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Innovative and Industrial Performance in Pharmaceutical R&D, a Management Control Perspective

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In this paper management control is related to innovative and industrial performance in 14 non-biotech pharmaceutical companies. The study consisted of questionnaires, sent to the heads of the different research departments of European research laboratories of leading pharmaceutical companies, combined with structured interviews with the R&D Directors of the companies. Given the limitations of a cross-sectional design and a relatively small study population, the following conclusions are tentatively drawn. Firstly, clear contrast has been found in the effectiveness of personnel, resources and external control, dividing the more from the less than average performers. Especially the strength of personnel control proves to be an important dividing parameter. Secondly, clear contrast has been found in research process control between discovery and development. In the highly uncertain environment of discovery, intensive 'in house' communication proves to be an important dividing parameter between less and more than average performers. However, in the more certain environment of development, the level of planning and the communication with marketing and production in the project team meetings is an important parameter dividing the more from the less than average performers.

Key words—management control, R&D, performance

INTRODUCTION

TECHNOLOGICAL INNOVATION HAS become one of the main drivers of competition, propelling new firms to the forefront and eroding the competitive advantage of well-established firms [20]. Especially in the 'science based' industries [16], like the pharmaceutical industry, innovation has become essential for long term survival. The necessity to innovate has led to the development of acceptably safer and more effective drugs. Increasing innovative effort is being put into complex therapeutic areas (like cancer and multiple sclerosis), requiring a degree of sophistication in methodology and basic scientific knowledge, which is without precedent

in pharmaceutical industry. However, increasing strict regulations, regarding the efficacy and safety of drugs, has reduced the time to recoup past research expenditures considerably [21]. Taking into account the policy of most national governments to reduce medical costs by influencing drug prices, for instance by stimulating the prescription of less costly generic drugs, pharmaceutical innovation gradually has become a high risk investment area. It is the aim of this paper to analyse the differences in innovative and industrial performance from the perspective of management control.

DEFINITIONS

Pharmaceutical innovation

In the context of this paper, pharmaceutical innovation is taken to mean the whole R & D-process, starting with the discovery of the lead compound (a chemical compound with assumed therapeutic efficacy), and the succeeding development process aiming to bring this lead to the market, and the post marketing surveillance activities, aiming to improve the product (e.g. search of side effects with low and moderate incidence, and improvements in drug delivery). In Fig. 1 an outline is given of the research

1. **Discovery phase**
   Before the discovery phase starts, strategic choices are made regarding research projects, based upon an evaluation of therapeutic and commercial significance and scientific attainability. Around 10,000 chemical compounds in the 'random screening' and 500 to 1,000 in the 'rational drug design' approach have to be synthesized and tested for therapeutic activity in pharmacological or animal models. The discovery phase ends with the finding of the lead compound.

2. **Pharmacological development phase**
   The pharmacological development phase starts with further pharmacological screening and characterization of the active substance. Pharmacokinetical research into degradation speed and acute and subacute toxicity along with mutagenicity tests are done, and the synthesis of the active substance for clinical testing is performed. Also a patent dossier is submitted to the authorities.

3. **Clinical development phase I, II, III**
   In the clinical development phase I, dose-effect relationships, duration of effects and side effects are tested in 50 to 100 healthy volunteers. In phase II the first controlled clinical trials are carried out on patients (about 200 to 400). In phase III the double blind randomized clinical trials are executed on a great number of patients in (academic) hospitals in different countries, to demonstrate therapeutic efficacy and to establish contra-indications, side effects with a relatively high incidence and optimal dosage. This phase ends with the presentation of the registration dossiers to the authorities.

4. **Registration and launch phase**
   In this phase the test dossiers are examined by the authorities for approval of the drug to be launched to the market. During the registration period the designing and building of the production facilities and manufacturing process continues, the marketing plan is formulated and the training of the sales force starts. In this way the larger pharmaceutical companies are able to launch a new drug within months after registration.

5. **Clinical development phase IV**
   After launch the post marketing surveillance starts to trace side effects of drugs with low and moderate incidence, and to investigate the possibilities of broadening the indication area.

Sources: 3,9,11,23 and this study.

Fig. 1. Description of the innovation process in the pharmaceutical industry.

activities in the different phases of the innovation process.

The R&D-process until registration is composed of three phases, which differ considerably in the character of the research activities. The process starts with the discovery phase, in which the screening and testing for the finding of the lead compounds is done, and in recent years more and more basic research is put into the biomolecular background of diseases. Although the use of new techniques in discovery, like biomolecular modelling, has made the searching for the lead compound less fortuitous, the research work in the discovery phase is still highly unpredictable. Contrary to this, the toxicological and clinical testing in the pharmacological and clinical development phases can be planned according to strict schedules. Whereas the research work in the pharmacological development phase is largely done 'in house', the clinical testing is done in hospitals. Therefore, the main task of the R&D-staff in the clinical development phase is the monitoring of the clinical trials.

Management control and performance

In Table 1 an outline is given of the variables used in this study. In the following a more general account is given of their theoretical background.

Management control is the process by which managers assure that resources are obtained and used effectively and efficiently in the accomplishment of the organization's objectives [2, p. 27]. Anthony conceives management control as the planning and control level between strategic planning (goal formulation) and operational control (assuring that specific tasks are carried out). Management control is divided into system, process and external control. System control refers to the control over the personnel and material resources of the system (the research laboratory). Personnel control is measured by the assessed effectiveness of the human resources management, and resources control by the estimated pace of the administrative procedures. Process control describes the control over the research process, and is assessed by planning

Table 1. The definition of size, management control and performance

Size	
Sales	World wide sales of ethical drugs in 1991 in US $billion
R & D-expenditures	Worldwide R&D-expenditures in 1991 in US $million (also derided into expenditures for drug discovery, and expenditures for pharmacological and clinical development, and post marketing surveillance (phase IV clinical trials, no patent and registration costs)
System control (personnel and resources control)	
Effectiveness	Subjective assessment of the heads of different research departments in company laboratories of the effectiveness of personnel policy, appointment, promotion and career planning (Likert's 5-point scales, higher values indicate a more positive assessment)
Adequacy	Subjective assessment of the adequacy of the size of the laboratory budget and facilities (e.g. advanced equipment, literature facilities, Likert scales, higher values indicate a more positive assessment)
Administrative control	Rapidity of administrative procedures, regarding appointment and procurement of equipment {US$50,000, Likert scales, 1 = (more than) a year; 5 = (less than) a month}
Process control	
Planning	Subjective assessment of the importance of short and middle range planning by higher management (Board of Directors, strategy department, Likert scales, higher values indicate a more positive perception)
Frequency	Frequency of project team meetings in discovery and in development {Likert scales, 1 = (less than) once in six months; 5 = (more than) once a week, research process communication}
Attendancy mix	Attendancy of project team meetings: only scientific staff of the own research department, or also researchers of the other R&D-phases {e.g. pharmacological development in case of discovery; clinical development in case of pharmacological development; or marketing and production in case of a clinical development department (Likert scales, higher values indicate more diversity in attendancy)}
External control	
International comm.	Frequency of international contacts with scientists and physicians on congresses and workshops {Likert-scales, 1 = (less than) once a year; 5 = (more than) once a month}
Innovative performance	
Number of patents	The average annual number of patents for new synthetic chemical compounds, submitted world wide with first priority date from 1985 to 1991, absolute and divided by the annual expenditures for discovery
Length of development	Length of the development phase, the average time span between patenting of the lead and the registration of the drug (in years^{-1})
Industrial performance	
Growth rate	The annual growth rate of the company, both organic growth and growth through acquisition
Operating profit margin	Operating result/revenues. Operating result = result after deduction of normal operating charges and before financial income and expenses, taxes etc. Revenues = net turnover including other operating revenues, change in stocks and capitalized costs

and research process communication (frequency and attendancy mix). External control refers to the control over the environment [19], and is assessed by international communication.[1]

The number of patents for new synthetic chemical pharmaca with first priority date submitted world wide from 1986 to 1991, is used as the performance measure for the discovery phase. The data were obtained by using the Pharmdoc Section of the World Patents Index Database of DERWENT Publications. Only compound patents (patents for NCEs, New Chemical Entities), and not process or formulation patents have been considered in this study. A compound patent gives protection for a group of closely related biochemical compounds. In order to assess whether the patents were submitted for NCEs and not for minor variants of drugs of other companies ('me too patents') or pharmaceutical or therapeutical extensions of existing drugs (for instance an improved version or a new indication area), the CAS-registration numbers (Chemical Abstract registration of new chemical compounds) were checked. Only those compounds were selected, of which the CAS-number indicated that they were new at the time of patenting.

Because the primary interest of this paper is to get a better understanding of the work of the proprietary innovative efforts of a company, joint development of a drug by two or more companies and in- and outlicencing (to buy the right to use a patent from or to sell this right to a competitor) have not been studied. For the same reason 'biotechnological' patents (immune-diagnostics, oligo- and polypeptides and DNA- and RNA-sequences) have not been taken into consideration. Another problem is the possible difference in patenting policy (timing and scope) between companies. Basberg [4] and Pavitt [17] indicate that some companies play for safety and apply for a patent in an early stage of the innovative process, while others wait longer. The first strategy decreases the risk that a competitor submits a patent for a similar compound, but increases the patents fees and translation costs and can put a competitor on the track. The second strategy has complementary (dis)advantages. In a previous paper, the authors concluded on the basis of the structured interviews, that the patent strategy of the companies was comparable [14].

The length of the development process is used as a measure of the efficiency of the development phase. In order to obtain comparable data, the Research Directors were asked to give an estimation of the maximum time span between the patenting of the lead compound and the introduction of the registered drug on the prescription drug market, for anti-hypertensive and anti-ulcer drugs. These drugs were chosen because the development-process is neither relatively short (antibiotics) nor very long (anti-psychotics). In five companies the reported length was checked for ten drugs which were launched after 1987. In all cases the findings proved to be in agreement, the period between patent submission and launch being 1–2 years shorter than the reported maximum length of the development-process. The finding of the lead precedes patent submission, so the time span of patent submission to launch will always be somewhat shorter.

Innovation, although essential, is not enough to reach the goal of attaining long term profitability for the company. It is obvious that without an adequate marketing and sales structure an innovative drug would never reach its full profit potential. Therefore, measures of industrial performance are also used in the present study: the annual growth rate, and the operating profit margin.

Hypotheses

It is expected that the different management control variables will show a positive association with one or more of the performance variables. It is expected that the industrial performance variables will reflect management control at large, and will primarily be related to elements of system and external control, and will not be closely related to process control. Contrary to

[1] de Leeuw's requirements for effective control [13] has been used to decide whether the control variables used in this study are sufficient to cover the concept of control: for effective control the controller must define a goal for the system and have a model of the system or at least a good understanding of the system to be controlled, must have sufficient information about the system and the environment, and must have enough measures of control at its disposal. In this study goal setting and having a model are referred to as planning, system information as research process communication and environmental information as external control. The measures of control are referred to as personnel and resources control. So it can be concluded that the control variables used in this study sufficiently cover the concept of effective control, as proposed by de Leeuw.

this, the innovative performance parameters are expected to be primarily related to process control. The differences in the research activities between discovery and development are expected to be reflected in this relationship. It is expected that the relatively high task uncertainty [6] in the discovery phase, connected with the unpredictability of research activities, will be reduced by intensive contacts, internally with colleagues in the discovery phase and externally with scientists and physicians on congresses. So it is expected that the frequency of research meetings and international communication will be dividing parameters between less than average and more than average performers.

In the relatively certain environment of the development phase it is expected that the level of planning and the attendancy mix will prove to be important parameters, dividing the more than average from the less than average performers. Concerning research process communication, in recent years the pharmaceutical companies work more and more with project teams in order to attain attuning between the different phases of R&D, and between R&D, marketing and production. In the project team meetings, researchers of the different phases of the R&D-process, and staff members of marketing and production, discuss the ongoing research projects on a regular basis. Especially in the late pharmacological and the clinical development phases, intensive contact in project teams with marketing and production are thought to be essential in order to get a drug to the market as soon as possible. Also in the development phase international communication is essential. But here the primary goal is to broaden the contacts with physicians, in fact the clients of the companies and the executioners of the clinical trials and to broaden the communication with other international pharmaceutical companies to provide a learning curve for eventual marketing of the new product. In Table 2 an outline of the hypotheses is given.

Table 2. The predicted associations of management control and innovative and industrial performance

	Patents number	Development length	Operating profit margin	Growth rate
System control	+	+	+	+
Process control				
Planning	*	+	*	*
Frequency	+	*	*	*
Attendancy mix	*	+	*	*
External control				
International communication	+	+	+	+

+ a positive correlation of the management control variable with the performance variable concerned predicted. *No specific correlation predicted.

Data analyses

For the assessment of the different management control variables, Likert's 5-point scales were used. After the data-collection a factor analysis was performed. Cronbach's α [7] was calculated for the individual sub-scales to find out whether they corresponded with the variables defined, and to check for the internal consistency of the items, supposed to measure a single concept. In all cases Cronbach's α was sufficiently high (>0.75), to warrant confidence in the internal consistency. In order to prevent eventual co-variation of size and management control with performance, size was entered first in the multivariate analysis, and before the management control variables were entered. In order to warrant objectivity the performance variables were measured by use of bibliometric measures and public information (year reports etc.) and checked by the research management concerned.

For clarity of presentation all bi-variate relationships are presented using Spearman Rank Correlation and One-way ANOVA. Non-parametric analysis of group means, using the Kruskal–Wallis test, does not alter the conclusions. For the description of management control in Table 5, from each constructed variable, that item is selected which reflects the average of the construct. The multi-variate associations are measured on the ranking numbers with a neural network. The neural network uses the iterative steepest descent technique, with exponential sum formula, based upon series expansion, to approach the minimum error solution. It is developed for usage in cases in which other numerical modelling methods (like multiple regression) perform poorly, due to insufficient or singular data [12]. The neural network divides the data into two groups: a model set of 80% and a test set of the remaining 20%. First, the neural network builds a model on the data of the model set, then this model is tested on the data of the test set. Because of the relatively small study sample, the choice of the test set can influence the results considerably. Therefore four independent runs of the neural network have been executed, using different

model and test sets, and an additional run without a test set, to get maximal statistical power. Because of their general use in multi-variate analyses, in this paper the terms 'explained variance' and 'F-value' are used. Strictly speaking, they relate only to predicted (mostly linear or transformed to linear) relationships. The neural network, however, is designed to model all kinds of linear and non-linear relationships. However, in the present study only linear and curvi-linear relationships are measured, because of the small size of the study sample.

Data collection and response

In 1992 twenty large and medium-sized pharmaceutical companies with major research laboratories in the EC were approached. The companies were selected on the basis of their (world wide and European) sales volume of ethical pharmaceutical drugs, and on their innovative capacity, measured by the number of R&D-staff and the number of patents submitted with a European priority. In order to prevent a selection bias based on the use of only quantitative data, 14 leading Dutch Clinicians in Universities and large Health Research Institutes were asked to name the most innovative drugs introduced to their specific therapeutic areas. The information obtained in this inquiry generally supported the quantitative selection. Only one company was added on the basis of the qualitative judgment.

Fourteen companies agreed to participate, including the company selected on qualitative grounds (a response rate of 70%). Ten of them are among the top 20 companies, ranked according to world wide ethical drug sales in 1991. Furthermore, 25% of all pharmaceutical patents submitted with a European priority from 1985 to 1991, originate from the companies in this study (in total around 1500 companies, universities and institutes submitted patents in this period).

Twenty-two structured interviews were held with the Directors of Discovery, and Pharmacological and Clinical Development (1–2 interviews per company). In addition, in 10 companies questionnaires about personnel, budget and research policy, were submitted to the heads of the different research departments. In total 59 questionnaires were sent, of which 38 were returned (3–4 questionnaires per company laboratory, an individual response rate of 64%).

RESULTS

In Table 3 an estimate is given of the length of the different phases of the R&D-process, the percentage of the R&D-budget spent on these phases, and the number of compounds investigated per phases. The data are based on literature and were checked in the structured interviews. The total length of the R&D-process from the start of the discovery phase until the final launch of the drug is 7–13 years. Most of the time is spent on development (6–11 years), half of it on clinical trials. As a consequence, the largest part of the R&D-budget is spent on clinical development, 30–55% of all R&D-costs going to phase I to IV clinical trials. About one-third of the costs of the phase IV clinical trials, are paid from the development budget, and two-thirds comes from the marketing budget of the company. Of course, the discovery phase can take much longer than the average 1–2 years presented in Table 3, if success fails to come. In recent years pharmaceutical companies use parallel development, in order to gain time in the development phase. For instance, at the same time as the clinical trials are executed, the long scale biological testing for chronic and subchronic toxicity continues and the upscaling for production starts. In recent years the screening and testing methods in the discovery phase have improved tremendously. On the one hand, specialized firms have computerized the screen-

Table 3. An estimation of the length, the percentage of the R&D-expenditures, and the number of chemical compounds under research, in the different phases of the innovation process

	Length (years)	% R&D exp.	No. of compounds
1. Discovery phase	1–2	20–30	10,000/500–1000
2. Pharmacological development phase	2–3	25–30	20–50
3. Clinical development phase I, II, III	3–5	15–30	10 (I), 4–5 (II), 1–2 (III)
4. Registration and launch phase	1–3	3–5	1
5. Clinical development phase IV	—	15–25	1

Sources: [22, 24] and this study.

Table 4. Study base description of size and performance. Average of all companies in the study ($n = 14$), and of smaller vs larger companies {median split of ethical drug sales, mean and (standard deviation) and $F_{\text{-oneway ANOVA}}$}

	Average all companies	Smaller companies	Larger companies	F-value
Size				
Sales ($m)	3372 (1913)	1755 (655)	4989 (1184)	38.9****
R&D-expenditures[a] ($m)	540 (248)	280 (101)	723 (97)	28.7***
Innovative performance				
Number of patents	73 (62)	34 (6)	124 (58)	14.4***
Length of development (years)	9.3 (2.1)	10.5 (1.76)	8.0 (1.58)	6.0**
Industrial performance				
Growth rate (%)	10.5 (4.5)	9.4 (3.9)	11.9 (5.1)	0.8
Operating profit margin (%)	23.6 (11.2)	16.6 (12.3)	28.2 (8.4)	3.2

[a]Discovery 126 (70) $m; development 390 (209) $m.
***$P < 0.001$; **$P < 0.01$; *$P < 0.05$.

ing and testing procedures to such an extent that large numbers of varieties of a chemical compound with assumed therapeutic efficacy delivered by a pharmaceutical company can be randomly synthetisized and tested, without human interference. On the other hand, the use of new techniques, like Biomolecular Modelling, supported by Nuclear Magnetic Resonance (NMR) and Scanning Tunnelling Microscopy techniques has made a more targeted approach possible. In this approach much smaller quantities of compounds (500–1000) have to be screened and tested. DiMasi *et al.* [8] estimated the average total R&D-cost per approved NCE as high as $114 million.

In Table 4 an outline is given of the average values of the size and the performance variables, used in the present study. Because the size is a very determining factor, a comparison of smaller vs larger companies is made (median split). The average sales-volume of ethical drugs world wide of the companies in the study is large, nearly $3.5 billion per company. However, the differences are considerable. The smaller companies have about half this size, whereas the larger companies have a sales-volume of nearly $5 billion. The companies spend on average 15.7% of the sales volume on R&D, the smaller ones somewhat more than the larger ones (16.3% vs 15%). 25% of the R&D-expenditures is spent on discovery, and 75% on pharmacological and clinical development. The companies grow vigorously at about 10% a year. The larger companies submit more patents than the smaller ones, not only in absolute figures (124 vs 34 patents a year), but also relative to their R&D-investment (9.6 vs 2.7 patents per $10 million per year). The operating profit margin is high, the operating result being nearly 25% of the total revenues, 16.6% in smaller vs 28.2% in larger companies. The length of the development process was on average 9 years 4 months. In the smaller companies it was on average 10.5 years, whereas in the larger ones it was much shorter, only 8 years.

In Table 5 an outline is given of the different management control variables. On average, the

Table 5. Study base description of management control (Likert's 5-point scales). Average of all companies ($n = 10$), and of companies with a relatively low {$< 17\%$ ($11.1\% \pm 4.5\%$), $n = 4$} vs companies with a relatively high operating profit margin {$> 28\%$ ($31.9\% \pm 2.9\%$), $n = 6$, mean and (standard deviation) and $F_{\text{-oneway ANOVA}}$}

	All companies	Operating profit margin relatively low	Operating profit margin relatively high	F-value
Personnel control				
Effectiveness	3.33 (1.02)	2.33 (0.80)	3.87 (0.87)	6.13*
Resources control				
Adequacy	3.56 (0.63)	3.22 (0.75)	3.62 (0.94)	0.36
Administrative control	3.48 (1.26)	2.42 (0.72)	3.67 (1.43)	1.90
Process control				
Planning	3.78 (1.57)	3.70 (1.08)	3.82 (1.30)	0.02
Frequency	3.07 (0.88)	3.06 (0.83)	3.08 (0.45)	0.00
Attendancy mix	2.37 (0.51)	2.34 (0.41)	2.37 (0.55)	0.01
External control				
International communication	3.46 (1.31)	3.08 (0.44)	4.06 (0.89)	6.98*

*$P < 0.05$.

Table 6. The Spearman rank correlations of size ($n = 14$) and management control ($n = 10$) with size and performance

	Sales	Patent number	Development length	Operating profit margin	Growth rate
Size					
R&D-expenditures	0.92	0.66	0.74	0.65	0.49[a]
Personnel control					
Effectiveness	0.50	0.36	0.43	0.71	0.44
Resources control					
Adequacy	0.43[b]	0.24	0.54	0.51	0.30
Administrative control	0.14	0.17	0.42	0.39	0.05
Process control					
Planning	0.31	0.06	0.62	0.42	0.19
Frequency	0.44	0.75	0.30	0.08	0.48
Attendancy mix	0.18	0.13	0.66	0.18	0.80
External control					
International communication	0.25	−0.02	−0.26	0.73	0.06

The underlined numbers are statistically significant ($P < 0.1$, 2-tailed test).
[a]R&D-expenditures spent on development is significantly correlated with growth rate (0.58).
[b]Adequacy is significantly correlated with R&D-expenditures (0.67).

subjective assessment of the different management control variables is rather positive. Both for the effectiveness of personnel policy, the adequacy of resources, and the importance of planning by higher management, the average assessment on a 5-point scale, is clearly above three. Also the administrative procedures are executed with pace; even larger reallocations do not take more than 3–6 months. On average once a month project team meetings are held. International communication was intense, on average every 3 months scientists attend congresses or workshops. The parameter of industrial performance, the operating profit margin, showed significantly more association with the different management control variables than size and is therefore presented in Table 5. The strength of all management control variables is somewhat lower in the companies with a low operating profit margin than in the companies with a high operating profit margin. Especially the assessed effectiveness of personnel control and the strength of international communication are significantly higher in the companies with a high operating profit margin. Concerning process control, however, the differences are very small. The R&D-staff in the companies with a relatively low operating profit margin are negative about the effectiveness of personnel and administrative control. In both cases the mean values of the answers lay clearly below 3 (see also Tables 6 and 7).

Table 7. Percentage explained variance of performance by size, and management control ($n = 10$)

	Patent number	Development length	Operating profit margin	Growth rate
Size				
R&D-expenditures (%)	44	52	43	24
Personnel control				
Effectiveness (%)	18	4	17	3
Resources control				
Adequacy	—	—	—	—
Administrative control (%)	—	—	11	—
Process control				
Planning (%)	—	2	—	—
Frequency (%)	14	—	—	—
Attendancy mix (%)	—	5	—	52
External control				
International communication (%)	—	—	10	—
Total (%)	76	63	81	79
R^2 model set (%)	79	59	80	79
R^2 test set (%)	53	85	82	75
F-value	6.44*	4.89*	5.19*	6.95*

*$P < 0.05$.
—, Variable does not associate significantly with performance.

Innovative and industrial performance

In Table 6 the Spearman Rank Correlations of size and management control with the variables of innovative and industrial performance, are presented.

The management control variables are hardly mutually correlated. The size of the R&D-expenditures, however, is significantly correlated with effectiveness of personnel control and adequacy of resources (data not shown). As was already shown in Table 4, the size of the R&D-expenditures is very significantly correlated with sales. It is also significantly correlated with both the innovative performance variables and the industrial performance measure operating profit margin. Dividing the R&D-expenditures in expenditures for discovery and for development hardly altered the correlations with number of patents and the development length, respectively. The R&D-expenditures spent on development, however, were significantly correlated with growth rate. The effectiveness of personnel control was significantly correlated with operating profit margin. Concerning resources control, the assessed adequacy of resources was positively associated with the R&D-expenditures. Further, the variables of resources control were not significantly correlated with any of the performance variables. Of the process control variables, frequency of research meetings was positively correlated with the number of patents and the attendancy mix with development length and growth rate. Concerning external control, international communication proved to be positively correlated with operating profit margin.

In Table 7 the multi-variate analyses of the size and management control variables with the different performance variables are presented. For all performance measures neural network models could be established, 60–80% of the variance could be explained by the size of the R&D-expenditures and the different management control variables. In all cases the test set fit was above 50% and the F-value was significant. As could be expected, also in the multi-variate models size contributed most, more than 50% of the explained variance. Only for growth rate was this percentage lower, namely 30% of the explained variance. Of the management control variables, the effectiveness of personnel control was the most important factor. All performance measures were associated with effectiveness of personnel control in the multi-variate models. The link of the other management control variables with the different performance measures was less clear. Administrative control and international communication were associated with operating profit margin, planning and attendancy mix with development length and frequency of research meetings with number of patents. Only attendancy mix was very significantly associated with growth rate; 70% of the explained variance of growth rate could be attributed to this variable.

DISCUSSION AND CONCLUSIONS

Despite the difficult environmental situation, in general the companies in the present study performed well, both in terms of absolute sales volume and in terms of operating profit margin. Probably partly forced by the economic situation, the companies grew vigorously in the past 5 years. In general, the R&D staff are positive about the management control situation in their company. However, if we concentrate on the low performers in terms of operating profit margin, the picture changes. In the less than average performing companies the judgement of the effectiveness of personnel and administrative control was clearly more negative and the intensity of international communication was clearly lower than in the more than average performers. As predicted, the operating profit margin was hardly correlated with process control. Interestingly, also in universities and institutes personnel, administrative and external control were found to correlate positively with the performance variables, reflecting their primary mission: (basic) research in universities and (applied) research in institutes [15]. Possibly, the operating profit margin not only provides the best reflection of the quality of the mission of pharmaceutical industry, but also for the sector of R&D. This is in accordance with the conclusion of van Engelen [10] for the marketing sector. However, it should be remembered that the operating profits of a company can depend on only one or two major products, or on a variety of products. Thus strict comparisons of profit performance with innovation may not be justified.

The predicted differences between discovery and development are also recovered in the results. The large task uncertainty in discovery

is assumed to be reflected in the positive correlation of frequency of research meetings with the number of patents, while in the relatively certain development phase a positive correlation was found of shorter development length with planning and attendancy mix. The very significant correlation of the industrial performance variable growth rate with the process control variable attendancy mix, however, was not expected. This high correlation probably originated from the association of this performance variable with the R&D-expenditures spent on development (see Table 6). Apparently the recent strategy to concentrate on development, in order to introduce drugs with small improvements on a regular basis [24], becomes more and more rewarding.

The size of the R&D-expenditures explains part of the variance in all the innovative and industrial performance variables. This could be expected for the 'size dependent' variables, such as the number of patents and the development length. More interesting is the observation that also 'size independent' variables, such as the innovative performance measure: number of patents relative to R&D-investment, and the industrial performance measures: operating profit margin and growth rate, are positively correlated with size. All these measures can be separately criticized on good grounds. Some critical considerations about the operating profit margin have already been mentioned. Furthermore, the observation that larger companies submit more patents may partly be due to a more prudent patent policy, the patent fees and translation costs constituting a smaller part of their R&D-budget. However, when all measures are combined they point in the same direction, that economies of scale can be observed in pharmaceutical innovation. Therefore it appears that the recent strategy of increasing concentration by mergers and joint ventures and strategic alliances, is also justifiable from the viewpoint of economics of scale in pharmaceutical innovation. In a previous paper of the authors this point is discussed in more detail [14].

The effectiveness of personnel control proves to be the most important management control factor dividing the more than average from the less than average performers. Although this conclusion should be interpreted with some caution, because the R&D staff in the better companies are likely to respond more positively than their colleagues in the less performing ones, this finding could be of special importance for research management. In the structured interviews the Research Directors indicated that, more than the material incentives, getting recognition for scientific efforts was an important driving force for R&D staff. In a previous paper of the authors the existence of a scientific ladder was already mentioned as one of the possible factors associated with success in pharmaceutical innovation [14]. Although eventual co-variation of size and management control was prevented by entering size as the first variable in the multi-variate analysis, it still can be argued that the causality may be the opposite way than we suggest for. The more profitable companies can afford to spend more on elaborate laboratory equipment, have more frequent international contacts and can have quicker procurement and appointment procedures. A cross-temporal analysis would be necessary to settle this point. However, even the smallest company in this study had an annual sales volume of ethical drugs of over $1.0 billion and an R&D-budget of around $200 million. So it may be expected that spending budgets will not be so much of a bottleneck for procurement, appointment and international travelling. Also the consistency of the results presented in this paper with previous studies [e.g. 1, 5, 18, 25, 26] leads us to prefer our interpretation.

It should be considered that the analyses in this paper are far from complete, because of the relatively small study population and the use of a cross-sectional design. Therefore the following characteristics of a successful pharmaceutical research laboratory are tentatively given: (1) much attention is paid to human resources management; (2) the administrative procedures are carried out quickly; (3) there is a flexible adjustment to changing situations; (4) much attention is paid to the building and maintaining of an (international) network; (5) the research process in the discovery phase is characterized by intensive 'in house' communication; (6) in the development phase much attention is paid to planning and communication with marketing and production. Of course these findings are not new. Numerous researchers have pointed to the importance of the human factor in research [e.g. 1, 18, 25]. Also the importance of flexible procedures and networking are stressed in many studies [e.g. 5, 26]. This is the first time, how-

ever, that they are found separately in different R&D-environments, indicating their crucial role in pharmaceutical innovation.

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REFERENCES

1. Allen Th (1977) *Managing the Flow of Technology.* MIT Press, Boston.
2. Anthony RN (1965) *Planning and Control Systems. A Framework for Analysis.* Harvard University, Boston.
3. Ballance R, Pogány J and Forstner H (1992) *The World's Pharmaceutical Industries: an International Perspective on Innovation, Competition and Policy.* UNIDO. Elgar, London.
4. Basberg B (1987) Patents and the measurement of technological change: a survey of the literature. *Res. Policy* **16,** 131–141.
5. Biemans WG (1992) *Managing Innovation within Networks.* Routledge, London.
6. Cohen MD and March JG (1974) *Leadership and Ambiguity: the American College President.* McGraw-Hill, New York.
7. Cronbach LJ (1970) *Essentials of Psychological Testing.* Harper & Row, New York.
8. DiMasi JA, Hansen RW, Grabowski HG and Lasagna L (1991) Cost of innovation in pharmaceutical industry. *J. Hlth Econ.* **10,** 107–142.
9. Duncan Reekie W and Weber MH (1979) *Profits, Politics and Drugs.* Macmillan, London.
10. van Engelen JML (1991) The role of information systems in marketing success. In *Business Strategy and Information Technology* (Edited by Sutherland E and Morieux Y), pp. 72–85. Routledge, London.
11. Fitzgerald JD (1992) Technology transfer issues in licensing pharmaceutical products. *R&D Mgmt* **22,** 199–208.
12. Hoptroff RG, Bramson MJ and Hall TJ (1991) Forecasting economic turning points with neural nets. *IEEE* **1,** 347–353.
13. de Leeuw ACJ (1979) The control paradigm is an aid for understanding and designing organizations. *Progr. Cybernet. Syst. Res.* **5,** 93–100.
14. Omta SWF, Bouter LM and van Engelen JML (1994) Managing industrial pharmaceutical innovation, a comparative study of management control and innovative effectiveness in European and Anglo-American companies. *R&D Mgmt.* In press.
15. Omta SWF and van Engelen JML (1993) A comparative study of management and organization of biomedical and pharmaceutical research in universities, research institutes and companies. *Proceedings 6th NOBO Research Meeting*, Rotterdam, pp. 97–105.
16. Pavitt K (1984) Sectoral patterns of technical change: towards a taxonomy and a theory. *Res. Policy* **13,** 343–373.
17. Pavitt K (1988) Uses and abuses of patent statistics. In *Handbook of Quantitative Studies of Science and Technology* (Edited by van Raan AFJ). Elsevier, Amsterdam.
18. Pelz D and Andrews FM (1976) *Scientists in Organizations. Productive Climates for Research and Development*, 2nd edn. Wiley, New York.
19. Pfeffer J and Salancik GR (1978) *The External Control of Organizations.* Harper & Row, New York.
20. Porter ME (1985) *Competitive Advantage, Creating and Sustaining Superior Performance.* Free Press, New York.
21. Redwood H (1987) *The Pharmaceutical Industry: Trends, Problems and Achievements.* Oldwick Press, Felixstowe.
22. Schwartzman D (1976) *Innovation in the Pharmaceutical Industry.* The Johns Hopkins University Press, Baltimore.
23. Taggart JH and Blaxter TJ (1992) Strategy in pharmaceutical R&D: a portfolio risk matrix. *R&D Mgmt* **22,** 241–254.
24. Taggart JH (1993) *The World Pharmaceutical Industry.* Routledge, London.
25. Twiss BC (1992) *Managing Technological Innovation.* Longman, London.
26. Volberda HW (1992) Organizational flexibility. Change and preservation. Ph.D. thesis, Wolters Noordhof, Groningen.

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