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Managing industrial pharmaceutical innovation, a comparative study

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Abstract

In this paper the results of a survey into the organizational and managerial factors influencing outcome in industrial pharmaceutical R&D are presented. The study consists of structured interviews with research directors of fourteen large and medium sized pharmaceutical companies, combined with quantitative and qualitative questionnaires. A systems theoretic approach has been used to postulate the relevant entities and the relations between them. The basic assumption has been that pharmaceutical R&D can be viewed upon as a conversion process in which information (knowledge) and R&D-input (chemical compounds) are converted into R&D-output (chemical compounds with information, namely about therapeutic efficacy and possible side-effects on patients), while control of this conversion process is exercised by R&D-throughput (scale, structure, management control, communication and coordination). The main conclusion is, that a number of managerial and organizational differences can be distinguished, in terms of speeding up product development and adjustment to market needs, dividing the outstanding from the average innovative companies. The analyses suggest that the motivation of scientific staff is one of the major success parameters. Also the perceived quality of coordination in terms of planning and evaluation is an important predictor of success in pharmaceutical R&D. The positive effect of coordination however, seems to be partly lowered by too frequent meetings. For three of the larger companies in the sample the data suggest that at R&D-expenditures of 12-15 percent of sales the companies has to put so much effort in the Development process, especially in large scale clinical trials, that the innovative potential could become at risk.

INTRODUCTION

Drug regulation and pricing have put strong pressure on the cost-benefit ratio of industrial pharmaceutical R&D. The increasing governmental regulatory demands regarding efficacy and safety of drugs have extended the R&D-process considerably. In the sixties in general the period between the finding of the 'lead' - a chemical compound with assumed therapeutic efficacy- and the introduction on the prescription drug market was about five years. Nowadays it takes more than ten years to do the pharmaceutical research, the toxicological and clinical testing needed, to bring a 'lead' to the market. The R&D-expenses have increased accordingly. Because a patent is submitted on the 'lead', while earnings start only ten years later, the effective patent protection time fell back from an average of thirteen years around 1965 to eight to ten years in the middle of the 1980s [Redwood, 1987]. 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, it is clear that increasing pressure has been put on pharmaceutical industry. In this paper the results will be presented of a study in fourteen large and medium sized companies in order to determine some important organizational and managerial factors influencing success, in terms of speeding up product development and better adjustment to market needs, in industrial pharmaceutical R&D.

In this paper at first the question will be answered whether or not 'economies of scale' occur in pharmaceutical R&D? Taggart [1992] refers to studies based upon figures of the 1950s in which 'diseconomies of scale' were established substantially below the largest R&D-effort. Later research
in the 1970s reported constant or increasing returns to R&D-scale. Taking into account the increased pressure on pharmaceutical R&D, it is even more interesting to establish the present-day situation. Further the results of a multivariate analysis, using the neural network method, will be discussed, providing a better understanding of the relative importance of the different factors influencing outcome. For the eight larger companies, which spend more than 375 million dollar on R&D in 1991, the annual figures of the pharma sales, R&D-expenditures and number of patents submitted, were collected for the period 1985 till 1991. On the basis of these data a time series analysis was executed. The results are also presented in this paper.

METHODS

In this research project a systems theoretic approach has been used to postulate the relevant entities and the relations between them. The basic assumption has been that pharmaceutical R&D can be viewed upon as a conversion process in which information (knowledge) and R&D-input (chemical compounds) are converted into R&D-output (chemical compounds with information, namely about therapeutic efficacy and possible side-effects on patients), while control of this conversion process is exercised by R&D-throughput (scale, structure, management control, communication and coordination). At first the R&D-process will be examined in more detail, then the variables used in this paper will be discussed.

The industrial pharmaceutical R&D-process

In figure 1 the different phases in the industrial pharmaceutical R&D-process are presented using the model of the double unit cell [van Engelen 1989], a combination of a control situation and a value chain as described by Porter [1985].

Figure 1

In the discovery phase the research concepts are elaborated and 5 to 10,000 chemical compounds are synthesized on a laboratory scale and screened for therapeutic activity in a biological or animal model. This phase has an average duration of one to two years, but sometimes it can take many years. The phase ends with the discovery of the 'lead'. The pharmacological development phase starts with further pharmacological screening and characterization of the active substance in 20 to 50 compounds. Pharmacokinetical research into degradation speed and acute and subacute toxicity along with mutagenicity tests are done. Then follows the synthesis of the active substance at the technical level of the 10 to 15 compounds which go further in clinical testing. Patenting is carried out in this phase, which has an average duration of 2 to 3 years. In the clinical research 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 a total of 200 to 400 patients with approximately 5 compounds. In phase III the controlled trials continue with only one compound. The double blind randomized clinical trials are executed among a great number of patients in (academic) hospitals to demonstrate therapeutic efficacy and to establish contra-indications, side effects with a relatively high incidence and optimal dosage. In recent years the larger firms work more and more with parallel development. So, at the same time that the clinical trials are executed the long scale biological testing for chronic and subchronic toxicity continues and the up-scaling for production of the
drug starts. This phase takes 3 to 4 years and ends with the presentation of the relevant pharmacological and toxicological data and the results of the clinical trials to the authorities. The registration phase involves the control of the test dossiers by the authorities for approval of the drug on the market and takes approximately 2 years. 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. After launch the post marketing surveillance starts to trace side effects of drugs with low and moderate incidence which were not discovered during clinical testing [Fitzgerald 1992, Taggart 1992 and 1993 and this study].

Operationalization of variables

In table 1 an outline is given of the operationalization of the predictor (through puts) and the criterion variables (output).

Table 1

For the assessment of the variables personnel control and coordination Likert-scales are used. The scales for the assessment of research management are based upon the questionnaires used in the 'Philips Natlab', the others were newly developed. After the data collection the internal consistency of the scales was calculated. Cronbach's $\alpha$ being sufficiently high (> .75) to warrant confidence in the consistency [Swanborn, 1987]. The multivariate analyses are done with the neural network method. It utilizes an intricate fitting method, which uses the iterative steepest descent technique to approach the minimum error solution. It is developed for usage in cases in which other numerical modelling methods perform poorly, due to insufficient or singular data [Hoptroff, 1991]. The method is based upon the division of the data in a model set and an independent test set. In this study the data of two companies were used for the independent test set. Changing model and test set did not influence the outcome of the calculations significantly. The parameters measured at interval and ordinal level are analyzed by use of non-parametric ranking methods.

Data collection

In 1992 the research laboratories of the ten largest Anglo-american and 'continental' pharmaceutical companies (average sales per company in 1991: 4.5 billion dollar) were approached for this study. In addition ten research laboratories of medium sized European companies (average sales: 2 billion dollar) were selected. The study consists of structured interviews with the Directors of the Research and/or Development and Clinical Research Divisions (mostly Members of the Board), combined with quantitative and qualitative questionnaires, regarding personnel, budget and research policy. Seven large and seven medium sized companies agreed upon participation. Two large and two medium sized companies only supplied general information regarding sales, R&D-staff and research management, while in ten companies also specific information regarding structure, management control and communication could be obtained. In total 22 interviews were held and 38 questionnaires returned (response rate of 65%). The patent analysis revealed the representativity of the companies in the sample. Twenty-five percent of the pharmaceutical patents submitted with a European priority from 1985 till 1991 originated from one of the companies in this study.
RESULTS

Economies of scale

It can be expected that the total R&D-expenditures and the pharma sales in a given year are more or less related, because the annual R&D-budget is at least partly based on the volume of sales in the previous year. In order to get an idea about this relation the total R&D-expenditures in 1991 are compared with the pharma sales in the same year of the companies under study. As shown in figure 2 a S-curve emerges ($r^2 = .94^{**}$, $N=14$). Apparently larger pharma sales are only partly converted into higher R&D-expenditures. The curve rises until the pharma-sales reach approximately 4 billion dollar. After that the R&D-expenditures rise only moderately, from about 700 to a maximum of 875 million dollar, while the pharma-sales rise to approximately 7 billion dollar.

Figure 2 Sales of pharmaceutical products and the total R&D-expenditures per company in 1991 (both in million US dollar)

Sources: Annual reports of the pharmaceutical companies at issue and Taggart (1993)

In order to examine the efficiency of the R&D-process in terms of absolute R&D-output in relation to scale, the average annual R&D expenditures of 1988 till 1991 are plotted against the average number of pharmaceutical patents submitted in the same period. As shown in figure 3 an exponential equation emerges ($r^2 = .87^{**}$, $N=14$) starting at around 180 million dollar, going up to around 700 million dollar, while the annual number of patents rises from 10 to 175.

Figure 3 Average number of patents for new chemical compounds submitted world wide versus the average annual R&D expenditures (in million US dollar) per company from 1988 till 1991

Sources: World Patent Index and Taggart (1993)

In order to examine whether a difference in R&D-efficiency could be established between larger and smaller companies a t-test was done. The larger companies (sales volume above 3 billion US dollar, $N=7$) in this study not only submitted more patents in the absolute sense than the smaller companies (less than 2.5 billion US dollar), but also related to their R&D-investment (15 versus 9 patents per 100 million dollar R&D-expenditures). Also the number of therapeutic areas in which the different pharmaceutical companies are doing research increased with the size of the R&D-expenditures, from 5-6 therapeutic areas in the smaller companies till 8-9 in the larger ones.

Figure 4 Length of the R&D-process (in years) versus the number of R&D-staff per company in 1991

Sources: see figure 2

The length of the R&D-process is one of the most important R&D-parameters.

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$a$ 2-tailed significance $^{***} p < .001$, $^{**} p < .01$, $^* p < .05$
influencing the profitability of a pharmaceutical company. The better a company succeeds in reducing the length of the R&D-process, the more successful it will be. Therefore in figure 4 the length of the R&D-process is plotted against the total number of R&D-staff world wide. There proves to be a significant correlation, the more scientific and analytical personnel is appointed, the shorter the duration of the R&D-process ($r^2=.75$, $N=11$). At first the length of the R&D-process is dropping fast from 15-16 years at around 1500 R&D-staff members to 11-12 years at 3000 staff members, then the curve approaches to a R&D-length of around 10 years at around 5000 R&D-staff members.

Multivariate analyses

In order to get a better understanding of the association of the different managerial and organizational factors in relation to the world wide sales of pharmaceutical products, in table 2 the results of the modelling sessions by means of the neural network are presented. At first a modelling session was executed including all predictor variables. The parameter which contributed least was omitted. After the first session resources control, after the second session structure and after the third external communication, was omitted. The results of the fourth modelling session are presented in table 2. The volume of the R&D-expenditures proves to have the largest impact on pharma sales, followed by the perceived quality of personnel control (human resource management), R&D-process communication and coordination.

Table 2

In table 2 the results of the modelling session without R&D-expenditures are presented between brackets. The model and test set fit being around 15% and 30% lower than with the R&D-expenditures included in the model. The t-value of personnel control rises, while those of R&D-process communication and perceived quality of coordination stay relatively constant. Because of the ordinal type of most of the scales used in this study, the 'strength of the association' of the different R&D-parameters with sales has no uniform interpretation. Therefore only the direction of the association is discussed here. If the direction of an association is positive it may indicate that a company which pays less attention to that factor may consider intensifying it. If the relationship is negative, it may indicate an overexposition in at least part of the companies studied. The association of the R&D-expenditures, personnel control and coordination with pharma sales is positive. The association with structure (percentage of research in the total R&D-process), resources control and communication is negative.

For the eight larger companies in the sample, which spend 375 million dollar or more on R&D in 1991, the association of the R&D-expenditures as percentage of pharma sales and the number of patents submitted in the period of 1985 till 1991, was calculated. For four companies a model could be drawn up. In three cases both the model and the test set fit were above 85%. In one case the test set fit was very good (above 95%), but the model fit was significantly lower (around 60%). For three companies the data indicate an optimum of the number of patents submitted at a R&D-investment of 12-15 percent of pharma sales. In the fourth company the number of patents goes up exponential with higher R&D-investment. The model stops just below 13 %, so a deflection at a higher percentage is possible.
DISCUSSION AND CONCLUSIONS

Economies of scale

There proves to be a relation between the R&D expenditures and the sales of pharmaceutical products of the companies in this study, the larger companies spending more than the smaller ones. This was expected because the annual R&D-budget is partly based on the sales in the previous year. The increase of the R&D-expenditures with the size of the company goes hand in hand with the increase in the number of patents submitted world wide. However, if we focus on the R&D-expenditures as a percentage of sales, the larger firms spend relatively less than the smaller ones. Also the number of therapeutic areas is larger and the duration of the R&D-process is shorter in the larger companies. Taking into account that also the relative investment per patent is lower in the larger companies, empirical confirmation has been found for the theoretical supposition that 'economies of scale' would appear in pharmaceutical R&D.

The shorter duration of the R&D-process in the larger companies can of course mainly be attributed to the greater size of the R&D-staff and budget. In the structured interviews some Research Directors gave as a further explanation, that larger companies have more possibilities for parallel development. It is relatively easy to shift R&D-staff between projects. According to the model developed by Grabowski and Vernon [1987] each year an innovative drug can be launched earlier, counts for three years of additional patent protection. For, as a drug has been longer on the market, the chance increases that a new innovative drug will push it from the market. Or, as a research director claimed in one of the structured interviews: 'Each day a potential best selling drug will reach the market earlier, yields 200,000 dollar for the company'. For smaller companies it will become more and more difficult to meet the strict requirements of the authorities regarding 'quality control' of the R&D-process. The recent integration process in pharmaceutical industry, expressed by a number of merges, strategic alliances and joint ventures, joint research and joint marketing [for instance Elfferich, 1992] appears to be justifiable, also from the viewpoint of the efficiency of the R&D-process.

The curve in figure 3, linking the R&D-expenditures and the number of patents submitted, starts at around 180 million US dollar, which could suggest that such an amount is minimally needed to keep up the whole pharmaceutical R&D-process. This amount corresponds with the bottom line of the following, very rough calculation based upon the information of the Research Directors. For the Research and Development of a new drug 200 to 300 million dollar is needed. Roughly speaking, one in every four drugs is successful on the prescription drug market and once in every four years a pharmaceutical company develops a successful drug. Taking into account that the successful drugs count for the profitability of a pharmaceutical company, it can be calculated that a minimum annual R&D-expenditure of 200 million dollar is needed to keep up the innovative potential (200 million dollar per new drug times four to get a successful drug divided by four years). A further qualitative judgement of the data suggests that a minimum investment of 50-60 million dollar a year is needed to keep up in-house innovative research. Only one division of a conglomerate spends less on Research, the Research Director indicating that discovery was partly done in another Division and incrementing was the main task. The data suggest that for Development the threshold lies more than twice as high than for
Research, namely at about 110-125 million dollars a year. Three smaller companies reporting expenditures of around this size. However, further research is needed to confirm these data systematically.

Multivariate analyses

The R&D-expenditures appear to explain most of the variance in pharma sales. From the results in table 2 can be seen that especially personnel control and R&D-process communication and, although to a lesser extent, coordination are the most important organizational and managerial parameters influencing pharma sales. A relatively flat organization like a R&D-laboratory however, provides less possibilities for promotion in terms of responsibility. Some Research Directors suggested in the structured interviews that in such an environment, remuneration by means of scientific promotion, incentives like shares or options for extra-ordinary achievements and publications as one of the aspects in salary determination, could be of great importance to keep scientific personnel motivated.

The pharmaceutical R&D-process, executed in different laboratories, often situated in different countries, needs strong coordination, in order to connect the different phases in the R&D-process as smooth as possible. Therefore it is not surprising that coordination in terms of perceived quality of planning and evaluation has a positive impact on pharma sales. On the other hand the negative association of the factor R&D-process communication with sales indicates that, at least in part of the companies, the communication seems to be somewhat exaggerated. Indeed some of the Research Directors reported in the structured interviews that time was lost with too frequent meetings. As one of the Research Directors stated: 'It is not quite clear whether the project teams have speeded up the R&D-process. Indeed, the communication between the different phases in the R&D-process has been improved and also with marketing and production, but the number of meetings has increased accordingly.'

The results show that the association of structure with pharma sales is minimal. If the company spends a higher percentage of the R&D-budget on Research the consequences seem to be slightly negative. Inverted it means that a weak positive correlation was found with the percentage of the R&D-budget spend on preclinical and clinical Development. But the association is so small that it does not supply a basis for management decisions. Resources control, reflecting the flexibility in the allocation of resources, is not predicted by the model as a positive factor influencing pharma sales. Also the strength of the association with pharma sales is very limited. This is surprising, because flexibility is often mentioned as a major factor in rising productivity. Apart from the multi-purpose and therefore often indistinct use of the term flexibility (see for instance Volberda, 1992), the reason for this finding can be that flexibility may stand on bad terms with human resource management. The positive effects of flexibility might be overruled by the negative effects on the motivation of scientific personnel. Especially in research it can be very demotivating to be drawn away from a topic. As one of the Research Directors stated: 'Most pharmaceutical companies concentrate their efforts on a few therapeutic areas. Of course this is inevitable, because of the huge investment needed for the preclinical and clinical development of a new drug. But the freedom to give the scientists in basic research the possibility to, at least partly, concentrate on own ideas, has proven to lead to several new products, which otherwise never would have been invented.'
An indication that this is the case could be, that univariate analysis has pointed out that personnel and resources control are not correlated in the study sample.

For three of the larger companies an optimum curve arises when a time series analysis is made of the relative annual R&D-investment and the number of patents submitted in the same period. For a fourth company an exponential curve arises. For these companies the volume of sales was constantly rising in the period under study. Also the R&D-expenditures were rising in the absolute sense, although sometimes faster and sometimes slower than the volume of the pharma sales. As was mentioned in a former article of the authors (Omta et al 1993), the number of patents submitted by the larger companies stayed constant for most companies or was only slightly rising in the period under study. This in clear contrast with the smaller companies which submitted significantly more patents at the end of the period. This is probably due to a further concentration of efforts to a limited number of therapeutic areas, as was often mentioned in the structured interviews. Also a change in the patent strategy of the larger companies could be involved, in that sense that companies wait longer before patents are submitted in order to reduce costs and to shorten the period between patent submittance and market launch, in order to prolong the effective patent protection period.

The modelling parameter 'number of patents' only concerns the discovery part, the first two to three years of the R&D-process. Two third to three quarter of the R&D-expenditures however, is spent on the Development-process. The Research Directors indicated that in recent years especially the costs of the large scale clinical trials went up rapidly. Research and Development are coupled in time, in that sense that research efforts leading to potential interesting patents will risen the Development costs in the succeeding years. Therefore the results presented above can probably be best explained by the consideration that for the largest companies in the sample holds, that the number of potential interesting patents that is generated at a R&D-expenditures to sales ratio of around 13 percent is so large that it requires an investment in the Development-process to such an extend, that Discovery and by that the innovative potential, could become at risk.

MANAGEMENT IMPACT

Provisionally the following practical implications for R&D-management can be abstracted from the results presented in this paper.

1. The data suggest that the motivation of scientific staff is one of the major success parameters, in terms of speeding up product development and adjustment to market needs, in industrial pharmaceutical R&D. Because in a flat organization like a R&D-laboratory, the possibilities for promotion in terms of responsibility are limited, remuneration in terms of promotion on the bases of scientific merits and other incentives for scientific staff could be considered.

2. The necessary further concentration on fewer therapeutic areas could lower the innovative potential. Therefore it might be considered to give scientific staff in basic research the opportunity to spend part of their time on promising research in areas of their own choice.

3. The data suggest that tight planning and evaluation are important success parameters in industrial pharmaceutical R&D. Indeed the Development process deserves strong coordination. However, the positive effect seems to
be at least partly lowered by too frequent meetings.

4. The data suggest that a minimum annual R&D-expenditure of around 200 million dollar is needed to keep up innovative Research and Development. Above around 750 million dollar 'economies of scale' seem to appear in pharmaceutical R&D.

5. For three of the larger companies in the sample the data suggest that above R&D-expenditures of 12-15 percent of sales the companies has to put so much effort in the Development process, especially in large scale clinical trials, that Discovery and by that the innovative potential, could become at risk.

It should be considered that the picture arising from this study is far from complete, given the inherent limitations of a survey and the limited number of companies analyzed. However, the study supplies interesting management concepts which could be used as starting points for in depth studies in individual companies.

ACKNOWLEDGEMENT

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P₀ = the finding of the 'lead', chemical compound with assumed therapeutic effect; P₁ = 'lead' with pharmacokinetic and toxicological testing reports, start of clinical testing, first on volunteers, later on patients; P₂ = submittance of registration dossiers to the authorities; P₃ = registration and launch; P₄ = post marketing surveillance (post launch control on side effects of drugs).

G = goal setting; A = accounting; C = communication; R = research management; I = input; T = transformation; O = output.
Table 1: List of predictor and criterion variables and their operationalization

<table>
<thead>
<tr>
<th>Predictor variables</th>
<th>Operationalization</th>
</tr>
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<tbody>
<tr>
<td><strong>Scale</strong></td>
<td></td>
</tr>
<tr>
<td>Structure</td>
<td></td>
</tr>
<tr>
<td>Personnel control</td>
<td>World wide R&amp;D-staff (scientific and technical and analytical support staff 1991 in full time equivalents, fte’s)</td>
</tr>
<tr>
<td>Resources control</td>
<td>Percentage research in the total R&amp;D-process</td>
</tr>
<tr>
<td>Communication</td>
<td>Subjective assessment of the efficacy of staffing policy, effects of reorganization and career planning (higher values indicate a more positive perception)</td>
</tr>
<tr>
<td>R&amp;D-process communication</td>
<td>Rapidity of resource allocation procedures (in months)</td>
</tr>
<tr>
<td>External communication</td>
<td>Frequency of formal contacts with staff members of marketing, production and the strategy department (times per month)</td>
</tr>
<tr>
<td>Coordination</td>
<td>Frequency of contacts with colleagues of other companies, scientists and physicians on congresses (times per year)</td>
</tr>
<tr>
<td></td>
<td>Subjective assessment of the importance of short and middle range planning and the intensity of evaluation by the main office (higher values indicate a more positive perception)</td>
</tr>
<tr>
<td><strong>Criterion variables</strong></td>
<td></td>
</tr>
<tr>
<td>Pharma sales</td>
<td>World wide pharmaceutical sales in billion US dollar 1991</td>
</tr>
<tr>
<td>R&amp;D-output</td>
<td>Number of patents of synthetic chemical compound with assumed therapeutic efficacy submitted world wide from 1985 till 1991</td>
</tr>
<tr>
<td></td>
<td>Length of the R&amp;D-process, the average time span between patenting and the launch on the prescription drug market (in years)</td>
</tr>
</tbody>
</table>

1 Likert scales
WORLD WIDE SALES OF PHARMACEUTICAL PRODUCTS AND TOTAL R&D-EXPENDITURES
PATENTS FOR NEW CHEMICAL COMPOUNDS VERSUS THE R&D EXPENDITURES

Number of patents

R&D-expenditures
LENGTH OF THE R&D-PROCESS (years) VERSUS THE NUMBER OF R&D-STAFF

LENGTH of R&D-process

R&D-staff
Table 2 The association of the different organizational and managerial parameters with pharma sales (t-values'), between brackets the associations with pharma sales if scale is excluded from the model (N = 10 companies).

<table>
<thead>
<tr>
<th>Predictor variables</th>
<th>Association with pharma sales</th>
<th>t-value</th>
<th>direction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scale (R&amp;D-exp.)</td>
<td></td>
<td>15-22</td>
<td>positive</td>
</tr>
<tr>
<td>Structure</td>
<td></td>
<td>*</td>
<td>negative</td>
</tr>
<tr>
<td>Management control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personnel control</td>
<td></td>
<td>8-12 (13-14)</td>
<td>positive</td>
</tr>
<tr>
<td>Resources control</td>
<td></td>
<td>*</td>
<td>negative</td>
</tr>
<tr>
<td>Communication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R&amp;D-process comm.</td>
<td></td>
<td>7-9 (6-9)</td>
<td>negative</td>
</tr>
<tr>
<td>External comm.</td>
<td></td>
<td>*</td>
<td>negative</td>
</tr>
<tr>
<td>Coordination</td>
<td></td>
<td>5-6 (5-8)</td>
<td>negative</td>
</tr>
</tbody>
</table>

* parameter omitted because of low association with pharma sales (t-value below 2.5).

1 t-value = mean partial derivative of criterion variable w.r.t. predictor variable x standard deviation of predictor variable / standard deviation of residual error.

The range of the t-values presented in table 2 is based upon the results of five runs of the neural network, using different model and test sets. The range of the R² of the different runs was as follows. If scale is included in the model: R² model set = 85-92% and R² test set = 91-99%. One run provided less reliable results (R² model set = 69% and R² test set = 84%). The t-values were comparably lower, t=5 for R&D-exp., t=4 for personnel control and t=2 for R&D-process communication and coordination. If scale is excluded from the model the model and test set fits are lower: R² model set = 73-79% and R² test set = 61-63%, one run provided a test set fit of 89%.