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Innovation Options and Profitability of Pharmaceutical Brand Manufacturers

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Abstract. Much research exists covering clinical development success rates, development costs of new drugs, and market launch impact on stock market valuation of companies, but little systematic work has been done to establish the impact of research input on new product launches and, in turn, their impact on profitability of drug manufacturers. This article investigates these relations using data from the world's largest pharmaceutical brand manufacturers and their product launches in the US over a period of more than 25 years. The objective is to determine the impact of innovation intensity on innovation output intensity and of innovation output intensity on profitability. It is shown that there is a complete lack of evidence that launches of New Molecular Entities (NMEs) necessarily lead to higher profitability, suggesting that many launches of NMEs are not particularly successful from an economic point of view. Furthermore, it was found that intangible knowledge assets acquired by company mergers and acquisitions do often not live up to their valuation. This leads to the conclusion that such intangible assets seem to be overpriced on average. The more and more frequently used strategy of launching new drugs without NMEs like combination drugs or extension of indications increased short-term profitability making this a valid approach to avoid setbacks when patent protection of blockbuster drugs expires.

Keywords: Drugs; Pharmaceutical industry; Product innovation; Profitability; Research and development

1. Introduction

The importance of pharmaceutical product innovation for human life has been demonstrated many times, e.g., by the factual elimination of many life-threatening diseases like the plague, tuberculosis and smallpox. Vaccine development during the recent pandemic once more showed the importance and the capabilities of pharmaceutical development as well as the enormous development costs and high risks of failure. There have been many investigations on how to create innovation (Berawi, 2021), improve certain drug formulations (Timotius et al., 2022), increase sustainability (Zaytsev et al., 2021), as well as improve drug supply chains (Goodarzian et al., 2021). However, this vast amount of literature does not address the issue that therapeutic and economic success of a new drug are separate things, despite sometimes staggering prices for new drug therapies. Drug development has always been known to be notoriously difficult and time-consuming (Scherer, 2010). Recently there is a growing concern about the profitability of market introduction of new drugs originating from longer development times and shorter market exclusivity for companies developing such drugs (Berndt et al., 2015; Lietzan, 2018).

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On the other hand, consumers and politics complain about rising drug expenditures and high drug prices by far exceeding development costs (Costantini & Walensky, 2020; Fleming, 2019). Considering both perspectives and their potential implications corporate management needs to carefully access options and the related risks and potential business performance to adapt development direction and innovation strategy accordingly (Pisano, 2015). This work aims at providing guidance to this assessment by quantifying the impact of different choices for innovation on corporate profitability.

2. Literature Review

Pharmaceutical product development is characterized by little advanced knowledge about the molecular drug properties necessary to achieve the desired physiological effect (Taalbi, 2017). High coupling of properties not only within the drug but also in different molecular pathways triggering physiological drug response makes the development of new active ingredients, in many cases, a more or less random search with limited probability of success (Garzón-Vico et al., 2020; Saint-Hilary et al., 2018). Furthermore, a unique feature of drug innovation is the mandatory combination of a tangible item and a precise labelling describing the desired physiological effect, both essential to the product and subject to rigorous clinical testing before market approval and product launch (Lietzan, 2018). In fact, in the pharma market, a product introduction may consist of adding a different indication to the drug's packaging or package leaflet, making the drug assessable for additional patients by a seemingly minute change.

Past literature mainly focused on drugs containing so-called new molecular entities (NMEs), the most difficult and expensive product innovation case in drugs (Light & Warburton, 2011). In contrast to this particular focus, drugs without new molecular entities account for the vast majority of drug launches, not only at generics manufacturers but also for brand manufacturers (see below in Sample and Data). Still, some authors like Schuhmacher et al. (2016) consider only drugs launched containing a new molecular entity for innovation efficiency, which greatly neglects the innovativeness of combination drugs or galenic improvements. Furthermore, although NMEs might achieve the most important breakthrough in the treatment of certain diseases, extensions of current drugs to new indications are also important product innovations in the pharmaceutical industry.

From a process point of view, product development steps in drug development are highly regulated and supervised by the regulatory bodies responsible, in the case of the United States, the Food and Drug Administration (FDA). Despite this strict regulation, the corresponding estimated costs, especially of the last steps in drug development, vary considerably between sources (DiMasi et al., 2016; Light & Warburton, 2011). Overall development costs depend not only on targeted disease and type of development, but also on temporal distribution of spending and interest rates used to calculate the accumulated cost (Scherer, 2010). In addition, companies continuously increased their R&D spending and overall innovation output measured as new drugs launched over the last decades (OECD, 2019). Schuhmacher et al. (2016, 2021) identified in this context external innovation by licenses or acquisition of rights as main source of NME launches in the last two decades. However, even with increasing R&D spending, the pharmaceutical industry generates excess returns (Sood et al., 2021). Tay-Teo et al. (2019) determined R&D investment as a source of additional turnover for new cancer drugs.

Several investigations looked at the relationship between innovation and corporate success. Fazlıoğlu et al. (2019) found a positive impact of innovation on productivity on a corporate level. Visnjic et al. (2016) differentiated between product innovation and service business model innovation both in the short-term and in the long-term, respectively. They

found a significant and robust positive effect of product innovation on long-term profitability measured as EBIT margin coupled with a degree of short-term performance sacrifice. Artz et al. (2010) identified a positive impact of product innovation measured as number of announcements of new products on return on assets and sales growth. Similar to these findings Ernst et al. (2016) described a positive impact of patent information and protection management on profit margin and annual sales growth. Feyzrakhmanova & Gurdgiev (2016) noticed a positive impact of blockbuster drugs in a company's product portfolio on the market value. In contrast to that, they also noticed that an increase in R&D expenditure has a negative short-term impact on market capitalization. Leahy (2011) used the different turnover ratios to explain profitability in the pharmaceutical industry, thereby basically using one financial success indicator to explain another. Reversing the perspective, Shaikh et al. (2021) considered profitability as determinant of current research in the pharmaceutical industry.

Still, while most of the evidence supports the positive impact of innovation on corporate success, many investigations found other relations or no significant positive association between innovation activities and firm performance at all (Bockova & Zizlavsky, 2016). Furthermore, only very few studies exist focusing on large companies within a single industry, the focus of this investigation.

3. Methods

3.1. Hypothesis Development and Research Framework

This investigation differentiates between two different sources of innovation: internal and external sources. Intangible assets from the acquisition of either entire companies or their intellectual property alone are used as surrogate for innovation acquired externally. In accordance with the literature, the two product innovation types considered in this publication are drugs with and without NMEs. Based on these fundamental considerations, it is hypothesized that innovation input from both sources positively impacts both product innovation types (H1a to H2b), as illustrated in Figure 1.

Following Artz et al. (2010), both types of product innovations are expected to influence profitability positively. However, it is evident from research that there is a lag from R&D spending to innovation activities like patent filing and sales impact (Ernst, 2001). Furthermore, revenues from new drugs vary considerably during the drug's life cycles, especially for new molecular entities (Dubois et al., 2015; Teramae et al., 2020). According to Robey & David (2017), the time to peak sale for new molecular entity prescription drugs launched in the US had a median of approximately six years. Drug launches can be expected to impact profitability in a time-dependent manner, i.e., influenced in the short term by higher cost at limited turnover and in the longer run by increasing economies of scale. This publication assumes that drug launches' impact on profitability is positive, both short-term and long-term, regardless of the drug type launched (H3a to H4b, see Figure 1).

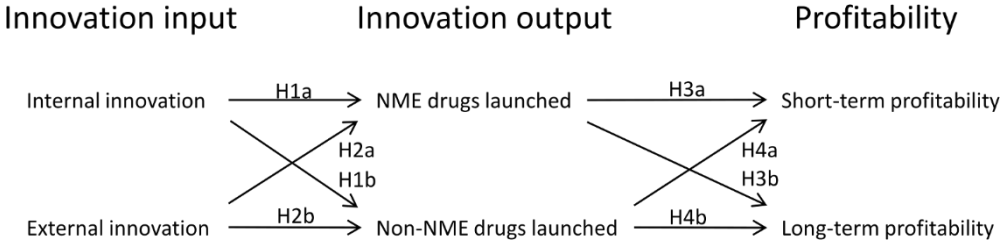

Figure 1 Research Framework Using Multivariate Panel Modelling

3.2. Multivariate Modelling

The research model from above was tested using multivariate linear modeling. Monetary measures refer to USD of the year 2000 and are adapted accordingly. Technological change or progress is implemented in the model as the average of drugs containing new molecular entities launched per year over the last three years divided by the total market volume of prescription drugs. Product introductions are used as proxy for rivalry in the market or competitive intensity (Ball et al., 2018), operationalized as the annual number of new drugs launched in the last three years divided by the market size of prescription drugs over the same period. Market growth calculated as moving average over three years adjusted to USD of the year 2000 was tested as model variable but eliminated due to lack of significance. Company-specific indicators include innovation input intensity, measured as moving average R&D intensity over five years (R&D expenses of last five years divided by sales). External innovation is measured by intangible asset intensity, which comprises acquired licenses or rights as well as identifiable intangible assets from corporate acquisitions (Lim et al., 2020). Innovation output intensity as dependent variable is measured as the average number of drugs launched in the last five years containing NMEs or no NMEs, respectively, divided by net sales. When employed as an independent variable in modeling impact on profitability, differentiation between short-term and long-term effects on profitability was achieved using the most recent five years (short-term), and the preceding five-year (long-term) interval. Financial resources of companies are measured using financial leverage. Profitability is investigated in two dependent variables relative to turnover and assets employed. The respective variables used are earnings before interest and taxes (EBIT) margin or return on sales (ROS) and return on assets (ROA).

Corporate size was used as control variable measured as logarithmic corporate turnover in billion USD (Artz et al., 2010). Innovation output intensity investigated as NME and non-NME drug launch intensities are derived from countable occurrences per financial year. Therefore, panel modeling was performed using quasi-Poisson distributions for the models describing innovation output as drug launch intensities (Munos, 2009). Fixed effect within modeling was chosen since the primary objective was to investigate the impact of company-internal choices regarding product innovation. External factors impacting innovation efficiency like the regulatory environment changed within the period under investigation (Riedel, 2021), so a two-way model was used. Profitability measures followed a Gaussian normal distribution and were treated accordingly. Furthermore, no overall profitability development was noticeable, leading to a one-way gaussian within the panel model.

3.3. Sample and Data

The sample consists exclusively of multinational companies from democratic countries. The overall sample contains data from 29 top brand manufacturers from the pharmaceutical industry covering the financial years 1990-2018. If not identical to calendar years, the numbers of financial years were assigned according to the major portion of the respective financial year. The companies selected were large companies with more than one billion USD turnover in 2018.

Financial company data were extracted from Refinitiv Eikon. General economic data were extracted from the database of the World Bank using the respective indicators (WorldBankOpenData, 2020). The database Drugs@FDA (Drugs@FDA, 2020) was used as a further data source to determine the number of new products launched by the pharmaceutical companies in the US market (Zeukeng et al., 2018). The database covers drug products approved since 1939 and is updated daily.

A summary of the data of the panel and descriptive statistics are presented in table 1.

Table 1 Descriptive Statistics

	Mean	Std. Dev.	Min	Max
NMEs per market volume [USD billion]$^{-1}$	0.24	0.15	0.11	0.61
New drugs per market volume [USD billion]$^{-1}$	3.36	0.69	2.54	4.97
Avg. R&D intensity last five years	0.15	0.05	0.03	0.60
Share of intangible assets	0.12	0.13	0.00	0.67
Log (Net sales) [USD 2000 billion]	1.72	1.49	-4.83	4.05
Drugs with NME last five y per turnover	0.14	0.68	0.00	11.39
Drugs with NME 5-9 years ago per turnover	0.07	0.14	0.00	1.13
Drugs without NME last five years per turnover	0.55	3.72	0.00	59.91
Drugs without NME 6-10 years per turnover	0.14	0.36	0.00	3.23
Average return on sales (ROS) 5 years	0.22	0.11	-0.74	0.45
Average return on assets (ROA) 5 years	0.07	0.04	-0.05	0.26

The companies investigated are multinational companies originating from democratic countries worldwide. The regional distribution of the investigated brand manufacturers from the pharmaceutical industry is the following: twelve originate from the EU and Western Europe, eight from North America, and nine from East Asia. The resulting panel is unbalanced due to different corporate ages as well as availability of financial data.

Overall, in the period investigated, 26,569 drugs, including different active ingredient concentrations, application forms, or formulations, were approved newly or for new indications in the US market, of which 2356 (8.87%) were launched by the companies investigated in the sample. Of all drugs launched, 1833 included 911 new molecular entities, 671 (36.61%) of which, containing 298 NMEs, were launched by the companies from the sample.

4. Results and Discussion

3.1. Innovation Input and Product Launches

Results of linear panel modeling of the innovation output for testing hypotheses H1a to H2b are shown in Table 2.

Table 2 Innovation Output Dependency from Innovation Input

Variable	NMEs	non-NMEs
Avg. R&D intensity last 5 years	3.35*** (0.58)	12.31*** (1.79)
Intangible Asset share	0.10 (0.21)	-2.66*** (0.64)
Log (Net sales) [USD 2000 billion]	-0.35*** (0.05)	-1.57*** (0.15)
R^2	0.28	0.42
R^2 adj.	0.19	0.35

The superscript *** denotes the significance level $P \leq 0.001$. Values in brackets indicate the respective standard errors.

It was found that coefficients for average R&D intensity over five years were positive and highly significant in linear models for both NME and non-NME drug launch intensity for confirming hypotheses H1a and H1b, which is at least for NMEs supported by previous investigations. Schuhmacher et al. (2021) found a similar relationship for NMEs comparing accumulated R&D spendings of large brand manufacturers. However, the positive impact of R&D intensity on non-NME drug launch intensity suggests a simultaneous increase in drugs

derived from known active pharmaceutical ingredients (APIs) like new combination drugs, new formulations, or new application forms.

Intangible asset share showed a more mixed influence in modeling. While for NME output intensity no significant correlation was found, the coefficient for non-NME drug output intensity was significantly negative, thereby effectively disproving H2b. The lack of significant impact of intangible asset share from mergers and acquisitions or licensing on NME output seems to contradict findings on the origin of NMEs launched by brand manufacturers (Schuhmacher et al., 2016; Schuhmacher et al., 2021). This discrepancy can be attributed to several factors: Firstly, in this investigation intensities were used instead of absolute numbers. In consequence, if one company buys another company to acquire the rights for one or several NMEs, intensities only change if the proportion between turnover of the second company and the number of NMEs is different from the proportion of the first company prior to the acquisition. Secondly, companies might use mergers and acquisitions as a last resort when their NME pipeline is rather empty at the end of patent protection of their current drugs despite their R&D efforts. In this case, due to the company-internal perspective of the model, the drug launch intensity will not necessarily be higher than previously without acquisition, and no statistically significant positive impact will be noticed. Still, the finding does certainly not imply that external acquisition of proprietary technology cannot be beneficial or even necessary for product innovation.

Furthermore, models displayed a significant negative impact of corporate size on innovation output intensities. This finding corresponds to previous reports on inefficiencies in large pharmaceutical companies (Munos, 2009).

3.2. Product Launches and Profitability

Coefficients resulting from investigating the relation between innovation output in terms of drug launch intensity and profitability are displayed in Table 3.

Table 3 Profitability Dependency on Innovation Output

Variable	ROS	ROA
NMEs per turnover last 5 years [bn USD]$^{-1}$	3.28 (3.00)	-1.42 (1.52)
NMEs per turnover 6-10 years ago [bn USD]$^{-1}$	0.58 (0.75)	0.52 (0.38)
non-NMEs per turnover last 5 years [bn USD]$^{-1}$	6.49*** (1.34)	3.18*** (0.68)
non-NMEs per turnover 6-10 years ago [bn USD]$^{-1}$	-0.15 (0.22)	-0.08 (0.11)
Avg. R&D intensity last 5 years	-48.47*** (9.65)	-12.55* (4.89)
Intangible Asset share	-9.07* (3.69)	-6.34*** (1.87)
Log (Net sales) [USD 2000 billion]	1.63 (1.01)	2.33*** (0.51)
NMEs per market volume [USD billion]$^{-1}$	-7.14 (9.16)	7.41 (4.64)
New drugs per market volume [USD billion]$^{-1}$	1.57 (0.76)	-0.85* (0.38)
R^2	0.25	0.17
R^2 adj.	0.18	0.09

The superscripts * and *** denote different significance levels: * $P \leq 0.05$; *** $P \leq 0.001$. Values in brackets denote the respective standard errors.

Innovation input is significantly negatively correlated to profitability regardless of the indicator used. Since R&D intensity is a cost factor, the negative impact on profitability for brand manufacturers is not surprising. The negative impact of intangible asset share might indicate that such acquired assets are normally overpriced. If the acquiring company bought these assets at a competitive price achieving their usual returns, the negative impact

of depreciation of the acquired intangible assets on profitability would be compensated by the saved R&D expenses, and the overall effect should not be statistically significant.

Findings for the relation between profitability and innovation output are much more difficult to interpret. Modelling of profitability for brand manufacturers revealed a significant negative impact of R&D intensity as well as intangible asset share on profitability.

However, the lack of significant impact of long and short-term NME launch intensity was most noticeable. This leads to the conclusion that H3a and H3b are not true. In addition, overall ROS of the manufacturers in the sample combined increased over time while NME launch intensity and non-NME launch intensity decreased (see Figure 2a-c). Furthermore, no significant correlation could be identified when looking at the change of return on sales against the change in five-year average NME launch intensity (see Figure 2d). Even distinct events like NME launches after several years without launch of new NMEs did not significantly impact profitability (data not shown). In the few cases where substantial differences were found, these could be attributed to other factors than the recent NME launches.

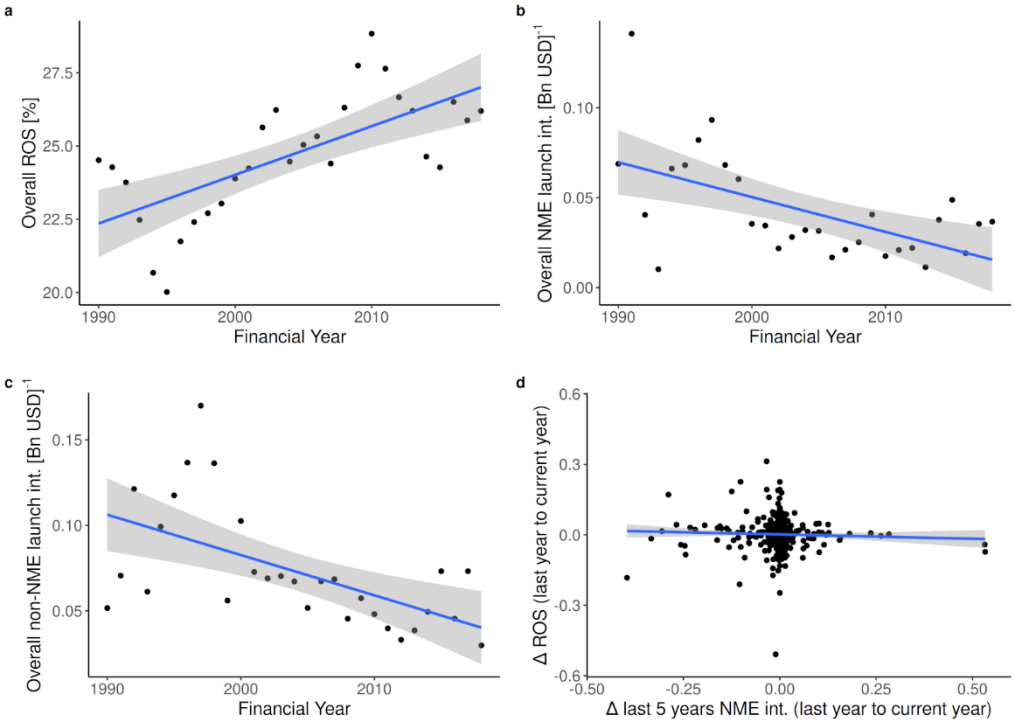

Figure 2 Development of ROS and drug launch intensity and their relation

In addition, substantial differences exist between the highly controlled clinical environment during clinical research and the standard-setting in a normal physician's office. Considering these dissimilarities and the high probability of failure even in pre-launch research, it seems reasonable to assume that even after market launch, new drugs often might live up neither to the promised medical benefit nor to the financial expectations.

In contrast to NME launch intensity, non-NME launch intensity significantly increased short-term profitability. This can be interpreted as confirmation of the R&D approach of launching combination drugs or extension of indications by brand manufacturers. Another effect potentially responsible for this association might be the launch of altered versions of drugs running out of patent protection to extend their exclusivity.

Corporate size impact in the model was only significantly positive for return on assets. Larger brand manufacturers achieve a higher return on assets, suggesting a more efficient use of their assets.

However, the current model used is limited in its predictive power, as indicated by the correlation coefficients. Innovations considered in this article cover drugs, including biological products, approved in the United States but do not include products like vaccines, blood, and blood products, or cellular and gene therapy products. No indications of drugs launched were included in the analysis. The market size for prescription drugs was used as surrogate for the overall drug market size, which might be considered a fair approximation but is certainly far from perfect.

Future research could improve the quality of the model by using a larger sample size and incorporating variables for different drug indications. Other potentially interesting parameters to add might be the number and duration of clinical trials. The differentiation between NME-containing drugs and non-NME-containing drugs might be enhanced by introducing new categories for combination drugs, applications for new indications, or both. In addition to that, orphan drug status might be of particular interest. Still, while the impact of innovation outcome on profitability in the pharmaceutical industry is an interesting topic, every product innovation, including NMEs, is a unique undertaking with a different setting. Another aspect to consider is that launches of NME-containing drugs are comparatively rare occurrences even for the largest companies, resulting in a high probability of overfitting a model if too many factors are included.

4. Conclusions

The outcome of this investigation suggests a lack of sufficiency of product innovation in terms of NME drug launches for increased profitability. While successful innovation in terms of market launches of new products might be considered a necessary condition for increased profitability, other conditions must be fulfilled as well for economic success. Furthermore, the results show the limited prognostic power of companies or their employees and the high risk of technological and economic failure of drugs containing new molecular entities. From a management point of view, the main implication is that intangible assets acquired by company mergers and acquisitions, assets swaps, or licensing deals might be considerably overpriced, suggesting a more careful approach to intangible asset valuation. However, external acquisition of proprietary technology can still be beneficial or even necessary for product innovation. Launching drugs without NMEs can be considered as one measure to increase short-term profitability of brand manufacturers, making this a potential approach to avoid setbacks when patent protection of blockbuster drugs expires.

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