Joint Discussion Paper Series in Economics

by the Universities of

Aachen · Gießen · Göttingen
Kassel · Marburg · Siegen

ISSN 1867-3678

No. 13-2018

Martin Backfisch

The Development of Firm Size and Innovativeness in the Pharmaceutical industry between 1989 and 2010

This paper can be downloaded from
http://www.uni-marburg.de/fb02/makro/forschung/magkspapers

Coordination: Bernd Hayo • Philipps-University Marburg
School of Business and Economics • Universitätsstraße 24, D-35032 Marburg
Tel: +49-6421-2823091, Fax: +49-6421-2823088, e-mail: hayo@wiwi.uni-marburg.de

The Development of Firm Size and Innovativeness in the Pharmaceutical industry between 1989 and 2010

Martin Backfisch[1]

Version: 14 April 2018

Within the last decades, there have been many technological and regulatory changes in the pharmaceutical industry. Some of these developments facilitate the innovative activities of large firms, while others foster small firms. It is therefore surprising that the implications of these changes in the pharmaceutical industry have not often been studied empirically. We contribute to the question of firm size and innovativeness in the pharmaceutical industry in presenting a brief review of the literature on innovative activities with a focus on the relation of different firm sizes in the pharmaceutical industry and present own empirical findings. Our results with project data from a broad range of firms show that the innovative activities of small firms measured by the share of their projects on all research projects have been rising strongly between 1989 and 2010. Further, the share of small firms on new drugs has been constantly increasing in this period. On the other hand, project success rates are lowest for small firms, while the rate of projects already discontinued in the preclinical phase is highest for them. We discuss these results and find that the reasons behind these developments are crucial to understand the innovative performance of the industry within the last 20 years.

Keywords: pharmaceutical R&D; drug development; success rates; firm size

JEL Classification: O32, L65

1. Introduction

Within the last decades, there have been many changes in the pharmaceutical industry. In the 1980s, the biotech boom lead to the entry of many small, start-up biotech firms. In the 1990s and the early 2000s, major changes in the technologies of drug discovery took place, for instance the methods of high throughput screening and the decoding of the human genome. Further, the regulatory standards have constantly been increased by regulatory authorities like the US Food and Drug Administration (FDA) and firms made many efforts to increase R&D efficiency, e.g. by mergers and acquisitions. Some of these developments facilitate the innovative activities of large firms, while others foster small firms. It is therefore surprising that the implications of these changes in the pharmaceutical industry have

[1] Duale Hochschule Baden-Wuerttemberg Center for Advanced Studies (DHBW CAS), Heilbronn, and Philipps University Marburg, Germany

not often been studied empirically. We will contribute to this question in presenting a brief review of research on industry evolution in the pharmaceutical industry with respect to firms' innovative activities with a focus on the relation of different firm sizes in the industry. We will present own empirical results concerning the development of the innovative activities of small, medium-sized, and large firms during the period 1989-2010. Our data from Pipeline provided by Informa Healthcare contains pharmaceutical R&D projects from a broad range of different firm sizes. Innovative activities within the different firm size groups are measured by the shares of each firm size group on the total number of R&D projects. We also look at the growth rate of the number of projects within each group to study the dynamics of the innovative activities within the industry.

Further, the question whether small or large firms are "better" in innovation is discussed by a large body of literature. We sum up arguments indicating a positive relation between firm size and innovation. Capital market imperfections, fixed cost spreading and the role of cumulative knowledge and past experience of firms point to a positive relation between firm size and innovation. Other arguments rather point to a negative relation between firm size and innovation, such as bureaucracy and management failures increasing with firm size, and the risks of R&D outsourcing. The existence of both large and small firms in the industry points to the fact that there is no optimal firm size. Empirical studies on this question focus either on the input side (R&D investments, spending) or on the output side of innovation (drug output, project success rate). In our descriptive analysis, we will both focus on the development of the input and the output side of innovation. Innovative input is measured as the number of R&D projects undertaken by different firm size groups. Output is measured as the share of introduced drugs by these firm size groups. We also analyze the development of the project success rate. The success rate is calculated as the number of successful projects within a specific study period divided by the total number of projects (successful and unsuccessful) within this period. The success rates of the different empirical studies in the literature are not comparable to each other as different data sets from different samples of firms and different definitions of small and large firms are applied. All these studies do not regard the development of the success rate over time. We will contribute to the success rate literature in analyzing the development of the success rate of worldwide projects for different firm size groups between 1989 and 2010. Additionally, we analyze the development of project discontinuation in the preclinical stage and the share of each firm size group on innovation output. To the best of our knowledge, the development of various indicators of the innovative activities of pharmaceutical firms of different sizes has not been studied before for such a long period of time.

The paper is organized as follows: in the next section, we briefly sum up the changes in the pharmaceutical industry during the last two decades and discuss their possible effects on the innovative activities of small and large firms. Further, we review some arguments in favour or against

a positive relation between firm size and innovation. We also discuss these arguments with respect to the pharmaceutical industry and look at the empirical literature on this question. In section 3, we present our own empirical results on the development of innovative activities of the different firm size groups, the success rate, preclinical discontinuation and innovative output. In section 4, we sum up and discuss our results and conclude.

2. Innovation and Firm Size

2.1. The Pharmaceutical Industry

Innovation in the pharmaceutical industry means discovering new compounds with a desirable effect on biological targets and to develop these drug candidates to introduce them on the market. Firms have to know about the development of molecules with required characteristics and match these with biological receptor knowledge (Dosi and Nelson 2010, p. 67). Molecules “dock on” receptors to take a specific effect. Drug development takes place within a regulated process during which the compound has to prove safety and efficacy before it can be brought to the market (Cockburn and Henderson 2001). Discovery as well as development processes are characterized by high uncertainty about the right discovery methods to obtain suitable problem solutions (Comanor and Scherer 2013).

During the last two decades, the industry has undergone several developments that may have changed the relation of small and large firms in the industry. The development of genetic engineering led to the entry of many small biotech firms during the 1980s while basic research and linkages to universities gained in importance (Grabowski and Vernon 1994, Galambos and Sturchio 1998, Malerba and Orsenigo 2015). During the 1990s, the Human Genome Project aimed at decoding the human genome. On the other hand, the development of platform technologies such as combinatorial chemistry and high throughput screening made “industrialized R&D” (Pisano 2006) more feasible, where large and “classical" firms rather profit. (Malerba and Orsenigo 2015). Large firms have increased their mergers and acquisitions (M&A) activities to retrieve new knowledge concerning drug development. However, the larger M&A activities had no effect on approval rates for new medical entities (Munos 2009). Munos shows that firms engaging strongly in M&A activities even lag behind firms that have not. Further, the share of new biotech drugs developed by small firms increased from 23% in the 1990s to 70% in 2006.

There have also been regulatory changes in the first decades of the 2000s. The Critical Path Initiative by the FDA tried to bring together capabilities of academia, industry, and government to foster basic research and the translation of basic research findings into new drugs (Kaitin and DiMasi 2010). This may have supported the innovative activities of small biotech firms or research based university spin-

offs. On the other hand, after the withdrawal of Vioxx by Merck & Co. in 2004, regulatory standards have been raised by the FDA Amendment Acts enabling the FDA to demand risk evaluation before approval and post market clinical studies when safety issues are present (Kaitin and DiMasi 2010). Higher regulation is increasing the entry barriers for small firms as development costs are increased by these further studies and reports. The knowledge of how to fulfil regulatory requirements is built cumulatively over a long time, favoring large firms with a large track record of drug research and development projects.

2.2. Theoretical considerations

The question of the relation between firm size and innovation goes back at least as far as the works by Schumpeter. In earlier works, Schumpeter considers the importance of the innovative entrepreneur as the main source of innovation (Schumpeter "Mark I", cf. Fagerberg *et al.* 2011). Later on, Schumpeter proposes that innovation is mainly conducted by large firms (Schumpeter "Mark II"). Based on these considerations, a large body of literature has tried to inquire the relation between firm size and innovation on the firm level.

There are some arguments for a positive relation between firm size and innovativeness. We highlight three of these arguments. First, capital market imperfections can be easier mitigated by large firms in generating higher internal funds than small firms. Capital market imperfections may as well be present in the pharma industry. However, venture capital startups and government funding play a large role in biotech. Teece (2010) argues that today the innovative power of venture capital-funded firms and the financing by public equity markets (especially in biotech and internet companies at an early stage) is very important such that size is mitigated as an important determinant of successful innovations.

Second, R&D expenditures are fixed costs. When a firm has higher sales, the expenditures are spread over a larger amount of output reducing costs per unit (Klepper 1996). Particular for process innovations reducing costs of production, this is a valuable approach favouring large firms with a larger production. Cohen and Klepper (1996) suggest that the "fixed-cost spreading advantage" is dependent on the appropriability abilities of the firm. In an empirical study, Klepper and Simons (2005) find empirical support for the advantages of fixed cost spreading for product markets in automobiles, televisions, tires and penicillin. Transformed to the pharmaceutical industry, with a larger project portfolio size, the fixed parts of research expenditures are spread over a larger number of projects and over larger expected sales such that the costs per project are decreasing (DiMasi *et al.* 1995, Petrova 2014). Small (entrant) firms do not have the same advantages from fixed costs spreading. Cohen and Klepper (1996) argue that the advantages of fixed-cost spreading are higher when appropriablity conditions are good. As patent protection of new, promising compounds is strong and therefore there

is high appropriability in the pharma industry, this suggests that large pharma firms profit strongly from fixed-cost spreading.

Third, the cumulativeness of knowledge describes to which degree new knowledge piles up on already existing knowledge. It can be defined as the future probability of innovation success conditional on past success (Dosi and Nelson 2010). When large firms are the most experienced ones in the industry, they have advantages in innovation compared to small firms when the cumulativeness of knowledge is high. In the pharmaceutical industry, there are strong learning effects such that the experience in a given field is increasing with the experience gathered in the past. Long-term market presence and a research history makes firms more effective in drug development within these fields (Chandy *et al.* 2006). Many empirical studies show that firms' prior experience with innovation projects is good for innovation success (van der Panne *et al.* 2003). During the innovation process, firms reduce the uncertainty and do not only learn about promising approaches of drug discovery, but also on the subsequent development of drugs during clinical trials, trial management, and satisfying regulatory standards speaking in favour of a high cumulativeness of knowledge and competence building (Orsenigo *et al.* 2001). Knowledge – and its cumulativeness – is not restricted to technological knowledge about drug discovery and development. Knowledge must also be built for the whole drug development, application and approval processes (i.e., how to satisfy regulators). As Pisano (2006) puts it, knowledge and experiences in conducting trials are complementary downstream assets required to be successful in innovation. Therefore, cumulativeness of knowledge is not only restricted to technologies of drug candidate discovery, but includes knowledge about fulfilling the standards of regulation authorities (Orsenigo *et al.* 2001). Danzon *et al.* (2005) argue that experience in clinical development produces knowledge in trial design and management as well as improved relations to regulators which is positive to successful clinical trials. According to many authors, the regulatory requirements have risen over the past decades (e.g. Kola and Landis 2004, Munos 2009; Scannell *et al.* 2012). Therefore, higher requirements of regulation lead to higher entry barriers for new, small firms to enter the pharmaceutical industry (Gambardella *et al.* 2000). Entrants have to build higher competences to successfully master the regulatory approval process.

The cumulativeness of learning in a static environment would mean that after building sufficient knowledge about methods and problem solutions, the discovery of new drug candidates becomes a standard process with reliable and established search methods. Scientific progress has led to new methods used by many firms such that a large number of chemical compounds and their effects on biological targets can be checked (Orsenigo *et al.* 2001). However, as there are new methods and technologies occurring, the search space has become larger and deformed such that the environment for compound discovery is not static but highly dynamic. After decades of drug discovery and

development, there is still a high technical risk to find compounds meeting regulatory approval standards, leading to lengthy and expensive search processes (DiMasi 2014). It is therefore not clear per se that the most experienced and largest firms have an advantage over small, rather unexperienced firms.

There are also arguments stating there is no positive relation between firm size and innovation. For example, the loss of managerial control or excessive bureaucracy or hierarchies within larger firms may hinder effective R&D efforts and therefore undermine innovation success. In larger corporations, the benefits from individual efforts may not be fully seen or captured by individual researchers leading to a drop in their incentives to be creative (Cohen 2010). In the pharmaceutical industry, short-term goals are incompatible with scientific creativity, leading micro-management of R&D by managers with little scientific and medical expertise, which may reduce R&D productivity (Paul *et al.* 2010). Further, pharma firms are said to believe R&D costs can be cut without reducing R&D output, while it is not clear if this is possible (Scannell *et al.* 2012). There is a lack of investments in capacities to turn biological discoveries into new drugs (Cockburn 2006). Recently, R&D spending has increased, albeit there are large variations across firms (Arrowsmith 2012).

Firms aim to introduce drugs into the market as soon as possible to earn returns from their innovation (Comanor and Scherer 2013). Patent protection and higher returns when the firm is first on the market lead to the incentive to be fast in developing drugs. One method to become faster can be outsourcing which is growing already since the 1980s. Monitoring and data management is sourced out to contract research organisations (CROs). Knowledge-intensive projects are rather developed by internal teams, whereas data-intensive projects are rather outsourced to CROs (Azoulay 2004). Azoulay highlights that outsourcing is a key decision considering the question who decides which employees or teams are working on a specific R&D project. In the case of outsourcing, this decision is taken away from the development firm to the CRO. There is a risk for firms to make the wrong decision which projects are outsourced. In the pharmaceutical industry, small start-up firms – often started as university spin-offs – believe in "their" compound and are passionate in developing it for market introduction, while in large firms, portfolio management is more strictly based on financial rationales, such that outsourcing of development is more present in large firms. The risks attributed to outsourcing therefore may be more present for large than for small firms.

Finally, there is a wide range of different firm sizes within most industries.[2] However, the coexistence of firms with different firm sizes does not automatically mean that large firms have no advantage over small firms. The question rather is, whether small firms persist over time. For example, not many small

[2] See Dosi and Nelson 2010 for references to the wide literature on this aspect.

biotech entrants in the pharmaceutical industry have persisted over a long period of time. But those who have persisted also became large in the meantime (Cockburn 2006; Mittra 2007). In this context, the continuity hypothesis by Chandler (1997) states that the set of large incumbent firms in an industry remains stable as these have developed skills and built resources in the past to adopt and adapt to new technologies. This hypothesis has also been criticized: Louca and Mendonca (1999) and Freeman and Louca (2001) show that with each wave of technical change, newcomer firms have added to the group of incumbent firms. It is also noteworthy that only few of the largest firms remain at the top throughout multiple waves of technical change.

2.3. Empirical Findings

Based on the considerations on the relation of firm size and innovativeness, many empirical studies tried to answer the question whether firm size is positive or negative for innovation. Early studies analysed the relation between firm size and R&D investments, i.e., the input side of innovation. They come to the conclusion that innovative input measured as research personnel increases or R&D investments increase more than proportional up to a certain threshold and then rise proportionally with firm size. These findings by Scherer (1965a, 1965b) have been confirmed by other researchers and have become the consensus view in the early 1980s (Cohen 2010). With some exceptions, industry-level studies find a proportional relation between R&D and firm size among R&D performing firms in most industries. Through the mid-1990s, the finding of proportionality between R&D spending and firm size was interpreted such that firm size was not advantageous to the conduct of R&D. Scherer (1984) extends the finding of proportionality from R&D expenditures to patent counts as an innovative output measure. Several other studies also came to the conclusion that there is no advantage to firm size for innovation output and that the R&D productivity is even declining in firm size (Cohen 2010). More distinguished, Pavitt *et al.* (1987) find a U-shaped relation between firm size and innovativeness: small firms with less than 1,000 employees and very large firms with more than 10,000 employees have the highest R&D productivity measured as number of innovations per employees.

However, Cohen (2010, p. 140) points out that the interpretation of these patterns – namely the reasons behind these findings – is less clear and raises many questions. It is puzzling that R&D spending increases proportional with firms' size, however R&D productivity is declining with size. Some scholars argued that smaller, especially start-up, firms are better in innovating than large incumbents which could be one reason for a higher R&D productivity of small firms. Griliches (1990) argues the diminishing returns of R&D productivity should be interpreted cautiously as the result may be resulting from sample selection and measurement error. Small firms are heavily selected into the studied samples as they have to be "successful" to exist and to be included in statistical samples, while

unsuccessful young firms die early and are not selected into any firm sample (see also Bound *et al.* 1984). Further, formal R&D is less relevant for small firms such that organized R&D activities are rising with firm size.

There is good reason to argue that innovation is industry- or sector-specific. In a noteworthy account, the taxonomy by Pavitt (1984) aims to identify different regimes of industry types and industry dynamics. One class of industries are "science-based", where innovation opportunities coevolve with advances in basic and applied sciences (Dosi and Nelson 2010, p. 85). These industries are microelectronics, informatics, bioengineering and drugs, i.e., the pharmaceutical industry.

We now have a closer look on empirical findings their innovativeness. Some empirical studies find that a less than proportionate rise in R&D spending with firm size is found for drug development (Grabowski 1968; Mansfield 1964). This suggests a disadvantage to firm size for the conduct of R&D in the pharmaceutical industry. Contrary, Acs and Audretsch (1990, 1991) find that the relation between firm size and innovation varies across industries while small firms are most innovative in less capital-intensive industries. As innovation in the pharmaceutical industry is based on large upfront investment and drug development is process oriented, this would suggest an advantage for large firms.

Henderson and Cockburn (1996) show that research expenditures of firms are positively associated to the number of important patents which points to the existence of economies of scale. However, the authors also find limits to the economies of scale and scope. They argue these limits are based on problems of bureaucracy and geographical dispersion of research groups within firms. Cockburn and Henderson (2001) define innovation success as obtaining regulatory approval for a drug. The scale effect is positive but becomes insignificant when firm scope, measured as the number of therapeutic areas where the firm is active, is controlled. When firm indicator variables are included, both size and scope become small and insignificant. Cockburn and Henderson also control past experience within the therapeutic class, which is positively connected to drug approval. The authors argue that other characteristics than scope are at work, such as firms' productivity, organizational structure and decision-making procedures which are all covered by the firm dummies such that the effect of scale and scope is mitigated. There seems to be no advantage of large firms in the discovery of new drugs, whereas in drug development, including clinical research and the fulfilment of regulatory requirements, large firms have an advantage as they have successfully developed the complementary downstream assets (Pisano 2006) to be successful drug innovators.

Arora *et al.* (2009) use a sample of 3,311 projects from 329 firms entering clinical trials between 1980 and 1994. The scale of the research program (i.e., the number of projects for each aggregated disease class) has a negative effect on innovativeness. This is interpreted by the authors such that large

research programs are conducted by firms to increase the probability that one of these projects will eventually become successful. In this case, all other projects are discontinued as it is only important to a firm to get one drug in the respective market ("portfolio effect", Arora *et al.* 2009, p. 1,648). As in this explanation more projects are discontinued than in a smaller research program, the *measured* innovation success is decreasing while the underlying reasons are based on rational firm choices. Chandy *et al.* (2006) study how firms transform patented compounds into new drugs on the market using US patent data from 1980 to 1985. The authors find that firms' performance of the conversion of patents into introduced drugs is highest in firms with a moderate number of patents, i.e. there is an inverted u-shaped relation between the size of a firm's patent portfolio and drug development performance. Further, Chandy et al. measure firm experience in the respective therapeutic areas by using the number of patents within respective areas 1960 to 1980 and show that firms' prior experience has a significantly positive effect on the success rate.

There are some studies analyzing the success rates of pharmaceutical R&D projects for different firm sizes. The success rate is given by the number of successful drug development projects divided by all drug developments undertaken for the respective study periods. Success is measured as approval by the regulatory authority to market the developed drug for a given disease. DiMasi *et al.* (1995) apply U.S. project data from 1970 to 1982 with 93 self-originated projects in clinical trials from 12 US-owned pharma firms. Firm size is measured as pharmaceutical sales at the beginning of the study period. For large firms, DiMasi et al. find a success rate of 0.279, for medium-sized firms of 0.174 and for small firms of 0.238. The result points to a U-shaped relationship between firm size and innovation success. The authors discuss this result as suggestive that large firms have superior research programs with a "more rational 'discovery by design' approach" (DiMasi *et al.* 1995, p. 209). However, they do not discuss why the smallest firms in the sample do have a larger success rate than medium-sized and large firms.

Abrantes-Metz *et al.* (2004) use data of 3,146 projects with clinical trials starting between 1989 and 2002. While the average success rate is 0.264, the authors find that firm size measured as the number of projects per firm in development in phases I, II, and III is positively connected to the success rate of pharma projects. The highest differences in success rates are found for phases II and III such that differences in firm size seem to be most relevant in later stage development with advantages for large and mid-sized firms. Danzon *et al.* (2005) apply project data containing over 1,900 projects in clinical trials between 1988 and 2000 from over 900 pharmaceutical and biotech firms in the U.S. The authors find no significant effect of total experience for phase I trials, but for phase II and phase III trials adding to the finding of Abrantes-Metz *et al.* (2004) that success rates differ especially for later stage development. The authors argue that firms with low experience levels can easily finish phase I trials

for safety, but find it difficult in the more complex phase II and phase III trials focusing on dosage and statistical evidence for efficacy. The complementary assets large firms possess seem to be most relevant in later stages of development.

DiMasi (2014) uses data on 1,734 projects first in clinical trials between 1993 and 2004. Firm size is measured in sales. The author finds a success rate of 0.169 for the top 10 firms, 0.203 for the top 11 to top 20 firms and 0.231 for the top 21 to the top 50 firms such that smaller firms yield higher success rates. However, the result only holds for self-originated compounds (excluding licensed compounds). Contrary, Pammolli *et al.* (2011) estimate a probability of success for small firms to be 0.061 whereas the probability of success for large firms is estimated to be 0.075. Small firms are defined as having less than 14 projects in development, which is the sample average number of R&D projects in development. While the difference in the success probabilities between these groups is not large, the result is based on a sample of firms much broader than the one of DiMasi (2014).

Empirical studies focus either on the input side (R&D investments, spending) or on the output side of innovation (drug output, project success rate), and present result on different firm size groups. The empirical literature on innovation in the pharmaceutical industry mostly does not directly refer to the theoretical arguments considering the relation between firm size and R&D. Notable exceptions are the studies by Henderson and Cockburn referring to economies of scale and scope. While some industry studies come to the conclusion that there is a negative relation between firm size and innovativeness in the pharmaceutical industry (Grabowski 1968, Mansfield 1964), others suggest there is a positive relation (Acs and Audretsch 1990, 1991). Studies on the success rate of drug development projects do not find clear cut results either. DiMasi (2014) finds a negative effect of firm size on the success rate, whereas results by (Abrantes-Metz *et al.* 2004) suggest there is a positive relation. Danzon *et al.* (2005) find evidence for a positive effect at least for clinical development phases II and III. In the study by DiMasi *et al.* (1995), there is a U-shaped relation between size and success rate such that the smallest and the largest firms have the highest success rates.

The success rates of the presented studies are not comparable to each other as different data sets from different samples of firms and different definitions of small and large firms are applied. Overall, these studies do not regard the development of the success rate over time. We will therefore contribute to the literature in analyzing innovative input as well as innovative output and focus on the development of different innovation indicators over time. With our detailed data set including a broad range of firms we are able to study the development of these indicators between 1989 and 2010.

3. Empirical Results

3.1. Data and Measures of Innovativeness and Firm Size

We use data from the Pipeline project data base provided by Informa Healthcare. The data includes commercial drug candidates of all firms conducting R&D programmes worldwide. Preclinical information on projects is provided as far as information is available in the public domain. Information on clinical development phases is included from regulatory trial reports, market communication of the firms, company contacts, and other sources following the projects until market launch or discontinuation takes place. We use the "lead compound definition" of a pharmaceutical project, i.e. a project is defined as the development of a compound for one or more diseases.[3]

The first projects in the data go back to the early 1980s. However, we only included projects with the first entry "new product" in the project history. This is done to exclude projects added to the data base at a later stage of development.[4] Our sample thus contains 17,787 R&D projects started since 1989. The latest complete year of observations is 2011. We further excluded projects started in 2011 such that the minimum development time of a project is one year. Therefore, the latest project start date in our sample is 2010. 1,706 projects were still in development at the end of our observation period such that it is unknown whether these projects will eventually be a successful or a discontinued project. These censored projects have been excluded from the sample as there is no information on project success available. In doing so, we assume that results for the comparison between different firm size groups are not affected, i.e. that censored projects have the same success probability for different firm size groups. Overall, the data is a comprehensive sample of projects for drug candidates from a time span of more than 20 years. The data contains projects from 2,605 firms and is therefore well suited to study the development of innovative activities within the industry for different firm size groups over a long period of time.

Innovative activities have many aspects. We therefore look at the development of four different indicators. First, we apply the development of the share of R&D projects of each firm size group on all R&D projects conducted within a period as an indicator of innovative activates or innovation input. We complement this by the growth rate of the number of projects originated within each firm size group between the periods. Second, we analyse the success rate for projects originated within each firm size group as measure of innovation productivity. A project is defined as a success when the compound is introduced as a drug to the market for at least one disease indication. Therefore, when more than one

[3] For a discussion on the lead compound definition, see Hay et al. (2014).
[4] Abrantes-Metz *et al.* (2004) also choose this approach.

indication can be treated, the introduction for the first indication is taken. Note that the compound is not required to be introduced by the originating firm. In case of licensing or acquisition, the compound may also be introduced by the licensee/acquiring firm. The share of licensed projects in the sample is 17.3 percent. A project is defined as discontinued when there is no ongoing development reported for at least one of the disease indications in the last 12 to 18 months. The success rate is the share of all successful projects on all projects originated within a given firm size group and within the time period studied. Third, we analyze the shares of projects discontinued in the preclinical stage for different firm size groups. Differences with respect to preclinical discontinuation may point to some specific problems firms have within the preclinical (drug discovery) phase. In the preclinical phase, firms aim to discover active compounds which are efficacious and show no toxic effects (Scherer 2010). While clinical phases start with a formal Investigational New Drug (IND) filing at the US Food and Drug Administration (FDA), the preclinical phase is rather informal and less regulated. Therefore, higher rates of project discontinuation are less attributed to regulatory requirements or the cumulative knowledge to be built for drug development with respect to fulfilling regulatory requirements, but with the technology to discover suitable compounds itself. Further, there is reason to suppose that the selection mechanisms in the preclinical stage differ between large and small firms. Guedj and Scharfstein (2004) argue that in biotech startup firms, only a small number of compounds is in development. These have to be pushed into clinical trials to produce good news for investors and the market. By contrast, large firms have a higher number of compounds to choose from and no such specific interest in particular compounds. Therefore, larger firms are expected to select projects more strictly at the preclinical stage than small firms. Another aspect is that it is difficult to reproduce results from preclinical research in order to explore and develop new theories for further study (Freedman *et al.* 2015). This may be especially difficult for small firms when they do not have enough resources to reproduce preclinical results from other studies in their field of development, making the development of promising compounds for clinical research more difficult. Fourth, we look at the share of introduced drugs originated by each firm size group. While the success rate is a productivity measure comparing input and output of the drug development process, the share of introduced drugs shows how drugs resulting from successful projects originated by each firm size group within a specific time period contribute to the innovative output of the industry. All these measures are based on the mere counting of projects. It would be preferable to know more about these projects, e.g. about the R&D investments for each projects, their strategic meaning to the firm, whether the drug in development is first-in-class or a minor improvement and which market potential it has. Unfortunately, all these indicators are not available in our data. We nevertheless think that the variables are a starting point in assessing the development of input and output aspects of innovative activities in the pharma industry.

There are classical firm size measures like sales or the number of employees. These measures are not only related to the innovative activities of firms, but also to other activities like marketing, management and accounting. When R&D investments or the size of the innovation project portfolio are applied as firm size measures they rather focus on the size of the innovative efforts. As we want so study the latter we use the number of projects a firm originates during the study period from 1989 to 2010 as an indicator of firm size. In doing so, we follow Abrantes-Metz *et al.* (2004), Pammolli *et al.* (2011) and DiMasi (2014) who measures firm size as the number of projects firms have in development. Although not perfectly correlated with classical firm size measures such as number of employees or turnover, the project portfolio size indicates the scale of drug development undertaken by the firm. Long-term market presence and a research history makes firms more effective in drug development within these fields (Chandy *et al.* 2006). Danzon *et al.* (2005) also argue that experience can be measured as number of compounds a firm has developed in the past. A larger R&D portfolio therefore suggests that the firm has more experience in drug development in general and in the specific fields it is active in. We stated in section 2.2 that cumulativeness of knowledge and experience is one possible reason for a positive effect of firm size and innovation performance. Further, the pharma industry consists of different firm types: established pharmaceutical firms and biotech companies. Whereas established producers were founded in the early 20th century, the first biotech company, Genentech, was founded in 1976 (Arora *et al.* 2009). While established firms are often also considered to be large, biotech firms are mostly small startup firms. However, there are also established biotech firms with considerable size nowadays. Therefore, with some caution, firm size can be considered to roughly distinguish established, traditional firms from small biotech startup firms.

To sum up, size measured as the number of R&D projects conducted by the firm does not only measure the size of firms or their research efforts, but also experience in conducting innovation projects or the type of the firm. Whereas large firms tend to be established pharma firms with a long track record of experience in innovation projects, small firms are rather start-up companies with less experience. As we do not control these different aspects of firm size, they are all inherent in our firm size measure which has to be recognized when interpreting the empirical results of our study.

3.2. Share and Growth of R&D Projects

The 17,787 drug development projects in the sample are conducted by 2,605 firms. We divide the sample into four groups of firms using the number of projects a firm has started between 1989 and 2010. The 25 firms with the largest project portfolio size (“Top 25”) are only 1 percent of all firms, but have a share of 32.2 percent on all projects in development (see Table 1). Their portfolio sizes range from 75 to 663 projects. The top 25 firms are put into an own group of “very large firms” to check

whether there are additional size effects at the upper end of firm size. The group of large firms consists of 77 firms with portfolios between 21 and 73 projects. Medium-sized firms have started 6 to 20 projects between 1989 and 2010, having a share of 29.6 percent on all R&D projects. Small Firms only started up to 5 projects over the whole study period. However, as the sample share of small firms is 75.3 percent, the share of projects conducted by this firm group is almost 25 percent. On the one hand, there is a small number of large firms with a high number of R&D projects. On the other hand, there is a large fraction of medium-sized and small firms, contributing to over 50 percent of all pharmaceutical R&D projects.

One point deserves attention. We do not look at each subperiod studied later on to define the firm size groups. Rather, we look at the whole study period to put firms in different size groups. In doing so, we evaluate ex post how certain groups of firms acted during the whole study period. For example, it need not necessarily be that a top 25 firm has been among the 25 largest firms within each subperiod. Further, mergers and acquisitions have an effect on the firm size grouping. Projects of a small firm which is acquired by a larger firm at some point during the study period count to the projects of the acquirer. When studying project growth rates, these may be induced by organic growth or by the acquisition of other firms.

Table 1: Descriptive Statistics of Firm Groups by Portfolio Size

				Number of Projects		
Firm Size Group	**No. of Firms**	**Share of Firms**	**Share of Projects**	**Min**	**Max**	**Mean**
Top 25 Firms	25	0.010	0.322	75	663	228.800
Large Firms	77	0.030	0.140	21	73	32.377
Medium Sized Firms	541	0.208	0.296	6	20	9.730
Small Firms	1,962	0.753	0.242	1	5	2.197
Sum	2,605	1.000	1.000			

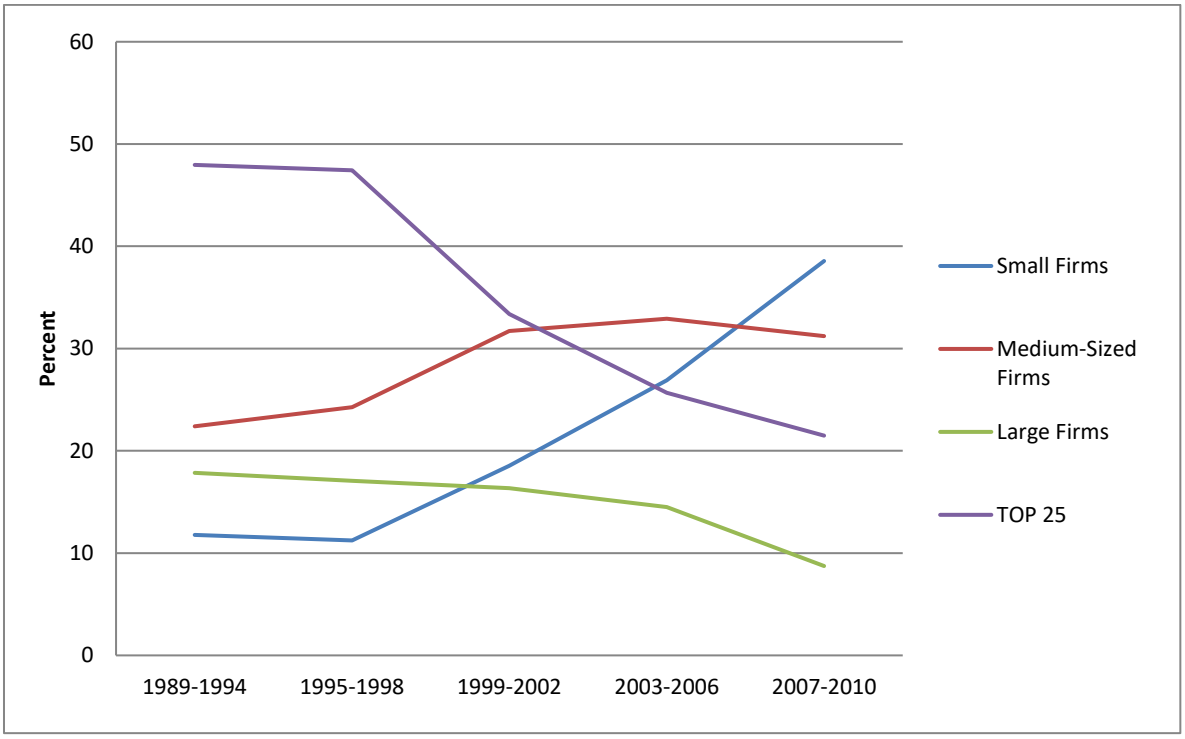
Source: Informa Healthcare Pipeline Pharma Data; figure by the author; N = 17,787 drug development projects

Looking at the development over time, we observe that the share of projects originated by the top 25 declines from 47.4 percent to 21.5 percent between 1989 and 2010. In the same period, the share of projects from small firms rises from 11.8 percent to 38.6 percent (see Figure 1).

We use the growth rate of the number of projects in each firm size group to inquire the development of the innovative activity in the industry over time (see Table 2). For the sake of convenience, we use the terms “period 1” for the period from 1989 to 1994, “period 2” for the period between 1995 and 1999, and so on. The overall growth rate of the number of projects between period 1 and period 2 is very high (87.8 percent). Subsequently, growth is declining strongly: For the next two periods, the growth rate is decreasing to 10.7 and 6.9 percent, respectively. Between period 4 and period 5 the

growth rate is only1.9 percent. Hence, during the study period, the number of projects is growing steadily, however, growth is heavily slowing down.

Figure 1: Share of Projects by Firm Portfolio Size Classes



Source: Informa Healthcare Pipeline Pharma Data; figure by the author

The growth rate within the different firm size groups is especially large between period 1 and period 2 for all groups. It ranges between 78.2 percent for small firms and 101.3 percent for medium-sized firms. The following periods, however, show a very distinct pattern of growth for the different firm size groups. For the top 25 firms, the number of projects is decreasing by 21.7 percent between period 2 and period 3, followed by more moderate decreases in the next two periods. The growth rate of projects originated by large firms is decreasing from 81.7 percent between period 1 and period 2 to 6.7 percent between period 2 and period 3. For the two most recent periods, the number of projects is decreasing by 3.9 and 36.3, respectively. The number of projects originated by medium sized firms is still growing strongly between period 2 and period 3 (44.3 percent). Growth is slowing down to 10.2 percent between period 3 and period 4 and turning negative between period 4 and period 5 (-2.7 percent).

The growth pattern of projects from top 25, large and medium-sized firms can be described by three steps: initially large growth, followed by smaller growth, and eventually negative growth. However, the timing of this pattern seems to be different. While for the top 25 firms, initial growth is followed by an immediate decline in the number of projects (already between period 2 and period 3), while the decline takes place one period later for large firms (between period 3 and 4), and still another period

later for medium-sized firms (between period 4 and 5). The development of the number of projects seems to be lagging behind for smaller firms: the strategy of top 25 firms to radically cut the number of projects started between period 2 and period 3 may have been observed by large and medium-sized firms and transferred to the own project portfolio in the subsequent periods.

Table 2: Success rates by firm portfolio size group:

			Period Project start				
Firms	**Variable**	**All Projects**	**1989-1994**	**1995-1998**	**1999-2002**	**2003-2006**	**2007-2010**
			(Period 1)	**(Period 2)**	**(Period 3)**	**(Period 4)**	**(Period 5)**
All Firms	Success Rate	0.054	0.182	0.069	0.042	0.033	0.016
	Number of Projects	16,081	1,703	3,198	3,540	3,785	3,855
	Growth Rate No of Projects	-	-	0.878	0.107	0.069	0.019
	Share of successful projects	1.000	1.000	1.000	1.000	1.000	1.000
TOP 25 Firms	Success Rate	0.076	0.205	0.071	0.052	0.053	0.026
	Number of Projects	5,508	821	1,527	1,195	1,026	939
	Growth Rate No of Projects	-	-	0.8599	-0.2174	-0.1414	-0.0848
	Share of successful projects	0.483	0.542	0.493	0.422	0.432	0.393
Large Firms	Success Rate	0.065	0.206	0.079	0.033	0.034	0.028
	Number of Projects	2,350	301	547	584	561	357
	Growth Rate No of Projects	-	-	0.817	0.068	-0.039	-0.364
	Share of successful projects	0.182	0.200	0.196	0.129	0.152	0.164
Medium Sized Firms	Success Rate	0.035	0.128	0.057	0.032	0.019	0.011
	Number of Projects	4,688	383	771	1,113	1,227	1,194
	Growth Rate No of Projects	-	-	1.013	0.444	0.102	-0.027
	Share of successful projects	0.189	0.158	0.201	0.245	0.184	0.213
Small Firms	Success Rate	0.036	0.157	0.068	0.046	0.030	0.010
	Number of Projects	3,535	198	353	648	971	1,365
	Growth Rate No of Projects	-	-	0.783	0.836	0.499	0.406
	Share of successful projects	0.146	0.100	0.110	0.204	0.232	0.230

N = Number of Projects (1,706 projects still in development by end of observation period 2010 are excluded)

Top 25 firms: The 25 firms with the largest project portfolios; Large Firms: the 75 firms following the Top 25 firms in size of project portfolio; Medium Sized Firms: the xx firms with smaller portfolios than large firms excluding small firms; Small Firms: bottom quartile of firms with the smallest project portfolios

The growth rate pattern of small firms is different to the patterns of all other firm size groups. For small firms, we firstly observe an increase in the growth rate from 78.3 percent between period 1 and period 2 to 83.6 percent between period 2 and period 3. Note that for all other firm size groups, a very large decrease in the growth rate has been observed. After period 3, we also observe a decline in the project growth rate originated by small firms, however growth remains at a high level and does not turn into negative growth. Between period 3 and period 4, the number of projects increases by 49.9 percent, and between period 4 and period 5, the number of projects is still growing with a high rate of 40.6 percent.

While the empirical result is striking the question remains what contributed to this development. Market entry in the pharmaceutical industry is based on high up-front investments serving as entry barriers to the market (Gassmann *et al.* 2008). However, Munos (2009) observes a growing number of firms during the 1980s and the 1990s, driven by growing amounts of venture capital and the rise of small biotech start-ups. Our data does not allow to observe the development during the 1980s. But since the end of the 1990s and the first decade in the 2000s our data shows a rise in the number of firms implied by the rising share of projects originated by small firms. In the study period, regulatory standards increased. Further, the development of platform technologies and the growing importance of "industrialized R&D" suggests that large firms would gain advantages in innovative activities. Eventually, several merger waves in the industry occurred. Contrasting with this development, we observe that many more small firms are active in the industry nowadays as the share of projects originated by small firms has been growing strongly. Especially technological changes and the decoding of the human genome during the early 2000s and the increasing importance of basic research and university linkages seem to favour the entry of small firms. "micropharma" firms with less than 20 employees, founded with a background from academia become more important in today's pharma industry innovation model as large firms fail to innovate and to take risks for the development of innovative drugs but rather in-license promising drug candidates discovered by small firms (Barden and Weaver 2010). The rising share of projects originated by small firms are in line with the arguments given by Barden and Weaver.

This result implies that the concentration of R&D within the industry is decreasing over time. R&D is conducted more decentralized within a larger number firms in more recent years. When many independent small firms search in more directions than a small number of large firms, this development is positive for the industry such that a broader search space for new possible drug compounds is covered. This has two aspects: first, more different ways of treatment for the same disease are independently tested, thereby increasing the possibility to find one successful treatment. Second, drug development for a wider range of diseases is conducted. While innovative activities within the industry have become broader during the last two decades, it is not said that these activities lead to a more successful development of drugs. We will cover this question in the next sections on the success rate, preclinical discontinuation, and the number and share of introduced drugs originated by different firm size groups.

3.3. Success Rates

We now look at the success rate which is the share of successful projects on all projects started in a specific time period. Overall, the top 25 firms have the largest success rate with 0.076, followed by

large firms with 0.065. Medium-sized and small firms have a lower overall success rate of 0.035 and 0.036 (see Table 2). Considering the development over time, the success rate of all firm size groups is decreasing. There is a large drop in success rates between period 1 (1989 to 1994) and period 2 (1995 to 1998). In period 1, the top 25 firms and the large firms have similar success rates of 0.205 and 0.206. The success rate of medium-sized firms is 0.128, whereas projects of small firms show a success rate of 0.157.

For all firm size groups, the success rates decrease strongly in period 2 and range between 0.078 (large firms) and 0.057 (medium-sized firms). After period 2 (1998), the success rate is still decreasing within all firm groups. For the top 25 firms, the rate is stabilizing at around 0.052 in period 3 and period 4, but finally decreasing to 0.026 in period 5. The same pattern is observed for large firms: in period 3, the success rate decreases to 0.033, staying at 0.034 in period 4. In period 5, the rate is decreasing to 0.028. Hence, both for top 25 and large firms, the rate stabilizes in periods 3 and 4 and decreases in period 5. Contrary, we do not observe this stabilization in periods 3 and 4 for medium-sized and small firms. For these firms, the rate is decreasing for from 0.032 to 0.019 (medium-sized firms), and from 0.046 to 0.030 (small firms). In period 5, the success rate is 0.011 for medium-sized firms and 0.010 for small firms. There is no stabilization in periods 3 and 4, the success rate is rather steadily decreasing.

One reason for the stabilization of success rates for top 25 and large firms between 1999 and 2006 may be the decreasing number of projects of Top 25 firms and the only moderately increasing number of projects of large firms. A lower number of projects seems to be resulting from a stricter assessment of projects and a selection on the basis of their success probability. The largest firms have succeeded in this “screening” strategy and selected projects more strictly, as Guedj and Scharfstein (2004) propose.

In general, the success rates of top 25 and large firms are higher than the success rates of medium-sized and small firms within nearly all periods. There is one exception to this observation: in period 3 (1999 to 2002), the success rate of small firms is 0.046 and lying above the rate of large firms (0.033). This one exception may be a reason for the project growth rate being still very high between the two most recent periods. The success rate was larger for small firms than for medium sized firms and even large firms. Many other potential entrants with promising compounds from basic or publicly supported research could have observed the high potential of these projects finally leading to larger success rates and started their own projects, resulting in a further increase in projects by small start-up firms.

We therefore find empirical evidence for a positive relation between the R&D portfolio size and innovative productivity in the pharmaceutical industry measured by the success rate. We do not correct censoring such that projects still in development at the end of the observation period are

dropped from the sample. In doing so, the success rate for the most recent periods is under-estimated. As we noted above that the share of small firms on the total number of projects is rising, this would imply that the success rate estimates are most downward biased for smaller firms. Therefore, cautious interpretation of the results for the most recent period is necessary. However, we found that also within earlier periods, smaller firms showed to have smaller success rates.

Our findings are in line with Pammolli *et al.* (2011) who analyse a sample with a broad range of firm sizes and over a similar time period. Abrantes-Metz *et al.* (2004) as well as Danzon *et al.* (2005) also find a positive relation between the number of projects and project success. For the 1970s and 1980s, DiMasi *et al.* (1995) find a U-shaped relationship, while DiMasi (2014) finds a negative relation between firm size and success rate. However, the latter result only holds for self-originated compounds. While all findings except those from Pammolli *et al.* (2011) are based on earlier periods or small samples including only a low number of firms, our findings are based on projects from a broad set of firms. The analysis over five subperiods allows to track changes of the success rate within different firm size groups over a long period of time.

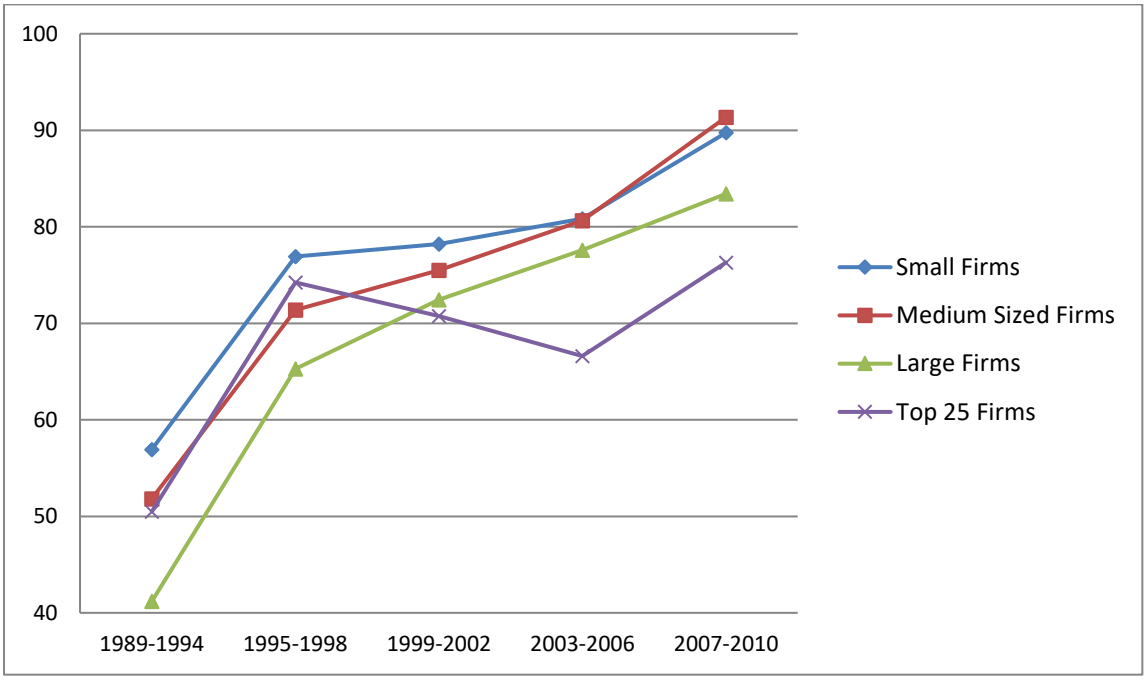
Above, we argued that capital market imperfections, the possibilities of fixed-cost spreading over a larger range of projects, and the high cumulativeness of knowledge in the pharmaceutical industry contribute to a positive relation between firm size and innovativeness. These effects seem to be outweighing the factors leading to a negative relation between firm size and innovation, such has loss of managerial control, management failures and the risks of outsourcing. The advantage of firm size is also based on the fact that our firm size measure is reflecting experience in conducting R&D projects. This effect dominates and points to the fact that cumulativeness of knowledge considering drug discovery technology and the conduct of drug development projects with respect to regulatory approval is very important in the industry. While the success rate is declining for all firm size groups, experience is an important asset for Top 25 and large firms contributing to higher success rates and innovativeness of these firm size groups.

3.4. Preclinical Discontinuation

Next, we focus on the selection of preclinical projects for clinical development. This selection marks an important milestone for a drug development project as compounds are first tested in humans then. Promising effects of these compounds on the biological target have been found during preclinical studies such that firms decide to go on testing them with respect to efficacy, toxicity, and side-effects in Phase I trials. The selection of projects for clinical testing is connected to the development of the success rate as the selection patterns indicate the overall quality of (preclinically) started projects. In our data, the share of preclinical discontinuations increases from 0.505 to 0.763 for the top 25 firms

(see Figure 2). For large firms, the share increases even stronger from 0.412 to 0.834. The rise in early project discontinuation is also prevalent for medium-sized and small firms. The share is highest for medium-sized firms rising from 0.518 in period 1 to 0.913 in period 5. Small firms start at a higher preclinical discontinuation rate than medium-sized firms in period 1. In period 5, the rate of preclinical discontinuation is comparable between small (0.897) and medium-sized firms (0.913).

Figure 2: Share of Projects Discontinued in Preclinical Stage by Firm Portfolio Size



Source: Informa Healthcare Pipeline Pharma Data; figure by the author

For established, large firms, especially the top 25 firms, a higher preclinical discontinuation rate is grounded on stricter selection of projects for clinical trials as proposed by Guedj and Scharfstein (2004). Large firms have many R&D projects to select from. Arora *et al.* (2009) hypothesize that selection of projects is based on expected profits and research costs of a research program. The authors argue that economies of scale at the research program level are present such that firms with larger research programs have lower costs per project, making firms less selective. Our result of increasing preclinical discontinuation within the top 25 firms (and large firms) therefore also indicates that research costs have increased during the study period leading firms to discontinue projects earlier in development. The strategy to conduct more parallel projects as backup compounds in clinical seems to be too expensive and therefore has lost some of its importance, indicated by the rise in preclinical discontinuation for top 25 and large firms between the two most recent time periods.

To the best of our knowledge, the development of preclinical discontinuation of projects for different firm size groups over time has not been empirically analyzed before. Preclinical discontinuation rates are highest for small and medium-sized firms. This result is not in line with Guedj and Scharfstein

(2004), who propose that large firms select their projects more strictly than small firms. This points to other factors being present here. Barden and Weaver (2010) illustrate the rise of “micropharma” firms with less than 20 employees, founded with background from academia. They state that small firms can take more risks for really innovative products; higher risk means larger probability of discontinuation. Our results suggest that failure occurs already in the preclinical stage. Further, R&D expenditures cannot be attributed to a large portfolio of projects, i.e. there is no fixed-cost spreading leading to economies of scale. We have argued that regulation of the preclinical phase is less strict than in the clinical phases. Therefore, experience is not only relevant for the clinical development process and for meeting regulatory standards, but also for drug discovery technologies. Additionally, it is difficult to reproduce preclinical results as a source of new knowledge, which may be especially a problem for small firms.

Capital market imperfections and lacking resources often lead to project discontinuation already in the preclinical stage for projects originated by small firms. Financial problems during the preclinical stage may be a problem especially for small firms as well. Orsenigo (2001) emphasizes that at least in Europe, the conditions of university-science links, lacking scientific and industry base and lower availability of venture capital makes life difficult for small biotech startup firms. Funding of startups has to be high: $250,000 to 500,000 for initial funding; $1m to $5m for later funding (Barden and Weaver 2010). Our results may point to the fact that a large fraction of firms does not qualify to be funded by venture capitalists. Khanna (2012, p. 1,092) also states that most small biotech companies are “cash-starved” and these startup firms either grow, license their discovered compounds or perish. The very high rate of preclinical discontinuation we find for small firms is therefore likely to be driven by financial constraints A failure in the discovery of promising compounds for clinical development may result in bankruptcy of the small firm. This also leads to the discontinuation of development of other projects within this small firm, increasing preclinical discontinuation rates among them again. It is difficult for small start-up firms to establish in the industry and the large number of discontinued projects of new coming firms is piling up large sunk costs for the industry as a whole.

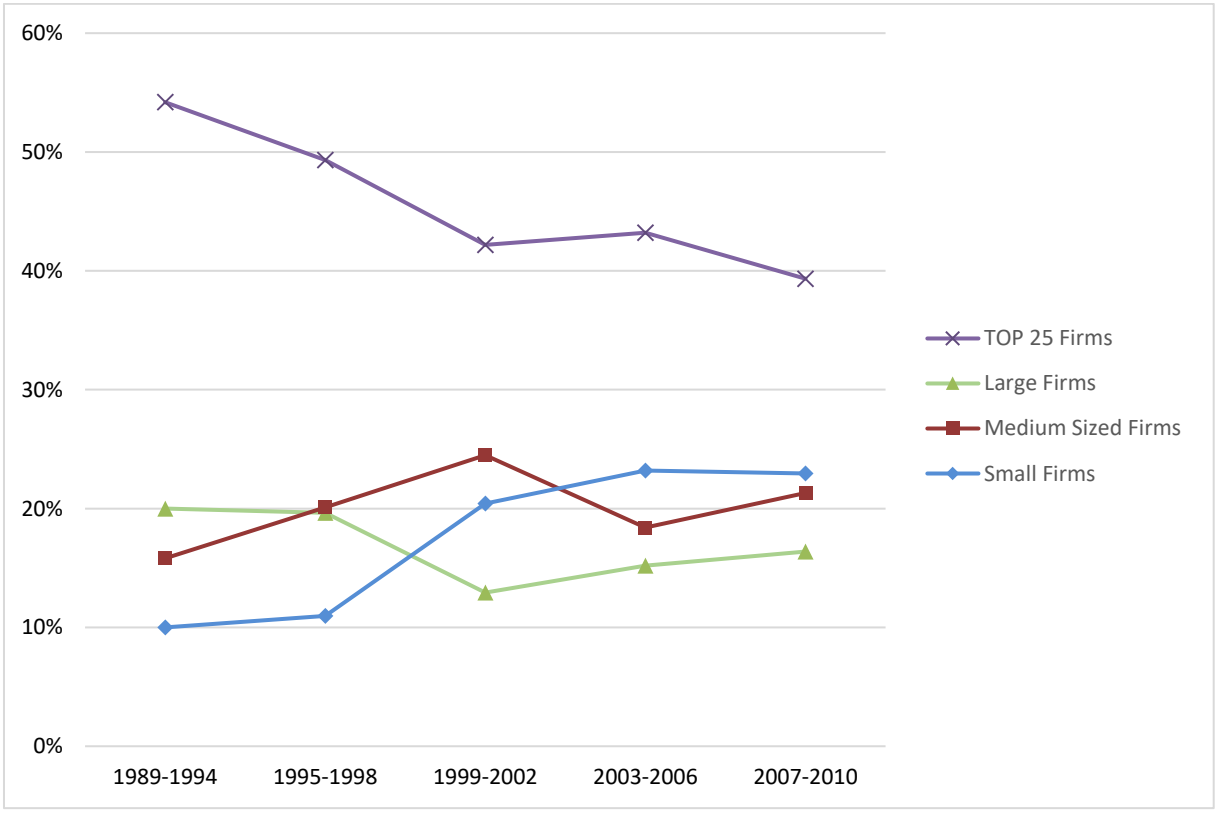
3.5. Successful Projects

While the success rate is a relative success measure, the number of new drugs is an absolute measure of the drug output of the industry. Note that the focus is on the innovation output of each firm size group as a whole. It may be the case that the group of small firms introduces more drugs within a given period than the group of large firms although the success rate is lower for smaller firms. The underlying reason for this is that the number of small firms is much higher than the number of large firms. This indicator therefore both considers changes in the success rate and changes in the number of firms

within each group over time. We look at the development of the *share* of each firm size group on the total number of new introduced drugs within each time period to show the relation of new drugs originated by different firm size groups.

The share of the top 25 firms on the number of new drugs is 0.542 in period 1 and decreases to 0.393 in period 5 (see Figure 3). Still almost 40 percent of the whole new drug output comes from the 25 largest firms in the industry. Looking at the large firms, the share is 0.200 in period 1, then decreases but stabilizes at a lower share of 0.164 in period 5. A different development is observed for medium-sized firms, where the share on the total number of new drugs is steadily increasing from 0.158 in period 1 to 0.245 in period 3 and then decreasing and stabilizing at 0.213 in period 5. Small firms only contribute to 10 percent of all new drugs in period 1. This share only slightly increases to 11 percent in period 2. From 1999 to 2002 (period 3), the share almost doubles to 0.204 and converges to around 0.23 from period 4 on. Therefore, the share is rising from 10 percent to almost 25 percent between 1989 and 2010. Especially the doubling of the share on new drugs in period 3 is striking. It can be explained by both the strongly increasing number of projects (growth rate of 83.4 percent) and the relatively high success rate of 0.046 in this firm size group within this period.

Figure 3: Share on successful projects by Firm Portfolio Size Group



Source: Informa Healthcare Pipeline Pharma Data; figure by the author

Over the study period, medium-sized firms and small firms have increased their share on the total number of projects, whereas the share of top 25 and large firms decreased. There seems to be a trend

towards a higher innovation output (measured as new drugs) by medium-sized, and, above all, small firms. Our results are in line with Munos (2009) who finds a steady decline in the share of new drugs (NMEs) introduced by large firms and an increasing share of new drugs introduced by small firms. Munos names two reasons for the increasing share: first, the number of small firms has increased strongly, and, second, the mean number of new drug output by small firms has risen strongly since 1995. Our findings are in line with these observations. This result does not reflect that many small firms have problems in developing compounds that are suitable for clinical development. From the analysis of the success rate and the preclinical discontinuation pattern, we see here that despite these problems, the group of small firms has an increasing higher share of new drug output in the industry. Not only on the input side, described by the number of drug development projects, but also on the output side of new drugs, small firms are gaining importance. However, while on the one hand, medium-sized and small firms have an ever-larger share on the innovative output of new drugs in recent times, the innovative output of top 25 firms and large firms is still very large: 55 percent of the new drugs are still introduced by the largest firms. Therefore, large firms remain an important driver of innovation within the industry.

4. Discussion of Results and Conclusion

We studied the development of innovative activities, productivity and output of different firm sizes in the pharmaceutical industry in a time span of over 20 years, a period where major technological and regulatory changes took place in the industry. In our analysis, we found that the share of projects originated by small firms has increased strongly between 1989 and 2010. While the number of projects increased for all firm size groups between the first two periods (1989 to 1994 and 1995 to 1998), the number of projects develops very different for large and small firms afterwards. While the number of projects originated by the top 25 firms and the large firms is decreasing strongly, the number of projects by small firms is increasing until the end of the study period. Clearly, R&D projects in the industry have become more decentralized. Many small firms conduct more independent experiments and can independently search in more directions than a small number of large firms. However, the success rate for small firms has found to be lower for medium-sized and small firms than for the top 25 and the large firms in our sample. This finding provides strong evidence for the interpretation that experience and the cumulation of knowledge considering both technological drug development and regulatory approval as well as the advantage of fixed-cost spreading over many projects is an advantage to be innovative in the pharmaceutical industry. Large firms therefore need to develop less projects to bring successful drugs to the market. Our findings are in line with Pammolli *et al.* (2011) who analyses a broad sample over a similar time period. Many small firms have difficulties to discover compounds suitable for clinical drug development. This interpretation is also supported by the analysis

of preclinical discontinuation rates. While preclinical discontinuation is increasing during the study period in general, the discontinuation rate is highest for small firms. However, as many more projects in the industry are originated by small firms nowadays, they eventually have a larger share on drug output nowadays. Not only on the input side, described by the number of drug development projects, but also on the output side of new drugs, small firms are gaining importance. However, the innovative output of top 25 and large firms is still very high as 55 percent of the new drugs are still introduced by the largest firms. Large firms also remain an important driver of innovation within the industry.

The relation of firm size and innovativeness is often discussed in the economic literature. It is therefore surprising that the development of innovative activities in the pharmaceutical industry have not often been studied empirically with respect to firm size. Our study is the first to provide comprehensive evidence on the innovative activities in the pharmaceutical industry over a time span of over 20 years – based on projects from a very broad range of different firm sizes. The striking result is that the industry is becoming more and more decentralized over time. The share of projects under development as well as the share of the drug output originated by small firms has been strongly increasing during the last 20 years. At the same time, it is puzzling that the success rate for projects originated by small firms is lower than the success rate for projects started by large firms. We did not correct for censoring when analyzing the success rates, assuming that the share of censored projects is the same for each firm size group. As in recent years, more projects are started by small firms, those are probably over-proportionally affected by censoring. It is likely that we under-estimate the success rate of more recent projects originated by small firms as relatively more and more projects are started by small firms. However, the success rate is lowest for small firms already in earlier periods. Further, the very high rate of projects from small firms already discontinued in the preclinical phase is also an indicator of a lower success probability of projects started by small firms.

The technological development in the industry generated much new knowledge. The higher number of small firms can search independently in various directions within the increasing search space. From this point of view, the rising importance of small firms is good for the innovativeness of the industry as a whole. On the other hand, lower success rates and higher preclinical discontinuation are at first glance negative. However, the reasons behind this development is not quite clear. Small firms may take more risks than larger ones, resulting in lower success rates and a higher risk of preclinical discontinuations. However, risk taking is a strategical firm decision and does not seem problematic for innovation. Indeed, many qualitatively high and effective drugs could be based on the discovery and development of “risky” compounds. On the other hand, when missing experience and financial difficulties are the main reasons behind the performance of small firms, this would be worrisome. These problems of small firms, often biotech startups, are already prevalent in the preclinical discovery

phase. Many startups do not qualify to be sufficiently financed by venture capital. However, despite these problems, the group of small firms has an increasing share on the output of new drugs. These considerations show that the reasons behind the development of the indicators are crucial and that still more research on these reasons is necessary to fully understand how the innovative development of the industry could be supported best by regulators and economic policy. This research can be based on qualitative studies but also on broad data sets of firms of different sizes – if available.

Discontinued projects induce sunk investment and increase the costs of drug development from the industry perspective. The increasing share of small firms on drug output suggests that smaller firms become more important, however large firms remain to have high shares on drug output. The qualitative assessment of our results could be improved by addressing the question whether drug introductions nowadays cover broader disease fields than in earlier times and whether the quality of new drugs has increased significantly. Further, we could not assess the financial background, i.e. the rate of return of investments in R&D. It could be the case that small firms show lower success rates but have in total smaller development costs or higher returns from more innovative drugs than large firms. The analysis of the development of the financial performance by firm size would yield interesting insights on the question whether the industry as a whole nowadays incurs on total higher sunk costs due to the lower success rate or a higher number of projects discontinued already in the preclinical phase.

References

Abrantes-Metz*, et al.*, 2004. *Pharmaceutical Development Phases: A Duration Analysis*. FTC Working Papers 274. Washington, D.C.: Federal Trade Commission.

Acs, Z.J. and Audretsch, D.B., 1990. *Innovation and Small Firms*. Cambridge, MA: MIT Press.

Acs, Z.J. and Audretsch, D.B., eds., 1991. *Innovation and Technological Change: An International Comparison*. New York, NY: Harvester Wheatsheaf.

Arora, A.*, et al.*, 2009. A Breath of Fresh Air? Firm Type, Scale, Scope, and Selection Effects in Drug Development. *Management Science*, 55 (10), 1638–1653.

Arrowsmith, J., 2012. A decade of change. *Nature Reviews Drug Discovery*, 11 (1), 17–18.

Azoulay, P., 2004. Capturing Knowledge within and across Firm Boundaries: Evidence from Clinical Development. *The American Economic Review*, 94 (5), 1591–1612.

Barden, C.J. and Weaver, D.F., 2010. The Rise of Micropharma. *Drug Discovery Today*, 15 (3-4), 84–87.

Bound, S*., et al.*, 1984. Who Does R&D and Who Patents? *In:* Z. Griliches, ed. *R & D, patents, and productivity*. Chicago: University of Chicago Press, 21–54.

Chandler, A., 1997. The United States: Engines of Economic Growth in the Capital Intensive and Knowledge Intensive Industries. *In:* A. Chandler, F. Amatori, and T. Hikino, eds. *Big Business and the Wealth of Nations*. Cambridge, MA: Cambridge University Press, 63–101.

Chandy, R*., et al.*, 2006. From Invention to Innovation: Conversion Ability in Product Development. *Journal of Marketing Research*, XLIII, 494–508.

Cockburn, I.M., 2006. Is the Pharmaceutical Industry in a Productivity Crisis? *Innovation Policy and the Economy*, 7, 1–32.

Cockburn, I.M. and Henderson, R.M., 2001. Scale and scope in drug development: unpacking the advantages of size in pharmaceutical research. *Journal of Health Economics*, 20 (6), 1033–1057.

Cohen, W.M., 2010. Fifty Years of Empirical Studies of Innovative Activity and Performance. *In:* B.B. Hall and N. Rosenberg, eds. *Handbook of The Economics of Innovation, Vol. 1*: Elsevier, 129–213.

Cohen, W.M. and Klepper, S., 1996. A Reprise of Size and R & D. *The Economic Journal*, 106 (437), 925.

Comanor, W.S. and Scherer, F.M., 2013. Mergers and innovation in the pharmaceutical industry. *Journal of Health Economics*, 32 (1), 106–113.

Danzon, P.M., Nicholson, S., and Pereira, N.S., 2005. Productivity in pharmaceutical–biotechnology R&D: the role of experience and alliances. *Journal of Health Economics*, 24 (2), 317–339.

DiMasi, J., 2014. Pharmaceutical R&D Performance by Firm Size: Approval Success Rates and Economic Returns

. *American Journal of Therapeutics*, 21, 26–34.

DiMasi, J.A., Grabowski, H.G., and Vernon, J., 1995. R&D Costs, Innovative Output and Firm Size in the Pharmaceutical Industry

. *International Journal of the Economics of Business*, 2 (2), 201–219.

Dosi, G. and Nelson, R.R., 2010. Technical Change and Industrial Dynamics as Evolutionary Processes. *In:* B.B. Hall and N. Rosenberg, eds. *Handbook of The Economics of Innovation, Vol. 1*: Elsevier, 51–127.

Fagerberg, J., Mowery, D.C., and Nelson, R.R., eds., 2011. *The Oxford handbook of innovation*. Oxford: Oxford Univ. Press.

Freedman, L.P., Cockburn, I.M., and Simcoe, T.S., 2015. The Economics of Reproducibility in Preclinical Research. *PLoS biology*, 13 (6), e1002165.

Freeman, C. and Louca, F., 2001. *As Time Goes By: From the Industrial Revolution to the Information Revolution*. Oxford: Oxford Univ. Press.

Galambos, L. and Sturchio, J., 1998. Pharmaceutical Firms and the Transition to Biotechnology: A Study in Strategic Innovation. *Business History Review*, 72, 250–278.

Gambardella, A., Orsenigo, L., and Pammolli, F., 2000. *Global Competitiveness in Pharmaceuticals: A European Perspective*. Report Prepared for the Directorate General Enterprise of the European Commission.

Gassmann, O., Reepmeyer, G., and von Zedtwitz, M., 2008. *Leading Pharmaceutical Innovation: Trends and Drivers for Growth in the Pharmaceutical Industry.* 2nd ed. Berlin, Heidelberg: Springer.

Grabowski, H.G., 1968. The Determinants of Industrial Research and Development: A Study of the Chemical, Drug, and Petroleum Industries. *The Journal of Political Economy*, 76 (2), 292–306.

Grabowski, H.G. and Vernon, J., 1994. Innovation and Structural Change in Pharmaceuticals and Biotechnology. *Industrial and Corporate Change*, 3 (2), 435-449.

Griliches, Z., 1990. *Patent Statistics as Economic Indicators: A Survey*. Cambridge, MA: National Bureau of Economic Research.

Guedj, I. and Scharfstein, D., 2004. *Organizational Scope and Investment: Evidence from the Drug Development Strategies and Performance of Biopharmaceutical Firms*. NBER Working Paper No. 10933.

Henderson, R.M. and Cockburn, I.M., 1996. Scale, scope, and spillovers: the determinants of research productivity in drug discovery. *RAND Journal of Economics*, 27 (1), 32–59.

Kaitin, K.I. and DiMasi, J.A., 2010. Pharmaceutical Innovation in the 21st Century: New Drug Approvals in the First Decade, 2000–2009. *Clinical Pharmacology & Therapeutics*, 89 (2), 183–188.

Khanna, I., 2012. Drug discovery in pharmaceutical industry: productivity challenges and trends. *Drug Discovery Today*, 17 (19-20), 1088–1102.

Klepper, S., 1996. Entry, Exit, Growth, and Innovation over the Product Life Cycle. *The American Economic Review*, 86 (3), 562–583.

Klepper, S. and Simons, K.L., 2005. Industry shakeouts and technological change. *International Journal of Industrial Organization*, 23 (1-2), 23–43.

Kola, I. and Landis, J., 2004. Can the Pharmaceutical Industry Reduce Attrition Rates? Opinion. *Nature Reviews | Drug Discovery*, 3, 711–715.

Louca, F. and Mendonca, S., 1999. *Steady Change: the 200 Largest US Manufacturing Firms in the Twentieth Century*. Working Paper No. 14/99. Lisbon: CISEP-ISEG, UTL.

Malerba, F. and Orsenigo, L., 2015. The Evolution of the Pharmaceutical Industry. *Business History*, 57 (5), 664–687.

Mansfield, E., 1964. Industrial research and development expenditures: Determinant prospects, and relation of size of firm and inventive output. *Journal of Political Economy*, 72, 319–340.

Mittra, J., 2007. Life science innovation and the restructuring of the pharmaceutical industry: merger, acquisition and strategic alliance behaviour of large firms. *Technology Analysis and Strategic Management*, 19 (3), 279–301.

Munos, B., 2009. Lessons from 60 years of pharmaceutical innovation. *Nature Reviews Drug Discovery*, 8 (12), 959–968.

Orsenigo, L., 2001. The (Failed) Development of a Biotechnology Cluster: The Case of Lombardy. *Small Business Economics*, 17, 77–92.

Orsenigo, L., Pammolli, F., and Riccaboni, M., 2001. Technological change and network dynamics Lessons from the pharmaceutical industry. *Research Policy*, 30, 485–508.

Pammolli, F., Magazzini, L., and Riccaboni, M., 2011. The productivity crisis in pharmaceutical R&D. *Nature Reviews Drug Discovery*, 10 (6), 428–438.

Paul, S.M.*, et al.*, 2010. How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nature Reviews Drug Discovery*.

Pavitt, K., 1984. Sectoral patterns of technical change: Towards a taxonomy and a theory. *Research Policy*, 13, 343–373.

Pavitt, K., Robson, M., and Townsend, J., 1987. The Size Distribution of Innovating Firms in the UK: 1945-1983. *The Journal of Industrial Economics*, 35 (3), 297-316.

Petrova, E., 2014. Innovation in the Pharmaceutical Industry: The Process of Drug Discovery and Development. *In:* M. Ding, J. Eliashberg, and S. Stremersch, eds. *Innovation and Marketing in the Pharmaceutical Industry: Emerging Practices, Research, and Policies*. New York: Springer, 19–82.

Pisano, G.P., 2006. *Science Business: The Promise, the Reality and the Future of Biotech*. Cambridge, MA.

Scannell, J.W.*, et al.*, 2012. Diagnosing the decline in pharmaceutical R&D efficiency. *Nature Reviews Drug Discovery*, 11 (3), 191–200.

Scherer, F.M., 1965a. Firm size, market structure, opportunity, and the output of patented inventions. *American Economic Review*, 55, 1097–1125.

Scherer, F.M., 1965b. Size of firm, oligopoly, and research: A comment. *Canadian Journal of Economics and Political Science*, 31, 256–266.

Scherer, F.M., 1984. *Innovation and Growth: Schumpeterian Perspectives*. Cambridge, MA: MIT Press.

Scherer, F.M., 2010. Pharmaceutical Innovation. *In:* B.B. Hall and N. Rosenberg, eds. *Handbook of The Economics of Innovation, Vol. 1*: Elsevier, 539–574.

Teece, D.J., 2010. Technological Innovation and the Theory of the Firm. *In:* B.B. Hall and N. Rosenberg, eds. *Handbook of The Economics of Innovation, Vol. 1*: Elsevier, 679–730.

van der Panne, G., van Beers, C., and Kleinknecht, A., 2003. Success and Failure of Innovation: A Literature Review. *International Journal of Innovation Management*, 7 (3), 309–338.