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Martin Backfisch

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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

Have Pharmaceutical R&D Project Success Rates Decreased?

A Critical Review and New Empirical Results

Martin Backfisch[1]

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In the context of the ongoing debate about an innovation crisis in the pharmaceutical industry, we study the success rates of pharmaceutical R&D projects as a measure of innovative productivity. The empirical literature suggests success rates have been decreasing during recent decades. We critically review this literature and only find few studies with a focus on the development of success rates over time. Further, the empirical analysis of success rates imposes difficulties with respect to methodological aspects like data censoring, the definition of success, and the range of firms included in the samples. These difficulties are generally not discussed by the literature. We therefore discuss these issues when critically reviewing the empirical studies and complement this discussion with own empirical results. While most other studies use samples containing a small number of firms and cover just a short time period, we use a broad sample containing firms of different sizes over an observation period of more than 20 years (1989-2010). Descriptive results suggest a declining success rate of pharmaceutical projects during recent years. Correcting for censored observations shows there has been a stabilization of success rates, but at a lower level than before. The main underlying reason for a lower success rate is the start of many more projects in more recent time periods. Results from hazard rate models even suggest there has only been a temporary drop in the success rate for projects between 1995 and 2002.

Keywords: pharmaceutical R&D; drug development; innovation; success rates

JEL Classification: O32, L65

1. Introduction

The pharmaceutical industry has undergone many changes during the last three decades. In the 1990s and early 2000s, important technological advances took place in parallel. The decoding of the human genome and the progress in bioinformatics and synthetic and structural biology lead to the entry of many small biotech firms (Malerba and Orsenigo 2015). There has also been progress in more "traditional" technologies like combinatorial chemistry and high-throughput screening, advancing "industrialised R&D" (Pisano 2006). The latter development was the basis for the development of blockbuster drugs with high revenues, what in turn made high R&D investments possible (Martin et al. 2009). However, the positive image of the industry ended with the turn of the century. Despite the aforementioned advances, the

[1] Baden-Wuerttemberg Cooperative State University Center for Advanced Studies, Heilbronn, and Philipps University Marburg, Germany

number of new drugs per year has been widely constant within the 1990s and the first decade of the 2000s (Munos, 2009; Malerba and Orsenigo 2015). At the same time, R&D costs increased dramatically. While DiMasi et al. (1991) estimate the cost per new drug to be $ 231m in 1987 dollars, DiMasi et al. (2016) estimate the respective figure to be $2,558 million in 2013 dollars. This development lead to a debate about an innovation crisis in the pharmaceutical industry. In this context, there is a broad empirical literature studying different innovation indicators. We will focus on the success rate which 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 rate is a measure of innovative productivity and can be interpreted as the probability that a pharmaceutical research project started by a firm will be successfully introduced to the market.

Many empirical studies present results on the success rates within different time periods. At first glance, empirical results suggest that success rates have been decreasing during recent decades. However, only few authors study the development of the success rates over time. They rather present evidence on the success rate within a certain time period. To infer the development over a longer time period, one has to compare different studies. This comparison, however, is problematic as different definitions of an R&D project are applied in the different studies, which in turn has an effect on the resulting success rate. Further, the success rates are not comparable across studies as they apply different data sets. Most results are based on data sets limited to projects of the leading pharmaceutical firms, not reflecting the structure of the industry with many small and medium-sized firms. It is surprising that there is almost no critical discussion in the literature about project definition, success rate definition, and the firms included in the sample. We critically discuss these issues to present a broad view on methodological aspects of the empirical analysis of success rate development over time.

Our review of the empirical literature also shows that most authors do not study the development of the success rate over time. Contrary, we present own empirical results on the development of the success rate over a period of over 20 years, investigating whether the rate has really decreased like the literature suggests. When this development is studied, censored projects have to be accounted for. Projects are censored when it is not clear whether the project is a success or a failure at the end of the observation period. When censoring is not handled, these projects are dropped from the sample. As the development process is lengthy for successful drugs, these do not have “enough time” to be launched to the market before the end of the observation period. In more recent time periods, relatively more potential launches than discontinuations are dropped from the sample and the success rate is under-estimated for these periods. Censoring has to be handled correctly as otherwise a decline in the success rate may be solely based on statistical reasons. There is no empirical study with projects starting later than 1994 which handles censoring.

We use a sample from the Pipeline data base from Informa Healthcare. This data set has not been utilised in this context before. It contains pharmaceutical R&D projects started between 1989 and 2010 by a broad range of large, medium-sized, and small firms and allows a comprehensive study of the development of the success rate in this time period. We complement this analysis by reviewing the development of the number of diseases a project is developed for and the project development time indicating the efforts firms undertake for drug development. Additionally, we estimate a hazard rate model to study the changes of the success rate within different time periods for a "representative" R&D project where all other project characteristics are held constant. In doing so, we can further identify reasons for the observed changes in the success rate over time. To the best of our knowledge, the development of the success rate over time has not yet been analysed in such a comprehensive way over such a long time period. Our study therefore adds to the understanding of the development of the success rate over time.

The paper is structured as follows: In section 2, the empirical literature on the success rates of pharmaceutical R&D projects is critically reviewed. The aforementioned issues of project definition, range of firms included in the sample, and the lack of an analysis over time are discussed. Based on this discussion, we develop our own empirical study in sections 3 and 4. In section 3, we describe the data and descriptively analyse the development of the success rate over five time periods. Further, we estimate success rates correcting for right-censoring of the data. In section 4, we complement these findings with results from hazard rate models. In section 5, the results are summarized and discussed. Directions for further research are given.

2. Empirical Studies on Success Rates: A Critical Review

2.1. Empirical Literature Review

There is a large literature on R&D productivity and innovativeness in the pharmaceutical industry. We focus on the empirical literature analysing success rates defined as the share of successful research projects on the sum of successful and discontinued projects within a given time period. The development of the project success rate over time is one indicator for the innovativeness in the industry. Cockburn and Henderson (2001) present results from projects in clinical trials (phase I) between 1960 and 1990 by 10 pharmaceutical firms, finding a success rate of 0.25, i.e. one out of four projects has been approved by the US Food and Drug Administration (FDA). DiMasi *et al.* (1995) use a sample of projects first in clinical trials between 1970 and 1982 and find that large firms have a success rate of 0.279, medium-sized firms of 0.174, and small firms of 0.238. Arora *et al.* (2009) include projects from 1980 to 1994 and find – like Cockburn and Henderson – a success rate of 0.25 as well. In a similar time period, DiMasi (2001) studies sub-periods of three years. Whereas from 1981 to 1983, the success rate is 0.232, it decreases to 0.205

Table 1: Literature Overview

Author(s)	Country	Period	Project and Firm info	Project and Success Definition	Success Rate
Abrantes-Metz *et al.* (2004)	U.S.	1989-2002	3,146 projects in clinical trials Set of firms not indicated, but presumably broad set of firms	Compound-disease definition project success: regulatory approval	**0.264**
Adams and Brantner (2006)	U.S.	1989-2002	3,181 projects in clinical trials set of firms not indicated	Lead compound definition success: regulatory approval	**0.24**
Adams and Brantner (2010)	U.S.	1989-2002	2,245 projects in clinical trials 183 publicly traded firms in the pharmaceutical industry	Lead compound definition success: regulatory approval	**0.2556**
Arora et al. (2009)	U.S.	1980-1994	3,311 projects in clinical trials 329 firms	Lead compound definition success: regulatory approval	**0.25**
Arrowsmith (2012)	N/A	2002-2008	Number of projects not indicated; Projects in clinical trials 6 major,8 mid and other companies	Lead compound definition project success: market launch	**0.10** (2002-2004) **0.05** (2006-2008)
Cockburn and Henderson (2001)	Europe, USA	1960-1990	708 projects in clinical trials 10 pharmaceutical firms covering the range of major R&D-performers	Lead compound definition success: regulatory approval	**0.250**
Danzon et al. (2005)	U.S.	1988-2000	Data from R&D Insight database from Adis International: over 1.900 projects in clinical trials over 900 pharmaceutical and biotech firms	Compound-disease definition success: regulatory approval	**0.3913**
DiMasi (2001)	U.S.	1981-1992	508 compounds in clinical trials 24 firms,	Lead compound definition project success: regulatory approval	1981-83: **0.232** 1984-86: **0.205** 1987-89: **0.222** 1990-92: **0.172**
DiMasi (2014)	worldwide development; approval for U.S. market	1993 -2004	1,734 compounds Top 50 pharmaceutical firms by sales in 2006 projects at least in phase I (clinical trials)	Lead compound definition project success: regulatory approval	**0.169** (Top 10) **0.203** (Top 11-20) **0.231** (Top 21-50)
DiMasi *et al.* (1995)	U.S.	1970-1982	93 self-originated projects in clinical trials 12 US-owned pharma firms	project definition: not reported project success: presumably regulatory approval	Large firms: **0.279** Medium firms: **0.174** Small firms: **0.238** (self-originated compounds)
DiMasi *et al.* (2010)	U.S.	1993-2004	1,738 projects in clinical trials Top 50 pharmaceutical firms by sales	Lead compound definition project success: regulatory approval	**0.16** (self-originated compounds) **0.19** (self-originated and licensed compounds)
Hay *et al.* (2014)	U.S.	2003-2011	7,372 projects in clinical trials 835 companies	Compound-disease definition project success: regulatory approval	**0.104** (lead and nonlead indications) **0.153** (only lead indications)
Kola and Landis (2004)	Europe, U.S.	1980-1998	No. of projects not indicated; projects in clinical trials; Top 10 drug companies during 1991-2000	Lead compound definition project success: regulatory approval	**0.11**
Pammolli *et al.* (2011)	Europe, US, and Japan	1990-2007	30,527 compounds from preclinical phase on (NMEs, including biologicals); Set of firms not indicated	Lead compound definition project success: regulatory approval	**0.071- 0.086** (depending on firm/project characteristics)

Source: table by the author

between 1984 and 1986, rises again to 0.222 between 1987 and 1989 and drops to 0.172 between 1990 and 1992. Results by Kola and Landis (2004) on clinical projects suggest this decline has continued during the later 1990s: projects started between 1980 and 1998 show a success rate of 0.11. This rate is lying well below the findings of the studies considering the earlier time periods.

Results by Danzon *et al.* (2005) contradict this decline in the success rate. In their study, projects first in clinical trials between 1988 and 2000 show a success rate of 0.39 contradicting previous findings of smaller success rates. Contrary, three studies with clinical projects in a similar time period (1989 to 2002) use samples from the same database and find success rates of 0.264 (Abrantes-Metz *et al.* 2004), 0.240 (Adams and Brantner 2006) and 0.256 (Adams and Brantner 2010). DiMasi (2014) analyses clinical projects started from 1993 to 2004 and finds rates of 0.169 for top 10 firms, 0.203 for top 11-20 firms and 0.231 for top 21-50 firms. While in this study no overall success rate is given, DiMasi *et al.* (2010) find a success rate of 0.19 for projects starting clinical trials within same time period. Pammolli *et al.* (2011) study projects started between 1990 and 2007 and come to different results: the success rates vary between 0.071 and 0.086. Table 1 summarizes the findings.

More recent projects are analysed by Arrowsmith (2012) and Hay *et al.* (2014). Arrowsmith (2012) finds a success rate of 0.10 for projects starting clinical trials between 2002 and 2004 which is steadily declining to 0.05 for project starting between 2006 and 2008. This result suggests a very low success rate for projects starting clinical trials in the first decade of the 2000s. Hay *et al.* (2014) analyse projects first in clinical trials between 2003 and 2011 and find a success rates of 0.104 and 0.153, depending on the definition of a pharmaceutical project.

The presented studies suggest that the success rate of pharmaceutical R&D projects lay between 0.20 and 0.25 from the 1960s to the early 1990s and fell then to 0.17 (DiMasi 2001) and eventually to 0.11 at the end of the 1990s (Kola and Landis 2004). However, other studies including projects started in the 1990s and early 2000s find higher success rates of around 0.25 (Abrantes-Metz *et al.* 2004; Adams and Brantner 2006). In a similar period, different studies come to varying success rates of 0.390 (Danzon *et al.* 2005), 0.190 (DiMasi 2014) and 0.071-0.086 (Pammolli *et al.* 2011). The results by Arrowsmith (2012) and Hay *et al.* (2014) with projects stared more recently also show there is a large difference in the success rates found by different studies.

Whereas for projects started between around 1990 and 2000, there are a number of studies coming to different results, the earlier time periods are not covered by more than one study. Therefore, the reliability of the results from projects from the 1960s to the end of the 1980s can be questioned as there is no confirmation of the results by other studies. A confirmation would, however, be necessary given the large differences in the success rates of studies with projects from the 1990s to the early 2000s and from the early 2000s to 2010. The question is why the empirical studies find large differences in success rates

for similar time periods. In the following, we will discuss two major aspects contributing to the variability in the results of the empirical studies. First, the definition of the success rate may differ. Second, the samples strongly differ according to the selection firms whose projects are included in the sample. Based on this discussion, we propose how the development of success rates over time can be studied suitably.

2.2. Problem 1: Success Rate Definition

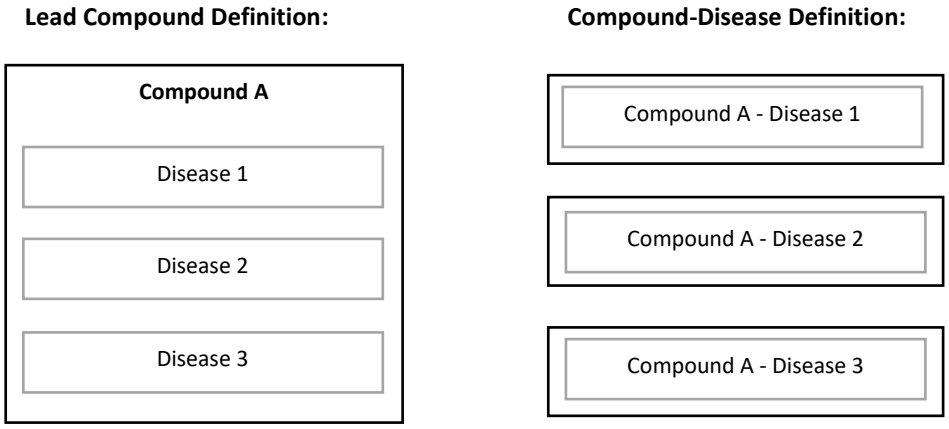
The results of the presented studies differ and cannot easily be compared to each other. One reason for a lack of comparability is a different definition of the success rate. There are three major aspects when defining project success rates: the definition of "success" itself, the definition of the "project" and the projects included in the sample. While a success can be the market launch in at least one country, it could also be a success when the filing of a new drug application (NDA) at the regulatory authority is done. While gaining the successful approval of a regulatory authority to market the drug is the last step in the clinical development procedure, defining success as actual market launch goes one step further. In the latter definition, the approval from the regulatory authority is given *and* the drug is launched to the market. Most of the empirical studies reviewed above define success as the approval of the regulatory authority to market the drug. The only exception is Arrowsmith (2012), regarding actual market launch. We do not expect a large difference between the approval by a regulatory authority and the market launch itself, i.e. the rate of approved drugs being launched is high. Nevertheless, when regarding market launch itself, remaining uncertainties about the introduction of a novel drug to the market is eliminated.

Second, the empirical literature uses two definitions of a pharmaceutical R&D project. In the lead compound definition, a project is the development of a drug candidate compound for the treatment of one or more diseases. Contrary, in the compound-disease definition, a project is defined as the development of a compound for the treatment of one specific disease, i.e. each compound-disease combination is a project on its own. Figure 1 shows the difference between these definitions for a compound A suitable to treat three diseases. In the lead compound definition, the R&D project consists of the development of compound A to treat three diseases. In the compound-disease definition each combination of compound and disease indication is a project on its own. With the exception of Danzon *et al.* (2005), Arora *et al.* (2009), and Hay *et al.* (2014), all of the reviewed studies use the lead compound definition.

Danzon *et al.* (2005) state that their approach using the compound-disease definition possibly estimates larger success rates than studies using the lead compound definition. However, we do not embrace this interpretation and come to the same conclusion as Hay *et al.* (2014). In the compound-disease definition, a success is given by the introduction of a compound to treat one specific disease. Contrary, in the lead compound definition a project with a compound in development for more than one indication is already

a success when it is launched for the first of these indications. For the remaining indications, the compound may not be developed successfully. This is, however, not reflected by this definition, hiding the failures for remaining indications. For this reason, the lead compound definition leads to larger success rates than the compound-disease definition.

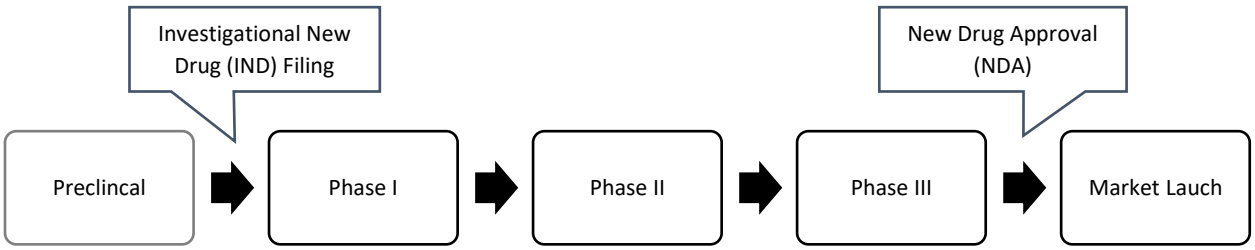
Figure 1: Two Possible Definitions of Pharmaceutical Projects



Source: figure by the author

Third, as the success rate is defined as the share of successful projects on all projects in the sample, it also depends on the selection of projects included. This is intuitive for the exclusion of projects not reaching the clinical phase. When these preclinically discontinued projects are excluded, the success rate is larger, but is only referring to projects reaching at least the clinical stage. This difference is crucial for the interpretation of the findings on success rates.

Figure 2: Stages in Drug Development (simplified)



Source: PhRMA (2014); figure by the author

In the USA, the clinical stage is starting with an Investigational New Drug (IND) Application at the FDA (see Figure 2). With the exception of Pammolli *et al.* (2011), all of the reviewed studies include only projects reaching at least clinical trials (phase I). Pammolli *et al.* (2011) are also including projects not reaching clinical trials in the sample. To economically assess the development efforts of pharmaceutical firms, all projects initiated by pharmaceutical firms should be included in the sample, if possible, as projects discontinued in the preclinical stage are costly without recouping these investments. The focus on clinical

trial projects in large parts of the literature seems to ground on a lack of data on preclinical projects. In most data sets, there is only information on projects available when they enter the clinical stage as before firms are not obliged to report data to regulatory authorities. Note, however, that while the inclusion of preclinical projects is favourable, the success rate results by Pammolli *et al.* (2011) between 0.071 and 0.086 cannot be compared to the success rates of the other studies. A comparison would be possible if the share of preclinical projects entering clinical trials was given. However, the authors do not indicate this share.

2.3. Problem 2: Firms included in the Sample

The difference in the groups of firms included in the study sample is an important aspect leading to differences in the result on success rates. For example, Arrowsmith (2012) uses a set of only 14 companies. These are not only top performing firms, but six major and eight mid-sized and other firms. The author gives no information on the number of projects such that we cannot infer for which kinds of firms the declining success rate between 2002 and 2008 applies. A comparison to the results of other studies is not possible.

Most studies focus on small samples of projects from the top performing firms in the industry. Cockburn and Henderson (2001) use 708 projects of only 10 pharmaceutical firms representing the range of major R&D performing firms in the industry. Given the long study period (projects started between 1960 and 1990) their data is most likely limited to the top pharmaceutical firms. DiMasi *et al.* (1995) use a sample restricted to 12 US-owned firms, including only 83 projects with self-originated new chemical compounds. The reliability of the findings from this study can be heavily doubted. DiMasi (2001) also uses a narrow sample of 24 firms, but the number of projects is larger (508 projects). The data set of DiMasi (2014) covers the 50 largest pharma firms and 1,734 projects. Similarly, DiMasi *et al.* (2010) use 1,738 projects from the top 50 firms. Kola and Landis (2004) use data on an unspecified number of projects from the 10 biggest drug companies from 1991-2000. While these studies give an impression of the success rate of the top performing firms, a comprehensive view of the whole pharmaceutical industry cannot be given. The results are limited to the largest firms in the industry.

There are some studies using broader data sets. Adams and Brantner (2006) analyse 3,181 projects. The authors, however, do not indicate the size of the firms included in the sample. Abrantes-Metz *et al.* (2004) can be criticized for the same reasons: they use data on 3,136 projects, however the firm sizes remain unclear. Adams and Brantner (2010) use projects from 183 stock market listed firms, restricting the sample by excluding non-listed firms. Arora *et al.* (2009) focus on 3,311 projects from 329 firms. While the studies not clearly indicate which firms are included, the larger number of projects and firms suggests that at least medium-sized firms are included as well.

Pammolli *et al.* (2011) and Hay *et al.* (2014) use the largest data sets with the broadest range of firms included. However, Pammolli *et al.* (2011) do not indicate the number of firms or firm characteristics like their size. The sample includes 30,527 compounds starting preclinical development between 1990 and 2007. Hay *et al.* (2014) use 7,372 projects from 835 firms, including small biotech companies as well as specialty firms. The range of firms is the largest among all reviewed studies. At the same time, the authors use the data set containing the most recent projects compared to other studies. The projects have all been first in clinical trials between 2003 and 2011.

Whereas large firms are the driver of pharmaceutical innovations brought to the market, many projects originate from small firms and are brought forward in clinical development by larger firms via licensing. This business model in the industry is not covered by studies only including the industry's top performing firms. Especially, the whole discovery and development efforts of small firms are neglected or only enter the analysis by licensed-in projects of top pharmaceutical firms. Therefore, studies analysing large samples and including more than the top innovating firms should be preferred to studies investigating smaller samples of firms when the development of the pharmaceutical industry is assessed.

The most reliable studies including at least mid-sized firms are Abrantes-Metz *et al.* (2004), Adams and Brantner (2006), Arora *et al.* (2009), and Adams and Brantner (2010). Remarkably, despite taking into account different sets of firms, these studies all find success rates of around 0.25 for projects started between 1989 and 2002 (Arora *et al.* 2009: 1980 to 1994). For the time periods of the late 1980s and early 2000s, a success rate of 0.25 for projects reaching clinical development provides a reliable estimate for large and mid-sized firms. However, these studies all focus on drugs developed for the US market. Pammolli *et al.* (2011) contributes more recent results for the period 1990 to 2007. However, the success rates between 0.071 and 0.086 cannot be compared to the rate of 0.25 found by previous studies as the sample of Pammolli *et al.* (2011) also contains projects discontinued in the preclinical stage. Further, small firms and also projects for the European and the Japanese drug market are included. Hay *et al.* (2014) include small firms as well and analyse more recent projects, coming to a success rate of 0.153 (in the lead compound definition). As the authors focus on drugs for the US market, these results could be compared to those of Abrantes-Metz *et al.* (2004), Adams and Brantner (2006), Arora *et al.* (2009), and Adams and Brantner (2010). However, this comparison is again limited by the fact that these four studies only include large and mid-sized firms. Therefore, it cannot be clearly inferred whether the drop to a smaller success rate of 0.153 is based on an ongoing decline of success rates over time or on the inclusion of small firms in the sample.

2.4. Change of Success Rates over Time

In section 2.1, we pointed out there is a possible development trend in success rates from 0.25 found by some studies for the 1990s and early 2000s to 0.153 found by Hay *et al.* (2014) for more recent projects. However, we saw in sections 2.2 and 2.3 that these results are difficult to compare. While most of the empirical studies use projects in clinical development and use the lead compound definition, the range of firms included is different. The two studies with the broadest range of firms (Pammolli *et al.* 2011 and Hay *et al.* 2014) cannot be compared to each other as Pammolli *et al.* (2011) also include projects discontinued in the preclinical phase. Therefore, the changes in the success rate found by different studies should be interpreted with caution. It would be preferable to review the development of success rates over time within one study rather than across different studies. Within one study the definition of the success rate and the firm set would be the same and the development over time could be traced reliably.

Besides the study by DiMasi (2001) with projects started from 1981 to 1992 and restricted to large firms, only Arrowsmith (2012) presents a within-study analysis of more than one time period, suggesting success rates have gone down from 0.1 (2002-2004) to 0.05 (2006-2008). However, as stated above, the author only relies on a restricted sample of 14 firms and does not indicate how many projects are included. For these reasons, we cannot rely on these results to assess changes in the success rate.

Table 2: Results from Pammolli *et al.* (2011)

Categories	1990-1999	2000-2007
Chronic vs. Acute Diseases	0.072	0.071
Lethal vs. Non-Lethal Diseases	0.088	0.085
Small vs. Large Organisations	0.084	0.071
Biotech vs. Non-Biotech	0.072	0.071
Rare vs. Widespread Diseases	0.072	0.075

Source: (Pammolli et al. 2011); author's own calculations

Pammolli *et al.* (2011) present changes in the project portfolios depending on different categories (see Table 2). Changes in the overall success rate can be computed for projects started between 1990 and 1999 and projects started between 2000 and 2007. The results only show minor changes in the overall success rate. However, Pammolli *et al.* (2011) do not present specific success rates for each time period. The authors assume a constant probability of success. The changes in success rates are merely based on a different composition of the project portfolios concerning the different categories of projects with different – but constant – probabilities of success. For this reason, these results are only of little relevance when studying changes in the success rates over time.[2]

[2] Pammolli *et al.* (2011) also presents the change in attrition rates of projects started from 1990 to 2004. Attrition rates are increasing in all preclinical and clinical phases, however, cannot be translated easily to success rates. For example, for projects

To sum up, the presented empirical studies are not suitable to get a comprehensive view on the development of success rates over time. There is no single study including recently started projects and tracing the development of success rates over time for a sample of projects from a wide range of firms. Studies on earlier periods until the end of the 1980s rely on small sets of firms, being mostly the top firms in the industry, limiting findings to this group of firms. Most of the studies for the end of the 1980s until the early 2000s can be compared and include at least mid-sized firms as well in the sample. Studies using data on recently started projects are rare. Comprehensive studies with projects from a wide range of firms are Pammolli *et al.* (2011) and Hay *et al.* (2014). These studies use a broad sample of projects from a wide range of firms. However, the results cannot be compared to each other and do not show the development of the success rate over time. In the following section, we will therefore analyse the development of success rate of pharmaceutical projects over time in a data set covering the long period of projects started between 1989 and 2010. The sample includes a broad set of projects from a wide range of firms. We are able to evaluate and discuss the change in the success rate for projects started in five different sub-periods and discuss the contribution and limitation of these findings in more detail than has been done before.

3. An Empirical Analysis of Success Rates

3.1. Data

We use a sample from the Pipeline data base from Informa Healthcare. The data contain the progress of drug candidates in R&D programmes around the world and from all research and development active firms with the aim of commercial drug development. The data contains information on projects in preclinical development as far as information is available in the public domain and follows the projects throughout clinical development phases until market launch or discontinuation. All diseases a drug candidate is developed for are covered. Included drug candidates are – among others – human therapeutics, human vaccines, novel formulations of existing drugs, and reprofiled drugs for novel uses. Generics, over-the-counter (OTC) drugs, and veterinary drugs are excluded.[3] A research project is only included when a specific therapeutic focus is present and when it is company-based or from non-industrial

started in 1990, the attrition rate in the preclinical phase is 0.65, i.e., 65 percent of projects are discontinued during the preclinical phase. This does – however – not mean that the success rate of this phase is 0.35. This number relates to all projects in the sample, including projects still in the pipeline. As explained above, the success rate is defined as the relation between successful projects and successful and discontinued projects (excluding project still in the pipeline at the end of the observation period). Therefore, calculating the success rate of 0.098 for projects started in 1990 and 0.014 for projects started in 2004 computed as the multiplication of the phase specific "success rates" are rather lower bounds of success rates, whereas in the more recent sample, more projects being still in the pipeline are expected. The estimate for the most recent sample is likely to be more downward biased than the estimates for the earlier sample.

[3] A complete list of inclusions and exclusions of research activities are given in Table A 1 in the Appendix based on Informa Healthcare (2012).

sources with early licensing opportunities. In other words, all projects in the database have a commercial focus.

Table 3: Number of Observations by Subsamples

Begin Year Periods:	1989- 1995	1995-1998	1999-2002	2003-2006	2007-2010
No. of obs. all projects (incl. preclinical phase)	1,714	3,239	3,638	4,092	5,104
No. of projects still in pipeline in 2010 (censored)	*11*	*41*	*98*	*307*	*1,249*

Source: Informa Healthcare Pipeline Pharma Data; author's own calculations.

Projects are kept in the data set when they are no longer in development. Project information is updated from any kind of information in the public domain or from company contacts. Entries in the data base go back to the early 1980s. However, we included only projects with the first entry "new product" to exclude projects added to the data base at a later stage of development.[4] This leaves us with 17,787 R&D projects started since 1989. Our sample was drawn during May 2012, such that 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.[5] The latest project start date in our sample is 2010 being the end of the observation period. Overall, we have a comprehensive data set of projects for drug candidate compounds for a time span of more than 20 years and not limited to large firms. Instead, the data also contains mid-sized and small firms with only a small number of R&D projects covering the research activities of the whole industry.

For the subsequent analysis, we use samples of projects in the preclinical as well as clinical phases. Although most empirical studies only use projects that have at least reached clinical trials (phase I) and exclude projects discontinued at the preclinical stage, we include these projects in parts of the analysis and compare the results with those from the sample of clinical projects. Projects still in development at the end of the observation period in 2010 have been excluded from the sample in this section as these are neither launched nor discontinued yet. In doing so, we lose 1,706 observations (see Table 3). Note that the loss of observations is attributed differently to the subsamples based on project begin year. The largest number of censored projects is contained in the last period with projects started between 2007 and 2010. In addition to the success rate, we look at the project length and the number of diseases a drug candidate is developed for to gain some further insights on changes of two key project characteristics over time.

[4] Abrantes-Metz *et al.* (2004) also choose this approach and take only projects for which an entry date is available.

[5] One year is a very short time for a project to be successfully completed and the share of discontinued projects is very large for these short projects. However, note that we also include reformulations or new indications for already existing drugs which have a much shorter development time than novel drugs.

3.2. Definition of the Success Rate

The success rate is defined as the share of successful research projects on the sum of successful and discontinued projects within a given time period. We use the lead compound definition of a project, i.e. a pharmaceutical R&D project is defined as the development of a compound for the treatment of one or more diseases (see section 2.2). As was discussed above, the lead compound definition leads to larger success rates than the compound-disease definition. The compound-disease definition would be preferable to define a project. When a compound is developed for the treatment of different diseases, safety and efficacy has to be proved for each of the diseases during the regulated development process. There may be differences in the efficacy of a compound in treating each of the targeted diseases. Further, project development is rather discontinued for specific diseases than for compounds as a whole. However, we cannot observe the development status for each compound-disease combination in the data such that we have to use the lead compound definition. The difference between lead compound and compound-disease definition is limited by correlations between the success probabilities for specific indications. These correlations are likely to be high as toxicity and side-effects are bound to the compound under development. For example, when the development of the compound for one specific indication has to be discontinued due to toxicity it has to be discontinued for the other indications as well.

A project is defined as a success when a drug resulting from this project is actually launched in at least one country.[6] By contrast, in the empirical literature success is mostly defined as the approval of a regulatory authority to launch the drug. However, in section 2.1, we discussed there is no large difference between these two definitions. Note that in the lead compound definition, a project is already defined as a success when a drug is introduced for one of the indications.

A project is defined as discontinued when there is no ongoing development reported for each of its disease indications in the last 12-18 months. Unfortunately, this is not a very precise definition, but it is likely that most of these projects are not developed any further. We cannot, however, exclude that development is going on after this time span.[7] In the lead compound definition, a project is only a failure when it is discontinued for all disease indications the compound is developed for. Compared to the compound-disease definition, a failure occurs later in time except for the case when development for all indications is discontinued at the same point in time. When a compound is still in the pipeline for at least one disease at the end of the observation period (2010), the project is excluded from the data set and does not turn up in the analysis, although it has failed to be a success for other diseases. Therefore, this project definition leads to an over-estimation of the success rate and we should keep in mind that our

[6] Note that a development success does not automatically mean commercial success, as a drug may only be commercially successful when introduced in more than one country. Further, we do not measure any development costs for and revenues generated by drugs such that we focus on technological success rather than on commercial success.

[7] In section 4, we will handle this issue with the application of hazard rate analysis.

results on success rates rather represent upper bounds. The exclusion of projects still in development by the end of 2010 also generally leads to an over-estimation of the success rate as the exclusion reduces the total number of projects in the sample.[8]

3.3. Results

We look at five subsamples whereas projects are attributed to the subsamples by begin year. We find evidence that the success rate of projects is decreasing strongly. Whereas the success rate is 0.18 for projects started between 1989 and 1994, it decreases to 0.069 for projects started between 1995 and 1998 and to 0.041 for projects started between 1999 and 2002 (see Table 4). The rate is even lower for projects started most recently and lies at 0.033 (2003-2006) and 0.016 (2007-2010). The decreasing success rate is based on two factors: first, the absolute number of launched projects is decreasing over time. Second, the number of discontinued projects is strongly increasing.

Table 4: Descriptive Statistics by Project Begin Year Periods

Variable	Total			Project Begin: 1989-1994			Project Begin: 1995-1998		
	Launched	Discont.	Sign. Diff.	Launched	Discont.	Sign. Diff.	Launched	Discont.	Sign. Diff.
Success Rate	0.0536			0.1803			0.0685		
	(0.225)			(0.385)			(0.253)		
No. of Diseases in Project	3.181	1.394	***	3.319	1.707	***	3.434	1.499	***
	(3.776)	(0.950)		(3.759)	(1.306)		(4.634)	(1.176)	
Project Length	5.810	4.592	***	7.371	11.02	***	6.046	6.445	n.s.
	(3.882)	(3.877)		(4.384)	(4.651)		(3.788)	(4.008)	
No. of Obs.	862	15,219		306	1,391		219	2,978	

(Continued) Descriptive Statistics by Project Begin Year Periods (Clinical Sample)

Variable	Project Begin: 1999-2002			Project Begin: 2003-2006			Project Begin: 2007-2010		
	Launched	Discont.	Sign. Diff.	Launched	Discont.	Sign. Diff.	Launched	Discont.	Sign. Diff.
Success Rate	0.0415			0.0330			0.0158		
	(0.200)			(0.179)			(0.125)		
No. of Diseases in Project	3.442	1.359	***	2.864	1.347	***	1.590	1.274	***
	(3.333)	(0.894)		(3.308)	(0.838)		(0.938)	(0.675)	
Project Length	5.678	4.868	***	3.600	3.307	*	1.918	1.774	
	(2.804)	(2.975)		(1.809)	(1.911)		(0.862)	(0.928)	
No. of Obs.	146	3,391		125	3,657		61	3,796	

*Mean values; standard errors are given in parentheses; column "Sign.": significant difference between means of launched and discontinued projects using a simple mean difference test (*** significant at 1 percent)*
Source: Informa Healthcare Pipeline Pharma Data; author's own calculations.

As we included also projects discontinued in the preclinical phase, the success rate results can only be compared to those of Pammolli *et al.* (2011). We find an overall success rate of 0.053, being lower than the range of 0.071 to 0.088 found by Pammolli *et al.* (2011). Note, however, that Pammolli *et al.* (2011)

[8] On the other hand, censoring leads to an under-estimation of the success rate, while the downward bias is larger in more recent time periods.

present results for the period 1990 to 2004. When we restrict our sample to a similar period (1989 to 2002), we get a success rate of 0.08, lying within the range of these findings. To compare our results to those from Hay *et al.* (2014), we also calculated success rates excluding projects discontinued in the preclinical phase from the sample. The overall success rate in this clinical sample is 0.213, lying above the result of Hay *et al.* (2014). The authors study the period 2003-2011. For a similar period (2003-2010), we find a success rate of 0.148 lying slightly below this result. In total, our results on overall success rates for similar periods than those studied by Pammolli *et al.* (2011) and Hay *et al.* (2014) are comparable to their findings.

Table 5: Descriptive Statistics by Project Begin Year Periods (Clinical Sample)

Variable	Total			Project Begin: 1989-1994			Project Begin: 1995-1998		
	Launched	Discont.	Sign. Diff.	Launched	Discont.	Sign. Diff.	Launched	Discont.	Sign. Diff.
Success Rate	0.213			0.331			0.233		
	(0.409)			(0.471)			(0.423)		
No. of Diseases in Project	3.181	1.827	***	3.319	2.021	***	3.434	1.976	***
	(3.776)	(1.526)		(3.759)	(1.616)		(4.634)	(1.835)	
Project Length	5.810	7.347	***	7.371	12.32	***	6.046	8.777	***
	(3.882)	(4.287)		(4.384)	(4.070)		(3.788)	(3.630)	
No. of Obs.	862	3,193		310	626		219	722	
No. of Precl. Projects excluded	12,026			767			2,257		
Share of Precl. Projects excluded	0.748			0.450			0.706		

(Continued) Descriptive Statistics by Project Begin Year Periods (Clinical Sample)

Variable	Project Begin: 1999-2002			Project Begin: 2003-2006			Project Begin: 2007-2010		
	Launched	Discont.	Sign. Diff.	Launched	Discont.	Sign. Diff.	Launched	Discont.	Sign. Diff.
Success Rate	0.159			0.148			0.148		
	(0.366)			(0.355)			(0.356)		
No. of Diseases in Project	3.442	1.804	***	2.864	1.712	***	1.590	1.459	n.s.
	(3.333)	(1.484)		(3.308)	(1.282)		(0.938)	(1.060)	
Project Length	5.673	6.779	***	3.600	4.562	***	1.885	2.487	***
	(2.795)	(2.590)		(1.809)	(1.725)		(0.839)	(1.063)	
No. of Obs.	147	775		125	719		61	351	
No. of Precl. Projects excluded	2,618			2,941			3,443		
Share of Precl. Projects excluded	0.740			0.777			0.893		

*Mean values; standard errors are given in parentheses; column "Sign.": significant difference between means of launched and discontinued projects (*** significant at 1 percent)*
Source: Informa Healthcare Pipeline Pharma Data; author's own calculations.

Comparing the full sample containing preclinical projects to the sample of clinical projects yields further insights. In the full sample, the success rate is declining from 0.033 for projects starting between 2003 and 2006 to 0.016 for projects starting between 2007 and 2010. By contrast, in the clinical sample the success rate is not decreasing and lies at 0.148 for both periods (see Table 5). This result shows how crucial the

definition of the success rate is when its development is studied over time. When the success rate is the share of all *clinical* projects being introduced to the market, we observe a decline from 0.331 to 0.159 between 1989 and 2002 and a subsequent decline to 0.148, remaining constant in the two most recent periods. This result suggests the decline in the success rate of clinical projects has been mitigated or even stopped for projects started from 2002 onwards.

By contrast, when the success rate is defined as the share of launched projects on all development projects including preclinical projects we find a strong decline in the success rate from 0.18 to 0.016 throughout all studied periods. There is no indication that the decline has stopped during recent periods. The decreasing success rate is based on the increasing number and share of discontinued preclinical projects. While 767 of those projects have been started between 1989 and 1994, representing a share of 45 percent on all projects within this period, this number is increasing to 3,443 projects, representing a share of 89.3 percent on all projects (see Table 5).

Above we argued that preclinical projects should be taken into account as these are not costless to firms and reflect part of the development efforts for new drugs. The costs occurring in this phase of drug discovery and development cannot be neglected. These costs are attributed to a larger number of preclinical drug candidate compounds screened and mostly discontinued before entering clinical development. In our data, we observe a substantial rise in number and share of projects terminated in the preclinical phase during our study period, suggesting firms recently start a larger number of preclinical projects per drug being introduced to the market. While this reflects rising research efforts attributed to more compounds in the preclinical phase, the costs of these efforts are limited since most of these compounds are not brought into costlier clinical studies.

We now turn to the number of disease indications per project as an indicator of the market potential of a compound. Each indication can be seen as a submarket where there is a chance to launch a drug for this indication. The development of the number of diseases per project has – to the best of our knowledge – not yet been studied in the literature. Regarding discontinued projects, the number of diseases is declining steadily from 1.71 (1989 to 1994) to 1.27 (2007-2010, see Table 4). In the clinical sample, the number of diseases per discontinued project is also steadily declining from 2.02 (1989-1994) to 1.46 (2007-2010). Note that the number of diseases is larger in the clinical projects sample within each period. This corresponds with our interpretation that firms limit the development efforts in the preclinical phase. This is done in focussing only on a small number of diseases. For launched projects, the number of diseases is significantly higher than for discontinued projects within each sub-period (see Table 4). From 1989 to 2002, the average launched project is developed for 3.3 to 3.4 disease indications. Then the number of diseases is decreasing to 2.8 and 1.6 in the two most recent periods. In the clinical sample, the

development pattern of the number of diseases per project is similar to the development in the full sample.

While the number of diseases is found to be a positive success factor as it is on average larger for launched than for discontinued projects, there is also a general development towards projects targeting less disease indications from 2003 on. This might suggest that firms generally focus on fewer indications per project and have changed their development strategies as a reaction of the decreasing success rate in the mid-1990s and early 2000s. It might however be as well the case that in recent years, a larger share of specialised firms focusses on projects with fewer disease indications being successful with this strategy. There are more projects started and eventually discontinued leading to a lower success rate. However, at the same time projects in more recent years are developed for a lower number of diseases limiting the costs of development and the sunk costs incurred by discontinued projects.

From 1999 onwards, launched projects significantly last longer than discontinued projects indicating that many unsuccessful projects are discontinued relatively early (see Table 4). There is no significant difference in project length for projects started between 1989 and 1994 or even a significantly longer project duration for discontinued projects started between 1995 and 1998. By contrast, in the clinical sample launched projects last significantly *shorter* than discontinued projects from 1999 on. For example, launched projects started between 2003 and 2006 on average last 3.6 years whereas discontinued projects last 4.6 years before their development is stopped. These results suggest that in clinical development, discontinued projects are stopped rather late in more recent years. Successful projects can be moved through the clinical pipeline faster than unsuccessful projects. Assuming a longer development time indicates larger development costs, there is a limitation in sunk costs by the discontinuation of many projects in the preclinical phase in more recent years. However, for clinical projects sunk costs are increasing. Taken together, the overall direction of the development of sunk costs over time is unclear.

3.4. Estimated Success Rates

Our data contain censored observations in each subsample. This relates to all projects being still in development at the end of the observation period 2010 where we do not know whether the project will be launched or discontinued in future. In section 3.3, we simply dropped these observations from the data set. This way, the samples for more recent time periods are biased towards projects with a shorter duration. Projects started between 2007 and 2010 only had up to five years to be launched to the market or to be discontinued, whereas projects started between 1999 and 2002 had up to nine years. The bias is especially present in the full data set also containing project discontinued in the preclinical phase. Here, the average project length is higher for launched than for discontinued projects for the three most recent time periods (see Table 4). For this reason, relatively more potential launches than discontinuations are

dropped towards the end of the observation period. We can illustrate this by looking at the average project length. It is decreasing both for launched and discontinued projects. While the average project length for projects started between 1989 and 1995 is 7.4 years, it drops to 1.6 years for projects started between 2007 and 2010. This clearly shows a bias towards favouring shorter projects.

Only a small number of the reviewed empirical studies offer some treatment of censoring. Adams and Brantner (2006) do discuss censoring, but do not apply suitable methods to handle it. Cockburn and Henderson (2001), DiMasi (2014), Kola and Landis (2004), Abrantes-Metz *et al.* (2004), and Arrowsmith (2012) do not offer any handling of censoring as well. Danzon et al. (2005) look at the transition of projects from one phase to the next one. When no phase transition during the observational period is observed, the project is defined to be a failure. This, however, leads to a downward bias of the success rate for more recent projects as projects started later only have a shorter time to make a phase transition. Therefore, this approach does not handle the censoring bias.

Arora *et al.* (2009) restrict the sample to projects with begin years no later than nine years before the end of the observation period. They argue that most of these projects will be discontinued or launched by the end of the observation period. Applying this approach would mean to restrict our study to the first three periods where we can observe a drop in the success rate in the full as well as in the clinical sample. However, the projects started most recently started could not be included. As we want to look at the scarcely studied recent time periods, this approach is not helpful for us.

DiMasi (2001) is the only study applying hazard rate analysis to estimate success probabilities. Whereas the author finds current descriptive success rates to be decreasing from 1981 to 1992, the predicted success probabilities are increasing.[9] However, while the end of the observation period is 1999, only success probabilities for projects started no later than 1992 are estimated. Further, the sample only contains projects for self-originated compounds, i.e. the effects of licensing – being quite common in pharma – are not recognized such that the results cannot be generalised to different kinds of projects.

We use two versions of a Cox model to predict the success probability of censored observations in the full sample, i.e. projects still in development in 2010.[10] In the first model, no explanatory variables are used to predict the success probability. In the second model, the number of disease groups the project is developed for, firm portfolio size, squared firm portfolio size and the disease group of the project are included as explanatory variables. In the model without explanatory variables, we predict a success probability of 0.107 for censored projects, whereas in the model with explanatory variables the predicted success probability is 0.097. The predicted success probabilities are used to calculate the number of

[9] The author uses two events, being market approval or project discontinuation as competing failure events, i.e. applies a competing risk analysis.

[10] The Cox model is described in more detail in section 4.1.

launches expected from censored projects. This number is added to the already launched projects and divided by the total number of projects started in the respective time period. Note that different to section 3.3 the total number of projects does include censored observations now.

Table 6: Success Rate Estimations (All projects)

All Projects	Total	1989-1994	1995-1998	1999-2002	2003-2006	2007-2010
Estimated Success Rate (Cox)*	0.059	0.182	0.069	0.043	0.039	0.038
Estimated Success Rate (Cox with X)**	0.058	0.182	0.069	0.043	0.038	0.036
Number of Obs.	17,787	1,714	3,239	3,638	4,092	5,104
thereof: No. of censored Obs.	*1,706*	*11*	*41*	*98*	*307*	*1,249*
Estimated *No. of Successes (Cox)*	*1,045*	*311*	*223*	*158*	*158*	*195*
Estimated *No. of Successes (Cox with X)*	*1,027*	*311*	*223*	*157*	*155*	*182*

**Success Probability of censored observations has been estimated by Cox model without explanatory variables to be 0.107.*
***Success probability of censored observations has been predicted to be 0.097 by Cox model with the following explanatory variables: Number of broader disease groups project is developed for, firm portfolio size (number of projects by firm), firm portfolio size squared, 14 disease groups as in section 4.*
Source: Informa Healthcare Pipeline Pharma Data; author's own calculations.

For the sample of all projects, the predictions for the first three time periods are not substantially different from descriptive results. This is not surprising since the number of censored observations is limited in the first three periods. Especially in the most recent period, the predicted success rates are larger than the descriptive ones. We still see a decline in the success rate from 0.182 (1989-1994) to 0.069 (1995-1998), and to 0.043 (1999-2002, see Table 6). However, the decline in the success rate from 0.043 (1999-2002) to 0.039 (2002-2006) is smaller than in the descriptive section. Further, we only observe a minimal decline in the success rate for projects started between 2003 and 2006 to the success rate of 0.038 in the subsequent period. By contrast, in the descriptive analysis we observed that a success rate less than half as large (0.016). The predicted success rates suggest that the rate has dropped from the mid-1990s to the early 2000s, but that this decline slows down and stops in the two most recent periods.

Considering the number of predicted successes, we find that this number is going down from 311 (1989 to 1994) to around 150 for 1999 to 2002 and 2003 to 2006. From 2007 to 2010, the number of predicted successes is increasing again to 195 projects, indicating the innovative output of the industry may be recovering again. However, this result should be viewed with caution as the rise in the number of launches is only prevalent in one period. Whether the recovery is sustainable cannot be answered at this point in time yet.

4. Hazard Rate Analysis

In the descriptive analysis, we cannot show connections between two variables of interest while controlling other factors. When we want to investigate how the year or period of project begin is connected to project success, we should control possibly confounding factors. We now use hazard rate analysis to handle both censored observations and to estimate partial effects of project begin year on the

project success probability. To the best of our knowledge, hazard rate analysis with the inclusion of project begin as explanatory variable and additional control variables has not been done before in the context of pharmaceutical R&D projects.

4.1. Method

Hazard rate analysis focusses on the time until an event occurs.[11] The time until an event occurs is a random variable denoted as *T*. In our case, the launch of a project as drug on the market in the first country is the event we study. A project is at risk until the event occurs. The event is called "failure" in technical terms. In our case, a successful, launched project has "failed" in terms of not surviving, i.e. being in development any longer. The project is no longer at risk then. The term "failure" should not be connected to a discontinued project from the descriptive part of this study. When a project is not launched during the observation period, we assume it to be censored. This is the case for projects still in development at the end of the observation period and projects where no development has been reported for 12-18 months. Note that the latter have been handled as discontinued project in the descriptive analysis. However, the definition of discontinued projects applied in the descriptive analysis has the drawback that the discontinuation itself is not reported in the data. A project's status is set to "no development reported" when there is no information on ongoing development for 12-18 month. After this time, a firm may still decide to continue the project and it may eventually become a success. This may rather be the case on more recent projects, as it is more and more unlikely for a project where no development is reported for a long time. We have no information whether a project where no development is reported will become a market launch or will be discontinued in future. Handling these observations as censored is the best way to include them into the hazard rate analysis.

The hazard function *h(t)* is the hazard of a project failing after time *t* given it has survived until *t*. Denoted by the random variable *T* (time until the event of failure occurs), the hazard function is given by[12]

$$h(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T < t + \Delta t | T \geq t)}{\Delta t}.$$

In our case, the hazard rate gives the conditional probability a pharmaceutical project is launched to the market instantaneously after time t, given it has been in the pipeline until t. There are different forms of how the hazard rate can be applied leading to different classes of models. The Cox model is a semi-parametric approach as the hazard function is given by:

[11] For a more detailed introductory treatment of hazard rate analysis see Kleinbaum and Klein (2005).

[12] See Kleinbaum and Klein (2005).

$$h(t, \mathbf{X}) = h_0(t)\, e^{\sum_{i=1}^{p} \beta_i X_i}$$

Note there is a baseline hazard $h_0(t)$ common to all observations. The baseline hazard is not further specified but is scaled by the exponential term, dependant on the variables in X_i. Note that the exponential term is not dependent on survival time t.[13]

4.2. Variables and Test of Proportional Hazards Assumption

We now describe the variables included in X_i and how their effects on the hazard rate are estimated. Our main variable of interest is the project begin year. In one version of the model, we include the begin year as linear term. In a second version of the model, we use indicator variables for the time periods to handle possible nonlinearities. The distribution of project begin years is right-skewed as the share of projects is ever increasing for more recent periods. 9.6 percent of projects are started before 1995 (see Table 7). The share is constantly rising to 28.7 percent of projects started between 2007 and 2010.

We further include the number of diseases a compound is developed for as an indicator of market potential. Note, however, that the reflection of market potential by the number of diseases is a very imperfect measure as we cannot infer how large the market potential for each disease is. In other words, a project aimed at only one disease, which could not effectively be treated before (e.g. Alzheimer's disease) would clearly have a higher market potential than an anti-depressant, where already many drugs are on the market. A larger number of diseases a compound is developed for may as well serve as a kind of "insurance" for the compound to be introduced at least for one or some of the disease indications. The insurance effect is limited by the correlation between reasons for discontinuation for the different diseases, e.g., if a compound shows toxicity, this affects the success probability for all diseases. On average, a compound within a pharmaceutical research project is developed for 1.53 diseases (see Table 7). The maximum number of diseases is 41, being quite large. 72.5 percent of projects aim at one disease and 17.2 percent of projects are developed for two diseases. 2.7 percent of projects aim at developing a compound for the treatment of five or more diseases.

The disease group variables indicate whether the different diseases a compound is developed for are from different disease groups. 9.7 percent of drug development projects aim at diseases from two different

[13] We also estimate a Gompertz model which does specify a functional form of the baseline hazard. In the Gompertz model, the hazard rate is given by

$$h(t, \mathbf{X}) = h_0(t)\, e^{\sum_{i=1}^{p} \beta_i X_i}$$

with $h_0(t) = e^{\gamma t}$. Note that different to the Cox model, the baseline hazard h_0 is now specified. Depending on the value of γ, the hazard rate is constant $(\gamma = 1)$, decreasing $(\gamma < 1)$ or increasing $(\gamma > 1)$ over time. The results do not substantially differ from those of the Cox model. Results are available from the author upon request.

diseases groups, whereas in 3.1 percent of projects the compounds are even developed for three or more disease groups. Compounds for diseases from different disease groups are expected to have a higher "insurance" effect as the reasons for discontinuation may be less correlated than for diseases in the same disease group. However, this kind of "insurance" is costly, as the low share of projects developed for more than one disease group shows. Further, the development of a drug candidate compound for different disease groups is limited by the characteristics of the compound itself.

Table 7: Descriptive Statistics of Model Variables

Variable	Mean	Standard Deviation	Minimum	Maximum
Project Begin Year	2002	5.3950	1989	2010
Project Begin: 1989-1994	0.0964	0.2950	0	1
Project Begin: 1995-1998	0.1820	0.3860	0	1
Project Begin:1999-2002	0.2050	0.4030	0	1
Project Begin: 2003-2006	0.2300	0.4210	0	1
Project Begin: 2007-2010	0.2866	0.4530	0	1
Control Variables				
Number of Diseases Project aims at	1.5280	1.3730	1	41
Project aims at one disease	0.7250	0.4470	0	1
Project aims at two diseases	0.1720	0.3770	0	1
Project aims at three diseases	0.0530	0.2240	0	1
Project aims at four diseases	0.0226	0.1490	0	1
Project aims at five or more diseases	0.0274	0.2970	0	1
Two Disease Groups	0.0978	0.2970	0	1
Three or more Disease Groups	0.0302	0.1710	0	1
One Disease Group	0.8720	0.3340	0	1
Vaccine	0.0908	0.2870	0	1
Project is Licensed	0.1730	0.3780	0	1
Natural Origin	0.0352	0.1840	0	1
Biological Origin	0.2620	0.4400	0	1
Chemical Origin	0.7028	0.4571	0	1
Firm Portfolio Size (No. of projects)	118.7	184.1	1	663
Firm Portfolio Size (Squared)	47,982	102,830	1	439,569
Disease Group Indicators				
Alimentary-Metabolic	0.1350	0.3420	0	1
Blood and Clotting	0.0449	0.2070	0	1
Cancer	0.1960	0.3970	0	1
Cardiovascular	0.0956	0.2940	0	1
Dermatological	0.0490	0.2160	0	1
Genitourinary	0.0444	0.2060	0	1
Hormonal	0.0057	0.0755	0	1
Immunological	0.0218	0.1460	0	1
Infectious Disease	0.2080	0.4060	0	1
Musculoskeletal	0.0934	0.2910	0	1
Neurological	0.1820	0.3860	0	1
Parasitic	0.0132	0.1140	0	1
Respiratory	0.0577	0.2330	0	1
Sensory	0.0271	0.1620	0	1
Analysis Time (tvc model)	4.5650	3.8380	1	21
Observations	17,787			

Source: Informa Healthcare Pipeline Pharma Data; author's own calculations

We also include the project portfolio size as the number of projects a firm develops during the whole study period (1989-2010). There is a discussion of economies of scale and scope in drug development (see Cockburn and Henderson 2001). DiMasi (2014) finds higher success rates for small firms suggesting there are either no scale or scope effects or these are over-compensated by other – negative – effects of firm portfolio size. We include a squared term to allow a nonlinear size effect. It is likely there is a positive effect of size up to some certain degree. After this turning point, size is becoming detrimental, e.g. by increasing coordination costs. The average firm is developing 118.7 projects over the whole observation period. Note however, there is a large standard deviation. In fact, the lowest quartile of firms is only developing up to 5 projects, whereas the top 25 firms have at least 75 projects in their pipeline.

Further, indicator variables for the drug being a vaccine, licensing of projects, project origin (natural, biological, chemical) and 14 broader disease groups are included in the model.

The proportional hazards (PH) assumption is central to the Cox model. Looking at the hazard rate of two sets of covariates*, X** and *X* shows that the hazard ratio between the hazard ratio of the two sets of covariates is constant over time when proportional hazards are assumed:[14]

$$\begin{aligned}\widehat{HR} &= \frac{\hat{h}(t,\mathbf{X}^*)}{\hat{h}(t,\mathbf{X})} \\ &= \frac{\hat{h}_0(t)\exp\left[\sum \hat{\beta}_i X_i^*\right]}{\hat{h}_0(t)\exp\left[\sum \hat{\beta}_i X_i\right]} \\ &= \exp\left[\sum_{i=1}^{p} \hat{\beta}_i (X_i^* - X_i)\right]\end{aligned}$$

The statistical test shows no indication of the begin year or the different periods of project start to violate the PH assumption. Contrary, we find evidence that the number of diseases and the indicator variables for three or more disease groups and for vaccines are violating the PH assumption (see Table A 2 in the Appendix). The statistical test further shows the disease groups dermatological and hormonal to violate the proportional hazards assumption. To handle the violations of the PH assumption, we use time varying covariates in including interaction terms of the violating variables with analysis time t.[15] For these variables, the assumption of a constant hazard ratio over time is relaxed.

[14] See Kleinbaum and Klein (2005, pp. 107-108)

[15] We also estimated models containing the interaction of the violating variables with a dummy variable when analysis time is larger than 3 years (being the median duration of a project in the sample). The results are not substantially different to the interaction with analysis time as such.

4.3. Results

We estimate effects of the covariates on the hazard rate of pharmaceutical projects being launched to the market. For this reason, we refer to the "success probability" of projects rather than to the hazard rate. Note that the success probability is the *instantaneous* probability of success to be introduced instantly after time *t** conditional on the project still being at risk at time *t** while the success rate above is just constructed as the total number of launched projects divided by all projects in the sample (not regarding censored projects). The project begin year is significant at the 1 percent level. A later project start by one year is associated with a 2.5 percent lower success probability to launch the project in the market. While this effect is rather low, in the long run it would pile up to a 22.3 percent lower success probability for projects started ten years later than a comparable project (see Table 8). However, this interpretation assumes a linear effect of the project begin year. Evidence from a second model including begin year periods calls this assumption into question.

Compared to the base group of projects started between 2007 and 2010, projects started between 1995 and 1998 have a 36.5 percent lower success probability. Projects started between 1999 and 2002 even have a 40.4 percent lower success probability compared to the base group (see Table 8). Projects started before 1995 and between 2003 and 2006 do not show a significant difference in the success probability compared to the base group. Results suggest there is only a temporary effect of the project begin year on the success probability for projects started between 1995 and 2002. Afterwards, the success probability is resuming to the original rate.

The number of diseases a project is developed for has a significantly positive effect on the success probability. One more disease is associated with an increase in the success probability by 5.7 percent. Given that one more disease means one more market with additional sales potential and a higher "insurance" against a total project failure, the effect is rather small. The considerations on market potential and "insurance" effects are based on the notion that each disease within a project is an independent submarket, while the potential and insurance effect is limited by the interdependence of the diseases. Most often, the diseases a project is developed for are from the same broader disease group, suggesting a high interdependence of success factors, resulting in a lower effect on the success probability when the number of diseases increases. Further, our results suggest that the "insurance" effect is also small, pointing to the fact that the success probabilities for the single diseases within a project depend mostly on the same factors such that the discontinuation for one disease very likely leads to the discontinuation for other diseases in the project as well.

Firm portfolio size yields a highly significant positive effect. When a firm develops one more project the success probability increases by 0.3 percent. Developing 10 more projects would increase the success probability by 3 percent. Note, that the squared term of firm portfolio size is significant but very small.

Table 8: Results of Cox models

Variables	Model 1	Model 2
Project Begin Year	**0.983****	
	(0.00779)	
Project Begin: 1989-1995		0.910
		(0.144)
Project Begin: 1995-1998		**0.635*****
		(0.101)
Project Begin:1999-2002		**0.596*****
		(0.0964)
Project Begin: 2003-2006		0.836
		(0.135)
Number of Diseases Project aims at	**1.052*****	**1.057*****
	(0.0178)	(0.0182)
Two Disease Groups	0.908	0.921
	(0.234)	(0.238)
Three or more Disease Groups	**0.250****	**0.246****
	(0.141)	(0.139)
Vaccine	**2.428*****	**2.392*****
	(0.601)	(0.592)
Project is Licensed	**4.021*****	**4.114*****
	(0.292)	(0.300)
Firm Portfolio Size	**1.003*****	**1.003*****
	(0.000607)	(0.000607)
Firm Portfolio Size (Sq.)	**1.000*****	**1.000*****
	(1.05e-06)	(1.05e-06)
Natural Origin	1.119	1.161
	(0.207)	(0.215)
Biological Origin	**0.738*****	**0.730*****
	(0.0669)	(0.0664)
<u>Disease Groups</u>		
Alimentary-Metabolic	1.244	1.211
	(0.242)	(0.236)
Blood and Clotting	1.261	1.228
	(0.293)	(0.286)
Cancer	0.728	**0.718***
	(0.144)	(0.142)
Cardiovascular	1.460*	1.448*
	(0.291)	(0.289)
Dermatological	**2.177****	**2.142****
	(0.699)	(0.687)
Genitourinary	**2.474*****	**2.482*****
	(0.512)	(0.514)
Hormonal	**19.66*****	**20.01*****
	(15.85)	(16.10)
Immunological	1.071	1.070
	(0.301)	(0.301)
Infectious Disease	1.109	1.113
	(0.217)	(0.218)
Musculoskeletal	0.933	0.914
	(0.196)	(0.192)
Neurological	1.359	1.325
	(0.260)	(0.254)
Parasitic	1.330	1.276
	(0.458)	(0.441)
Respiratory	1.184	1.170
	(0.256)	(0.253)
Sensory	1.210	1.208
	(0.318)	(0.317)

(Continued): Results of Cox models (Time Varying Covariates)

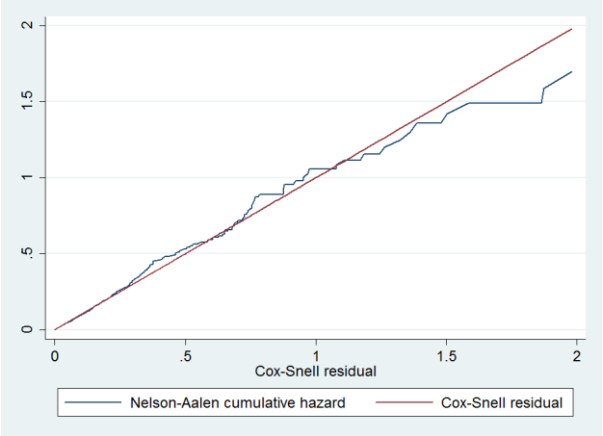
Time Varying Covariates; Time Function:	t	t
Number of Diseases Project aims at	**1.011*** **	**1.011*** **
	(0.00237)	(0.00239)
Two Disease Groups	0.986	0.984
	(0.0264)	(0.0264)
Three or more Disease Groups	**1.166*** **	**1.168*** **
	(0.0446)	(0.0447)
Vaccine	**0.848*** **	**0.849*** **
	(0.0375)	(0.0375)
Disease Group: Dermatological	0.933*	0.933*
	(0.0370)	(0.0369)
Disease Group: Hormonal	**0.472** **	**0.468** **
	(0.157)	(0.155)
Observations	17,787	17,787

*Standard Errors in Parentheses; significance: *** 1 percent / ** 5 percent * 10 percent*
Source: Informa Healthcare Pipeline Pharma Data; table and calculations by the author

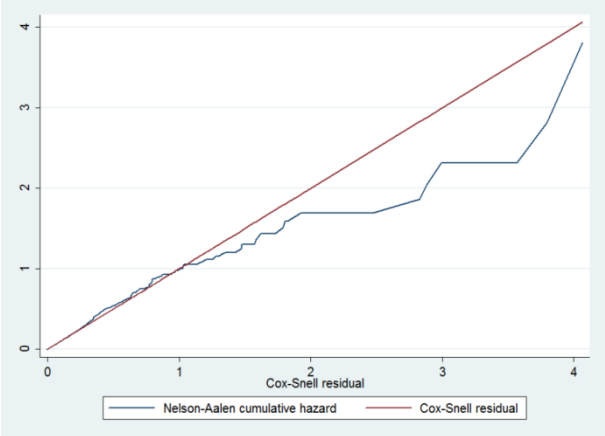
The result of 0.999996 shows the squared term effect is negative such that the positive effect of firm portfolio size is diminishing in the number of projects. This result suggests there is some scale effect which is, however, limited. A more thorough analysis of economies of scale and scope in drug development could be fruitful, but is beyond the scope of this paper.

Figure 3: Nelson Aalen Cumulative Hazard against Cox-Snell Residuals

Model 1 (Begin Year)



Model 2 (Begin Year Periods)



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

Projects with a licensed compound show a success probability almost four times as large as projects without licensing. Projects being licensed for the development by other firms are screened by them beforehand. The result suggests that screening is effective in selecting projects with a larger success probability. When the project is licensed to more than one firm, each R&D project for the drug development can be viewed as an independent experiment, increasing the probability of success. If one firm ceases development, other firms may go on. This effect is limited by the reasons leading to the

discontinuation of projects. For example, when the compound shows to be toxic, all developing firms will discontinue development.

Projects with compounds of biological origin have a 27 percent lower success probability than projects of chemical origin. In biotech, more drug candidate compounds are needed to introduce one drug successfully to the market. Projects with natural origin, on the other hand, do not have a significantly different success probability than projects of chemical origin. We plot the graphs of the Nelson-Aalen cumulative hazard function against Cox-Snell residuals to get a measure of the model's goodness-of-fit. The two lines should lie close to each other to indicate a good fit. It can be seen that both for model 1 and model 2 the Nelson-Aalen estimates first lie close to the diagonal line indicating the Cox-Snell residuals and then divert from this line (see Figure 3). The 99th percentiles of the Cox-Snell residuals and of the Nelson Aalen cumulative hazards both lie around 0.36. In this range the estimated Nelson Aalen cumulative hazard is very close to the Cox-Snell residual value and our model fits the data very well.

The results from hazard rate analysis support our findings from the analysis of success rates in section 3. While the decrease of the success rate for projects started between 1995 and 2002 is found in section 3 as well, we do not find a recovery of the success rate after 2002 to the higher earlier success rates as hazard rate analysis results suggest. We rather see a stabilization of the success rate at a low level. The different results can be explained by the differences in the definition of success rate and hazard rate ("success probability") on the one hand. On the other hand, the application of control variables in the Cox model leads to a different interpretation of the results for different begin year periods. While the results from the model can be interpreted to apply for projects with similar characteristics, the success rate analysis in section 3 does not control different project characteristics. Taken together, both results suggest that the project characteristics changed in a direction favouring a lower success rate. For example, the number of diseases, being found to have a positive effect on the success probability is lower for more recent projects. When these characteristics are not controlled, the success rate is going down, but stabilizing for projects started more recently as has been found in section 3. Controlling these factors leaves us with a temporary decrease in the success probability between 1995 and 2002 that are not explained by other variables included in the model. The question remains what caused the decrease in the success rate and whether the shift towards projects with characteristics leading to a lower success probability is strategically done by firms or forced by external factors, contributing to an innovation crisis.

5. Discussion

In the context of the discussion on the innovation crisis in the pharmaceutical industry, we critically reviewed the literature on the R&D project success rate as a productivity measure of the industry. The review of the empirical literature revealed that most studies do not correctly address methodological

aspects like project definition and censoring. Further, the studies largely differ by the range of firms included in their samples such that they lack comparability. Most studies do not analyse the development of the success rate over time. In order to contribute to the ongoing discussion about the innovation crisis in the pharmaceutical industry we performed a comprehensive descriptive analysis and applied methods of hazard rate analysis on the development of R&D project success rates. While most other studies use samples containing a small number of pharmaceutical firms and only covering a short time period, we use a broad sample of different firm sizes with projects from an observation period of more than 20 years. We track the development of the success rate within five sub-periods.

The descriptive analysis suggests a declining success rate of pharmaceutical projects during recent years. However, when we estimate success probabilities of the projects still in development at the end of the observation period in 2010, we find a stabilization of the success rate at a lower level than before. The estimated number of projects introduced to the market is rising in the most recent period. Results from hazard rate models suggest there has only been a temporary drop in the success rate for projects started between 1995 and 2002. This result is not comparable to the descriptive results as other project characteristics are controlled. In the descriptive analysis, we showed that at least one important factor promoting project success – the number of diseases a project is developed for – is decreasing. This in turn leads to a lower success probability per se as can be seen from the results of hazard rate models. We pointed out that the underlying reason for a lower success rate is the start of many more projects in more recent time periods. At the same time, the share of projects discontinued already in the preclinical phase has risen substantially.

When interpreting our results with respect to the innovation crisis discussion, one should bear in mind that the success rate is only one indicator besides, for example, R&D investments, the number of new drugs introduced, and the degree of drug novelty. While we estimate an increase in clinical success rates and an increase in the number of new drugs, the question remains whether the crisis will soon be over. We surely do not have enough information to answer this question. Given the new possibilities the advancing knowledge in biotechnology, genetics, and bioinformatics, we should expect a higher increase in the success rate or the number of new drugs than has been found. Further, real innovation would mean more than just substituting drugs when patent protection is ending, but to come up with more new drugs providing a real additional value to patients.

While we highlighted the development of the success rate very comprehensively in our study, an economic theory on the project success rate and its role in pharmaceutical innovation is still lacking. The economic reasons for the decline in success rates have not yet been thoroughly discussed by the existing empirical literature on success rates. The studies are mainly focused on giving estimates on success rates, not discussing their meaning or changing external factors such as technology, regulation or firm strategies.

The development of a sound economic theory on the development of the success rate is beyond the scope of this paper and left open to further research. There are, however, various contributions in the literature with a pharma-based theoretical background. We will present selected aspects here and discuss how our results relate to the reasons brought forward by this literature.

We found that the success rate is under pressure due to the strongly increasing number of drug development projects. However, the higher number of projects started in total is not necessarily a crisis phenomenon. Contrary, the rising number of projects rather indicates there is more innovative activity than in earlier times. Scientific progress makes it possible to screen many more compounds at the same time (e.g., high throughput screening, see Scannell *et al.* 2012). While these methods have been criticized in bringing too many projects with toxicity or side-effects into clinical phases our data on clinical development do not support this view: In the three most recent time periods of projects started between 2003 and 2010 we find a relatively stable success rate of 0.17 to 0.18 in the clinical sample. However, our data does not allow studying this in detail as we have no information on the discovery and development methods firms use in the preclinical phase. This leaves room for further research on the connection between the strong increase in the number of preclinical discontinuations and the relatively stable success rate concerning clinical projects.

Regarding the exploration of technological fields in search of suitable drug candidate compounds, some authors argue that the easiest drugs to develop have already been introduced leaving only drugs that are more difficult to develop (see, e.g. Scannell *et al.* 2012). A decline in success rates of new drugs can be explained this way, however, we oppose this view. For example, the antibacterial effects of penicillin or the anti-inflammatory effects of corticosteroids found in earlier years were far from obvious or easy to develop (Scannell *et al.* 2012). Further, this view is based on a static search space. However, technological progress especially in biotech and molecular development lead to a highly dynamic search space. New fields occur where new drug candidate compounds are feasible for development. These need not be more difficult to discover and develop than compounds found in earlier decades. Indeed, the increasing number of projects started during time may be an indicator of a dynamic search space.

According to many authors, the regulatory standards have increased over the past decades with regard to quality requirements of new drugs (e.g. Kola and Landis 2004; Munos 2009; Scannell *et al.* 2012). However, this would mean the requirement of a drug to be a pharmaceutical innovation has been lower in the past. Therefore, in the past drugs were considered to be innovative whereas the same drugs would be no innovation anymore nowadays and innovativeness has never been higher before. The larger success rates of project started earlier would then just mean that the industry's innovativeness has been over-stated in the past. Firms have to build competences with regard to the regulated drug development process. This does not only mean to have knowledge and experience about the technologies of discovery

and development of drug candidate compounds but also to gain knowledge about fulfilling the standards of regulation authorities (Orsenigo *et al.* 2001). When new firms enter the industry, they first have to build competences on regulation standards suitable to get the drug through development and eventually to the market. Higher regulatory requirements increase this entry barrier for new firms (Gambardella *et al.* 2000).

Last, firms' choice of risk is worth looking at. Firms are more and more focusing on therapeutic areas where there are no established compounds yet (Pammolli *et al.* 2011). These are disease field where the probability of success is lower.[16] This way, firms avoid competition and focus on markets without incumbent firms. Targeting new mechanisms of action, however, has a higher risk of failure (Kola and Landis 2004). There is evidence that research efforts have been reoriented towards more difficult targets in areas where success rates are lower (Pammolli *et al.* 2011). The result is low competition both in the market and for the market. When success rates are low and one firm is already in later stage development of a drug, other firms can observe this and will not choose the same area. A lower overall success probability by a change in firms' choice of risk is not negative from a firm view as long as the firms' expected costs and revenues are reasonable. Without having financial data about the eventual returns of launching drugs in riskier, but less competitive fields, this cannot be evaluated. However, there is a concern from a regulators point of view. First, firms switch to more risky fields to avoid competition. When a firm is successful in competition for the market and launches a drug for a certain disease, it has no incentive to further improve the drug's quality. There are no competitors as these are expected to refrain from risky development. Second, when all firms switch to more risky fields, more firms develop drugs for more risky fields and the success rate is decreasing in total.

There are firm strategies to mitigate the higher risk of project failure in more risky disease fields, e.g., firms can develop more than one compound for the same disease in parallel projects. In doing so, there are backup compounds to step in when difficulties occur in the development of the lead compound. For this reason, parallel development increases the probability that at least one of the projects will eventually become a success (e.g., Comanor and Scherer 2013).[17] When one compound passes the clinical development process and is launched in the market the development of others is stopped. When more and more parallel backup projects within firm pipelines are started, more of these projects are discontinued later on as well, and the observed success rate decreases. There is, however, some limitation to the development of parallel compounds for the same disease. The more parallel projects are

[16] For example, project discontinuation duet to a lack of efficacy is more prevalent in therapeutic areas where animal models of efficacy are rather unpredictive. These are central nervous system and oncology, showing higher failure rates in phases II and III (Kola and Landis 2004).

[17] For a more general discussion on the economics of parallel research and development, see Nelson (1961) and Abernathy and Rosenbloom (1969).

developed, the higher the costs are, such that firms have to balance the higher probability of a successful market launch with the higher costs of parallel development. Further, parallel projects only offer a higher probability of introduction for a specific disease when the success factors of these projects are only moderately correlated (Girotra *et al.* 2007). Otherwise, the discontinuation of one project due to a specific factor would lead to the discontinuation of the other parallel projects as well. In our data, we observe a higher number of projects started and discontinued eventually. Our results show that the predicted number of successful projects is first decreasing and then increasing again, while the number of discontinued projects is heavily increasing. A large share of these projects may be backup compounds for the riskier compounds in development nowadays. The increasing predicted number of launched projects shows that the mitigation of higher risk by backup compounds yields some success and the innovative output of the industry is recovering. However, the increase in the predicted number of launches is only observed for the last period of projects started between 2007 and 2010 and comes at the cost of a higher number of discontinued projects serving as backup compounds. Whether this recovery in innovative output of the industry is sustainable, cannot be answered at this point in time yet. Further, we did not study whether a higher number of discontinued projects are backup compounds leaving this question open for future research.

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Appendix

Table A 1: Included Projects and Firms

Drugs	*Pipeline covers novel drug candidates intended for prescription use in humans. Therapeutics, vaccines, novel drug formulations and their technologies and certain in-vivo diagnostics are covered.*
Inclusions	• Human therapeutics • Human vaccines • Biosimilars • Prescription drug candidates • NCEs, novel biologicals and natural products • Novel formulations of existing drugs • Reprofiled drugs in development for novel uses • Novel drug formulation technologies • Certain drug-like in-vivo diagnostics • Drug candidates in active development since 1980
Exclusions	• Generics • Over-the-counter (OTC) drugs • Veterinary drugs • Devices • In-vitro diagnostics • Nutraceuticals and nutritional products • Cosmetics • Pharmacological and screening tools • Biomarkers • Drugs which were already fully launched worldwide by 1980 • Drugs which ceased development before 1980
Companies	*Pipeline covers companies (and their subsidiaries) directly involved in developing drugs listed on the database. Both originators of drugs and licensees/collaborators directly involved in development are included, with further details of areas/territories of responsibility as appropriate. Manufacturers, Contract Research Organizations (CROs), suppliers, distributors, investors and funding bodies are not covered.*
Inclusions	• Companies originating drug projects • Licensees and collaborators directly involved in drug development • Non-industrials with licensing opportunities, or which are sole developers of drugs intended for commercialization • Areas of responsibility/territories assigned to originators and licensees/collaborators
Exclusions	• Manufacturers • CROs • Suppliers • Investors and government funding bodies • Academics/non-industrials (unless they are sole developer, or have projects available for licensing) • Financial details of licensing agreements • Financial figures/funding information

Source: Informa Healthcare 2012, pp. 1-2; summary table by the author

Table A 2: Test of Proportional Hazards Assumption, Cox model

Variable	Rho	Chi-Squared	sign.	P-Value	Rho	Chi-Squared	sign.	P-Value
Project Begin Year	-0.293	0.99		0.321				
Begin Year: 1989-1994					-0.026	0.61		0.435
Begin Year: 1995-1998					-0.017	0.24		0.622
Begin Year: 1999-2002					0.059	2.89		0.089
Begin Year: 2003-2006					0.013	0.15		0.703
Number of Diseases Project aims at	0.142	**11.63**	***	0.001	0.148	**13.45**	***	0.000
Two Disease Groups	0.023	0.34		0.562	0.018	0.26		0.610
Three or more Disease Groups	0.076	**4.35**	*	0.037	0.075	**4.22**	*	0.040
Vaccine	-0.136	**13.11**	***	0.000	-0.134	**12.79**	***	0.000
Project is Licensed	0.061	3.23		0.072	0.054	2.49		0.115
Natural Origin	-0.062	3.38		0.066	-0.037	1.30		0.254
Biological Origin	-0.027	0.57		0.452	0.043	1.73		0.188
Firm Portfolio Size	-0.035	1.14		0.286	-0.062	3.36		0.668
Firm Portfolio Size (Squared)	0.040	1.49		0.222	-0.027	0.55		0.457
Disease Groups								
Alimentary-Metabolic	-0.561	2.47		0.116	-0.054	2.31		0.128
Blood and Clotting	-0.020	0.31		0.565	-0.017	0.23		0.628
Cancer	-0.028	0.56		0.456	-0.027	0.52		0.469
Cardiovascular	-0.019	0.27		0.605	-0.015	0.17		0.677
Dermatological	-0.073	**4.10**	*	0.043	-0.071	**3.83**	*	0.050
Genitourinary	-0.059	2.67		0.102	-0.057	2.49		0.114
Hormonal	-0.118	**11.82**	***	0.001	-0.119	**12.04**	***	0.001
Immunological	0.010	0.07		0.787	0.010	0.08		0.781
Infectious Disease	-0.036	0.92		0.338	-0.034	0.84		0.358
Musculoskeletal	0.006	0.03		0.863	0.008	0.06		0.810
Neurological	-0.019	0.27		0.604	-0.016	0.20		0.655
Parasitic	-0.006	0.03		0.853	-0.005	0.02		0.876
Respiratory	-0.038	1.11		0.293	-0.037	1.06		0.303
Sensory	-0.060	2.94		0.086	-0.058	2.78		0.096
global Test		**84.00**	***	0.000		**44.10**	**	0.0074

Time: Rank (t)

Degrees of freedom: individual variables: 1; global test: 24
*Significance: *** 0.1 percent / ** 1 percent * 5 percent*
Source: Informa Healthcare Pipeline Pharma Data; table and calculations by the author