 6 in Table 1) explains: "we work directly with basic research, we have a lot of input into the pre-development process, selection of compounds in terms of their solid state characteristics, desirable properties from a pharmaceutical formulation point of view." (Scientist at MNC1, p.116 of our transcript). As one set of hypotheses is formulated and tested, additional new compounds may be discovered which may lead to further hypotheses and tests. In other words, the drug R&D process is not linear from basic research to marketing as depicted in Table 1, but is characterized by considerable backtracking between the various steps. The interactions between scientists are very frequent, fraught with uncertainty as to the outcome and usefulness of the research and create both valuable tangible and intangible assets. One scientist at MNC1 explains: "We don't know what causes various kinds of liver toxicity and until we can get the biology sorted out we cannot design in vitro assays... to sort out the compounds on the basis of their likelihood to cause various types of toxicity. So it all has to be done with animals; some types of toxicity are specific to some species of animals, even to some sexes, and the pattern that emerges with a series of compounds of one structural type might not be applicable to compounds of different structural type; we have no predictability." (p.113 of our transcript). He adds: "This is one of the things that I think a lot of people who are not working in the sciences may not totally understand. There are thought experiments that you can do and you can try and predict outcomes but the

actuality of the thing is always determined by the data generated. That sometimes is not as predictable as you would like it to be. You cannot think about all the variables that go into even the simplest of systems. So... I think that rational drug design is obviously very admirable. It's more than a great idea, it's a move in the right direction. It applies as much rationality to your programs as possible. But, you're not going to be able to predict 100%... of the outcome. You're always going to have things that happen that nobody really foresaw and you look back in hindsight and say that there is no way that we could have predicted that outcome... There is a certain amount of good luck involved... you have to have the breaks; if you don't have the breaks in drug development you may have great difficulty in getting any compound." (pp.117–118 of our transcript). These scientists need to work in close proximity to allow the free exchange of information among themselves. Once the drug is on the market, the involvement of chemists in the development of the new drug does not end. They may be asked to synthesize other molecular combinations of the new drug to eliminate unwanted side effects.

Since large gaps still exist in our theoretical knowledge and in our understanding of the relationship between chemical structure of a new compound and biological activity, compounds must be thoroughly tested by the firm's clinicians before they are deemed safe. Thus, the safety and efficacy of the compound are uncertain until late in the development process. As a result, a contract selling patent rights to the new compound is extremely complicated to write, making the transfer of the new chemical compound from an independent laboratory to the firm difficult, risky, and costly.

Second, firms are returning to the old trial and error method of drug discovery because the rational drug design approach has not yet proven its superiority. In order to carry out this kind of research a firm needs a vast library of molecules. Since research is highly empirical a considerable number of iterations is needed between stages of the R&D process. As a result, once a library of molecules is available, it is almost impossible to separate stages of research by contracting out certain of these stages and carrying out others in-house. All the interviewees in our sample agreed, for example, that knowledge about cell receptors was far from being sufficiently developed to allow new drugs to be discovered by designing a molecule that would fit exactly in the target receptor.

3.2. R&D architecture for dealing with organizational failures

Doing successful research requires more from firms than carrying out well the steps we have just described. Many discoveries in the pharmaceutical industry are serendipitous. They happen outside the original field of inquiry of a particular research program. The firm's scientists must realize the significance of an unusual observation and convince managers that a new unexpected avenue should be pursued. In successful pharmaceutical firms an atmosphere is thus created where, although scientists focus on targets, they are free of blinders and free to pursue new leads as long as good science results. A wise R&D strategy recognizes the need to blend rigour and intuition, combining focus on the target with readiness to follow leads into other avenues. Mintzberg (1989, p.33) describes such a strategy as one where "errors become opportunities, and limitations stimulate creativity." Hiring the best researchers and giving them the best possible tools is not enough to guarantee a major breakthrough. A scientist at MNC3 explained, "[MNC3] was a small

company and all of a sudden we have a small company making billions of dollars so they took the approach that 'well we've got time, let's build this huge facility, hire topnotch scientists and work on new drug discovery from a really academic approach.' Unfortunately, it didn't work all that well. The research going on at [MNC3] is topnotch, first rate, a lot of really good innovative publications coming out of it. Unfortunately, none of the compounds are making it to development as quickly as possible." (MNC3, p.5 of our transcript). Our case studies point to three requirements for the R&D strategic architecture that will successfully counter organizational failures. These are focus, openness, and incentives. The extent to which each of these themes was encountered in our interviews is summarized along with the results of the survivor test in Table 2. The most successful of the multinationals, MNC1, is strong in each of these three areas. The other firms exhibit varying degrees of strength. We discuss each of these ideas in turn.

A well-run R&D operation maintains a careful balance between too much focus at the various stages of the R&D process, the result of a product orientation, and too little focus, the result of a curiosity or knowledge generation objective. While in industry the institutional objective is clearly to discover products, this cannot be achieved without a strong foundation of basic research. Thus, pharmaceutical firms must be in a position to expand knowledge in areas of interest, just like academic researchers, but at the same time must not hesitate to drop research projects that will not lead to profitable products. The need to balance too little and too much focus comes into play again at the development stages of the R&D process when a firm must decide which and how many active compounds it will take through the development process and how many it will abandon. One interviewee mentioned the inability to throw away interesting compounds as a major reason for lack of success. Although this firm had very creative research and discovered many interesting compounds, it spread itself too thin by refusing to throw away the least promising ones and was unable to bring many of the more promising ones to market because it could not manage the development process of so many compounds simultaneously.

Basic research in a pharmaceutical firm is more focused than in a university laboratory because in an industrial setting a compound must eventually emerge from that research, deadlines must be met, and sometimes management dictates to scientists the type of research they must carry out. The balance between focus and lack of it is very difficult to maintain. Too much focus stifles creative researchers and is ultimately self-defeating. Too little focus allows scientists to wander off from the institutional goals for the research, often sacrificing potential profits. Some of the firms in our sample have found the right balance, whereas others are still searching for it. A scientist at MNC1 explains, "In the case of the [MNC1] approach, the programs are extremely well focused programs. When a compound essentially runs into problems with toxicity or efficacy in the clinical or safety studies, the studies are terminated." (MNC1, p.50 of our transcript). However, a scientist at MNC3 told us, "MNC3 has left a very open approach to R&D to people on new drug discovery, etc. and we're paying the price for it now. We've created a university atmosphere within the company and are clearly not getting the compounds that we need for the future, so we have to change the approach." (MNC3, pp.12–13 of our transcript).

To keep research focused at MNC1, every scientist in the lab prepares a list of yearly objectives. These objectives include all the steps needed to push forward the development

of a new compound. Progress is also monitored through regular meetings and short monthly reports. All this monitoring keeps the pressure on scientists and allows information about research programs to spread to every scientist involved in them. At the end of the year these objectives are compared to accomplishments, and discrepancies must be explained.[8]

A second requirement for dealing with organizational failures in the conduct of R&D is the need to maintain openness between disciplines, particularly between biology and chemistry. This point has two aspects. First, following the rise of biology in the 1970s and 1980s in the discovery and design of new drugs, chemistry is making a comeback. Pharmaceutical firm laboratories are best able to break the barriers between disciplines by putting biologists and chemists to work on discovering, designing and fabricating new drugs, regardless of their original academic affiliation. Teams of scientists from various disciplines work best in parallel, rather than as a relay. The advantage of the parallel organization is that it forces each discipline to be integrated with every other within a research program. In addition, because specialists from different backgrounds study the same problem, anomalous observations are more easily recognized and investigated. This opens the firm's R&D laboratory to serendipitous discoveries which might be ignored in a laboratory where research programs are carried out by groups of scientists working on a problem, one discipline at a time. At MNC1 a group working on a project can include from two to twenty people from various disciplines. These researchers interact on a daily basis individually or as a group, exchanging ideas, suggesting new approaches and influencing the evolution of the research. Each researcher typically works on one project only, although some exceptions can be found in cases of projects which are in an introductory phase, needing some support but not yet a full-time effort.

The second aspect of openness has to do with receptivity to new, "off-the-wall" ideas from different subgroups within the company. Many separate decisions must be made to encourage the creativity of the firm's scientists. This begins with the hiring of scientists. At MNC1 an attempt is made to find people who, while specialized in their disciplines are also able to understand developments in related disciplines. In addition, development scientists have to be able to communicate with those doing basic research. A scientist at MNC1 explains, "... that is one thing that [MNC1] does very well in that the development people do indeed talk with the basic researchers. In essence our focuses are different and if we don't explain what each of us needs to do within the framework of the company you may get a compound but if it is not a good candidate for dosage form development, basically you have gotten one group to do its job and the next group really can't begin. So the two have to communicate." (MNC1, p.13 of our transcript). This facilitates the integration of the various disciplines and combats the diseconomies of scale that inevitably arise when large groups of people work together.

None of our interviewees was able to give us a size threshold where diseconomies of scale arise, although some firms operate laboratories with more than one thousand scientists. The optimal size of a pharmaceutical lab is influenced by the need to bring

[8]In another industry, Hewlett–Packard carries out evaluations called "in-process project retrospective reviews" at the end of each major phase of an R&D project. These reviews are used to make sure that projects are progressing satisfactorily. See Graves et al. (1991) for a more detailed discussion.

together scientists doing biology, chemistry, animal studies and safety assessment among other subjects. Our interviewees told us that this means having between 150 and 200 scientists in one lab.[9] This smaller size lab forces scientists to do a number of tasks or be "jacks-of-all-trades" in the words of one senior scientist interviewed. Such an environment fosters interaction and cooperation, and keeps scientists creative and interested.

Some firms in our sample deal with organizational failures by decentralizing their research geographically. Giving a world-product mandate to a laboratory in a particular country on research in a specific therapeutic area allows a group of scientists to work in a smaller, less bureaucratic laboratory. Less time is spent on paper shuffling and meetings and more time is devoted to productive research. Many of our interviewees agreed that decentralization of R&D was a positive trend, likely to continue.

The location of the lab is important. Being close to other labs and universities fosters interaction and facilitates relationships among researchers. One scientist at MNC1 noted, "People come on their way to New York and back and forth, and we have many, many people coming here; I mean noted chemists and scientists." (MNC1, p.10 of our transcript). To maintain contact with outside researchers and keep an open mind about new ideas, scientists at some of the firms in our sample have joint appointments with universities. Seminar series in all disciplines bring in visiting scientists on a regular basis. For example, at MNC1 three or more seminars are offered each week. Collaborative research with academics is also done. Coop students are offered positions in the lab for four month terms. University professors on sabbatical are encouraged to arrange long-term research visits.

Publishing articles in the professional literature is part of the evaluation of scientists for promotion at MNC1. One of the scientists at MNC1 puts it this way: "If people are going to progress in [MNC1]'s lab... they are going... to be recognized outside of [MNC1] as top scientists. Otherwise, they are not going to progress." (MNC1, p.11 of our transcript). This comes in addition to meeting objectives within their research programs. The decision to allow submission of a paper to a journal is made very fast and does not have to go through two or three levels of management. To encourage scientists to look for ideas off the beaten track, it is important to allow a certain amount of freedom in the area they study. MNC1, for example, balances the need for focus to obtain a patentable drug with the desire for freedom to keep scientists creative, by allowing these researchers to spend between 10 and 20% of their time working on their own curiosity-driven projects.

Finally, to fight organizational failures some firms use competition between laboratories as a spur to improved performance. We found in our sample examples of firms signing long-term R&D contracts with university laboratories or other firms which are ahead of the firm's own scientists in an area of interest to the firm, and using the competition with these laboratories as a way of enhancing the work of its own scientists. For example, Merck–DuPont Pharmaceutical is a joint venture of Merck and DuPont which operates in all therapeutic areas with compounds invented by DuPont but

[9]Graves and Langowitz (1993) find that pharmaceutical firms experience decreasing returns to scale in R&D as the level of R&D expenditures rises. This study can be contrasted with those of Vernon and Gusen (1974), Schwartzman (1976).

developed and marketed by Merck. This venture competes with Merck itself and creates a benchmark against which the firm can measure itself.

A third requirement for dealing with organizational failures in the conduct of R&D is the creation of appropriate incentives. In at least two of the firms in our sample, MNC1 and MNC3, there are two pathways for promotion: the research path and the management path. The two are paid equally to allow scientists to remain in research positions, but still rise in the hierarchy. MNC1 gives stock options to almost everyone who participated in the discovery and development of a new compound. This program reaches all the way down to bench chemists. These stock options cannot be exercised until the compound passes various regulatory hurdles on its way to government approval. If the research does not yield a marketable product, MNC1 rewards its scientists based on the spreading of useful knowledge, through for example, the publishing of research results in a refereed journal.

It is interesting to note that the pharmaceutical industry is not the only one where the role played by cross-functional R&D teams has become essential.[10] In the electronics hardware industry, at Hewlett–Packard (HP) for example, marketing, manufacturing, and R&D managers work together to define, design, manufacture and market new products. As opposed to using concepts such as focus, openness and incentives to combat the threat of organizational failures in the pharmaceutical R&D process, HP uses concepts such as break-even time, post-introduction product reviews, in-process project retrospective reviews and quality function deployment to foster cross-functional work in its own R&D process (see Graves et al., 1991, Takei, 1981, Cooper et al. 1990, Roberts, 1989, Roussel et al. 1991). The major difference between the pharmaceutical/biotechnology and the electronics hardware R&D process is that in addition to having to face market uncertainty about whether or not the drug will sell after it is approved, pharmaceutical/biotechnology firms must deal with the very strong probability that no new compound will emerge at all from the R&D process. Issues relating to safety, efficacy and increasingly also cost-effectiveness of treatment add a large dimension of uncertainty. Therefore, it is very difficult to predict which compound will succeed and which will fail.

Researchers at the University of Sussex (1972, pp.4–9) have studied 29 successful and 29 unsuccessful innovations and found that five factors were sufficient to distinguish successful from unsuccessful innovations. These are understanding user needs, marketing, efficiency of the development effort, effective use of outside technology, and project leaders with more seniority and authority.

Similarly, in a comparison of the British and German machine tool industries, Parkinson (1984) finds that the greater success of German machine tool manufacturers is accounted for by greater direct involvement with customers in the design and development of new machine tools, machine tools designed to individual customer specifications, superior technical quality in product design, better contacts with university and research institutions and well organized and informed customers. These factors play a role in the pharmaceutical/biotechnology industry as well. However, in pharmaceutical R&D, the path to a product is far less direct and much longer, often taking between 8 and

[10]We are grateful to an anonymous referee for suggesting this point.

12 years. Uncertainty remains until very late in the R&D effort,[11] and continues even after the product has been approved for marketing. This last element of uncertainty stems from the cost containment measures recently introduced by governments, third party payers and employers. In today's economic environment pharmaceutical products must not only be safe and effective, but also cost-effective in comparison with other forms of treatments. Pharmaceutical companies must now increasingly provide pharmacoeconomic or outcome studies to managed care organizations before these organizations will agree to reimburse patients for the cost of the product.[12] Canada has just published national guidelines for pharmacoeconomic studies which will eventually become law (Canadian Coordinating Office for Health Technology Assessment, 1994). These studies are required by law in Australia. Many other countries such as France, the UK, the US will also soon require pharmaceutical companies to provide this type of analysis alongside the medical information obtained in clinical trials.

3.3. Exceptions to the vertical integration rule for R&D

We have discussed the limitations of rational drug design and shown that as a result of these limits, close links among the first four stages of the R&D process are required. Yet some exceptions exist. Six firms in our sample, Monsanto, SmithKline, Squibb, Upjohn, Connaught and Allelix, have signed long-term joint venture R&D contracts with universities to perform basic research.[13] Interviews with the firms in our sample reveal three motives for these agreements: low transaction costs, the need to catch up in a specific area of research and governmental policies. The importance of these motives for each of the firms in our sample is reported in Table 3.

The first motive occurs when the relevant biological and chemical theories are advanced enough that the action of a particular compound on the target molecule can be predicted accurately. Under those conditions transaction costs analysis predicts that firms are able to isolate the first four stages in the R&D process and use market contracts in addition to hierarchical governance. A scientist at Canadian Firm 1 puts it this way, "... the scientist has got something that fits your immediate strategy. This is in the case where you are trying to manufacture or move towards an end product you've targeted. It's going to take you seven years and here is somebody who has some technology that will short-circuit the thing – bring it forward two or three years." (Canadian Firm 1, p.21 of our transcript). The CEO of Canadian Firm 2 argues, "The other one of our strategies about research is really to form strategic alliances with universities. We don't aim to be in basic research. We link up with universities for the initial product. We determine what the

[11]There are examples of products which failed late in phase 3 clinical testing after 10 years or more of work and many tens of millions of dollars spent. See the stories of biotech firms Centocor, Cortech, Glycomed, Magainin, Medimmune, Regeneron and Synergen in Hamilton (1994). DiMasi et al. (1991) provide estimates of the costs and risks of drug discovery. It is too soon to tell what the impact of the new pharmacoeconomic guidelines will be on the introduction of new drugs (see, Scherer, 1993).

[12]Genentech's TPA, for example, was at first rejected by many third party payers as being too expensive in comparison to competing treatments. It was only after a major outcome study that Genentech was able to show the benefits of TPA, despite the high cost per dose.

[13]Tapon (1989) has argued that R&D transactions with university partners do not suffer as much as with independent laboratories from the effects of opportunism.

Table 3
Exceptions to the vertical integration rule

	MNC1	MNC3	MNC4	MNC5	Canadian Firm 1	Canadian Firm 2	MNC2	Canadian Generic Firm
Low transaction costs	○	*	*	○	*	*	*	○
Catch-up/window on science	○	*	*	*	*	*	*	○
Governmental policies	*	*	*	*	*	*	○	○

* Means that the interviewees specifically mentioned this variable in their description of their firm's R&D process.
○ Means that this concept was not mentioned.

product might be and then we take it in-house and begin to apply our technologies which are production oriented. We do the development I would call it." (Canadian Firm 2, p.8 of our transcript). A firm may also find it convenient to work with outside sources to explore a greater variety of models for particular diseases than it is willing or able to develop itself. A scientist at MNC3 explains, "Building animal models and human models of disease is a difficult thing to do and it's not worthwhile for a pharmaceutical company developing all of these different models for small experiments to see if a compound is useful in various indications." (MNC3, pp.10–11 of our transcript). Sometimes, despite scientists' best efforts and the recruitment of the most able researchers, a dead end is reached. At that point firms try to join forces with another organization that has been successful where it failed. Most of the time these links are ad-hoc and cover one project, one class of molecule, or one particular group of experts. It is understood that the link lasts only as long as the project, and ends with it.

The second motive occurs when a firm has to catch up in an area of research and is looking for a partner who will act as a teacher or mentor. One of the scientists at an MNC in our sample referred to this as "opening a window on emergent technology." A scientists at MNC3 explains, "... I would say the big part of collaborative research with the university is when we are targeting a therapeutic area that we are interested in and we have some expertise in but, we want to supplement our expertise." (MNC3, p.10 of our transcript). A scientist at MNC2 argues, "The effort there was to develop an umbrella agreement with Harvard... to gain a window on science. ... Inside talk at [MNC2], as in many companies, was sort of an expression that described [these long-term R&D agreements with university laboratories]. I think it was 'a window on emergent technology'." (MNC2, p.8 of our transcript). In this circumstance, the independent university laboratory helps the firm establish its own research in a new area by teaching it new techniques. This has been especially true recently for established pharmaceutical firms with a chemistry-based research which needed to add new capabilities in biology. The executives we interviewed acknowledge that they are playing catch-up in the areas of science covered by these contracts and that they see some of these links as a quick and

cheaper way of establishing research programs and rapidly learning about new fields.[14] The goal is eventually to bring this research in-house. The evidence for this statement is provided by the acknowledgement on the part of our interviewees that their firms are simultaneously building up their research capability in-house in the areas covered by the long-term university agreements.

The third motive for firms to link up with university laboratories is to satisfy governments in host countries. For example, France regulates the price of drugs and approves the scientific aspects of new drug submissions. When a firm introduces a new drug in France, it must negotiate the entry level price with the government. In order to obtain a higher price, a firm may pledge to spend money on research in France. The quickest and most effective way of launching a research program when none exists is to link up with a reputable university laboratory. The relationship may develop into a long-term link, or the relationship may go nowhere and the research program may be brought back in-house. France is not alone in demanding that research be done in its territory. Canada and the UK are using similar policies. Some executives we interviewed saw this last motive as very significant. They argue that in the past, some countries have used control on prices of new drugs or return on investment to extract concessions on prices of other drugs, or on manufacturing and now on research. Canada extracted promises from the pharmaceutical industry to increase the level of spending on research to 10% of Canadian sales by 1996 in return for changes to the Canadian Patent Act. A scientist at MNC4 explains, "These [long-term R&D joint ventures with university laboratories] are mechanisms or ways in which the company can increase its R&D efforts and at the same time create a presence in jurisdictions where it would not normally have a presence in research and development, because, of course research is primarily conducted at the company based in [the United States], Japan, and the United Kingdom. There is a two-fold kind of situation. There is a political rationale behind this as well as a scientific rationale." (MNC4, pp.1–2 of our transcript).

4. Conclusions

We started this research with the belief that progressive pharmaceutical companies were opening up their R&D process by contracting out basic research and sometimes applied research to external laboratories (university or independent). What we found was the opposite. First, by understanding better how the pharmaceutical R&D process is carried out, we realized that the costs of market failures associated with contracting R&D externally are very high. This is the reason that vertical integration into R&D is the solution of choice for leading pharmaceutical firms. Second, we learned about the organizational design measures adopted by firms to combat the organizational failures from which vertically integrated firms inevitably suffer. These were focus, openness, and incentives. Third, we did find that six of the firms in our sample (MNC2, MNC3, MNC4, MNC5, Canadian Firm 1, Canadian Firm 2) used external contracting for certain R&D

[14]Trust is an important element in these relationships. Ring and Van de Ven (1992) discuss the link between governance structure, trust and risk.

projects. However, this does not disprove our finding that vertical integration is the normal solution of choice for pharmaceutical R&D. We found that the reasons for these firms' choice fell into three stable categories: low transaction costs associated with external R&D, catchup or window on emergent technology, and governmental policies. The firms in our sample, with the exception of the Canadian generic producer, are all well-established research-oriented brand-name manufacturers. Although they compete in different therapeutic areas, their strategic focus is the same: to discover and develop break-through products. They are not all equally successful. At the time of our interviews (1989–1992) MNC1 was independent and successful; MNC2 was talked about as a takeover target; MNC3 was about to be taken over by another brand-name manufacturer; MNC4 was regularly mentioned as a takeover target; MNC5 merged with another brand-name manufacturer; Canadian Firm 1 was taken over by another brand-name manufacturer; Canadian Firm 2 was owned by a small group of investors among which were other brand-name manufacturers and their managers; and Canadian generic firm was privately-owned. Thus, the vertical integration result held despite the different circumstances, strategic focus, and industry positioning in which these firms found themselves.

Acknowledgements

We gratefully acknowledge the financial support of the Ontario Centre for International Business, at the University of Toronto, and the encouragement of Dr. A.M. Rugman. We also wish to thank the executives of Merck Frosst, SmithKline, Upjohn, Monsanto/Searle, Squibb, Allelix, Connaught, and Novopharm who participated in our study. Without their help and generosity this paper could not have been written.

References

Canadian Coordinating Office for Health Technology Assessment, 1994, Guidelines for economic evaluation of pharmaceuticals: Canada, 1st edn., November, Ottawa.

Comanor, William S., 1986, The political economy of the pharmaceutical industry, Journal of Economic Literature, 4(3), 1178–1242.

Cooper R.B., et al., 1990, Applying quality assurance to R&D projects, Quality Progress 23(7) 21–26.

DiMasi J.A. et al., 1991, Cost of innovation in the pharmaceutical industry, Journal of Health Economics 10(2) 107–142.

Gibbins, M., A. Richardson and J. Waterhouse, 1989, The management of corporate financial disclosure: Opportunism, ritualism, policies and processes, unpublished manuscript, Department of Accounting, Faculty of Business, University of Alberta, February 16.

Grabowski, Henry G., 1989, Innovation and international competitiveness in pharmaceuticals, Working Papers in Economics no. 89.03, Department of Economics, Duke University.

Grabowski, Henry G. and John Vernon, 1990, A new look at the returns and risks to pharmaceutical R&D, Management Science, 36(7), 804–821.

Graves, S.B.,W.P. Carmichael,D. Daetz and E. Wilson, 1991, Improving the product development process, Hewlett-Packard Journal, 71–76.

Graves, S.B. and N.S. Langowitz, 1993, Innovative productivity and returns to scale in the pharmaceutical industry, Strategic Management Journal, 14(8), 593–605.

Hamilton, J., O'C., 1994, Biotech an industry crowded with players faces an ugly reckoning, Business Week, No. 3391, September 26, pp.84–92.

Henderson, R., 1994, Managing innovation in the information age, Harvard Business Review, 72(1), 100–105.

Henderson, R.M. and K.B. Clark, 1990, Architectural innovation: The reconfiguration of existing product technologies and the failure of established firms, Administrative Science Quarterly, 35, 9–30.

Hill, C.W.L. and G.S. Hansen, 1991, A longitudinal study of the causes and consequences of changes in diversification in the pharmaceutical industry, 1977–1986, Strategic Management Journal, 12, 187–199.

McGahan, Anita M., 1994, Industry structure and competitive advantage, Harvard Business Review, 115–124.

Merton, R.K., 1957, Social theory and social structure, rev. and enlarged, (The Free Press, Glencoe, IL).

Merton, R.K. and P.L. Kendall, 1956, The focused interview, American Journal of Sociology, 51, 541–557.

Mintzberg, H., 1989, Mintzberg on management, (Free Press, New York).

Parkinson, S.T., 1984, New product development in engineering: A comparison of the British and West German Machine Tool Industries, (Cambridge University Press, Cambridge, UK).

Pisano, G.P., 1990, The R&D boundaries of the firm: An empirical analysis, Administrative Science Quarterly, 35, 153–176.

Pisano, G.P., 1991, The governance of innovation: Vertical integration and collaborative arrangements in the biotechnology industry, Research Policy, 20, 237–249.

Ring, P.S. and A.H. Van de Ven, 1992, Structuring cooperative relationships between organizations, Strategic Management Journal, 13(7), 483–498.

Roberts, G.W., 1989, Wipe out R&D waste, Quality Progress, 22(1), 54–57.

Roussel, P.A., K.N. Saad and T.J. Erickson, 1991, Third generation R&D, (Harvard Business School Press, Boston).

Scherer, F.M. and David Ross, 1990, Industrial market structure and economic performance, 3rd edn. (Houghton-Mifflin, Boston).

Scherer, F.M., 1993, Pricing, profits, and technological progress in the pharmaceutical industry, Journal of Economic Perspectives, 7(3), 97–115.

Schwartzman, David, 1976, Innovation in the pharmaceutical industry, (Johns Hopkins University Press, Baltimore, MD).

Schneiderman, H.A., 1991, Managing R&D: A perspective from the top, Sloan Management Review, 32(4), 53–58.

Stigler, G.J., 1958, The economies of scale, Journal of Law and Economics, 1, 54–71.

Takei, F., 1981, Productivity improvement in engineering work – the 'EPOC' campaign in a Japanese company, Engineering Management International, 1, 23–28.

Tapon, F., 1989, A transaction costs analysis of innovations in the organization of pharmaceutical R&D, Journal of Economic Behavior and Organization, 12, 197–213.

University of Sussex Centre for the Study of Industrial Innovation, success and failure in industrial innovation: Report on Project Sappho by the Science Policy Research Unit, 1972.

Vernon, John M. and Peter Gusen, 1974, Technical change and firm size: The pharmaceutical industry, Review of Economics and Statistics, 56, 294–302.

Williamson, O.E., 1975, Markets and hierarchies: Analysis and anti-trust implications, (Free Press, New York).

Williamson, O.E., 1985, The economic institutions of capitalism, (Free Press, New York).

Williamson, O.E., 1991, Strategizing, economizing and economic organization, Strategic Management Journal, Vol. 12, Special Issue, Winter, pp. 75–94.