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Drug Life Cycles in the Pharmaceutical Industry

Empirical Detection and Consequences for R&D Profitability

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Abstract

Reliable forecasts of brand sales are fundamental to a value based evaluation of R&D projects in the pharmaceutical industry. The paper describes a cross sectional and time series analysis of sales data over one decade in four major segments of the market for cardiovascular drugs. The seven leading countries except for Japan are covered in the study. We estimate over 200 product life cycles using a very flexible mathematical model to account for a variety of PLC shapes. Life cycles are then clustered on the basis of estimated regression coefficients. As a result this analysis leads to the detection of an international product life cycle classification. This typology gives useful insight into the success and market determinants in the segments under investigation. Moreover, it turns out that the order of entry is not only crucial to achieve a certain market share level but also to the shape of the drug life cycle. The paper provides first findings on this subject. Consequences for the economic evaluation of innovative products are drawn according to their prototypical life cycle. In this context we conduct a simulation study to show the impact of the PLC shape on the net present value. Management implications on effective R&D strategies in the light of cost containment efforts are shown at the end.

1 Introduction

The total costs of developing and introducing a New Chemical Entity (NCE) into a market is by now reported to amount up to $ 500 million. Even if this figure represents only the top of pharmaceutical R&D product spending the estimates are still high with around $ 200 to 250 million. Taking into account that reported R&D expenses also cover the costs of abandoned projects, new products require considerable revenues during their effective pay back period of 15 to 20 years.

In the past product managers were able to set prices at a level that would ensure the repayment of the direct as well as the indirect product investment. With regard to worldwide governmental cost containment efforts this is no longer true. Companies will have to change their evaluation rules of R&D projects in order to achieve an efficient position in the future innovation process. This change essentially focuses on value based computation techniques. Reliable forecasts of future cash flow streams are fundamental to these techniques.

Hence, estimating the sales and cash flow potential of a new product is a major problem. The well-recognized product life cycle model offers a useful framework for analyzing the development of sales and turnover. While every marketing manager should be familiar with the heuristic power of product life cycle theory, little attention is given to the empirical investigation of today's global pharmaceutical markets.

The PLC describes and characterizes "the phases of development of a product from its introduction in the market until its withdrawal" (Polli 1968, S. 17). Empirical proof of PLCs has been given in a whole series of studies for many different branches and product categories (e.g. Easingwood 1988; Midgley 1981; Harrell/Taylor 1981; Thorelli/Burnett 1981; de Kluyver 1977; Polli/Cook 1969; Polli 1968; Brockhoff 1967; Cox 1967). The best-known of these empirical studies on PLCs of pharmaceuticals was carried out in the United States a while ago (Cox 1967). *Cox* studied the sales trends of 258 ethical drugs that had been launched on the U.S. market between 1955 and 1959. He extracted six PLC types which, except for one type, he reduced after further moni-

toring in subsequent years to the form of a fourth-degree polynomial as "the basic curve form of the ethical drug industry" (Cox 1967, p. 383). However, *Cox* also classified three types of linear sales trends as product life cycles. This is not in line with our model and may at best be taken as an indication for identifying the PLC stage. In addition, we may assume that it would be of limited use if we applied empirical findings of more than 30 years ago to the totally changed situation of today's pharmaceutical markets.

2 Detection of a Life Cycle Typology for Pharmaceuticals

2.1 Research Design

The following broad-based empirical study covers most of the global market for cardiovascular drugs (CV drugs) in the period from 1983 to 1993. It shall make a contribution towards overcoming our lack of knowledge about the properties of pharmaceutical PLCs.

In a first study, the PLCs at hand are estimated using a regression approach. We resort to a theoretical PLC model here but are not interested in the generalizability and validity of the regression model or its estimated coefficients. Ordinary least squares is exclusively used as a method to determine an unbiased mathematical representation of the underlying empirical PLCs; so it is only the reliability of the measurement in terms of its coefficient of determination that is relevant for our further studies.

The PLCs thus determined are examined for possible similarities and differences in study #2. We hope to derive a typology with which we can categorize PLCs of cardiovascular drugs worldwide. As we have no information about meaningful relations between the products that would suggest a typology and cannot infer such information, we have to use explorative methods such as cluster analysis. This technique is to produce a valid and robust PLC typology.

If we succeed in detecting a consistent PLC structure in the CV segment, the PLC types identified and empirically corroborated can provide important product management information for the anticipatory assessment of new products. However, a prediction of the

PLC type of the new product is a major prerequisite. The time of maximum sales and thus the length of the growth phase are of particular concern in this context. This period is important for pharmaceutical companies doing research as it makes the greatest contribution to the payback of R&D expenses. In study #3, a regression approach is applied to check whether the time of maximum sales has changed systematically in the PLC of a NCE over the last years.

The result that late mover NCEs have very short growth phases has enormous consequences for strategic product and program planning. For this purpose we identify their typical life cycle and draw conclusions about their long-term profitability through a simulation study in chapter 3. Managerial implications are shown at the end (chapter 4).

2.2 Data

Following the customary classification worked out by IMS, the leading international market research agency, we have examined CV drugs in the following product classes:

- antiarrhythmics,
- beta blockers,
- calcium channel blockers, and
- ACE inhibitors.

The products examined were launched in at least one of the five big European markets and/or the United States in the period from 1982-1990. The six countries covered by our study represent about two thirds of the world's pharmaceutical market. By turnover, the cardiovascular market segment is the most important one of the global drug market, and the above four product classes stand out in this segment because of the size of their turnover. The reference quantity for the PLC of the drugs is their sale expressed in standard units. These standard units are the respective smallest counting units for a drug. While solid drugs are counted by the piece, liquid quantities are converted so as to be comparable to solid drugs. Time is measured in years.

We needed data ranging into the downward phase of the life cycle to get a sufficiently precise idea of the individual course of a PLC. To ensure this, we stipulated that sales in the last year under review should have declined to at least 70% of the peak value, or entered a new life cycle (e.g. through a relaunch). The sales trends examined were standardized based on a uniform maximum value of 25,000 counting units to ensure their comparability. Furthermore, we set the condition that the drugs had to have reached a minimum market share of at least 0.5% in their respective NCE class during their life cycle, a threshold value that was to ensure that the drugs examined had at least some market relevance. Finally we adjusted the data by excluding re-importers (a non-productive trade), which had an effect for Germany and the U.K. only. 212 life cycles were included in our analysis.

2.3 Study 1: Product Life Cycle Estimation

In accordance with our model of the PLC concept, we assume that there is a reconstructible relation between the time t and the sale y of a product. However, we do not intend to make an empirical contribution to the discussion about the general validity of the PLC concept by our estimating life cycles (for more information, see Brockhoff 1967; Polli/Cook 1969; Hoffmann 1972; Pfeiffer/ Bischof 1974; Dhalla/Yuspeh 1977; Day 1981). The regression results obtained for each unit of study are exclusively meant for descriptive purposes and for generating new variables which provide the basis for the cluster analysis at the next step of our study. What we are interested in here is just the accuracy of the PLC measurements. The coefficient of determination R^2 is the classical goodness of fit measure to assess the overall reliability of regression-analytical measurement approaches. The ordinary least squares method we use for estimation can sometimes produce inefficient or unstable results due to autocorrelation of the residuals and collinearity of the predictor variables, especially in the case of time series data. Such distortions can be corrected by more powerful algorithms applying a generalized least squares approach or the maximum likelihood principle which are based on less restrictive assumptions. Quite frequently, however, the results deviate only marginally from the OLS estimations. So we will continue to use the OLS method, not least for the sake

of research economy, as long as it produces results with a high accuracy of measurement, i.e. an R-square value greater than 0.8.[1]

It is important for estimating the PLC curves to formulate a useful mathematical model that is sufficiently flexible to adapt to the manifold empirical curves. Several proposals for selecting a suitable growth function have been made (Cox 1967, p. 382f, Brockhoff 1974, pp. 1764-1766, de Kluyver 1977, p. 24). The mathematically most flexible approach was introduced by *de Kluyver* and can be expressed as follows:

$$(1) \qquad y_i(t) = a_i t^{b_i} Exp\left[-\left(c_i t + d_i t^2 + f_i t^3\right)\right] Exp\left[u_i(t)\right], \qquad \text{for } t \geq 0$$

y_i - sales of product i
a_i, b_i, c_i, d_i, f_i - regression coefficients
u_{it} - error term

After a log transformation, (1) becomes accessible for an estimation by ordinary least squares.

Most of the 212 estimated PLC curves match the empirical trends extremely well. The predictor variable 'time' can explain 95% of the sale variance for roughly 4/5 of the population. This provides an adequate basis for the subsequent classification of the CV segments in terms of typical PLCs that were examined.

2.4 Study 2: Cluster Analysis

We cannot imagine as yet how the mass of estimated PLC curves can be characterized concisely or which exemplary trend curves best reflect the structure of the population. The pattern of relations among the objects can only be disclosed using an adequate multivariate technique. Cluster analysis is the proven method for such issues.

[1] All subsequent analyses are therefore based on the estimated life cycle curves with $R^2 \geq 0.8$. We also reduced the total sample by 15 cases that were below 0.9 but the results remained the same.

2.4.1 Clustering Method

The relevant cluster variables for the research design chosen are the estimated regression coefficients, i.e. the parameters of the sales-over-time function. It is widely known that the results of a cluster analysis quite frequently show a sensitive response to the decisions taken in the process of analysis. Several synopses are now available which discuss the application and problems of cluster analysis (e.g. Sharma 1996; Backhaus et al. 1996; Hair et al. 1992; Punj/Stewart 1983). The "correct" practice of carrying out a cluster analysis has not yet been finally settled, but recently criteria were developed based on empirical comparisons and extensive simulation studies that can make its use more robust. These studies are discussed in *Punj* and *Stewart* (1983) who also make recommendations for a modus operandi.

First of all, the selection of the cluster variables and the similarity measure seems to be of some importance (Green/Rao 1969; Morrison 1967). Theoretical considerations alone suggest that the choice of the relevant cluster variables can greatly influence the results as these variables provide the explanation for the existence of groups in the set of data. Therefore, their selection should always be based on a conclusive derivation of their discriminatory potential. The estimated parameters of the growth function from (1) represent cluster variables which give a directly mathematical description of the curve of a PLC.

As regards the similarity measure, *Punj* and *Stewart* (1983) draw the conclusion that its selection has little or no distorting effect on the result, especially when a nonhierarchical clustering method is used. We chose Euclidean distance as the probably most common metric measure of similarity. Additionally, *Kaufmann* and *Pape* (1984) require scale invariance for metric measures of distance. This requirement is met by the parameters of our growth function.

The selection of the data fusion algorithm has by far the greatest potential effect on the final result of clustering (Sharma 1996; Hair et al. 1992; Punj/Stewart 1983; Milligan 1980). Hierarchical methods have the advantage that they do not require given initial

cluster seeds. In addition, the dendrogram as a structural reflection of the agglomeration process helps to identify the clusters and any outlier objects. But this is paired with the great disadvantage that once an element has been assigned with a cluster, such assignment cannot be reversed during the hierarchical clustering process. This may have a fatal impact on the derivation of an optimum solution.

Hierarchical cluster analysis is characterized by a great variety of methods which, however, do not all comprise similar desirable properties for grouping. The average linkage method and the minimum variance method are considered reliable fusion algorithms, the latter being particularly associated with Ward's method (Punj/Stewart 1983; Milligan 1980). But if compared to nonhierarchical algorithms these methods are much more susceptible to outliers, faulty specification of variables or other errors (Milligan 1980). Nonhierarchical procedures such as the k-means algorithm will only provide superior results if no random cluster seed points are set. A combination of hierarchical and nonhierarchical methods is proposed as a way out of this dilemma so that these two types of methods are not considered competing alternatives but complementary methods (e.g. Punj/Stewart 1983; Sharma 1996).

In the further course of our study, we therefore decided to use a multistep approach that first involves two hierarchical methods. The single linkage algorithm has the specific property of summarizing cases with very great distances in small groups, so that in a first step any outlier objects were to be identified. We could exclude 14 outliers from the further analysis. The subsequent agglomeration using Ward's method first pointed to a 3-6 cluster solution. In particular, these clusters were identified by the elbow criterion. Average linkage and Complete linkage clustering methods partly resulted in modified object assignments but also pointed to a solution range of 3 to 6 clusters.

2.4.2 Results

A further problem of cluster analysis is to determine the optimum number of groups. *Milligan* and *Cooper* (1985) compared numerous approaches that were meant to support the decision but could not identify a method that proved optimal across studies. Despite the varied and sometimes sophisticated procedures to compare various cluster solutions,

face validity appears to be an outstanding choice criterion. In most cluster analyses used in marketing, it is difficult to compare group characteristics due to their multivariateness. The level of complexity simply goes beyond our imagination. In our case, the parameters of a mathematical function with only one independent variable represent the object properties and facilitate the graphical representation of PLCs in a two-dimensional space. Thus a visual inspection of the discriminating power of the cluster solutions based on the PLC types identified can easily be carried out.

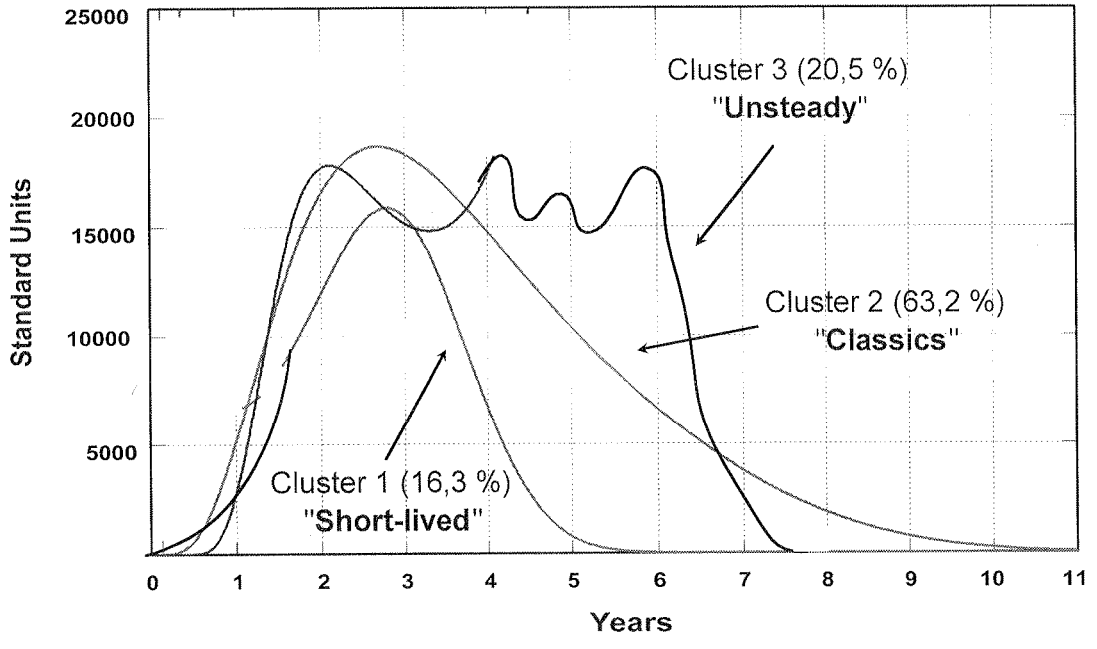


Figure 1: Schematic PLC Shapes for the Three Cluster Solution

We discussed our results with managers working in the pharmaceutical industry. As a result we found that the solutions with four, five, or six clusters included additional PLC types that were only marginally different from the others. Thus we decided to divide life cycles into three clusters (Figure 1) which were finally calculated using the nonhierarchical k-means method and specifying the initial cluster seeds obtained from applying Ward's method before. Table 1 shows the means and standard deviations resulting from the grouping.

Table 1: Mean Values and Standard Deviations of the Three Cluster Solution

CLUSTER		A	B	C	D	F
1 (n = 30)	Mean	3.6109	-4.3188	-5.9695	.7372	1.645E-02
	Standard Deviation	4.1158	3.5200	4.3012	1.2806	.2649
2 (n = 117)	Mean	11.1453	4.8307	2.7856	-.2309	1.217E-02
	Standard Deviation	2.1913	3.3429	2.4040	.6081	8.796E-02
3 (n = 38)	Mean	19.9482	15.7109	13.5865	-1.6592	6.499E-02
	Standard Deviation	3.8621	5.8048	5.0025	1.4301	.2214
Total (N = 185)	Mean	11.7316	5.5819	3.5844	-.3673	2.371E-02
	Standard Deviation	5.7974	7.3009	6.8949	1.2076	.1620

2.4.3 Validation

After a face validity test, the variables selected (regression coefficients) prove to be useful segmentation criteria in accordance with which the heterogeneous population can be divided into more homogeneous groups. A number of methods and goodness of fit measures is available for the statistical evaluation of cluster-analytical solutions (Milligan/Mahajan 1980; Milligan 1981; Sharma 1996). But cluster analysis is known to employ heuristic methods. The solutions it yields do not necessarily represent a global optimum. In addition, the distribution of the various test statistics proposed is unknown. Strictly speaking, we cannot make any statements regarding the degree of certainty to which the results can be generalized. In our study, we will use validity measures which, on the one hand, are based on the principle of decomposing variance, and on the other hand include criteria of discriminant analysis.

ANOVA Criteria. The variance-analytical criteria are mainly based on the assumption that the grouping itself makes a contribution to explaining the variance of the set variables. Our cluster solution therefore represents nothing else but the treatment levels of a multivariate variance analysis (MANOVA) in which the segmentation is the explanatory variable and the segmentation criteria are the variables to be explained. Assuming a multivariate normal distribution of the estimated regression coefficients and their equal variance-covariance matrices across all groups, we obtain a highly significant

MANOVA result (Wilks' lambda = .217 at 10 and 358 degrees of freedom). Therefore, the variance in the variables A through F can systematically be put down to the cluster solution.[2] Furthermore it should be ensured that the dependent variables are correlated in the MANOVA case, which is commonly checked using Bartlett's test for sphericity. This test confirms the highly significant intercorrelation at $\chi^2 \approx 2{,}838$ and 14 degrees of freedom. In addition, Table 2 shows the results of a univariate variance analysis (ANOVA) which confirm the explanatory potential of the cluster solution for all variables except for F.

Table 2: ANOVA - Results

Variables		Sum of squares	df	Mean Sum of squares	F-value	Significance level
A	Between Groups (Combined)	4584.079	2	2292.040	260.694	.000
	Within Groups	1600.154	182	8.792		
	Total	6184.233	184			
B	Between Groups (Combined)	6905.433	2	3452.717	216.509	.000
	Within Groups	2902.396	182	15.947		
	Total	9807.829	184			
C	Between Groups (Combined)	6614.548	2	3307.274	282.218	.000
	Within Groups	2132.833	182	11.719		
	Total	8747.380	184			
D	Between Groups (Combined)	102.197	2	51.098	55.982	.000
	Within Groups	166.122	182	.913		
	Total	268.318	184			
F	Between Groups (Combined)	.082	2	.041	1.570	.211
	Within Groups	4.746	182	.026		
	Total	4.827	184			

[2] Proof of multivariate normality is known to be difficult. As the univariate normal distribution of the variables is necessary though not sufficient, the general remedy is to check this property. After inspecting the variables using Q-Q plots, we can maintain the assumption of a normal distribution. It is known, by the way, that a violation affects the statistical power rather than the α-error (Sharma 1996 and the references quoted there).
The assumption of homoscedasticity is conventionally checked using Box's M-test. This, however, is a highly sensitive test for larger samples ($N > 100$) and signals a violation of the assumption even at smallest departures from multivariate normality (Mardia 1971). So the equal variance-covariance matrices are rejected for our application. But in view of the comparatively small F value of 6.239 and satisfactory inspection of the Q-Q plots this should have no meaningful impact on our results.

Another variance-analytical consideration leads us to validity criteria that can be interpreted as goodness of fit indices in accordance with the regression analysis. It is assumed here that the variance of the variables in the tested sample can be broken down into a segment-specific (σ^2_w) and a segmentation-related portion (σ^2_b). If the between groups sums of squares of the variables as indicated in Table 2 are pooled and related to the total pooled sum of squares, a measure is obtained with values between 0 and 1 which has also been termed R-square (RS) in the relevant literature. RS in our case is .73, which is a good value.

It is, however, a setback of this criterion that it uses variables for evaluating goodness of fit which have no explanatory power at all, i.e. are in no way related to the cluster solution obtained. One should ask in such cases why these obviously useless variables are included in the evaluation. If they are not considered useful for segmentation from a theoretical point of view, it should be accepted that the respective objects cannot be segmented based on this/these variable(s) in combination with the powerful discriminant criteria. We, therefore, suggest a partialized treatment with variable-specific coefficients of determination and develop an approach resulting from general measurement theory considerations (see appendix for technical details). As a result we pool the estimated group-specific variance of a variable taking into account the group sizes and relate it to the overall estimated variance of the total sample. Our variable-specific coefficient of determination r_k can be expressed as follows:

$$(2) \qquad r_k = 1 - \frac{\sum_g \left(\frac{n_g}{N}\right) \cdot \hat{s}^2_{gk}}{\hat{s}^2_k} = 1 - \frac{N-1}{N} \cdot \frac{\sum_g \sum_i \frac{n_g}{n_g - 1} \cdot \left(\bar{x}_{gk} - x_{gki}\right)^2}{\sum_i \left(\bar{x}_k - x_{ki}\right)^2}$$

x_{ki} - observation i of variable k
n_g - size of group g
N - total sample size
$\hat{s}^2$ - estimated variance

Table 4 shows clearly that a group-specific variation of variables A to C is fairly well covered by the segments determined. The coefficients of determination > .7 indicate

this, although this is not yet a perfect segmentation (r = 1) which only exists for a one case/one segment solution. Parameter D is not completely convincing, but it still contributes to the cluster solution with r = .38. The variance observed in variable F, however, cannot be put down to segment-specific effects.

Discriminant Criteria. The hypothesis that the division into groups can be put down to the discriminatory power of the cluster variable is now checked using goodness of fit criteria from discriminant analysis rather than variance-analytical measures. Using a linear discriminant analysis under the same assumptions as the variance analysis (see Footnote 2), two discriminant functions can be estimated. Only the first function is significant and explains 99% of the variance (Table 3).

The F-value based selection of variables within a stepwise discriminant analysis is said to point to the relative importance of the discriminant variables very much in the same way as the size of the mean standardized discriminant weights (e.g. Backhaus et al. 1996).

Table 3: Linear Discriminant Functions

Discriminant Function	Eigenvalue	% Variance	Canonical Correlation	Wilks' Lambda	Chi-Square	df	Significance level
1	3.310	99.0	.876	.225	220.997	10	.000
2	.033	1.0	.178	.968	4.778	4	.311

A stepwise discriminant analysis function in SPSS results in only two discriminatory variables, C and D. The decision in favour of C and D is also clearly suggested considering the standardized discriminant coefficients in Table 4. But the standardized coefficients should be interpreted with great caution if there are collinear relations among the variables (Sharma 1996; Huberty 1984). We have shown with Bartlett's test for sphericity that such relations obviously exist in our case. Orientation to the discriminant loadings should produce more valid results (Sharma 1996; Hair et al. 1992; Dant/Lumpkin/Bush 1990; Huberty 1984).

The interpretation of the discriminant loading is based on the concept of principal component analysis. The discriminant functions represent the factors here which reduce any correlative relations that may exist among the variables to only a few dimensions. To calculate the discriminant loadings, we determine the pooled correlation between discriminant variable and discriminant score. Based on the values from Table 4, at least the meaning of D can be seen in relative terms. Variables A to C each show a high correlation with the first discriminant function, which leads us to assume that they strongly correlate among each other as well. Such correlation indeed is statistically evident with values for Pearson's correlation coefficient $\rho > .85$.

Table 4: Discriminant Coefficients Estimates

Variables	F-value[b]	Significance level	r_k	Standardized discriminant coefficients		Discriminant loadings[a]	
				Function 1	Function 2	Function 1	Function 2
A	21174	0.00	.74	-.41	-5.27	.96	.06
B	170.20	0.00	.70	-.88	-6.87	.92	-.10
C	230.45	0.00	.75	3.12	16.00	.83	-.20
D	52.26	0.00	.38	2.13	11.65	.07	.66
F	2.40	0.09	.02	1.02	6.14	-.46	-.51

Hit ratios	
Analysis sample	91.5 %
Holdout sample	96.9 %
Leave-one-out cross validation	90.8 %
Maximum chance criterion	63.2 %
Proportional chance criterion	46.7 %

[a] correlation between discriminant variable and canonical discriminant function
[b] ANOVA statistics only for analysis sample (153 cases)

Apart from the discriminatory power of individual variables, we were interested in the predictive quality of the discriminant functions determined. This can easiest be checked using the hit ratio. This value, however, will always be somewhat improved if the information of the total sample is included in the estimate. If the samples are sufficiently large, external validity can be increased by splitting them into an analysis sample for calibrating the coefficients and a holdout sample. The holdout sample serves as external validation set, while the prediction is based on the calculated discriminant coefficients of the analysis sample (Crask/ Perreault 1977). Empirical studies with econometric applications frequently split the sample in accordance with the 50/50 rule (e.g. Brent Richie/McDougall/Claxton 1981; Hanssens 1980; Hornik 1982; Neslin/Shoemaker

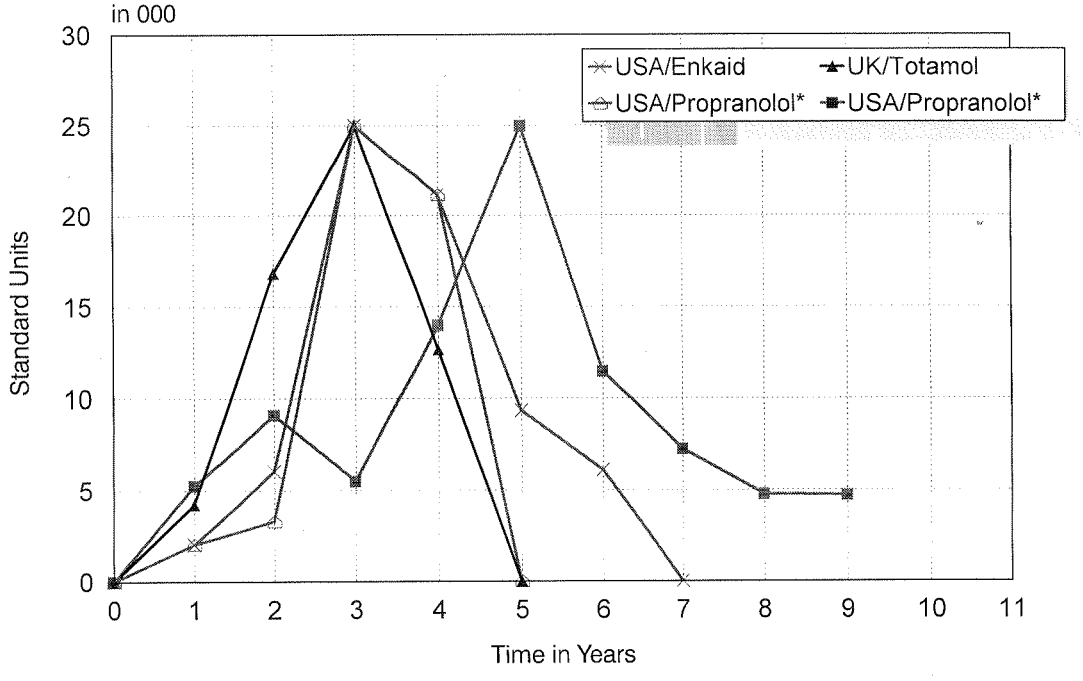
1983). The 1:2 rule is also quite common (Press/Wilson 1978; Bearden et al. 1981). *Steckel* and *Vanhonacker* (1993), however, convincingly argue using extensive simulation studies that the optimum size of the holdout sample as a function of the change in statistical power increases up to a sample size of 60 and then drops again. But a 50/50 split is below optimum even with N = 60. Based on these findings, we selected a random assignment of 25% of all cases to the holdout sample for our study. If there are not enough cases available, this can be remedied using a leave-one-out cross validation (Lachenbruch 1967; Huberty 1984). Each of the *n* cases is used once here as external validation set.

We have reached a high overall hit ratio for both approaches in our study as illustrated by Table 4. The comparison is on the one hand based on the maximum chance criterion that provides a classification probability if only the highest random assignment rate is important, regardless of the group. This maximum a priori probability simply results from the frequency of the cases in the greatest cluster. If the group sizes vary and it is desired to hit more than just the greatest group correctly, the proportional chance criterion should be employed. This criterion adds up the squared relative group sizes.

A comparison of these criteria with our classification rates across the external validation sets demonstrates the superiority of the discriminant solution. *Hair et al.* (1992) further demand a classification rate which is at least 25% better than the results yielded by the proportional chance criterion if the total sample is used for the estimation. This is no problem for our sample. As a result we can present a very good cluster solution in terms of discriminant analysis as well. It should also be noted here that a pilot study involving about 60 PLCs on the U.S. market resulted in an identical PLC structure at slightly changed group sizes. This empirically confirms the reliability of the cluster solution and corroborates the PLC typology we found from this perspective.

2.4.4 *Interpretation*

The generic PLC types described below represent an idealized curve. The PLCs in Figure 1 are a structural reflection of the drugs in one group and represent the smallest common denominator of their empirical cycles. It should be noted that the PLCs shown here are based on a smoothed growth function. The congruence with the observed sales refers to the structure rather than to the sales level at any given point in time. Thus the sales development towards the end of a PLC is usually somewhat underestimated in Figure 1, which can probably be explained by the relatively low sales figures in the degeneration phase. The focus is on the generic form of the PLC, especially the length and slope of the increase in the growth phase and the time of maximum sales, and is supported both by the theoretical and the empirical curves.



* propranolol is a generic name

Figure 2: Typical Sales Histories in Cluster 1

***Cluster 1*: The "Short-lived"**

This cluster includes 30 objects of study or 16.3% of the population. The "short-lived" represent a life cycle with a mean *lifetime* of *5-7 years*. A typical feature of this cluster is the *peaked curve* of the PLC which quite resembles a normal cycle. Another characteristic is the relatively *slow growth*. As a rule, the 10,000 units sold threshold

(standardized sales data) is reached only after two years; for an average lifetime of 6 years this means that just 40% of the maximum sales was effected by the end of the first third (see Figure 2).

***Cluster 2*: The "Classics"**

Cluster 2 is the largest group and includes 117 items of study (63.2% of the life cycles examined). As the sales cycles of the drugs in cluster 2 resemble the ideal-typical image of the PLC concept, this group shall be termed the "Classics". The life cycle of the "Classics" is the longest of the three groups and amounts to an average *11-14 years*. Their form mainly corresponds to that of a positively skewed normal distribution. A *strong growth* is characteristic for these PLCs, while 4/5 of the maximum are effected after two years or 1/6 of their lifetime (see the empirical cycles in Figure 3).

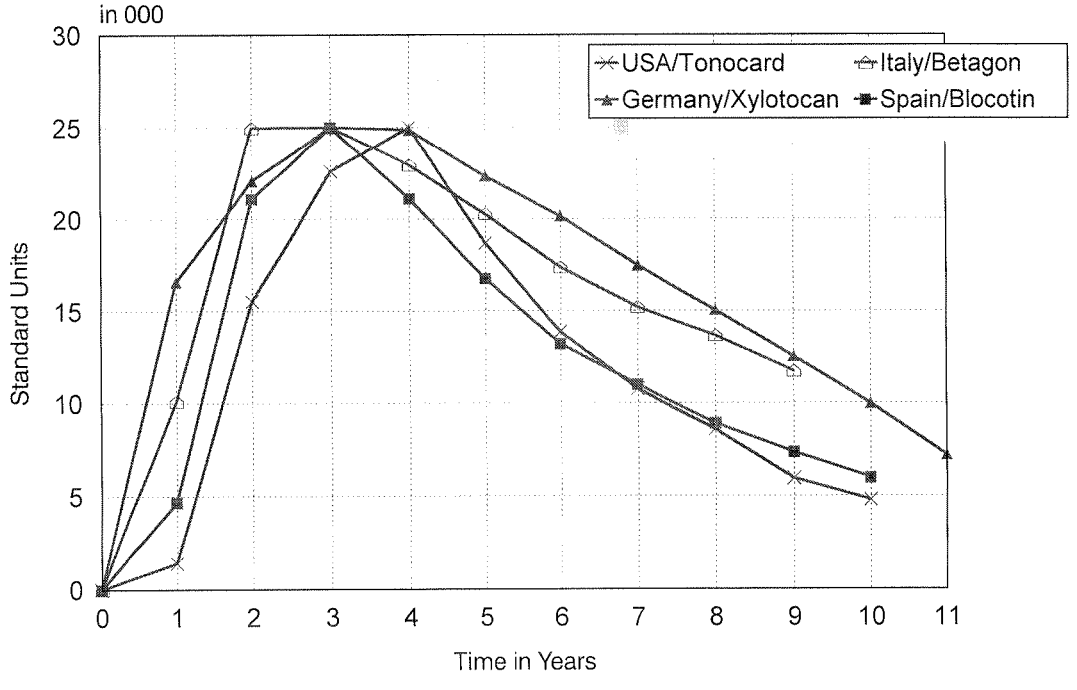


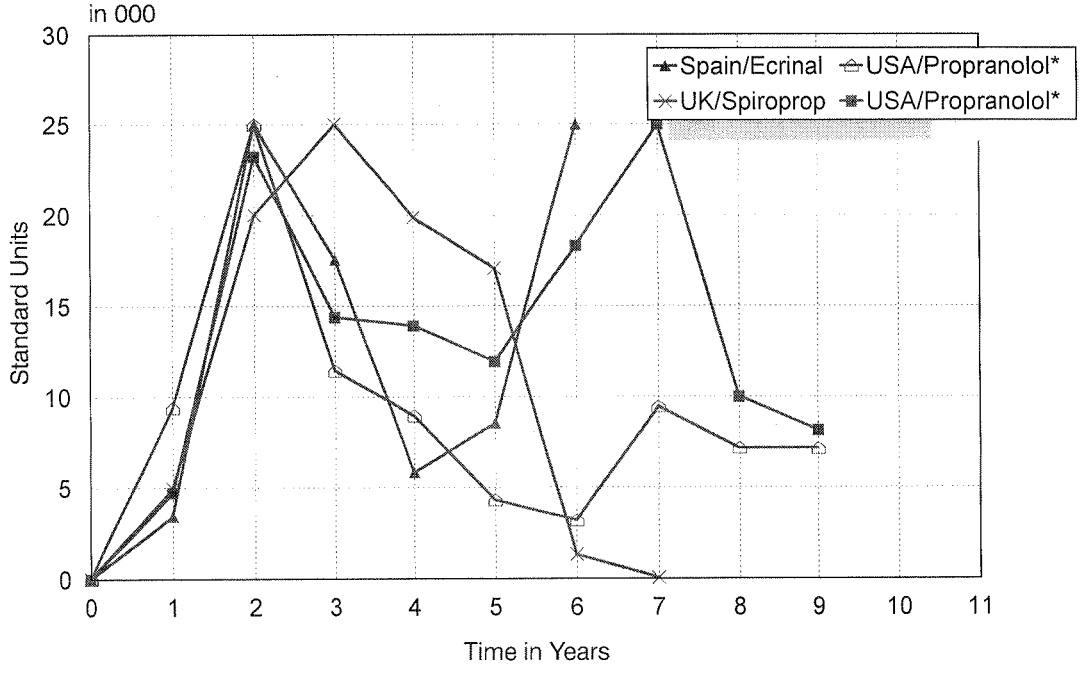
Figure 3: Typical Sales Histories in Cluster 2

This is the typical cycle for the vast majority of the original drugs examined which were launched in the CV segment in the 1980s, distributed either as own brand or as licensed product copy. The fact that the maximum sale is reached very fast certainly is a major finding which was not expected in this form. 54% of 45 innovative drugs in cluster 2

reached their peak after the third year, another 21% after the fourth year since their respective product launch, i.e. a total of 75% of these NCEs.

***Cluster 3*: The "Unsteady"**

20.5% of all life cycles examined or 38 elements are included in this group. There is no definite peak in their cycle, and little resemblance to the ideal type. The "Unsteady" thus do not fit into *any fixed cycle pattern*. The major anomaly here is that there are no patterns for the maturity phase (flatness, skewness), the time of reaching maximum sales and the number of "recycles". Quite a few of these PLCs are characterized by *several cycles*, the majority has at least one. There seems to be just one similarity of these PLCs: Their *growth phase* is relatively *short*. Quite frequently the peak value is reached as early as after the second year. Life expectancy is *6-8 years*. Thus a totally unpredictable unsteady and short cycle is typical of the PLCs in cluster 3 (see Figure 4).



* propranolol is a generic name

Figure 4: Typical Sales Histories in Cluster 3

2.5 Study 3: Shortening of the PLC Growth Phase

The empirical finding that the PLC types reach their sales peak after a relatively short time is somewhat surprising in our eyes. Although it fits well into the explanatory pat-

tern of shortening PLCs, a growth phase of only 2-3 years for drugs used in the treatment of chronic diseases is astonishing. We asked experts from the industry for a forecast of the time of maximum sales for newly launched products in the CV segment. Estimations varied between 8 and 10 years, which is too much to be interpreted as a random variation of the results. The estimates, however, only referred to NCEs. We have proved elsewhere that the clusters 1 and 3 are mainly determined by generics while cluster 2 shows the typical cycle for innovative products (Fischer/Crisand 1996). But even the NCEs in cluster 2 reach their maximum on average after only 3-4 years.

Exceptions to this rule are the pioneers and some of the early followers which show a slow rise and reach their maximum only after about eight years (see Figure 5). As the sample includes two older product classes, we do not have enough complete time series of pioneers to define them as a cluster in its own right.[3] Still, there are also indications of a shift in the time of maximum sales to the first years after product launch in the case of breakthrough innovations (e.g. Captopril and Enalapril in France and the United States, respectively).

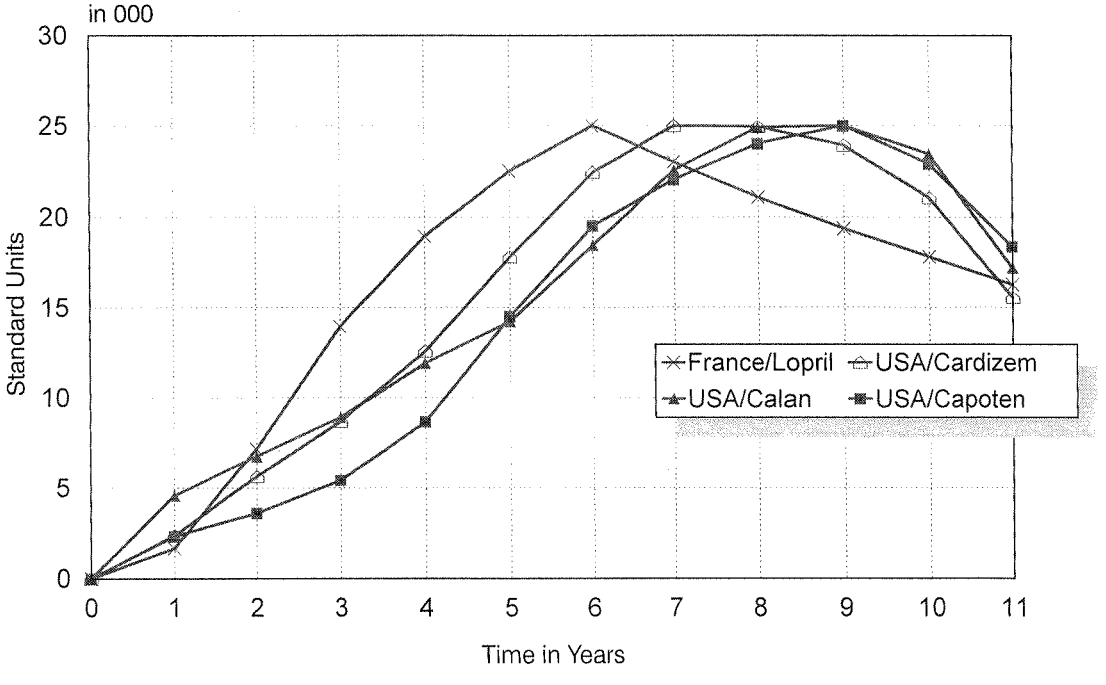


Figure 5: Typical Sales Histories of Pioneer Products

[3] The composition of the sample as regards innovative drugs and generics is otherwise representative.

But we have to ask ourselves why the PLC cycles of innovative drugs show that much differences. In some cases, the maxima of pioneers and me-toos are six years apart. It has been known for some time from strategic management research that there is a close relation between the order of entry and the market share (Bond/Lean 1977). Empirical findings attest pioneers a clear market share bonus which amounts to about 40% compared to the second entrant (Kalyanaram/Robinson/Urban 1995; Berndt et al. 1994; Kalyanaram/Urban 1992; Urban et al. 1986). Some of these empirical studies made explicit reference to pharmaceuticals (Bond/Lean 1977; Urban et al. 1986; Berndt et al. 1994). Our observations lead us to the conclusion that there is not just a relationship between the order of entry and the market share but also a link to the PLC. We think that, at least for NCEs, a later entry into the market results in systematic shortening of the growth phases. Some first considerations shall now substantiate this hypothesis theoretically and empirically.

A major reason for the long growth phase of pioneer drugs in our opinion results from the high perceived risk that doctors are facing when they prescribe new products. The customer potential is much faster penetrated with product launches that are based on a known and proven technology with only marginal use benefits than with genuine innovations. Doctors clearly see a lower risk when handling and applying just new products rather than new product concepts (e.g. ACE inhibitors). Experience in applying such a product has to be built slowly and inhibits the diffusion rate. The experience gained seems to be a factor that is process rather than product-related in tendency (Gatignon/Robertson 1993; Oren/Schwartz 1988; Jensen 1982).

Moreover, the competitive pressure increases with the number of competing products. If a new supplier enters the market too late, this supplier will have to use relatively greater marketing resources to maintain a hold in the market and to win market shares (Bowman/Gatignon 1996; Parker/Gatignon 1994; Robertson/Gatignon 1986). Launching a new pharmaceutical product generally involves high marketing expenses which are reduced after 1 to 2 years. But this leads to a decline in attraction power that provides the competitive edge and nourishes growth.

We studied the length of the growth rate for all Ca-antagonists and ACE inhibitors that were newly launched in all six countries from 1980 to 1990 to underpin our hypothetical statements. Both Ca-antagonists and ACE inhibitors are the most innovative and doubtlessly the most attractive segments of the cardiovascular drug market. We had to exclude only five new brands launched at the end of this decade out of a total of 55 because a PLC maximum could not yet be determined. The drug with the greatest market relevance, usually the offer of the innovator, was included in case of a co-marketing contract. In most cases, however, the original brand and the licensed product copy showed nearly identical development patterns. We measured the length of the growth rate until the time of maximum sales was reached and formulated the following hypothesis for the empirical validation:

New product launches take increasingly less time at the end of the decade to reach their maximum sales figures.

If τ represents the time of maximum sales, we can express the relation outlined in a mathematical equation as follows:

$$(3) \qquad \tau = f(t) \cdot Exp[u(t)] = a \cdot b^t \cdot Exp[u(t)],$$

where $a \geq 0$, $\frac{df(t)}{dt} = \frac{a \cdot b^t}{\log_b e}$ and $\frac{d^2 f(t)}{dt^2} = \frac{a \cdot b^t}{(\log_b e)^2}$.

Apparently, b should be constrained to $0 < b < 1$ to allow for a degressive trend in $f(t)$. Indeed, the OLS estimation with 48 degrees of freedom yields a BLU estimator of .88 (t = -13.52). R^2 is .79. There should be no autocorrelation of residuals at a Durbin-Watson value of 1.85. Figure 6 once again illustrates the relationship we determined empirically.

Moreover, we cannot prove a suspected relation between the growth phase and the length of effective patent life in our sample. A decline in sales in the year of launching the first generics or in the subsequent year was observed in just four cases. We can thus conclude that our hypothesis has been confirmed in a first empirical check.

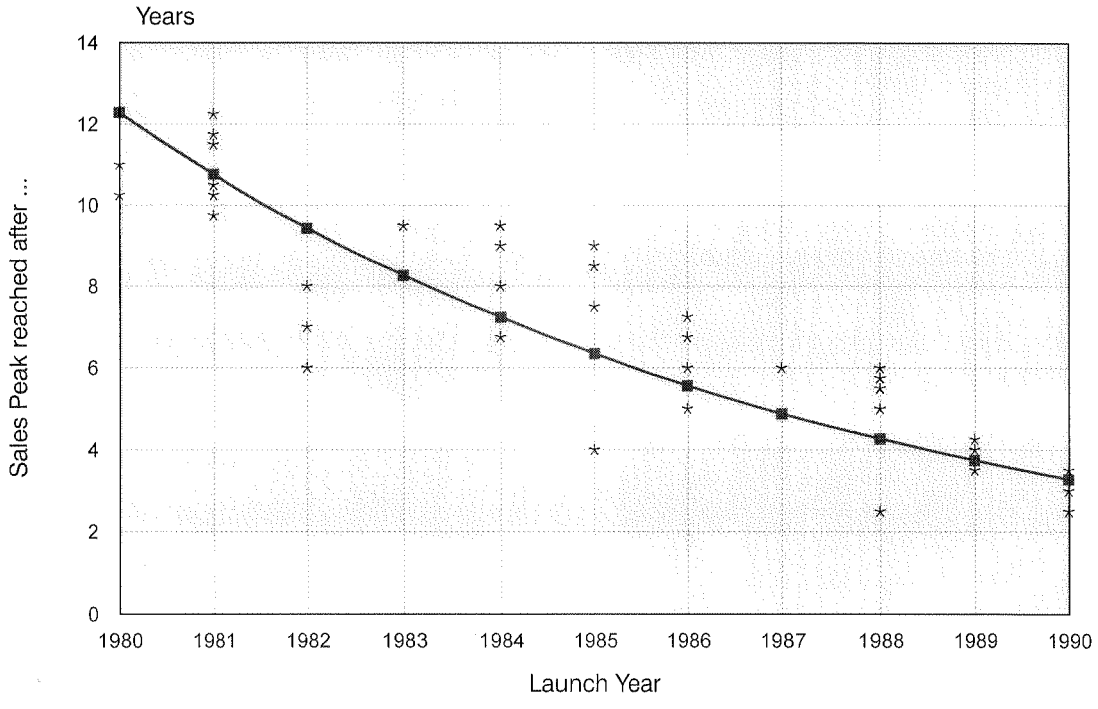


Figure 6: Shortening of the Growth Phase for NCEs between 1980-1990

3 Valuing Late Mover Drugs

The fact that NCEs in Cluster 2 have very short growth phases has enormous consequences for strategic product and program planning. Still about 70% of the NCEs do not comprise a high degree of novelty. They are generally late movers with an anticipated sales development as in Cluster 2. A simulation study shall now demonstrate the impact of this sales structure on the value creation potential of an NCE.

The value creation potential of NCEs is analysed based on their net present value (NPV). The NPV is the only correct criterion for valuation as it is future-oriented on the one hand and based on cash flows on the other. Furthermore, the cost of capital (CoC) reflects both risk bonus expectations of the private investors and the financial risk structure of the company.

Let p_t be the product's price in period t, x_t the respective quantity, c_t the amount of direct out-of-pocket costs per unit and f_t the product related but fixed marketing and manufacturing expenditures in t. $R\&D_{PV}$ denotes the capitalized R&D costs at product launch and r the Weighted Average Cost of Capital. Then the common computation of the net present value (NPV) in discrete terms would read as:

$$(4) \qquad NPV = -R\&D_{PV} + \sum_{t=0}^{T}\left[\left(p_t - c_t\right)x_t - f_t\right](1+r)^{-t}.$$

Empirical studies of the spread of methods used for evaluating and selecting R&D projects indicate that value based techniques frequently take a major or even dominant position in practical application (Liberatore/Titus 1983; Watts/Higgins 1987; Sanchez 1989).

3.1 Assumptions of the Profitability Analysis

A great number of empirical studies was published in the past few decades that deal with the profitability of the research-intensive pharmaceutical business. A great portion of these studies was dedicated to the specific problems of efficient R&D management (Sheck et al. 1984; Mattison/Lasagna 1988; Graves/Langowitz 1993; DiMasi 1995; Di Masi/Grabowski/Vernon 1995; Bierly/Chakrabarti 1996) and the determination of average R&D costs for a new pharmaceutical (Wiggins 1987; Mansfield 1987; Jensen 1987; DiMasi et al. 1991, 1995; OTA 1993). Another part of the studies focused on estimating the return on R&D investment and risks (Grabowski/Vernon 1982, 1990, 1994; Joglekar/Paterson 1986; Woltman 1989; OTA 1993; Baber/Kang 1996; Myers/Howe 1997). The recently published works, in particular, provide a good basis for supporting the simulation study with plausible data. In addition, we checked each assumption for its reflection of economic reality with experts from the pharmaceutical industry.

Market and Product Class Characteristics. While the cited profitability studies rely on a representative sample across all product classes and determine the average net present value or internal rate of return as the target variable, we will now focus on just one significant product class and derive break even sales and break even market shares

resulting from a target NPV of zero. The empirical basis is provided by the market for ACE inhibitors that was opened in 1981 with an innovation by Bristol Myers-Squibb and has been among the segments with the largest growth and sales ever since then. Merck & Co. followed in 1984 with a second NCE. It was only at the end of the 1980s that a greater number of other companies entered this market, increasing the amount of globally available NCEs to 15 until 1996. These product launches are what we categorize as a late mover NCE that would have a typical life cycle as in Cluster 2.

We used in our simulation quarterly data from 1987 to 1996 on global turnovers, sales, and spending on advertising and promotion. All figures are shown in real dollar values of 1997. The cost-of-living index of the years 1987 to 1996 was used as deflator. Foreign currencies were converted based on dollar parity at the end of 1996. Thus the results of our simulation are not distorted by inflationary or exchange rate influences.

Global Sales. The PLC is at the core of the profitability analysis, which clearly differs in this respect from existing studies. These works did not differentiate any further according to the sales curve of an NCE. Most of them used a rough estimate of the uniform turnover development in the U.S. market both for pioneer and for me too-NCEs as the basic model. Sales of foreign subsidiaries were taken into account through a sales multiplier (Grabowski/Vernon 1990, 1994; Myers/Howe 1997). We, however, base our study on the sales development of a newly introduced ACE inhibitor following the pattern of Cluster 2. We did not estimate turnover trends. But there is a coherence of turnover and sales due to the very low price variation, which justifies our assumption. Furthermore, we assume a sequential entry into the world market over three years in the following order: U.S. and France in the 1st year, Italy and Germany in the 2nd year, and the United Kingdom and Spain in the 3rd year. This reflects the average number and entry order of nations for the ACE inhibitor market. The Japanese market was frequently avoided when late movers launched their new products - presumably because the entry barriers are rather high. In addition, four out of the eleven NCEs marketed in Japan are domestic products that were only introduced into this market.

Grabowski and Vernon assume a life cycle of 20 years in their 1994 study. Our PLC estimate reveals an international supply period of 17 years. We have pointed out that our PLC estimates could show greater inaccuracies in the years before market withdrawal. We therefore determined a residual value from the average real sales amounting to $ 30 million for another 8 years after the 17th year. Thus, we arrive at a market period of 25 years, an assumption on which a previous study by Grabowski and Vernon (1990) was based as well.

R&D Costs. The studies by DiMasi and colleagues provide detailed information on the out-of-pocket costs in each phase of the pharmaceutical R&D process (DiMasi et al. 1991, 1995; DiMasi 1995). These average costs take into account the phase-specific error rates of abandoned projects. The technical failure risk of the drug development process is thus directly included in the R&D costs through empirically determined success probabilities.[4] Capitalization of the phase-specific costs over 12 years for the time of market launch yields the overall R&D investment for one NCE. Taking into account a correction factor for differences between the therapeutic areas (Grabowski/Vernon 1982), we use capitalized R&D costs after tax of $ 223 million. So we follow the estimate by Myers and Howe (1997) who resort to figures by DiMasi et al. (1991) but use a differentiated concept for determining the cost of capital. However, contrary to them we adjust our estimate for pre-launch investment in production facilities which we include in the overall manufacturing investment. The R&D costs furthermore contain the capitalized costs of ongoing research after product launch which mainly include line extension activities.

Cost of Capital. The R&D costs include the technical failure risk of the product development process. The market risk and the obligation to provide sufficient capital for developing a new pharmaceutical and establishing it in the market have to be compensated through the cost of capital rate. The nominal (real) cost of capital for pharmaceuti-

[4] The empirical estimates of success probabilities for projects according to DiMasi include to some extent projects abandoned based on economic criteria. Part of the business risk should therefore be covered herein. It may be assumed, in particular, that the available estimates of R&D costs are consistent with those determined according to an option price based approach. After successfully passing a stage in development a project is far enough "in the money" that it will go through the subsequent phase of development as well. See also Myers and Howe 1997.

cal companies in the 1990s is an average 14% (10.5%) according to Myers and Shyam-Sunder (1996). Similar values are used by Grabowski and Vernon (1990, 1994). These figures, however, do not reflect the actual amount of the cost of capital over the whole R&D process and the marketing period. Myers and colleagues correctly argue that the average R&D costs were predetermined at the beginning of the development process, thus representing a kind of mortgage (Myers/Shyam-Sunder; Myers/Howe 1997). This "mortgage" should also be considered when calculating the cost of capital (future costs) for predetermined expenses, for which the authors assume a real interest rate of 6%. They estimate the real cost of capital (revenues) to be 9% for the risky marketing period. Unlike Myers and colleagues, we further assume predetermined launch investments consisting of manufacturing and marketing/promotional expenditures based on expert opinions. Accumulated for our global base scenario, these amount to $ 225 million (after taxes) at the time of first international market launch.

Marketing/Promotional and Manufacturing Expenditures. Pharmaceutical companies typically spend 1.5 to 2 times their annual R&D expenditure on marketing and promotion activities. Marketing investment in a global product launch is considerable and exceeds the associated R&D costs. Based on statements by experts and the advertising/promotional data we have, we assume cumulative pre-tax expenses for all six nations in the year prior to and after the product launch in the amount of $ 109 million per year. These expenses are reduced to 50% by the fifth year, and to 30% in the 8th year; from the 10th year, they make up about 10% of the sales volume. These figures are included in our analysis in accordance with the share of the various nations in the advertising and promotional costs, and in the global market entry order described. Our estimate of the total marketing investment after tax finally is $ 414 million, which is about 1.8 times the R&D investment.

We follow the approach by Myers and Howe (1997) to estimating the investment into the construction of production and logistics facilities. They take into account scaling effects. We iteratively determine the pre-tax expenditure in manufacturing for our data which total $ 180 million. 50% of the expenses are incurred in the year prior to and after product launch. The rest is distributed over the subsequent five years. The sales mini-

mum is reached in the 5th year, so that the last expenses represent necessary replacement investments. The result is $ 115 million after tax in the base case.

Cash Contribution Margin and Tax Rates. In agreement with Myers and Howe and experience gained by managers, we base our study on a 65% cash contribution margin. This is determined after deducting 10% from sales for manufacturing costs, 12.7% for inventory, 18.9% for accounts receivable, and adding 6% for accounts payable. This margin is further reduced by tax actually paid. We assume that globally operating pharmaceutical companies utilize international tax benefits. The effective marginal tax rates are in the range from 33% to 38% internationally. Only Germany clearly deviates (46%) in the period under review. We determine an international sales weighted tax rate from the national effective tax rates and apply it to both sides of the income statement.

Off-patent and line extension sales. The meaning of the generic competition has greatly increased in recent years. Patent expiry for a pharmaceutical can result in considerable sales drops if aggressive imitators appear in the market. We do not consider here a negative generic sales multiplier for two reasons. On the one hand we focus on late mover NCEs that are less important to possible generic competitors due to their generally low sales potential. On the other hand our PLC estimate also includes potential influences from generic competition after the patent for a substance has expired. The same applies to line extensions that are included in consolidated form in the PLC estimate curves. Line extensions, e.g. in the form of slow release applications, were a typical element of product line policy for the product classes examined which none of the companies could refrain from. We did not find any large differences in the records with regard to the product differentiation degree of the NCEs (Fischer/Crisand 1996).

3.2 Results

We assume in our simulation that a new ACE inhibitor was launched worldwide between 1987 and 1989 in the sequence mentioned. The NCE develops in accordance with the life cycle type from Cluster 2. Under the assumption of an average cash contribution margin the sales curve also dominates the development of cash revenues. The share of

sales variance that can be put down to price modifications is relatively low in our data. Note that the variance σ^2 of the sales G from a time series can easily be decomposed in its price and quantity components after a linearizing log transformation:

$$(5) \qquad \sigma^2_{\ln G} = \sigma^2_{\ln p} + \sigma^2_{\ln x} + 2\,Cov(\ln p, \ln x).$$

Thus with $\sigma^2_{\ln p}$ we measure the portion of sales variance that can exclusively be put down to price modifications. The price-related sales variance was on average very poor for our quarterly data.

Table 5 clearly shows the strong effect of reaching an early PLC maximum on covering the overall product investment. The contribution to recovery ψ is dropping sharply over time. We define ψ as:

$$(6) \qquad \psi(r) = \frac{\sum_{t=0}^{\hat{t}} (p_t - c_t) x_t (1+r)^{-t}}{\sum_{t=0}^{T} (p_t - c_t) x_t (1+r)^{-t}}, \quad where\ \hat{t} \le T.$$

Under the assumption of p_t - $c_t \ge 0$, $\forall\ t$, ψ is a monotonic function increasing in t und r. The value is zero at market launch and equals one when the product is withdrawn from the market. The specific sales structure of our PLC type thus requires a high cash return as early as in the first years after product launch. As regards the cost of capital in the base case, 50% of the product-specific investment has to be covered after only four years. The condition is, however, that sufficient cash revenues are generated with the underlying absolute sales levels in each period. In other words, the PLC may also have influence on sales targets that materialize in absolute sales levels or market shares.

The last column of Table 5 shows the break even market shares, which from the third year (marketing in all six countries) are identical with the break even market shares in each country as long as their contribution to sales matches the share of the national market volume in the overall market volume. It is obvious that great market shares have to

be reached and secured in the first years. Thus the break even market share is 8.1% in the second year and climbs to more than 10% in the subsequent four years. Only in the 12th year after product launch can the market share be allowed to drop below 5%.

Table 5: Baseline Break Even Analysis (rounded figures, after tax)[a]

Time in years	Target-NPV recovery in %	Discounted cash revenues in mill. $	Nominal cash revenues in mill. $	Total break even sales in mill. $	Total market sales volume in mill. $	Total break even market share in %
1	1.7	12.9	14.0	33.4	1360	2.5
2	8.6	50.6	60.1	143.3	1759	8.1
3	20.7	90.4	117.0	279.2	2141	13.0
4	35.9	112.3	158.5	378.2	2569	14.7
5	50.2	106.0	163.1	389.2	2915	13.4
6	62.4	90.5	151.7	362.0	3173	11.4
7	72.5	75.0	137.1	327.0	3342	9.8
8	80.8	61.4	122.4	291.9	3563	8.2
9	87.4	49.1	106.6	254.4	3634	7.0
10	92.4	37.2	88.0	248.0	3589	6.9
11	95.9	25.9	66.7	188.1	3686	5.1
12	98.1	16.2	45.7	128.8	3790	3.4
13	99.2	8.7	26.8	75.6	3903	1.9
14	99.8	4.0	13.3	37.6	4024	0.9
15	100.0	1.3	4.6	12.9	4156	0.3
16	100.0	0.3	1.2	3.5	4298	0.1
17	100.0	0.0	0.0	0.0	4451	0.0

[a] national price index deflated 1997 $

Total R&D investment:	223 mill.	Cost of capital (future costs):	6 %
Total marketing investment:	414 mill.	Cost of capital (revenues):	9 %
Total manufacturing investment:	115 mill.	Cash contribution margin:	42 %
Residual value:	12 mill.		

A minimum market share of 10% is an ambitious goal in the pharmaceutical business. In the six markets studied, only three ACE inhibitors launched first reached a market share of more than 10% over a period of four years or longer. From 1987 to 1997, they represented on average more than 70% of the market volume. As a total of ten NCEs were introduced globally and considered here this means that only 30% of new launches reach a positive net present value. This result is consistent with the findings of other profitability studies which discovered a highly skewed distribution of returns. Only the top three deciles included NCEs with a positive NPV (Grabowski/Vernon 1990, 1994; Myers/Howe 1997).

These figures show clearly what challenges a later product launch faces in terms of securing market shares. The order of entry effect has always been strong in the pharma-

ceutical business (Bond/Lean 1977; Urban et al. 1986; Berndt et al. 1994). Without a doubt it represents a serious market entry barrier which apparently is either not yet perceived or not accepted by many companies. A sensitivity analysis shows (Table 6) that the greatest influence on the net present value besides the cost of capital (revenues) is exerted by marketing activities, i.e. the efficiency of sales promotion and pricing. They can reach three times the effect of measures to increase R&D efficiency. However, if the acceleration of the R&D process results in an NCE that is introduced as an early follower or even pioneer into a new market, the leverage on NPV cannot be topped.

Table 6: Sensitivity Analysis (rounded figures)[a]

	Model input	Peak break even share in %	Point elasticity of break even share
Baseline		**14.7**	
R&D costs			
10 % increase	245 mill.	15.1	0.28
10 % decrease	201 mill.	14.3	0.28
Marketing/Promotional expenditures			
10 % increase	455 mill.	15.5	0.56
10 % decrease	373 mill.	13.9	0.56
Manufacturing expenditures			
10 % increase	126 mill.	15.0	0.20
10 % decrease	104 mill.	14.5	0.18
World residual sales (per year)			
33 % increase	40 mill.	14.6	-0.01
33 % decrease	20 mill.	14.8	-0.01
Tax rates (weighted average tax rate)			
10 % increase	0.39	15.2	0.31
10 % decrease	0.32	14.3	0.28
Cash contribution margin/Pricing			
10 % increase	0.72	13.4	-0.92
10 % decrease	0.58	16.4	-1.13
Cost of Capital (revenues)			
10 % increase	0.10	16.2	1.00
10 % decrease	0.08	13.4	0.89
Cost of Capital (future costs)			
10 % increase	0.07	14.2	-0.38
10 % decrease	0.05	15.3	-0.41

[a] national price index deflated 1997 $

4 Management Implications

The sales structure over time is still one of the most important factors that influence the net present value of a new product (Day/Fahey 1988). If we compare – assuming con-

stant cash flows per unit of revenue – the areas below the curves in Figure 1, it becomes evident that cluster 1 is completely encompassed by the life cycle of cluster 2. Cluster 2 is typical for late mover drugs which have higher absolute sales levels compared to the average generic drug dominating the two other groups of our typology. PLCs following the pattern of cluster 2 are thus more attractive as they comprise the highest net present value. But this is only true as long as the R&D expenses can be compared. The products in cluster 3 are unimportant due to their much lower market share.

However, the innovative drugs in cluster 2 have to pay back huge R&D expenses. The fact that the sales peak is reached fast forces the companies to gain high market shares as early as in the first years after the product was launched. But the product margins will be typically lower in this phase due to the high costs of the product launch. Later periods can thus no longer be used to compensate lost margins as sales are going to be clearly lower due to the PLC structure.

The opportunities to compensate potential drops in sale through a fairly high introductory price are also declining. In view of the worldwide cost containment efforts in the health sector, launches of new products will mostly be evaluated based on their therapeutical cost-benefit ratio. Top prices can no longer realized in the foreseeable future. The influence of the sales structure, i.e. the PLC, on the net present value is increasing.

Pharmaceutical companies can only escape this cycle if they are among the first to launch a new drug on the market. This requires a high innovation rate with all its consequences for the structure and management of the R&D division. This race also requires a critical mass in R&D which most companies do not have and which has recently resulted in increased M&A. The only way out left for companies that do not wish or are unable to participate in the innovation race are other markets. This can be achieved, on the one hand, through a rigorous globalization that does not just affect the triad markets. On the other hand, pharmaceutical companies are offered great opportunities for growth in disease management. In this sector, quite unlike their traditional spheres of activities, we can expect less resistance on the part of the institutions that bear the costs in the health sector.

Appendix

In this section we derive the coefficient of determination r_k for a metric cluster variable k from general measurement theory.[5] We are aware of the limitations of cluster analysis, i.e. the distribution properties of the proposed test statistics are not known. Hence, statistical inferences about the outcome of the clustering procedure cannot be made.

The purpose of cluster analysis is to establish a sample based empirical representation of a hypothesized segmentation as regards to some prior defined variables and objects. Segmentation itself is assumed to be the main source of systematic variation in the data. Thus, we can decompose the observed value of a cluster variable k into a systematic part that is due to segmentation and a second one which is random in nature. Symbolically,

$$(7) \qquad X_O = X_S + X_R,$$

where X_O denotes the observed score, X_S the systematic or true score and X_R the error score. Segmentation is not a continuous predictor variable. We, therefore, determine the expected value of x conditional upon the membership g of object i. The expected value of the observed score then is:

$$(8) \qquad E\left(X_O \middle| G = g\right) = E\left(X_{Sg}\right) + E\left(X_{Rg}\right).$$

The value of X_S is provided by cluster analysis through the centroid of cluster g, i.e. $X_{Sg} = \frac{\sum_i x_{gi}}{n_g}$ and consequently $E\left(X_{Sg}\right) = \frac{\sum_i x_{gi}}{n_g}$. The mean value of variable k in cluster g is simply the smallest denominator to which all group and variable specific information can be reduced. As in general measurement theory, the expected value of the random error component is assumed to be zero. It directly follows from the definition of the mean that $E\left(X_{Rg}\right) = 0$ always holds for (8). If the membership is not known we can predict x_i as follows:

$$(9) \qquad E\left(X_O\right) = \sum_g p_g \left[E\left(X_{Sg}\right) + E\left(X_{Rg}\right)\right],$$

where p_g is the relative group size resulting from cluster analysis or the a priori probability of object i belonging to group g, respectively. As $E\left(X_{Rg}\right) = 0$ we have $\sum_g p_g E\left(X_{Rg}\right) = 0$.

Like in regression theory a measure of the goodness of fit would take into account how much of the variance in the data is attributed to systematic variation relative to total variation. The variance of the observed score from (7) is:

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[5] A good review of basic concepts in measurement theory for the social sciences is given in Campbell (1976) and Kerlinger (1973). See also Peter (1979), p. 7.

$$(10) \quad \mathrm{var}(X_O) = \mathrm{var}(X_S) + \mathrm{var}(X_R) + 2\,\mathrm{cov}(X_S, X_R).$$

By assumption the covariance between X_S and X_R must equal zero which is always true in our case since X_S is a nonstochastic outcome of the clustering procedure and $E(X_R) = 0$. Our coefficient of determination r thus reads as follows:

$$(11) \quad r = \frac{\mathrm{var}(X_S)}{\mathrm{var}(X_R)}.$$

Since X_S is a discrete random variable we calculate its variance according to:

$$(12) \quad \mathrm{var}(X_S) = \sum_g \left(X_{Sg} - \overline{X}_S\right)^2 p_g$$

and derive r_k from the sample data as follows:

$$(13) \quad r_k = \frac{N-1}{N} \frac{\sum_g n_g \left(\bar{x}_{gk} - \bar{x}_k\right)^2}{\sum_i \left(x_{ki} - \bar{x}_k\right)^2}.$$

$\overline{X}_S$ defines the mean calculated from the cluster centroids. As the groups are disjunct and together comprize the whole sample their mean can also be directly computed from the total sample, i.e. $\overline{X}_S = \bar{x}_k$ for a variable k. Another description of r_k is based on:

$$(14) \quad r = \frac{\mathrm{var}(X_O) - \mathrm{var}(X_R)}{\mathrm{var}(X_O)}$$

or

$$(15) \quad r = 1 - \frac{\mathrm{var}(X_R)}{\mathrm{var}(X_O)},$$

respectively.

According to (12) and (15) we derive the formula for r_k after some transformation:

$$(16) \quad r_k = 1 - \frac{N-1}{N} \cdot \frac{\sum_g \sum_i \frac{n_g}{n_g - 1} \cdot \left(\bar{x}_{gk} - x_{gki}\right)^2}{\sum_i \left(\bar{x}_k - x_{ki}\right)^2}.$$

The goodness of fit index is restricted to values between 0 and 1. r_k reaches the value of one if the number of clusters corresponds to the number of objects in the total sample, i.e. $G=I$. This is the special case of perfect segmentation. If we have only one group, i.e. $G=1$, a r_k of zero results indicating that there is no segmentation in the data.

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