# Knowledge sources, patent protection, and commercialization of pharmaceutical innovations

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Abstract:

This paper investigates different types of innovations (from radical to incremental) in the pharmaceutical industry by studying bibliometric data of drugs approved by the United States Food and Drug Administration (FDA), looking at time-to-market aspects, knowledge sources of these innovations, and protection strategies. Scientific knowledge stemming from the public sector is found to be important for all innovations. Nevertheless, radical innovations build on a higher degree on basic research, and they build on a significantly higher share of own prior scientific research than do incremental innovations. Furthermore, each drug is shown to be accompanied by, on average, about 19 journal publications and 23 additional patents. Additional patent filings peak when the commercialization of the drug is in reach. Firms do not differ among the various types of innovations regarding the amount of additional patent filings, but rather with the speed of filing these patents. Finally, this work contributes to the improvement of future econometric analyses that aim to link bibliometric indicators such as patent or publication counts to firm success.

Key words: time lags, event study, Tobin's q, radical innovations, drug lifecycle management, technological trajectories



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## 1. Introduction

This paper examines the knowledge base, knowledge protection and commercialization speed of different types of innovations in pharmaceuticals: radical innovations, technological breakthroughs, market breakthroughs, and incremental innovations. First, the impact of scientific and technological knowledge generated by both public research institutions and the firm that brings the innovation to market is investigated. Second, drug lifecycle management activities of these firms are analyzed and discussed.

The findings presented in this paper aim to contribute to a better understanding of technological trajectories within firms, also known as corporate technological traditions (Achilladelis (1993)); they contribute to the stream of literature on radical innovations and their emergence, as well as to a better understanding of the drug lifecycle management activities of firms. Finally, the paper provides empirical data for the time-lag between research, development, and commercialization that may serve as a basis for conducting research on (technological) capabilities, knowledge stocks, and other aspects in strategic management theories that are widely operationalised by bibliometric indicators such as publication and patent counts.

This work is organized as follows: section 2 explains the background of the paper and develops several hypotheses. Section 3 explains the methodology, section 4 provides details on the dataset, and section 5 presents the results. Conclusions and limitations follow in section 6.

## 2. Theoretical background and hypotheses

### 2.1 The emergence of different types of innovations

Innovations emerge along the evolution of technological trajectories which have been discussed in the literature on several levels.On the macro level Kondratev (1926) proposed his theory of long waves with its (technology-driven) economic cycles, ranging over

several decades, once popularized by Schumpeter (1934). On the meso level, technological trajectories (Dosi (1982)) describe how technological fields evolve, and which implications can be drawn for the industry relying on such fields. On the micro or firm level, Achilladelis (1993) discusses the concept of corporate technological traditions, thus examining how technological trajectories affect the creation of innovations within single firms.

The emergence of a technological trajectory is triggered by a technological paradigm or discontinuity which is often related to scientific discoveries, while incremental innovations emerge through continuous technical change afterwards (Dosi (1982), Dosi (1988), Godoe (2000)). Technological trajectories can be modelled via S-curves, which can be considered to be either the performance of a new technology over time (see e.g. Christensen (1997), Sood and Tellis (2005)) or the cumulative number of innovations within that cycle. Here, the emergence of a technological trajectory goes hand in hand with the birth of new technology fields, with a flood of incremental innovations emerging over the course of the trajectory, following some discontinuous innovations from the beginning (Achilladelis et al. (1990), Achilladelis (1993), Andersen (1999)).

In the literature on innovation types, a more specific definition of innovation types than discontinuity or incremental innovation has evolved. Chandy and Tellis (1998), Sorescu et al. (2003), and Chandy et al. (2006) distinguish innovations according to the novelty of the underlying technology and the technology's impact on the market; incremental innovations rely on minor changes in the technology base and deliver low extra benefits to customers. In contrast, ceteris paribus a high level of customer benefits represents a market breakthrough. If, however, customer benefits are low but there is a novel technology base, then it is a technology breakthrough. Radical innovations are based on both a novel technology base and substantial customer benefits (for an illustration, see Table 1).

*{Insert Table 1 about here}*

### 2.2 R&D in pharmaceuticals and biotechnology

The different phases of drug development and the creation of innovations take place across various institutions nowadays. Universities and public research institutes perform the bulk of basic research for understanding the underlying principles of substances. Biotechnology firms engage in applied research, while pharmaceutical firms have focused their downstream capabilities on further developing[*] the methodologies and substances found, for instance, by universities or biotechnology firms towards marketable drugs (see e.g. Achilladelis and Antonakis (2001), Gambardella (1995) Henderson et al. (1999), Grabowski and Vernon (1994)). The fundament of this process is that the pharmaceutical industry performs basic research on a moderate level to be able to understand and absorb externally generated knowledge (Cohen and Levinthal (1989), Cockburn and Henderson (1996), Gambardella (1992), Rosenberg (1990)) and, in doing so, widely cooperates with public labs (Gambardella (1995), pp. 48-81) or biotechnology firms (which are a frequent acquisition target). In order to quickly absorb externally generated knowledge and convert it into products, industrial researchers frequently work on topics similar to their colleagues in publicly funded labs (Hicks et al. (1996), Narin and Rozek (1988)). Pharmaceutical companies publish extensively (European Commission (2003), pp. 310-311, Hicks (1995), Koenig (1983)) because their papers serve as tickets to (scientific) information networks (Cockburn and Henderson (1998), Hicks (1995)). Simultaneously, the freedom to publish as an employee within a company attracts good scientists (Healey (1978), Rubenstein (1989), pp. 48-49) and is promoted by many firms (Zucker and Darby (1997)). As a consequence, those firms with a policy to publish are more successful than others (Henderson and Cockburn (1994)).

[*] The differences between basic and applied research as well as development are laid out in the OECD Frascati manual.

Finally, about 80 percent of all pharmaceutical products and about 45 percent of all processes are patented (Arundel and Kabla (1998)). Overall, patent protection is particularly effective in this industry (Gambardella (1995)), playing an important role for preventing imitation (Levin et al. (1987)). Typically, patenting occurs when new chemical and potentially useful compounds are synthesized, applications for them are identified, and manufacturing processes are developed.

### 2.3 The roots of innovations

Narin et al. (1997), for instance, found that almost 80 percent of the references from US patents in pharmaceuticals relate to science published by public sector institutions. Mansfield (1991) observed that about 20% of drugs could only be developed with substantial help from recent academic research. So since many path-breaking discoveries are made in publicly funded research labs, it seems likely that the relevant knowledge to create radical innovations and technological breakthroughs also stems from there, and external public sources are the primary base for creating these two types of innovations rather than internally generated knowledge.

*Hypothesis 1: Radical innovations and technological breakthroughs build on more public sector knowledge than market breakthroughs and incremental innovations.*

As Rosenberg and Nelson (1994) remark, only about sixty percent of the research conducted in the public sector is basic, while the rest is more applied, and in some domains rather developmental work. As discussed in section 2.1, Dosi (1988), Ayres (1988) and Godoe (2000) remark that the beginning of a technological trajectory is frequently triggered by science-based discoveries. Science can be applied, but also basic, exploring the fundaments of discoveries and phenomena, which are pivotal for many applied tasks. These more applied tasks often already take place in line with incremental technical change on the technological trajectory, and they may lead to incremental innovations. So

not all research conducted in the public sector appears to be of equal importance to radical innovations and technological breakthroughs; basic research appears to be of particularly high relevance. These arguments lead to the next hypothesis:

*Hypothesis 2: Radical innovations and technological breakthroughs build on more basic scientific knowledge than market breakthroughs and incremental innovations.*

Firms should absorb, process, and further develop such outside-generated basic scientific knowledge to create radical innovations and technological breakthroughs. Kiernan (1991), for instance, denotes that basic research alone, except in biotechnology, was seldom the direct base for new drugs. This means that in particular, incremental innovations and market breakthroughs, which represent the bulk of all drugs, should build on own prior scientific and technical work to a much higher degree than the two former types of innovations. In the light of these arguments and the previous hypotheses it is proposed:

*Hypothesis 3: Radical innovations and technological breakthroughs build on less own prior scientific and technical work than market breakthroughs and incremental innovations.*

**2.4 Drug lifecycle management**

If a drug finally has been developed, firms apply different strategies for the further development and protection of pharmaceutical innovations in order to prevent imitation by competitors such as generic drug makers. These practices are known as drug lifecycle management or 'evergreening'. According to Howard (2007), a number of consecutive patents for new combinations, uses, formulations, manufacturing processes, or molecules follow the original (basic) patent. They aim not only to reduce manufacturing costs but also to extend the area of application of the drug or to improve its current state in order to offer patients a migration path to 'better' medicines. However, not all evergreening

activities aim to achieve a benefit over generic competitors. As Chong and Sullivan Jr (2007) observe, already approved drugs (or drugs that had failed in later clinical studies for certain indications) are a valuable search field for new applications: since clinical studies already exist, the drug development process can be not only much cheaper but also faster, which offers a substantial benefit for both drug makers and patients.

The stream of additional patents is accompanied by various papers, reporting novel applications of the drug in fundamental research. However, pharmaceutical firms have to deliver results from various clinical studies in order to achieve market approval in several countries. According to Figure 1, the spectrum of studies a firm has to conduct for achieving market approval is quite broad. It therefore seems likely that most of the papers deal with clinical studies for authorities in a variety of countries that reflect measures to show safety and efficacy of the drug or even further improvements of it. Therefore it is proposed:

*Hypothesis 4: The stream of papers following the basic patent and published by the same firm is primarily clinical.*

Since radical innovations are more valuable than the other types of innovations (Sorescu et al. (2003)), it is assumed that, in the context of drug lifecycle management, firms should be eager to apply for more additional patents than in the case of the other types of innovations in order to, first, expand protection legally by creating patent fences and, second, fully exploit the technological and market potential of newly found and approved substances:

*Hypothesis 5: Radical innovations lead to more subsequent patent filings by the same firm than in the case of the other types of innovations.*

In pharmaceuticals, the path from basic research towards marketable drugs is standardized, starting with the synthesis of the compound, various clinical studies representing feedback loops for the actual development process, and - last but not least - market approval. The

path is long-lasting (see Table 2 for empirical studies on the time-lag between compound synthesis and commercialization such as market approval) and associated with substantial risk ex ante regarding the commercially relevant output of R&D activities, where only a small fraction of all synthesized compounds finally enters the market. Figure 1 exemplifies this process with various characteristics for the United States Food and Drug Administration (FDA).

*{Insert Figure 1 and Table 2 about here}*

The high level of uncertainty regarding the success of developmental projects would make it extremely costly for firms to employ drug lifecycle management activities early on. Instead, they should start when the likelihood is relatively high that a drug will finally be marketed. According to the studies in Table 2, market introduction of a drug takes place about eight to fourteen years after compound synthesis.

This finally leads to the following hypothesis:

*Hypothesis 6: Drug lifecycle activities such as further patenting and publishing of scientific papers occur when the likelihood is high that the drug will contribute to firm success.*

The possible importance of a drug can be recognized relatively early during the development stage of a drug when first clinical studies indicate a high benefit for patients (see e.g. Katzenstein and Grossman (2001)). However, during ongoing clinical trials the drug may show adverse side effects which may finally prevent its market introduction. Nevertheless, if high benefits for patients are in sight, firms may already start their lifecycle management activities early, taking greater risks while envisioning greater chances. In other cases with low extra benefits of the drug, early lifecycle management activities may be appropriate when the risk of failure is lower and, ceteris paribus, market introduction is more likely to take place.

*Hypothesis 7: Additional drug patents are filed earlier for radical innovations and market breakthroughs.*

*{Insert Table 3 about here}*

## 3. Methodology

The focus of my analysis lies on drugs approved for the United States, the world's largest market for pharmaceutical products (BPI (2004)).

### 3.1 Differentiating innovations

Drugs are distinguished in this paper into radical innovations, technological breakthroughs, market breakthroughs and incremental innovations as was done by Sorescu et al. (2003) or Chandy et al. (2006). The differentiation relies on practices by the FDA for classifying drugs according to the novelty of their chemical substance (i.e. new chemical or molecular entities (NMEs) vs. updates, i.e. substances that already have been under review by the authority) and therapeutic potential which determines review speed (priority review for drugs fulfilling a high medical need vs. standard review). NMEs with priority review are defined as radical innovations, NMEs with standard review as technological breakthroughs, updates with priority review as market breakthroughs, and updates with standard review as incremental innovations. See Table 4 for an overview.[†]

*{Insert Table 4 about here}*

### 3.2 Retrieval and computation of data

For testing the hypotheses, bibliometric data of both papers and patents is employed, reflecting both scientific and technical developments. Table 5 briefly summarizes which data were analysed and where they were obtained from.

For evaluating hypothesis 1, the origin of the patent and nonpatent references cited within the basic patents was assigned to two categories. The first category, the public sector, comprises all universities, medical schools, private non-profit research institutes, and

[†] Employing this scheme for differentiating between different types of innovation also received criticism since in practice the benefits from priority reviewed drugs are not necessarily higher than from standard review drugs (Cohen (2005)).

hospitals, but also institutions like the National Institute of Health or the National Cancer Institute. Private firms constitute the second category.

The knowledge base of the innovations was checked via backward references to patents and papers found in the drugs' basic patents, while the scientific base of an innovation was characterised by the nature of its nonpatent references. Here, only scientific articles were taken into account: no books, manuals, etc. The 'basicness' of the articles (hypothesis 2) was assessed by means of the CHI Research/ipIQ journal classification (Narin (1976), Narin et al. (1976)), relying on the type of journal where the article is published. The four-levels of the classification range from *clinical observation* (level 1) to *clinical mix, clinical investigation*, and *basic research* (level 4), and the share of articles from the last category was calculated.

*{insert Table 5 about here}*

In order to test H3, both applicants and inventors of the basic patents were compared to those authors and inventors mentioned in the patents and publications cited therein, and the share of self-references was then calculated.

Time-lags were computed via the priority date of patents and the publishing date of papers, where for the latter the entry date into the database was used as a proxy.[‡] In either case, the priority date of the basic patent served as a baseline since it represents a proxy for the point in time when the important synthesis of the compound took place.

To assess hypothesis 6, the time-lag between developmental activities and commercialization of the basic patent was computed in order to compare it to further patenting and publishing activities. For confirming H6, the development-commercialization lag should come close to the peak of overall patenting and publishing

[‡] The Chemical Abstracts database is updated on a weekly basis, so a bias here seems to be negligible.

activities. Commercialisation was measured by an event-study approach. Three different indicators were chosen here: sales growth, impact on market value (as expressed by changes of Tobin's q), and FDA market approval. All three are widely employed to measure firm success (e.g. Baum and Wally (2003), Desarbo et al. (2005), Wiklund and Shepherd (2003), Lang and Stulz (1994), Tanriverdi and Venkatraman (2005), Wernerfelt and Montgomery (1988)) or the impact of new product introductions (Sorescu et al. (2003)).

For a sales signal, the product launch had to have occurred within the triad region (North America, Europe, and Japan), which was accountable for 75-90 percent of the world market sales throughout the observation period (BPI (2004), Reiß et al. (1997), p. 13). Therefore, the year for the sales signal was chosen when the drug was launched either in the United States, Japan or two countries out of the following four: France, Germany, Italy, and the United Kingdom, the world's largest pharmaceutical markets (VFA (2006)).

Tobin's q, in contrast, is continuously influenced over time since any information with potential impact on firm value is represented immediately in the firm's stock price according to the efficient market hypothesis (Fama (1970), Fama (1991)). To assess this stream of information, all potential information on a drug published in business and industry-news related publications stemming from the PHARMAMarketLetter database were tracked, comprising information from press releases, health care journals, interviews, conferences, etc. from 1992 to the present.[§] More specifically, changes in the stock price over a three-day time window were computed, from one day prior to the publication of the press release, etc. to two days thereafter, as was used by Francis et al. (1992) and Sorescu

[§] Publishing dates of papers and patent granting dates were not directly taken into account. However, publicly traded firms are obliged to publish relevant information with impact on business activities, such as news on the outcome of approvals by several drug approval authorities, coupled with news on the outcome of clinical trails. Important patents and papers should therefore be cited in press releases, etc. and on this way appear in the business and industry literature.

et al. (2003). This data was adjusted for the expected stock market return, i.e. general stock movements of the Dow Jones Industrial Average Index, the leading stock market index in the world. The absolute value of these changes was subsequently calculated, since the goal was to measure the points in time when the highest impact on Tobin's q can be expected. These data were used for weighting the events with the sum of the absolute values per year, yielding a weighted impact index.

In order to elicit differences among the four types of drugs, analysis of variance with a post-hoc Scheffé-test was performed for all drugs. For those cases where multiple events per drug (such as various journal publications per drug) were obtained, the distribution of events based on all events of all drugs was computed, not only based on mean values per drug.

**4. The sample**

For the years 1999-2004, the FDA approved, in total, 154 NMEs (including 28 orphan drugs), and 306 updates (including eleven orphan drugs). All orphan drugs which only target a small population and, therefore, are financially only of limited importance for a company were excluded, even though the FDA grants extended monopoly rights in exchange for marketing such a drug. In the next step, this dataset was narrowed by about 50 percent when excluding all drugs where no stock quotes were available, e.g. because the firms were privately held or due to mergers and acquisitions that led to a delisting of the company. The timeframe for product launches was set to 1990-mid 2007.[**] Drugs that were both approved between 1999 and 2004 as updates *and* NMEs due to product lifecycle management activities were excluded, as well as all with missing data. As a result, 64 drugs with complete data could be identified: 21 updates and 43 NMEs. According to the

[**] Going back further than 1999 here means that drugs may also have been launched in other countries than the US prior to the approval by the FDA.

definition of Sorescu et al. (2003), the sample comprises 17 radical innovations, 26 technological breakthroughs, three market breakthroughs, and 18 incremental innovations. Since the numbers per class of innovations are, in some cases, relatively small, tests were conducted for two groups of innovations, namely radical innovations and technological breakthroughs on the one hand, and market breakthroughs and incremental innovations on the other, as the hypotheses have been formulated.

## 5. Results and Discussion

### 5.1 Roots of innovations

In H1 it was proposed that radical innovations and technological breakthroughs build on more public sector knowledge than market breakthroughs and incremental innovations do. Even though the data shows that there is such a difference, this hypothesis can be rejected because the results are not significant; neither between the two aggregated groups of innovations nor between the four single types (see Table 6). This holds true for both scientific and technical knowledge (i.e. incorporated in papers and patents respectively). Public sector knowledge therefore seems to be equally important for all of them. Remarkably, more than two thirds of all papers cited within the patents come from the public sector, while this is the case for less than ten percent of all patents (as indicated by the mean values in Table 6).

*{Insert Table 6 about here}*

It was postulated in H2 that radical innovations and technological breakthroughs build on more basic scientific knowledge. In Table 7 the results are presented, indicating that the scientific research cited within the basic patents is more basic for the first group of innovations, confirming the hypothesis. This underlines that many radical innovations build on scientific paradigms (which are certainly basic science-oriented) as proposed by Dosi (1988). The more detailed analysis of the four different types of innovations suggests that the difference is only significant between radical innovations and incremental ones.

This highlights the importance of basic research for drugs that turn out to be cornerstones of the pharmaceutical industry.

*{Insert Table 7 about here}*

The own prior knowledge base was a further issue in this investigation. According to H3, it was postulated that radical innovations and technological breakthroughs build less on own prior scientific and technical work than market breakthroughs and incremental innovations. Table 8 reveals that for scientific knowledge (papers), the relationship is inverse, but not statistically significant. With respect to technical work (patents), the expected relationship is found, but the results lack significance as well. So hypothesis 3 has to be rejected.

*{Insert Table 8 about here}*

The data sample was rather small, which may be the reason that no significant results could be obtained for H1 and H3. To conduct robustness checks, the sample was expanded by adding data on 44 randomly selected drugs from the same time period that were registered at the FDA by firms for which no financial data was available, and my hypotheses so far were re-tested. The results (not shown) change in two cases. First, radical innovations build on a significantly higher degree ($p<0.1$) on publicly available *technical* knowledge than do technological breakthroughs. The latter rely on much less technical knowledge than the four other groups. It was checked whether they simply comprise more patent references than the other groups, so that a similar absolute number of public references as the other innovation types would yield a much lower relative value here, but this is not the case. Interpreting the overall findings for knowledge stemming from the public sector (equal importance of scientific knowledge, more importance of technical knowledge for radical innovations) in the light of the results from H2 (i.e. radical innovations are based on significantly more basic research), ceteris paribus more *applied scientific research* from the public sector seems to be relevant for the other types of innovations. The phenomenon

of technical knowledge observed here deserves attention in future research. Since patents in pharmaceuticals are very science-based, the boundaries between scientific and technical knowledge may be blurry, and the results relating to patent references may be an artefact of the measurement instruments here.

The second finding in the robustness check is that radical innovations and technological breakthroughs build significantly more on own prior scientific work than market breakthroughs and incremental innovations do ($p<0.05$). So it becomes obvious that absorptive capacity, rooted in own research activities, is much more important for creating radical innovations than for other types of innovations. Therefore pharmaceutical firms that cut internal research activities run the risk of losing their abilities to come up with radical innovations that might turn into blockbuster drugs in the future.

### 5.2 Publishing and patenting activities over the course of time

It was hypothesized in H4 that the stream of papers following the basic patent and published by the same firm is primarily clinical. In total, about 400 different journals were identified, representing about 1,400 articles. The CHI Research/ipIQ classification covered about 75% of these journals, and 84% of all articles.[††] The results can be found in Table 9. It becomes obvious that more than 80% of all articles relate, in fact, to clinical research, with a strong emphasis on clinical investigation. So Hypothesis 4 can be confirmed. Additionally, the results from Table 9 were tabulated against the different types of innovations (see Table 10). Here, descriptive statistics suggest that particularly radical innovations tend to lead to basic research activities to a higher degree than other innovations do.

*{Insert Tables 9 and 10 about here}*

[††] One third of the missing articles appeared in foreign-language journals not classified by CHI Research/ipIQ.

Hypothesis 5 proposed that radical innovations lead to more subsequent patent filings by the firm that developed/marketed that drug than in the case of other types of innovations. The results, which corroborate hypothesis 5, can be found in Table 11. While radical innovations lead to about 17 subsequent patent filings, there are, on average, 25 other patent filings for the other three types of drugs. The same holds true for differentiating the results further. It was assumed that the data may be biased here: since the search was conducted on documents based on the Chemical Abstracts registry number, the results for those innovations relying on updates (i.e. incremental innovations and market breakthroughs) may contain data from NMEs as well. The differentiation on the basis of NMEs (radical innovations and technological breakthroughs) should, however, be unbiased in this case. Still, no significant difference was found. Pharmaceutical firms therefore seem to apply similar lifecycle management strategies for all major drugs.

*{Insert Table 11 about here}*

For determining H6, first the lag structure between basic patent and its commercialisation was computed, starting with inspecting the results from analysing the sales signal. According to Table 12, there is an average time-lag of about eleven years, while the different types of drugs do not vary significantly from each other here (see Table 13).[‡‡] For an effect on Tobin's q, the distribution of drug-related news was first considered. On average, they appear about twelve years after the basic patents' priority date, and the time is slightly shorter for NMEs. News related to standard-review updates are published after significantly more time, while priority-review updates appeared after significantly less time. The weighted data, in contrast, yields a mean value of 11.74 years, with no

[‡‡] Since drugs usually do not receive peak sales already in the first year on the market, a stronger sales signal can certainly be expected two or three years afterwards (for statistics on the development of drug sales, see Grabowski and Vernon (1990)).

significant difference between the types of drugs.[§§] Finally, FDA approval occurs, on average, 12.61 years thereafter, and there was no significant difference in the lag structure between the various types of drugs. So my previous results appear to be quite robust.[***]

*{Insert Tables 12 & 13 about here}*

To assess H6 and H7, I next compare these lags to further patenting and publishing activities. According to Table 14, additional patent applications appear, on average, eleven years after the basic patent, and additional papers for radical innovations are published, on average, after twelve years. Finally, both activities peak when commercialisation is in sight, confirming H6. While additional patents for radical innovations and market breakthroughs are filed significantly earlier than for technological breakthroughs and incremental innovations (see Table 15), I checked the same for publications, and found that additional papers for radical innovations are published, on average, twelve years after the basic patent, which is significantly earlier than in the case of technological breakthroughs. So these findings support H7, confirming that applicants seek to add additional patent applications timely for drugs with a high market potential. Firms therefore seem to differentiate their lifecycle strategies not by the amount of additional patents but rather by the speed of their application.

*{Insert Tables 14 and 15 about here}*

The confirmation of the lag in the order of 11 to 12 years between compound synthesis and its commercialisation also has implications for empirical research on technological capabilities, knowledge stocks, and other aspects in strategic management theories that are

[§§] The data used for measuring the impact on Tobin's q, however, is biased threefold: first, due to the many mergers and acquisitions, complete stock price data could only be obtained for about 83 percent of all drugs. For the remaining ones, data was obtained for, on average, 80 percent of all news events. Second, the PHARMAMarketLetter database comprises information from 1992 onwards; only 40 percent of the basic patents were filed thereafter. So were the missing data included, the peak would instead shift towards shorter lags. But third, the dataset is also biased towards drug-related news that will occur in the future since many drugs are still on the market.

[***] For a discussion on the magnitude of the impact on Tobin's q, please see Appendix I.

widely operationalised by bibliometric indicators such as publication and patent counts. For instance, De Carolis (2003), Hirschey and Richardson (2004), Schoenecker and Swanson (2002) employed relatively short time lags in the order of zero to three years between patenting activities and firm success. The results presented in this paper suggest that here the effect of additional patenting activities was primarily captured. In order to fully assess the impact of patenting activities on firm success in pharmaceuticals, including important basic patents, the long lag structures in this industry suggest employing either lags on the order of the mean plus one standard deviation, yielding a timeframe of about 16 to 19 years, or the calculation of patent *stocks*, which were, for instance, used by DeCarolis and Deeds (1999), Hall et al. (2004) and Klavans and Deeds (1997).

*{Insert Table 16 about here}*

## 6. Conclusions and limitations

This study investigated the pharmaceutical industry which is, much more than other industries, dependent on scientific advances as well as work done in the public sector. Such work, particularly of scientific kind, is equally important for all types of drug innovations. Looking at the basicness of the scientific research it was uncovered that radical innovations here build on more basic scientific knowledge than do incremental innovations, confirming that new technological trajectories are rooted in scientific discoveries as described by Dosi (1982). Radical innovations and technological breakthroughs build on prior own scientific work to a higher degree than do market breakthroughs or incremental innovations, but this does not hold true for own prior technical work, i.e. own patents serving as the basis for new drugs. So absorbing externally-generated knowledge works quite well within pharmaceutical firms, and conducting own scientific research is instrumental in this industry for generating radical innovations and technological breakthroughs. As Tijssen (2004) found, the level of basic research stemming from industry has been declining in

recent years. This may also have an impact on bringing radical innovations onto the market in the future.

The time-lag between filing a basic patent on a compound and its commercialisation as a drug is, at 11 to 12 years, on the order of what other studies have found before. It was shown that additional patent filings as well as publishing activities of firms occur at about the same time, so firms foster their developmental activities once marketing of the drug is about to start. The stream of papers following the basic patents consists of about 19 papers on average and is primarily clinical. On average, 23 additional patents are filed per basic patent over time, which may, to some degree, contribute towards a patent thicket around the basic patent. There is no significant difference in the number of these additional patents among the different types of innovations, but those relating to radical innovations and market breakthroughs are filed significantly earlier. This may imply that firms speed up their development process in the light of high expectations regarding market success. After all, these findings help us better understand the drug development process in the pharmaceutical industry, particularly knowledge generation and protection.

The results encounter the typical limitations with respect to the use of bibliometric data and stock market-related information for event studies as described, for instance, by Chaney et al. (1991). Another limitation is that drugs which failed in clinical trials for which no information was available were excluded. One could assume that inventions of drugs which failed in the approval process would deliver interesting insights for theories on innovation as well. However, per definitionem, these are solely inventions, not innovations, since they cannot be marketed (Schumpeter (1939), Freeman and Soete (1997)). Future research should address other industries as well. As they are less science-dependent than pharmaceuticals, one could assume that the importance of basic science as a source of radical innovations might be lower there. Instead, one would expect a higher

importance of more applied research in other industries. Future studies could also dive further into the definition of basic research, which can be differentiated into pure and use-inspired basic research according to Stokes (1997), a differentiation which cannot be made with the ipIQ/CHI research journal classification which was employed as a measurement instrument here. A hypothesis to be tested in this context may be that pharmaceutical firms tend to conduct use-inspired basic research in the sense of Stokes (1997). The effects of creating patent thickets or clusters for single drugs could also be worth more thorough investigation, but also integrating information from journal articles in order to investigate the nature of R&D races.

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Figure 1: Schematic view of the new drug development process in the pharmaceutical industry (source: Mathieu (2005), p. 162, modified with data from PhRMA (2007). *: 20-100 volunteers).

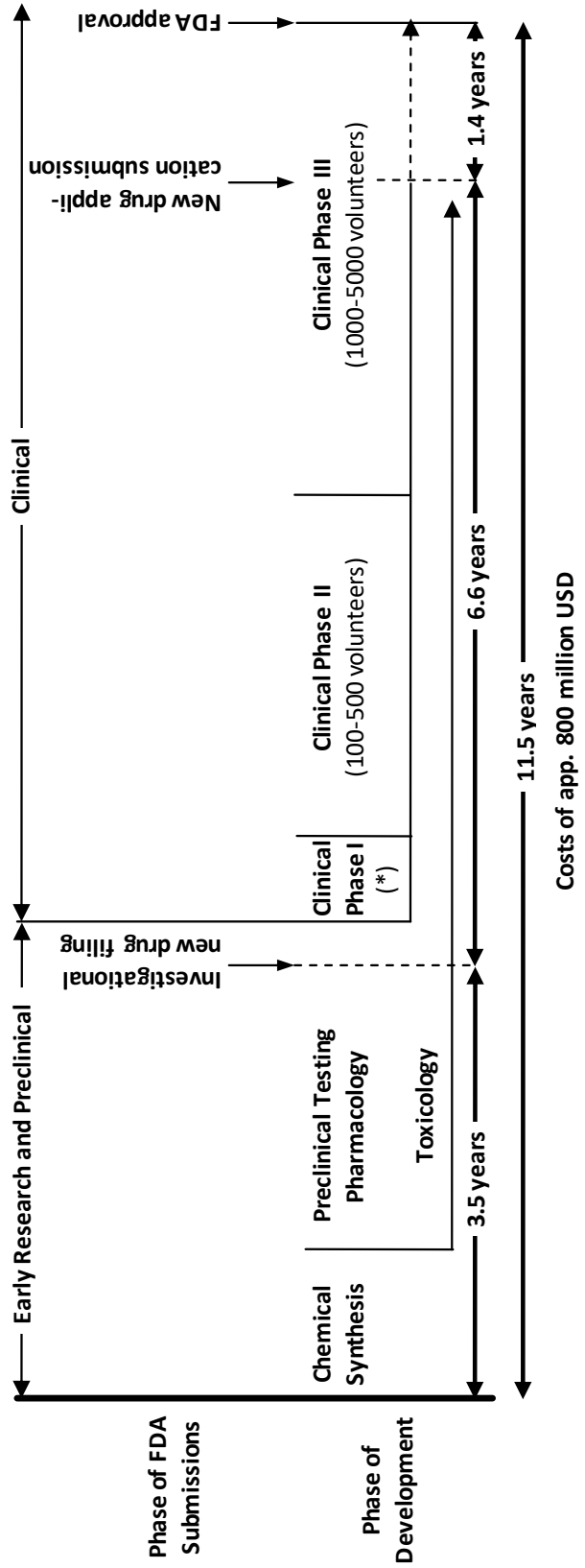

Table 1: Types of innovations.

| | | Customer need fulfilment per dollar | |
|---|---|---|---|
| | | Low | High |
| Newness of technology | Low | Incremental innovation | Market breakthrough |
| | High | Technological breakthrough | Radical innovation |

Source: Chandy and Tellis (1998), p.476.

Table 2: Overview about studies investigating lag structures between research, development, and product introduction

| Source | Scope of research | Points of reference | Results |
|---|---|---|---|
| Cockburn and Henderson (1996) | Sample of 15 drugs, missing values | Key enabling discovery, synthesis of major compound, commercialization | First phase: 22 years, second phase: 8 years, in total: 28 years |
| Comanor and Scherer (1969) | Patents from 57 US pharmaceutical companies from 1955-1960 | Patent priority, commercialization | Three years |
| DiMasi (2001) | New Chemical and Biopharmaceutical Entities approved by the FDA between 1963 and 1999 | FDA approval date, further information from surveys not specified | On average, about 14 years from synthesis to market approval in the 1980s and 1990s |
| Chandy et al. (2006) | 603 FDA-approved drugs | Patent filing to FDA approval | 9.6 years |
| Achilladelis and Antonakis (2001) | Radical innovations in pharmaceuticals | Start of R&D to commercialization | 8-10 years |
| Mansfield (1991) | Patents from 76 US companies, including 6 pharmaceutical companies<br>Data from 1975-1985 | Research results, commercialization | 7 years, but 9-10 in pharmaceuticals |
| Mansfield (1998) | Same as above | Research results, commercialization | 5-6 years, but 6-8 in pharmaceuticals. |

Table 3: Overview of hypotheses

| H# | Explanation |
|---|---|
| H1 | RIs and TBs build on more public sector knowledge than MBs and IIs. |
| H2 | RIs and TBs build on more basic scientific knowledge than MBs and IIs. |
| H3 | RIs and TBs build on less own prior scientific and technical work than MBs and IIs. |
| H4 | The stream of papers following the basic patent and published by the same firm is primarily clinical. |
| H5 | RIs lead to more subsequent patent filings by the same firm than in the case of the other types of innovations. |
| H6 | Drug lifecycle activities such as further patenting and publishing of scientific papers occur when the likelihood is high that the drug will contribute to firm success. |
| H7 | Additional drug patents are filed earlier for RIs and MBs. |

(RI – radical innovation; TB – technology breakthrough; MB – market breakthrough; II – incremental innovation)

Table 4: Types of innovations according to the FDA drug status.

| | | Therapeutic potential | |
|---|---|---|---|
| | | Standard review | Priority Review |
| Chemical Composition | Update | Incremental innovation | Market breakthrough |
| | NME | Technological breakthrough | Radical innovation |

Source: Sorescu et al. (2003), p.88.

Table 5: Data and its sources

| Data | Source |
|---|---|
| Drug names, chemical composition, therapeutic potential, approval date | FDA website |
| Year and country of market introduction, chemical abstracts (CA) reference number, drug owner/licensee* | Pharmaprojects database |
| Bibliographic data of patents and publications including patent priority data | Chemical Abstracts (CA) |
| Patent family data | Derwent World Patents Index database |
| Inventor and assignee data, inventor backward references to patents and papers** | Esp@cenet and PATONline databases |
| 'Basicness' of journals | CHI Research/ipIQ Journal classification |
| Inventor/author data including affiliation | Web of Science, Scopus, various publishers online archives |
| Publishing data of business and industry news | PHARMAMarketletter database |
| Financial data | Yahoo Finance |

* Licensee data was also included since many drugs are out-licensed for certain markets, while information from licensees may have an impact on licensors market success.
** Inventors' references stemming from full-text documents better reflect spillovers than examiner citations frequently found in patent databases (Jaffe et al. (2000), Tijssen et al. (2000)).

Table 6: Hypotheses tests H1 – public knowledge (share of public institutions among cited references per innovation patent)

| Type of innovation | RNPL | | | | | | | | RPL | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | Mean | Std.-Dev. | p (two-tailed T-Test) | F-value | Significance of difference (Scheffé-test, p-values) (b) | (c) | (d) | n | Mean | Std.-Dev. | p (two-tailed T-Test) | F-value | Significance of difference (Scheffé-test, p-values) (b) | (c) | (d) |
| Radical Innovations + Technological Breakthroughs | 35 | 0.608 | 0.327 | 0.641 | - | - | | | 36 | 0.068 | 0.199 | 0.248 | - | - | | |
| Market Breakthroughs + Incremental Innovations | 14 | 0.653 | 0.294 | | - | - | | | 15 | 0.026 | 0.058 | | - | - | | |
| (a) Radical Innovations | 14 | 0.665 | 0.253 | - | 0.342 | 0.848 | 0.999 | 1.000 | 14 | 0.143 | 0.296 | - | 1.967 | 0.207 | 0.989 | 0.263 |
| (b) Technological Breakthroughs | 21 | 0.570 | 0.318 | - | (0.795) | | 0.987 | 0.901 | 22 | 0.020 | 0.074 | - | (0.132) | | 0.934 | 1.000 |
| (c) Market Breakthroughs | 3 | 0.639 | 0.127 | - | | | | 1.000 | 2 | 0.100 | 0.141 | - | | | | 0.926 |
| (d) Incremental Innovations | 11 | 0.656 | 0.368 | - | | | | | 13 | 0.014 | 0.035 | - | | | | |
| Sample size | N=49 (Patents without nonpatent references and missing values excluded) | | | | | | | | N=51 (Patents without patent references excluded) | | | | | | | |

RNPL – Reference to Nonpatent Literature; RPL – Reference to Patent Literature

Table 7: Hypotheses tests H2 basicness of scientific knowledge (share of nonpatent references that are basic research according to ipIQ/CHI Research Journal Classification)

| Type of innovation | Basicness of RNPL | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | n | Mean * | Std.-Dev. | p (two-tailed T-Test) | F-value | Significance of difference (Scheffé-test, p-values) (b) | (c) | (d) |
| Radical Innovations + Technological Breakthroughs | 36 | 0.547 | 0.356 | 0.006 | - | - | | |
| Market Breakthroughs + Incremental Innovations | 13 | 0.229 | 0.285 | | - | - | | |
| (a) Radical Innovations | 15 | 0.651 | 0.339 | - | 3.636 | 0.494 | 0.318 | 0.033 |
| (b) Technological Breakthroughs | 21 | 0.473 | 0.357 | - | (0.020) | | 0.753 | 0.313 |
| (c) Market Breakthroughs | 3 | 0.244 | 0.423 | - | | | | 1.000 |
| (d) Incremental Innovations | 10 | 0.225 | 0.262 | - | | | | |
| Sample size | N=49 (Zero-values and missing data excluded) | | | | | | | |

Table 8: Hypotheses tests H3 – share of own prior knowledge (references to self-generated patents/papers)

| Type of innovation | RNPL | | | | | | | | RPL | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | Mean | Std.-Dev. | p (two-tailed T-Test) | F-value | Significance of difference (Scheffé-test, p-values) (b) | (c) | (d) | n | Mean | Std.-Dev. | p (two-tailed T-Test) | F-value | Significance of difference (Scheffé-test, p-values) (b) | (c) | (d) |
| Radical Innovations + Technological Breakthroughs | 36 | 0.228 | 0.310 | 0.184 | - | - | | | 36 | 0.429 | 0.405 | 0.426 | - | - | | |
| Market Breakthroughs + Incremental Innovations | 15 | 0.106 | 0.258 | | - | - | | | 15 | 0.519 | 0.371 | | - | - | | |
| (a) Radical Innovations | 14 | 0.257 | 0.319 | - | 0.659 | 0.976 | 0.845 | 0.682 | 14 | 0.489 | 0.393 | - | 0.346 | 0.918 | 1.000 | 0.997 |
| (b) Technological Breakthroughs | 22 | 0.210 | 0.310 | - | (0.581) | | 0.926 | 0.842 | 22 | 0.319 | 0.417 | - | (0.792) | | 0.987 | 0.833 |
| (c) Market Breakthroughs | 3 | 0.083 | 0.144 | - | | | | 0.999 | 2 | 0.500 | 0.141 | - | | | | 1.000 |
| (d) Incremental Innovations | 12 | 0.111 | 0.284 | - | | | | | 13 | 0.522 | 0.398 | - | | | | |
| Sample size | N=51 (Zero-values and missing data excluded) | | | | | | | | N=51 (Patents without patent references excluded) | | | | | | | |

RNPL – Reference to Nonpatent Literature; RPL – Reference to Patent Literature

Table 9: Distribution of the articles across different journal types according to the CHI Research/ipIQ journal classification.

| Level | Description | Number of Journals | Number of articles |
|---|---|---|---|
| 1 | clinical observation | 29 (10%) | 70 (6%) |
| 2 | clinical mix | 72 (24%) | 333 (28%) |
| 3 | clinical investigation | 125 (42%) | 614 (53%) |
| 4 | fundamental research | 75 (25%) | 152 (13%) |

Table 10: Distribution of the articles of the different types of drugs across different journal types according to the CHI Research/ipIQ journal classification.

| Type of innovation | CHI Research/ipIQ journal classification level | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| Radical Innovations (NME - priority review) | 5% | 30% | 46% | 19% |
| Technological Breakthroughs(NME – standard review) | 8% | 27% | 53% | 12% |
| Market Breakthroughs (Updates - priority review) | 5% | 30% | 49% | 15% |
| Incremental Innovations (Updates – standard review) | 8% | 32% | 49% | 11% |

Table 11: Hypotheses tests H5 – additional patent applications

| Type of innovation | additional patents | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | n | Mean | Std.-Dev. | p (two-tailed T-Test) | F-value | Significance of difference (Scheffé-test, p-values) (b) | (c) | (d) |
| Radical Innovations | 17 | 16.64 | 13.02 | 0.095 | - | - | | |
| Other types of innovations | 47 | 25.28 | 27.36 | | - | - | | |
| Radical Innovations + Technological Breakthroughs | 43 | 14.84 | 14.64 | 0.002 | - | - | | |
| Market Breakthroughs + Incremental Innovations | 21 | 39.67 | 31.92 | | - | - | | |
| (a) Radical Innovations | 17 | 16.65 | 13.02 | - | 7.175 | 0.978 | 0.029 | 0.071 |
| (b) Technological Breakthroughs | 26 | 13.65 | 15.74 | - | (0.000) | | 0.013 | 0.012 |
| (c) Market Breakthroughs | 3 | 58.67 | 11.93 | - | | | | 0.446 |
| (d) Incremental Innovations | 18 | 36.50 | 33.28 | - | | | | |
| Sample size | N=64 | | | | | | | |

Table 12: Descriptive statistics for time differences [in years]

| | Total observations | Number of drugs | Mean | Median | Std. Dev. | Min | Max |
|---|---|---|---|---|---|---|---|
| Market introduction (per drug data) | 64 | 64 | 10.89 | 10 | 5.02 | 0 | 23 |
| Tobin's q: Business news. weighted with change in stock price (total news) | 3441 | 63 | 11.74 | 11 | 5.78 | -3 | 34 |
| Tobin's q: Business news (unweighted) (total news) | 3441 | 63 | 12.17 | 12 | 5.66 | -3 | 34 |
| FDA approval year (per drug data) | 64 | 64 | 12.61 | 12 | 6.87 | 0 | 30 |

* Positive values originate from related patents that were mentioned by the Pharmaprojects database. There were five of these cases in the sample.

Table 13: Descriptive statistics for time differences [in years] and ANOVA results

| | Type of innovation | Total observations | Number of drugs | Observations per drug | F-Value (p-value) | Mean | Std. Dev. | Significance of difference (Scheffé-test, p-values) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | (b) | (c) | (d) |
| Market introduction (per drug data) | (a) Radical Innovations | 17 | 17 | - | 1.363 | 11.53 | 4.06 | 0.999 | 0.492 | 0.781 |
| | (b) Technological Breakthroughs | 26 | 26 | - | (0.263) | 11.73 | 4.57 | | 0.432 | 0.652 |
| | (c) Market Breakthroughs | 3 | 3 | - | | 6.67 | 2.08 | | | 0.800 |
| | (d) Incremental Innovations | 18 | 18 | - | | 9.78 | 6.37 | | | |
| Business news. weighted with change in stock price (total news) | (a) Radical Innovations | 30.35 | 17 | 1.79 | 2.023 | 12.21 | 4.24 | 0.623 | 0.690 | 0.874 |
| | (b) Technological Breakthroughs | 31.55 | 25 | 1.26 | (0.116) | 10.29 | 4.89 | | 0.981 | 0.212 |
| | (c) Market Breakthroughs | 6.67 | 3 | 2.22 | | 9.26 | 4.83 | | | 0.408 |
| | (d) Incremental Innovations | 27.92 | 18 | 1.55 | | 13.46 | 7.71 | | | |
| Business news (unweighted) (total news) | (a) Radical Innovations | 893 | 17 | 52.5 | 50.443 | 11.95 | 4.35 | 0.637 | 0.000 | 0.000 |
| | (b) Technological Breakthroughs | 1158 | 25 | 46.3 | (0.000) | 11.63 | 5.02 | | 0.000 | 0.000 |
| | (c) Market Breakthroughs | 340 | 3 | 113.3 | | 9.88 | 4.29 | | | 0.000 |
| | (d) Incremental Innovations | 1050 | 18 | 58.3 | | 13.71 | 7.13 | | | |
| FDA approval year (per drug data) | (a) Radical Innovations | 17 | 17 | - | 1.281 | 12.23 | 4.96 | 0.989 | 0.927 | 0.672 |
| | (b) Technological Breakthroughs | 26 | 26 | - | (0.289) | 11.50 | 5.75 | | 0.965 | 0.403 |
| | (c) Market Breakthroughs | 3 | 3 | - | | 9.33 | 3.79 | | | 0.609 |
| | (d) Incremental Innovations | 18 | 18 | - | | 15.11 | 9.55 | | | |

Table 14: Descriptive statistics for time differences [in years]

| | Total observations | Number of drugs | Mean | Median | Std. Dev. | Min | Max |
|---|---|---|---|---|---|---|---|
| Further related patent applications (total patents) | 1471 | 64 | 10.99 | 10 | 7.01 | -21 | 31 |
| Journal publications (as contained in Chemical Abstracts) (total journal publications) | 1208 | 61 | 12.15 | 12 | 6.62 | -4 | 32 |

* Positive values originate from related patents that were mentioned by the Pharmaprojects database. There were five of these cases in the sample.

Table 15: Hypothesis tests H7 - Descriptive statistics for time differences [in years] and ANOVA results

| | Type of innovation | Total observations | Number of drugs | Observations per drug | F-Value (p-value) | Mean | Std. Dev. | Significance of difference (Scheffé-test, p-values) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | (b) | (c) | (d) |
| Further related patent applications (total patents) | (a) Radical Innovations | 283 | 17 | 16.6 | 21.159 | 9.42 | 5.63 | 0.000 | 0.306 | 0.000 |
| | (b) Technological Breakthroughs | 355 | 26 | 13.7 | (0.000) | 11.77 | 6.05 | | 0.000 | 0.964 |
| | (c) Market Breakthroughs | 176 | 3 | 58.7 | | 8.16 | 4.69 | | | 0.000 |
| | (d) Incremental Innovations | 657 | 18 | 36.5 | | 12.01 | 8.15 | | | |
| Journal publications (as contained in Chemical Abstracts) (total journal publications) | (a) Radical Innovations | 305 | 16 | 19.1 | 45.516 | 12.10 | 4.75 | 0.001 | 0.000 | 0.841 |
| | (b) Technological Breakthroughs | 335 | 25 | 13.4 | (0.000) | 14.19 | 7.01 | | 0.000 | 0.006 |
| | (c) Market Breakthroughs | 173 | 3 | 57.7 | | 7.38 | 5.42 | | | 0.000 |
| | (d) Incremental Innovations | 395 | 17 | 23.2 | | 12.54 | 6.98 | | | |

Table 16: Hypotheses and results

| H# | Explanation | Results | Interpretation |
|---|---|---|---|
| H1 | RIs and TBs build on more public sector knowledge than MBs and IIs. | *Rejected*. RIs build only significantly more on technical public sector knowledge than do TBs. | Public science triggers the development of RIs. |
| H2 | RIs and TBs build on more basic scientific knowledge than MBs and IIs. | *Partially confirmed*. Comparing the four innovation types, RIs are based significantly more on basic science than IIs. | Basic science is pivotal for RIs. |
| H3 | RIs and TBs build on less own prior scientific and technical work than MBs and IIs. | *Rejected*. RIs and TBs build on more own prior scientific work than MBs and IIs. | Own scientific work is necessary to a) possess the absorptive capacity to benefit from public science and b) convert this knowledge by own scientific activities into RIs. |
| H4 | The stream of papers following the basic patent and published by the same firm is primarily clinical. | *Confirmed* | Firms predominantly seek new applications for their innovations once they have developed them, Further fundamental investigations on them are rare. |
| H5 | RIs lead to more subsequent patent filings by the same firm than in the case of the other types of innovations. | *Rejected* RIs are protected by fewer additional patents than other types of innovations. | Data relating to MBs and IIs may be biased. If solely comparing RIs and TBs, there is no significant difference. So the amount of additional patents does not seem to be a differentiation criterion. |
| H6 | Drug lifecycle activities such as further patenting and publishing of scientific papers occur when the likelihood is high that the drug will contribute to firm success. | *Confirmed*. Both patenting and publishing activities peak around the time when market introduction takes place. | Firms start to devote more resources to patent protection and further developments of their innovative products once market approval is in sight. |
| H7 | Additional drug patents are filed earlier for RIs and MBs. | *Confirmed.* Additional patents for RIs and MBs are filed significantly earlier.<br>Additional papers are published significantly later for TBs; papers for MBs are published the earliest. | Firms prioritize their resources in a way that they file additional patents earlier in cases where they expect a fast market entry. |

(RI – radical innovation; TB – technology breakthrough; MB – market breakthrough; II – incremental innovation)

**Appendix I: The impact of FDA approval on stock performance**

While computing the impact of FDA approval on market value of the firm, it was found that, even though previous studies cited in the methodology section of this paper demonstrated the contrary, in more than 50 percent of all cases the stock price dropped at the approval date, while the average change is negative (see Table A). Obviously, in a substantial amount of cases the FDA narrowed the scope of field of application for the drug contrary to investor expectations.

Table A: Approval date: Impact on stock price change

| | Observations | Mean | Std.-Dev. | Min | Max |
|---|---|---|---|---|---|
| Positive changes at approval date | 29 | +3.75% | 3.4% | +0.1% | +14.9% |
| Negative changes at approval date | 34 | -3.85% | 4.4% | -20.1% | -0.2% |
| Average change (positive and negative values) | 63 | -0.35% | 5.5% | -20.1% | +14.9% |
| Average change (absolute value) | 63 | +3.8% | 4.0% | +0.1% | +20.1% |

N=63

Relative to other stock price changes, the absolute value of the changes at the approval date is 30 percent higher than the mean change over the whole observation period (see Table B), so the approval date can, indeed, be considered as an important date for impact on market value. Nevertheless, the absolute value of the stock price change at the FDA approval date reaches only 35 percent of the highest change in the observation period, implying that there is a substantial amount of information with higher importance than the actual approval. Since weighting the different news events with stock price-change data yielded a shorter time-lag, obviously important information is released relatively early, such as reports on clinical studies, describing the therapeutic potential of the corresponding drugs. Because the results here should have a high impact on the likelihood of FDA approval, parts of the changes in market value take place prior to the actual approval date.

Table B: Change at approval date vs. change at other events

| | Mean | Std.-Dev. | Min | Max |
|---|---|---|---|---|
| Approval change divided by mean change of the drug over all industry news. etc. | 1.30 | 1.13 | 0.046 | 5.143 |
| Approval change divided by maximum change of the drug over all industry news. etc. | 0.35 | 0.39 | 0.009 | 2.068 |

N=63