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Letter from the Editor

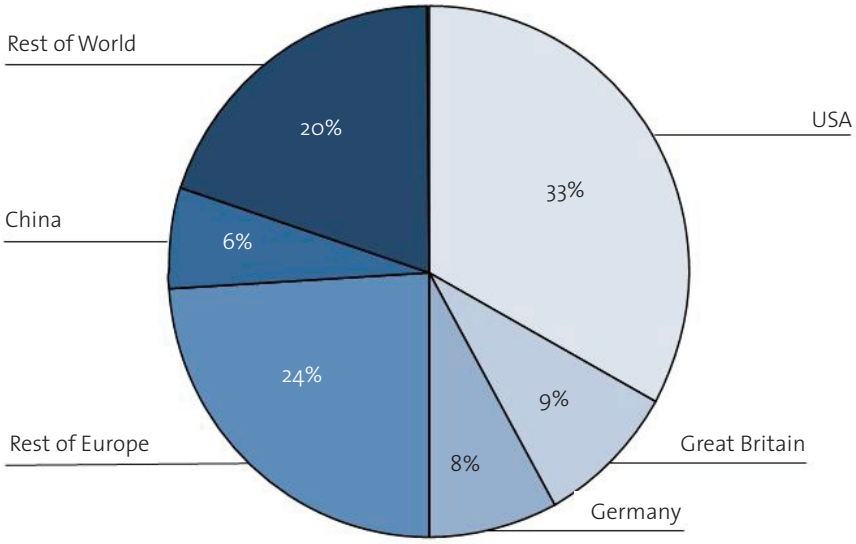
The Journal of Business Chemistry – Five issues of covering the latest trends in research and practice

While chemistry has never been short of inventions, the commercialization of these inventions into innovations requires a completely different set of skills. Many of the problems occurring in this process no longer deal with natural sciences alone but are rather related to topics from the field of business administration. However, natural scientists often lack a profound economic knowledge, while at the same time economists rarely understand the chemistry behind the business. Against this background, the Journal of Business Chemistry (JoBC) was founded in 2004 to serve as the next step of academic progress within the field of business chemistry.

As frequent readers might have noticed, the fifth volume of the JoBC's printed edition appears in a completely new layout. We would like to take this opportunity to highlight some of the recent developments around the journal.

Offering a discussion forum for researchers and practitioners from different backgrounds, the journal attracts readers from all over the world, as illustrated in Figure 1.

Fig. 1: Approximated composition of the Journal of Business Chemistry's readership.



The Journal of Business Chemistry mirrors the whole diversity of the field of business chemistry as the list of all articles published so far shows (see below).

At the website "www.businesschemistry.org", all issues of the JoBC are available for download free of charge to offer a fast and convenient access to newest research insights. Several hundred visitors of the website each month demonstrate the demand for a medium that addresses questions at the intersection of business and chemistry.

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We believe that the still very young research field of business chemistry will continue to grow in importance, as the increasing specialization in all parts of the economy calls for interdisciplinary approaches to solve complex problems. With the Journal of Business Chemistry, researchers and practitioners from the chemical and neighbouring industries have a platform to share and discuss new insights into research questions from the field of business chemistry.

We would like to thank all authors and reviewers for their contributions. Now enjoy the new layout and reading the first issue of the Journal of Business Chemistry in 2008. If you have any comments or suggestions, please send us an email at contact@businesschemistry.org.

Prof. Dr. Jens Leker
Editor-in-Chief
Benjamin Niedergassel
and Clive-Steven Curran
Executive Editors

Journal of Business Chemistry

Commentary

REACh: A European chemicals regulation with global intersectoral consequences

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First of all what is the meaning of REACh? REACh stands for Registration, Evaluation, Authorisation and Restriction of Chemicals and is the new Chemicals Regulation of the European Parliament and Council which entered into force on June 1, 2007. The background of REACh´s coming into force is that our current European chemical system has a lack of information of the existing chemicals, which cover today more than 97% of the market. The current chemical system consists of more than 103,800 chemicals, round about 100,000 existing chemicals, so called EINECS (European Inventory of Existing Commercial Chemical Substances) and 3,800 "new chemicals", ELINCS (European List of Notified Chemical Substances). The impact on human health and environment of the EINECS chemicals has not been yet checked until today. REACh should close this gap by fulfilling the protection of human health and environment, the increase of transparency throughout the whole chemical supply chain, the transfer of responsibility from public authorities to the chemical industry, a harmonized system for EINECS and ELINCS, the substitution of hazardous substances and last but not least the avoiding of animal tests.

All actors along the European chemical supply chain have duties and responsibilities under REACh. Any European producer who manufactures a substance on its own, in preparations or articles in quantities of one tonne or more per year within the European Community is obliged to submit a registration dossier to the Agency. The polymers are exempted from REACh, but the monomers have to be registered. In case that a European manufacturer or agent imports chemical substances, formulations or articles in quantities of one tonne or more per year in the European Community, he has also to register under REACh.

In cases where substances/preparations/monomers are produced or imported in quantities of ten tonnes or more per year, the manufacturers or importers have to conduct a chemical safety assessment (CSA) and to create a chemical safety report (CSR). If manufacturers/importers are producing/importing hazardous substances/preparations, the manufacturers/importers have to create additionally an exposure scenario (ES). To ensure the safe use of chemical substances/preparations, downstream users are obliged to inform the producer/importer about the application and working conditions, so that the manufacturer/importer can create an individual chemical safety report or respective risk management measures. In case that a manufacturer will not add an application of one of his downstream users to his CSR, the downstream user has to register by himself under REACh. In case that the market participants will not fulfill the duties under REACh the consequence can be summarized with Art. 5 of the REACh Regulation: "No data, no market"!

At first view the Regulation´s definition may give the impression that REACh applies only to chemical raw materials and the chemical industry, but REACh´s impact is much larger. The next concrete example should demonstrate this. A producer of chemical raw materials supplies barium sulfate to a formulator. This formulator produces a formulation for coatings, which is sold to downstream users like the automotive industry, plastic industry, textiles, electronics etc. Each of the mentioned down-stream

users integrates the supplied formulation again in diverse applications and product lines. The intermediate or end product is again determined for the local market (European) but also for the export and therefore if some chemical raw materials will not be registered under REACh the whole supply chain has to be examined. Alternative suppliers (EU and Non-EU producers), substitutions of chemical raw materials or even new formulations have to be taken into account.

Although REACh is a European Regulation the consequences will be global. REACh will cause enormous costs, which have to be considered as an investment for future business. In case that the predicted REACh costs will surpass the margin, the result of a cost-benefit analysis will be: no registration. This means immediate streamlining of the product portfolio. A progressive streamlining of the product portfolio would happen in the case that a product will be registered, but the price increase is so high that it will cause a significant decrease in demand. A restructuring of the product portfolio would have dramatic consequences for many industry sectors all over the world – as it is primarily low volume specialties that are the engine for innovation (Research & Development).

Non-European producers have to ensure their business in Europe by choosing the right option for the registration. Non-Community manufacturers cannot register their substances/formulations/articles directly as REACh is a European Regulation and the obligation under REACh should primarily apply to European actors. There are three options for Non-European producers:

1. Importer
2. Legal Entity
3. Only Representative

In case that the importer will take care of the registration under REACh, the Non - European manufacturers have to take into account that the importer who will register will be the owner of the registration no. Then the Non-European manufacturer is completely dependent on his agent and cannot appoint another one. The second aspect is that the importer, who has registered a substance under REACh can use another supplier (if the substance identity is the same) and the first supplier, here the Non-European producer will be out of the market.

The second option which can be used by Non-European producers to maintain their business in Europe is a “legal entity” within Europe. A legal entity could be a daughter company in Europe, which could take over the responsibility for the pre-registration and the registration. Nevertheless resources and know-how are needed for REACh and as the REACh time schedule is quite short the know-how could not be first build up but has to be promptly available. Last but not least the Regulation offers Non - European producers a third option to ensure their business in Europe, namely to appoint a natural or legal person, so called "only representative" (Article 8) to fulfill their obligations under REACh. The advantage of an "only representative" is the flexibility and the independence which Non-European manufacturers maintain as they will own the registration no. An additional advantage is the higher protection of sensitive information – like Intellectual Property - and thus better control of know-how. By the way the Non-European producer can profit from an anonymous appearance in SIEF and consortia. EU manufacturers or EU importers can also appoint a fully responsible "third-party representative" to comply with the obligations under REACh.

REACh will definitely have important business effects: product portfolios – not only within the chemical sector – will be restructured, production locations may be shifted and REACh will have a significant influence on financial figures. In future the commercial due diligence for any Mergers & Acquisitions project will also comprise a REACh check of the whole company. The conclusion: REACh is a European Chemicals Regulation with global intersectoral consequences.

Journal of Business Chemistry

Research Section

Patterns of collaboration along the bio-pharmaceutical innovation process

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Literature has widely acknowledged that creating a tight network of collaborations is an unavoidable strategy for innovative biotech firms. However, few contributions have focused so far on how collaborations along the bio-pharmaceutical innovation process are organised in practice. The paper attempts to cover this gap by investigating, on a large empirical base which covers the years 2000-2005, the adoption of different organisational modes of collaboration in the bio-pharmaceutical industry. A framework of analysis, identifying the relationship between organisational modes and the phases of the drug discovery and development process, has been developed and assessed in the industry. This has allowed to disclose the determinants of adoption of different organisational modes of collaboration and their relationship with the typology and size of partners involved. In this respect, the paper also contributes to the ongoing debate about Open Innovation, examining its organisational implications.

Introduction

The advent of biotechnology in the '80s deeply revolutionised the R&D and innovation process in the pharmaceutical industry. In contrast with the traditional "monolithic" approach centred on chemical pharmacology, biotechnology requires the capability to handle and integrate a number of scientific disciplines and technologies, e.g. genetics, immunology, biochemistry, general medicine, computer science, physics and optical science (Byerlee et al., 1999; Powell, 1998). This had two major, although strictly interrelated, effects: on the structure and the division of labour within the pharmaceutical industry, as well as on the management and organisation of the bio-pharmaceutical innovation process.

On the one side, the advent of biotechnology paved the way for the birth and proliferation of new biotech companies, highly specialised on few scientific disciplines and focused on the development of a very narrow set of technologies (e.g. bioinformatics, High-Throughput-Screening), or committed to specific tasks (e.g. screening, lead optimisation) of the revolutionised innovation process, which is still undertaken in large part within the boundaries of established pharmaceutical firms (Chiaroni et al., 2008; Chiesa, 2003; Malerba and Orsennigo, 2002; Muffatto and Giardina, 2003).

On the other side, for both small biotech firms and traditional pharmaceutical companies, it became hardly impossible to effectively and efficiently manage the whole innovation process within their own boundaries, because of the high number of scientific and technological competencies to be contemporarily mastered. As a result, building a network of inter-organisational R&D collaborations that acts as a coordination means among different actors (e.g. new biotech companies, established pharmaceutical firms, but also universities, research centres, science parks), each contributing to the innovation process with its own competencies and technological assets, turned out to be a strategic imperative (Chiesa and Toletti, 2004; Niosi, 2003; Powell et al., 1996). In

recent years, partially as a consequence of the globalisation of markets and the increasing diffusion of biotech applications, R&D collaborations along the bio-pharmaceutical innovation process have gained further momentum and nowadays they represent one of the key drivers of industry growth (Baum et al., 2000).
As a result, literature has widely investigated the topic from several different, although complementary perspectives (Deeds and Hill, 1996; Dussauge and Garrette, 2000; Gulati, 1998). This paper contributes to this stream of research, focusing on biotech firms operating in the pharmaceutical industry by empirically analysing: (i) the extent to which biotech firms adopt collaborations in the drug discovery and development process; (ii) the organisational modes selected for these collaborations; (iii) the type of external partners involved; (iv) the evolution of the organisational modes and of the type of external partners along the different phases of the bio-pharmaceutical innovation process.
This paper is believed to add also to the recent debate on Open Innovation (Chesbrough, 2003; Chesbrough et al., 2006; West et al., 2006). In particular, it is one of the few contributions, to the best of our knowledge, that provides some insights on the degree to which biotech firms conform to the Open Innovation philosophy, studying their attitude to exploit collaborations with external partners, and on the different organisational modes through which the Open Innovation paradigm is implemented.
The paper is structured as follows. The next section briefly reviews the literature on R&D collaborations in the bio-pharmaceutical innovation process and the Open Innovation model, whereas the third part describes the research strategy adopted in the paper. The fourth section reports and discusses the results of the empirical analysis; finally, some conclusions and future directions of research are outlined.

Collaborations in the bio-pharmaceutical innovation process and Open Innovation: a literature review

R&D collaboration can be defined as the practice through which a firm establishes a relationship with an external organisation with the purpose of improving the performance of its R&D processes (Chiesa and Toletti, 2004). Literature has widely acknowledged that the creation of a tight network of R&D collaborations with a range of external partners is an unavoidable strategy for innovative companies in the bio-pharmaceutical industry (Barbanti et al., 1999; Fontes, 2003; McKelvey et al., 2003; Niosi, 2003; Powell et al., 1996; Salman and Salves, 2005). The development of a novel drug according to the new biotech-based R&D process requires, indeed, the convergence of many sources of knowledge and skills. Therefore, networks of collaborations turn out to be an effective means of industrial organisation along this complex R&D process.
As a result, scholars have claimed that the formation of strategic R&D collaborations is a key factor explaining the survival and growth of smaller biotech firms (Audretsch and Stephan, 2001; Niosi, 2003) focusing either on the development of supporting technologies or on specific tasks of the whole R&D process. At the same time, however, strategic R&D collaborations also explain the growth of large "traditional" pharmaceutical companies. Establishing a network of collaborations with innovative biotech firms, large pharmaceutical companies have succeeded in facing the challenges of the socalled "biotech revolution" and in keeping their dominant position in the industry. Moreover, as suggested by Powell et al. (1996), in the bio-pharmaceutical industry this network of collaborations increasingly involves partners different from biotech or pharmaceutical companies, such as universities, public research laboratories and private investors.
In recent years, there has been an unprecedented growth in strategic R&D collaborations in high technology, and especially science-based industries. This trend is particularly evident in biotechnology, as shown by practitioners and consulting companies operating in this field (Burrill&Company, 2005; Ernst&Young, 2004; Ernst&Young, 2005; Ernst&Young, 2006).
As a result, several scholars have been investigating the topic, covering a wide array of aspects. The largest part of the contributions on collaborations in the bio-pharmaceutical innovation process focuses on: (i) the impact of collaborations on the innovative performance of the focal firm (Baum et al., 2000; Deeds and Hill, 1996; Gulati, 1998; Lerner et al., 2003); (ii) the impact of collaborations (and particularly of in-licensing) on the productivity of large pharmaceutical companies (Laroia and Krishnan, 2005); (iii) the role of partners' complementarity of assets (resources, capabilities, or knowledge competences) on the forms selected for collaborations (Helfat, 1997; Liebeskind et al., 1996); (iv) the reasons for success and failure in R&D collaborations (Dussauge and Garrette, 2000; Lane and Lubatkin, 1998).
Although this body of literature is extensive, relatively scarce attention has been paid so far to the problem of how R&D collaborations along the bio-pharmaceutical innovation process are orga-

nised in practice. In particular, literature shows that a wide spectrum of organisational modes can be adopted for R&D collaborations, ranging from mergers & acquisitions, through joint ventures, alliances and outsourcing, to licensing agreements (Chiesa, 2001). Nevertheless, no systematic attempt has been made to empirically evaluate the extent to which biotechnology firms use these alternative organisational modes, and whether some sort of specialisation along the stages of the bio-pharmaceutical innovation process is in place. Furthermore, the typology of partners with which biotechnology firms collaborate in the different phases of the innovation process has been the subject of sparse research, too, although it seems a critical determinant of a collaboration's success (Chiesa and Manzini, 1998). These issues will be dealt with at length in this paper.

As pointed out in the previous section, this paper is believed to contribute also to the ongoing debate on Open Innovation, the new paradigm for the management of innovation which conceives the firm as an open system that purposefully and systematically leverages the resources of external organisations in order to support the generation and exploitation of its innovative capabilities (Chesbrough, 2003). Academic and managerial research on this topic has been extensive (for an up-to-date bibliography on this issue see the web site: http://www.openinnovation.net); nevertheless, an important gap can be identified that is relevant in the light of the objectives of this paper, i.e. the scarce attention dedicated to the organisational and managerial implications of this new model.

It should be noted in fact that the Open Innovation paradigm, as discussed by Chesbrough and colleagues, has a very general nature, since it basically captures the underlying logic at the roots of most innovative firms' choices in the area of technology management. However, companies that are willing to implement the Open Innovation "philosophy" need to select specific organisational modes through which they can leverage their knowledge-abundant external environment. The choice of how to organise the firm's R&D collaborations is one of these critical implementation issues. Scholarly literature has not addressed this topic systematically and in-depth so far, besides a few attempts to discuss the most appropriate intellectual property strategies (Chesbrough, 2003) and performance metrics (Chesbrough, 2004) for supporting Open Innovation, or to study the criteria affecting the choice of the governance mode for external technology sourcing (van de Vrande et al., 2006). Moreover, anecdotic evidence is available about how most innovative and successful enterprises have been managing and organising their transition towards Open Innovation. For instance, Huston and Sakkab (2006) describe the different types of networks and the strategic planning process which are at the heart of Procter & Gamble's Open Innovation approach, which is called "Connect & Develop"; Kirschbaum (2005) explains how the multinational life cycle and performance materials company DSM has built a teamwork and entrepreneurial culture for opening up its innovation process. Nevertheless, a structured theory of the managerial and organisational enablers of the Open Innovation paradigm has not yet been developed.

This paper will help make a step further in this direction. Studying the adoption of different organisational modes for R&D collaboration in the biotech industry, it will contribute to disentangle the issue of how firms practically implement the Open Innovation paradigm. Adopting the taxonomy suggested by Chesbrough and Crowther (2006), we will distinguish between two different types of inter-organisational relationships, according to the purpose for which they are established: (i) "inbound organisational modes" (e.g. licensing-in, acquisitions, R&D contracts and research funding, alliances), which have the purpose to access technical and scientific competences owned by external partners for improving the focal firm's innovation performance; (ii) "outbound organisational modes" (e.g. licensing-out, spinning-out of new ventures, provision of technical and scientific services), which have the purpose to commercially exploit technological opportunities developed within the focal firm.

Finally, although the paper is primarily focused on the issue of R&D collaborations organisation, it is one of the few literature contributions (Fetterhoff and Voelkel, 2006) that provides some empirical evidence of the adoption of the Open Innovation paradigm in the bio-pharmaceutical industry. This gap in the existing literature about Open Innovation is relevant since the biotechnology, and especially the bio-pharmaceutical industry, show several characteristics that make them a fertile ground for the diffusion of Open Innovation and hence for the study of the latter's managerial and organisational implications. In this respect, it is worth remembering its extraordinary technology intensity (DeCarolis and Deeds, 1999), the complexity of the innovation process and the heterogeneity of the competences it requires (Powell et al., 1996), the pivotal role in the development of the industry of technology transfer

mechanisms (Madhock and Osegowitsch, 2000), the intensity of relationships between biotech firms, universities and research centres (Owen-Smith et al., 2002) and the birth of a venture capital market, at least in Anglo-Saxon countries, specialised in supporting biotech ventures (Powell et al., 2002).

In conclusion, this brief literature review highlights the potential relevance of the managerial and research implications of this paper, both in respect to the traditional literature about collaborations in the biotechnology industry, as well as to the recent debate on Open Innovation.

Research methodology

In order to achieve the objectives of this paper, a two-step research strategy has been adopted. The first step aims at developing a reference framework to identify the critical "inbound" and "outbound" organisational modes and their relationship with the different stages of the bio-pharmaceutical innovation process. The framework, taking into account the peculiarities of innovation activities undertaken by biotech companies, allows supporting the subsequent empirical analysis. In the second step, the framework was applied to a longitudinal empirical data set, in order to test its initial validity.
As far as the first step of the research is concerned, a panel study was organised, involving 20 people (business development managers, R&D directors, chief executive officers of biotech companies, as well as academics and consultants with a significant experience in the field) among the most representative companies of the Italian biotech industry. The full list of participants in the

Table 1 List of participants in the panel study (*)

Organisation	Position
Amgen	Corporate Affair Director
Assobiotec – Italian association of biotech companies	Director
ATA – Advanced Technology Assesment	Life Science Senior Consultant
Axxam	Chief Executive Officer
Bioindustry Park Canavese	Business Development Manager
Bioxell	Chief Executive Officer
Blossom Associates	Chief Executive Officer
Ernst&Young	Senior Industrial Specialist Health Sciences
Gentium	Chairman and Chief Executive Officer
GlaxoSmithKline	Manager
MolMed	Business Development Manager
MolMed	Chief Executive Officer
MolMed	Director R&D
Newron	Chief Executive Officer
NicOx	Chief Executive Officer
Roche	Head of External R&D Policy
Siena Biotech	Chairman and Chief Executive Officer
Toscana Life Sciences	Business Development Manager
Università degli Studi di Milano	Director of the Department of Pharmacological Sciences
Università degli Studi di Milano-Bicocca	Full Professor of the Department of Biotechnology

(*) The names of the participants in the panel study have been blinded for confidentiality reasons.

panel study is reported in Table 1.
Two rounds of interviews were conducted directly by the authors. Each round allowed to accomplish a main task, respectively: (i) to share and validate a model of the actual sequence of phases that constitute the whole drug discovery and development process in the bio-pharmaceutical industry; (ii) to identify, for each of the above phases, which of the organisational modes identified by the literature are more suitable to be implemented by biotech firms. The determinants of each choice have been discussed and related to the characteristics and peculiarities of the biotech industry.
As a whole, the panel study allowed the authors to develop a framework for investigating the "inbound" and "outbound" organisational modes adopted by biotech firms for collaborating with external partners.
In the second step of the research, we selected the first 20 pharmaceutical biotech firms worldwide (considering their market capitalisation at the end of December 2006, Table 2) and, for each company, we documented the organisational modes they used in the various phases of the drug discovery and development process as well as the type of external partners they collaborated with. Some further details on the empirical investigation are provided below concerning (i) the selection of the sample, (ii) the time period covered in the analysis, (iii) the type of data collected, and (iv) the data sources.
First, it is worth mentioning that the selection of the top 20 biotech firms in terms of market capi-

Table 2 List of companies in the sample

Name	Market Capitalisation 29th December 2006 ($billion)
Genentech	85.8
Amgen	85.7
Gilead Sciences	32.0
Celgene	19.8
Genzyme	17.7
Biogen IDEC	17.7
Serono	12.7
Medimmune	7.9
Elan	5.8
Amylin Pharmaceuticals	5.6
Vertex Pharmaceuticals	5.0
Cephalon	4.8
Millennium Pharmaceuticals	3.6
ImClone Systems	2.7
PDL BioPharma	2.6
Human Genome Sciences	1.7
MEdarex	1.7
Alkermes	1.6
BioMarin Pharmaceuticals	1.6
MGI Pharma	1.5

talisation is consistent with the purpose of the paper. This is true for a twofold reason: on the one side, companies listed on public stock exchange markets also have to disclose information about their R&D activities, thus allowing to access relevant information about their collaborations; on the other side, firms in the sample represent the top players in the industry and are therefore more suitable to highlight relevant trends and best practices in the management of innovation processes. The time period chosen for the analysis covers the years from 2000 to 2005, attempting to balance the relevance for the research objectives of the collected information with the efficiency of procedures for data gathering. Furthermore, it should be noted that the year 2000 represents in almost all the cases the starting point of documentations and archival records for the firms in the sample. Collected data concern:

- the number and typology of different organisational modes for collaborations (as identified in the research framework developed through the panel study) adopted by the firms;
- the phase of the drug discovery and development process to which each of the above modes refers;
- the typology of partners involved. In this case, we classified external partners along two dimensions: (i) type of organisation (i.e. pharmaceutical firms, biotech firms – further distinguished into product and platform firms, according to the well known taxonomy (Chiesa and Chiaroni, 2004), universities and research centres); (ii) size (i.e. small-medium and large firms)[1];
- the therapeutic area (where applicable and following the classification proposed by the Biotechnology Industry Organisation) within which the object of the collaboration can be classified (i.e. the target disease of a new drug).

As primary source of data, the annual reports of the selected firms in the time period 2000-2005 were analysed. Nevertheless, in order to verify the gathered data, they have been triangulated with information drawn from professional databases and reports (Recombinant Capital, Biospace Directory, Canadian Biotech).

As far as the reliability of the data is concerned, it should be highlighted that, for the purpose of the paper, the identification of general trends is far more relevant than the completeness of the information for each single firm. Indeed, even if the completeness might be ensured by the fact that firms in the sample are listed on public stock exchanges, it is anyhow reasonable to expect that if there are omissions they are rather equally distributed in the sample, thus not affecting the results of the analysis. Nevertheless, it is clear to the authors that achieved results have to be further validated on a larger empirical base in order to prove their statistical relevance.

Patterns of collaboration in biotech

In this section of the paper the results of the empirical investigation are presented. Specifically, the next paragraph describes the framework of analysis developed through the panel study. In the second part of the section, the outcome of the longitudinal inquiry is discussed at length.

Patterns of collaboration in biotech: framework of analysis

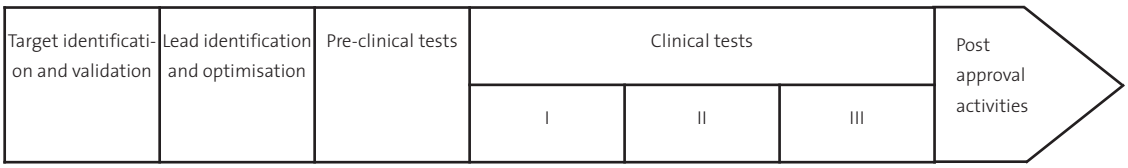
During the first round of interviews, participants in the panel study were first asked to discuss the structure of the drug discovery and development process in the bio-pharmaceutical industry, as it is reported in the literature (Chiaroni et al., 2008; Chiesa, 2003; Chiesa and Chiaroni, 2004; Gassmann and Reepmeyer, 2005; Muffatto and Giardina, 2003). The purpose was to reach a consensus about the number and the content of the phases to be included in the framework for the subsequent analysis of collaborations. The structure of the process suggested by the panel of experts is reported in Figure 1.

A brief description of the phases comprised by the framework follows:

- target identification and validation. Target identification has the purpose to identify a gene or a protein or a sequence of both (target), which is thought to be the pathogenic of a selected disease. Target validation, which follows immediately, concerns the study of the identified target with the purpose to: (i) define the interactions between the target and the whole human organism; (ii) check if there are intellectual property rights already claimed regarding the identified target, e.g. through accessing public databases like NCBI in the US;

1) We used and purposefully adapted the criteria suggested by the EU (European Commission Recommendation, 2002) for classifying firms on the basis of their size. Specifically we classified a company as: (i) small-medium, if the number of workers is < 250 and the revenues € 50 m; (ii) large, if the number of workers is > 250 and the revenues > € 50 m. These criteria obviously do not apply to universities and research centres.

Figure 1 Structure of the drug discovery and development process in the biotech-pharmaceutical industry for subsequent analysis



- lead identification and optimisation. After assessing the genetic base of the disease's evolution, scientists need to identify the compound that has the desired effects in treating the selected disease (lead identification). This compound actually represents the active principle of the future drug. The lead optimisation activity, finally, adds to the lead the necessary excipients (i.e. substances included in the drug formulation) in order to protect, support or enhance the stability of the active principle and to increase patients' compliance;
- pre-clinical tests. This activity studies, especially through in vivo testing, the mechanisms of absorption, distribution, metabolism, excretion and toxicology of the new drug, with the purpose to evaluate its effects on animals. Before entering clinical trials, a first approval by public authorities is required;
- clinical tests. These trials directly involve human patients and are usually divided into three steps: phase I, phase II and phase III. In phase I, researchers test the new drug in a small group of healthy people (20-80) to evaluate its safety and to determine a safe dosage range. In phase II, the new drug is tested on a larger group of people (100-300) affected by the target disease to evaluate its effectiveness in patients and to determine the common short-term side effects and risks. Finally, the phase III involves an even larger group of patients (1,000-3,000) to confirm the effectiveness of the new drug and to evaluate its overall benefit-risk relationship. If all the three phases are successful, public authorities have to approve the new drug to allow it to be marketed;
- post-approval activities. These comprise the purchasing, production, logistics, marketing & sales and post-marketing tests for the new drug. In particular, post-marketing tests involve the monitoring of the drug's performance along its whole life-cycle, with the purpose to delineate additional information on its risks, benefits and optimal use in the middle-term.

In the second round of expert interviews, the "inbound" and "outbound" organisational modes of collaborations were discussed, with the purpose to spot which specific modes are used by pharmaceutical biotech firms along the different phases of the development process. The interviewed managers recognised that "inbound" organisational modes take place mainly in the preclinical phase of the drug discovery and development process, i.e. target identification and optimisation, lead identification and validation and pre-clinical tests. In other words, it is chiefly on these stages that biotech companies get into contact with external organisations for leveraging their innovation efforts and accessing their highly specialised knowledge and competences. Instead, "outbound" organisational modes take place mainly in the second part of the process, i.e. in the clinical tests and post-approval activities. It is in these stages, in other words, that biotech firms generally collaborate with external organisations for commercially exploiting the results of their own innovation activities. This suggests the possibility to distinguish between two distinct macro-phases in the pharmaceutical biotech drug discovery and development process, called "generation" of innovation - where inbound organisational modes of collaboration prevail - and "exploitation" of innovation - where outbound organisational modes are mainly present (Figure 2).

The separating point between the generation and the exploitation macro-phases was identified at the transition from pre-clinical to clinical tests. Because of the intrinsic characteristics of the biotech innovation process, in fact, it is only at the end of pre-clinical tests that drug candidates acquire the properties that allow them to be commercially exploited. Before this point, the drug discovery and development process is mainly a "trial-and-error", internal effort characterised by extreme uncertainty and unpredictable outcomes. Once the first approval by the public authorities is obtained, at the end of pre-clinical tests, development risk is lower: the process becomes

Figure 2 Generation and Exploitation of innovation in the pharmaceutical biotech drug discovery and development process

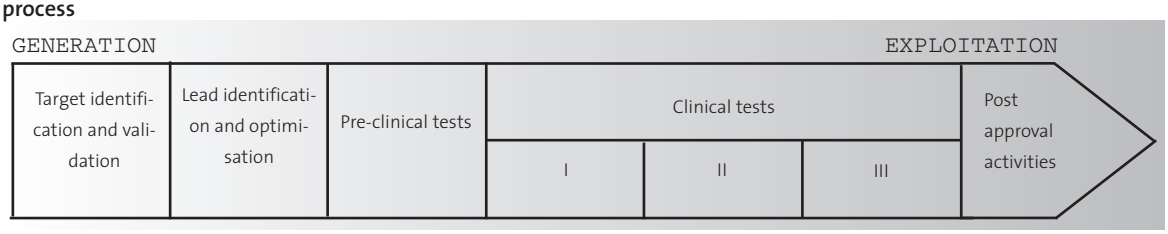
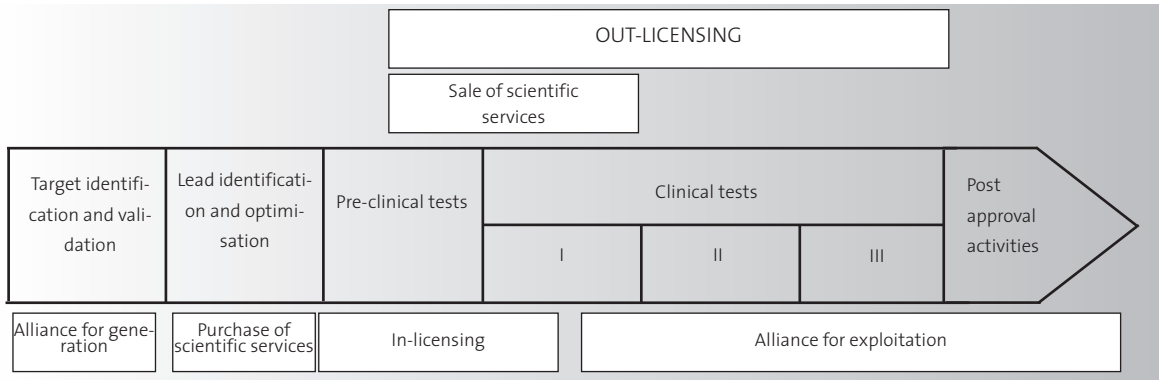


Figure 3 Organisational modes of collaboration and their position along the phases of the drug discovery and development process



much more formalised and externally visible. At this point, therefore, actual possibilities for external commercial exploitation can be identified and pursued. Nevertheless, interviewed managers recognised a certain degree of overlapping between the generation and exploitation phases (Figure 2). This is due to the fact that, according to the characteristics of the drug under development: (i) commercial exploitation sometimes can start earlier than the end of pre-clinical tests (e.g. out-licensing of a candidate that has not completed these trials yet); (ii) the leverage on the innovative efforts of other organisations can continue beyond this limit (e.g. in-licensing of a candidate that has already completed phase I of clinical tests).

Finally, the interviews allowed identifying the specific organisational modes that pharmaceutical biotech firms use to collaborate along the phases of the drug discovery and development process:

Organisational modes of collaborations for the generation of innovation:

- alliance for the generation of innovation. In this case the biotech firm establishes a partnership (without equity involvement) with other biotech firms, pharmaceutical companies, universities or other research centres, in order to pursue a common innovative objective (e.g. the validation of a genetic target);
- purchase of scientific services. The biotech firm externalises a specific phase of its innovation process to a specialised provider (e.g. the lead optimisation activity), under a well-defined contractual agreement (for further details on the role of technical and scientific services in the biotech industry see Chiaroni et al., 2008);
- in-licensing. The biotech firm acquires the right to use a specific drug candidate from another biotech firm, a pharmaceutical company or a university.

Organisational modes of collaboration for the exploitation of innovation:

- alliance for the exploitation of innovation. In this case the biotech firm partners with another company (a biotech firm or, more often, a big pharma) for accessing some complementary assets (e.g. production capacity or distribution channels) required to commercially exploit the new drug;
- supply of scientific services. The biotech firm provides third parties (typically, other biotech firms) with technical and scientific services that leverage the outcome of its discovery efforts;
- out-licensing. The biotech firm licenses out, usually to other biotech or pharmaceutical companies, the right to use a new drug candidate that it has discovered and developed.

Figure 3, according to the results of the panel study, schematically describes the specific pha-

ses of the pharmaceutical-biotech drug discovery and development process in which these organisational modes of collaborations prevail.
The next section reports and discusses the results of the longitudinal analysis, that was undertaken applying this framework.

Patterns of collaboration in biotech: evidence from the empirical analysis

The analysis of the data of the top 20 pharmaceutical biotech firms leads to interesting results concerning the patterns of collaboration in the bio-pharmaceutical industry.
First of all, it is possible to highlight a general trend (as reported in Table 3) analysing the evolution of the number of times in which organisational modes of collaboration have been adopted by firms in the sample.

The number of items recorded in the sample, 794 in total with an average for each firm of nearly 40, is significant and demonstrates, supporting the results of the extant literature on the field, the relevance of collaborations as a mean for biotech companies to sustain their business. Moreover, if the number of collaborations is assumed as a rough measure of the openness of the innovation process (as it indeed represents the number of actors involved in the biotech firm's innovation network), the above mentioned empirical results support also the hypothesis that the biotechnology industry (and in particular the biopharmaceutical industry) is a fertile ground for the adoption of the Open Innovation paradigm.
However, it should be noticed that the trend declines from 168 items in 2000 to 113 items in 2005. As far as the determinants of this trend are concerned, at least the following two can be highlighted: (i) the impact of the overall economic context, with the blow up of the Internet (and high tech) bubble in the year 2000 and the economic downturn following terrorist attacks in 2001, reducing the availability of financial resources for biotech firms; (ii) the progressive evolution towards the maturity stage of some basic technologies (e.g. gene mapping and analysis, production of monoclonal antibodies). The former point implies an overall reduction of the innovative effort (and therefore of the number of collaborations) by biotech firms that are constrained by limited resources. The latter point implies, on the one side, the increasing concentration of the supply with a lower number of organisations offering those technologies and, on the other side, a push for larger product biotech firms towards internalising mature technologies into their own boundaries. In both cases this results in a reduction of the number of times in which firms look at external organisations to complement their internal assets and competences.
A further step of the analysis concerns the evo-

Table 3 Total number of organisational modes of collaboration by year

Organisational modes of collaboration Number per year (%)	2000	2001	2002	2003	2004	2005
Generation of innovation	97 (57.7%)	85 (62.0%)	71 (59.2%)	79 (63.7%)	85 (64.4%)	76 (67.3%)
Exploitation of innovation	71 (42.3%)	52 (38.0%)	49 (40.8%)	45 (36.3%)	47 (35.6%)	37 (32.7%)
Total	168	137	120	124	132	113

lution of the organisational modes of collaboration in the two identified macro-phases of generation and exploitation of innovation. Table 3 shows the clear prevalence of organisational modes of collaboration in the generation phase. They account, indeed, on the whole sample for nearly 62%, with a growth over the time period considered, from nearly 58% in 2000 to more than 67% in 2005. This implies a clear tendency of biotech firms in cooperating with external organisations in their innovation process and particularly in the generation phase, where the quest is more relevant for innovative products (and enabling technologies) able to support the business development of top players. As a consequence, the relative weight of organisational modes of collaboration in the exploitation phase declines in the time period considered, from more than 42% in 2000 to nearly 33% in 2005.

Table 4 presents in more detail the different modes of collaboration in the generation and exploitation phases of innovation. First of all, it is possible to highlight the relative weight (among the modes for the generation of innovation) of in-licensing, which increased from 18.6% in 2000 to more than 30% in 2005. It is interesting to notice that this growth is mostly due to a substitution of alliances with in-licensing agreements. Top players in the industry, indeed, operating as product firms (i.e. developing new drugs), have to continuously fill their product pipelines in order to remain competitive in the market and to sustain their growth against traditional pharmaceutical firms. As far as biotech firms grow and are

Table 4 Organisational modes of collaboration by typology and by phase

Organisational modes of collaboration Number per year (%)	2000	2001	2002	2003	2004	2005
Generation of innovation						
Alliances	54 (55.7%)	41 (48.2%)	30 (42.3%)	28 (35.4%)	34 (40.0%)	28 (36.8%)
Purchase of scientific services	25 (25.8%)	25 (29.4%)	23 (32.4%)	25 (31.7%)	31 (36.5%)	25 (32.9%)
In-licensing	18 (18.6%)	19 (22.4%)	18 (25.4%)	26 (33.0%)	20 (23.5%)	23 (30.3%)
Exploitation of innovation						
Alliances	34 (47.9%)	25 (48.1%)	17 (32.1%)	12 (29.3%)	23 (48.9%)	21 (56.8%)
Supply of scientific services	11 (15.5%)	13 (25.0%)	4 (7.6%)	2 (4.9%)	3 (6.4%)	3 (8.11%)
Out-licensing	26 (36.6%)	14 (26.9%)	32 (60.4%)	27 (65.8%)	21 (44.7%)	13 (35.1%)

able to use revenues from directly marketed drugs to finance their own R&D activities, they tend to adopt more in-licensing modes. Indeed, in-licensing is relatively more "expensive" than alliances but at the same time allows both to reduce the risk of competencies spill-over and to better protect intellectual property. It also ensures a better control and independence of the biotech firm in the management of the drug discovery and development process. The above remarks are further supported by the fact that the majority of in-licensing (respectively 24%, 15% and 12%) refers to products in major therapeutic areas of oncology, cardiovascular diseases, and central nervous system diseases, where competition with traditional pharmaceutical and other biotech firms is fiercest and where top players actually focus.

As far as organisational modes of collaboration in the exploitation phase of innovation are concerned, it is interesting to notice the relative growth of alliances (mostly co-manufacturing and co-marketing agreements). A suitable explanation for this trend is the increasing need for biotech firms (and particularly for product biotech firms) to expand their geographical coverage to reach customers on a worldwide basis. Alliances, indeed, are mostly (56% on average) signed with pharmaceutical companies, operating with a world-scale productive and distributive capacity.

An interesting up-and-down trend in the average weight can be also recognised in out-licensing (decreasing from nearly 37% in 2000 to more than 35% in 2005, but with peaks of more than 60% in 2002 and 2003). The analysis of out-licensing requires further details on therapeutic areas. In 43% of the cases, out-licensing refers to products in major therapeutic areas (oncology, cardiovascular diseases, and central nervous system diseases), whereas the remaining 57% is distributed in a plethora of minor therapeutic areas (e.g. allergy/immunology, metabolic diseases, infectious diseases, respiratory diseases, genito-urinary diseases). The determinants of the adoption of out-licensing, indeed, are rather different in the two cases. In the former cases, biotech firms adopt out-licensing as a second-best after alliances when they are not able to reach autonomously the market or are unable to find a suitable partner. In the latter cases, on the contrary, biotech firms adopt out-licensing to profit (actually in a typical Open Innovation approach) from products whose development is not coherent with their core business, i.e. with their focus in terms of therapeutic areas.

A final remark on the organisational modes of collaboration for the exploitation phase concerns the declining weight of the supply of scientific services (from 15.5% in 2000 to 8.1% in 2005). This trend is again related to the natural evolution of biotech firms. In their initial stages, they are forced to supply services (particularly technological services) to create a revenue stream able to support R&D activities. Once products reach the market, revenue streams from ancillary activities becomes less relevant and biotech firms tend to concentrate their efforts in the development process of new drugs.

The empirical evidence on the organisational modes adopted by biotech firms along the phases of the drug discovery and development process supports the model developed through the panel study (and shown in Figure 2). Concerning the macro-phase of generation of innovation it is possible to highlight that:

- on average, more than 60% of the alliances for the generation of innovation are concentrated in the phase of target identification and validation. As identified in the model, indeed, in this activity the contribution of external sources of innovation is particularly relevant as they allow biotech firms to complement internal competences in basic research;
- purchase of scientific services is concentrated in the lead identification and optimisation (48%), where it is specifically concerned with the access to technological platforms for lead optimisation. The remaining part refers to clinical tests (mainly to CROs) and, only marginally (7%) to post approval activities;
- in-licensing, that represents the main tool for filling the product pipeline and increasing the rate of introduction of new drugs into the market, progressively shifted in the time period considered from pre-clinical tests (that in 2000 represented nearly 80% of cases) to clinical tests. In-licensing in phase I (and eventually in phase II) of clinical tests represented in 2005 nearly 40% of the cases. In-licensing of products that are in later phases of the process significantly reduces the risks of development. At the same time, however, in-licensing in later phases of the process is more "expensive", as the acquirer usually pays the more the less risky the product is, and therefore only more mature firms are able to use this mode.

Concerning the macro-phase of exploitation of innovation, it is to notice that:

- nearly 50% of the alliances in this phase are related to post-approval activities, where there is a quest for expanding geographical coverage by biotech firms;
- supply of scientific services, even if quite marginal, is concentrated almost only in the preclinical and clinical (phase I) tests, where bio-

tech firms may exploit particularly their technological base to offer support services mainly to other biotech firms;
- in the case of out-licensing, the distinction between products in major therapeutic areas versus those in minor therapeutic areas is clearly related to the phase of the process where out-licensing takes place. In particular, out-licensing for products in minor therapeutic areas concentrates mainly in pre-clinical tests (from 40% in 2000 to nearly 70% in 2005). This reduces the financial effort (and risk) for biotech firms in developing products that are out of their main business scope and, at the same time, allows firms to find an effective way to profit from these products. Out-licensing for products in major therapeutic areas, on the contrary, is even more pursued in the later phases of the process (and particularly in phase II and III of clinical tests, 45% and 23% in 2005 up to 38% and 15% in 2000, respectively), thus highlighting the attempt of biotech firms to increasingly reach autonomously mainstream markets.

Finally, it is possible to analyse the typology of external partners involved in collaborations and their evolution along the different phases of the bio-pharmaceutical innovation process. The concept of "typology" of partners has already been discussed in the third section. However it is worth remembering here that this concept comprises both a qualitative characterisation (distinguishing between pharmaceutical firms, product biotech firms, platform biotech firms, universities and research centres) and a quantitative characterisation (distinguishing between small-medium and large companies). Analysing the organisations with which biotech firms in our sample have established collaborations, the following typologies of partners emerged:
- large pharmaceutical firms. This typology comprises traditional pharmaceutical firms, i.e. those operating in the industry since before the advent of biotechnology with a long tradition in "chemical-based" pharmacology. All pharmaceutical firms found in our database are large firms. This is not surprising, however, and for a twofold reason: on the one side, pharmaceutical firms are on average older and more mature than biotech firms and, on the other side, they represent, in the large majority of cases, the "natural" partner for large biotech firms searching to expand their geographical and/or market coverage. It seems obvious that large pharmaceutical companies fit better with the latter purpose;
- product biotech firms. Product biotech firms are those firms that have as a main business goal the development and marketing of new drugs. These firms are very similar in nature to the top players in the industry and according to their different stage of development, we found product biotech firms that are either of large or small-medium size in our databases. More in particular, 80% of product biotech firms are small-medium companies, whereas the remaining 20% are large companies;
- small-medium platform biotech firms. This typology comprises biotech firms involved in the development of enabling technologies for the drug discovery and development process. It is noteworthy that only small and medium size companies of this typology are found in our database. However, this appears reasonable considering the nature of their business. The large majority of platform biotech firms, indeed, operates on a small scale, offering a set of technologies to product biotech firms in a limited geographical area (usually within an industrial cluster);
- universities and research centres. This typology comprises the other external organisations involved in the process of drug discovery and development.

Table 5 summarises the results of the analysis. In particular, for each organisational mode of collaboration the number of times (measured by the relative percentage) a given typology of partner is involved is reported.

Within the macro-phase of generation of innovation, small-medium companies (and more particular small-medium product biotech companies) clearly prevail, with an average percentage of occurrence of nearly 66%. The reason behind this evidence is the willingness of top players in the industry to sustain their drug development process through accessing most innovative scientific competencies (alliances), technological assets (purchase of scientific services) and products (in-licensing). Small and medium-size companies, indeed, even if usually started around a very innovative and high potential idea, in most cases do not have the financial resources nor the complementary assets needed to sustain on their own the whole process of development. Therefore, they become an attractive partner for larger biotech companies, which can also exploit their bargaining power in setting the terms of the organisational mode of collaboration.

Further on, it is interesting to notice the relatively marginal role played by universities and research centres, which on average account for about 8% of all partners. This may appear to be

Table 5 Organisational modes of collaboration by typology of partners

	Large companies		Small-medium companies		
Organisational modes of collaboration Percentage	Pharmaceutical firms	Product biotech firms	Product biotech firms	Platform biotech firms	Other (universities and research centres)
Generation of innovation					
Alliances	12%	11%	55%	13%	9%
Purchase of scientific services	11%	6%	27%	52%	4%
In-licensing	22%	16%	37%	13%	12%
Exploitation of innovation					
Alliances	33%	25%	29%	9%	4%
Supply of scientific services	35%	15%	45%	4%	1%
Out-licensing	43%	20%	29%	6%	2%

in contrast to a large part of the literature (among others Chiesa, 2004; Malerba and Orsenigo, 2002) claiming the pivotal role of universities and research centres in generating biotechnology innovation and in sustaining the creation of new biotech firms (academic spin-offs). In this case, however, the reason has to be found in the peculiar characteristics of the sample, including only the largest biotech firms. These companies, indeed, prefer to collaborate with other companies, which have already started the process of development of the new product (maybe with an academic origin), rather than with universities and research centres that usually conduct only very basic research. On the one side, this approach reduces the risk of the innovative process (as initial stages of development had already succeeded) and, on the other side, even if more expensive, it is viable for large companies that can exploit financial resources generated from marketed products. In the macro-phase of exploitation of innovation, large companies (particularly pharmaceutical firms) play a pivotal role, representing on average nearly 57% of total partners involved in collaborations. Looking in closer detail at the single rows of the Table 5, it is possible to highlight the following:

- in the alliances for the exploitation of innovation, as already discussed, top biotech industry players mostly need reliable partners to expand their geographical and/or market coverage, through complementing their existing market assets. Large pharmaceutical firms, which usually already operate on a worldwide basis, represent the best solution for this purpose. Otherwise, co-marketing agreements can be signed with other product biotech firms to join forces in distribution and selling activities (large product biotech firms) or to exploit a particular geographical or therapeutic focus (small-medium product biotech firms);
- in the supply of scientific services again the role of large pharmaceutical firms (and more general of large companies) appears to be of relevance. The support by these firms is usually related to clinical tests. It should be noticed, however, that small and medium product biotech firms account for the largest relative share (45%). This is mainly due to the fact that they usually offer pre-clinical tests services to third parties, thus attempting to sustain their research effort with an ancillary stream of revenues. This activity is usually abandoned once business maturity is reached (as the low percentage of large product biotech firms involved demonstrates). Finally, the marginal role of platform biotech firms, usually more focused on technology supply for initial research activities, has to be mentioned;
- in the out-licensing agreements, large pharmaceutical companies gain the "lion's share" still exploiting their competitive advantage (that is however fast eroding) in complementary assets in respect of top biotech industry

players, particularly in major therapeutic areas. Small and medium product biotech companies, on the contrary, are the best partners for out-licensing agreements that involve new drugs for those minor therapeutic areas that fall out of business scope of top industry players.

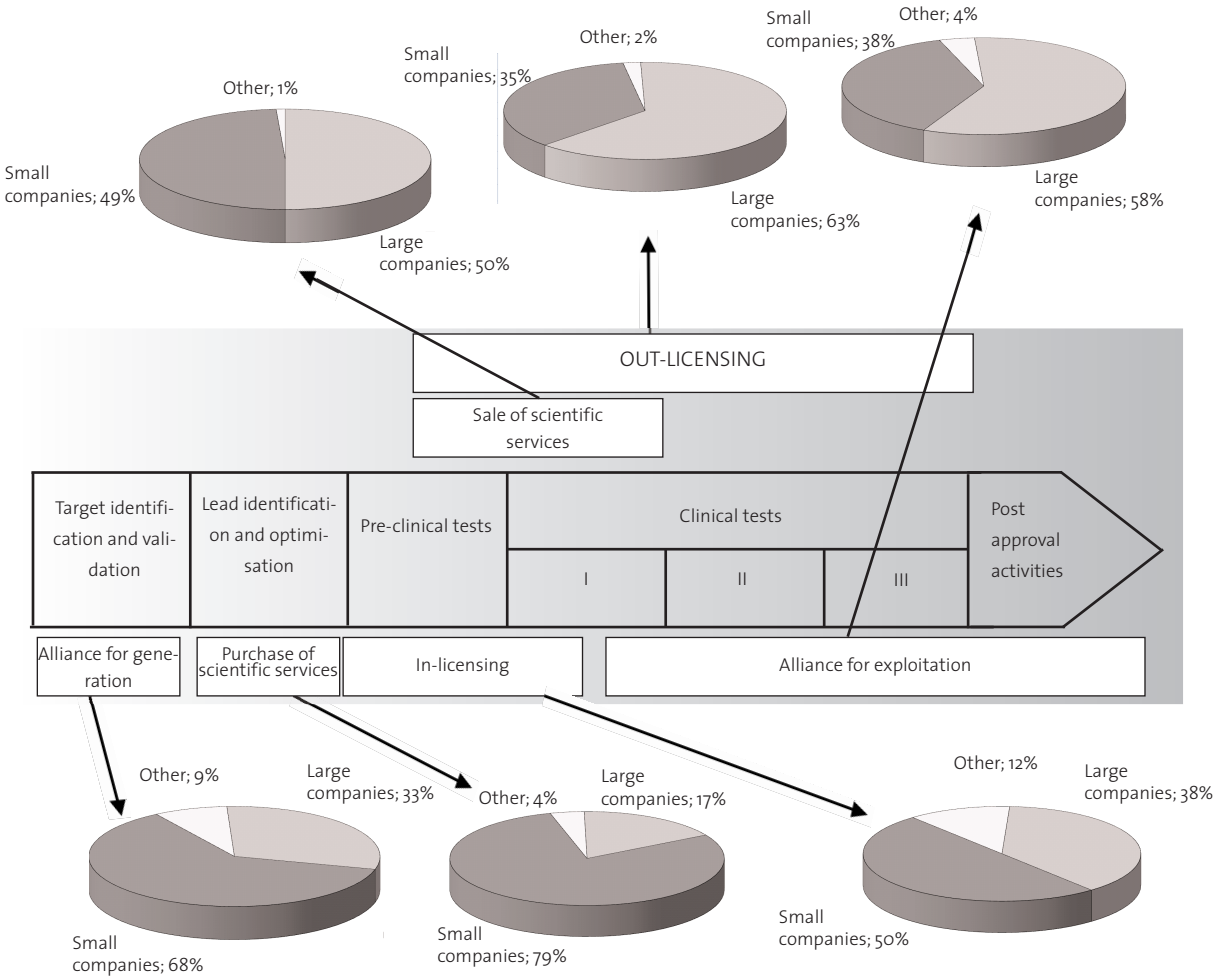
A clear pattern of evolution can be therefore recognised in the typologies of partners involved in organisational modes of collaboration. In the macro-phase of generation of innovation the innovative contribution of small and medium companies (both product and platform firms) is of paramount importance, whereas in the macro-phase of exploitation of innovation large companies prevail exploiting their strength in existing complementary assets. This is consistent with the already discussed evolution of the organisational modes of collaboration in the two macro-phases.

Figure 4 is a comprehensive picture of the results of the analysis and schematically represents the evolutionary pattern. It is worth mentioning that the variety of partners involved, of organisational modes adopted and their evolution along the pharmaceutical biotech drug discovery and development process are a clear example of the adoption in the industry (or at least by its top players) of the paradigm of Open Innovation.

Conclusions

The paper contributes to the on-going debate on the role of collaborations in the bio-pharmaceutical industry. In particular, it systematically and longitudinally assesses the extent and variety of organisational modes of collaboration adopted by biotech firms, the relations among different

Figure 4 Size of partners by organisational modes of collaboration and by phase of the pharmaceutical biotech drug discovery and development process



organisational modes, the phases of the drug discovery and development process, and the typologies of partners involved. Moreover, it represents one of the first attempts to study the adoption of the Open Innovation paradigm in a definite industry.

A framework of analysis has been developed through a panel study, identifying different organisational modes of collaborations and their relations with the phases of the bio-pharmaceutical innovation process. The framework has then been applied to a longitudinal empirical base including data about the collaboration of top 20 worldwide industry players, in the time period 2000-2005.

The results of the analysis allow to initially assess the framework and to discuss the determinants of the adoption of different organisational modes of collaboration and the role of different typologies of partners. In particular, the paper highlights that the peculiarities of the biotech industry (e.g. the articulation of the innovation process and its typical risk pattern, the business focus of biotech firms towards major therapeutic areas, the problems related to the management of IPRs) are crucial to analyse the pattern of evolution of organisational modes of collaboration and also represent the key to understand the typology (and particularly the size) of partners involved in collaborations. The overall picture resulting from the empirical analysis supports the idea that the biotech industry is a clear example of industrial sectors where the Open Innovation paradigm is in place.

Nevertheless some limitations of the research should be addressed in future research. In particular, it is necessary to further investigate whether and how the composition of the sample, which includes only large product biotech firms (i.e. firms developing new drugs), affects the results. It might be possible to argue, e.g. that platform biotech firms are less compelled with the need to fill their product "pipeline" and therefore have a different approach to collaborations, or that smaller firms adopt in- and out-licensing strategies that are different (or even exactly the opposite) from those of large firms.

However, the authors believe this paper represents a valuable basis for future research and managerial discussions in the field.

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Research Section

The spatial dynamics of the European biotech industry- a NEG approach with vertical linkages

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After a period of consolidation, the European biotech industry faces new challenges in the course of increasing internationalization, especially in terms of the EU Eastern enlargement. On one hand, the accession of the new member states opens the emergence of new research, production and sales opportunities. On the other hand, the increasing competitive pressure may imply an essential risk for local biotech firms. Against this background, the paper reviews the potential development of the European biotech industry with respect to its spatial structure. On the first stage, the present industrial situation as object of investigation is described and evaluated with respect to a further model implementation. In this context, the article introduces the findings of an online survey concerning international trade, conducted with German biotech firms in 2006. On the second stage, the results are completed by the outcomes of a numerical simulation within the New Economic Geography (NEG), considering vertical linkages between the biotech and pharmaceutical industries as an agglomerative force. The analysis reveals only a slight relocation tendency to the European periphery, constrained by market size, infrastructure and factor supply. Based upon the findings, the paper concludes with suggestions for economic policy in terms of research and location promotion.

Introduction

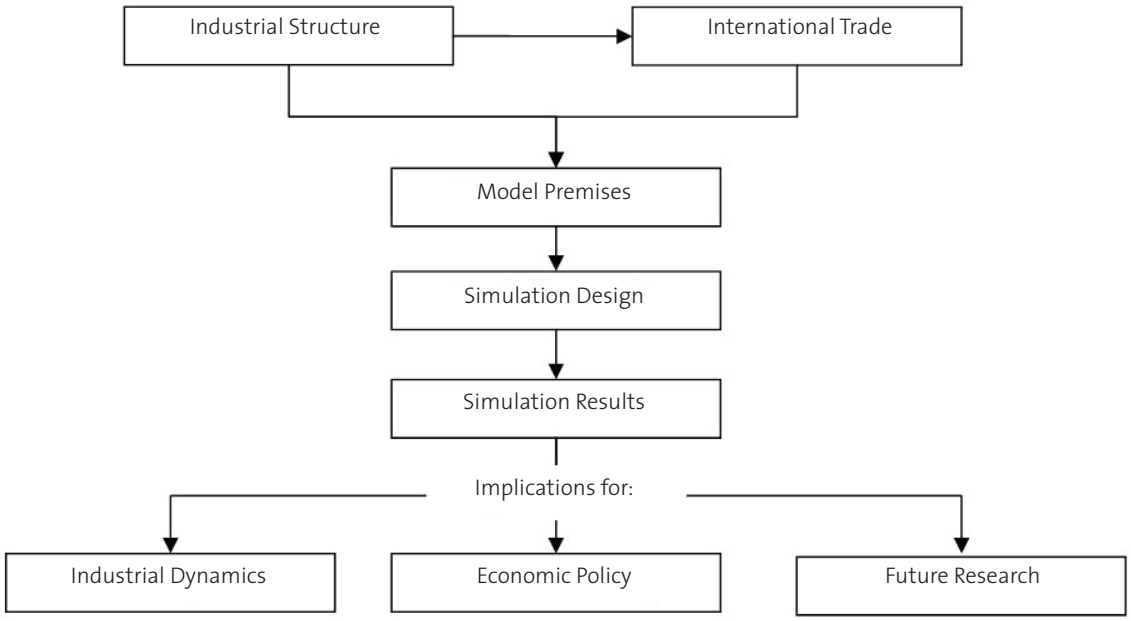
Significant changes in spatial concentration and specialization of European industries accompany the EU integration process. The empirical study of Midelfart-Knarvik et al. (2000) reveals that since the 1970s, medium and high-tech industries have been characterized by increasing dispersion. In this context, the geographical concentration of the pharmaceutical industry shows a particularly sharp decrease: 12% of the production was relocated from Germany and Italy to Denmark, the UK, Ireland and Sweden. Against the background of strong sectoral interdependencies between the biotech and pharmaceutical industries, changes in the economic geography of biotechnology may be expected as well.[1]

In the course of the EU enlargement in 2004, European industries did not only face enlarged sales markets, they also faced alternative production and research locations. In this context, it is debatable if the efforts of economic policy, especially in Germany, France and the UK, to establish a growing biotech landscape are endangered by a potential relocation to acceding countries in Central and Eastern Europe (CEE).[2] This risk appears

1) The term biotech(nology) follows the definition according to the OECD (2005): "The application of science and technology to living organisms, as well as parts, products and models thereof, to alter living or nonliving materials for the production of knowledge, goods and services." Analogously, a biotech company is: "... defined as a firm engaged in key biotechnology activities such as the application of at least one biotechnology technique (...) to produce goods or services and/or the performance of biotechnology R&D (...)".

2) With regard to the diffuse common definition of the term CEE, here it synonymously refers to the EU accession countries only.

Figure 1: Structure and Approach of the Present Article



to be imminent in the light of the dynamic economic growth, increasing foreign direct investments, and increasing hightech exports from CEE countries. In contrast, the acceding countries show substantial deficits in research infrastructure, proprietary developments of products and processes, purchasing power, and in the supply of highly qualified labour.

Against the background of these questions, this paper aims to make a quantitative contribution within this debate addressing on the central issue: To what extent does the EU enlargement have an impact on the spatial formation of the European biotech industry?

Although the location and agglomeration of biotech firms have been analyzed in a wide range of scientific publications, the spatial dynamics of the European biotech industry as a whole appears to be a blind spot against the multitude of country studies.[3] Therefore, this paper aims to make a quantitative contribution using a numerical simulation of a standard model of the New Economic Geography (NEG). In combination with the empirical results of primary and secondary statistics, this approach allows to construct a scenario for the future development of the European biotech geography. This requires a consideration of the industrial structure and determinants of foreign trade.

As the study of Midelfart-Knarvik et al. (2000) demonstrated and intensely discussed in the regional economic literature, the impact of inter-industrial linkages on agglomeration dynamics has significantly increased.[4] In this regard, Central and Eastern European locations attract downstream sectors to an increasing degree. This implies also a stronger relocation of the biotech industry in its essential capacity as an upstream supplier for the pharmaceutical and medical sectors. Therefore, this paper aims to fertilize the discussion of spatial restructuring within the context of sectoral interdependencies between the biotech and pharmaceutical industries.

Figure 1 represents the approach of this analysis. In the first steps, comprised in section 2, the paper provides the analytical base and legitimization of the model assumptions underlying the numerical simulation in section 3. Because of the central importance of the vertical integration of the biotech industry within the pharmaceutical supply chain, the sectoral interdependencies are the focus in characterizing the real object of investi-

3) See for country studies e.g. Cooke (2001) for UK, Corolleur et al. (2003) in the context of France, Dohse (2000) for Germany.

4) See Amiti (1998), Hummels et al. (1998), Markusen and Melvin (1984), Porter (1990) as an exemplary listing of empirical studies concerning vertical linkages.

Table 1: European biotechnology industry (2004), data from EuropaBio (2006)

Country	Firms	Turnover (€ m)	R&D exp. (€ m)	Employees
Austria	44	481	345	2,842
Belgium	84	606	315	3,654
Czechia	63[11]	-	-	-
Denmark	117	5,396	824	18,461
Finland	66	568	91	2,160
France	223	2,197	589	9,142
Germany	572	3,421	1,244	24,134
Greece	5	2	2	131
Hungary	16[6]	38[7]	-	394[8]
Ireland	41	982	277	2,900
Italy	51	286	284	2,654
Netherlands	51	286	284	2,654
Norway	41	81	80	931
Poland	13[9]	180[10]	-	946[11]
Portugal	17	36	8	256
Spain	81	260	214	2,201
Sweden	138	854	367	3,942
Switzerland	90	2,367	795	1,990
UK	457	4,522	1,557	21,134
Total	**2,266**	**67,733**	**9,816**	**101,156**

gation. In the following section, based on the specification of real economic facts of the preceding segment, the paper identifies the structure of international trade within the European biotech industry as a major determinant of its spatial formation.

In this context, the article refers to the results of an online survey, conducted by the department Innovation and Growth of the University of Lueneburg and supported by two major industrial associations.[5] A detailed presentation of the survey results associated with an extensive analysis of the biotech industry and its foreign trade activities are discussed in Kranich (2007) and in a working paper for the survey results (Kranich, 2007).

Based upon the empirically established model assumptions, Section 3 sets up a standard NEG model incorporating vertical linkages(Venables, 1996). This model provides the basis for the simulation study of the EU-15+10 enlargement. Finally, Section 4 discusses the results and draws conclusions for: i) potential industrial development paths; ii) economic policy in terms of location and research promotion; and iii) for further research concerning the spatial dynamics of the European biotech industry.

The European Biotech Industry

Industrial Structure and Vertical Integration

In 2004, the European biotechnology industry counted about 2,200 firms generating a total tur-

5) Federal Association of the Pharmaceutic Industry in Germany (BPI), German Association of Biotechnology Industries (DIB).

7) EuropaBio (2006).

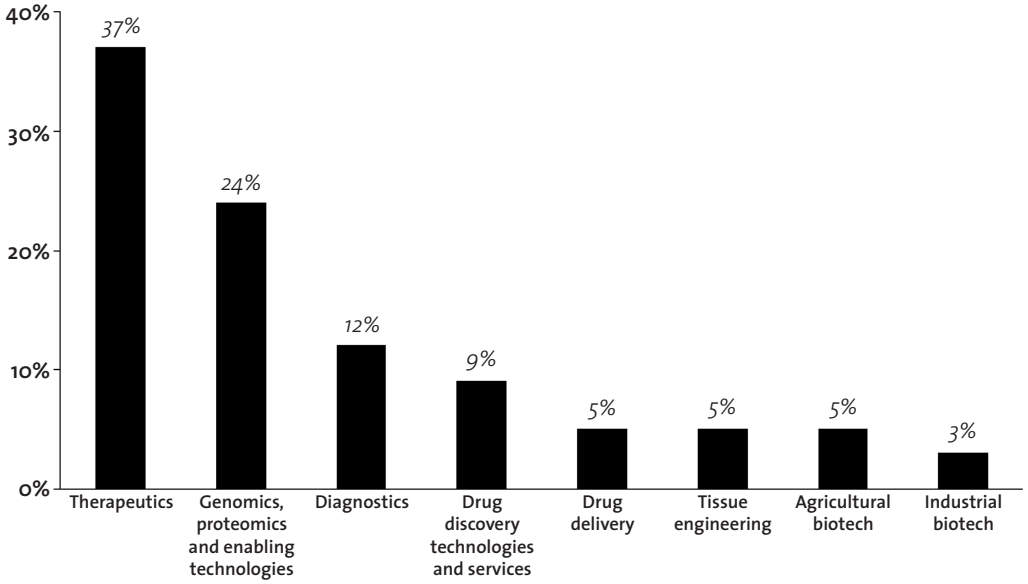
8) Rough estimation based upon Proventa (2004).

9) OECD (2006).

10) Polish Information and Foreign Investment Agency: Biotechnology Sector in Poland 2004.

11) South Moravian Innovation Center (2007).

Figure 2: Percentage of firms with respect to biotech applications in Europe (2005)[13]



nover of € 22 bn (EuropaBio, 2006). Germany, the UK, and France occupied the leading positions in terms of firm number (Table 1).

Furthermore, with respect to turnover, Denmark and Switzerland joined the leading group, which can be traced back to the presence of large multinational corporations. In general, it is apparent that the leading Western European agglomeration areas are also occupied by the larger part of biotech companies. This conclusion corresponds also with the results of Allansdottir et al. (2002). The authors draw a similar picture of the spatial concentration of the European biotechnology using patent statistics. The study reveals that the most innovative regions in terms of patents are in Germany, France, the UK, the Netherlands and Italy. Another remarkable result is that the leading positions correlate to the spatial concentration of downstream sectors (material sciences, organic chemicals, pharmaceuticals and polymers). Furthermore, several studies emphasize the role of local universities and research institutions as well as the supply of a highly educated workforce for the emergence and growth of biotech clusters.[12]

Summarizing, these results allow the conclusion that: i) the local conditions in R&D infrastructure and capacities; ii) the size of sales markets; and iii) the connection to the (pharmaceutical) downstream sector play an important role for the spatial formation of biotechnology. In this context, the relevance of location factors depends upon the level of geographical aggregation. In international terms, the degree of industrialization, the consumer as well as the downstream market size, and the connection to global markets determine the extent of national biotech industries. On the national level, only few regions benefit from the local presence of biotech firms. In contrast, the occurrence of regional clustering is restricted to national agglomeration areas characterized by high performing endowments of research facilities and highly skilled labor.

Turning to the cross-sectional orientation of the European biotech industry, Figure 2 shows the percentage of firms with respect to the fields of biotechnological application. In this context, Pharmaceuticals and Enabling Technologies (platform technologies), with 37% and 24%, respectively, are the outstanding categories. Overall, the figure indicates the superior importance of the pharmaceutical sectors for the biotech industry, which legitimates the simplification of the simulated supply chain in section 3, consisting of the pharmaceutical industry as a single downstream sector for the biotech industry.

A common attribute of the majority of biotech firms is the small and medium firm size. According to the OECD survey (2006), the share of companies with less than 50 employees lies between

12) See e.g., Audretsch and Stephan (1996), Feldman (2000), Stuart and Sorenson (2003).
13) Ernst & Young (2006)

63% (Belgium) and 86% (Germany). Only few large Life Science Corporations (LSC) dominate the biotechnology industry in Europe.[14] These firms attend different markets, primarily for pharmaceuticals but also for chemicals, health care and consumer goods. In Germany, for instance, approximately 30 firms, covering a share in total biotech sales of nearly 70%, occupy this category.

Also in contrast to the majority of core biotech firms, the LSCs are vertically integrated in all stages of the value-added chain from R&D until distribution. In addition, these companies interact with biotech core firms in ways such as the purchase of intermediate inputs, contract research, sales cooperation, and license agreements. In general, the representative core biotech firm is small or medium sized, operating as an intermediate supplier of products, knowledge (licenses and patents) or external knowledge production (contract research) for the pharmaceutical and medical industries. The vertical separation of these upstream and downstream sectors is relatively stable while both industries have recently experienced a period of horizontal consolidation. In this context, Pisano (1990) considers the vertical division of labor between core biotech and established firms in the pharmaceutical industry. The paper concludes that, though both sectors show a tendency for vertical integration due to transaction costs and the need for technology adaptation by the downstream sector, these endeavors are limited by capital restraints of the core biotech firms and a longsome know-how accumulation process within established downstream firms.[15]

In addition, any more arguments for vertical separation may be supplemented. Since the 1980s, public technology promotions, on one hand, and the increasing availability of venture capital, on the other hand, have advanced the emergence and growth of biotechnology out of the fundamental research in academic facilities. Due to high fixed cost in R&D and production, as well as the extensive research risk, only a few core biotech firms succeeded in becoming established as fully integrated units. The technological gap of the LSCs with respect to biotechnology forwarded their demand for biotech products and services, especially in the form of contract research, and strengthened the division of labour between both sectors. Since the industrial consolidation in the course of the collapse of the stock market bubble in 2001, many biotech companies had financial shortages. In consequence, the firm population decreased by market exits, mergers and acquisitions. Another result was the adjustment of the business models to a stronger focus on services and technologies rather than proprietary development, production and distribution. Finally, these factors resulted in an increased vertical separation between core biotech and life science industries at increased sectoral interdependencies.[16]

Based upon these results and the findings of existing literature, the relationship between the core biotech industry and LSCs is characterized by: i) the demand for biotech intermediate products and services of the life science industry; ii) the LSCs as competitors for fully integrated biotech firms; iii) the make or buy decision of LSCs with respect to biotech services and intermediates; and iv) the intensity of competition within the biotech industry.

In consequence, an increasing independence of the LSCs from the core biotech industry may be expected for the future, assuming an unchanged market condition. The crucial factor for this development is the tendency of the LSCs to (re-)integrate biotech R&D as a core competence, which is primarily dependent upon the (anticipated) market size for biotech products and applications. This mainly concerns activities, which could not be integrated in default of technological knowledge but are of strategic importance for (pharmaceutical) corporations. In contrast, activities with a high degree of homogeneity, low economies of scale, or minor demand (i.e., specialized services) may be unaffected by the integration propensity of LSCs. Furthermore, a reduction of public technology promotion and hence a reduction of subsidization of core biotech firms would decrease cost advantages of outsourcing biotech activities, which finally reinforces the integration tendency of the life science industry.[17]

Concerning the opposite dependency of the biotech core industry upon the LSCs, it is necessary

14) Life Sciences are qualified as "...any of the branches of natural science dealing with the structure and behaviour of living organisms" (WordNet: http://wordnet.princeton.edu/perl/webwn?s=life%20science). In these categories particularly fall biochemistry, nutritional sciences, medical technology, pharmacy, environmental technology. The term life science corporation (LSC) follows the definition of Ernst & Young (2000), which is also used by the German Federal Statistical Office (2002): large corporations of the life science industry are firms with more than 250 employees, which do not focus on biotechnology as the only business segment, but undertake intensive R&D efforts for products and processes of modern biotechnology or achieved an annual turnover of more than € 10 m with modern biotech products. In contrast, core biotech firms primarily work with the use of modern biotechnological processes and firm size is smaller than the thresholds of the LSCs.

15) See also Audretsch (2001).

16) See Kranich (2006) for a theoretical discussion of allocation in vertically linked industries.

17) This hypothesis was also confirmed by experts in personal interviews.

to differentiate with respect to different firm types, again. Generally, the increasing concentration in the downstream sector implies a further shifting of market power to the LSCs from the biotech core firms in their capacity as either intermediate suppliers or fully integrated competitors. In this context, it is noted that with respect to market segment and degree of differentiation, the impact of increasing concentration on the biotech sector may vary. On one hand, the fields of biotech products and services are quite heterogeneous, with the result that, on closer examination, the industry disaggregates into separate submarkets with frequently oligopolistic structures. Because of the wide range of biotechnological applications and the innovative potential, customers in different industries prefer a certain degree of diversity in terms of products, processes and suppliers. In consequence, it may be a successful business strategy to focus on a few segments rather than to compete on a homogenous or large-scale production. A vertical acquisition of core biotech companies by LSCs is an exception and conceivable, if the take-over: i) represents an opportunity for vertical restraint with respect to downstream competitors; ii) grants access to strategically important know-how, licenses and patents; or iii) is beneficial due to strong complementarities between intermediates and final products and services.[18]

International Trade

For evaluating the impact of international trade on the German biotech industry, our department conducted an online survey in 2006. The target audience contained 810 firms consisting of German biotech core companies, equipment suppliers, and LSCs that were compiled by address files of the industrial associations, as well as internet and database search. The subject matters of the survey were led by the central questions: To what extent are biotech firms involved in foreign trade? What significance do the emerging countries Brazil, Russia, India, China (frequently abbreviated BRIC) and the Eastern EU accession states have in terms of sales market, research and production location?
In this context, the survey was structured into five parts: A) the location factors of German biotech firms within Germany; B) international activities of the industry in terms of R&D, production and sales; C) opportunities and risks of globalization for the interviewed firm with a focus on BRIC and Eastern Europe; D) opportunities and risks due to globalization for the overall German biotech industry; and E) information about the interviewed firm with respect to size, business focus, region and age.
The firm survey was accompanied by an expert survey with 106 persons from industry, politics, industrial associations and science.[19] Both questionnaires were identical except for firm specific questions. The online survey represents the first study concerning the internationalization of (German) biotech firms. Because the survey primarily asked for qualitative evaluations, the significance of the results cannot be statistically proved. Nevertheless, the outcome appears to be valid in consideration of the feedback rates, which are 12% of firms and 27% of experts, as well as the representative cross-section in terms of application field, firm size and firm age. The expert survey was conceived to check the answers of firms from a different point of view, especially concerning country evaluation and interpretation of firm response.
In the context of this paper, the online survey confirms the major importance of the location factors for biotech firms (Germany), as discussed in the previous subsection. For international activities, the survey concludes that the most important determinants are: i) the enlargement of sales markets; ii) the unification of admission standards (the reduction of market entry barriers); and iii) the access to technological knowledge of research institutions.
The study reveals that biotech companies participate to a high degree in international trade. About 66% of the firms generate a turnover of at least 30% abroad, where 34% of the firms gain more than 70% of their annual turnover by the export business. Despite the high trade intensity, the majority of firms (41%) realize only less than 10% of their turnover beyond Europe. This implies that the foreign sales of the German biotech industry focuses on Western Europe as indicated in table 2, which shows the rankings of foreign countries preferred by German biotech firms. The percen-

18) See e.g., Martin (1993), pp. 242-260 for a discussion of vertical integration.
19) The addresses of experts have been provided by the German Association of Biotechnology Industries (DIB).

Table 2: Ranking of the most important countries for German biotech companies with respect to R&D, production and sales activities[20]

Pos.	Sales	Production	R&D
(1)	Switzerland (55%)	USA (9%)	USA (17%)
(2)	Austria (51%)	China (7%)	China (14%)
(3)	USA (50%)	UK (5%)	Russia (14%)
(4)	Others Europe (43%)	Slovakia (4%)	Austria (14%)
(5)	UK (42%)	Hungary (4%)	Netherlands (12%)
(6)	France (39%)	Netherlands (3%)	UK (12%)
(7)	Netherlands (38%)	Brazil (3%)	Hungary (11%)
(8)	Canada (34%)	Canada (3%)	Switzerland (10%)
(9)	Japan (33%)	Others America (3%)	Japan (9%)
(10)	Belgium (31%)	India (3%)	Australia (5%)

tages in brackets represent the relative frequency of firms, which established a relationship to the corresponding country. In this regard, the indications summarize the foreign activities in terms of their varying intensity. In respect of sales, for instance, the foreign activities range from pure exporting, sales corporations to own subsidiaries; concerning R&D this contains (bilateral) contract research or own foreign R&D facilities.

With respect to sales, the most important destinations are in Western Europe: Switzerland, Austria, the UK, France and the Netherlands. Regarding the foreign engagement in terms of production, the results confirm the statements of trade theory, where the trade volume is determined by spatial closeness and the market size of foreign trade partners. This explains the high relevance of the Western European countries, on the one hand, and the importance of North America, where the USA represents the largest global pharmaceutical market, on the other hand. In terms of production, it is apparent that Western European countries are underrepresented. which can be traced back to their geographical closeness to Germany in which the largest part of manufacturing for the European market is located. Furthermore, countries featuring a large (expected) market size but are distant from Europe, e.g., USA or China, tend to be supplied by local production. For R&D, the biotechnological leader, the United States, is closely followed by China, Russia and Western Europe. This implies that R&D activities follow not only the research potential and infrastructure, but also the market size and manufacturing, which explains the relatively strong correlation to the production ranking. This relocation dependency may be an evidence for strong vertical linkages between R&D and production (or downstream sectors).

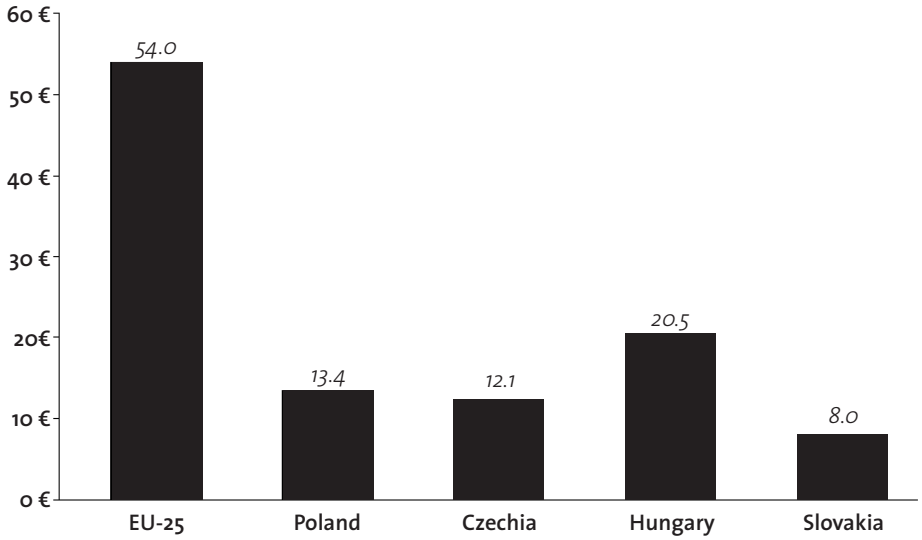
In the survey we explicitly asked for an evaluation of the BRIC and CEE countries in terms of their competitive position and biotech market potential. The majority (60%) of the survey participants consider the role of competitors from the emerging countries China and India as relevant. In contrast, about 69% attribute a meaningful market potential to those countries. Overall, the questioned firms plan to expand their sales activities in the emerging BRIC (65%), followed by 32% and 9% that intend to establish R&D or production capacities.

Regarding the EU accession states, about 63% of the responding firms assess the competitive risk from the CEE countries as unimportant or almost unimportant. With respect to the market potential, a clear rating is not available. About 48% of the firms assess the market size as relevant - opposed to 45%, which see no potential in Eastern Europe. Nonetheless, 61% of German biotech firms plan an extension of sales in the CEE countries, as well as 32% in R&D and 9% in production. The importance of the CEE countries, in terms of biotech upstream activities, particularly concerns Hungary and Slovakia, as also shown in Table 2.

These results raise the question: What factors are responsible for the relatively weak position of the CEE countries compared to the BRIC

20)The data contain any kind of activities from pure export to own (sales) establishments in relative frequency. Multiple answers were possible.

Figure 3: Labor unit costs of the pharmaceutical industry in the largest CEE countries in comparison with the EU-25 average (2004)[23]



states?

At first, the economic potential in the CEE countries is restricted in several ways: the low market size and purchasing power, the below-average research infrastructure in comparison with Western Europe, as well as the scarce supply of highly qualified biotechnologists. Furthermore, the Eastern European research locations are suffering from two dilemmas: first, the geographical closeness to the industrialized European core implies that highly skilled R&D can be undertaken without leaving the core. The case is different in China and India, where the immense market potential and the spatial (and political) distance requires a local establishment. Second, the European integration process promotes the interregional mobility of workers. The income and professional perspectives are significantly better in Western Europe, which makes highly skilled specialists leave peripheral regions to look for job opportunities in the core.[21]

With respect to the pharmaceutical industry as a downstream sector for biotech companies, further barriers for development occur. Although the pharmaceutical industry has recently been characterized as a dynamic development, the total market size accounts just for 6% of the European Union. In this context, Poland plays with € 3.8 bn , the largest part of the CEE countries, followed by Hungary (€ 1.9 bn), Czech Republic (€ 1.6 bn), and Slovenia (€ 672 m).[22] In 2003, the local pharmaceutical industry in the CEE countries achieved revenues of € 5.3 bn. The largest Eastern European manufacturer with 202 firms is Poland, ahead of Hungary with 102 firms. A major part of sales growth can be attributed to the imports of multinational corporations (via sales branches) and locally produced generics. Therefore, it can be concluded that local manufacturing predominantly supplies local markets so that the competitive risk from the CEE countries is relatively low. Competitive advantages in labour costs have a lower impact due to high capital and technology intensity in the biotech and pharmaceutical sectors, which was also confirmed in personal expert interviews. According to expert opinions (survey and interviews), the expansion of international biotech activities in the CEE countries is currently constrained to production and services of standardized products and processes, especially in the field of clinical testing and automatic screening.

Opposed to these dampening factors for an

21) This corresponds also with the results of empirical studies; see e.g., OECD (2002).

22) EUROSTAT database

23) Data source: EUROSTAT, industry code: NACE DG244 (Manufacture of pharmaceuticals, medicinal chemicals and botanical products), indicator code: vg1210 (Labour cost per employee -Unit labour cost).

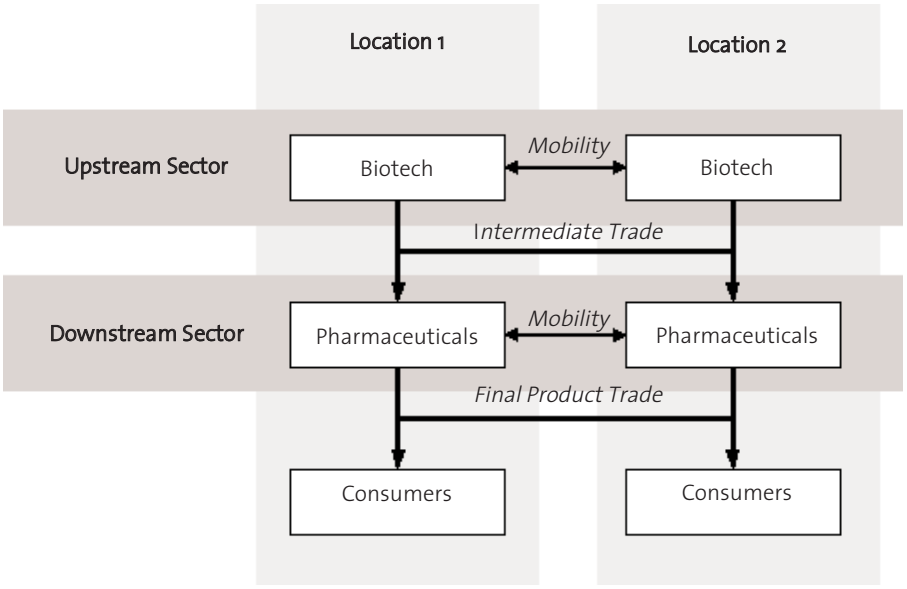
eastward relocation, the spatial formation of the biotech industry is also dependent upon the dynamics of the pharmaceutical sector. Although this downstream sector is currently weakly established in the CEE states, it sensitively responds to national wage differences. Figure 3 shows the labor unit costs of the pharmaceutical industry (2004) for Poland, Czechia, Hungary and Slovakia compared to the EU-25 average, which is about onefourth of the Eastern accession states.
These cost advantages imply a motive for an eastward relocation of pharmaceutical firms. In the course of the EU integration process, trade barriers between European countries have fallen, which has made it profitable to attain the large Western European pharmaceutical markets from distant low cost locations. A spatial shifting of the pharmaceutical industry, characterized as being the relevant market for biotech firms, involves also a relocation tendency of the corresponding upstream sector via vertical linkages. This linkage driven development may entail increasing spatial technology diffusion that could (partially) compensate the technological gap of the CEE research facilities. Against this background, the next section introduces a modeling framework for quantifying the spatial dynamics of the European biotech industry from this vertical linkage perspective.

Simulation

The Model

The New Economic Geography, initially introduced by Krugman (1991), provides explanations for industrial agglomeration based upon increasing returns and imperfect competition. Based upon classical economic geography models (e.g., Christaller, 1933; Lösch, 1940), the first proceeding, commonly referred to as the core-periphery mode", explains industrial agglomeration with respect to regional mobility of workers. Later on, the theoretical debate was extended by the implementation of vertical linkages as a further agglomerative force, as discussed in the first section, where Krugman and Venables (1995) as well as Venables (1996) provided seminal papers.
For modeling the European biotech industry, this paper picks up the latter model roughly illustrated in this section.
The Venables model considers a simple supply chain consisting of an upstream sector providing a downstream sector with intermediate products while this downstream sector supplies consumer with final products. Both such vertically linked industries are spread across two spatially separated locations (Figure 4). Both industries produce a continuum of differentiated goods by the use of labour, while the downstream sector additionally employs the output of the upstream sector as a further input factor. The downward arrows between sectors and consumers indicate these commodity flows. Both types (intermediate and

Figure 4: Schematic Diagram of the Venables model



final products) are internationally tradable signified by the sectoral cross-links labeled by 'trade'. The firms in both industries are competitive monopolists, so that due to increasing returns and (technical) preference structure, one firm produces only one differentiated variety.

The market supply attends to a representative private household, which demands not only the whole consumer good continuum, but also a homogenous outside good, which can be considered, as all these goods, which are not in the focus of this model. The allocation between both sectors is characterized by mutual interdependencies, which are also referred to as forward and backward linkages. The forward linkage, also called demand linkage, describes the dependency of the upstream industry upon the downstream industry: the larger the downstream sector, the larger is the relevant market for the intermediate sector. The backward linkage, also described as cost linkage, results from the price index effect: the more firms produce in the upstream sector, the higher is the competitive pressure implying decreasing intermediate prices, which finally decrease the procurement costs of the downstream industry. It is applied for both mechanisms: the larger the first sector is, the larger is the other.

In the framework of the NEG, the spatial distance between locations is represented by trade costs (usually Samuelson iceberg costs), which are dependent upon the value of goods exported from location r to location s. Trade costs involve not only transportation costs but also every cost arising from international trade. These include tolls and import taxes, insurance rates, labour and storage costs, etc., and additionally efforts caused by lingual and cultural differences or varying legal conditions, but are difficult to quantify.

Against this background, not only local market size and production costs influence the location decision of firms, but also the amount of trade costs. The higher the trade costs, the stronger firms tend to locate at the larger market for reducing the costs of spatial transfers. In contrast, at low trade costs, local cost advantages become more important than local market size.

The model results in two spatial distribution functions, ν^u and ν^d, where the first one describes the spatial spreading of the upstream industry, and the second one of the downstream industry.[24] The distribution of an industry is measured by the ratio of sectoral output in location s to the corresponding output in location r. For an example, if ν^u takes the value 5, the total output of the upstream industry in location s is five times higher than the output of the same industry in location r, implying that the upstream industry geographically concentrates in s.

In this context, equation (1) represents the spatial distribution of the upstream industry dependent upon several exogenous parameters and the distribution of the downstream industry, ν^d:

$$\nu^u = \frac{\nu^d\left[t^\sigma - \left(\alpha^u\right)^{\sigma-1}\omega^\sigma\right] - t\left[\left(\alpha^u\right)^{\sigma-1}\omega^\sigma - t^{-\sigma}\right]}{\left[t^\sigma - \left(\alpha^u\right)^{1-\sigma}\omega^{-\sigma}\right] - \nu^d t\left[\left(\alpha^u\right)^{1-\sigma}\omega^{-\sigma} - t^{-\sigma}\right]} \quad (1)$$

Equation (1) reveals two mechanisms. First, it contains the forward linkage, which implies that the distribution of the downstream sector positively determines the distribution of the upstream sector. Second, we find parameters representing the production situation in both locations: α and ω. The first one is the ratio of production coefficients in location s to location r reflecting productivity differences. The second one, ω, defines the ratio of wages in both locations and can be interpreted as the wage differential.[25] In general, the location with lower production costs is the location with a smaller consumer market, and thus, with a lower concentration of downstream firms. This, in turn, reduces the motivation of upstream firms to move to the location characterized by cost advantages. The tension between those opposing mechanisms is determined by the level of trade costs, t, with the result that, at a certain degree of trade integration, one force exceeds the other one. In the extreme, where international (intermediate) trade is costless, the upstream industry totally agglomerates in the country with lower production costs.

Equation (2) describes the spatial distribution of the downstream industry with respect to the distribution of the upstream industry.

$$\nu^d = \frac{\eta^d\left[t^\sigma - \left(\alpha^d\right)^{\sigma-1}\left(\xi^d\right)^\sigma\right] - t\left[\left(\alpha^d\right)^{\sigma-1}\left(\xi^d\right)^\sigma - t^{-\sigma}\right]}{\left[t^\sigma - \left(\alpha^d\right)^{1-\sigma}\left(\xi^d\right)^{-\sigma}\right] - \eta^d t\left[\left(\alpha^d\right)^{1-\sigma}\left(\xi^d\right)^{-\sigma} - t^{-\sigma}\right]} \quad (2)$$

Similarly as in equation (1), the outcome is dependent upon the backward linkage and local produc-

24) The superscripts are mnemonics for upstream and downstream.

25) The parameter σ represents the constant elasticity of substitution. The higher the value the more homogenous are the differentiated intermediate and final products. Because this variable is not of major importance for this paper, it is henceforth neglected.

tion and cost conditions. In this context, the variable ξ defines the relative downstream costs that are the procurement costs for intermediates in the ratio of location s to r, again:

$$\xi^{d} = \omega^{1-\mu}\left[\frac{t^{1-\sigma} + \omega^{-\sigma}\left(\alpha^{u}\right)^{1-\sigma} v^{u}}{1+\omega^{-\sigma}\left(\alpha^{u}\right)^{1-\sigma} v^{u} t^{1-\sigma}}\right]^{\frac{\mu}{1-\sigma}} \quad (3)$$

This expression depends upon the wage differential, trade costs, the size of consumer markets, μ, and finally upon the distribution of the upstream industry. The level of trade costs determines the relevance of the upstream industry distribution. With decreasing trade costs, the concentration of the downstream industry becomes increasingly independent of the location of upstream firms. Under specific conditions, a potential outcome is the total geographic specialization, where upstream and downstream industries totally agglomerate in different locations.
The interaction of mechanisms summarized in the functions (1) and (2) allocate an equilibrium distribution of both sectors, where the intersection of the corresponding graphs defines one or multiple equilibrium states. In the following subsection, we adapt the modeling framework to the case of the European biotech and pharmaceutical industries.

Simulation Design

Within the simulation study, the Venables model is utilized to analyze the impact of the European enlargement in 2004 (EU15+10) upon the European biotech industry. In doing this, the following facts, presented in the second section, are explicitly taken into account: i) the strong focus of biotech firms on upstream activities incorporating R&D and the production of intermediates; ii) the dominance of the pharmaceutical industry as a major application field; iii) the great importance of inter-European trade; and iv) the spatial concentration of industries in the Western European countries. Based upon these facts, we make the following assumptions:

- The biotech core industry is considered an upstream sector of the pharmaceutical industry as indicated in Figure 4.
- Both sectors have access to the same labour market.
- Because only a singular supply chain is modeled, the partial-analytical version of the Venables model is used implying exogenous wages and income.
- We summarize the Western European countries (AT, BE, CH, DE, DK, FR, GB, IT, NL) to one location, referred to as the core region, and the residual European states (E, FI, GR, IE, PT, NO, SE) to a second location, defined as the peripheral region.[26]

This approach allows not only an analysis within a two-location version but also a modeling of the European Eastern enlargement by adding the CEE countries to the periphery.
All in all, this simulation design raises several problems: i) the Venables model does not incorporate R&D activities so that corresponding expenditures fall in production fixed costs; ii) capital as an important input factor, especially in the pharmaceutical industry due to high development costs of new agents, are neglected; iii) the model does not involve the decisive public research infrastructure; and iv) the agglomeration forces are ascribed to vertical linkages only, but not to factor mobility, for instance.
Nonetheless, this approach features convincing advantages with respect to the present case. The markets for biotech products and services as well as pharmaceuticals are fragmented to a high degree, which can be traced back to the relative low substitutability between products on the one hand, but also to the distinctive consumer preference for diversity, on the other hand. In addition, due to patents and property rights, temporary niche markets appear, which only few firms provide. The choice of monopolistic competition sufficiently takes account for the structures in both sectors. Furthermore, both industries are characterized by increasing returns, principally in R&D and production. It may be held again to the missing implementation of explicit R&D activities and associated demand effects that the Venables model describes basic agglomeration dynamics of vertically linked industries; this is also valid in the biotech and pharmaceutical industries. The simulation results, which can be interpreted as agglomerative potential, will be completed by the impact of entrepreneurial R&D and public research policy.

Simulation Results

Figure 5 and Figure 6 illustrate the simulation outcomes as well as the comparative-static analysis based upon the simulation parameters in Table 3. Figure 5 shows the distribution of secto-

26) The countries are assigned to the categories by means of their spatial distances and the annual turnover of the pharmaceutical industry (2004).

Table 4: Simulation parameters

Variable	Description	Value	Comments
η^d	Relative expenditures for pharmaceutical output	5.6709 4.7018	Pharmaceutical turnover, ratio core: periphery (before and after enlargement)
α	Relative production coefficients	0.9110 0.8914	Calculated from the average factor productivity, ratio core: periphery, (before and after enlargement)[a]
ω	Wage differential	1.2638 2.3552	Labor unit costs, ratio core: periphery, (before and after enlargement)
μ	Cost share of downstream industry for intermediates	0.0716	Ratio of biotech wage bill + purchases of goods and services to total costs of the biotech industry[b]
σ	Substitution elasticity	9.53	Hummels (1999), table 4

Source: Own calculations, data: EUROSTAT

a Here the ratio of locations is inversed because the gross value-added per each output unit is equal to the reciprocals of the production coefficients. Average factor productivity = input / output = (production value – gross value added) / production value. It is assumed the same productivity for biotech and pharmaceutical industry.

b The costs of biotech industry are calculated from data of Ernst & Young (2004).

ral output in the ratio core to periphery with respect to trade costs. Here, ν^b stands for the distribution of the biotech instead of upstream industry and ν^P for pharmaceutical in terms of the downstream industry. Both marks indicate the calibrated trade costs level for the period before and after the EU Eastern enlargement in 2004. This means for "EU-15" that before the European enlargement in 2004, both industries very spatially concentrated in the same degree: the biotech and pharmaceutical industries were 5.8 times stronger agglomerated in the European core compared to the periphery.

The trade cost values for "EU-15" and "EU-25" are indirectly determined from the real ratio of sectoral turnovers for 2003 and 2005, while the distributions are functions of trade costs.

The Eastern enlargement implies for the European Union not only a larger common economic area, but also a simultaneous convergence of legal conditions, an increasing expansion of transportation infrastructure, an abolition of tolls and import regulations, and decreasing average trade costs with increasing trade volume.

With decreasing trade costs, the spatial concentration of both sectors, characterized by a decreasing ratio, declines to the benefit of the peripheral countries. Furthermore, the biotech industry shows a stronger relocation to the periphery compared to the pharmaceutical industry, apparent at the divergence of the sectoral distribution on the left hand side of the figure. This implies that the pharmaceutical sector features an increasing relative specialization at a decreasing spatial concentration in comparison to the upstream sector. The reason for this development is the stronger sales market orientation of the pharmaceutical industry: the expenditures for respective products in the Western European states are almost five times higher than in the periphery (Table 3, first line).[27]

Figure 6 shows the simulation results with respect to a change in the relative wages (again: core to periphery).

The European enlargement is associated with an increasing wage differential from 1.2 to 2.3, in consequence of the accession of the CEE countries. It is apparent that the current and the past wage differential lie in a relatively inelastic range of the sectoral distribution function. The spatial concentration does not respond to an increasing (decreasing) wage differential until the value is above 3.5 (below 0.5). Only in a situation beyond these values, the figure shows relative specialization and a tendency to a symmetric outcome (increasing asymmetry). In the course of econo-

27) Multiple equilibria, a central feature of NEG models, do not occur in this parameter setting. For trade costs (basically defined to be greater than 1) which are below 2.3, the model loses its validity: countries become more and more regions.

Figure 5: Relative distribution (core to periphery) of pharmaceutical and biotech industry (measured in the relative turnover), before and after EU enlargement, with respect to trade costs.

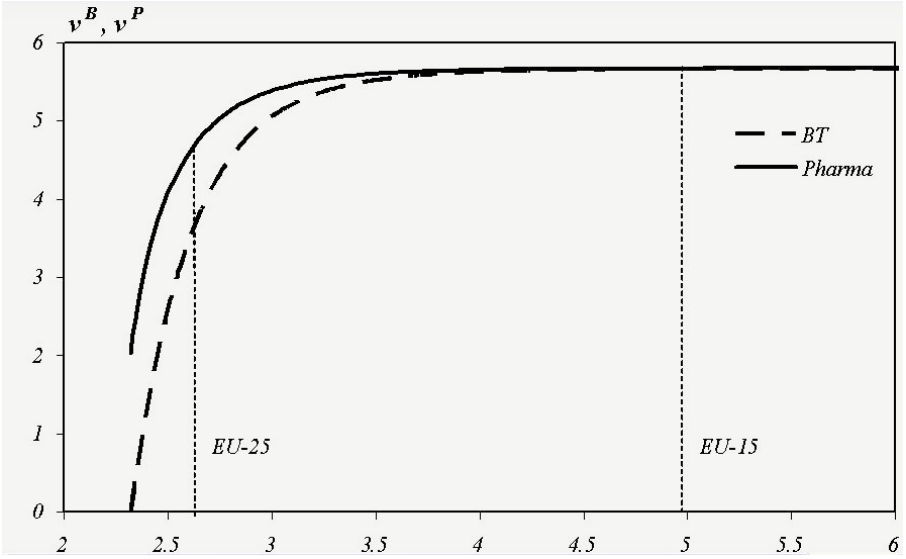
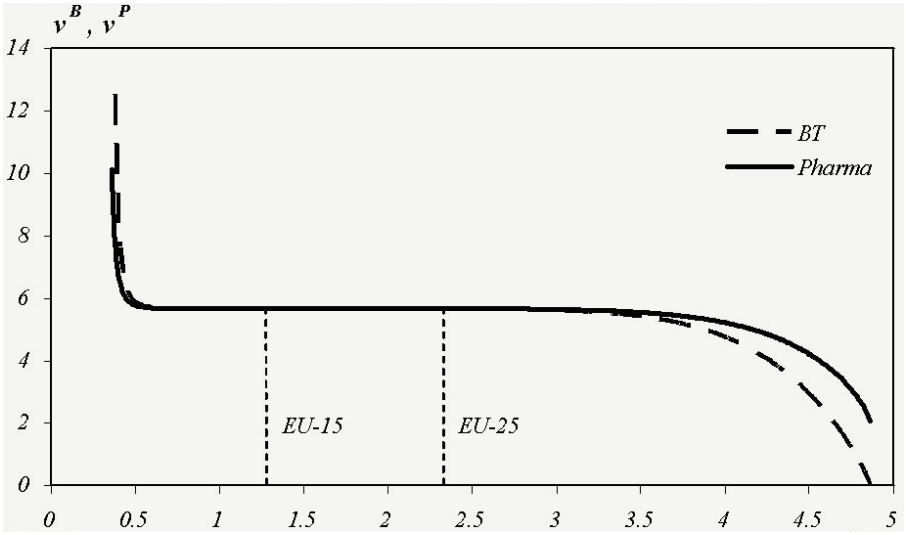


Figure 6: Relative distribution (core to periphery) of pharmaceutical and biotech industry, before and after EU enlargement, with respect to wage differential.



mic integration, a convergence of wages and income is expected within the EU, which corresponds with a limiting wage differential of 1. With respect to figure 6, the economy moves from a wage ratio of 2.3 leftward to 1 without affecting the spatial distribution of both sectors. The reason for the rigidity is the strong forward linkage between biotech and pharmaceutical linkages, which more than compensate differences in local production costs. This means that the dependency of the biotech industry upon the pharmaceutical industry, which primarily orientates on the larger core market, has a stronger impact on the location decision than lower wages in the periphery.

Discussion and Conclusions

Considering the simulation, the results provide two central messages. First, the strong vertical linkages between biotech and pharmaceutical

industries compensate the dispersive impact of wage differentials across European countries. Because the European core features the larger consumer market, it primarily determines the downstream sector distribution, which exerts a strong attraction for the biotech industry. Wage differentials within the real parameter domain do not have an impact on the concentration of both the biotech and pharmaceutical industries.
The second implication is the sensitivity of sectoral distribution with respect to the level of trade costs. The simulation shows that a further decrease results in an increasing relocation of both industries to the European periphery. In the face of this outcome, the concerns, that public investments in the core get lost by a relocation of the biotech industry, appear to be justified. However, this conclusion requires a further discussion. One point of critics is addressed to the simulation design. In this context, the partial-analytical approach implying exogenous income and wages may provide a relevant dampening effect for the industrial relocation. On the one hand, there is the limited supply of highly qualified labour and the research infrastructure in the periphery, which is not included in the model but represents crucial location determinants, as shown in the previous section. The supply of skilled labour and R&D facilities in the CEE countries are restricted by mobility as well as low capacities for public investments in the capital-intensive biotech and pharmaceutical research. On the other hand, a further limitation stems from the model design: the periphery is considered as one common location implying a homogeneous economic area. In reality, the periphery disaggregates into spatially separated countries arranged like a ring around the core. Some peripheral countries are quite distant from each other so that the underlying assumption of costless intraregional trade is questionable. Nevertheless, this argument may be countered by several empirical studies concerning the exports of peripheral countries, e.g., the Eastern European states.[28] The largest part of the peripheral exports concentrates on trading with the core while the intraperipheral flows of trade are relatively low. Without these distortions, the spatial production network would be much more filigree; furthermore, the market size of the periphery would be significantly reduced, which works against dispersion.
Summarizing and turning back to the central question posed in the first section, a restrained relocation tendency from the European core to the periphery results for both, the biotech and pharmaceutical industries. Restrictions in labour, infrastructure, and technology supply considerably dampen the industrial shifting. Along with the low peripheral market size (for both sectors), only moderate changes arise in the spatial distribution.
Against the background of these results: What can be concluded for economic policy?
Baldwin et al. (2003) summarized central issues of the NEG with regard to economic policy. Nonlinearities, thresholds, and discontinuities determine agglomeration, and thus an efficient economic political intervention. As shown in the previous section, the current wage differential is in an inelastic range of sectoral distribution, which also will not be left at complete convergence. Public intervention via price or factor cost subsidization for promoting industrial agglomeration potentially requires enormous expenditures in which legitimization is questionable with respect to proportionality and economic efficiency. Therefore, it is important to note that, with decreasing trade costs, the efficiency of agglomeration stimulating instruments is increasing.
From the viewpoint of regional policymakers, political options are even more restricted due to financial and hierarchical constraints. In addition to lower public budgets, a conflict of regional and supraregional interests develops. While industrial agglomeration is desirable for local policy, on the national or supranational level, these ambitions lead to industrial dispersion and a loss of spatial efficiency due to lower economies of scale. The solutions proposed for this dilemma refer to spatial specialization implying the emergence of industry- or technology-specific clusters. The basic idea is to compensate missing spatial economies of scale by competitive advantages due to specialization. This approach is debatable with respect to the following facts:

- Biotech products and services find use only in few applications, which are dominated by the medical and pharmaceutical sectors.
- The biotech industry disaggregates in many small-scale niche market and technology fields, which are not inevitably interconnected. This implies that endogenous agglomeration tendencies by spillover effects are lower as they would be for a more homogenous industry.
- The vertical linkages between biotech and pharmaceutical industries are strong in such a way that the upstream industry primarily orientates on the location of the downstream industry. The pharmaceutical industry is agglomerated in the European core as a result of

28) See e.g., Ando and Kimura (2006).

larger sales markets. A spatial separation of the sectors implies an immense subsidization of peripheral regions, public investments in a highly qualified labor supply and sufficient infrastructure.

- Without supranational coordination, regional (national) politics may be conflicting what is associated with a loss of spatial efficiency and common welfare.

In the context of these conditions, a final and general recommendation for economic policy is not possible because the political trade-off between spatial economies of scale and regional equality depends upon the aversion to asymmetry of the European population. As demonstrated by Charlot et al. (2004), the industrial core is almost able to compensate the periphery for welfare losses resulting from agglomeration. This implies interregional transfers as realized by the European Regional Development Fund (ERDF), for instance. The related question is: For what purposes should these interregional investments be applied? With respect to the present case, a promotion of peripheral industries is reasonable if these industries do not only feature comparative cost advantages, but also low trade costs and major economic importance in terms of output and employment. For Eastern Europe, this may concern industries with a relative high labor intensity, distinctive product or process standardization, and large-scale production. However, a further consideration of an optimal European technology mix requires a comprehensive analysis of the European industries and may be subject for future research. In this context, the outcomes of this paper suggest a further consideration of public technology promotion in their capacity as location factor, potential spillover effects between biotech firms as a relevant agglomeration force on the regional level, as well as the international mobility of biotech researchers as a destabilizing impact for the European periphery.

What can finally be concluded for the theoretical background? First, simulation and empirical results confirm the statements of the NEG. Models of the classical trade theory predict that regional differences in terms of production costs tend to converge and economic activities to disperse. In contrast, modern approaches by the NEG as well as the New Trade Theory emphasize agglomeration based upon increasing returns and imperfect markets and the corresponding differences regarding wages, income and factor endowments. However, this paper reveals that the core-periphery structure of European industries may remain, in spite of increasing trade integration and decreasing wage differentials. Exogenous asymmetries between countries, e.g., in terms of country size, suggest an attractive field for future research - despite the loss of analytical convenience given by symmetric countries. Second, the reason for the success of the NEG is the potential to provide quantitative statements compared with alternative location theories. In consequence, case studies and econometric analysis of the spatial formation of industries may be complemented by a stronger use of numerical simulations, especially in the context of multi-country frameworks.

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Practitioner's Section

The growing importance of covering payment risks in the chemical industry

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The first dark clouds are gathering on the economic horizon of the chemical industry and may cause an unattractive dip in otherwise impressive growth. With the oil price remaining high, concerns that global economic growth is cooling and ever fiercer competition, the outlook is gloomy. There is also uncertainty about the reform of the European Community Regulation on chemicals, REACH, the financial impact of which is still impossible to predict for most companies. Such lists of possible causes of an economic slowdown often fail to mention the risk of bad debts, which may result in considerable financial difficulties for companies or, in the worst case scenario, lead to insolvency. However, providing security against the risk of payment default should always be on the agenda. This is particularly relevant in view of the growing importance of trade credit, a fact reflected by the winter 2007 Payment Practices Barometer recently published by Atradius. In addition, payment practices have deteriorated in some countries and sectors in Europe.

Trade credit as a competitive factor

More and more frequently, customers do not pay for goods supplied until such time as they have sold them on and have therefore posted their own sales. This means that in some cases suppliers have to wait a long time for their money. During this time, they are faced with the risk of non-payment. According to the survey findings, guarantees and delivery upon advance payment have become less common. Only 15% of the companies surveyed in Germany insist on advance payment whereas eighteen months ago, this figure amounted to 37%. Guarantees are now relevant in only 4% of business transactions (summer 2006: 14%). The findings of the survey also highlighted the effects of increasing competitive pressure at national and international level. Suppliers need to adapt to the payment terms of their customers if they want to keep customers. These and other findings of the Atradius Payment Practices Barometer underscore once again how important it is for companies to secure receivables due, in order to prevent financial distress in the event of non-payment by their customers. This also applies to the chemical and pharmaceutical sectors, especially since – as described at the beginning - prospects for the coming years are no longer as promising as they have been in the past. Accordingly, a rise in the incidence of non-payment is to be expected.

Deterioration in payment practices in the chemical industry

In summer 2007, Atradius carried out the first sector-based analysis of the two Payment Practices Barometers available at the time, summer 2006 and winter 2006/2007. The result showed that payment discipline dete-

Figure 1 Payment duration in the chemical/pharmaceutical industry
How many days does it take, on average, for business partners to settle their debts?

Source: Atradius

riorated in most European business sectors within the space of nine months. This is also true of the chemical and pharmaceutical industries. The average time between receiving an invoice and payment increased from 50 to 59 days. Respondents also took a considerably more critical view of the sector in terms of late payments and complete non-payments.

The breakdown of the sector analysis by the individual countries surveyed provides a slightly more differentiated picture. In this comparison, the chemical and pharmaceutical sectors in Germany, for example, score much better. On average, payments were made within 45 days. However, companies exporting to other European countries waited significantly longer for their money. Chemical and pharmaceutical companies in the UK took an average of 50 days to pay invoices. French customers in the same sectors even waited 67 days before honouring their debts. Exporters supplying customers in the Italian chemical and pharmaceutical industries waited the longest, with invoices being paid after 84 days on average (Figure 1).

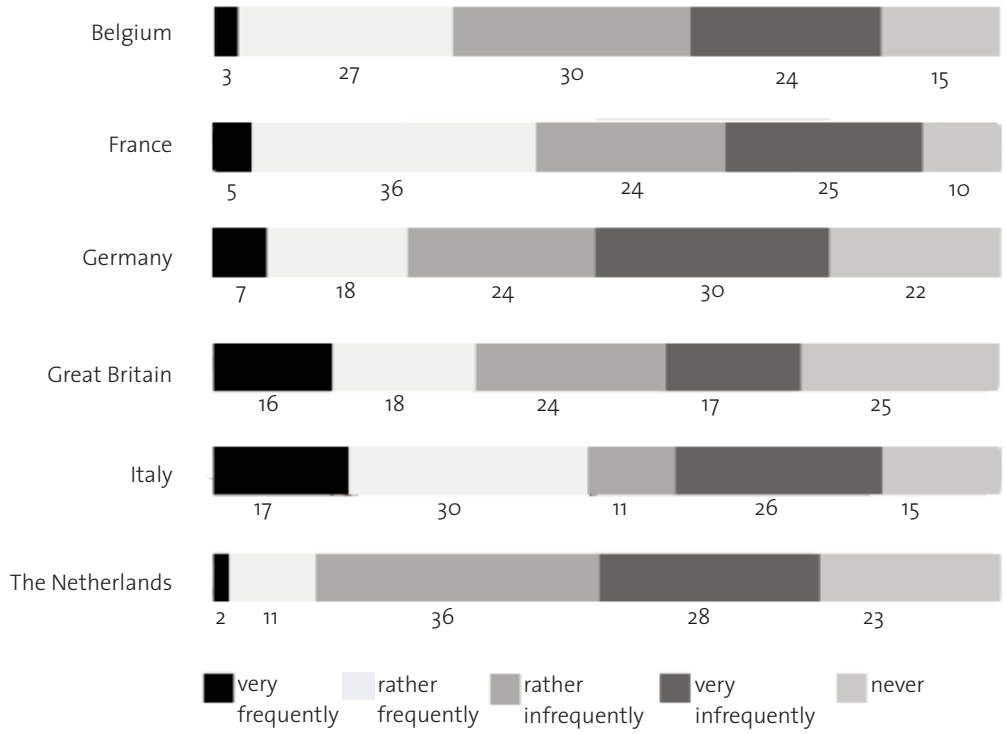
German chemical and pharmaceutical companies were given comparatively high scores by their business partners in Germany and abroad when these were asked about payment delays and complete non-payments. Payment delays occurred only in relation to one in four invoices. The situation is very different with regard to exports to other countries. Delays were most frequently experienced regarding deliveries to Italy, where almost half of the invoices (47%) were not paid within the agreed period of time. In France, this figure was similarly high (41%; see also Figure 2).

Caution advised regarding exports to other industries

The chemical and pharmaceutical sectors in Germany receive relatively good ratings for their payment practices. It is also worth consulting the Payment Practices Barometer to establish how long business partners in other sectors in Germany and abroad wait to pay invoices.

In Germany, the services, transport, technology, research and electronics sectors also achieve comparatively high scores. On average, suppliers waited 39 days to have their invoices paid. The food industry took 3 days longer to pay. The manufacturing industry scored average (44 days), along with the automotive sector (45 days). The clothing industry (48 days) and furniture industry (58 days) are towards the bottom of the league table, with the public sector in last place after a marked gap – government offices and local authorities took almost ten weeks to pay invoices. Incidentally, this is by no means the maximum in a European comparison. Companies supplying the public sector in Italy waited approximately 3 months (104 days) to receive payments. Suppliers to the following sectors in European countries also had to wait patiently for payment of their invoices: automotive (94 days) and clothing (91 days) in Italy, trade/wholesale (70 days) and retail (69 days) in France and the public sector in the UK (66 days). Comparing the times recorded in the two Payment Practices Barometer surveys conducted in summer 2006 and winter 2006/2007, it is evident that the average time for the payment of outstanding invoices recorded in

Figure 2 Payment delays in the chemical/pharmaceutical industry
How often were outstanding debts only paid after some delay?



Source: Atradius

the later survey was longer for almost all of the sectors.

High risk of non-payment

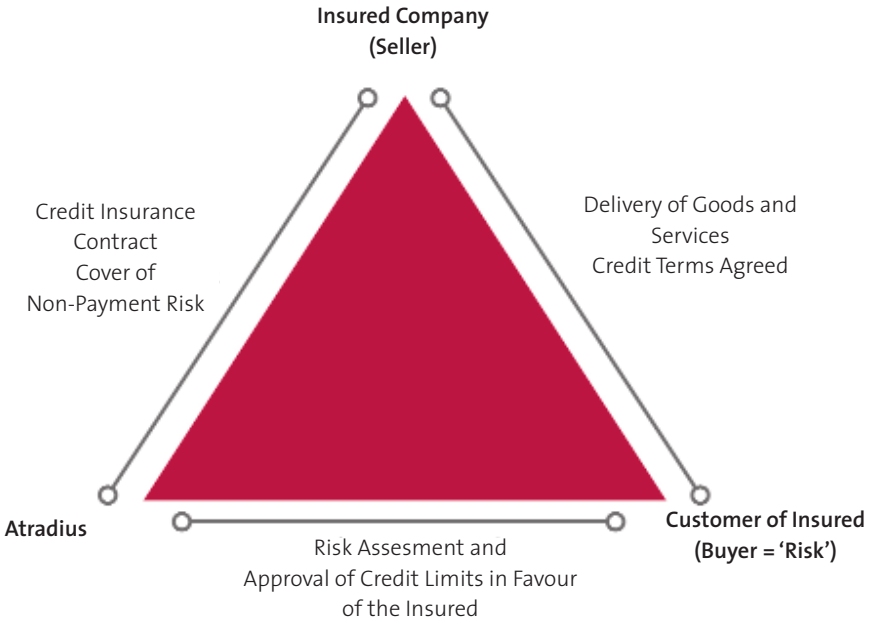
While allowing long periods for payments is common practice in some sectors and also accepted in some cases, actual non-payment of receivables is more than just annoying and in the worst case may jeopardise the existence of a company. A simple calculation illustrates this fact. If a supplier is left with one invoice worth € 50,000 unpaid, assuming a sales return of 5%, he would have to generate an additional € 1 m to absorb the non-payment of this one invoice. For small and medium-sized companies, in particular, one unpaid invoice can impact heavily on the income statement of the relevant financial year.
German companies supplying the following sectors in other European countries should analyse business partners carefully and obtain comprehensive information about their creditworthiness:

- manufacturing industry in France: 11% of respondents indicated that payment problems with representatives from the sector occurred "very frequently" or "relatively frequently";
- technology, research and electronics in Italy: payment delays occurred "very frequently" in 6% of cases and "relatively frequently" in 3%;
- pharmacies and hospitals in the UK: an average of 7% defaulted on payments "very frequently".

Credit insurance provides instant liquidity

Credit insurers regularly check the creditworthiness of customers on behalf of their clients and hedge against specific risks or the complete portfolio of receivables. These risks include customers' inability to pay, exchange rate fluctuations and political risks in the export business. The credit specialists have the required expertise and can rely on a worldwide network of sector experts to assess the financial strength of customers as accurately as possible.
Hedging the portfolio of accounts receivable is

Figure 3 The credit insurance triangle



Source: Atradius

often a prerequisite for obtaining a loan from the main bank, particularly in connection with major projects where companies require sales financing. The bank will only give the green light for the financing of imminent orders once a credit insurance policy with a cover note is in place. If one party is unable to meet its liabilities, or unable to meet these on time, the credit insurance kicks in, preventing any negative impact on the liquid funds and earnings of the company by providing compensation promptly (please refer to Figure 3 regarding the tripartite relationship in credit insurance).

Summary

In an increasingly competitive market environment, which is coupled with the intensifying international credit crisis, it is virtually impossible for companies to avoid granting trade credit and allowing long periods of time for payments to be made. However, this is risky since non-payment will occur time and again. In addition, payment practices in some sectors and countries are far from ideal, with invoices remaining unpaid for weeks. These days, the traditional means for companies to protect themselves against non-payment by customers, such as delivery upon advance payment or granting guarantees, are accepted only by a minority of business partners. This makes it all the more important for companies to hedge their complete portfolio of receivables where possible. Credit insurance companies have developed sector-specific solutions to prevent the worst case scenario of a financial collapse of companies through no fault of their own but caused by their customers' inability to pay.

Atradius Credit Insurance has published three Payment Practices Barometers for the B2B segment to date. In each of the surveys carried out in summer 2006, winter 2006/2007 and winter 2007, a total of 1,200 participants, who are responsible for the receivables management in their companies, were questioned about the payment behaviour of their business partners in Germany, Belgium, France, the UK, Italy and the Netherlands. An interim evaluation of the 15 major economic sectors in Europe was published in July 2007. The surveys were conducted by Psychonomics AG in Cologne (summer 2006, winter 2006/2007 and sector evaluation in July 2007) and Heliview Research in Breda (winter 2007) respectively.

Atradius is a leading credit insurer with total sales

of € 1.3 bn and a 24% share of the global credit insurance market. The company insures trade transactions worth € 400 bn a year against the risk of non-payment and offers products and services relating to risk transfer and receivables management. With 3,500 staff and more than 90 offices based in 40 countries, Atradius has access to information about the credit quality of 45 million companies across the globe and makes more than 12,000 credit limit decisions every day. Atradius has an A rating from Standard & Poor's (outlook stable) and an A2 rating from Moody's (outlook stable).

Journal of Business Chemistry

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Comments

If you have any comments on articles of the previous issue you are welcome to send them to us as a separate submission. The comments are revised only by an Executive Editor and might be published in the next issue if they suit the academic discussion.

Thank you for your contribution!

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