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International Society for Research on Innovation and Change in Health Care Systems
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Mail questions to: Martina Eckardt (martina.eckardt@andrassyuni.hu) or to Stefan Okruch (stefan.okruch@andrassyuni.hu), Andrássy University Budapest, Hungary, H-1088 Budapest, Pollack Mihály tér 3

Co-evolutionary Innovation Patterns in the Pharmaceutical Industry since 1888

Oliver Eger
University of Augsburg
Universitätsstr. 16, D-86135 Augsburg, Germany
Email: oliver.eger@wiwi.uni-augsburg.de

Horst Hanusch
University of Augsburg
Universitätsstr. 16, D-86135 Augsburg, Germany
Email: horst.hanusch@wiwi.uni-augsburg.de

Andreas Pyka
University of Bremen
Hochschulring 4, D-28359 Bremen, Germany
Email: pyka@uni-bremen.de

ABSTRACT

This paper examines the relation between the innovation output from universities and the innovation output from industry on a historic-empirical data base in the pharmaceutical industry. We suggest a stable cross-country pattern of innovation output to exist where public funded universities act as a trigger for new scientific developments, opening the way for a new industry to emerge. Our results highlight the importance of publicly funded basic research for future socio-economic benefits.

Key Words: Basic science, innovation, economic development, pharmaceutical industry, history, co-evolution

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1. Introduction

Since the last two decades pharmaceutical industries are confronted with tremendously increasing R&D costs accompanied by a decreasing rate of innovative success. Given this increasingly difficult development the long term mechanisms linking innovation and industry development are of outstanding significance for industry as well as for policy actors. The aim of our paper is to analyze these long run relationships between public and private innovation processes and industry development for the German pharmaceutical industry for the last 110 years. Applying the Neo-Schumpeterian approach of industry dynamics the mechanisms determining the interplay between scientific-technological and economic development and the emerging patterns of co-evolution are in the centre of interest.

Because of endogenous links between knowledge creation and economic development Neo-Schumpeterian Economics provides the adequate framework for our empirical research. Advances in science and progress in technology are the key drivers for economic development. In particular we are combining three strands of literature in our empirical model which are highly complementary: The theory of technological paradigms und trajectories (Dosi 1982), the theory of technological regimes (Nelson /Winter 1982, Malerba /Orsenigo 1997) and the theory of industry live cycles (Gort /Klepper 1982, Klepper 1997).

Technological paradigms allow for the analysis of the knowledge spheres, whereas the theory of industry life cycles covers the industrial sphere; the two approaches can conceptually be linked by the approach of technological regimes. Beginning with the idiosyncratic scientific-technological features of the pharmaceutical industry, we will connect industry dynamics and structural changes drawing on insights of the ILC theory.

Two historical databases are created, containing active pharmaceutical ingredient data as an indicator for innovative activities, as well as firm data on entry and exit processes in order to deviate industry life cycles. While the firm data base contains only German pharmaceutical companies, the innovation data also covers new ingredients from all relevant pharmaceutical producing countries. An outstanding feature of the two data bases is their long time horizon encompassing more than 100 years of industry development starting in 1888. This allows us to examine a rather complete record of the techno-economic development of this important industry.

Generally we have two aims in mind:

(i) We want to improve our understanding of innovation driven economic development. On a sector level this has to be done by describing and analyzing long-run time-series depicting the technological as well as economic dynamics. (ii) The improved understanding of these co-evolutionary forces is supposed to lead to conclusions which might support and guide decision processes in industry and politics. This, in particular holds with respect to the ongoing debate about decreasing innovation performance in the pharmaceutical industry and the ongoing concentration processes in this industry. Concerning the ISRICH network, we are interested in a particular part of the health care system, namely the production of pharmaceuticals and the determinants driving their evolution.

The present paper examines one aspect of these evolutionary determinants in detail: It analyzes the interrelations between university research and private research performed in the pharmaceutical companies. What are the specific relations between basic science and applied research in the field of pharmaceuticals and how do they mutually influence each other? Is there a specific direction of influence from one source to the other? Has basic research a stimulating influence on the innovation output of the industry? And, consequently, does public funded research affect the economic evolution of the pharmaceutical industry?

The impact of science on the economic development is an old and well investigated research area. In the post-war-area Richard Nelson (1959) and Kenneth Arrow (1962) triggered this prolific field of research and inspired lot of research until today. The writings of Nelson and Arrow are considered the starting points of economists engaged in the economics of science and innovation and addressing the meaning of basic research on economic growth and social welfare: Whereas Arrow claims that the market allocation of resources within the scientific system has to be inefficient, because of the public good nature of sciences' outcome, Nelson is emphasizing the economic impact of science and its contribution to economic growth and welfare. Our work is embedded in this literature and should strengthen its insights by an empirical analysis with a very long historical time horizon covering the whole record of innovation output from the beginning of the pharmaceutical industry at the end of the 19th century until today. In particular, our studies are covering innovation processes on the technological side as well as entry and exit processes on the economic side.

The paper is structured as follows: the second section gives a short overview on the literature concerning questions of the relation between science, innovation and the economic realm. The third section starts with a description of our innovation database, followed by some descriptive results. The final section discusses the results and gives an outlook for future research

2. Science, Innovation and the Economy

A huge literature on the connection of science, innovation and the economy exists. It is beyond the scope of our paper to give a complete overview. In the following sections, we do only outline the most important contributions structuring the field.

Following the seminal contributions by Arrow and Nelson mentioned above, Nathan Rosenberg (1974) emphasizes the fundamental importance of science for the economy concerning the demand as well as the supply side. His starting point is the work of Jacob Schmookler (1966). Here Schmookler, by empirically studying several American industries, shows the overwhelming importance for innovation of the demand side. In particular, Schmookler stresses the high correlation between the number of inventions in one industry and the volume of sales. Schmookler argues, that the need and therefore the demand for certain goods triggers innovative activities in the respective fields. In his view, inventions are not limited by scientific or technological restrictions, but by the economic dimension of demand. As long as there is demand, science and technology generate adequate solutions automatically. Following this view, innovation activities can fully be explained with the help of economic variables (Rosenberg 1974, 91-94).

Rosenberg generally agrees with the importance of the demand side, but also gives a strong argument stressing the fundamental role of science itself. Rosenberg argues that science and technology have also an internal logic concerning development; this internal logic also shapes the direction and timing of inventions, resulting in different cost structures for innovation activities in different industries. To illustrate this, he points to the fact, that scientific disciplines have different rates of advance. For example, because of the high state of development in mathematics and astronomy, the need for navigation techniques in the sixteenth and seventeenth century could be satisfied at this time, whereas the undoubtedly similar existing need for better medical treatments could not. The scientific base for improvements in medicine and pharmaceuticals e.g. knowledge on bacteriology, biochemistry or organic chemistry was far away any realistic possibility contributing to advances. Scientific development does not take place shaped only by economic (demand) forces, but within a historical path with opportunities and restrictions within its specific scientific discipline (Rosenberg 1974, 97-101). No matter how much money would have been spend in the year 1800, neither a wide-spectrum antibiotic nor a satellite to be send in the space could be constructed. In economic terms: the supply of certain products was completely inelastic, i.e. elasticity is zero at all levels of prices (Rosenberg 1974, 107). Rosenberg concludes that besides such extreme cases, when the supply elasticity is larger than zero but smaller than infinity, or when the scientific fundamentals for an innovation are existent, the costs for a science dependent invention are declining with growing scientific knowledge. These decreasing costs then justify the public funding of basic research. Because there are different states of development in different scientific disciplines at one time, the supply curve for inventions in every discipline is different, i.e. the innovation costs structure is different. By this Rosenberg highlights the crucial role of science for economies by pointing on its inner logic as well as the economic consequences with respect to demand and supply.

With respect to the role of scientific knowledge for economic development the work of Keith Pavitt has to be mentioned. Pavitt (1991) states, that the intensity of knowledge transfer from basic science to applications or technology differs among industries and scientific fields, an idea not un-related to the different science-driven innovation-supply- curves introduced by Rosenberg. An example for a very strong relationship offers the pharmaceutical industry. Besides the direct impacts from science via technology to economy, Pavitt emphasizes two further influential relationships: training or skills and unforeseen applications. Being engaged in basic research strengthens the capabilities of the involved researchers which is of significant importance for firms searching innovative capabilities on the labour markets. Furthermore, often underestimated, scientific research, undertaken without any explicit profit motivation, historically has shown to be an important source of innovation. Finally, Pavitt addresses absorptive capacities which are created by basic research. Absorptive capacities have to be considered as a broader concept than originally conceived by Cohen and Levinthal (1989), who introduced absorptive capacities as a by-product of regular firm R&D. In order to benefit from potential cross-fertilization effects between seemingly unrelated technologies (Pyka 1999) a much broader understanding of absorptive capacities is necessary and being engaged in basic research is an important source to create these competences.

Discussing from a historical perspective the role of American universities with respect to industrial innovation Nathan Rosenberg and Richard Nelson (1994) come to similar conclusions.

Without going into details of the evolution of the American academic system and the changing roles of university since the 19th century, the crucial point is that they find an increasing engagement in academic research by industrial sources since the last two decades. Based on this finding they focus on the problems this may cause for university research agendas. Universities should support industrial R&D, rather than substituting it. Especially in the pharmaceutical industry, which is close to basic science, industrial development is closely related to advances in science. Basic research undertaken in university research laboratories is supposed to offer new technological potentials to be exploited by the industrial actors and should not address specific R&D projects. To maintain this borderline between university research and industrial R&D industrial funding of universities needs to be controlled severely. This division of labour between basic scientific research and applied economic-driven research will lead to mutual benefits in the long run.

So far we stressed the relation between science and economy from a theoretical angle. The following paragraphs summarize important empirical findings. One of the most prominent advocates is Edwin Mansfield. In a often cited approach (Mansfield 1991) he tries to give answers to the following questions: (i) How much are technological innovations in different industries based on recent academic research? (ii) How long is the time lag between the beginning of this research and the outcome in terms of applicable products? And (iii) what is the social rate of return of basic research?

To answer these questions he conducted a survey of 76 randomly selected American firms. There he is addressing the question on the proportion of products and process introduced between 1975 and 1985 that could not have been developed without substantial delay in the absence of academic research. Relevant academic research is framed within a 15-years period prior to the innovation. In line with the theoretically and historically motivated research, Mansfield finds a large variance between different industries. Whereas the mean percentage for the industries was about 11% for products and processes that could not have been developed without the help of academic research, oil industry was lowest with 1%, and drug industry was highest with 27%. To measure the economic importance of these products and processes, the sales of products and cost reductions from the innovative processes are estimated for 1985. The resulting figures are impressing 24 billion dollars for products (or 3% related to total sales of the firms) and 7.2 billion dollars for processes (or 1% of the total costs). With respect to the time lag between first research activities at universities and innovation Mansfield also reports considerable differences between industries. The mean value over all industries is 7 years, the time lag e.g. in the drug industry is 8.8 years.

With respect to the social rate of return from academic research between 1975-1978 Mansfield estimated a value of 28%. However, he stresses that this figure is very tentative, although based conservative calculations. In a recent paper Diamond (2003) is adjusting Mansfield's figure to 40% (Mansfield 1992).

These figures underline the remarkable impact of science, especially in science-based industries like the pharmaceutical industry. These results also confirm the relative importance of scientific research compared with other input factors in production. Reducing the amount of basic research will clearly lead to a decrease of welfare benefits.

The above mentioned contributions give a coherent picture of the relationship between scientific advance and innovation. All of these studies emphasize the importance of scientific research for prolific economic development is common. It is also pointed out, that there are significant differences between the various industries. It is shown that the pharmaceutical industry is among the industries which benefit most from public funded scientific research. However, the empirical investigations focus only on the developments of the most recent past. Our research tries to connect the history-oriented perspective with the empirically guided research. We are interested in the specific patterns which can be found in the relation between science and economy in a historical perspective. Our historical data base allows for new insights in this respect. Our data base is suited to analyze the evolution of pharmaceutical innovations either by its source (e.g. public or private funded research) or by its national origin. This allows tracing back the sources of innovations starting from the very beginning of the industry until present days thereby mapping a historical micro based macro path and national specificities.

The next section starts with a brief description of available innovation data in pharmaceuticals and on our data base.

3. Data

3.1. General data basis

In order to find patterns in the historical development of the pharmaceutical industry and its particular relationship the scientific sector, we have compiled two data bases describing innovation and economic processes. The innovation data base contains active pharmaceutical ingredient data as an indicator for innovative activities. The economic data base collects firm entries and exits which allows depicting the industry life cycle of the pharmaceutical industry in Germany.

First we address the active pharmaceutical ingredient data. To build up the innovation data base, we explored various sources in order to find out, how useful they are for our questions.[1] Among others we scanned data from patent offices, public administration, scientific offices, trade associations, publications and pharmaceutical reference books. Altogether the situation concerning the question, how much active pharmaceutical ingredients ever have been developed world wide revealed to be unclear. The figures ranged between 1200 at minimum up to 12000 maximum. In order to clarify this puzzling finding we called several experts, in particular authors of reference books. The explanations we find for the large range of ingredients where:

- different definitions of pharmaceuticals (medical effects or any biological effect)

- a different treatment of substances which are only used in clinical trials, but never came to any practical applications

- ingredients just introduced in a few countries, but not world wide

The experts agree that it is impossible to find a well-defined solution to this problem. Additionally, many data sources proved to be inadequate because of covering only a short period, focussing on a particular topic, did not give any information of the introductory year, did not contain the information of the innovator (university or company) or the country of origin. Only the book written by Walter Sneader (1996) and the data he collected fit all of our requirements. Sneader offers an expert selection of the 1200 most important active pharmaceutical ingredients world wide since 1800, compiled especially to give an historical overview of the development and evolution in the pharmaceutical area. His data include information on the year of the invention or introduction of each substance and hints to the patent specification or scientific publication.

3.2. Innovation data base

The Sneader data are compiled to come to grips with the historical development and to give a historical overview of the evolution of pharmaceuticals. Sneader states in the preface of his book,

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[1] A detailed discussion of the data basis would cross by far the frame of this paper. I gave the details at my talk at the institute of public health and health economy, university of Augsburg, 16th of June, 2005, see manuscript p. 12 – 23. This details will be published in my forthcoming thesis; O.Eger.

that he aims to give a genealogical overview of the development of drugs. For this purpose he organises his book in six main groups of drugs, divided into 19 subgroups and 244 so called "drug prototypes". He adds a brief historical record of most of the about 1200 drugs or active pharmaceutical ingredients. These brief descriptions include information on the year of the drug release, which is either the date of introduction or the date of patenting or publication. Often patent numbers and the exact journal and date of publication are given.

Using Sneader's data collection as a starting point, we looked up for every substance the original patent specification, if the patent number is given. With patent numbers the specification can be collected easily from the European or US patent offices. By this inquiry we generate the necessary information on the institution of the invention (public funded institute, most often universities2 or private firms) as well as the country of invention. The procedure can be applied to scientific publications.

3.3. Results

Our final database has to be considered as an expert selection of around 1200 most important active pharmaceutical ingredients world wide since 1800, including their denomination, the year of patenting or publication, the institutional sources and the country of invention. In summary we count 29 countries. The five most important countries are: USA (31.9%), Germany (20.3%), UK (12.8%), Switzerland (11.1%) and France (6.3%). The five countries together cover 81.7% of all pharmaceutical active ingredients.

The shares of the universities' and firms' outputs measured by the total output of a country are given in the following table:

	USA	Germany	UK	Switzerland	France
University	27%	42%	30%	15%	44%
Company	73%	58%	70%	85%	56%

[2] The lion share of innovations from public funded institutions comes from universities. Also there are other public funded institutions where pharmaceuticals arose from, in the following we only use the term university because of linguistic simplification.

Table 1: percentage of innovation source (university or firm) in the five most important countries. Source: own data, based on Sneader data.

The following figures display the historical developments of the shares of university and company based innovations.

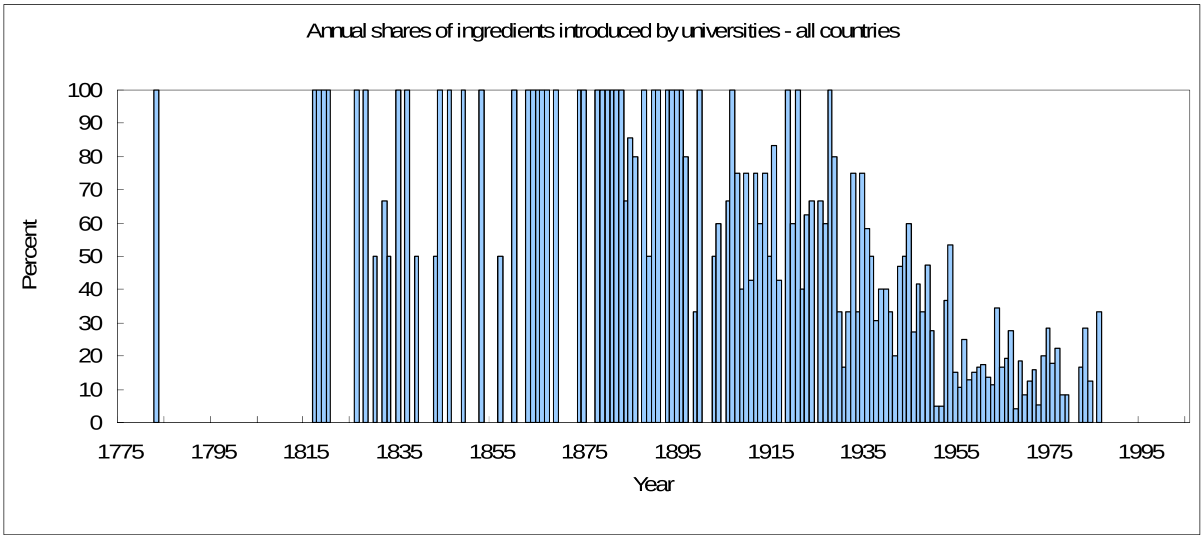


Figure 1: Annual percentage of all university ingredients in all ingredients. Source: own data, based on Sneader data.

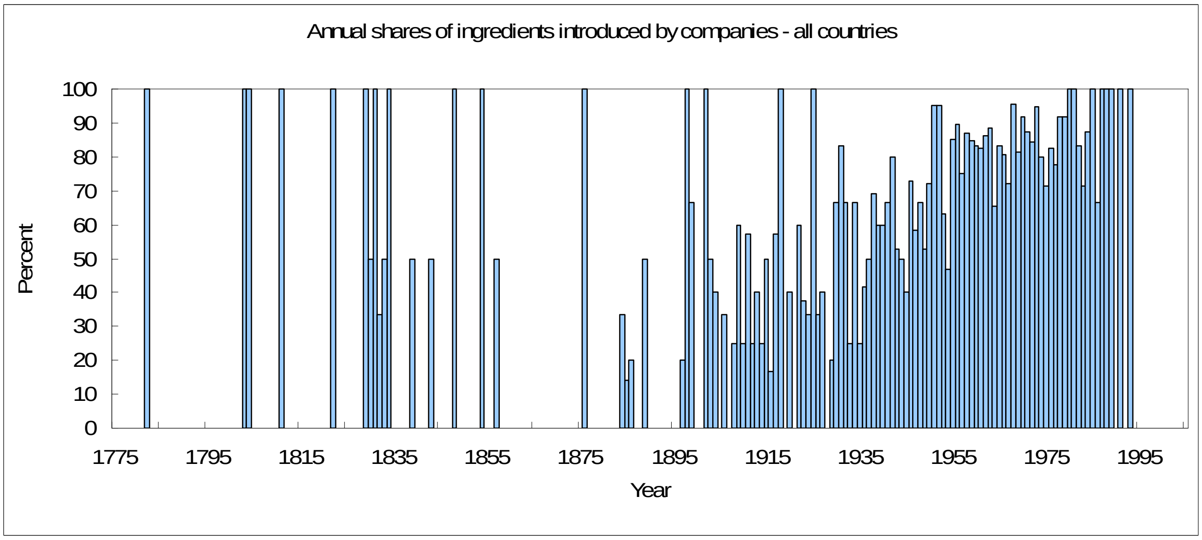


Figure 2: Annual percentage of all company ingredients in all ingredients. Source: own data, based on Sneader data.

The comparison of figures 1 and 2 shows that from the early days of the pharmaceutical industry at the end of the 19th century, the rise of pharmaceuticals stemming from companies continuously increases, whereas the share of active ingredients from universities developed almost contrariwise. Furthermore, before the onset of the industry the majority of substances came from universities.

In order to find out whether the patterns in innovation output in figures 1 and 2 can be traced back to the aggregation of the different countries, we disaggregate the data for each of the five most important countries listed in table 1.

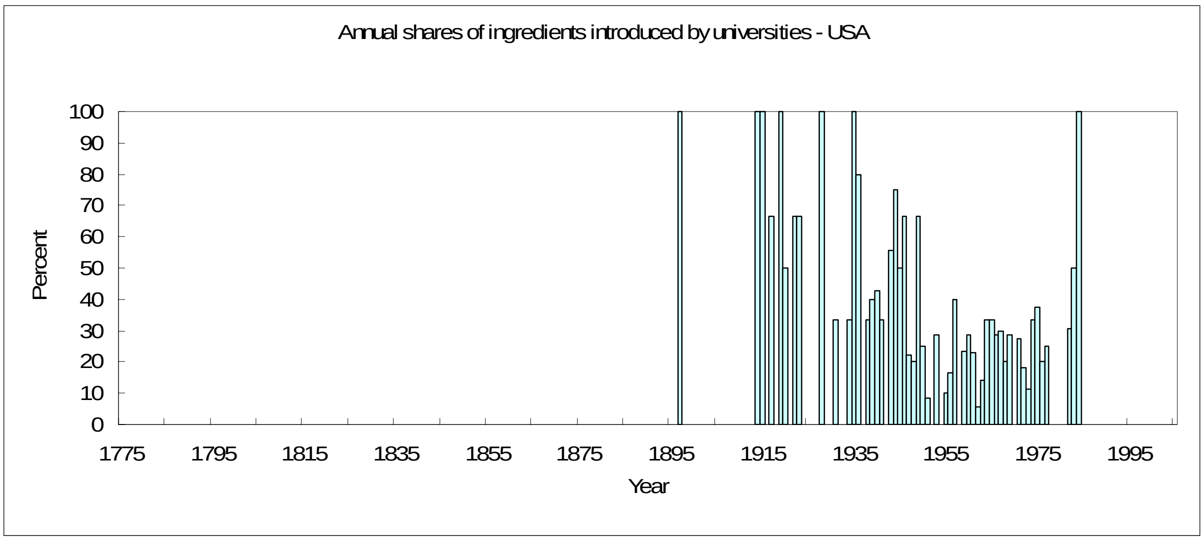


Figure 3: Annual percentage of all USA university ingredients in all USA ingredients. Source: own data, based on Sneader data.

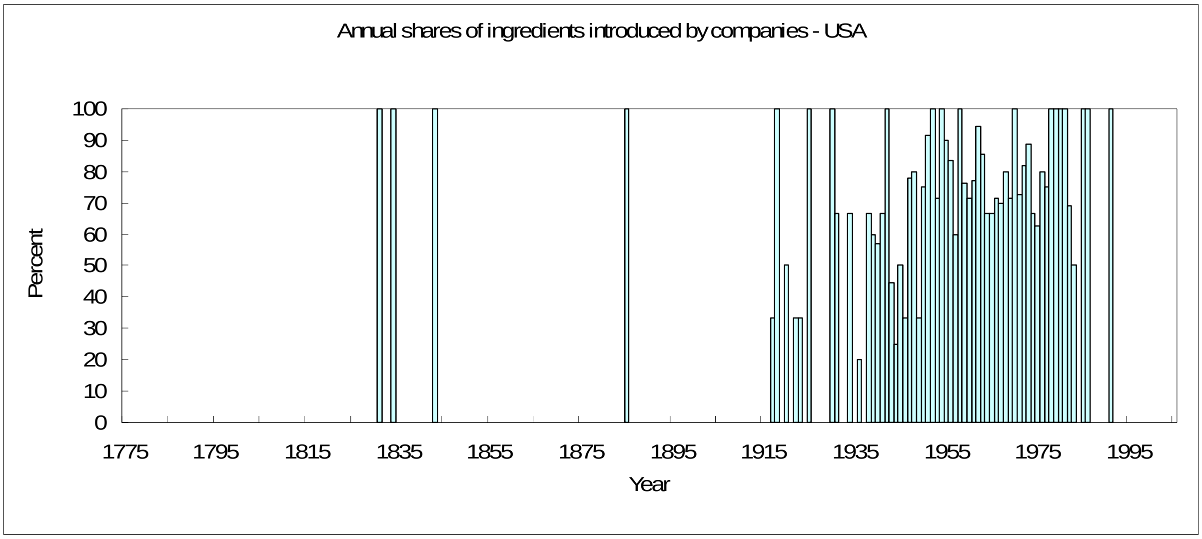


Figure 4: Annual percentage of all USA company ingredients in all USA ingredients. Source: own data, based on Sneader data.

It can be from seen from figures 3 and 4 that the development in the USA somewhat differs from the aggregated data. At the end of the 19th century there are only a few pharmaceutical innovations both from universities and from private companies. An increase in innovative output starts only after World War I. A possible explanation for the deviating pattern can be found in the historical development of U.S. universities. This is discussed in length by Rosenberg and Nelson (1994, 325, 338). They show that U.S. universities were much more application-oriented. The decentralized academic system which most often was locally funded specializes in practical and vocational problems. The focus was mainly on improving agriculture technologies and training of engineering skills. Sophisticated scientific problems were far less important in these early days. The universities were supposed to deliver problem solving techniques and a reasonable return to their owners. In consequence only a few activities were oriented towards basic research. This also holds for organic chemistry which is the most important scientific discipline concerning the development of a pharmaceutical industry. Compared to machine tools, agriculture etc. an immediate relation between organic chemistry and medical needs was not obvious end of the 19th century.

The particularities in the evolution of the U.S. academic system and in the U.S. pharmaceutical innovation data, support our arguments outlined in section 2. Without social institutions which are able to perceive the potentials of new emerging scientific knowledge and which support scientific advance without having immediate economic aims in mind, no prolific and crossfertilizing science-driven economic development can take place. In this respect our finding confirms the conclusion of Rosenberg and Nelson (1994): academic agendas should not follow too closely and exclusively the demands of the economic realm.

Besides the differences, also similarities can be seen in the comparison of the U.S. figures and the aggregated data. The similarities start with the beginning of 20th century when in the U.S. the different trend in development changes. Now the university output continuously decreases and the industry output steadily increases. This change in trends supports our hypothesis that university research can trigger a development in industry or even is the kernel of a completely new industry.

Another observation in our data is in line with Rosenberg and Nelson (1994, p. 338). In figures 3 and 4 one can see two small peaks in the university output after 1945 and a corresponding decrease in the industry output. This can be traced back to the structural transition in the funding of US universities after World War II where public funding enormously increased, in particular in fields of health and defence.

The second important country for pharmaceutical output, listed in table 1, is Germany. The respective data are displayed in figures 5 and 6.

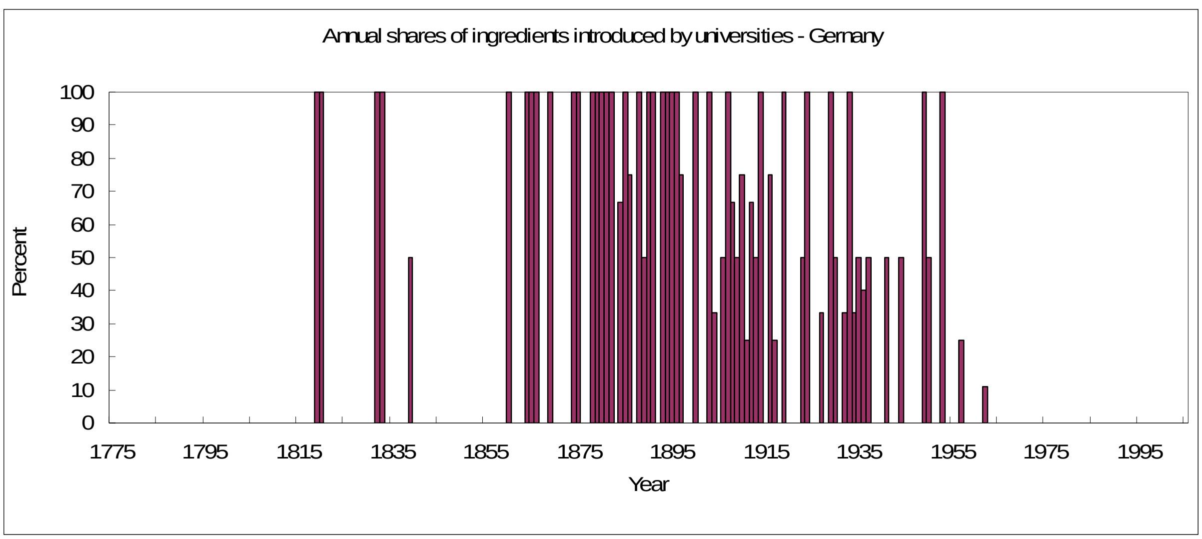


Figure 5: Annual percentage of all German university ingredients in all German ingredients. Source: own data, based on Sneader data.

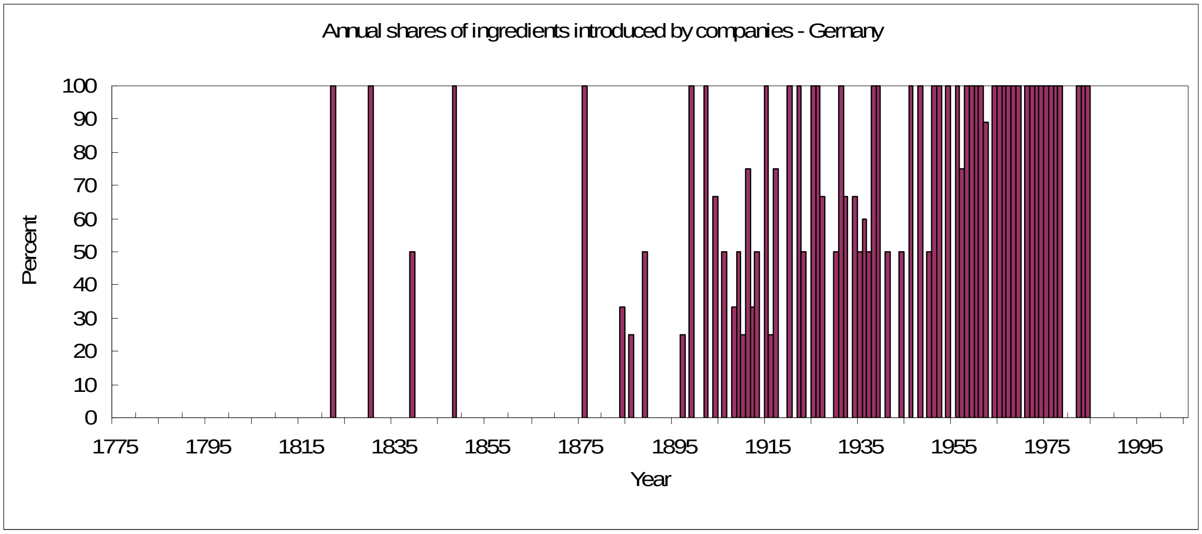


Figure 6: Annual percentage of all German company ingredients in all German ingredients. Source: own data, based on Sneader data.

University innovations begin to increase in the middle of the nineteenth century. This finding also conforms to the literature (Haas 1981, Drews 1998) which reports the start of first advances in modern pharmaceuticals in this period. In Germany we have a permanent decrease in university innovation accompanied by an increasing firm innovation output. The beginning of the industry output can be placed at the end of the 19th century (Drews 1998, 37). Compared to all other countries in our database, this is the earliest starting point in pharmaceuticals.

A potential explanation for the head start of the pharmaceutical industry in Germany has to be seen in the severe efforts in German universities indicated in figure 5. A similar record cannot be found for any of the other countries. This is accompanied by a further important institutional innovation in Germany, namely the German health insurance system which was founded end the 19th century. The introduction of a general health insurance strengthens the demand side (Drews 1998, 37). These simultaneous developments in Germany are close to the theoretical discussions given by Rosenberg (1974) and reported above: for prolific innovation processes the demand side is essential, however the supply side matter, too; without a sound science base no development takes off.

The remaining three countries in our data base are UK, Switzerland and France. Their development is displayed in figures 7 to12.

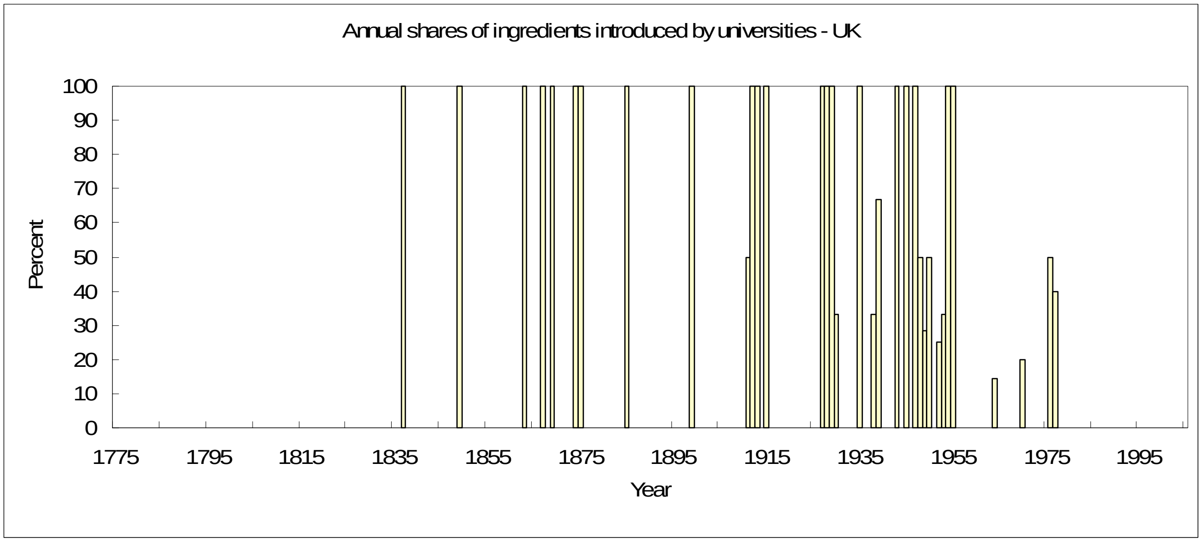


Figure 7: Annual percentage of all UK university ingredients in all English ingredients. Source: own data, based on Sneader data.

Figure 8: Annual percentage of all UK company ingredients in all English ingredients. Source: own data, based on Sneader data.

The starting point of industry activities in the U.K. is relatively late. Nevertheless the well known diverse trends in university and industry innovation are repeated in these figures. With accelerating industry efforts university output slows down.

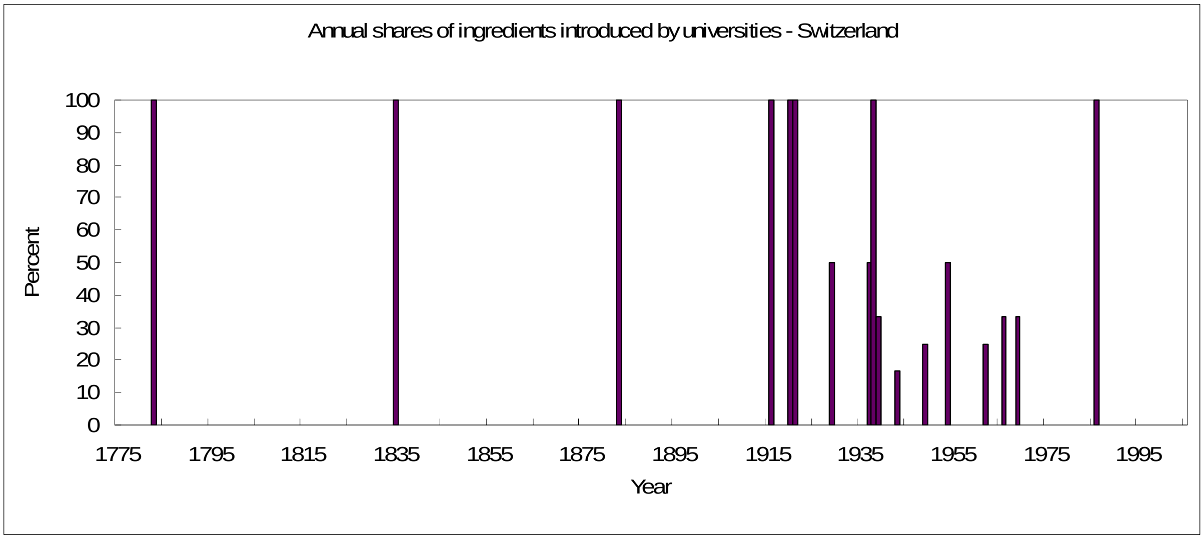
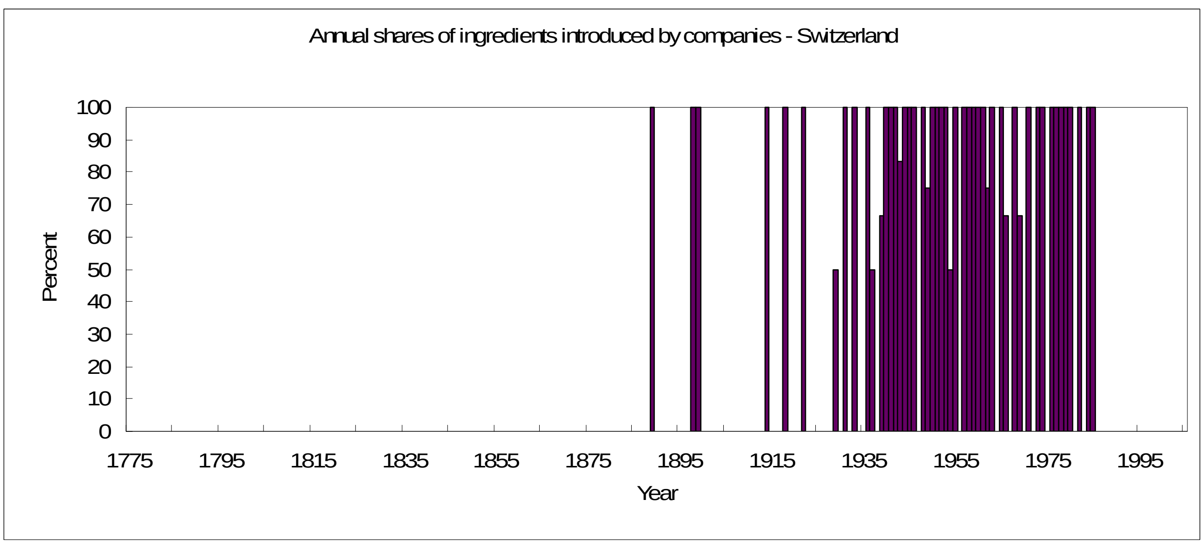


Figure 9: Annual percentage of all Swiss university ingredients in all Swiss ingredients. Source: own data, based on Sneader data.



Figur 10: Annual percentage of all Swiss company ingredients in all Swiss ingredients. Source: own data, based on Sneader data.

The developments in Switzerland are rather similar to the UK although one has to state that the university activities are not pronounced. Again university activities decrease over time and company activities increase.

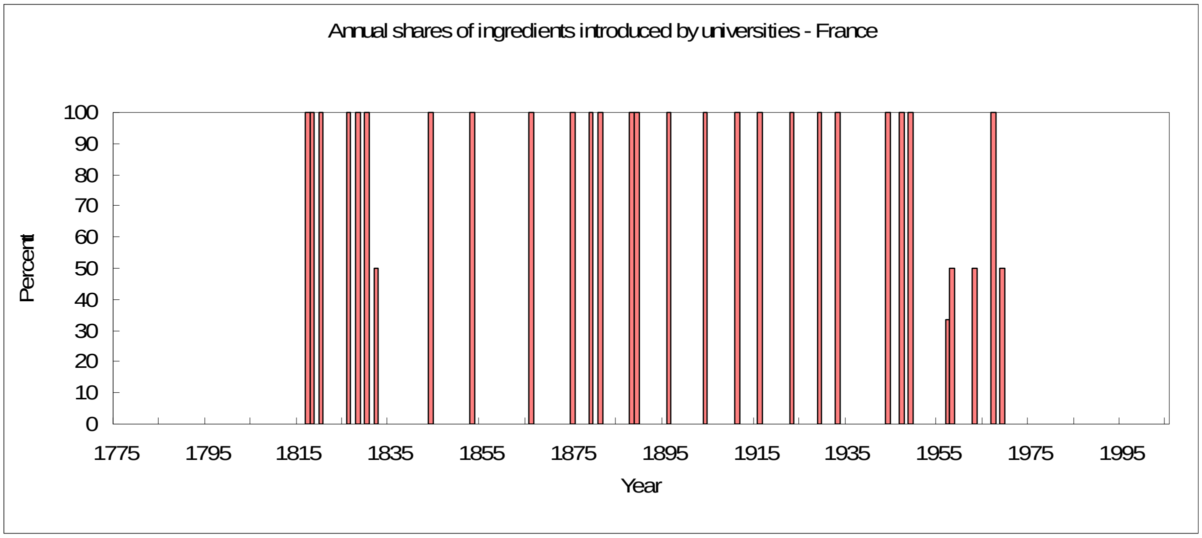


Figure 11: Annual percentage of all French university ingredients in all French ingredients. Source: own data, based on Sneader data.

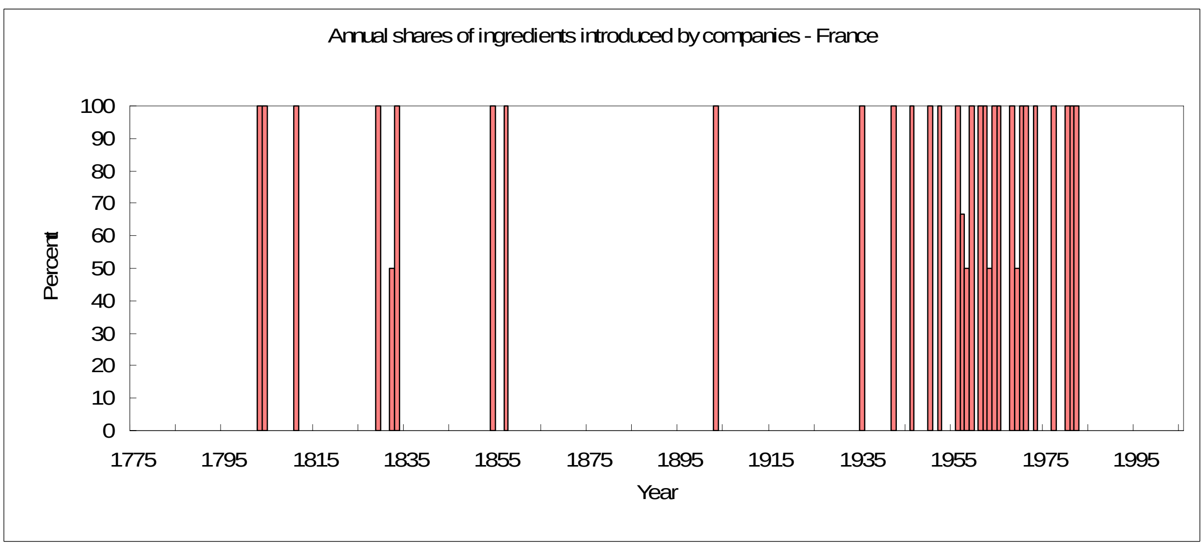


Figure 12: Annual percentage of all French company ingredients in all French ingredients. Source: own data, based on Sneader data.

In France we find a high level of industrial innovative activities relative to the other countries in the early periods. From the beginning of the 19th century until World War II, however, innovative activities are dominated by universities in France (see figure 11 and 12).

4. Conclusions

The aim of paper is to find patterns in the interaction of basic and applied research in the pharmaceutical industry. To summarize the results our data suggests a stable pattern with respect to the necessity of broad scientific research undertaken in universities for a prolific industrial development. This is shown for our aggregated innovation data as well as for the disaggregated levels for the different countries. Innovations generated by universities precede innovation from companies. With increasing industrial innovation activities the number of university innovations declines.

As these patterns can be found in all countries with significant innovation activities in pharmaceuticals national specificities do play only a minor role. In this sense Rosenberg (1974) has to be understood when he states that every science has its own rules and internal logic with respect to scientific advance. It is this internal logic which shapes the direction and timing of invention.

Our descriptive figures suggest a trigger mechanism of university research for the take-off of private innovation activities. Public funded research undertaken in universities acts as an ignition spark for the emergence of a new science-based industry. The more companies finally invest in search for new pharmaceuticals on the basis of the basic research results, the amount of innovation output shifts away from university to industry.

The deviation in U.S. data is additionally emphasizing the importance of basic science for the economic development in particular in science-based industries. The mission of U.S. universities in the 19th century was strengthening application oriented research in agriculture and engineering. These conditions were not favouring the provision of a sound scientific base necessary for a science-based industry to develop. Furthermore, the German case suggests, that it nevertheless is not only technology-push, i.e. basic research undertaken in universities but also demand-pull which positively shapes industry evolution. The early introduction of a health insurance system clearly favours the development of the pharmaceutical industry in Germany.

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