The interplay of regional systems of innovation, strategic alliances and open innovation

The Case of New Biotechnology Firms in the bioRegions of Flanders & Wallonia (Belgium)

Thèse présentée
en vue de l'obtention du grade
de Docteur en Sciences Économiques
et de Gestion par

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Atelier des Presses

Université de Liège - Atelier des Presses
Chemin des Amphithéâtres - Bât B7a
4000 Liège (Belgique)

Ouvrage mis en page par l'auteur
Imprimé en Belgique

D/2017/13.315/1
ISBN 978-2-930772-20-2

Acknowledgements

My sincerest and warmest thanks in finishing this PhD project go out to the following:

- Inge Verheyen, for her love, support and patience;
- Family, Friends and *Fools (= Believers)*;
- Prof. dr. em. Rik (baron) Donckels (KMO-Studiecentrum, KU Brussel);

- the **University of Liège** and in particular **HEC Liège – Management School**:
    - Prof. dr. Bernard Surlemont (Supervisor)
    - Prof. dr. Didier Van Caillie
    - Prof. dr. Fabrice Pirnay
- Prof. dr. Wim Vanhaverbeke (ESADE Business School, Barcelona; National University of Singapore; Universiteit Hasselt)
- Prof. dr. Michele Cincera (Université Libre de Bruxelles);

- Prof. dr. Marina Solesvik (Nord University, Norway);
- Prof. dr. Elina Gaile-Sarkane (Riga Technical University, Latvia).

Final version finished in "Le Laurier" (Apt – Luberon, France)

Résumé

Le coeur du projet de thèse doctorale est lié au start-ups technologiques dans le secteur des biotechnologies et les approches partenariales, c'est à dire, des questions de recherche par rapport aux enjeux stratégiques du secteur pharmaceutique et biotechnologique et à l'innovation ouverte.

Des recherches antérieures montrent que les performances en matière d'innovation sont associées au système, à la collaboration et à la mise en réseau. L'intérêt pour l'innovation ouverte est croissant. Il manque des études qui explorent l'interaction entre les systèmes régionaux d'innovation, la formation de grappes technologiques, les nouveaux modèles économiques parfois disruptifs, les partenariats stratégiques et les pratiques d'innovation ouverte.

Nous observons que les entreprises de biotechnologie se sont lancées dans l'innovation ouverte en se regroupant et en formant des partenariats de manière intensive pour innover à partir des connaissances existant à l'intérieur et en dehors de leur périmètre. L'accent de cet étude est mis sur l'interaction entre les nouvelles entreprises de biotechnologie en Belgique dans les bioRégions Flandres et Wallonie, les alliances stratégiques et l'innovation ouverte, dans un contexte de renforcement par le système régional d'innovation et grappes biotechnologiques.

La structure industrielle est dominée par les plus grosses entreprises pharmaceutiques mondiales, qui capitalisent plutôt sur des liens éphémères avec des sociétés de biotechnologie innovantes pour avoir un accès permanent à de nouveaux produits ou actifs (technologies, process, prototypes, produits) où qu'ils soient. L'innovation est diffusée en mondial et la dynamique contractuelle est très forte pour la capter et faire face à la compétitivité globale.

Les grands groupes pharmaceutiques mondiales bénéficient de la flexibilité, de l'agilité et du dynamisme des nouvelles entreprises de biotechnologie pour accélérer leur innovation dans un contexte concurrentiel et technologique mouvant et pour étoffer leur portfolio avec des solutions innovantes et souvent complémentaires (Alcimed, 2016b). Les nouvelles entreprises de biotechnologie s'appuient quant à elles sur les grosses entreprises pharmaceutiques pour accélérer leur croissance.

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① Setting the Scene

The Biotechnology Industry: the players and the dynamics

Modern biotechnology is a driving force and a full grown industry in the international economy with ongoing and rapid innovations in e.g. medical healthcare (pharmaceutical), agriculture, plants, food and beverages processing, animal healthcare, natural resources, environment, renewable energy, industrial processes and bioinformatics. Biotechnology is defined as the application of science and technology to living organisms, as well as parts, products and models thereof, to alter living or non-living materials for the production of knowledge, goods and services (OECD, 2005; 2006; 2009).

The emphasis of this dissertation is on the valorization of **red biotech**, i.e. all those biotechnology uses connected to medicine and healthcare applications. Red biotech includes producing vaccines and antibiotics, drug discovery, drug development and medical devices, molecular diagnostics techniques, regenerative therapies and the development of genetic engineering to cure diseases through genetic manipulation. It also includes services and technology platforms, bioinformatics or cheminformatics, contract research and contract manufacturing. It involves therapeutic areas such as oncology, immunology, diabetes, inflammation, alzheimer, parkinson, cardiovascular and rare diseases (orphan drugs).

From the 1980s onwards, the emergence of the field of biotechnology gave rise to the modern biopharmaceutical industry in which immunology, molecular biology, genetics and human genome sequencing now play an integral part of drug discovery and development (PhRMA, 2014), whereas the traditional pharmaceutical industry and its innovations are largely based on organic chemistry.

It was medical research, located principally in publicly funded government and university laboratories, which provided the more powerful focus for the development of third-generation biotechnology (Oakey et al., 1990), most notably in the area of genetic engineering (i.e. recombinant DNA or gene-splicing techniques and cell-fusion techniques, the hybrid cell or hybridoma) and the monoclonal antibodies, a protein that is created by the

host's immune system in response to a foreign particle called an antigen. Next generation biotechnology opens new frontiers in personalized medicine, advances in imaging and the use of powerful bioinformatics.

The global biotechnology economy is knowledge-based and a major engine for regional economic growth with clusters of biotechnology companies situated around major publicly-funded research universities and institutions. It is "a complex network of corporate players, dominated by large firms with strong marketing capabilities and start-up firms that focus on research and development" (Pereira, 2006). The direct participants of the biotechnology industry are science-based start-ups (Ebers and Powell, 2007), established biotechnology firms, large (big) pharmaceutical companies, universities, university and government funded scientific research, investors, suppliers and customers (Pisano, 2006).

The biotechnology industry faces a high-cost research and development, limited commercialization and constant technological change. The industry is characterized by a dynamic combination of the following features:

- geographical proximity (clustering);
- a strong science base: very research-intensive with long product development lead times;
- knowledge intensive: high quality of research and education;
- new biotechnology firms are often founded by academic scientists;
- a strong university-industry relationship and transfer;
- strong linkages and strategic alliances with universities, public and corporate research institutions, large companies and other biotechnology firms;
- capital-intensive: traditional venture capital and/or corporate equity investment (private equity);
- public equity: initial public offerings (IPOs); high-performing stock exchange;
- clear institutional and regulatory frameworks;
- heavy dependence on patents (patent legislation) and intellectual property rights;
- the patent cliff: the point in which patents run out, the past level of sales drops and generic replicas enter the market;
- high cost of commercialization;
- heavy regulation of drugs by governments and healthcare systems through approval processes and price controls (Rugman, 2005);

- different health systems in different countries;
- ethical clearance mandatory;
- aging population demanding improved healthcare;
- growing attention for open innovation and/or open source.

The commercial entities analyzed in this study can be described as dedicated biotechnology firms or **new biotechnology firms (NBF)**. They are "involved both in the research in the fields of life sciences (including biotechnology and biosciences) and in the exploitation of the research results" (PwC, 2011). Small biotechnology companies are mostly focused on research and development and only in some cases devoted to manufacturing and commercialization (Bianchi et al., 2011; Chiesa and Chiaroni, 2005). New biotechnology firms are playing an important bridging role at the interface between public sector research and industrial R&D in large pharmaceutical companies (Faulkner, 1989).

Academic spin-offs are a particularly important type of new company in the biotechnology industry. These companies serve as the main vehicles for exploiting biotechnology research. Spin-offs are a significant engine of direct commercialization of university intellectual property. Universities have become active participants in the science business, with the technology transfer from universities to the private sector through the creation of new biotechnology firms. They focus on specific pieces of the R&D value chain. They patent their discoveries. Their technology transfer offices actively seek commercial partners to license the patents. They partner with venture capitalists in setting up firms to commercialize the science emanating from academic laboratories. As Pisano (2006) indicates, the scientists are thus becoming biotechnology entrepreneurs.

According to Pirnay et al. (2003), European universities have dedicated growing attention to the strategic role of laboratories and research centers in fostering a region's capacity to innovate by creating and diffusing knowledge. Venturing is defined as starting up new organizations drawing on internal knowledge, i.e. it implies university spin-offs and corporate spin-outs (Van de Vrande et al, 2009). This is in line with the theoretical model (p. 14 – Fig. 3).

Originally based on university research, that led to major scientific and technological changes, nearly all of the small, biotechnology companies also started as new entrants to the pharmaceutical industry (Hagedoorn and Roijakkers, 2000). This is in line with the early work of Schumpeter

(1934), where small, independent entrepreneurial firms are viewed as major agents of innovative change within new industries.

Biotechnology firms use biotechnology to produce goods or services and/or to perform biotechnology R&D (OECD, 2015). Dedicated biotechnology firms are a subgroup of the biotechnology R&D firm. They devote at least 75% of their production of goods and services - or R&D - to biotechnology. A dedicated biotechnology firm is defined as a biotechnology active firm whose predominant activity involves the application of biotechnology techniques to produce goods or services and/or the performance of biotechnology R&D. Small, dedicated biotech firms play an important role in almost all fields of biotech applications, especially in healthcare (red) biotech.

Large pharmaceutical companies have a worldwide geographical presence with a portfolio of already marketed drugs (Bianchi et al., 2011). According to Chiesa and Chiaroni (2005), they progressively specialized downstream in the value chain (drug development, production, marketing), whereas upstream activities (drug discovery) have been the field of specialization of biotechnology firms.

Today, large pharmaceutical companies typically work in huge research networks with new and/or established biotechnology firms. The relation of the collaborations is mostly bilateral with the pharmaceutical company being the hub of the network (Gassmann et al., 2008). According to Sabatier et al. (2012), even though the discovery process has been transformed by biotechnology tools and by bioinformatics, it is still typically orchestrated by the fully integrated large firms, whose business models have evolved so as to fully integrate their internal and external competencies, with network orchestration as a particular capability.

The drug development pipeline is the engine that drives pharmaceutical companies. Their market valuations are based on prospected new drug approvals and expected new drug revenues. As Gassmann et al. (2008) pointed out, pipeline management is a key point of interest for big pharmaceutical companies, continuously seeking promising products to fill out their drug pipeline to balance their expiring patent terms.

The growth of large (big) pharmaceutical companies - such as Johnson & Johnson, Pfizer, Novartis, Roche, Merck & Co., Sanofi-Aventis, GlaxoSmithKline, AstraZeneca, Eli Lilly, AbbVie and others - is largely

fueled by external innovation and inorganic growth through acquisitions. Incumbent pharmaceutical companies often acquire medical biotechnology start-ups that have successfully passed critical stages in the FDA (Food and Drug Administration) approval process (Knockaert et al., 2015). They keep a watching brief on the progress of innovative new biotechnology firms while hiring them to perform contract research and development (Oakey, 2013).

The central task of most biotech companies is the development of drugs or new diagnostic methods. The large majority of firms working in medically oriented biotechnology are either still in the preclinical stage of therapeutic research or developing technology platforms in modern drug development. Muralitharan et al. (2011) points out that most biotechnology companies conduct research in the discovery phase I of a new drug and biopharmaceutical companies take the new drug through phases II-III-IV (i.e. post-approval) and market it globally.

The long path to a new drug generally takes place in six distinct steps (Germany Trade & Invest, 2012). Drug discovery research encompasses four subsequent steps: target discovery, target validation, hit identification, and lead optimization. An early step is the identification of the drug target, a molecular structure that is involved in a disease or condition and which can be accessed using active substances.

Subsequent drug discovery describes the process of finding a chemical or biological substance that alters the action of the drug target in a manner that improves the medical condition. Drug discovery is often a trial-and-error process in which fully automated systems are employed to perform screenings of millions of drug candidates. Lead compounds isolated in this procedure are typically tested for their pharmacology, and sometimes chemically modified to improve tolerability in the human body. Further drug development can then be split into two main stages: preclinical studies and the all-important clinical trials. Many companies active in contract research services cover more than one of these stages.

The clinical development timeline and the pharmaceutical supply chain are illustrated by Fig. 1. and Fig. 2 respectively.

Phase I (early human clinical trials); Phase II (medium-sized); Phase III (large-scale human tests).

Fig. 1 – Clinical development timeline (ThromboGenics, annual report 2009)

Pre-clinical studies (animal tests).

Fig. 2 – Pharmaceutical supply chain (Deutsche bank, 2010)

The period between discovery and production is only part of the total lead time involved in the complete innovation process. In many potential markets, notably therapeutic drugs, the testing required in order to meet safety requirements is time-consuming, costly and often uncertain. The prediscovery research, conducted predominantly in public sector institutions, is not conventionally costed into the innovation process (Oakey et al., 1990).

The biopharmaceutical value chain has as keystone the approval of a new drug by the dedicated public authorities, i.e. the FDA in the United States (Food and Drug Administration) and the EMA in the European Union (European Medicines Agency). Pre-approval activities concern the research and development in phases I-II-III, whereas post-approval (phase

IV) activities concern the large-scale production and marketing of a new drug. The point of approval by FDA and/or EMA represents the boundary between cash absorption (the so-called burn rate) and cash generation.

According to PhRMA (2015), the average R&D cost required to bring a new, FDA-approved medicine to patients is estimated to be $2.6 billion over the past decade (in 2013 dollars), including the cost of the many potential medicines that do not make it through the FDA approval. From drug discovery through FDA approval, developing a new medicine on average takes at least 10 years.

② The Conceptual and Theoretical Framework

Prior research shows that innovation performance is linked to system, collaboration and networking. This study develops an understanding of the interdependencies between regional biotechnology policies, bioclusters and regional growth in knowledge and technology intensive bioRegions.

The **focus of this study** is on the interplay between new and innovative biotechnology firms, the influence of strategic alliances (interfirm partnerships) with large (global) pharmaceutical companies and the role that open innovation might play in the further reinforcement of these relationships within regional biotechnology clusters (bioRegions).

The research is addressed from the point of view of :
① the **policy governance level** (i.e. regional systems of innovation);
② the **firm level** (i.e. new biotechnology firms and their large counter-parts, the big pharmaceutical companies). It provides a longitudinal perspective (1982, first Belgian biotech – 2016) to the biopharma industry.

This dissertation takes a closer look at the strategic alliances portfolios of these small and large firms, together with the fairly new open innovation practices, through a set of four related research papers.

The **first paper** on strategic links between high-tech firms in the biotechnology and micro-electronics industries sheds considerable light on the networking process. It was published in Small Business Economics (Segers, 1993). A large body of literature was reviewed with respect to new technology based firms. The paper builds on the strategic regional technology policies that have been adopted in Belgium since the beginning of the 1980s. The regional dimension of technology policy raises the question whether a relationship can be established between strategic technology policy and the emergence of new technology based firms in Flanders and Wallonia. The key research questions are closely linked to the technological and marketing relationships between large and small firms by means of interfirm technology partnerships, i.e. strategic alliances. In addition, the potential pitfalls were identified. A multiple case study design (Yin, 1984) was chosen to develop an understanding of the impact of strategic partnering on new technology based firm-survival and growth. To improve the reliability of conclusions, a small number of

cases on Belgian new technology based firms in the biotechnology and micro-electronics industries were analyzed for the construction of a theoretical model.

The **second paper** (Segers, 1996) covers the role of regions and the policy incentives of regional governments in supporting technology-based entrepreneurship by means of the strategic regional technology policies that were adopted in Belgium since the beginning of the 1980s: THIRF/DIRV in 1983 in Flanders and the Opération ATHENA in 1982 in Wallonia. It was published as a book chapter in Gomez-Mejia et al. (1996). A large sample of literature and definitions on new technology based firms and strategic technology partnering was presented. A survey and case study design were used to highlight the characteristics of and differences between common starters and high tech entrepreneurs in the biotechnology and micro-electronics industries. One of the principal conclusions was that the combination of a small firm's know how with a larger firm's resources opens opportunities for synergies that can contribute to both firm's competitive advantage and to the creation of a regional growth potential.

In the **third paper** – published in Journal of Global Entrepreneurship Research (Segers, 2015) – new technology based firm survival and growth are connected with strategic partnering alliances and open innovation within technology clusters. Strategic alliances in the biotechnology industry allow new technology based firms to gain a foothold in this high-cost, high-risk industry. The impact of strategic alliances and open innovation on the success of new biotechnology firms in Belgium is examined by developing multiple case studies of firms in regional biotechnology clusters. A longitudinal follow up of the Belgian biotech startup ecosystem is presented. The main conclusion is that the future of new biotechnology firms in Belgium lies in the effective establishment of strategic alliances. Despite their small size and relative immaturity, Belgian new biotechnology firms are able to adopt innovative business models by providing R&D and services to larger firms and openly cooperating with them through open innovation.

Finally, the **fourth paper** (Segers, 2016) elaborates on the interplay between regional systems of innovation, biotechnology clustering, closed and open business models and open innovation. The paper was published in Journal of Small Business & Entrepreneurship.

The survival and growth of Belgian new biotechnology firms is put in perspective with their involvement in strategic alliances and the emerging attention for open innovation within biotechnology clusters (bioRegions). With regard to the concept of bioRegions, a comparison is made between Belgium and Germany. The focus of the case study design is on a sample of 30 new biotechnology firms. An overview of good practices and benchmarks with respect to open innovation is added to supplement the case-based evidence.

The literature review of the 1993 and 1996 papers is fully updated in the 2015 and 2016 contributions. The conceptual framework from Segers (1993; 1996) is further adapted into the current model (Segers, 2015; 2016), bringing open innovation into the framework (Fig. 3).

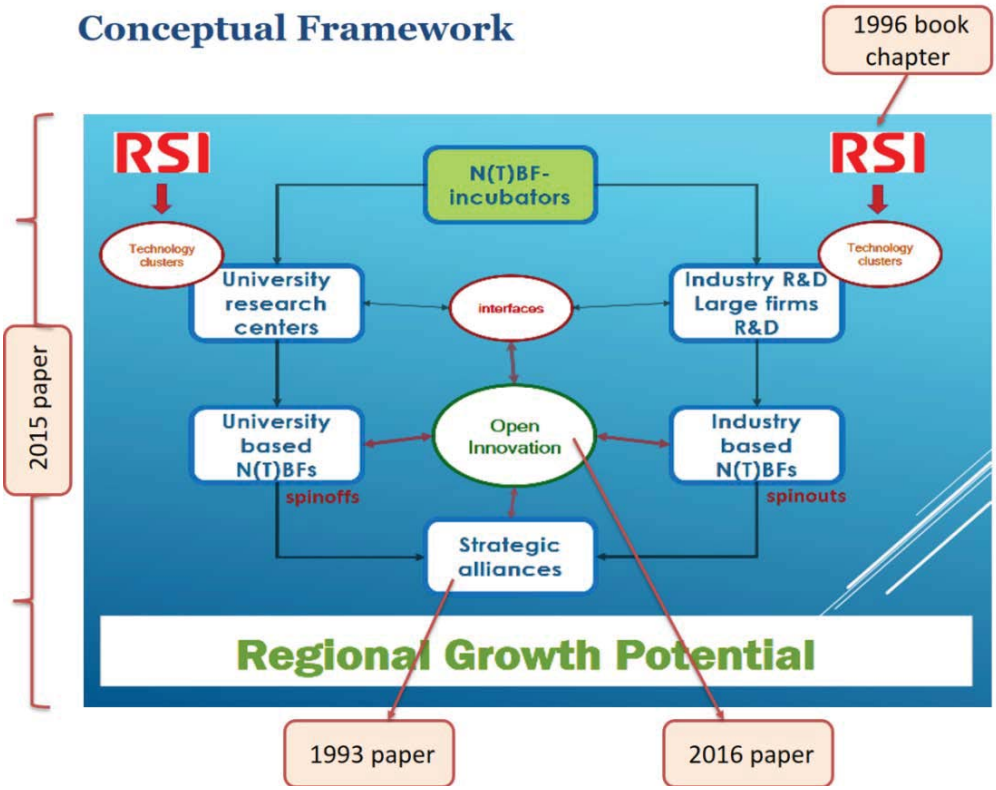


Fig. 3 – Conceptual framework

RSI: regional system of innovation | **NTBF**: new technology based firm | **NBF**: new biotechnology firm

Before proceeding, it is important to clarify the interplay of three theoretical approaches in this dissertation. The first approach explores biotechnology clustering from a regional systems of innovation viewpoint, "as an instance of rather strong sectoral, regional innovation systems capabilities, though integrated also to global knowledge supply and markets" (Cooke, 2002). The second and third approaches cover the strategic alliances and open innovation concepts. All these approaches focus on business model portfolio enhancement to maximize value creation-value capture and network dynamics.

The dissertation addresses four hypotheses, which will be tested by means of multiple case studies and the presentation of good practices and benchmarks in Chapter ③.

The **first hypothesis** relates to the systems of innovation theories.

H①: Regional systems of innovation (regional technology policies) have a significant impact on the creation of new biotechnology firms in Belgium.

Competitiveness, innovation and economic performance are highlighted on the supranational level (e.g. the Innovation Union flagship program in Europe and the OECD outlooks), the national level, the sectoral level and the regional levels. According to Capron and Cincera (1999), innovation systems are characterized by the close intertwining between several sub-systems that stress the following elements:

- institutional set-up;
- education and training structure and performance;
- science and technology (S&T) profile and base;
- industrial pattern;
- scope of interactions among institutions;
- degree of international integration of institutions.

The **national systems of innovation** (NIS) approach was originally conceived to explain the economic performance of nations and their international competitiveness (Asheim et al., 2011). NIS has a focus on national boundaries and on non-firms organizations and institutions. According to Capron and Meeusen (2000), the most salient characteristic of the NIS approach is its emphasis on networks. The national innovation system is defined by the OECD (1997) as a way to acknowledge "that the flows of technology and information among people, enterprises and institutions are key to the innovative process. Innovation and technology development are the result of a complex set of relationships among actors in the system, which includes enterprises, universities and government research institutions".

According to Malerba (2002; 2003), a **sectoral system of innovation** approach provides a design for innovation and technology policies. This approach focuses on three broad dimensions that affect the generation and adoption of new technologies and the organisation of innovation and production at the sectoral level:

- Knowledge, technological domain and boundaries: the specific knowledge base, technologies and inputs; also the dynamic complementarities;
- Agent (actors), interaction and networks: organisations and individuals (e.g. consumers, entrepreneurs, scientists); Organisations may be firms (e.g. users, producers and input suppliers) and non-firm organizations (e.g. universities, public research centers, financial institutions (e.g. venture capital companies), government agencies, trade-unions, or technical associations), including sub-units of larger organisations (e.g. R-D or production departments) and groups of organisations (e.g. industry associations);
- Institutions: a lot of institutions are national (such as the patent system and/or property rights), while others are specific to sectoral systems, such as sectoral labour markets or sector specific financial institutions.

Innovation is most effectively addressed at the regional level, as physical proximity fosters the partnerships between actors in both public and private sectors. The concept of **regional systems of innovation** has evolved into a widely used analytical framework generating the empirical foundation for innovation policy making (Doloreux and Parto, 2004).

The regional innovation system (RIS) is a normative and descriptive approach that aims to capture how technological development takes place within a territory, i.e. the region. The innovative performance of regions is improved when firms are encouraged to become better innovators by interacting both with various support organizations and firms within their region.

A rich body of literature has been developed since the early 1990s (Asheim, 2009; Asheim et al., 2013; Cooke, 1992; 1998; 2001; 2008; Cooke et al., 1997; 2006; Capron and Meeusen, 2000; Doloreux, 2002; 2005; Dohse, 2003; Edquist, 1997; 2005; European Union, 2014; OECD, 2011; Pessoa, 2012). Cooke (1992; 1998) provided a typology of different types of RIS. Much of the existing literature has focused on highly successful RIS and on regions characterized by a prevalence of medium- to high-technology industries.

The system of innovation approach focuses on the fact that firms do not innovate in isolation, but rather in collaboration and interdependence with other organizations such as other enterprises, universities and government research institutions. Autio (1998) distinguishes between a number of characteristics for a successful regional innovation system:

- the regional production structure displays clustering tendencies (Asheim and Gertler, 2006);
- the knowledge application and exploitation subsystem: innovative industries – innovative companies;
- the knowledge generation and diffusion subsystem: higher education institutions, research centers and other intermediaries. the OECD (2011) refers to knowledge hubs;
- intensive interactions between subsystems in terms of scientific and applied knowledge and human resources flows, including links with other (inter)regional and (inter)national institutions;
- high-quality infrastructures and institutional setting, including sufficient regional autonomy;
- regional policy actors.

At the regional level, the successful establishment of an efficiently operating industry sector through value-added growth, competitive advantage and an increase in employment takes place within geographically localized networks – called **clusters**. According to the best-known taxonomy of innovating firms, clusters can be categorized as science-based, scale-intensive, supplier dominated and/or specialized suppliers (Pavitt, 1984). A degree of openness is a key part of the comparative advantages that clusters offer over non-clustered locations (Oakey, 2013).

A cluster is "a geographical concentration of actors in vertical and horizontal relationships, showing a clear tendency of cooperating and sharing their competencies, all involved in a localized infrastructure of support" (Zechendorf, 2011). They include government agencies, public organizations, higher education and research institutions, cooperating companies, suppliers and financial structures. They compete and cooperate simultaneously within the same industry sector. Geographical proximity provides a platform for strong cooperation and the flow of knowledge and expertise between research institutions, companies and policy makers.

Cluster and technology policies are merely means for achieving regional growth. Technology policy is defined as the sum of all regional state measures promoting new or existing technologies for economic use in its widest sense (Sternberg, 2003). Innovation and technology policy could be supplemented by other types of policies, such as science policy, industrial policy, policies related to standards and IPR, and competition policy. This point highlights the importance of the interdependencies, links, and feedbacks among all of these policies, and their combined effects on the dynamics and transformation of sectors (Malerba, 2002). Audretsch et al. (2016) found that public cluster policies positively affect regional entrepreneurial activities, but only in part. The overall effect of government subsidization is rather low compared to the impact of local research intensive universities and the innovative milieu on new venture creation.

According to Laur (2015), regional authorities should encourage multi-faceted collaboration, in line with the "triple helix"-model by Etzkowitz and Leydesdorff (1997; 2000) which creates constructive and mutually reinforcing activities between (1) academia, government, and industry and

(2) between research and commercialization of technology (Kerry and Danson, 2016).

In summary, regional innovation involves diverse players, including clusters of higher education institutions (universities and university colleges), knowledge centers and research centers for fundamental, basic and applied research, business ecosystems for established companies and innovative startups, government institutions, technology transfer offices, investment funds and startup incubators and accelerators.

The **second and third hypotheses** are positioned within the subfields of the strategic alliances and the business model portfolios in the pharmaceutical-biotechnology regional and sectoral system.

H②: The development process of new biotechnology firms in the bioRegions of Flanders and Wallonia depends on setting up strategic alliances. Working closely together with international large (bio)pharmaceutical companies is beneficial to maximize value creation/value capture.

H③: Most of the new biotechnology firms in Belgium are unlikely to become fully integrated pharmaceutical companies.

The pharmaceutical-biotechnology industry has continuously adapted to its environment by increased in/outsourcing of research and development through **strategic alliances**. The term alliances covers several governance modalities ranging from relational contracting to licensing, to logistical supply-chain relationships, to equity joint ventures or to the complete merger of two or more organizations (Contractor and Lorange, 1988; 2002). In order for a strategic alliance and collaboration to be successful is for both parties to be able to transfer something distinctive to the other party: basic research, product development skills, manufacturing capacity, access to distribution and marketing. The primary goal when entering into collaborative agreements is the sharing of the costs of research and development and of the risks involved (Hamel et al., 1989; Gassman et al., 2008).

Oakey et al. (1990) point at the variety of inter-institutional research collaborations involving large firms with academia, with other large firms,

and with small companies, notably new biotechnology firms. Large firms use small firms as a window on leading-edge technological developments (with a view to possible acquisition), while small firms view large firms as sources of patronage and investment, providing control is not lost in exchange for financial support. In most traditional interfirm partnerships, smaller firms perform research and development for the larger firms or transfer innovations to them.

Interfirm competition is affected by increased technological development, innovation races and the constant need to generate new products (Hagedoorn, 2002). Consequently, one of the most significant developments in the structure of the global biotechnology industry is competitive collaboration (Gay, 2014) or collaboration networks characterized by co-opetition dynamics (Quintana-Garcia and Benavides-Velasco, 2004), networks involving multiple partnering activities (Mytelka, 1999) and integration with the global value chains (Cooke, 2003). Cooperation with direct competitors involves the trade-off between access to greater resources and the potential for loss of proprietary information or the creation of stronger competitors.

According to Pisano (2006), alliances mostly have a short-term focus, as priority is given to the deal, not to the building of joint long-term capabilities. The relationship is often centered on reaching specific, short-term milestones. On the other hand, Segers (1992) and others seem to expect that these networks of R&D collaboration in the biotechnology industry are of a more long-term nature because functionally specialized companies can easily maintain various relations with each other through distinctive transactions. This is expected to be a long-term affair that will affect the continuation of a network-like structure of innovation in the biotechnology industry for decades (Hagedoorn and Roijakkers, 2000).

Suarez-Villa and Walrod (2003) argue that most biotechnology firms in existence today might not have survived without the support provided by the many collaborative agreements that have developed in this industry. The high cost of commercialization make it unlikely that any new, small firm can succeed on its own. To overcome this challenge, many smaller firms enter into strategic partnership alliances with larger firms. Most large pharmaceutical companies find it cheaper not to do the expensive research themselves, but instead to fund academic entrepreneurs to do it.

A new biotechnology firm may be involved in drug discovery focusing on the identification of new drug targets, but may not have the necessary capital resources to take the drug candidate to market. The small biotechnology firm will therefore require a strategic alliance with a large pharmaceutical company to take the product to market (Hine et al, 2006).

Rothaermel and Deeds (2004) propose an integrated product development path for building alliances based on the exploration-exploitation framework by March (1991). Successful exploitation enables the firm to commercialize the knowledge gained through exploration. Exploration alliances focus on products in development, whereas exploitation alliances lead to products on the market.

Pharmaceutical companies use different modes of adaptation – from internal investments over a range of strategic alliances (Rybka et al., 2015) to acquisitions. The most important are:

- Research and development alliances

In the traditional outsourcing agreements in the early R&D stages, a large firm gives a smaller firm the information necessary to produce a defined item for the parent firm. In the case of research alliances, both partners focus on issues related to basic research and drug discovery. They usually intend to come up with new targets or compounds by leveraging their individual technology platforms, know-how or capital. According to Du et al. (2014), R&D partnerships also facilitate the implementation of open innovation.

According to Rothaermel (2001), typical research alliances of pharmaceutical companies include target identification partnerships with new biotechnology firms. The biotech firms' rationale to enter into research alliances with large pharmaceutical companies is to access distribution channels as well as capital for the cost-intensive clinical development activities (Gassmann et al, 2008).

Outsourcing some R&D activities to pharmaceutical service providers might lead to time and cost savings and access to new technologies and know-how. Besides biotechnology, genomics-based and other platform companies, the outsourcing partners include the contract service and manufacturing organizations (CRO and CMO);

- Joint ventures in R&D (Hamel et al., 1989)

Joint ventures typically focus on co-development or research for a special purpose or therapy area (joint research);

- In-licensing of intellectual property

Management of intellectual property used to be purely defensive. In current times it is becoming a critical enabler to access external ideas, and/or to profit from letting ideas go out to others (Chesbrough et al, 2016);

- Licensing agreements

whereby one partner licenses intellectual property for exploitation. The firms sell or acquire the rights to others' assets. In the biopharmaceutical industry, this generally involves target sourcing, or basic techniques, or biological materials that have application to more than one end product. These agreements mostly translate in annual user fees for access to proprietary assets. Licensing agreements may include a milestone structure in compliance with cooperation phases and define adaptable responses for positive and negative events which may occur in correlation with a milestone or to changed development or business needs;

- Marketing or distribution agreements

wherein firms embark on a joint marketing campaign or where the large pharmaceutical company uses its well-established distribution channels to distribute the new biotechnology firm's offering;

- Equity research alliances (Diao-Piezunka and Felitti, 2016)

through board participation and/or oversight, ensuring the investing firm's alignment and commitment to the research alliance;

- Spin-offs and divestitures of R&D activities that are either not sufficiently promising or do not fit into the business strategy;

- Mergers and acquisitions

M&A-activity is increasingly becoming a vehicle to grow revenue, especially for branded pharmaceuticals and medical device manufacturers (Jones Lang LaSalle, 2015).

The **fourth hypothesis** that is put forward in this dissertation is about the growing application of **open innovation** practices in the pharmaceutical-biotechnology regional and sectoral system.

H④: Belgian new biotechnology firms apply open innovation in their development and growth patterns, thus taking strategic partnering to a next level.

Open innovation is broadening the range of external technology sourcing – which was limited a decade ago to strategic alliance networks and the acquisition of external technology partners (Wang et al., 2011). Companies increasingly consider the use of external knowledge as a complement to inhouse innovative activities (Teirlinck and Poelmans, 2012).

The open innovation paradigm was introduced by Chesbrough (2003; 2006) and Chesbrough et al. (2006). Open innovation is an innovation paradigm shift from a closed to an open model. It is the opposite of the conventional, vertically integrated research and development model, in which companies rely heavily on internal knowledge and resources (Deloitte, 2015a; Chesbrough et al, 2006).

According to Chesbrough et al. (2006), "open Innovation is a new paradigm that assumes that firms can and should use external ideas as well as internal ideas and internal and external paths to market, as the firms look to advance their technology". Open innovation is defined as "the use of purposive inflows and outflows of knowledge to accelerate internal innovation, and extend the markets for external use of innovation, respectively". Open innovation is "a distributed innovation process based on purposively managed knowledge flows across organizational boundaries, using pecuniary and non-pecuniary mechanisms in line with the organization's business model" (Chesbrough and Bogers, 2014).

The open innovation model is criticized by Oakey (2013). Open innovation may not be readily appropriate for most high technology small firms for valid strategic reasons, intellectual property being a key asset, as confidentiality is often necessary to protect intellectual property rights gained through long-term, expensive, and risky development endeavors (Hossain, 2015; Hossain and Kauranen, 2016).

Chesbrough's work within this context tends to overestimate the potential for greater openness in terms of industrial R&D since a degree of openness has always existed, while at the same time underestimating the benefits of closed innovation systems (Wynarczyk, Piperopoulos & McAdam, 2013).

The central idea behind open innovation is that in knowledge ecosystems (Valkokari, 2015), companies cannot afford to rely entirely on their own research, but should instead buy or license processes or inventions (e.g. patents) from other companies. In addition, internal inventions not being used in a firm's business should be taken outside the company, through licensing, joint ventures, spin-offs (Chesbrough, 2003; Pustovrh & Jaklic, 2014). Companies use open innovation to source external knowledge, innovative ideas and technologies from outside the organization. Open innovation involves opening up R&D processes through pooling of collaborative activities and/or trading of intellectual property rights (Gassmann, 2006) and liberally sharing information, capabilities and intellectual property with other organizations, including competitors. A distinctive feature is that it may leave collaborators free to exploit a new technology in other, non-competing areas.

Under open innovation, large firms do not abandon the traditional vertically integrated approach, but rather augment their traditional R&D practices with inbound sourcing of external technologies throughout the product development process, as well as controlled outflows of internal technologies seeking new markets through outbound licensing (West et al., 2014). Findings by Gurău and Lasch (2011) indicate that the size of the firm, its organizational stage, its capability to develop partnerships and its capacity to identify partner organizations with complementary resources influence the capacity of biopharmaceutical firms to implement and manage open innovation systems.

The focus of this field of research is not only on open innovation practices in large firms. The open innovation approach is providing new ways for firms of all sizes to collaborate and interact. It is creating opportunities for (high technology) small firms. Hossain and Kauranen (2016) found that adopting open innovation by small and medium sized enterprises improves their overall innovation performance. Spithoven et al. (2013) argue that small and medium sized enterprises are more inclined to use different sets of open innovation practices than large firms. Wynarczyk (2013) argues

that the small and medium sized firms tend to put more emphasis on research and development teams than do their closed innovation counterparts.

At the heart of the open innovation model is the recognition that today, competitive advantage often comes from inbound as well as from outbound connections. Chesbrough and Brunswicker (2013) differentiate between inbound open innovation where external knowledge flows inside the firm, and outbound open innovation where knowledge flows outside the firm. According to Chesbrough and Crowther (2006), Gassman and Enkel (2004), Enkel et al. (2009), Michelino et al. (2015) and the European Union (2016) the concept of open innovation is constantly evolving. Open innovation has three dimensions, as illustrated in Fig. 4 and 5:

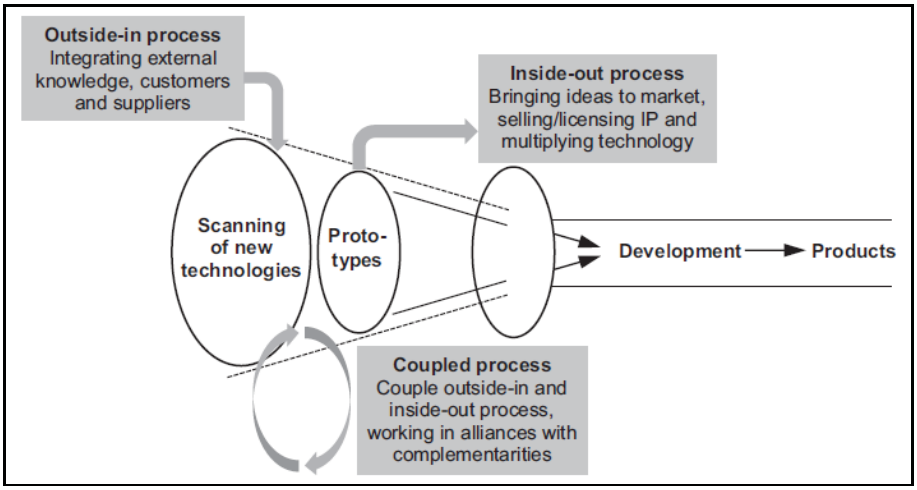


Fig. 4 – Open innovation model (Gassman and Enkel, 2004)

Fig. 5 – Open Innovation mechanisms (European Union, 2016)

1. Inbound open innovation or the outside-in process:

enriching the company's own knowledge base through the integration of suppliers, customers and/or external knowledge sourcing. Companies should not rely exclusively on their own research and development. The acquisition and transfer of external technologies, ideas and knowledge into the firm through research collaborations with universities, the use of innovation intermediaries, involvement of users (Von Hippel, 2005), customers, suppliers, business partners and even competitors (Remneland et al, 2016); in-licensing, mergers and acquisitions. Pittaway et al. (2004) emphasize the link between business network relationships with suppliers, customers and intermediaries and the innovative capacity of firms. Building absorptive capacity – firms' ability to sense, value, assimilate, and apply new knowledge – is a prerequisite for sourcing innovation from external sources. A higher absorptive capacity in small firms entails a higher propensity to engage in both research cooperation and research and development outsourcing (Teirlinck and Spithoven, 2013).

2. Outbound open innovation or the inside-out process:

earning profits by bringing ideas to market, the transfer of technology and knowledge (selling intellectual property) to external firms and their commercial exploitation through out-licensing, joint-ventures, venture spin-outs, etc. Outbound open innovation entails that firms do not only rely on internal paths to market, but also look for external organizations with business models that are better suited to commercialize a given technology (Chesbrough, 2002).

3. Coupled process:

this involves co-creation with complementary partners through alliances, cooperation, and joint ventures during which give and take are crucial for success.

In the early stages of research and development, open innovation offers a neutral platform for companies to jointly investigate emerging technologies, applications and business models while sharing risks and costs. According to Michelino et al (2015), the economic dimension of open innovation can be characterized by costs and revenues deriving from:

1. collaborative and contract development: collaborative agreements, development partners' reimbursements, cost or profit-sharing agreements, share of results of research associates, contract fees, development milestone payments and achievements, up-front payments and receipts;

2. outsourcing of research and development services.

Big pharmaceutical companies use in-licensing (inbound innovation) as a main contractual form. Conversely, biotech companies are in effect on the sell side of the open business model, i.e. out-licensing; value creation and outbound innovation. They typically gear toward explicit, short-term milestones. Muralitharan et al. (2011) point out that open innovation adds value to the development of new biopharmaceuticals, even if in joint research and development initiatives biopharmaceutical companies do not own the intellectual property and pay royalties for the jointly developed technology with the new biotechnology firms.

According to Remneland Wikhamn et al. (2016), Chesbrough and Chen (2015) and Damani (2013), big pharmaceutical companies now experience a greater push towards models of collaborative drug discovery and development. External knowledge is made available outside a firm through open innovation approaches, open source biotechnology, models of co-development and collaborative innovation (Tamoschus et al, 2015). Drugs sourced via open innovation have a higher chance of later-phase clinical success (Deloitte, 2015a).

With blockbusters running off patent and generics/biosimilars being launched, the paradigm shift in drug discovery is mainly motivated by the pressure on the pharmaceutical research and development pipeline (Tamoschus, 2014; Deloitte, 2015b). The growing regulatory demands by the FDA (Food and Drug Administration) and EMA (European Medicines Agency) translate into longer trials and higher costs. As revealed in Cooke (2007), data showed that the dedicated biotechnology firms were outperforming big pharma at a massively lower research cost for a larger number of new chemical entities. This was the point from which big pharma began a retreat from direct drug research and early exploitation in favour of entrenching the 'open innovation' relationship with specialist new biotechnology firms to the forefront.

③ The Case of New Biotechnology Firms in Belgium

In this chapter, the empirical evidence is presented for the regional biotechnology innovation system in Belgium. The focus is on the case-based evidence for biotechnology clustering in the bioRegions of Flanders and Wallonia, together with a longitudinal follow up of a sample of Belgian new biotechnology firms in the health-related (red) biotechnology subsector.

1 The institutional profile

Belgium is one of the founding and key member countries of the European Union. It is a small highly open knowledge based economy and is very open to international trade and foreign direct investment. The Belgian economy is strongly service-oriented and it has some internationally competitive technology sectors, such as pharmaceuticals and chemicals (OECD, 2014).

The three regions of the federal state of Belgium are Flanders, Wallonia and Brussels (capital district). A number of state reforms since the beginning of the 1980s – with the institutional reform act of 8 august 1980 and its subsequent amendments – triggered the development of the regional systems of innovation in Belgium over de past decades.

The institutional profile is of crucial importance in setting up policy instruments and to enhance framework conditions to stimulate research and development and innovation. It is a factor that should not be neglected because of the high level of autonomy that was given to the regions – so called federated entities - in the fields of economic policy, scientific research and (higher) education:

- the federal level is responsible for fiscal policy (taxes and incentives), labor market, social security, the national health system, the regulatory framework and intellectual property law;
- the regions bear the primary responsibility for science, technology, (higher) education and economic policy. As such, they control the main levers for innovation policy (Spithoven, 2013). The regions are the main source of scientific research support, innovation and business R&D support.

The above is of the utmost importance to understand the development and evolution over the past decades of the biotechnology industry in Belgium. Each of the regions set up and initiated top class organizations devoted to biotechnology.

2 Key biotechnology indicators

The pharmaceutical industry is one of the driving forces of the Belgian economy. According to the OECD (2006), for performance in innovation and industry development as measured by patent applications, the number of drugs in the pipeline, venture capital invested in biotechnology and the number of new biotechnology firms, Belgium is among the leading countries. Within the European Union, the pharmaceutical industry - in terms of value added - is highly concentrated in a number of countries (IWEPS, 2016): Germany (22.5%), United Kingdom (16%), France (12.4%), Ireland (10.8%), Italy (8.1%). Belgium accounts for 6.1% of European value added. The bioRegions of Flanders and Wallonia host a number of global players in medical research and development.

Belgium is a key player in Europe for biopharmaceutical research and development (R&D) and manufacturing. According to Essenscia (2015b), the Belgian pharmaceutical industry is highly R&D-intensive, with about 35% of the Belgian R&D conducted by pharmaceutical companies (Fig. 6a and 6b).

In 2011, the three largest business R&D spenders were pharmaceutical companies. In particular, 85% of the R&D in the top R&D sector (pharmaceuticals) is carried out by foreign-controlled affiliates. Furthermore, their R&D activities rely more on cooperation, exchange, outsourcing and subcontracting than their resident-controlled counterparts (Spithoven, 2013).

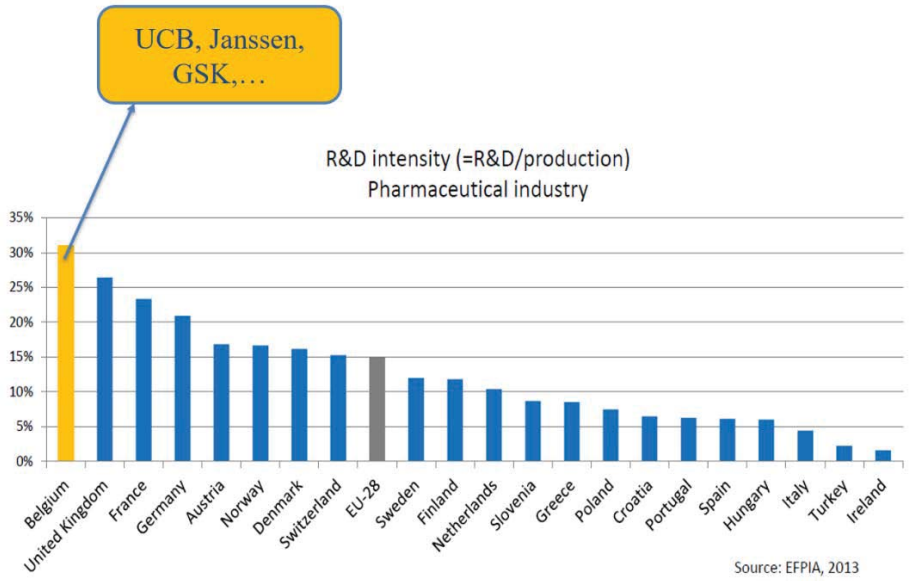


Fig. 6a – R&D Intensity (Essenscia, 2015b)

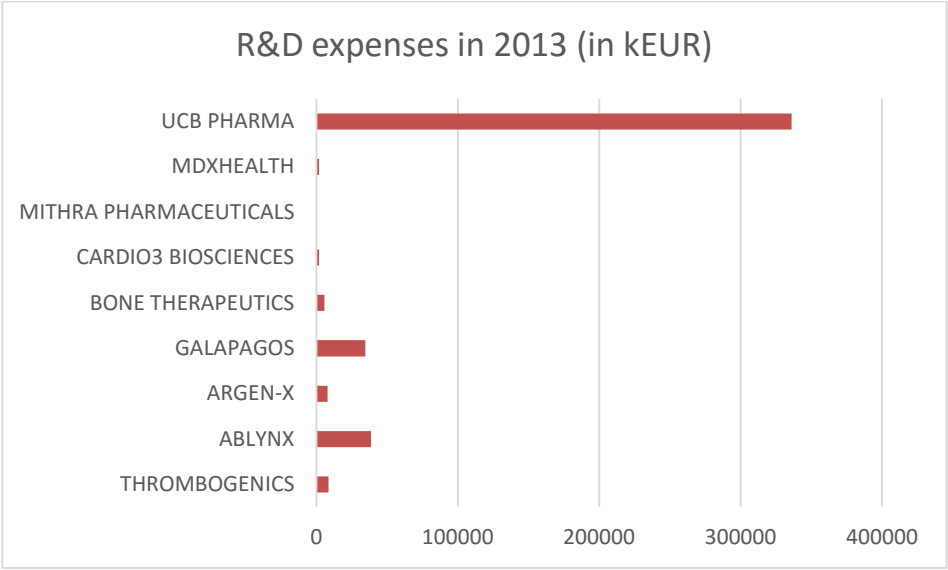


Fig. 6b – R&D expenses 2013 (Belgian Science Policy – Belspo, 2015)

Belgium was ranked in the top 10 of most innovative (bio)pharmaceutical valleys in the world in 2010. Pharma.be (2014) states that 30% of the European biotech industry (in value) is located in Belgium. Companies in the pharmaceutical industry in Belgium range from big pharmaceutical corporations to a large network of small and new biotechnology firms that specialize in all areas of biopharmaceutical fundamental and clinical research and manufacturing (Teirlinck and Poelmans, 2012).

Belgium ranks in the world top 10 in terms of patents applied for per capita from the European Patent Office (Essenscia, 2015a). Switzerland and Finland rank first and second. Direct employment amounted to 32.700 in 2014 (EFPIA, 2014), mainly in health-related biotechnology (80%) (Belgian Foreign Trade Agency, 2011). The percentage of dedicated biotechnology firms in Health is 58.3% for Belgium against 49.4% for Germany (OECD, 2015).

Belgium has the largest number of medicines in development in the world per capita. It is also a European leader in the number of clinical trials in phase I and II per capita. The Flanders bioRegion acts as a regional hub for pre-clinical trials (Ranger and Lawton, 2015). Belgium is a world center of vaccines R&D and manufacturing, both in Flanders (Flanders Vaccine Cluster) as in the Wallonia bioRegion (e.g. GlaxoSmithKline).

According to the Organisation for Economic Co-operation and Development (OECD, 2009; 2011; 2013), the number of biotechnology firms is the most widely available indicator but it is not the best measure of a country's activity in biotechnology, owing to large differences in firm size and R&D intensity.

The key biotechnology indicators of the OECD (2015) show that a considerable number of firms in Belgium are active in biotechnology (Table 1).

Key Biotechnology Indicators (OECD, 2015)					
Number of firms active in biotechnology, 2013 or latest available year					
OECD, Key Biotechnology Indicators, http://oe.cd/kbi, July 2015.					
	Biotechnology firms	Dedicated biotechnology firms	% dedicated	Year	Type of firm
United States	11 367	1 165	10,2	2012	Biotech R&D firms
Spain	2 831	554	19,6	2013	Biotech firms
France	1 950	1 284	65,8	2012	Biotech R&D firms
Germany	709	578	81,5	2014	Biotech firms
Belgium	350	127	36,3	2011	Biotech R&D firms
Netherlands	262	65	24,8	2010	Biotech R&D firms
Ireland	237	193	81,4	2011	Biotech R&D firms
Switzerland	233	134	57,5	2012	Biotech R&D firms
Finland	157	70	44,6	2011	Biotech R&D firms
Denmark	134	58	43,3	2013	Biotech R&D firms
Austria	128	95	74,2	2012	Biotech firms
Czech Republic	115	85	73,9	2013	Biotech R&D firms
Sweden	102	54	52,9	2013	Biotech R&D firms
Numerator: Number of biotechnology firms (production and/or R&D firms)					
Denominator: Total of biotechnology firms (production and/or R&D firms)					

Table 1 – Number of firms active in biotechnology, 2013 or latest available year (OECD, 2015)

The European Union's Regional Innovation Scoreboard (RIS) provides a comparative assessment of innovation performance across 190 regions of the European Union, Norway and Switzerland. Denmark, Finland, Germany, Netherlands, Sweden (2016) and Switzerland (2014) are the regional innovation leaders. Belgium, i.e. Flanders, Wallonia and Brussels, is categorized as a regional strong innovator.

According to the Regional Innovation Scoreboard (2014; 2016), for most countries, there is limited variation in regional performance groups, suggesting that regional and national innovation performance are linked. Austria, Belgium, Bulgaria, the Czech Republic, Hungary, Ireland and Romania show a relatively homogenous innovation performance as all regions in those countries are in the same performance group (EU-RIS, 2016).

Taking these countries into account, the following statistics apply for the selected RIS indicators (Table 2):

Country	R&D expenditure in the public sector		R&D expenditure in the business sector		Innovative SMEs collaborating with others		Patent Applications European Patent Office	
	RIS-2014	RIS-2016	RIS-2014	RIS-2016	RIS-2014	RIS-2016	RIS-2014	RIS-2016
Belgium	0,381	0,244	0,472	0,501	0,601	0,681	0,357	0,406
Flanders	0,406	0,269	0,505	0,536	0,672	0,818	0,404	0,470
Wallonia	0,322	0,195	0,531	0,624	0,600	0,527	0,409	0,460
Denmark	0,509	0,405	0,547	0,455	0,498	0,503	0,454	0,559
Finland	0,469	0,264	0,574	0,519	0,516	0,465	0,380	0,585
Germany	0,540	0,307	0,467	0,466	0,434	0,338	0,450	0,581
Netherlands	0,422	0,247	0,344	0,372	0,483	0,486	0,372	0,417
Sweden	0,502	0,299	0,566	0,510	0,576	0,430	0,475	0,568
Switzerland	0,428	n/a	0,626	n/a	0,301	n/a	0,587	n/a

Adapted from EU-RIS 2014 and EU-RIS 2016 (Eurostat Regional Statistics)
RIS: Regional Innovation Scoreboard

Table 2 – RIS indicators – adapted from EU-RIS 2014 and 2016

- R&D expenditures in the public sector (%)
R&D expenditure represents one of the major drivers of economic growth in a knowledge-based economy. As such, trends in the R&D expenditure indicator provide key indications of the future competitiveness and wealth of the EU. Research and development spending is essential for making the transition to a knowledge-based economy as well as for improving production technologies and stimulating growth.

- R&D expenditures in the business sector (%)
The indicator captures the formal creation of new knowledge within firms. It is particularly important in the science-based sector (pharmaceuticals, chemicals and some areas of electronics) where most new knowledge is created in or near R&D laboratories.

- Innovative SMEs collaborating with others (%)
This indicator measures the degree to which SMEs are involved in innovation co-operation. Complex innovations, in particular in ICT, often depend on the ability to draw on diverse sources of information and knowledge, or to collaborate on the development of an innovation. This indicator measures the flow of knowledge between public research institutions and firms and between firms and other firms. The indicator is limited to SMEs because almost all large firms are involved in innovation co-operation.

- EPO Patent Applications (per billion GDP/Regional Gross Domestic Product)
Number of patents applied for at the European Patent Office (EPO), by year of filing.

Belgium has a relatively high number of firms active in biotechnology compared to innovation leaders like Germany, Switzerland, Finland,

Denmark, Netherlands and Sweden. Belgium represents 16% of the European biopharmaceutical industry (Ranger and Lawton, 2015). It accounts for 7% of European biotechnology firms and 10% of R&D expenditures (OECD, 2011; 2014).

Business enterprise research and development expenditures on biotechnology as a share of total business sector R&D expenditure (BERD) is an indicator of a country's research effort. On average, it accounted for 5.7% of BERD in 2009 and 5.9% in 2011. With 19.4 % in 2011, Denmark spent the most on biotechnology R&D as a percentage of BERD, followed by Ireland (17.2%), Switzerland (12.6%) and Belgium (12.6%; 2009).

Denmark has the largest specialisation ratio in biotechnology followed by Singapore and Belgium. The revealed technological advantage as defined by the OECD is a country's share of patents in a particular technology field divided by the country's share in all patent fields. The index is above 1 when a positive specialisation is observed. Next to the United States (> 40%), Denmark, Belgium, Singapore and Canada all have a strong revealed technological advantage in biotechnology with more than 10% of their patent portfolio dedicated to biotechnology (OECD, 2009). An alternative measure of research focus on biotechnology is biotechnology R&D intensity, defined as biotechnology R&D expenditure as a share of total value added of the industry sector. This ratio was 0.31% for the USA, followed by Switzerland (0.28%), Ireland (0.27%), Belgium (0.26%) and Sweden (0.24%).

Finland, Belgium, Germany, Ireland, Austria and France have a high degree of public spending in biotechnology, whereas Sweden, Switzerland and the United Kingdom rely much more on private spending for research and development. The share of biotech funding of the total public funding of R&D is particularly high in Belgium, Ireland and Finland, but very low in Sweden, Switzerland and Denmark (Jonsson, 2007). Within Europe, Switzerland is frontrunner when it comes to public biotech market value, with Denmark in second place (Joos, 2015; Ranger and Lawton, 2015).

The Belgian biotech market capitalization accounts for 20 % of the European biotech market cap (shares outstanding x share price). Based on the average market value per company, Belgian public biotech companies even rank first. Belgium has the most venture capital available per dedicated biotech company, compared to other European Union countries.

3 The Flanders and Wallonia bioRegions

Biotechnology is developing in several forms such as **bioclusters and bioRegions**, i.e. regional clusters of life science activities and networks. For the purpose of this study, a bioRegion is defined by the definition of the European Commission (PwC, 2011; Zechendorf, 2008): "Any geographically meaningful entity which can, but has not necessarily, to be a political or administrative entity for which the promotion of biotech and/or life sciences has been defined as a priority. Such a bioRegion can, but need not, contain one or several bioclusters and biotech, bioscience, life sciences parks, which are supposed to interact in order to enhance their efficiency". Bioclusters in this study focus primarily on health-related biotechnology. They represent spatially (predominantly regionally) concentrated economic activities (Sternberg, 2003), where new biotechnology firms and large companies are mainly connected with the regional science infrastructure (research labs, universities, hospitals, etc.), as well as industrial associations and public institutions. Cooke (2013) argues that, without clusters of such expertise, a country can have no biotechnology industry.

A sectoral strategy for technological innovation reflects the desire to establish industries in sectors which allow interfacing university and technological research with the needs and/or the potential of the industry. From the beginning of the 1980s, there was a strong regional focus on programmes fostering network structures between science and industry. Regional policymakers in Flanders and Wallonia initiated successive regional technology policies. The basic purpose of these region-specific technology policies was to mobilize regional research and technology development resources in order to stimulate self-generating regional growth (Donckels and Segers, 1990). The emphasis was and still is on regional technology clustering, new technology based firm creation and on building international strategic alliances (interfirm technology partnerships).

In the early 1980s, the THIRF (Third Industrial Revolution in Flanders, 1983) and the Opération ATHENA (Wallonia, 1982) regional technology programmes were launched (Segers, 1987). Large government supported and financed science and technology campaigns were set up. Networked research centers and interuniversity poles were created to provide a strategic orientation for research (OECD, 2006).

Regional policymakers in Flanders and Wallonia gave a priority status to micro-electronics and biotechnology as the focal generic technologies. To support this process, the private sector created a support network of high technology product groups (Flanders) and "pôles de compétitivité" (Wallonia). Flanders established the Interuniversity Micro-electronics R&D Centre and the Flemish (interuniversity) Institute of Biotechnology. The Walloon government developed its poles of excellence, i.e. horizontal and vertical cross-boundary networks with academia and industry.

The first regional technology programmes were followed by successive science and technology programmes to prepare the Belgian and regional economy for the impact of new generic and disruptive technologies in new and specialist product-market niches: Flanders in Action/New Industrial Policy; Marshall Plan 4.0 Wallonia (fourth industrial revolution) and the new WALInnov (2016) program.

Region-specific technology policy (Segers, 1992; 1993) has been organized around the following focal points:

- the state of the art research potential in universities and other centers of excellence, together with substantial incentives for corporate research;
- the emergence of and support for new technology based firms in micro-electronics and biotechnology;
- cooperation and technology transfer between university research centers and small (new technology based) firms and large (established) companies;
- industry-academia research and technology development linkages.

Over the years, regional public authorities in Flanders and Wallonia have created a wide range of incentives for stimulating technological innovation and for assisting new technology based firms (Segers, 1996), such as:

- financial and fiscal incentives: a fiscal framework to encourage the flow of private risk capital into new ventures;
- tax incentives for research and development activities: patent income deduction and the new innovation deduction scheme (applicable to patents, copyrighted software, plant breeders' rights, orphan drug designations and data/market exclusivity for medicinal products); research and development tax credit; tax exemption for researchers;

- equity finance; access to seed, venture and growth capital;
- an active public market for trading of shares in new ventures (initial public offerings);
- government supported laboratories and industry specific collective research centers;
- infrastructural incentives: science parks and incubators in the proximity of universities for stimulating and assisting university spin-offs;
- a targeted policy of incentives to attract high-achieving and entrepreneurial scientists;
- retaining and attracting skilled manpower.

As Cooke (2002; 2013) stated, many regional governments are known to have important competencies and budgets in the field of biotechnology innovation. This is also true for Belgium, where biotechnology was chosen as a top priority sector to position the Flanders and Wallonia bioRegions at the forefront of European bioRegions. Government organizations, universities, public and private research institutions, venture capital/high risk finance providers, new biotechnology firms and existing large companies are the key players in the regional biotechnology clustering process.

The Belgian biotechnology model was clearly created as a university spin-off model. Strong collaboration between research institutions, universities, financiers and existing companies has resulted in many university spin-offs. The basic innovative activity occurs mainly in university based new biotechnology firms, i.e. small, new firms that are spin-offs from university research centers performing state of the art research. Networked research centers and interuniversity poles of excellence were created to provide a strategic orientation for biotechnology research (OECD, 2006). Venture capital companies actively participate in these new biotechnology firms. The funding of research and development is of major importance to new biotechnology firms. On the other hand, large and international (bio)pharmaceutical companies participate in or establish a variety of strategic alliances with university research centers and small university based new biotechnology firms.

In Flanders as well as in Wallonia the biotechnology and life sciences industries are represented by a number of regional government and private

sector network organizations that actively participate in the biotechnology clustering activities. This supports hypothesis **H1**:

> **H①**: regional technology policies (regional systems of innovation) have a significant impact on the creation of new biotechnology firms in Belgium.

Belgium (general)

- ✓ Essenscia (Belgian Federation for Chemistry and Life Sciences Industries) and Bio.be (the federation of Belgian companies active in the biosciences and part of Essenscia);
- ✓ Pharma.be (pharmaceutical industry);
- ✓ FPIM-SFPI (Federal Holding and Investment Company).

Flanders (region-specific)

- ✓ Dedicated university departments, science parks (bioincubators), technology transfer offices of Leuven, Ghent & Brussels;
- ✓ FlandersBio ("umbrella" networking and lobbying organization);
- ✓ Flemish Institute of Biotechnology (VIB: biotechnology research platform);
- ✓ Regional Investment Company of Flanders (GIMV); GIMV Life Sciences;
- ✓ PMV (Flemish investment and participation company);
- ✓ Biotech Fund Flanders (managed by PMV);
- ✓ Flemish Agency for Innovation and Entrepreneurship (VLAIO);
- ✓ Flanders Investment and Trade;
- ✓ Public and private venture capital companies (seed finance, venture and growth capital): e.g. Fund+ and V-Bio Ventures.

The Flanders Institute of Biotechnology (VIB) was created in 1996 as a unique biotechnology research platform. One of its key goals is technology transfer, i.e. to convert research results into commercial activities. The VIB unites life sciences departments and research centers from the main Flemish universities (Ghent, Leuven, Antwerp, Brussels, Hasselt), research parks, bio-incubators and bio-accelerators, academic hospitals and clinical research organizations. VIB has a substantial patent portfolio and takes part in a vast number of research and development and licensing agreements with

small and large biotechnology and biopharmaceutical companies based in Flanders, Europe or the United States.

Biotechnology and the pharmaceutical clusters in Belgium are closely linked to the chemicals industry. Several top pharmaceutical companies have large research and development operations in Flanders. Belgium's first biopharmaceutical company was founded in 1953 by dr. Paul Janssen. In 1961, Janssen Pharmaceutica became part of the Johnson & Johnson group of companies.

The Flanders Institute of Biotechnology has a diverse portfolio of spin-offs in red or green biotechnology, as is shown in Fig. 7.

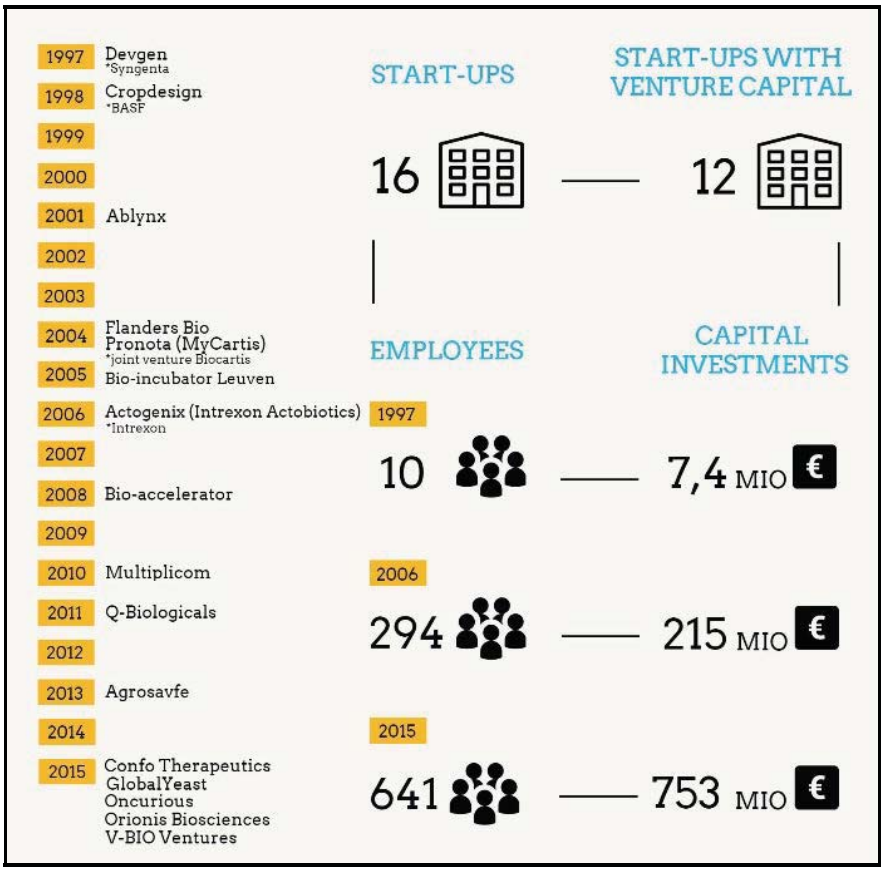


Fig. 7 – VIB Startups 1997-2015 (VIB, 2015)

VIB is an excellence-based entrepreneurial institution that focuses on translating basic scientific results into pharmaceutical, agricultural and industrial applications. Commercial exploitation of scientific results is achieved through the submission of patents. As part of an open innovation strategy, the Flanders Institute of Biotechnology advances technology in the academic community and industry. VIB brings new findings to technology platforms that are the basis for the creation of innovative new biotechnology firms (Euris, 2012).

Wallonia (region-specific)

- ✓ Dedicated university departments, science parks (bioincubators), technology transfer offices of Liège, Louvain-La-Neuve, Brussels;
- ✓ Direction générale opérationnelle de l'Economie, de l'Emploi et de la Recherche (DGO 6 - Science & Technology);
- ✓ Regional Investment Company of Wallonia (SRIW); seed finance & venture capital;
- ✓ Wallonia Biotech (bio-incubator);
- ✓ Welbio (Walloon Excellence in Life Sciences and Biotechnology);
- ✓ Wallonia Export and Foreign Investment Agency (AWEX);
- ✓ BioWin (BIOtechnologies Wallonie Innovation);
- ✓ WagrALIM cluster for the agro-industry;
- ✓ ARESA (the Walloon clinical cluster);
- ✓ GIGA (Interdisciplinary Cluster for Applied Genoproteomics);
- ✓ Walloon Cell Therapy Platform (public-private partnership);
- ✓ Public and private venture capital companies (seed finance, venture and growth capital): e.g. Sambrinvest, Meusinvest (Spinventure) and Fund+.

In Wallonia, the existing chemical and large pharmaceutical companies provided the industrial expertise necessary to leverage the results of the highly innovative research that was taking place in the university research centers. The Wallonia bioRegion is hosting a number of global players in medical research and development, such as GlaxoSmithKline (GSK Biologicals), UCB, Baxter (Baxalta), IBA and Eurogentec/Kaneka. The global companies are powerhouses that stimulate the entire sector in the region (DGTRE, 2008). They invest heavily in research programs, not only internally, but also externally through cooperation with local universities and young new biotechnology firms and university spin-offs. The leading sectors are healthcare and agricultural biotechnology.

In 2006, the Walloon Region launched the first "Marshall Plan for Wallonia", particularly focused on the pharmaceutical and biotechnology sectors. It is a regional government initiative to encourage sustainable growth in life sciences and biotechnology entrepreneurship. Five competitiveness hubs were identified; two of them are related to biotechnology: BioWin (life sciences, health) and WagrALIM (agri-business).

BioWin was set up in July 2006 within this context. It is the health competitiveness cluster of Wallonia, active in the main healthcare biotechnology sectors of (bio)pharmacy, cell therapy, radiopharmacy, diagnostics, biotechnology products, services (contract research organizations; contract manufacturing organizations), medical devices and equipment. It clusters a number of universities, research centers, higher education institutions and over 100 companies. BioWin facilitates the emergence and growth of new biotechnology firms, such as Delphi Genetics (DNA vaccines), WOW Technology (partner of Applikon Biotechnology), MDxHealth (molecular diagnostics) and iTeos Therapeutics (cancer immunotherapy). BioWin entered into partnership agreements with LyonBiopôle and EuroBioMed (France) and with the Shanghai Biopharmaceutical Industry Association and Juke Biotech Park.

Welbio (Walloon Excellence in Life Sciences and Biotechnology) is an interuniversity life sciences research institute. It aims at promoting scientific excellence in fundamental life sciences research and translating scientific achievements in medical, pharmaceutical and veterinary biotechnology applications.

The Walloon Region - via the Marshall Plan and its consecutive programs (Marshall Plan 2.Green and 4.0) - and BioWin have made major investments to create and support innovation in companies active in cell therapy. In 2011, the MaSTherCell platform was created. MaSTherCell - Manufacturing Synergies for Therapeutic Cells - is a cell therapy dedicated contract development and manufacturing organization. It is a technological platform for the clinical and commercial production of cell therapy products for third parties. This public-private-partnership platform will provide Wallonia with an innovative high-tech cluster to respond to the development needs of the growing number of cell therapy companies in Belgium. The platform is supported by the Walloon Region and Sambrinvest, and two private cell therapy companies, Promethera Biosciences and Bone Therapeutics.

4 The state of the Belgian new biotechnology firm

Qualitative research methods (Suddaby et al., 2015) play an essential role in testing the hypotheses put forward earlier in this dissertation, as drawn from the conceptual framework (p. 13). The selected research approach draws heavily on the concepts of multiple case study research design (Yin, 1984; 2009), given that the technology entrepreneurship in this study is conditioned by its context (Yin, 2012).

The dataset presented in **Table 3** is based on a longitudinal follow up of multiple case studies for the regional red biotechnology clusters in Belgium. The dataset contains a selection of 30 new biotechnology firms (spin-offs and spin-outs – including a number of stock-exchange-listed firms) in the bioRegions of Flanders and Wallonia, although some important cases for the Brussels region are included to supplement the total picture for Belgium on the country level.

The principal data collection method used here is the literature-based alliance counting (Hagedoorn, 2002): the field of research on strategic alliances and open innovation practices is characterized by relatively difficult access to data. Deal and licensing information is commercially sensitive (Deloitte, 2016). Studies of national or regional innovation systems, technical collaborations within industry can be mapped using literature-based surveys. Information on industry alliances is gathered through reviews of national and international industry media, business journals, financial newspapers, scientific research journals, trade magazines, corporate annual and/or financial reports, annual sector reports of public and private (network)organizations, prospectuses of initial public offerings, specialist information databases and industry directories.

A dataset for alliances may be compiled by querying and reviewing a mix of secondary data, such as specialized internet sites from Belgian and international financial media, i.e. leading sources for news releases and regulatory filings from Belgian new biotechnology firms and international large pharmaceutical companies. Using multiple data sources is indispensable to track effectively alliances made by companies, private or public, and ascertain the accuracy of the database. Major alliance databases are incomplete in that they do not capture all announced alliances and understate heavily the size of the industry, particularly regarding young companies (Gay, 2011).

The emergence and evolution over time of the selected 30 Belgian new biotechnology firms (non-exhaustive dataset) is put in perspective with:

① the strategic alliances portfolio with global large biopharmaceutical companies;

② the technology platform and product portfolio;

③ the growing open innovation practices coming into the relationship between the selected new biotechnology firms and their large counterparts.

For this purpose, Table 3 is supplemented with a number of good practices on open innovation for global biopharmaceutical companies and for Belgian new biotechnology firms.

The applicable business model portfolio strategy is discussed below.

INSERT TABLE 3 HERE (4 pages)

Table 3: Sample of Belgian new biotechnology firms and strategic alliances portfolio [n=30]
(**Red biotech**: (bio)pharmaceutical and biomedical, services, technology platforms and medical diagnostics | non-exhaustive: data YTD 12/2016).

New Biotech-nology Firm	Technology Platform	Product(s) Portfolio	Strategic Alliances	Acquisitions Takeovers	Region (Location)
ThromboGenics*	Ophthalmology (Ocriplasmin platform)	**Jetrea**	**Alcon (Novartis)** Bicyle Therapeutics Eleven Biotherapeutics		Flanders (Leuven)
	Diabetic retinopathy	*in-licensing* THR-687 ◄····· THR-409	Galàpagos*		
joint venture (spin-out)					
Oncurious	Oncology Orphan drugs	TB-403 (former Roche pipeline)	BioInvent International AB NMTRC (clinical trial network)		Flanders (Leuven)
Ablynx*	Nanobody technology platform (llama)	Vobarilizumab (ALX-0061) (RA) Ozoralizumab (RA) Caplacizumab (TTP) ALX-0171 (RSV)	AbbVie Eddingpharm; Taisho; Novartis; Merck KGaA; Algeta; Novo Nordisk; Genzyme; Merck & Co.; Boehringer Ingelheim.		Flanders (Gent)
Argen-X*	SIMPLE antibody platform (llama) Immuno-Oncology	ARGX-115 / GARP	Lonza (GS Xceed); LEO Pharma; Shire Pharmaceuticals; Eli Lilly; Bird Rock Bio (RuiYi). AbbVie		Flanders (Gent)
Galàpagos* *(joint venture of Tibotec-Virco & Crucell)*	Rheumatoid arthritis (RA) (inflammatory and autoimmune) Cystic fibrosis Osteoarthritis Disease-modifying antibodies	Filgotinib SilenceSelect platform / Ylanthia antibody technology	Gilead Sciences AbbVie Servier MorphoSys	01/2013: acquisition of Cangenix Biofocus + Argenta: drug discovery divisions (sold)	Flanders (Mechelen)
Fidelta (fee-for-service subsidiary)					
Tigenix*	Stem cells Cell therapy	**ChondroCelect** Cx601	Cellerix; Grifols; Lonza; Sobi AB; Biolife Solutions; Takeda	Cellerix *(reverse takeover)* Coretherapix	Flanders (Leuven)
Movetis* *(J & J spin-out)*	Gastroenterology	**Resolor**	**Shire**-Movetis	2010: Delisting takeover by Shire	Flanders (Turnhout)
Genticel*	Vaxiclase Platform - vaccines	ProCervix (HPV)	Serum Institute of India	Genkyotex *(reverse takeover)*	Paris and Toulouse (France)
Bone Therapeutics*	Stem cells Cell therapy	Preob Allob			Wallonia (Gosselies)
Promethera Biosciences	Stem cells Cell therapy	HepaStem H2Sreen; H3Screen Heparesc	Shire; Boehringer Ingelheim; Mitsubishi UFJ; Cell Innovation Partners	04/2016: acquisition of Cytonet	Wallonia (Mont-Saint-Guibert)

New Biotech-nology Firm	Technology Platform	Product(s) Portfolio	Strategic Alliances	Acquisitions Takeovers	Region (Location)
Celyad*	Stem cell therapy Immunotherapy	C-Cure NKR-2	Medisun; Institut Curie ONO Pharmaceutical	 Acquisition of OnCyte	Wallonia (Mont-Saint-Guibert)
Mithra* Pharmaceuticals *spinoff* **Uteron Pharma**	Intrauterine platform (contraceptiva) Intra-uterine device (IUD)	Women's health: **Estelle**; **Donesta** [Estetrol] Alyssa; Colvir; Vaginate Tibelia; Zoreline; MyRing.	GlaxoSmithKline Fuji Pharma Zheijang Xianju Pharmaceutical	Novalon Actavis plc (former Watson Pharma)	Wallonia (Liège)
ADx Neurosciences	Neurodegenera-tive disorders + companion diagnostics (Alzheimer – Parkinson)	Tau (biomarkers)	Quanterix Eli Lilly TauRx Therapeutics EuroImmun		Flanders (Gent)
MaSTherCell	Cell therapy platform cGMP manufacturing	Cell therapy products Re-generative medicine Type 1 Diabetes		Acquired by Orgenesis	Wallonia (Gosselies)
Confo Therapeutics	Camelid (llama) antibodies (nanobodies) CONFO platform	Confobodies G-Protein Coupled Receptors (GPCR)			Brussels
MDxHealth*	MSP molecular diagnostics (Urologic cancer) CLIA laboratory	**ConfirmMDx** SelectMDx PredictMDx InformMDx AssureMDx	Exact Sciences (Cologuard) LabCorp; Oncgnostics SouthGenetics; Sumitomo Merck & Co.; GSK; Roche; Pfizer Qiagen	 Acquisition of NovioGendix	Wallonia (Herstal)
Biocartis* *spinout* **MyCartis**	molecular diagnostics platforms Evalution (biomarker platform)	**Idylla** mini-lab Biomarker assays	Johnson & Johnson (Janssen) Abbott Molecular Fast-Track Diagnostics Microbiome ETPL (Exploit Technologies) A*STAR Merck KGaA; Amgen Thermo-Fisher Scientific	 MyCartis = Evalution (Biocartis division) **+** Pronota (takeover)	Flanders (Mechelen) Flanders (Gent)
Multiplicom	molecular diagnostics	MASTR products (assays)	EURenOmics Consortium	Agilent Technologies	Flanders (Niel)

Table 3 – page 2

New Biotech-nology Firm	Technology Platform	Product(s) Portfolio	Strategic Alliances	Acquisitions Takeovers	Region (Location)
ETheRNA	mRNA-based TriMix technology	TriMix-based immunotherapies	Boehringer Ingelheim Ventures Fund Progress Pharma (former Movetis)		Brussels (Jette)
Ogeda (Euroscreen)	G-Protein Coupled Receptors (GPCR)	Endometriosis (female health)	Pfizer Boehringer Ingelheim Novartis Pharma		Wallonia (Gosselies)
Asit Biotech*	Allergen-specific ImmunoTherapy (allergic rhinitis) ASIT+ Platform	gp-ASIT+ hdm-ASIT+			Brussels
Q-Biologicals (former Innogenetics – Fujirebio)	cGMP manufacturing of Biologicals	Recombinant proteins Monoclonal antibodies Vaccines	Artes Biotechnology Epirus Biopharmaceuticals (Bioceros) JSR Life Sciences Amatsigroup (AmatsiSEPS) Virbac Bayer CropScience		Flanders (Gent)
Complix	Alphabody Platform Oncology Autoimmune diseases	Cell Penetrating Alphabodies	Merck & Co. (MSD) Monsanto Company		Flanders (Diepenbeek)
ActoGeniX	Cellular therapeutics Allergen immunotherapy	ActoBiotics (biological drugs/ biopharmaceuticals)	Merck & Co. (MSD) Stallergenes Greer	Acquired by Intrexon Actobiotics	Flanders (Gent)
reMYND	Neurodegenera-tive disease (Alzheimer; Parkinson; Diabetes)	TAU-models RadarScreen	ProMIS Neurosciences Inc. (Amorfix Life Sciences)		Flanders (Leuven)

Table 3 – page 3

New Biotech-nology Firm	Technology Platform	Product(s) Portfolio	Strategic Alliances	Acquisitions Takeovers	Region (Location)
KitoZyme ⇩ *spinoff* *spinout* **Synolyne Pharma**	Plant-based Biopolymer Chitosan technology Medical devices	Chitosan-based hydrogel microbeads Vegetech Inside Arthrovisc			Wallonia (Herstal)
iTeos Therapeutics	Cancer immunotherapy (tumor biology)	Immuno-modulators	Pfizer ImaBiotech SAS		Wallonia (Gosselies)
Delphi Genetics	StabyDNA technology platform (antibiotic resistance)	Gene cloning DNA cloning Protein production Plasmid DNA vaccines	Merck & Co. (MSD) GSK Biologicals Sanofi-Aventis Eurogentec		Wallonia (Gosselies)

Global (bio) Pharmaceutical Company	Technology Platform	Product(s) Portfolio	Strategic Alliances	Acquisitions Takeovers	Region (Location)
UCB*  **UCB Ventures**	Neurology Immunology	**Zyrtec**, **Keppra** **Cimzia**, **Vimpat**, **Neupro** **Briviact**, Epratuzumab, Romosozumab	AstraZeneca; Pfizer; Bayer Neuropore Therapies; Lonza Oncodesign; Dermira Biogen Amgen	Celltech (UK) Schwarz Pharma (GER)	Brussels

* IPO Brussels and/or Paris and/or Amsterdam EURONEXT stock exchange listing AND/OR Nasdaq listing (*Galàpagos – Celyad – Tigenix*)

The following **conclusions** can be drawn **from Table 3**:

1 The biotechnology industry in Belgium is mapped around the major universities:

- the Flemish biotech valley is clustered near the Ghent – Mechelen – Leuven triangle;
- the Walloon biotech valley covers the Liège – Louvain-la-Neuve – Namur – Charleroi (Gosselies) axis.

2 Segers (2015; 2016) found a large number of strategic alliances and networks involving interfirm partnering activities between large and global biopharmaceutical companies like Johnson & Johnson, Pfizer, Novartis, Roche, Merck & Co., Sanofi-Aventis, GlaxoSmithKline, AstraZeneca, Eli Lilly, AbbVie and many others and Belgian new biotechnology firms in red biotechnology. The composition of a strategic alliances portfolio is essential in the early years of development.

The Belgian new biotechnology firms are either still in the preclinical stage of therapeutic research, developing targets and compounds in their early stages of existence or developing technology platforms in leading edge drug development. Most of them conduct research in the discovery phases I and/or II. They are involved in interactive collaborations (strategic alliances) with big pharmaceuticals, often with a co-creation goal: therapeutic targets, finding new molecules with a blockbuster potential, transforming the new molecule into a commercial drug.

3 Belgian NBFs apply a business model portfolio strategy to capture value from the proprietary technology and know-how. Sabatier et al. (2010) define a portfolio of business models as the range of different ways a firm delivers value to its customers to ensure both its medium term viability and future development. Business models can be balanced to ensure short or medium times-to-market. This is important for Belgian new biotechnology firms, as it is difficult for them to survive the long period without turnover and profit involved in longer-term models.

The new biotechnology firms rationale for this strategy is:

- the lack of infrastructure for late-stage clinical trials;
- the need for external investment capital for the cost-intensive clinical development activities (public – via initial public offerings – and private equity and venture capital);

- to access marketing and distribution channels;
- (in some cases) to create a viable exit strategy by means of acquisition by a big pharmaceutical company.

The business models most used are the technology platform model, the hybrid model, the royalty income model, the pure licensing model, the IPO financing model and the research services model. The technology platform business model generally focuses on the early drug development phases (molecule development). It leverages on licensing technologies and co-development partnerships. In the hybrid business model, the technology platforms are combined with services and the generation of a pipeline of products. The pipeline of products can be developed organically or through additional in-licensing or purchasing access to another's technology.

4 The case evidence for new biotechnology firms shows a high degree of dependence on milestone and success payments in the early stages of development (pecuniary incentives). The royalty income pharmaceutical company model covers platform and tool-based companies seeking to commercialize drug targets, services and technologies that can be sold or licensed to other companies. They research and develop new drugs, which they eventually license to a big pharmaceutical company in exchange for a royalty on sales. The large company finishes the research, produces the drug and commercializes it.

The **Argenx**-case in the Flanders bioRegion (De Tijd - Finance Avenue, 2016) is a good example of a business model portfolio maximizing shareholder value. Argenx captures value at different stages through:

a. platform deals with Shire and Bayer in the discovery stage;
b. product deals and thriving strategic alliances with Bird Rock Bio, LEO Pharma and AbbVie;
c. wholly owned antibodies in early & late clinical development.

Galàpagos on the other hand is capturing value in a very competitive landscape from a mix of top-level partnerships with a number of big pharmaceuticals for clinical trials on multiple indications of its lead products, such as Filgotinib (see Fig. 8).

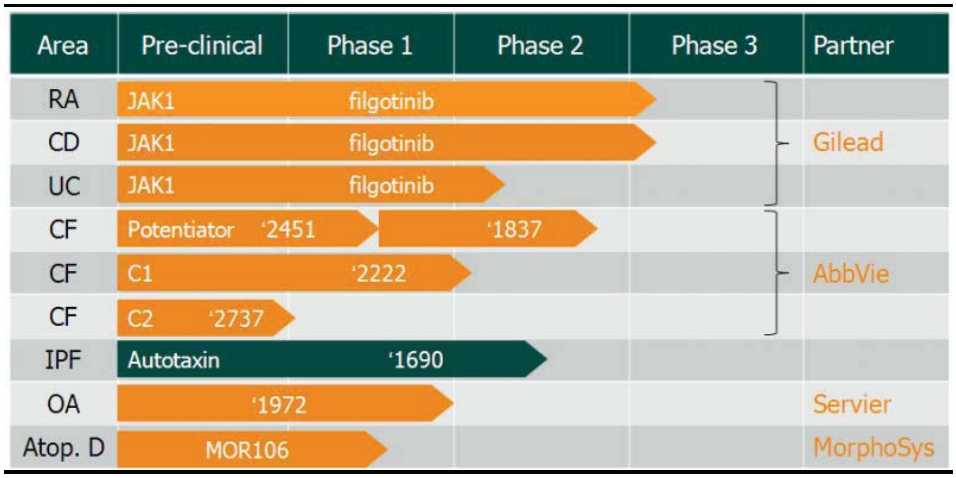


Fig. 8 – Galàpagos' pipeline (labiotech.eu, 2016)

5 Taking Dixon's (2011) framework on common business models in the biotechnology industry as a point of reference, the data from Table 3 suggest that few Belgian new biotechnology firms may be attributed to – possibly achieving – the fully integrated pharmaceutical company (FIPCO) model (see Fig. 9 below).

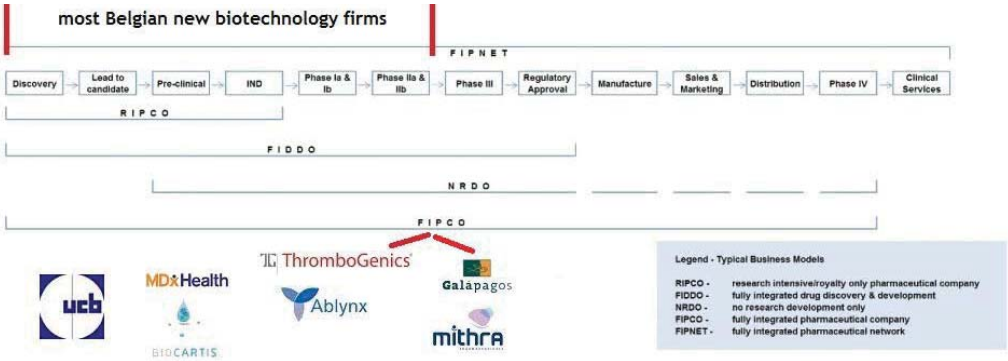


Fig. 9 – Common business models for Belgian new biotechnology firms

- With respect to the strategic alliances portfolio and the product pipeline, Galàpagos, Ablynx, Mithra Pharmaceuticals are the most likely to make it to the FIPCO model stage;
- The same holds for the molecular diagnostics niche firms MDxHealth and Biocartis;
- UCB made the transition to becoming a multinational global (bio)pharmaceutical company years ago, with a number of blockbuster products in its "old" and new product pipeline.

6 There is a clear duality as Belgian new biotechnology firms move from the research and development phase to the production and marketing of new products. The dilemma is whether to increase vertical integration within the company by producing and marketing the researched products themselves, or whether to license the products to a large pharmaceutical partner: examples are ThromboGenics, Ablynx, Argenx and Galàpagos.

7 Belgium may end up specializing in subsectors of red biotechnology, e.g.:
- Flanders bioRegion: nano- and antibodies (llama); molecular diagnostics;
- Wallonia bioRegion: cell therapy; women's health; molecular diagnostics.

The findings from the multiple case analysis of Belgian new biotechnology firms support hypotheses **H2** and **H3**:

H②: the development process of new biotechnology firms in the bioRegions of Flanders and Wallonia depends on setting up strategic alliances. Working closely together with international large (bio)pharmaceutical companies is beneficial to maximize value creation/value capture.

H③: most of the new biotechnology firms in Belgium are unlikely to become fully integrated pharmaceutical companies.

The regional biotechnology clusters are now embracing open innovation. Belgian new biotechnology firms are able to adopt innovative business models by providing R&D and services to larger firms and openly cooperating with them through open innovation. The open business models most used are:

- the open innovation-based research and development model;
- the networked model;
- collaborative discovery.

Some **good practices of open innovation** are emerging in global biopharmaceutical companies and in Belgian new biotechnology firms. They are presented below:

I. Global pharmaceutical companies have enrolled in open innovation strategies, policies and structures. One approach companies like Johnson & Johnson, Pfizer, Novartis, Roche, Merck & Co., Sanofi-Aventis, GlaxoSmithKline, AstraZeneca, Eli Lilly, AbbVie and others have been taking to replenish their drug development pipelines is not only investing in early-stage new biotechnology firms, but also opening innovation centers to help these companies grow. They have established corporate venture capital funds to make strategic investments in biotechnology or to invest in strategic pipeline management (Gassmann et al, 2008; PwC, 2010b). UCB (Belgium) launched UCB Ventures to this end in 2016.

1 Open source/Open access biotechnology

Most big pharmaceuticals have established some kind of open innovation platform with open access to data, the sharing of clinical trial data or data on newly approved medicines to researchers and scientists. Some good practices (Deloitte, 2015a; Nilsson, 2016) are found in:

- GlaxoSmithKline's open innovation strategy with a particular focus on the developing world;
- the Eli Lilly (Lilly) Open Innovation Drug Discovery program (open source drug discovery);
- Pfizer Centers for Therapeutic Innovation program;
- AstraZeneca/MedImmune's open innovation collaborations on target validation;
- the Sanofi Access Platform;

- the call for an oncology (cancer) research data sharing consortium that would include Repositive, AstraZeneca, Merck, Novartis and Pfizer (FierceBiotech, 2016).

2 Innovative Medicines Initiative

Public-private collaborations are providing researchers access to more open data than ever before (Chesbrough et al., 2016), with the promise of new treatments to follow. The Innovative Medicines Initiative is a partnership-focused public-private partnership aiming to boost pharmaceutical innovation in Europe and to speed up the development of better and safer medicines for patients. IMI (2010) is a joint undertaking of the European Union and the pharmaceutical industry association EFPIA. Large biopharmaceutical companies and small and medium-sized enterprises are working together with patients' organizations, research institutions, hospitals, regulatory agencies and industrial partners.

3 Open innovation at Bayer

Bayer's (2016) global open innovation approach offers different forms of cooperation (outside-in) along the value-chain, from traditional licensing agreements or strategic research alliances to public-private partnerships as well as its crowdsourcing program "Grants4Targets". Bayer HealthCare's (2014; 2015) CoLaborator and Grants4Apps partnering hubs and startup incubators and accelerators were set up to advance digital innovation in healthcare (Segers, 2016) and for the development of new therapeutic options.

4 BioMedX - Roche

The BioMedX innovation center is a collaboration model at the interface between academia and industry in the Heidelberg Technology Park in the Biotech Cluster Rhine-Neckar (BioRN) bioRegion in Germany. Innovations in the fields of biomedicine, molecular biology, cell biology, diagnostics and bioinformatics are explored within a strategic partnership network with biomedical research in an open innovation setting. Corporate pharmaceuticals like AbbVie, Roche, Boehringer Ingelheim and Merck are key players in this cluster. After a fully funded project term, successful projects are either internalized into the development pipeline of the respective pharma or biotech sponsor or spun off into an independent startup company. BioMedX partners with Roche in an open innovation research

alliance in biotechnology, nanotechnology and engineering. The goals are to develop new and faster diagnostic tests, speedier diagnosis and synergies with existing drug treatments.

5 AstraZeneca Open Innovation Platform

AstraZeneca and Sanofi announced an open innovation model in the search for new small-molecule medicines in several disease areas such as diabetes, cancer and cardiovascular conditions. They will exchange compounds from their respective proprietary compound libraries.

6 LEO Pharma - open innovation program

LEO Pharma focuses on dermatologic and thrombotic conditions. LEO is hastening its transformation to patient-centricity by experimenting and testing multiple new business models across the organization in such areas as patient services, payer engagement, pharmacy engagement, and more. The aim is to leverage the company's understanding of patients and engage them to co-create care solutions and future business models.

7 Allergan – Open science model

The open science-strategy depends heavily on letting the innovators do the heavy lifting on early research - sorting winners from losers - with a team at Allergan in place to handle late-stage development and regulatory efforts (Fiercebiotech, 2016).

8 Shire – Virtual collaboration model

Shire has implemented elements of an open, virtual and partnership-oriented concept: an open, collaborative and networked R&D model of 'early alliance' whereby pharmaceutical and biotechnology companies collaborate in early R&D. The biotechnology company provides the innovation, whereas the pharmaceutical partner contributes its capacities to discover and develop jointly an early drug candidate with the purpose of having access to the drug project later. Alternatively, it can use the early alliance to familiarize with a new technology or therapeutic area without investing too many resources (Schuhmacher et al., 2013).

II. Belgian new biotechnology firms

1 Johnson & Johnson (J&J)/Janssen Pharma – JLABS/JLINX-model

This is an example of a collaborative model where Johnson & Johnson created regional clusters of life sciences start-ups and innovation hubs. Johnson & Johnson (2015) launched its JLABS (Janssen Labs) network of biotechnology/life sciences incubators in San Diego, San Francisco, Boston, Toronto, Shanghai and London. The innovation hubs provide life science entrepreneurs and scientists with an open collaboration space (Weverbergh, 2013) for early-stage research in developing medical device and diagnostic technologies, consumer health care products and pharmaceuticals. The incubated life science start-ups are granted access to J&J's compound library and to its regulatory and commercial experts.

This approach enhances sourcing external innovation. Researchers working within the J&J-facilities do not work for Johnson & Johnson. Nor do their discoveries belong to J&J. Some of them even receive funding from J&J's competitors, such as Novartis, Pfizer and Bristol Myers Squibb (Fortune, 2016). Johnson & Johnson/Janssen Pharmaceuticals gain access to some valuable technology, scientific talents and entrepreneurs in the life sciences space in backing these startups and set up development collaborations that help accelerate their growth.

Building on this growing JLABS network, Johnson & Johnson (2016) opened JLINX at its Janssen Pharmaceuticals Campus in Beerse (Belgium). JLINX will focus on innovation in pharma and cross-disciplinary healthcare solutions (FierceBiotech, 2016). Robaczewska et al. (2016) examine the regionally embedded innovation ecosystem set up by Janssen. This approach goes beyond the traditional focus of open innovation as Johnson & Johnson/Janssen try to leverage external talent and expertise, share public infrastructure, raise funding and influence public policies.

2 Biocartis – Open architecture platform

The Belgian new biotechnology firm Biocartis (Mechelen, Flanders bioRegion) is active in molecular diagnostics, rapid cancer and virus tests. Biocartis is opening up its Idylla-platform for external developers and is working together with Janssen Diagnostics (Johnson & Johnson) and Abbott Molecular. The Evalution open architecture platform of MyCartis – a

spinout/division of Biocartis – enables MyCartis to engage in a strong industrial partnership with almost any company active in the field of bio-assay development.

3 GIGA cluster (Interdisciplinary Cluster for Applied Genoproteomics)

The GIGA ecosystem of thematic biotechnology research units (medicine, agronomic sciences,…) and technology platforms in the Wallonia bioRegion (Liège, Belgium) optimizes interactions and exchanges through open labs. The GIGA cluster is open to both academic researchers and private sector actors. A state of the art infrastructure is available for new biotechnology firms (start-ups, spin-offs, spin-outs). In addition, the FOREM-GIGA Biotechnology Training Center was created to work in close collaboration with academics and the biotechnology industry (GIGA, 2016).

4 ThromboGenics – Galàpagos alliance

ThromboGenics was established in 1998. The company developed over the years from a university spin-off of the University of Leuven to a fully integrated specialty pharmaceutical company, with a promising biotechnology-based pipeline (Belgian Foreign Trade Agency, 2011). Its primary goals are to develop and commercialize innovative therapies in ophthalmology (eye diseases, with a special focus on diabetes), cardio-vascular diseases and oncology (cancer).

From 2013 onwards, after the strategic turnaround - following a downturn in expected revenues from its FDA-approved (October 2012) lead product JETREA® (ocriplasmin-platform) - ThromboGenics evolved from a university spin-off to a fully integrated biopharmaceutical company and is now a clinical stage biotechnology company, taking its future prospects beyond its lead product JETREA®. In April 2015, the company's research and development activities in oncology (orphan drugs - pediatric cancer) were spun out into a separate entity, Oncurious NV, a joint venture with the Flanders Institute of Biotechnology (VIB).

In March 2016, ThromboGenics signed a global in-licensing agreement (inbound open innovation) with the Belgian new biotechnology firm Galapagos with respect to certain compounds to develop and commercialize THR-687 for the treatment of diabetic eye disease (diabetic retinopathy).

Two **benchmark-studies** underline the growing attention of open innovation in the biopharmaceutical industry.

1. Michelino et al. (2015) studied the degree of openness of big pharmaceutical companies such as Johnson & Johnson, Pfizer, Novartis, Roche, Merck & Co., Sanofi-Aventis, GlaxoSmithKline, AstraZeneca, Eli Lilly and AbbVie. Results through the analysis of annual reports show a negative correlation of openness degree with firm age, dimension and efficiency, with biotech companies being more open than pharmaceutical ones. Biotech companies are more involved in R&D transactions both inbound and outbound; they are also more involved in outbound IP transactions, while pharmaceutical companies are more involved in inbound transactions. In the biotechnology segment, the more the companies are open, the younger and smaller they are and the higher values of R&D costs per employee they have. In the pharmaceutical segment, not only the most open companies are the youngest and smallest with highest values of R&D per employee, but also R&D intensity and closed R&D intensity are significantly higher. Biotech companies have lower efficiency than pharmaceutical ones, and in mean, they show a decrease of EBIT (Earnings Before Interest and Taxes, i.e. the operational profits or losses), while pharmaceutical companies increase it.

2. Schuhmacher et al. (2013) analyzed the R&D models of pharmaceutical companies and categorized them with respect to their preference for innovation management. The preference in innovation management, defined as predominantly introverted or predominantly extroverted, was determined from strategic statements in the annual company reports and other investor relation information provided by the peer companies. The results indicate a predominantly introverted innovation management. The latter is characterized by a tendency to use entirely or predominantly internal know-how, knowledge and resources when managing R&D activities. GSK (strategic alliance with Mithra), Shire (Promothera and Argenx) and Takeda (Tigenix) were categorized as “extroverted”.

In Table 4, a number of new biotechnology firms from the Belgian sample are labelled as “fairly to very open”. The big pharmaceutical companies, including Belgian UCB, were all categorized as “hardly open”.

(New) Biotechnology firms	Clusters	Pharmaceutical companies	Clusters
Ablynx	**very open**	Abbott Laboratories	hardly open
BioInvent Int. *	very open	AstraZeneca	hardly open
Galapagos	**very open**	Boehringer Ingelheim	hardly open
Gilead Sciences**	fairly open	Bristol Myers Squibb	hardly open
ThromboGenics	**very open**	Eli Lilly	hardly open
Tigenix	**fairly open**	GlaxoSmithKline	hardly open
Biocartis/MyCartis	**very open**	Johnson & Johnson	hardly open
		Merck (US)***	hardly open
		Merck (DE)****	hardly open
		Novartis	hardly open
		Novo Nordisk	hardly open
		Pfizer	hardly open
		Roche	hardly open
		Sanofi-Aventis	hardly open
		Shire	hardly open
		UCB	**hardly open**

* BioInvent = partner of Oncurious (ThromboGenics)
** Gilead Sciences = partner of Galapagos
*** Merck US = Merck & Co. (Merck, Sharp & Dohme)
**** Merck DE = Merck KGaA

Table 4: adapted from Michelino et al. (2015)

The findings and benchmarks from above support hypothesis **H4**:

> **H④**: Belgian new biotechnology firms apply open innovation in their development and growth patterns. Open innovation is taking strategic partnering to a next level in the development process.

④ Conclusions

Building a sustainable and successful biotechnology company is still as challenging as ever. Developing a domestic biotechnology industry - and hence new biotechnology firms - can be influenced by regional policy. The pharmaceutical-biotechnology regional and sectoral innovation system is characterized as an international and dynamic network architecture involving numerous players engaged in drug discovery. Regional governments and dedicated public and private network organizations have supported emerging new biotechnology firms by providing critical resources and by promoting an institutional environment that has enabled partnerships between universities, highly specialized research centers, small science based academic spin-offs and corporate spin-outs and large global pharmaceutical companies. Both policy and big firms look at the new biotechnology firms from a strategic point of view. The policy objective is the emergence of new and sustainable firms in the region; the big firms objective is the filling or renewal of the pipelines of products.

Belgium has firmly established itself as an international red biotechnology country, with a world class biotechnology industry in the Flanders and Wallonia bioRegions. It has many of the ingredients for successful biotechnology and pharmaceutical activity: top-tier academic research, a commitment to public research funding, a heritage and presence of large pharmaceutical companies and a growing and relatively high number of new biotechnology firms. However, Belgium has few large biotechnology companies.

The Flanders and Wallonia bioRegion models are offering an “umbrella” for a sufficient amount of time for the Belgian new biotechnology firms to make it through the first stages of (pre)clinical development. New biotechnology firms are both beneficiaries and targets of strategic partnering alliances with large and global (bio)pharmaceutical companies. A number of the Belgian new biotechnology firms hold a nodal position as “most preferred partner” with multiple alliances in dynamic R&D networks. They have a high degree of integration into global technological networks through strategic alliances.

The biotechnology industry is characterized as extremely capital, knowledge and infrastructure intensive. Value is captured by continuously shifting business model portfolios – from closed to open and collaborative

– considering the development phases the firms are in. Strategic alliances and open innovation are commonly leveraged. Despite their small size and relative immaturity, some of the new biotechnology firms are able to adopt innovative business models by providing R&D and services to large biopharmaceutical companies and by cooperating with them through open innovation. The new collaborative model implies multiple projects and product portfolios, solid technology platforms and the ability of building competencies in all stages of the drug development process. Belgian new biotechnology firms rely heavily on licensing agreements, milestone or success payments and/or royalty payments on sales once the product is marketed.

The Belgian new biotechnology firms appear to face high difficulties in bridging the gap between their technological performances and the economic valorization of results. The long term challenge of Belgian new biotechnology firms is in making the transition from performing contract research to the independent manufacture and marketing of the products of research, given the fact that capability in production and downstream technology remains largely the prerogative of the global biopharmaceutical companies.

New biotechnology firms are longing for a safer passage through the "Valley of Death", the phase where the smaller research organization transforms from being a research company to a company that is engaged in the development of a pharmaceutical product. They focus on network orchestration and alliance management as necessary steps for keeping control of value capture mechanisms for their medium term viability and future development. Building and managing new business model portfolios and this way generating revenue streams is a strategy that has allowed Belgian new biotechnology firms to develop value propositions that balance the time lags between investment and revenues and to survive the long period without turnover and profit, provided they accept high levels of interdependency.

The global biotechnology (biopharma) industry is going through a paradigm shift in how medicines and therapies are discovered, developed and commercialized. The shift to more personalized medicines, as well as drug pricing pressures have driven pharmaceutical and biotechnology companies to increase their efforts in the hunt for new and smarter approaches to drugs and diagnostics development. The industry is becoming increasingly outcome-driven and patient centric.

A new distributed model of R&D has been introduced in big pharma to reduce costs and risks. External partnerships and outsourcing strategies – i.e. strategic alliances with new biotechnology firms and academia – are aligned with in-house efforts to generate innovative medicines. However, an adequate patent rights and data protection system is mandatory. Intellectual property rights protection is important, as it is directly linked to the ability of new biotechnology firms and pharmaceutical companies to potentially recuperate the significant investments needed for biopharmaceutical R&D and to provide the revenues needed to make up for the many R&D failures and continued investments in the future.

The biotechnology industry in the Flanders and Wallonia bioRegions has taken the network model to the extreme so that, right now, the goal of transitioning into an independent, fully integrated pharmaceutical company is rarely achieved, with the exception of UCB. Most of the new biotechnology firms in Belgium are unlikely to become fully integrated pharmaceutical companies, although there are promising examples like Galàpagos, Ablynx, MDxHealth, BioCartis and Mithra Pharmaceuticals. Some of these new biotechnology firms aspire to create high-quality knowledge jobs in their regional economy along the way.

The case-based evidence supports the assertion by Fisken and Rutherford (2002) that "while a small number of companies with access to a large supply of capital may be able to complete downstream integration and revert to the fully integrated pharmaceutical company model, the majority of biotechnology companies will instead need to further develop sophisticated relationship management skills in order to extract greater value from relationships with customers, collaborators and strategic partners".

Belgian new biotechnology firms are acutely aware of the possibility of a takeover. For some however, "merger & acquisition becomes the only viable option, or to partner certain rights away while keeping a strategic and economic interest in a product or technology for long-term growth" (Financial Times, 2016).

"Whatever road you go down, eventually you will find yourself in a partnership with a pharma company, either to buy you out or to commercialize your products."

[Tim Van Hauwermeiren, CEO ARGENX (FierceBiotech, 04/2016)]

⑤ Future Research Directions

This final chapter outlines some directions for future research, containing managerial as well as policy implications.

Biotech business models: one size does not fit all

When taking the longitudinal time frame of this study into account one of the most striking and ongoing evolutions is that of the business models applied in biotechnology. There is a large body of literature on business models – traditional and closed opposed to open – linking technology development to economic value creation (Porter, 1985; Chesbrough and Rosenbloom, 2002; Chesbrough, 2006; Sabatier et al., 2010; Osterwalder and Pigneur, 2010; March-Chordà and Yagüe-Perales, 2011; Muegge, 2013; Gassmann et al., 2014).

Gassmann et al. (2014) argue that a company's current business model becomes tangible by describing it in four dimensions: the customer (who?), the value proposition (what?), the value chain (how?) and the profit mechanism (why?). Themes such as cost reduction, business transformation, revenue generation and shareholder value proposition are commonly highlighted.

As Pisano (2006; 2007) argued, biotech needs a variety of business models. The dominant logic of the drug industry is product-based (Sabatier et al., 2012). Tomorrow's competitive advantage of companies will not be based on innovative products and processes, but on innovative business models. One of the key challenges of business model innovation is to overcome the dominant firm and industry logic (Sabatier et al., 2012; Gassman et al, 2014).

The closed business models (Fisken and Rutherford, 2002; Chesbrough, 2003; Chesbrough et al, 2006; Hine et al., 2006; Pisano, 2006; Pareras, 2008; Dixon, 2011; Gay, 2014) based on vertical integration, blockbuster drugs and physician preferences is under pressure by innovative patient-centered models (Cotter, 2006; Heidrick and Struggles, 2014; PhRMA, 2014; Deloitte, 2015b; Saias and Kapadia, 2016), making the company's drug development processes more patient-centric. It involves a shift from a product-driven approach towards a connected patient-centered healthcare ecosystem.

A wide range of open business models is emerging. They include different types of extensive collaboration and cooperation, open innovation, open source and open data sharing. A selection of these open business models are:

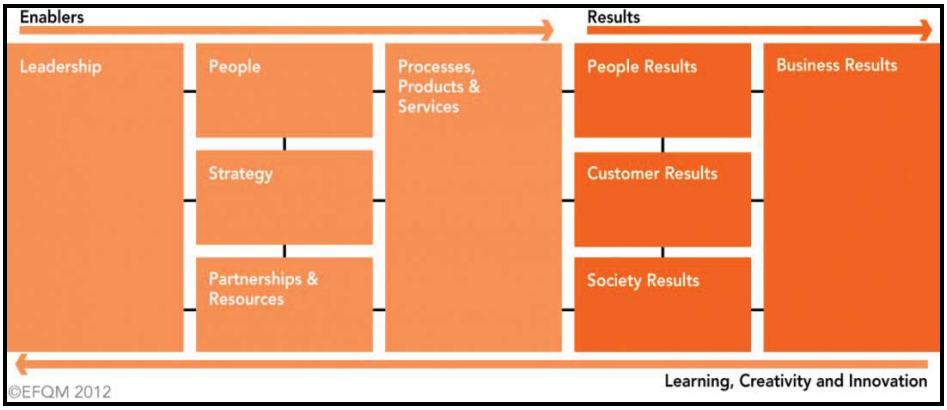
- open innovation-based research and development model (Reepmayer, 2005; Deloitte, 2015a);
- networked business model (Pittaway et al., 2004; Gay, 2014);
- collaborative discovery business model (Sabatier et al., 2012);
- IP-oriented business models (Pisano, 2006; Birch, 2016; Kerry and Danson, 2016; West and Olk, 2016);
- public-private partnership model (Stevens et al., 2016);
- product definition companies business model (Roth and Cuatrecasas, 2010);
- repurposing and technology brokering business model (Sabatier et al., 2010);
- virtual R&D collaboration model (PwC, 2010a; Sabatier et al., 2010; Dixon, 2011; Schuhmacher et al., 2013; Tamoschus et al., 2015);
- outcome-driven business model ("pay for performance") (PwC, 2010a);
- crowdsourcing business model (Alcimed, 2016a);
- bundling (biology, nano-technology and computational sciences in combination) (Sabatier et al., 2012);
- open source partnering through powerful bioinformatics (Sabatier et al., 2012; Tamoschus et al., 2015);
- patient engagement models (crowd research, research partnerships, co-design programs, patient communities and focus groups) (Allarakhia, 2015; Tamoschus et al., 2015).

The evolution towards patient-centricity warrants further research, both from a managerial as from a policy perspective, as it reflects the trend towards cost efficiency of healthcare systems and affordable public healthcare. This calls for coverage and reimbursement policies that support and encourage medical innovation and that value innovative medicines.

Applying the EFQM framework to biotechnology

A good complement to the diversity of biotechnology business models that were reviewed earlier would be the excellence model by the European Foundation of Quality Management (EFQM). The EFQM is a generic model that may also be applied to the biotechnology industry, the new biotechnology firms and the big pharmaceutical companies since it provides a framework that encourages cooperation, collaboration and (open) innovation.

One of the most positive aspects of the EFQM excellence model is the use of self-assessment. The EFQM has nine criteria grouped in 'enabler' and 'result' criteria: the enabler criteria are concerned with how the organization undertakes the key activities (leadership, policy and strategy, people, partnerships and resources, and processes) and the result criteria are concerned with what results are being achieved (customer results, people results, society results, and key performance – i.e. business – results).



Strategy is aligned with the needs and expectations of stakeholders. EFQM views processes as an enabler and evaluates how well a company designs and improves its processes to add value for its customers and stakeholders. According to Vallejo et al. (2006), the EFQM framework has many correspondences to a health care-specific framework. The experiences of the application of EFQM in health care are found mainly with respect to hospitals, clinical professionals and healthcare systems.

By extension, the EFQM excellence model can be applicable to the next generation biotechnology industry, with changing dynamics of pharmaceutical R&D because of patient centricity, uncertainty of reimbursement, demand for efficient healthcare systems and willingness to share risk.

Leadership, partnership development (alliances), customer focus and patient centricity are key issues:

- *leadership*: the creation and growth of new business; high technology entrepreneurship (entrepreneurial drive – innovativeness);
  leadership: one of the key strengths of the management of biotechnology firms and pharmaceutical companies is pipeline management (the generation of new products and services);
  leadership: the generation of new ideas and to encourage innovation and organizational development (creativity);
- *strategy*: choice and/or adaptation of the business model portfolio;
  strategy: management endorsement for open innovation;
  stakeholder focused strategy, i.e. a regular dialogue with the key stakeholder groups (patient's organizations, research institutions, hospitals, regulatory agencies and industrial partners);
- *partnerships*: manage and develop a strategic alliances portfolio (network dynamics);
- *processes*: create value for customers and patients.

The shift to more personalized medicines, as well as drug pricing pressures have driven pharmaceutical and biotechnology companies to increase their efforts in the hunt for new and smarter approaches to drugs and diagnostics development. Personalized medicine is a medical model enabling a more customized health care tailored to the individual patient and thus reducing healthcare costs (Academy of Medical Sciences, 2015). Healthcare systems are moving in the direction of "pay for performance", a system driven by outcomes. Some of the key results of the deployment of the strategy based on the needs and expectations of the key stakeholders are:

- *customer results*: the new business model of patient-centricity (p. 28) and the reduction of time to market of (new) products and services;

- *society results*: an improvement of the cost efficiency of the health care system (cost reduction, pricing and reimbursement; coverage and payment policies that value innovative medicines) is a key issue for the future of the biopharmaceutical/biotechnology industry.

  Relevant topics are new forms of public-private cooperation to facilitate access to medicines notably through managed entry agreements, coordinated access to orphan drugs, etc. The so-called Managed Entry Schemes could provide to decision-makers in reimbursement policy a window of opportunity for adding value to patients and society when new therapeutics are considered for introduction. Managed entry agreements constitute a special kind of contract which is concluded between the marketing authorization holders of an innovative medicinal product and the health insurance system in order to be included in the scope of pharmaceuticals whose costs are covered. Through these arrangements it is possible to speed up the market entry of new products while guaranteeing a close monitoring of their therapeutic benefits as well as of their effectiveness and/or relative efficacy (European Commission, 2014).

- *business results*:
  - the shareholder value: cash burn vs revenues out of royalties, milestone payments, number of patents,…;
  - the number and success rate of open innovation activities.

Interregional collaboration

The biotechnology industry is clearly shifting towards a more cooperative competitive (co-opetition) model. There are marked differences across the Flanders and Wallonia regions regarding technology policy-making. However, the analyzed indicators give evidence that the regions are more complementary than substitutable. This opens the case for cross-"border" alliances.

In an economic environment characterized by the techno-globalisation phenomenon, it would be profitable for regions to take advantage of their

geographic proximity as well as capitalizing their long-standing relational proximity (Capron and Cincera, 1999). Stimulating interregional cooperation agreements would make the regional systems of innovation highly efficient to the benefit of the both bioRegions (Segers, 1987). This could be achieved by:

- avoiding duplication of research projects and technological competition;
- stimulating joint inter-regional near-market research consortia;
- identifying and exploiting the added value of specific cooperative actions between bioRegions through the exchange of best practices and common strategies;
- building more (international) public-private partnerships;
- supporting a better integration between clusters of new biotechnology firms and large pharmaceutical companies into a "mega-cluster", both politically and financially;
- creating cluster organisations, which can support the development of European leader bioclusters to compete at international level;
- boosting technology transfer activities through the creation of an open architecture;
- closing the "co-ordination gap" between the separate regional departments and the multitude of public and private structures and organizations.

Generalizability

The conceptual framework and the findings of this study are transferable to rapidly advancing (niche) industries and emerging regional clusters, where disruptive business models are leading to new spin-offs and spin-outs that engage in alliance building and open innovation activities. In Belgium, this could be the case for a selection of the following technologies:

Biotechnology, nano-electronics and nanotechnology for health

The Leuven (Flanders) based Interuniversity Micro-electronics Centre (IMEC) is a world-leading public research institute in nano-electronics. It developed an IP-based orchestration model through multi-party research collaborations between public and private firms. IMEC aims to leverage

its industrial affiliation programs model to the life sciences industry in search of nano-electronic applications. This will lead to a dual-core, dual-site innovation ecosystem (Leten et al, 2013). IMEC is also a major partner of the Eindhoven based Holst Centre, working in an open innovation setting in a partnership model with industry – e.g. Philips Healthcare – and academia. It focuses on challenges in healthcare, sustainability and the internet of things.

Yaghmaie et al. (2016) describe the partnership network for the open innovation ecosystem in nano-electronics, the ecosystem map (Fig. 10).

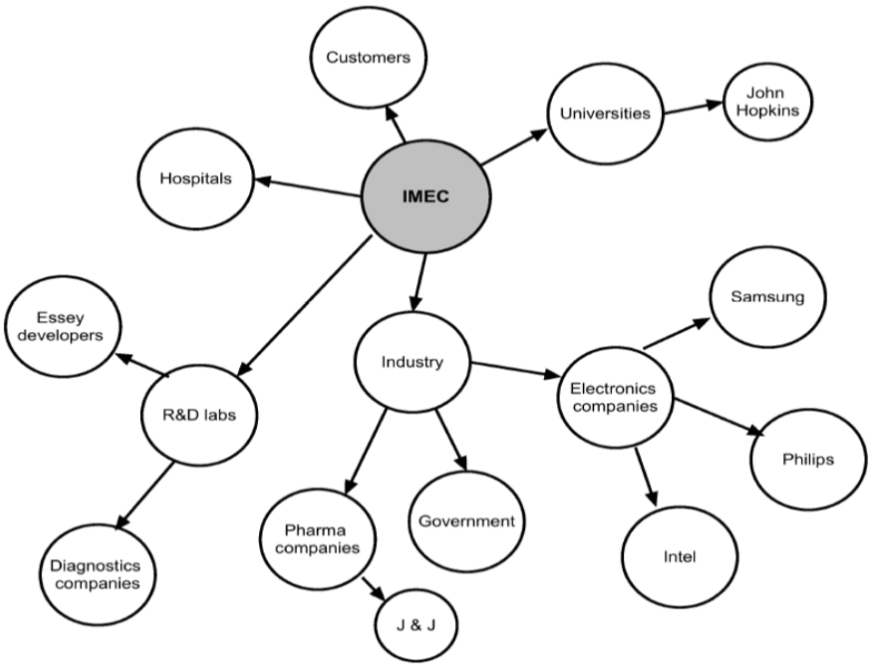


Fig. 10 – IMEC ecosystem map (Yaghmaie et al., 2016)

3D printing

Belgium is pioneering in a 3D printing ecosystem, with universities and research centers working closely together with new technology based firms. New startups like Materialise and LayerWise-3DSystems (both university spinoffs) are introducing new innovative business models for the 3D printing industry and working on disruptive possibilities of 3D printing technology for business and society.

Additive manufacturing software solutions and sophisticated 3D printing services can be applied in a wide variety of industries, including healthcare (3D bioprinting), automotive, aerospace, design and consumer products. Examples of key domains are the manufacturing of artificial implants, medical image processing, surgical simulations and the bio-printing of live stem cells, in cooperation with new biotechnology firms like Tigenix and MaSTherCell.

Aerospace open innovation ecosystem

As life sciences organizations move toward greater use of outsourcing in their business models, they may be able to learn from the airline (aerospace) industry (Saias and Kapadia, 2016). This industry is characterized by so-called value chain deconstruction: a focus on core business-critical competencies, together with the outsourcing of non-core activities. The outsourcing arrangements allow them to gain access to technology specialists that help them make the most of new innovations and models.

Airbus is enhancing its innovation process through the operation of a global network of accelerator facilities – called Airbus BizLabs (2016) – to speed up the transformation of ground-breaking ideas into valuable business propositions, all within an extended innovation ecosystem. This set-up has two primary methods for meeting its goal: accelerating the pace at which Airbus commercializes its own innovations; and drawing upon and developing more ideas from outside Airbus, including customers and companies from other business sectors.

This new open innovation approach by Airbus offers possibilities for the Belgian regional aerospace industry and for R&D and industrial collaborations between academia and small and large companies. The Belairbus consortium is a Belgian industrial partnership set up to allow Belgian companies to participate in the manufacturing of Airbus aircraft. The Flemish Aerospace Group (FLAG) and Skywin Wallonie are cluster organizations for enterprises active in the aerospace market. FLAG and Skywin were set up within the regional systems of innovation of the Flanders and Wallonia regions.

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Paper ① 1993 Strategic partnering between new technology based firms and large established firms in the biotechnology and micro-electronics industries in Belgium

Strategic Partnering Between New Technology Based Firms and Large Established Firms in the Biotechnology and Micro-electronics Industries in Belgium

Jean-Pierre Segers

ABSTRACT. There is an increased emphasis on New Technology Based Firms (NTBFs) and on Strategic Partnerships. The number of strategic partnerships between large, established firms and NTBFs has multiplied over the past few years, due to a growing trend towards technological and marketing relationships between large and small firms. In this contribution, the strategic — predominantly technology — partnering (also referred to as interfirm technology cooperation) experiences of a small number of Belgian NTBFs in the biotechnology and micro-electronics industries will be analysed. The analysis presented here derives from the region-specific technology policies in Belgium.

A multiple case study design was chosen to develop an understanding of the impact of strategic partnering on New Technology Based Firm-survival and growth in Belgium. To improve the reliability of conclusions in the research presented here, a small number of cases will be investigated for the construction of a theoretical model.

Introduction

In this contribution, the strategic — pre-dominantly technology — partnering experiences of a small number of Belgian New Technology Based Firms (NTBFs) in the biotechnology and micro-electronics industries will be analysed. Micro-electronics is taken here as a core technology instead of being defined as a subfield of information technology. This is due to the fact that the analysis presented here derives from the region-specific technology policies in Belgium (Segers, 1992), where technology policy efforts have been focusing on biotechnology and micro-electronics.

There is an increased emphasis on New Technology Based Firms (Bollinger *et al.*, 1983; Rothwell, 1983, 1984; Anglo German Foundation, 1988; Oakey *et al.*, 1988; Rothwell, 1990) and on Strategic Partnerships or Alliances (Contractor and Lorange, 1988; Doz, 1988; Knight, 1989; Syed Tariq, 1991). The number of strategic alliances between large established firms and small firms — in particular New Technology Based Firms (NTBFs) — has multiplied over the past few years. Small firms in general and New Technology Based Firms in particular are contributing a far greater share of the overall growth of the economy than has been recognized. Theoretically, the combination of a small firm's know-how with a larger firm's resources opens opportunities for synergies that can contribute to both firm's competitive advantage (Niederkofler, 1991) and to the creation of a regional growth potential (Donckels and Segers, 1990).

Research hypotheses and methodology

A multiple case study design (Yin, 1984; Niederkofler, 1991) was chosen to develop an understanding of the impact of strategic partnering on New Technology Based Firm-survival and growth in Belgium. To improve the reliability of conclusions in the research presented here, multiple cases will be investigated for the construction of a

theoretical model. Thereby, this research will follow Glaser's and Strauss' (1967) recommendation for the development of "grounded theory", which lets theory emerge from the data. One of the primary concerns in this study is to design a model based on empirical observations that captures as much as possible the "real world" of NTBF-creation in the biotechnology and micro-electronics industries in Belgium.

The hypotheses for the research presented here are as follows:

Hypothesis 1 Belgian NTBFs in their survival or growth phases gain from entering into a strategic technology partnership with large established firms.

Hypothesis 2 A number of potential partnership pitfalls can be identified. Therefore, a successful strategic technology partnership constitutes an optimization of the potential synergies and the dynamic complementarities between large, established companies and small — new technology based — firms.

Hypothesis 3 Strategic technology partnerships enable NTBFs to successfully commercialize their innovations and products and to significantly expand their future viability in terms of growth potential.

Review of literature

Before proceeding, it is important to clarify the meaning of the terms "New Technology Based Firm" and "Strategic Partnering". Small firms are a very complex and heterogenous population, especially in the case of innovation. As such, *New Technology Based Firms* are only a limited subgroup of the total population of start-ups. According to Shapero (1972) the tech starter is "an individual or a group, that takes the initiative in forming an organisation to produce a product and/or service in the area of high-technology, managing with relative autonomy and sharing the risk of success or failure". Rothwell and Zegveld (1982) state that small firms are responsible for a disproportionately large share of radical innovations in certain industry sectors. Bollinger *et al.* (1983) hypothesize that while regional policies do play a part in attracting high technology industries to an area, the greater influence lies in sector differences.

Oakey *et al.* (1988) define NTBFs as "small firms with a higher inherent innovative potential than large firms and small firms in general". They play an important role in the emergence of new, high technology sectors. A significant number of basic innovations have originated in small firms. Small firms often play an important role in industries characterized by a particularly high rate of growth and technological change. According to Schmidt (1988) NTBFs are "interpreted to include users and producers of new technologies including research and development, innovations (product-, proces-, . . .), diffusion and adoption measures . . . and it covers the phases of invention, modification and continuing information on new products, production processing, organizational methods and social or personnel innovations". Samson (1990) defines NTBFs in a narrow sense as science-started-ventures (scientist-turned-entrepreneurs).

Roure and Keely (1989) identified the following factors as important facilitators of technology availability or market opportunities in the process of the creation of NTBFs:

- The presence of 'incubator' type companies in the area
- Attractive potential market, if possibly, nearby
- Universities with a strong interaction with firms
- Government purchase contracts, research projects and incentives or subsidies to innovation

Figure I expresses the creation process of a New Technology Based Firm according to Roure and Keely (1989).

There is a growing trend towards technological and marketing relationships between firms. Partnerships and alliances are becoming more and more important in the light of an increasing globalization of markets and technology (O'Doherty, 1990). There is however, no consensus on the definition of *Strategic Partnering*. Partnering spans a continuum of working relationships. On the left end is the purely transactional relationship, i.e.

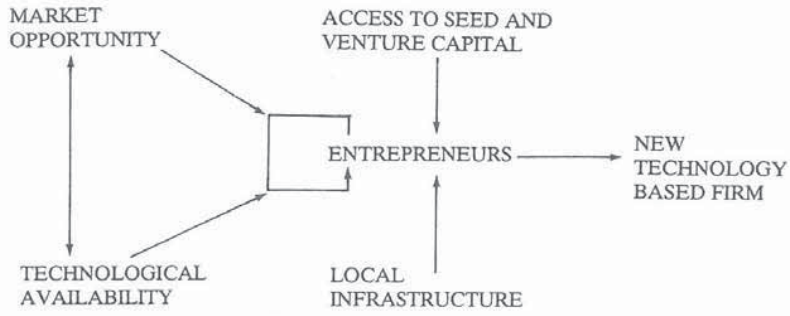


Fig. I. The new technology based firm.

exchange of product(s) for competitive prices. On the right end is the purely collaborative relationship, the ultimate in partnering where customer firm and supplier firm have strong "social, economic, service and technical ties over time ... thereby achieving mutual benefit" (Anderson and Narus, 1991). The lack of a clear definition makes it best to define the concept of strategic partnering as broadly as possible. Harrigan (1988) defines a strategic partnership as a cooperative agreement in which two or more businesses are actively involved in the management of a venture. The spectrum of agreement types varies from subcontracting and licensing over joint ventures and strategic alliances to consortia and acquisitions. The independence of the entrepreneur is usually decreased as one moves down the list (Knight, 1989). Strategic alliances are partnerships among firms that work together to attain some strategic objective. Joint ventures create a jointly owned entity, while nonequity forms of cooperation do not.

According to Doz (1988), partnerships usually offer large firms a channel to tap into the innovative and entrepreneurial potential of smaller companies. The strategic contributions of joint ventures are numerous (Contractor and Lorange, 1988): larger firms offer their smaller partners funds, established manufacturing facilities, distribution channels and general management skills (Knight, 1988; 1989). In most of the observed partnerships, smaller firms perform research and development for the larger firms and/or transfer innovations to them. The complementarity is obvious. However, Doz (1988) and Niederkofler (1991) point out that strategic partnerships have to deal with a number of managerial pitfalls. Research has shown that most partnerships fail to meet the objectives of the large established bureaucratic companies and their smaller, entrepreneurial partners. Partnerships are on the other hand more frequent, since the obvious alternative for it, i.e. acquisition of smaller firms, is the least likely to succeed of the partnership types and usually ends with the entrepreneurs leaving the large corporation, as Knight's research (1989) which was based on a sample of 140 NTBFs in Canada suggests. The alternative is to form a strategic partnership of alliance which is essentially a joint venture.

With respect to technology, Hagedoorn and Schakenraad (1990) limit strategic partnering to *interfirm technology cooperation*, i.e. those forms of inter-firm collaboration for which joint development of new technologies and or agreements aimed at improved innovative performance (on this behalf, see Kleinschmidt and Cooper, 1991) are at least part of the agreement. In that context, strategic partnering is defined as those agreements that focus on a long-lasting effect on the product-market positioning of the participating companies. The definition of terms as it is derived for the research presented here is as follows (see Table 1).

Rothwell (1983) states that the main advan-

TABLE 1
Definition of terms

1. New technology based firm		
▶ University spin-off	→	University based NTBF
	→	Science-started-venture
▶ Industry spin-out	→	Industry based NTBF
2. Strategic Partnering (Interfirm Technology Cooperation)		
▶ University spin-off		
+ Large established firm	→	Strategic (technology partnership)
▶ Industry spin-out		

tages of small firms are 'people embodied', while those of large firms are predominantly 'resource embodied'. Small NTBFs often enjoy the advantages of dynamic, entrepreneurial management embodied in a system that is flexible and highly responsive to change, and who are willing to accept financial, technological and marketing risk. Large firms contain the financial, technical and production resources that enable them to undertake innovation, but because of potential problems of bureaucracy, internal inertia and risk aversion, they often lack the dynamism and flexibility necessary for the initiation and successful conclusion of radical innovation. Small NTBFs tend to be run by technically trained individuals.

These firms often lack the management skills and other resources to successfully commercialize their innovations. Large firms, on the other hand, often lack the entrepreneurial talents to generate innovations to expand their product lines, using their superior resources, such as funds, established manufacturing facilities, distribution channels and general management skills (Knight, 1988; 1989). According to Acs and Audretsch (1989) a strategy of product innovation can at least partially compensate for the inherent size disadvantage of small firms. They found that the innovative strategy explains a significant proportion of the variation in the presence of small firms.

Van der Auwera and Eysenbrandts (1989) compiled a set of specific advantages of small versus medium/large NTBFs in Belgium (N = 130). Small NTBFs have a greater job flexibility and less hierarchy. The flow of information between management and production is faster. They have a better view over the innovation process. The organizational structure is more rapidly adapted to market needs or to new products. Small NTBFs have a direct relationship with suppliers and customers. They respond more rapidly to direct demand from abroad. Medium/Large NTBFs can recruit more easily specialists and know-how. They dispose of larger promotion- and marketing budgets. They have better options for product differentiation. There is an accumulation of information within the network of specialized units or departments of these firms. Relative to price, their bargaining position with suppliers is stronger. They dispose of a better infrastructure and better foreign contacts in the case of exportation. They have larger R&D-budgets.

From the above, it may be hypothesized that a successful strategic (technology) partnership constitutes an optimization of the potential synergies and the dynamic complementarities between large, established companies and small — new technology based — firms. Dynamic complementarities (Rothwell, 1983) are of major importance for the future perspectives of NTBFs. The rate by which an NTBF grows will be determined to a great extent by its ability for complementarity and the attached cost/benefit analyses. NTBFs can grow rapidly and through dynamic complementarities with other organisations (i.e. universities, other small — new technology based — firms, large firms), they can generate regional growth. However, their innovatory potential varies between sectors and across the industry cycle as does their growth creating potential (Rothwell, 1990). Many new discoveries and advances in science occur in universities and government laboratories, while the application of this new knowledge to commercial and useful public purposes depends largely upon action by large and small — new technology based — firms.

On the one hand, radical technological innovations often originate from state-of-the-art research, that is often conducted in small, new companies which are spin-offs from university research centres. The transfer of this know-how to large firms with more traditional technologies enables the latter to leapfrog their competitors. On the other hand, the large partner firms possess distinct strengths that are of vital importance to

their smaller partners, such as national or global systems of distribution channels and established reputations, which permit a rapid market penetration on a large scale. According to Niederkofler (1991), this logic explains why the number of strategic partnerships between established large companies and small — new technology based — firms has been on the rise.

Factors for assisting new technology based start-ups locally

Bollinger *et al.* (1983) describe a number of factors and policies that are most critical for countries that wish to encourage the growth of New Technology Based Firms. They are:

- Regional policy
- Sector differences and product versus process innovation
- Technology-oriented complexes
- Other factors such as information flow, existence of financial markets and capital constraints and government or large firm procurement procedures

However, for the purpose of this contribution, we limit ourselves to *region-specific technology policy in Belgium* (Segers, 1991). Technology policy in Belgium emphasizes the creation of infrastructures to promote and provide information on the importance of new technologies for industrial development, the purpose of which is to create an environment suitable for the mobilisation of all innovative forces in the region and to attract foreign investment. A sectoral strategy for technological innovation reflects the desire to establish industries in sectors which allow interfacing university and technological research with the needs and/or the potential of the industry. Consequently, region-specific technology policy has been organised around two focal points, i.e. the existence of a high potential for research in universities and other centres of excellence and the support for New Technology Based Firms.

A wide range of incentives have been created for stimulating the diffusion of technological innovation and for assisting New Technology Based Start-ups locally, such as financial and fiscal incentives including soft loans, capital grants and state guarantee, seed and venture capital funds, financing of pre-competitive and competitive research, prototype development aid, interest subsidies for R&D-loans, accelerated depreciation, government-supported laboratories and industry-specific collective research centres, infrastructural incentives, support for selected technologies, public sector procurement (national, European and international technology programs; on this behalf see Roscam Abbing and Schakenraad, 1991), science parks and innovation & incubation centres for stimulating and assisting university spin-offs and university based NTBFs. Regional technology policy measures have provided an important initial stimulus for the emergence of a number of New Technology Based Start-ups in generic technology industries in Belgium such as biotechnology and micro-electronics (Segers, 1992). Due to a growing trend towards technological and marketing relationships between large and small firms, interfirm technology cooperation (formalized in strategic technology partnerships) has become increasingly important for the survival and growth of a number of NTBFs in Belgium, as the case-based evidence will show.

Strategic partnering experiences of NTBFs in Belgium

As analyses of the emerging biotechnology industry in Belgium offers proof for the hypothesis that strategic technology partnerships may have a significant impact on the survival and growth of Belgian NTBFs. The basic inventive activity in the biotechnology industry in Belgium has occurred mainly in university based NTBFs (science-started ventures), i.e. small, new companies which are spin-offs from university research centres performing state-of-the-art research. Increasingly, venture capital companies have participated in or formed joint ventures with large international chemical or pharmaceutical firms, who are at a growing rate establishing joint ventures with university research centres and small university based biotech firms (on this behalf see also Faulkner, 1986 and Oakey, Faulkner, Cooper and Walsh, 1990). This logic has resulted in a number of strategic technology partnerships between Belgian NTBFs and established large international companies. Examples are:

- Plant Genetic Systems (Bel) with Japan Tobacco, Clause (France) and Hilleshög (Sweden)
- Corvas NV (Bel) with Plant Genetic Systems (Bel) and Corvas International, Inc. (USA)
- Eurogenetics (Bel) with Tosoh (Japan)
- IRE-Celltarg (Bel) with the Liposome Cy (USA)
- IRE-Medgenix (Bel) with Bio-Assay Systems (USA)
- Phytotec (Bel) with Native Plant International (USA)

The same logic is true for the micro-electronics industry in Belgium. Examples of recent strategic technology partnerships are:

- Imec (Bel) with Teknekron (USA)
- Mietec Alcatel (Bel) with Imec (Bel)
- Softcore (Bel) with Apple (USA) and Advent (Bel)
- Cobraïn (Imec spin-off) (Bel) and Matrix Integrated Systems, Inc. (USA)
- UCB Electronics (Imec spin-off) (Bel) with Japan Synthetic Rubber

In the following section, case-based evidence will be used to develop an insight into the relationships between Belgian NTBFs and their strategic (large) partners. Table 2 presents an overview of the cases on Plant Genetic Systems and Corvas NV (biotechnology industry) and on Imec and Mietec (micro-electronics industry) that will be discussed hereafter.

TABLE 2
Strategic partnerships between Belgian NTBFs and (large) established firms

Belgian NTBF	Strategic partner(s)	Agreement type
Plant Genetic Systems (Biotn)	▶ Corvas International Inc. (USA)[1]	▶ Partnership Spin-off Firm
	▶ Hilleshög (Sweden)	▶ Co-marketing and Licensing Agreement
	▶ Japan Tobacco	▶ Joint Venture
	▶ Clause (France)	▶ Joint Venture
Corvas NV (Biotn)	▶ Plant Genetic Systems (Bel) and Corvas International Inc. (USA)	▶ Product Development
Imec (Me)	▶ Teknekron (USA)	▶ Co-marketing Agreement
Mietec Alcatel (Me)	▶ Imec (Bel)	▶ Joint Venture

Biotn: Biotechnology Me: Microelectronics

[1] Corvas International, Inc. has also entered into a strategic alliance with Centocor, Inc. (USA). See Figure II.

Case I: Plant Genetic Systems

The case of *Plant Genetic Systems* is an excellent illustration of the impact of strategic technology partnerships on NTBFs in Belgium. Plant Genetic Systems (PGS) is a Belgian NTBF working on the leading edge of the new wave biotechnology industry. PGS originates initially from academic incubators, i.e. the genetic engineering laboratories of the universities of Ghent and Leuven. The same logic is true for other new biotech firms in Belgium. PGS is Europe's leading agricultural biotechnology company, renowned for its product development capabilities. The NTBF was founded in 1983 to develop new plants with high-added value traits. Through genetic engineering the company "designs" plants that offer major economic benefits to the food, feed, pharmaceutical and chemical industries. It currently employs over 125 people. Plant Genetic Systems was initially a technology driven company. Due to the strategic technology partnerships it has stepped into, PGS is becoming increasingly market driven.

PGS' business strategy shows the potential gains an NTBF can obtain by entering into one or more strategic technology partnerships. Its business strategy is to secure its position as a major supplier of its genetic engineered plants (hybrids) through extensive patenting of its commercially important technology. The company opens marketing channels for its products by establishing joint ventures, co-marketing agreements and licensing arrangements with large international seed companies. Plant Genetic Systems is now fostering dynamic complementarities between technology and science and the niche-markets it is positioning itself on.

For this purpose, PGS has entered into a number of strategic technology partnerships with leading American, Japanese and European large established chemical and/or pharmaceutical companies. In 1987, PGS signed a licensing agreement with Hilleshög A. B., the largest plant breeding and seed company in Europe. Benefits include access to markets for production that reaches the commercialization stage. In April 1989, PGS announced a major joint venture with Japan Tobacco, Inc., a 22 billion dollar corporation with interests in agribusiness and pharmaceuticals. Japan Tobacco currently owns 10% of PGS stock. Also in 1989, PGS signed a joint venturing agreement with the French seed giant Clause. In March 1991, Plant Genetic Systems entered into a strategic partnership agreement with the Californian biopharmaceutical company Corvas International, Inc. (see case 'Corvas NV'). In Table 3, the stepping stones in the start-up, survival and growth of Plant Genetic Systems are displayed.

TABLE 3
The stepping stones in the start-up, survival and growth of Plant Genetic Systems

NTBF-Incubators

- Genetic engineering laboratories of the State University of Ghent and the Catholic University of Leuven

Start-up-Phase

- Plant Genetic Systems (Bel): development stage company
- Technology driven
- Product development with high added value
- Absence of products

Survival-Phase

- Continuing operating losses
- Patenting of commercially important technology: hybrids
- *Strategic partnerships*:

1987: Co-marketing and licensing agreement with Hilleshög: plant breeding and seed company

1989: Joint venture with Japan Tobacco, Inc.: agribusiness and pharmaceuticals

1989: Joint venture with Clause (France): seed company

1991: Product development agreement with Corvas International, Inc. (USA): biopharmaceutical company. Partnership Spin-off: Corvas NV (Bel). Public stock offering (Nasdaq, February 1992).

- Technology/Market driven

Growth Phase (projected)

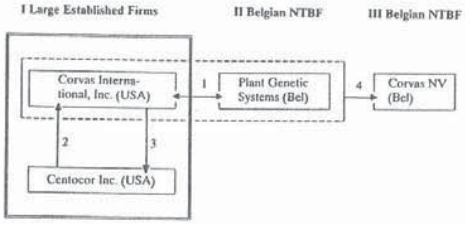
- Market driven
- Fully integrated manufacturing concern (as an independent venture?).

Case II: Corvas International Inc. and Corvas NV

Corvas International, Inc. (further abbreviated as Corvas Int.) is a biopharmaceutical company located in San Diego, California (USA), engaged in the design and development of a new generation of therapeutic agents in the field of thrombosis and associated vascular diseases. The company intends to commercialize synthetic drugs for the improved treatment and prevention of major cardiovascular diseases, including among others heart attack and stroke. The company has developed proprietary drug design technologies which have yielded several lead compounds. Its first drug candidate, Corsevin M, is currently in phase I clinical trials. Corvas Int. is a development stage company, founded in 1987. The company has not completed the development of any therapeutic product and, accordingly, has not begun to market or generate significant revenues from the commercialization of products. The company's strategy for the research, development and commercialization of certain of its products includes entering into various arrangements with corporate partners, licensors, licensees and others. Because Corvas Int. is focusing its resources on proprietary synthetic pharmaceuticals rather than on monoclonal antibodies, in November 1991 it entered into a strategic alliance with Centocor, Inc. in the area of monoclonal antibody products. In connection with this alliance, Centocor made an additional equity investment in Corvas Int. and in turn acquired a license to Corsevin M and an option to license other present or future monoclonal antibody products. Corvas Int. has retained exclusive commercial rights to all non-antibody products under development. All this is of major importance to Plant Genetic Systems since PGS seeks to strengthen its position in the market niche of biotechnological pharmaceuticals. In March 1991, Corvas Int. and Plant Genetic Systems entered into a strategic technology partnership agreement. Corvas Int. acquired certain assets and research and development projects of Plant Genetic Systems in

exchange for a certain amount of shares of preferred stock. The assets acquired included laboratory equipment and prepaid services. Corvas Int. conducts its proteïn engineering programs, including the research and development projects acquired from Plant Genetic Systems through its Belgian partnership spin-off *Corvas NV* to complement its medicinal chemistry programs in San Diego.

As Figure II clarifies, Plant Genetic Systems is indirectly related to Centocor, Inc. through the Centocor-Corvas Int. partnership and the Corvas Int.-PGS alliance via Corvas NV.



1 Strategic Technology Partnership
2—3 Strategic Technology Partnership
2 Equity Investment
3 Licensing Agreement (monoclonal antibody products)
4 Partnership Spin-off (proteïn engineering programs)

Fig. II. Plant Genetic Systems and Corvas NV.

Case III: Imec and Mietec

Micro-electronics is of strategic importance to every industrialised country, because integrated circuits are found in almost every product and production process. The R&D however is very demanding both in capital equipment as in manpower. The regional government of Flanders (Belgium) therefore created Imec as part of a science and technology programme to promote research and applications of micro-electronics, in the fields of very large scale integration systems design methodologies, advanced semi-conductor processing and micro-electronics education and training.

The *Interuniversity Micro-Electronics Centre (Imec)* is an originally science-started-venture. It currently employs over 370 people and was founded in 1984. It strengthens the research potential of the Flemish universities with electronic engineering departments (universities of Leuven, Ghent, Brussels, Antwerp and Limburg). Imec makes available state-of-the-art design software for integrated circuits by offering the possibility of fabricating custom and semi-custom integrated circuits and sensors and by carrying out joint national or international research projects, with or without industrial involvement. With other research institutions outside Belgium, Imec cooperates in large projects where the complementary know how of several laboratories is required. It carries out R&D for the European Space Agency and in the framework of the Jóint European Submicron Silicon Initative.

Imec has developed into a major independent research resource for industry. This has opened opportunities for university-industry linkages and for technology transfer. Several industrial companies have scientists working at Imec. Among the university-based research potential in Flanders cooperating with Imec are ESAT (Department of Electrical Engineering, Leuven), MICAS (Medical and Integrated Circuits and Sensors, Leuven), MI2 (Machine Intelligence and Imaging, Leuven), LEA (Laboratory of Electromagnetism and Acoustic, Ghent), LEM (Laboratory of Electronics and Metrology, Ghent), APD (Applied Physics Department, Brussels), IRIS (neural networks, . . . , Brussels).

In May 1986 the Imec-Spin-off Cell was created in order to strengthen the interaction between the research centre and the industry. To meet this objective, a number of actions have been developed such as the transfer of information to the industry with respect to potential industrial applications of technologies developed at Imec; an identification of industrial research needs in the field of micro-electronics; informing and supporting potential foreign investors of the research facilities and the contract research possibilities offered by Imec; licensing agreements for Imec technology and software with third parties for commercialisation of design, device modeling and measurement software. The major objective of the Imec-Spin-off Cell is however to identify the technologies that can lead to spin-offs. To do this, the spin-off cell helps to prepare market analyses, investment calculations and complete business

plans up to finding the appropriate required financial input either through seed or venture capital or by attracting industrial partners to set up (joint) industrial units based upon technologies developed at Imec. The spin-off cell spents a large effort on informing Belgian small firms on the different possibilities for benefiting from Imec's R&D-effort.

Imec helps to create a scientific environment needed by high tech companies to start, survive and grow. On the other hand, Imec can play an important role in the decision of micro-electronic companies to invest in Belgium. The latter creates opportunities for regional growth. An industrial research park together with an incubation and innovation centre is available in the proximity of Imec for the start-up of research-based firms and industrial research institutions.

In the Fall of 1991, Imec and the American company Teknekron signed a cooperative agreement for the joint marketing of products, technology and consultancy of micro-systems. The establishment of a mutual spin-off firm is under consideration. The strategic technology partnership will follow Teknekron's marketing approach in which potential customers point out potential applications of micro-systems. In November 1991, Imec stepped into a strategic technology partnership with *Mietec Alcatel.* Mietec is an industry based NTBF that develops, manufactures and markets technologies and products in the niche-market of ASICs (Application Specific Integrated Circuits). The company was established in 1983 by Bell Telephone Mfg., a Belgian subsidiary of Alcatel and by the Investment Company for Flanders. In January 1990, a 100% shareholding was acquired by the Alcatel Group, Europe's number one telecommunications company, to form the current Mietec Alcatel, that is now the group's strategic partner for micro-electronics. Mietec works together with Imec for all technology developments, especially in defining process steps and analysing techniques. Mietec participates with other companies and research labs in various European science and technology programmes.

One of Imec's strategic goals is to provide incentives for new industrial ventures based on technology (research and development) developed at Imec. Next to its strategic technology partnerships with Teknekron and Mietec, Imec has thus given rise to a number of new technology based start-ups in Belgium. They are:

- UCB-Electronics (1986)
- Cobraïn (1987)
- European Development Centre (1989)
- Soltech (1989)

In the course of 1990, Cobraïn entered into a strategic partnership with Matrix Integrated Systems, Inc. (USA) and UCB-Electronics closed a joint venturing agreement with Japan Synthetic Rubber.

In Figure III, the logic behind strategic partnering between Belgian NTBFs and large established firms is presented in a model based on empirical observations that capture as much as possible the "real world" of NTBF-creation in the biotechnology and micro-electronics industries in Belgium.

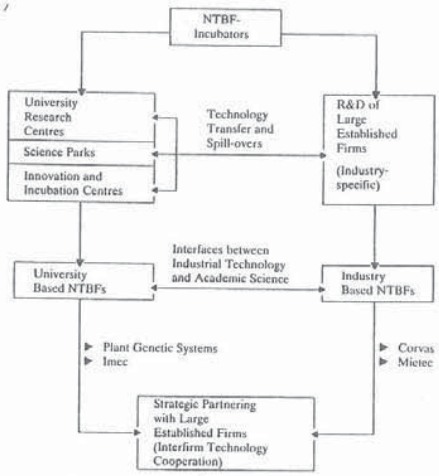


Fig. III. Strategic partnerships between (large) established firms and Belgian new technology based firms.

Conclusions

The data from the cases suggest that strategic technology partnerships can have a significant impact on New Technology Based Firms in Belgium that are in their survival or growth stages. The partnerships with established large firms offer

Plant Genetic Systems, Corvas NV and Imec/Mietec access to the superior resources of their strategic large partners. The research and development, marketing, financial and managerial resources are formalized in equity, product development, co-marketing and/or licensing agreements (*Hypothesis 1*). If these NTBFs are not able to establish strategic partnerships, they could encounter delays in introducing their products into certain markets or find that the development, manufacture or sale of their products in such markets is adversely affected.

A number of potential pitfalls can be identified for the survival and growth of these NTBFs:

- the absence of products
- the need for additional capital (seed and venture capital, public stock offering)
- continuing operating losses during the early stages of development
- no assurance of regulatory approval
- rapid technological change and competition
- uncertainty regarding patents and proprietary rights
- dependence on others: the amount and timing of resources that the strategic large partner(s) will devote to its contractual partnership responsibilities are not within the NTBF's control
- uncertainty about expected revenues that will be derived from the strategic partnership
- manufacturing, clinical trial and regulatory compliance capabilities of the NTBF and if not dependence of the strategic partner
- retention and attraction of key personnel

It is clear that a number of these potential pitfalls are directly linked to the involvement of the NTBFs in strategic (technology) partnerships (*Hypothesis 2*). The cases on Plant Genetic Systems, Corvas NV and Imec/Mietec seem to suggest that a workable strategic partnership constitutes an optimization of the potential synergies and the dynamic complementarities between the large, established firm and the small — new technology based — firm. However, despite the considerable success of these Belgian NTBFs in establishing strategic partnerships, the nature of the market involved, the long lead times and the uncertainty which characterizes these firms suggest that they are unlikely to become fully integrated manufacturing concerns — at least not as independent ventures. The new biotechnology firms reviewed here are heavily dependent on established companies, especially for marketing outlets, for manufacturing resources when they reach the commercialization stage and for continuing product development efforts. The microelectronics firms reviewed depend heavily on both public (national, European and international) and industrial R&D contracts and on the public research system. However, both types of NTBFs are important interfaces between industrial technology and academic science.

As stated earlier, the combination of a small firm's know-how with a larger firm's resources opens opportunities for synergies that can contribute to both firm's competitive advantage and to the creation of a (regional) growth potential. If the pitfalls mentioned earlier can be avoided by entering into a partnership agreement, the small — new technology based — firm will stand a better chance to expand its future viability in terms of successful commercialization of its innovations or products and of its growth potential (*Hypothesis 3*).

With respect to regional technology policy, the findings from above lead to the conclusion that stimulating and assisting NTBF-creation is best put within the framework of European and/or international technology programs and the effects of this for small countries such as Belgium.

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Paper ② 1996 Technology policy: the role of regions and new technology based firms in Belgium

TECHNOLOGY POLICY:
THE ROLE OF REGIONS AND NEW TECHNOLOGY-BASED FIRMS IN BELGIUM

Jean-Pierre Segers

INTRODUCTION

During the past few decades, there has been a growing acceptance of the key role that small businesses and technological innovation play in stimulating regional economic growth. According to Dufour (1988), "increasingly, governments have realized the dynamic combination of small business and technology development. By and large, however, New Technology Based Firms constitute a small number of a country's total industry and are predominantly the target of support among the industrialized countries." Consequently, regional policymakers have formulated a growing number of policy incentives to assist and to stimulate technological innovations in industry. As several authors recognize (e.g., Anglo German Foundation, 1988; Bollinger et al., 1983; Oakey, 1984; Oakey et al., 1988; Rothwell, 1983, 1984, 1990), the emergence of new high-technology industries has therefore led to a position where the encouragement of indigenous New Technology-Based Firm-creation has

become an undisputed goal of regional technology policy. There is a growing belief among regional policymakers that the small business in general and the New Technology Based Firm (NTBF) in particular are a realistic and potential source of regional economic growth. The openess of the technology-oriented small business towards technological development can lead to competitive advantages in local, national and international markets which can, in turn, lead to improved prospects of output, income and employment. However, despite a growing interest in indigenous NTBF formation and growth, there are many issues concerning their conception and development that remain unclear. Appendix I presents a selection of definitions and research on New Technology Based Firms.

CONCEPTUAL SETTING

The Belgian economy is dominated by the small business sector: 99 percent of all firms in Belgium are small businesses. Within this population, only a very small percentage are technology based firms (Donckels & Segers, 1990). In order to reach an understanding of the NTBF-phenomenon in Belgium, a combination of the survey and case study design (Yin, 1984; Niederkofler, 1991) was chosen. To improve the reliability of conclusions, the research presented here will follow Glaser's and Strauss' (1967) recommendation for the development of grounded theory, which lets theory emerge from the data. In Exhibit I, the research design from above is fit into a conceptual model that clarifies the basic goal of this contribution: to understand the creation process of New Technology Based Firms in Belgium, within the context of technology based regional policy. One of the primary concerns of this study is to design a theoretical model that captures the real world of NTBF-creation in Belgium. The validity of the model is supported by empirical observations.

THEORETICAL SETTING

Many new discoveries and advances in science occur in universities and government-supported laboratories, while the application of this new knowledge to commercial and useful public purposes depends largely on action by large and small—new technology-based—firms. According to Rothwell (1983, 1990), New Technology Based Firms (NTBFs) can play an important role during the early phases of industrial evolution. Dynamic complementarities (Rothwell, 1983) may exist between small and large firms during the industry cycle. Existing large firms provide much of the basic, state-of-the-art technology, venture capital and technically skilled personnel which are essential to new technology-based firm start-ups. The new technology based firms provide the risk-taking entrepreneurial drive and rapid market exploitation.

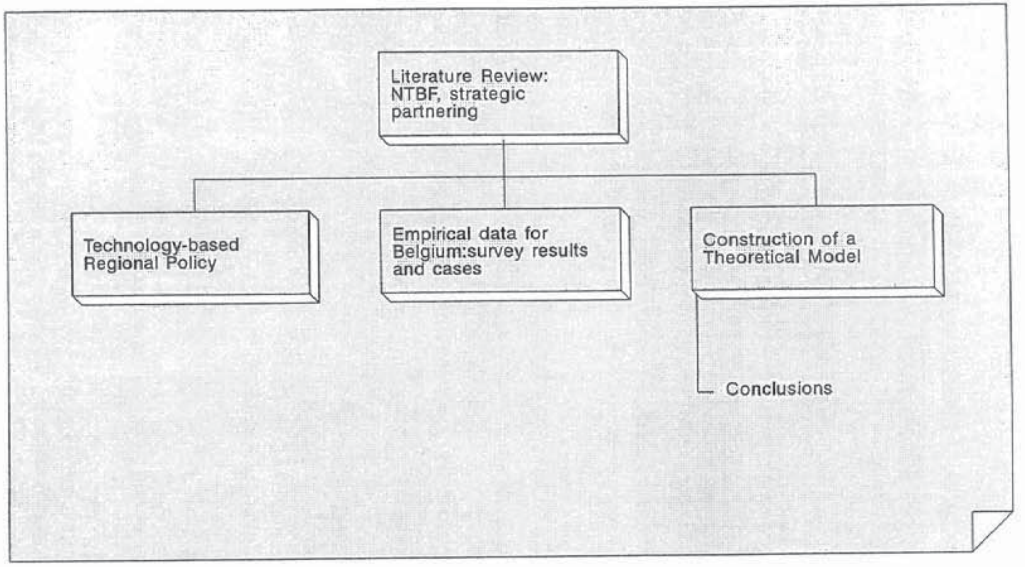


Exhibit I. New Technology Based Frims in Belgium
Conceptual Model

As the industries mature, scale economics become increasingly important in the mainstream activities and strong oligopolies are formed, leaving only specialist market niches for new and small firms. The latter then often turn to the production of "add-on's," once the product in question had reached the dominant design-stage (Abernathy & Utterback, 1982). Existing large corporations play the major initial role in invention, producing new devices largely for in-house use only. The major role in the initially rapid market diffusion of these new devices, however, is played by new, small but fast growing companies founded by technological entrepreneurs, often coming from established corporations, bringing with them a great deal of technological and applications know how. In this system of dynamic complementarities between large and small firms, the latter make a unique contribution in the rapid market diffusion and general commercial exploitation. Established technology-based large corporations can in turn be extremely effective in creating new technological possibilities. They are highly inventive. While they are adept at utilizing the results of their inventiveness in-house (new technology for existing applications), they are less well adapted to the rapid exploitation of their inventions in new markets (new technology for new applications). During the early phases in the evolution of a new industry the behavioral advantages of small scale are crucial. As the industry evolves, technological possibilities become better defined and market needs become increasingly well specified. The advantages of large scale begin to dominate. Comparative advantage shifts to the larger firms and the industry develops towards a mature oligopoly. NTBFs have been highlighted as a vehicle for high technology economic growth. Oakey et al. (1988) point out that in terms of emphasis during the 1950s and through to the mid-1970s, large firms generally were favored in preference to their small counterparts, and public policies emphasized industrial rationalization through the formation of national "flagship" companies in areas such as computers. It was felt that such large companies with a strong resource base were best suited to compete in world markets for advanced high technology products. However, from the mid-1970s onwards, during a period of structural economic change, public policy makers began increasingly to favor small firms. This shift in policy emphasis was largely based on the belief that small firms were potentially a more suitable (endogenous) vehicle for the economic renewal of less developed regions than were the branch plants of large firms (the traditional vehicle of regional policy) and that small firms had a higher inherent innovative potential than large firms. Since 1980, a number of governments in Europe have increasingly focused on stimulating the creation of NTBFs, which is a recognition of the important role such firms play in the emergence of new, high technology sectors (Dodgson & Rothwell, 1987). Technological progress is a necessary, but far from sufficient condition for business success. It is accepted that the regional economy, no less than the national or international economy, needs a continuous process of technical

change and innovation. The dynamics of this process will vary between regions. The technology acquisition behavior of local enterprises, their sources of supply and modes of access to technology will reflect the unique research and technology development environment of the region. But, improvements in the quality of this environment for local enterprises, either in local research and technology development generating capacity, or in the technology transfer and assimilation capabilities of the region will, ceteris paribus, help the economic performance of local enterprises and hence improve regional and national economic performance. The economic performance of a region is, therefore, a reflection of whether its enterprises are technologically innovative and dynamically growing, or technologically backward and declining (National Board for Science & Technology, 1987). The success of NTBFs is determined by the possibility to grow from a research-oriented firm to a fully integrated company with research, production and distribution facilities. The timing of this evolution is very important: too much time spent on technology-development can make it difficult for the NTBF to retain a credible commercial value and to obtain enough venture capital. This is a real danger in a focused strategy and a broad-based strategy. This is not so in the more commercial oriented early-product-strategy. However, NTBFs which follow this strategy are confronted with a highly competitive market because of their easy to imitate me-too-products (Van Dierdonck & Gemmel, 1990a, 1990b). There is a growing trend towards technological and marketing relationships between firms. Strategic Partnerships and Alliances (SPAs) have reached a growing status in the light of an increasing globalization of markets and technology (O'Doherty, 1990). The number of SPAs between (large) established firms and small firms—in particular NTBFs—has multiplied over the past few years. Theoretically, the combination of a small firm's know-how with a larger firm's resources opens opportunities for synergies that can contribute to both firm's competitive advantage (Niederkofler, 1991). Companies need increasingly to enter networks of alliances and cooperative arrangements ranging from R&D joint ventures to develop new products and processes, to technology licensing and transfer, to market exploration and marketing arrangements.

One of the most effective forms of cooperation is that between established companies with a well-functioning sales organization and a broad customer base, but in search of new products and services to ensure growth and young innovative firms which have developed new technologies, new products and/or new services, but which lack the sales channels to rapidly penetrate the market. According to Sommerlatte (1990), there are essentially three channels for innovation in an economy:

Innovation Channel 1. Technology and product innovation within large established corporations

Innovation Channel 2. Growth of young technology-based firms in competition with large established companies

Innovation Channel 3. Cooperation between established corporations and young technology-based firms

If established and young technology-based companies cooperate, be it in a supplier-customer relationship, or through cooperative agreements, then there is a good chance that the technological solutions are channelled through the marketing and sales organization of the established company and reach an existing customer base in an effective way. Small firms are more effective and inventive in certain technology areas and can realize technological solutions more rapidly, but they do not have the muscle to penetrate markets and to overcome acceptance barriers on their own. Appendix II offers a selection of research on strategic (technology) partnering.

TECHNOLOGY-BASED ENTREPRENEURSHIP IN BELGIUM

Belgium is a small country in Western Europe, a founding and key member of the European Union, its capital city Brussels hosts a large number of European and international organizations. The two main regions of Belgium are Flanders and Wallonia. A number of state reforms in the 1980s and 1990s have enabled the regional governments of Flanders and Wallonia to define regional (technology) policy. From the beginning of the 1980s onwards both regional governments initiated a number of science and technology programs aimed at the diffusion of new technologies in related (sub)fields of microelectronics, biotechnology and new materials. A sectoral strategy for technological innovation reflects the desire to establish industries in sectors which allow interfacing university and technological research with the needs and/or the potential of the industry. Consequently, region-specific technology policy has been organized around two focal points, that is, the existence of a high potential for research in universities and other emerging technology centers and the support for New Technology Based Firms. In general, a wide range of incentives have been created in Belgium for stimulating the diffusion of technological innovation. They are categorized in Exhibit II (Segers, 1992a). Priority in Belgiun regional policy is given to:

Support and continued development of emerging technology centers, which are the driving power for the development of new technology based industries in the regions.

Incentives for the corporate research potential in the 'new' industries.

Cooperation and technology transfer between university research centers and small (new technology based) and large firms.

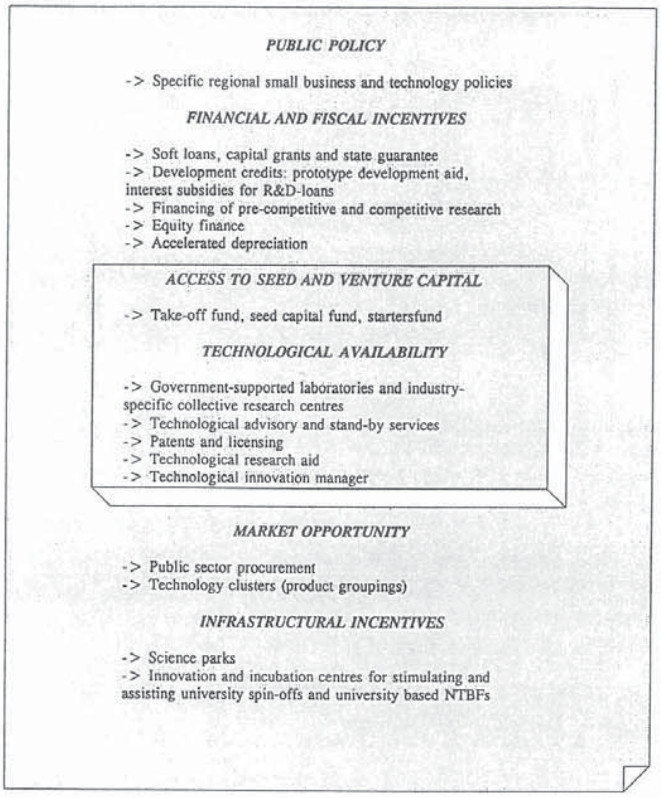


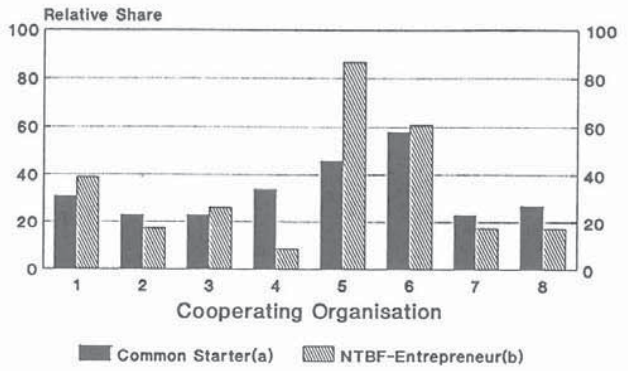
Exhibit II. Technology Based Regional Policy in Belgium
List of Policy Incentives

In Flanders, region-specific technology policy emphasizes the creation of infrastructures to promote and provide information on the importance of new technologies for industrial development. In 1982, the regional government of Flanders initiated the science and technology program "Dirv," Third Industrial Revolution in Flanders (Thirf), the purpose of which was to create an environment suitable for the mobilization of all innovative forces in the region and to attract foreign investment (see Segers, 1987). The focus of the "Dirv"-program was mainly on micro-electronics and to a lesser extent on biotechnology. In 1991, the "Dirv"-program was followed up by a number of specific technology programs focusing on generic technologies such as biotechnology, new materials and environmental technologies. The financial and infrastructural support of emerging technology centers (ETCs) is now one of the main instruments of regional technology policy in Belgium. This allows interfacing university research with the long term needs of private industry. ETCs are instrumental in providing a local capacity for technology transfer and application, for retaining and attracting skilled manpower, for improving national and international research and technology development linkages, for mobilizing regional research and technology development resources. Also in 1982, the regional government of Wallonia initiated the "Operation Athena," which was conceptually similar to the Dirv-program in Flanders. Recognizing the importance of diversification of its industrial fabric, the Walloon region-specific technology policy has been organized around the existence of a high potential for research in its universities and the support for technological innovation by a vast number of small businesses, which evolved around the traditional industries of the Walloon region (coal, steel, engineering and chemicals).

EMPIRICAL RESULTS

Our empirical verification for Belgium is based on research by Donckels and Segers (1990) into a number of characteristics of NTBF-Entrepreneurs such as educational level, product/market-orientation, socioeconomic networking, delegation, growth strategy and research and development. The following hypothesis was tested: "NTBF-Entrepreneurs differ significantly from common starters on a number of determinants that are of vital importance for the creation of a regional growth potential." As reference material, the results of the study "The New Entrepreneur" (Donckels et al., 1987) were used. The scope of the New Entrepreneur-survey (N= 400) was on the general profile and the managerial behavior of the common Belgian starter. These survey results are supported by case-based evidence for the emerging biotechnology industry in Belgium (Segers, 1992c). The findings of the survey by Donckels and Segers are of critical importance for the formulation of explicit growth-oriented and technology based regional policies in Belgium. The degree in which NTBF-

entrepreneurs will serve as a lever to regional development depends primarily on their dynamic behavior, on the development of environmental factors and on the intensity of the regional network and the specific position in it of the NTBF-entrepreneur. NTBF-entrepreneurs in Belgium are better educated than common starters. However, research by Donckels and Segers (1989) and Donckels et al. (1991) on the issue of entrepreneurship education in Belgium shows that specific entrepreneurship-oriented education and training are underdeveloped at the Belgian business schools and polytechnics. Most of the Belgian business schools are (quasi) exclusively manager-oriented. Curricula should be opened up to courses on entrepreneurship. A considerable number of starters dispose of well-developed technical skills, they had their education at technical high schools. Especially in these schools, entrepreneurship should be promoted. The professional background of NTBF-entrepreneurs differs from that of common starters on a number of issues. They become entrepreneurs after an employment in the private sector. Compared to common starters, they have had more important—often management—functions. They are often coming from established medium-sized or large firms. NTBF-entrepreneurs are more mobile than common starters. They have had more problems in the area of job satisfaction. The common starter is product-oriented. The NTBF-entrepreneurs are more market-oriented. The common starter is a 'craftsman'-type of entrepreneur, primarily interested in the technical product or production process. For the common starter, the most important motives to start are product orientation, the need to create something, takeover opportunities, a thorough knowledge of market and/or product and favorable prospects within the sector of activity. For the NTBF-Entrepreneur the main motives to start are a thorough knowledge of market and/or product, favorable prospects within the sector of activity, the need to create something, product orientation and tensions within the former employing company. Teamwork is crucial for the development of a successful new firm. Firms founded by a group with a mix of skills have better growth and survival potentials. This is especially true for the NTBFs, for which cooperation, delegation, networking and interdisciplinarity are essential. If this is the case, then there will be more know-how available throughout the firm. Throughout the innovation stages, the internal know how is an essential element. Radical innovations in particular are often the result of teamwork. NTBF-entrepreneurs are much better integrated in the socioeconomic network than common starters. Special attention is given to additional training and education, the relationship with supporting and service-rendering organizations and cooperation with suppliers. It is within the socioeconomic network that the synergistic relationship between small and large firms and the dynamic complementarities are being developed. The managerial behavior of NTBF-Entrepreneurs is clearly more professional than that of common starters. They are more



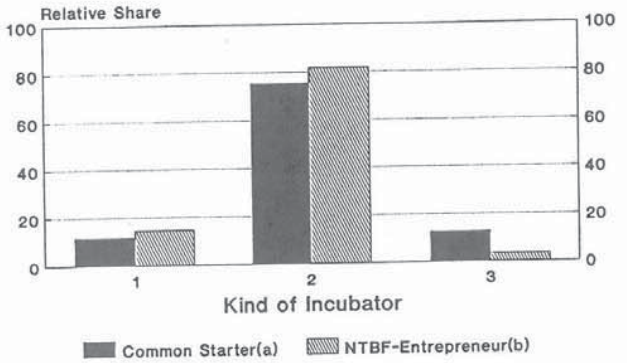
(a) N=400 - (b) N=32

Key: 1-University research centers
2-Private sector research centers
3-Study or engineering agencies
4-Technological advisory agencies
5-Customers
6-Suppliers
7-Large firms
8-Small firms

Figure 1. Cooperation in Research and Development

information-oriented and make better use of the available sources of information in their internal and external environment. There is also more delegation of tasks in these firms. NTBF-entrepreneurs are a dynamic factor within our economic system: they are more growth-oriented and clearly less dependent on local markets than are common starters. As is clear from Figure I, NTBF-entrepreneurs are clearly more open to research and development and are more oriented versus product innovation. Three groups of incubators were defined for common starters or NTBFs, that is, university-linked, industry-specific and government-supported incubators (see Figure 2). The survey results suggest that industry-specific incubators are the most important incubators for both common starters and NTBF-entrepreneurs. Government supported incubators are more important to common starters. Next to the industry-specific incubators, NTBF-entrepreneurs prefer university-linked incubators.

Regional policymakers in Flanders and Wallonia selected bio-technology and micro-electronics as the focal generic technologies for technology-based



(a) N=1060 - (b) N=89 (Multiple Answers)

Key: 1-University linked incubators
2-Industry specific incubators
3-Government supported incubators

Figure 2. Incubator Type and New Technology Based Firms

regional policy. The biotechnology and micro-electronics industries are particularly conducive to the formation of New Technology-Based Firms since the advancing new technologies are constantly creating new and specialist product-market niches together with opportunities for specialist sub-component manufacture. Three strong trajectories (Sharp, 1990)—that is, mainstream pathways of technological development—have emerged to date from the genetic engineering revolution. The first relates to pharmaceuticals, comprehending both human and animal health care. The second concerns agriculture. The third relates to diagnostics. The pharmaceutical sector is the leading "trajectory" in this new technology. It is a high value-added sector, where the potential returns are large enough to compensate for the high risk premium attached to novel developments. This trajectory took off on the basis of developments in recombinant DNA, that is, the implantation of foreign genes into micro-organisms, which subsequently proved capable of reproducing themselves. This process has led to products such as insulin and the human growth hormone. The focus of the pharmaceutical trajectory has now shifted to protein engineering—that is, methods by which proteins themselves can be "engineered" in such a way as to implant desirable or remove undesirable characteristics—to make drug delivery easier and safer. The next

step is that of "designer proteins," man-made proteins which are designed to incorporate particular therapeutic characteristics. In agriculture, the major breakthrough came in the early 1980s when the whole area of plant biotechnology was opened up. Since that time the "agricultural trajectory" has developed rapidly, with new varieties of hybrid plant seeds. The latter incorporate all kinds of desirable characteristics, from immunity to disease and/or pests, and early ripening, to the ability to withstand the use of general weedkillers. As a result the splicing and cloning of plant genes have become an area of major interest to the big agro-chemical companies, all of whom have now bought up seed companies with a view to developing hybrid species immune to their own particular brands of herbicides. The third area of intense activity is diagnostics. The main impetus to developments in this sector, that is, monoclonal antibodies, constitutes another, separate technological trajectory of the new biotechnology. Monoclonal antibodies derived from the search for a means of cloning individual antibody cells, since the specificity of antibodies had obvious applications not only in diagnostics, but in separation processes and drug targetting. This was the trajectory which, in commercial terms, took off most rapidly, since diagnostics is largely a matter of testing in vitro. It does not require the years of careful testing required of new drugs or new herbicides and pesticides. As a result this trajectory produced a product which could be easily marketed. Meanwhile, developments like antibody engineering are linking the monoclonal antibody trajectory back to the pharmaceutical trajectory. According to Sharp (1990), important convergences exist between the three main trajectories mentioned above. For example, although the pharmaceutical and agricultural trajectories are now distinct pathways, both took off with the discovery of recombinant DNA and both trajectories are much influenced by current developments in protein engineering. The diagnostics trajectory, which was built upon monoclonal antibodies, is now converging with that in pharmaceuticals through developments in antibody engineering. The biotechnology industry was formed by a cluster of entrepreneurial startups exploiting innovation-generating knowledge, which was generally produced elswhere (Audretsch & Acs, 1990). Biotechnology is particularly dependent on science. The actual scientific breakthroughs triggering the formation of the biotechnology industry were made during the first half of the 1970s. However, there was little recognition at this time that these scientific breakthroughs could have commercial applications. Genentech was the first new biotechnology firm to emerge in 1976. During the formative years of the biotechnology industry, a proliferation of small entrepreneurial high-tech start-ups quickly ensued Genentech's initial success. Kenney (1986a, 1986b) emphasizes that most of these entrants were motivated by an attempt to exploit the potential market value of major innovations. Virtually all of the firms in the industry are small and are specialized in a particular technology niche. Although there have been

numerous attempts by large established firms in the chemical and pharmaceutical industries to enter the biotechnology industry, they have generally been unsuccessful. Florida and Kenney (1988) attribute this to the inability of the large drug and chemical companies to attract and hold high quality scientists. As a result, these large companies have resorted to forming strategic partnerships with small firms. In fact, these large firms have often been a source of venture capital for new startups.

The basic inventive activity in the biotechnology industry in Belgium has occurred mainly in university based NTBFs (science-started ventures), that is, small, new companies which are spin-offs from university research centers performing state-of-the-art research. Increasingly, venture capital companies have participated in these firms. Large established (mostly foreign) firms in the chemical or pharmaceutical industries have established at a growing rate partnerships with emerging technology centers and their spin-offs. In turn, those NTBFs have entered into a growing number of interfirm agreements, predominantly strategic technology partnerships with large established firms (Segers, 1992b, 1992c). Faulkner (1986), Florida and Kenney (1988), Kenney (1986a, 1986b) and Oakey et al. (1990) witnessed the same trends in the United Kingdom and in the United States. According to Van Dierdonck and Gemmel (1990a, 1990b), almost all Belgian biotechnology firms have chosen for a focused or an early-product strategy. New Biotechnology Firms produce and distribute low-tech me-too products in order to generate cash flow to pay long-term research and to build up production and distribution facilities. In Belgium, the preference of many NTBFs for an early-product-strategy is quite logical considering the deficient financing framework: there is a deficient venture capital structure, an ineffective over-the-counter market and almost no R&D Limited Partnerships. Venture capitalists only invest in NTBFs after they have proven a growth-potentiality. Consequently, in the formative years, NTBFs have to rely on self-financing and eventually on the government taking on the role of venture capitalist.

The Regional Investment Company of Flanders is one example of a government institution providing venture capital. The Flanders Biotechnology Action Program (FBAP) focuses on precompetitive basic industrial research. The priority sectors of the FBAP are genetic engineering and micro-organisms, plant biotechnology, protein engineering, diagnostics and therapeutics. The relationship between technology based regional policy and emerging NTBFs in the biotechnology industry in Belgium is well illustrated by the histeriography of Plant Genetic Systems (PGS). PGS is a Belgian NTBF working on the leading edge of the new wave biotechnology industry. PGS originates initially from academic incubators, that is, the genetic engineering laboratories of the universities of Ghent and Leuven. The same logic is true for other new biotechnology firms in Belgium. PGS is currently one of Europe's leading agricultural biotechnology companies, renowned for its product development capabilities. The NTBF was founded in 1983 to develop new

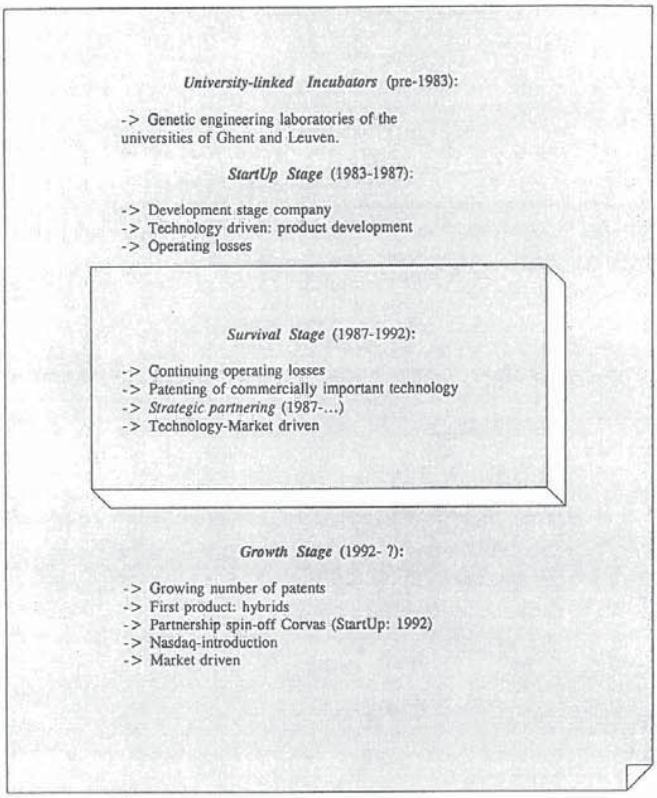


Exhibit III. Case Firm: Plant Genetics Systems Development Stages

plants with high-added value traits. Through genetic engineering the company "designs" plants that offer major economic benefits to the food, feed, pharmaceutical and chemical industries. It currently employs over 125 people. Plant Genetic Systems was initially a technology driven company. Its business strategy is to secure its position as a major supplier of its genetic engineered plants (hybrids) through extensive patenting of its commercially important technology. PGS is becoming increasingly market driven. The development stages of PGS are presented in Exhibit III.

Plant Genetic Systems is now fostering dynamic complementarities between technology and science and the niche-markets it is positioning itself on. For this purpose, PGS has entered into a number of strategic technology partnerships with leading American, Japanese and European large established chemical and/or pharmaceutical companies. The company opens marketing channels for its products by establishing joint ventures, co-marketing agreements and licensing arrangements with large international seed companies. In 1987, PGS signed a licensing agreement with Hilleshög A.B., the largest plant breeding and seed company in Europe. Benefits include access to markets for production that reaches the commercialization stage. In April 1989, PGS announced a major joint venture with Japan Tobacco, Inc., a 22 billion dollar corporation with interests in agribusiness and pharmaceuticals. Japan Tobacco currently owns 10 percent of PGS stock. Also in 1989, PGS signed a joint venturing agreement with the French seed giant Clause. PGS seeks to strengthen its position in the market niche of biotechnological pharmaceuticals. For this purpose, in March 1991, Plant Genetic Systems closed a joint product development agreement with the Californian biopharmaceutical company Corvas International, Inc. (Corvas Int.), a development stage company that was founded in 1987. Corvas Int. engages in the design, development and commercialization of synthetic drugs for the improved treatment and prevention of major cardiovascular diseases. Corvas Int. acquired certain assets and research and development projects from PGS in exchange for a certain amount of shares of preferred stock. To complement its medicinal chemistry programs in San Diego, California, Corvas Int. will conduct its protein engineering programs, including the research and development projects acquired from Plant Genetic Systems through its Belgian partnership spin-off firm Corvas NV. Corvas NV introduced an initial public stock offering on Nasdaq (New York Stock Exchange) in February 1992.

Another focal technology in Belgian regional policy is micro-electronics, in particular a small number of specific niches which still offer a growth potential in a market which has otherwise been long divided worldwide. Micro-electronics is of strategic importance to every industrialized country, because integrated circuits are found in almost every product and production process. The R&D however is very demanding both in capital equiment as in manpower. The regional government of Flanders (Belgium) therefore created the

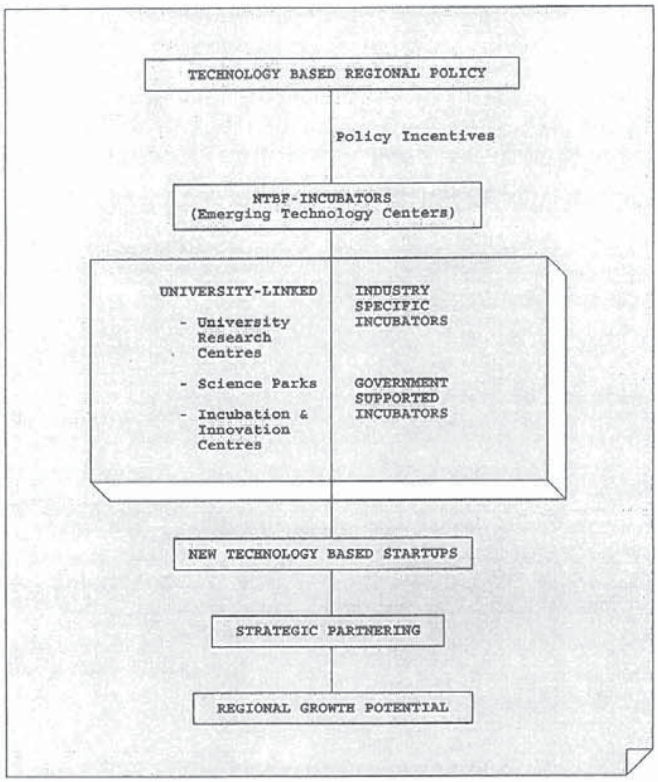


Exhibit IV. Construction of a Theoretical Model for Understanding NTBF Formation and Growth in Belgium

Interuniversity Micro-electronics Center (Imec) as a center of excellence to promote and support research and applications of very large scale integration systems design methodologies, advanced semi-conductor processing and micro-electronics education and training. Imec has developed into a major independent research resource for industry. This has opened opportunities for university-industry linkages and for technology transfer. Imec helps to create a scientific environment needed by high tech companies to start, survive and grow. On the other hand, Imec can play an important role in the decision of micro-electronic companies to invest in Belgium. The latter creates opportunities for regional growth. An industrial research park together with an incubation and innovation center is available in the proximity of Imec for the start-up of research-based firms and industrial research institutions. One of its strategic goals is to provide incentives for new industrial ventures based on technologies developed in-house. Imec has thus given rise to a number of new technology-based start-ups in Belgium. In the Fall of 1991, Imec and the American company Teknekron signed a cooperative agreement for the joint marketing of products, technology and consultancy of micro-systems. In November 1991, Imec stepped into a strategic technology partnership with Mietec Alcatel. Mietec is a Belgian NTBF that develops, manufactures and markets technologies and products in the niche-market of ASICs (Application Specific Integrated Circuits). The company was established in 1983 by Bell Telephone Mfg., a Belgian subsidiary of Alcatel and by the Investment Company for Flanders.

To conclude this section on technology-based entrepreneurship in Belgium, a theoretical model is presented in Exhibit IV that captures the logic behind NTBF formation and growth in Belgium, as it arises from the survey and case based data presented above.

CONCLUSIONS

Many new areas of technology are too small for large firms and too sophisticated for existing small firms. In the early stages of development, the commercial opportunities of scientific results or pre-competitive R&D are very often (willingly) neglected by large established firms. Organizations possessing the state-of-the-art knowledge then become incubators of New Technology-Based Start Ups. Technology based regional policy in Belgium increasingly focuses on the development and support of incubators for New Technology Based Startups. A wide range of incentives have been developed to support the emerging technology centers ("NTBF-Incubators") and the NTBFs that spin-off from them. Distinct differences have been identified between NTBF-entrepreneurs and common starters. NTBF-entrepreneurs differ significantly from common starters with respect to educational level, product/market-orientation, socio-economic networking, delegation, growth strategy, research

and development and the importance of incubators. NTBF-survival and growth may be significantly influenced by partnerships with established large firms. Strategic partnerships offer the small, new technology based, firm access to the superior resources of the strategic large partner(s). The research and development, marketing, financial and managerial resources are formalized in equity, product development, co-marketing and/or licensing agreements. If an NTBF is not able to establish strategic partnerships, it may encounter delays in introducing its product(s) into certain markets or find that the development, manufacture or sale of its product(s) in such markets is adversely affected. A number of (potential) pitfalls, closely related to strategic partnering activities, can be identified, such as the absence of products, the need for additional capital (seed and venture capital, public stock offering), continuing operating losses during the early stages of development, no assurance of regulatory approval, rapid technological change and competition, uncertainty regarding patents and proprietary rights, dependence on others—the amount and timing of resources that the strategic large partner will devote to its contractual partnership responsibilities are not within the NTBF's control, uncertainty about expected revenues that will be derived from the strategic partnership, manufacturing, clinical trial and regulatory compliance capabilities of the NTBF and if not dependence of the strategic partner, retention and attraction of key personnel. Despite the considerable success of Belgian NTBFs in establishing strategic partnerships, the nature of the market involved, the long lead times and the uncertainty which characterizes these firms suggest that they are unlikely to become fully integrated manufacturing concerns, at least not as independent ventures. The new biotechnology firms in Belgium are heavily dependent on established companies, especially for marketing outlets, for manufacturing resources when they reach the commercialization stage and for continuing product development efforts. The micro-electronics firms depend heavily on both public (national, European and international) and industrial research and development contracts and on the public research system. However, both types of NTBFs have proven to be important interfaces between industrial technology and academic science. The combination of a small firm's know-how with a larger firm's resources opens opportunities for synergies that can contribute to both firm's competitive advantage and to the creation of a regional growth potential. If the pitfalls mentioned earlier can be avoided by entering into a partnership agreement, the small—new technology based—firm will stand a better chance to expand its future viability in terms of successful commercialization of its innovations or products and of its growth potential, as is supported by the case evidence.

Appendix 1. Sample of Definitions and Research on New Technology Based Firms

REFERENCES	YEAR	COUNTRY	FOCUS
Abernathy & Utterback	1982	USA	Established Industry as Incubator for NTBFs
Anglo-German Foundation	1988	UK/FRG	Basic Characteristics of NTBFs
Bollinger et al.	1983	USA	Factors and Policies Most Critical for Encouraging the Growth of NTBFs
Bullock	1983	USA	Soft vs Hard Start-up of NTBFs
Donckels	1989	BEL	NTBF-Entrepreneurs vs Common Starters
Donckels & Segers	1990	BEL	NTBF-Enterpreneurs Versus Common Starters Regional Growth Potential
Doutriaux	1992	CAN	University Spin-Offs
Oakey et al.	1988	UK/USA	Innovative Potential Role in Emergence of High Technology Sectors Origin of Basic Innovations
Rothwell	1983	UK	Dynamic Complementarities
Rothwell	1984	UK	Role of NTBFs in the Emergence of New Technologies
Rothwell	1990	UK	Technology Transfer Infrastructure
Rothwell & Zegveld	1982	UK	Radical Innovators in Certain Industry Sectors
Roure & Keely	1989	USA	Creation Process of NTBFs Factors as Facilitators of Technological Availability and Market Opportunities

(continued)

Appendix 1. *(Continued)*

Samson	1990	USA	Science Started Ventures (University Spin-Offs)
Segers	1992a	BEL	Region-Specific Technology Policy and NTBF Start-Ups
Segers	1992b/1993	BEL	NTBFs and Strategic Partnering
Van Der Auwera & Eysenbrandts	1989	BEL	Specific Advantages of Small Versus Medium/Large NTBFs
Van Dierdonck & Gemmel	1990a/1990b	BEL	Role of NTBFs in the Diffusion Process of Innovations

Appendix II. Sample of Definitions and Research on Strategic (Technology) Partnering

REFERENCES	*YEAR*	*FOCUS*
Chesnais	1986/1988	Interfirm Agreements Spectrum
Contractor & Lorange	1988	Joint Ventures and Technology Partnerships Between Firms
Doz	1988	Technology Partnerships Between Larger and Smaller Firms
Harrigan	1988	Partner Asymmetries
Knight	1988/1989	Strategic Alliances for Entrepreneural Firms Spectrum of Agreement Types
Hagedoorn & Schakenraad	1990	Interfirm Technology Cooperation
O'Doherty	1990	Cooperation Phenomenon
Sommerlatte	1990	Cooperation Between Established Corporations and Young Technology Based Firms
Niederkofler	1991	Alliances and Managerial Pitfalls
Syed Tariq	1991	Strategic Alliances for Small Businesses
Segers	1992c	Strategic Partnering Between NTBFs and Large Established Firms in Biotechnology and Micro-Electronics

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Paper ③ 2015 The interplay between new technology based firms, strategic alliances and open innovation, within a regional systems of innovation context. The case of the biotechnology cluster in Belgium

Segers *Journal of Global Entrepreneurship Research* (2015) 5:16
DOI 10.1186/s40497-015-0034-7

Journal of Global Entrepreneurship Research
a SpringerOpen Journal

RESEARCH Open Access

The interplay between new technology based firms, strategic alliances and open innovation, within a regional systems of innovation context. *The case of the biotechnology cluster in Belgium*

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Abstract

Purpose: New technology based firm (NTBF) survival and growth are connected with strategic partnering alliances and open innovation within technology clusters. Strategic partnerships in the biotechnology industry allow new technology based firms to gain a foothold in this high-cost, high-risk industry.
In this article, we examine the impact of strategic partnerships and open innovation on the success of new biotechnology firms in Belgium by developing multiple case studies of firms in regional biotechnology clusters.
A longitudinal follow up of the Belgian biotech startup ecosystem is presented. We find that, despite their small size and relative immaturity, new biotechnology firms are able to adopt innovative business models by providing R&D and services to larger firms and openly cooperating with them through open innovation.

Design/methodology/approach: This is a theory-driven paper with suggested theoretical model and case study research design.

Originality/value: Although the literature on strategic partnerships is well developed, the majority of studies focus on large, established firms. There is absence of studies that look at strategic partnerships – and specifically the role of open innovation – in the development of small and innovative biotechnology firms. This article addresses this gap in the literature with a focus on new firms in the biotechnology cluster in Belgium, where there is a growing trend towards technological and market-driven relationships between large and small biotechnology firms.

Practical implications: Our conclusion is that the future of new biotechnology firms in Belgium lies in the effective establishment of strategic partnering alliances. In future research, the impacts of open innovation and novel business models warrant further attention.

Keywords: New technology based firms; New biotech firms; Strategic alliances/partnerships; Open innovation; Regional system(s) of innovation

Background

The application of new discoveries and advances in science towards commercial use and for public purposes depends mainly upon actions by entrepreneurs who create new technology-based firms.

Whether a broad or narrow definition is used, the evidence shows that new technology based firms constitute only a small proportion of the firms established each year in Belgium and in Europe. According to Storey and Tether (1998), NTBFs are thought to embody the technologies of the future which will provide secure employment opportunities for several generations. The quality of jobs provided in NTBFs are also thought to be significantly better than those in traditional activities.

There is also the role of NTBFs in industrial networks and technology clusters, in which they are thought to play an important part in the transfer of technologies and in strengthening the industrial fabric. However, in the life sciences industry (pharma, healthcare, biotechnology, medical devices, diagnostics) the high cost of commercialization make it unlikely that any new, small firm can succeed on its own. To overcome this challenge, many smaller firms enter into strategic partnership alliances with larger firms.

Although the literature on strategic partnerships is well developed, the majority of studies focus on large, established firms. There is absence of studies that look at strategic partnerships – and specifically the role of open innovation – in the development of small and innovative biotechnology firms. This article addresses this gap in the literature with a focus on new firms in the biotechnology cluster in Belgium, where there is a growing trend towards technological and market-driven relationships between large and small biotechnology firms.

For this research, a sample of stock-exchange-listed biotechnology firms in Belgium are screened and monitored. Most of these new biotechnology firms are unlikely to become fully integrated pharmaceutical companies, because they are heavily dependent on their large strategic partners, especially for:

- marketing outlets;
- resource manufacturing when they reach the commercialization stage;
- continuing product development efforts;
- licensing agreements;
- milestone payments.

Product and market characteristics, affecting firms' financing options, are important enablers or inhibitors (Knockaert et al., 2015). While aiming for sustainable growth, most of the new biotechnology firms in Belgium have not yet reached this level of maturity and are acutely aware of the possibility of takeover. The objective of this article is to develop an understanding of how strategic partnerships influence the development of these new and innovative biotechnology firms and the role that open innovation might play in the success of these relationships.

Research methodology

This study is structured as follows. The first section provides an overview – supported by the literature - of biotechnology business models to show how strategic

partnerships and open innovation are commonly leveraged in this industry and in the regional system of innovation policy framework. In the second section, we explore the biotechnology cluster in Belgium and present the longitudinal case based evidence for this cluster.

To investigate the impact of strategic partnering – and specifically the role of open innovation – on the growth and survival of new biotechnology firms, we employed a qualitative case study research design (Yin, 2009).

Our focus is new technology based firms - in particular new biotechnology firms - operating within the regional biotechnology clusters in Belgium. The data and findings are derived from personal interviews, company and public sector reports, IPO prospectuses, financial media coverage, OECD REGPAT databases, OECD and EU Outlooks and other available secondary data.

Methods

Biotechnology cluster in Belgium: the regional framework

Science and technology offer tremendous opportunities to innovate.

Biotechnology is defined as the application of science and technology to living organisms, as well as parts, products and models thereof, to alter living or non-living materials for the production of knowledge, goods and services. A number of biotechnological fields that have traditionally been distinguished include health, agriculture, food and beverages processing, natural resources, environment, industrial processing and bioinformatics (OECD 2009a). Next generation biotechnology opens new frontiers in personalized medicine, advances in imaging and the use of powerful bioinformatics.

The emphasis of this study is specifically on the valorization of red biotechnology. Red biotechnology brings together all those biotechnology uses connected to medicine. Red biotechnology includes producing vaccines and antibiotics, developing new drugs, molecular diagnostics techniques, regenerative therapies and the development of genetic engineering to cure diseases through genetic manipulation. Some relevant examples of red biotechnology are cell therapy and regenerative medicine, gene therapy, novel scaffolds, genomics, biomarkers, companion diagnostics and medicines based on biological molecules such as therapeutic antibodies.

The new biotech(nology) firm (NBF)

Biotechnology firms use biotechnology to produce goods or services and/or to perform biotechnology R&D. Dedicated biotechnology firms are a subgroup of the biotechnology R&D firm. They devote at least 75 % of their production of goods and services - or R&D - to biotechnology.

A dedicated biotechnology firm is defined as a biotechnology active firm whose predominant activity involves the application of biotechnology techniques to produce goods or services and/or the performance of biotechnology R&D.

The central task of most biotech companies is the development of drugs or new diagnostic methods. The large majority of firms working in medically oriented biotechnology are either still in the preclinical stage of therapeutical research or developing technology platforms in modern drug development. In general, biotechnology

companies conduct research in the discovery phase I of a new drug and biopharmaceutical companies take the new drug through phases II-III(IV, post-approval) and market it globally.

According to the OECD key biotechnology indicators (2009b); OECD 2011a; OECD 2013), the number of biotechnology firms is the most widely available indicator but it is not the best measure of a country's activity in biotechnology, owing to large differences in firm size and R&D intensity.

Business enterprise research and development expenditures on biotechnology as a share of total business sector R&D expenditure (BERD) is an indicator of a country's research effort. On average, it accounted for 5.7 % of BERD in 2009 and 5.9 % in 2011. With 19.4 % in 2011, Denmark spent the most on biotechnology R&D as a percentage of BERD, followed by Ireland (17.2 %), Switzerland (12.6 %) and Belgium (12.6 % in 2009).

The revealed technological advantage as defined by OECD is a country's share of patents in a particular technology field divided by the country's share in all patent fields. The index is above 1 when a positive specialisation is observed. In this regard, Denmark has the largest specialisation ratio in biotechnology followed by Singapore and Belgium.

An alternative measure of research focus on biotechnology is biotechnology R&D intensity, defined as biotechnology R&D expenditure as a share of total value added of the industry sector. This ratio was 0.31 % for the USA, followed by Switzerland (0.28 %), Ireland (0.27 %), Belgium (0.26 %) and Sweden (0.24 %).

Next to the United States (>40 %), Denmark, Belgium, Singapore and Canada all have a strong revealed technological advantage in biotechnology with more than 10 % of their patent portfolio dedicated to biotechnology.

With lesser, but bigger New Biotechnology Firms compared to its neighbour-countries, Belgium accounts for about 350 NBF's, i.e. 7 % of European biotech firms and 10 % of R&D expenditures (OECD 2011b; OECD 2014).

Within Europe, Sweden is frontrunner when it comes to public biotech market value. Belgium is in second place. Based on average market value per company, Belgian public biotech companies even rank first.

Suggested model

One of the primary concerns is to design a theoretical model or framework that capture(s) the real world of New Technology Based Firm-creation in Belgium. The validity of the model is supported by empirical observations and cased based evidence for New Biotech Firms.

The collaboration and strategic partnerships between universities and research institutions on the one hand, and the big pharmaceutical companies and biotechnology industry on the other hand opens up opportunities for the translation of innovative (academic) research into potential drugs, new therapies and medical diagnostics.

We screened a sample of stock-exchange listed new biotechnology firms (Table 1), which are representative for the Belgian biotechnology cluster and for the different business models described. These NBFs are representative for the different business models described.

Number of firms active in biotechnology, 2012 or latest available year

	Biotechnology firms	Dedicated biotechnology firms	% dedicated	Year	Type of firm
United States	6,862	2,178	31.7	2011	Biotech R&D firms
Spain	3,070	625	20.4	2012	Biotech firms
France	1,950	1,284	65.8	2012	Biotech R&D firms
Korea	937	370	39.5	2012	Biotech firms/Dedicated biotech R&D firms
Germany	700	570	81.4	2013	Biotech firms
UK	614	#N/A	#N/A	2013	Biotech firms
Japan	552	#N/A	#N/A	2013	Biotech firms
Australia	527	384	72.9	2006	Biotech firms
New Zealand	369	135	36.6	2011	Biotech firms
Belgium	350	127	36.3	2011	Biotech firms/Dedicated biotech R&D firms
Italy	300	166	55.3	2011	Biotech firms/Dedicated biotech R&D firms

OECD (2014), Key Biotechnology Indicators, http://oe.cd/kbi, October (adapted)

We expect to find that:

Proposition ① New biotechnology firms in the Belgian cluster will have to work together with international (bio)pharmaceutical firms to create substantial added value;

Proposition ② The success of future new biotechnology firms in Belgium will depend on setting up strategic partnering alliances and accommodating open innovation;

Proposition ③ Most of the new biotechnology firms in Belgium are unlikely to become fully integrated pharmaceutical companies, i.e. they are unlikely to adopt a product-based business model Fig. 1.

Biotechnology business models

To varying degrees, new biotechnology firms depend on strategic (technology) partnerships with other organizations or large firms. In most of the partnerships, the initial research and innovation developed by the smaller firms is transferred to their larger counterparts. According to Contracter and Lorange (1988; 2002), the term *alliances* covers several governance modalities ranging from relational contracting to licensing, to logistical supply-chain relationships, to equity joint ventures or to the complete merger of two or more organizations.

According to Porter (1985), "the business model outlines how a company generates revenues with reference to the structure of its value chain and its interaction with the industry value system". In the biotechnology industry, the business model for a new, small company is necessarily dependent on collaboration with other organizations. As Fisken and Rutherford (2002) explain: "for a biotechnology company, the business model serves to secure value from the company's proprietary technology and know-how and is currently often heavily reliant on large (bio)pharmaceutical or established biotechnology company customers, collaborators and partners".

Biotechnology companies have traditionally used a variety of business models to enter the life sciences, pharmaceutical, or healthcare markets. Fisken and Rutherford (2002) and Pareras (Pareras 2008a) distinguish between three key business models based on the value chain structure of the biotechnology industry:

Table 1 Belgian New Biotechnology Firms (red biotech) & Strategic Partnership Alliances

Firm Name	Technology Platform	Product/Portfolio	Strategic Partnerships/Alliances	Acquisitions/Takeovers	Location Region
ThromboGenics[a]	Ophthalmic medicines	Jetrea	Alcon (Novartis)Novartis		Flanders (Leuven)
↳	Oncology		Bioinvent Int. AB		
Oncurious					
Ablynx[a]	Nanobodies	Alpha-pharmaceuticals Caplacizumab Ozoralizumab	Merck & Co.; AbbVie; Eddingpharm; Novartis; Merck Serono; Shire; Eli Lilly; Algeta Genzyme; Taiso		Flanders (Gent)
Argen-X[a]	Nanobodies		Lonza (GS Xceed)LEO Pharma		Flanders (Gent)
Galàpagos[a]	Rheumatoid arthritis	Filgotinib	AbbVieGlaxoSmithKlineEli LillyJanssen Pharmaceuticals (J&J) Servier Roche Ono Pharmaceuticals	01/2013: acquisition of Cangenix (drug discovery) Biofocus + Argenta: drug discovery divisions (sold)	Flanders (Mechelen)
Tigenix[a]	Stem cellsCell therapy	ChondroCelec Cx601	Cellerix/Grifols Lonza	Cellerix (acquisition)	Flanders (Leuven)
Movetis	Gastroenterology	Resolor	Shire-Movetis	2010: public takeover by Shire	Flanders (Turnhout)
Genticel[a]	Therapeutic vaccines	ProCervix (HPV)			Paris and Toulouse (France)
Bone Therapeutics[a]	Stem cellsCell therapy	PreobAllob			Wallonia (Gosselies)
Promethera Biosciences	Stem cellsCell therapy		ShireBoehringer Ingelheim		Wallonia (Louvain-L-N)
Celyad[a] (Cardio3 BioSciences)	Stem cellsCell therapy	C-Cure		Oncyte (Celdara Medica, USA)	Wallonia (Mont-Saint-Guibert)
Mithra[a] Pharmaceuticals	Intrauterine platform	Estelle (Estetrol)	GlaxoSmithKline		Wallonia (Liège)
Uteron Pharma	Intrauterine platform			2013: Actavis (USA) <> 2015: buy back	Wallonia (Liège)
MastherCell	Stem cellsCell therapy			Orgenesis (USA)	Wallonia (Gosselies)
MDxHealth[a]	Molecular diagnostics	ConfirmMDx	Exact SciencesOncgnostics		Wallonia (Liège)
Biocartis[a]	Molecular diagnostics	Idylla	Johnson & Johnson Abbott Fast-Track Diagnostics		Flanders (Mechelen)

Table 1 Belgian New Biotechnology Firms (red biotech) & Strategic Partnership Alliances *(Continued)*

UCB[a]	Neurology/immunology	Zyrtec, Keppra	AstraZeneca Pfizer Amgen Bayer	Brussels
		Cimzia, Vimpat, Neupro	Neuropore Therapies	
		Brivaracetam, Epratuzumab, Romosozumab	Oncodesign	

[a]*BEL-Brussels and/or FRA-Paris (double) EURONEXT stock exchange listing*

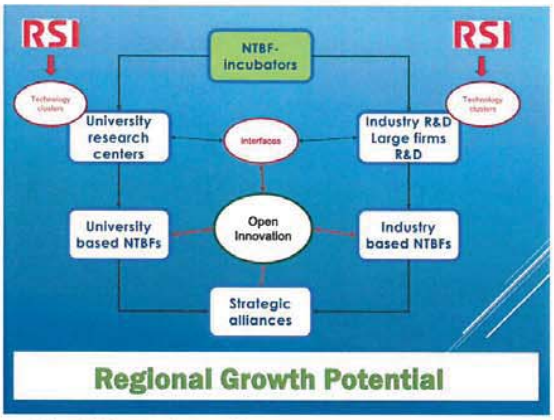

Fig. 1 theoretical model. RSI: regional system of innovation

1. Product-based: this vertical business model has its origins in the "fully integrated pharmaceutical company", where medicines are developed by the company from the point of discovery up to the end of clinical trials or up to approval. According to Fisken and Rutherford (2002) this business model "aims to generate value in progressing products along the drug development process and either licensing them out to pharmaceutical and top tier biotechnology companies or taking them straight through to commercialization."
2. Platform-based: with this business model, companies develop a set of tools or integrated technologies and license them out. Revenue can be generated relatively quickly through contract research and services. Thus, this business model reduce risk and the need for venture capital. Parares (Pareras 2008b) calls companies following this model "royalty income pharmaceutical companies". These small companies research and develop a new drug, which they eventually license to a large pharmaceutical company in exchange for a royalty on sales.
3. Hybrid: this is the dominant business model in the biotechnology industry. It is a hybrid of the product-based and platform-based business models and focuses on generating a pipeline of products. Investors benefit from reduced risks and the possibility of near-term revenue generation. In the hybrid business model, technology platforms are combined with services and the creation of products.

The choice of business model may depend on the type of innovation; indeed, Pisano (2006) distinguishes between "types of pharmaceutical innovations which call for vertical integration and which call for alliance-building and R&D outsourcing". However, for new, small technology companies the high risk and high cost of developing and commercializing a new product on their own make the platform-based and hybrid business models attractive.

Roth & Cuatrecasas (2010) defined a new paradigm for efficiently advancing new therapeutic products in the value creation chain. In their distributed partnering model for drug discovery and development, product definition companies (PDC) focus solely on advancing a portfolio of discoveries through the initial definition research phase. PDCs would acquire early stage discoveries from research institutions and invest in defining product applications with a goal of selling the successful ones to pharmaceutical companies for further development and delivery. The PDC business model focuses on identifying and licensing promising discoveries from research institutes (and biotech/pharma).

Open innovation

Companies are increasingly forced to join forces in complex regional innovation networks or startup/ spinoff ecosystems where they organize open innovation activities.

Open innovation and open business models are two concepts that have been launched by Henry Chesbrough (2003; 2006). It is a popular approach within innovation practice, in contrast to the traditional closed innovation strategies.

Oakey (2013) criticizes Chesbrough for exaggerating the applicability of open innovation systems because R&D is often long-term, expensive and always risky and requires necessary protection of outcomes. He argues that closed innovation is still an effective way for R&D investment (Hossain, 2015).

"Open Innovation is a new paradigm that assumes that firms can and should use external ideas as well as internal ideas and internal and external paths to market, as the firms look to advance their technology". Open innovation is defined as "the use of purposive inflows and outflows of knowledge to accelerate internal innovation, and extend the markets for external use of innovation, respectively" (Chesbrough et al., 2006). It implies collaborating with researchers, customers, suppliers – even competitors – as well as research institutions and universities.

The central idea behind open innovation is that, in our knowledge society, companies cannot afford to rely entirely on their own research, but should instead buy or license processes or inventions (e.g. patents) from other companies. In addition, internal inventions not being used in a firm's business should be taken outside the company (e.g., through licensing, joint ventures, spin-offs).

Various network forms of cooperation thus come into play to support the value creation process, such as strategic alliances, consortia, ecosystems and business/technology platforms.

At the heart of the open innovation model is the recognition that today, competitive advantage often comes from inbound as well as from outbound connections. Leveraging inbound connections means leveraging the discoveries of others: companies should not rely exclusively on their own R&D. Leveraging outbound open innovation means that, rather than relying entirely on internal paths to market, companies can look for external organizations with business models that are better suited to commercialize a given technology (Chesbrough, 2002).

The adoption of open innovation may be sequential, starting with customer involvement, followed by employee involvement and external networking, and ending with more "advanced" practices such as IP licensing, R&D outsourcing, venturing, and external participations (Van de Vrande et al., 2009).

A lot of research has been devoted to strategic alliances and innovation partnerships, such as the motives for, and the impacts of, collaboration (Contractor & Lorange, 1988; Segers, 1993). According to Solesvik & Westhead (2010), selection of the right partner is probably the most crucial aspect of open innovation success.

In most traditional partnerships, smaller firms perform research and development for the larger firms or transfer innovations to them. However, open innovation is changing the way these firms interact. In the early stages of R&D, open innovation offers a neutral platform for companies to jointly investigate new and emerging technologies and applications, while sharing risks and costs.

The open-innovation approach is providing new ways for firms of all sizes to collaborate, and it is creating opportunities for smaller companies. According to Weverbergh (2013), "cross pollination between the corporate and the startup world – whether through corporate accelerators, venturing or open innovation – is fast becoming the trend".

Open innovation and biotech clustering

The work of Su and Hung (2009) defines five critical success factors in the evolutionary process of a biotech cluster: (1) a strong science and industry base; (2) finance supporting mechanisms; (3) entrepreneurship; (4) social capital; (5) networking; with the later three factors being intertwined.

Davies et al. (2015) examine models of life sciences startups through presenting a science base in its role to facilitate new enterprise, alongside networking efforts to strengthen the region.

Basically, biotech firms have worked with the open innovation concept for many years now, using knowledge existing inside and outside the organisation. The new approach is that of clustering and intensive partnering. A number of recent examples underline this:

- Johnson & Johnson's pharmaceutical division, *Janssen* (Belgium), opened "Janssen Labs" (J&J, 2015) (i.e. concept labs and open collaboration spaces) in San Diego, Boston and Beerse (Belgium). This shared laboratory – and its open-plan office space –provides life-science entrepreneurs with an affordable environment for early-stage research and encourages interaction between startups. It enhances sourcing external innovation.
- Roche (Pharmaphorum (2015)) announced a new open innovation research alliance in biotechnology, nanotechnology and engineering to develop new and faster diagnostic tests. Roche is working together with Biomed X, a new open innovation lab. It hopes to produce speedier diagnosis and synergies with its drug treatments.
- Open source biotechnology in big pharma with open access to data, i.e. sharing of clinical trial data or data on newly approved medicines to researchers. This is already the case for Pfizer, Novartis, Sanofi, GSK, Johnson & Johnson.
- The Innovative Medicines Initiative (2010) http://www.imi.europa.eu/ is the largest public-private partnership aiming to boost pharmaceutical innovation in Europe and to speed up the development of better and safer medicines for patients. IMI is a joint undertaking between the European Union and the pharmaceutical industry association EFPIA. Large biopharmaceutical companies and small- and medium-sized enterprises are working together with patients' organisations, research organisations, hospitals, regulatory agencies and other industrial partners.

Strategic partnerships

The number of strategic partnerships between large, established firms and NTBFs has multiplied over the past decades, due to a growing trend towards technological and marketing relationships between large and small firms. The issue of the clustering of NTBFs relates to agglomeration economies, especially with regard to access to knowledge and information. Proximity is generally thought to enhance both formal and informal knowledge and information flows, between NTBFs and both universities/research institutes and other firms, especially the NTBFs customers which tend to be large firms. This in turn relates to the issue of networking, and the dynamic complementarities (Rothwell, 1983) between small and large firms in innovation. It is therefore the concept of strategic alliances, between small and large firms, with mutual benefits for both, which is stressed here.

(O'Doherty 1990a; 1990b) argues that "strategic partnerships and alliances perhaps represent the greatest need but also the greatest challenge for small firms and small countries". The challenges include both determining the strategic direction of the firm but also finding "suitable and willing" partners to collaborate with. In the biotechnology industry, open innovation might have a role play in meeting these challenges and in the success of the strategic partnerships, both from the perspective of new, small companies and established, large companies. As Nigel Sheail (Bayer Healthcare, 2012) says: "Partnering and even open innovation is becoming increasingly important for our industry in a world where health systems are undergoing profound transformations." According to the Holst Centre (2013), an independent open-innovation R&D centre, "due to the increased complexity of physics, life-sciences, materials, electronics, software, etc., the cost of R&D is growing faster than company revenues. The goal of partnering is to share ideas and efforts, cost and risk of R&D and to reduce the time to market of new product generations".

In most traditional partnerships in the biotechnology industry, smaller firms perform research and development for the larger firms or transfer innovations to them. However, open innovation is changing the way these firms interact. In the early stages of R&D, open innovation offers "a neutral platform for companies to jointly investigate new and emerging technologies and applications, while sharing risks and costs" (Holst 2013).

Regional systems of innovation - innovation ecosystems

Widespread research emphasizes the role of regional systems of innovation (RSI) in augmenting the competitiveness and performance of regions and companies. RSI can be defined as the ".. wider setting of organisations and institutions affecting and supporting learning and innovation in a region" (Asheim, 2009). The regional production structure or knowledge exploitation subsystem often displays clustering tendencies (Asheim & Gertler, 2006). Cooke (1992) in particular has pioneered the concept of the RSI.

Cooke et al. (2006) described the emergence of the Welsh Regional Science Policy which placed life Sciences and health as a challenge area to be tackled though the EU approach of Smart Specialisation, and the associated concentration of investment into excellence. The mix of industry and cluster policy development objectives was discussed by Cooke (2004) and more recently by Ketels (2013). Cooke and Leydesdorff (2006) point to the creation of infrastructure of excellence to provide basic and applied research capabilities, and in turn construction of regional competitive advantage.

Klepper (2011) points at the valuable agglomeration economies and the Marshall (1920) theory that suggests that firms cluster geographically because it is beneficial in

terms of better access to skilled labor (labor market pooling), specialized suppliers (shared inputs), and knowledge spillover from competing firms. Clustering facilitates learning from other firms, lowers transaction costs for firms and suppliers and enhances productivity.

According to Klepper, the following patterns are expected in industries subject to clustering:

- clusters begin with a successful diversifier;
- clusters experience a high rate of spinoffs;
- the leading firms in clusters are predominantly spinoffs of other leading firms in the cluster;
- spinoffs in clusters are more competent on average than spinoffs elsewhere and/or new firms/startups.

According to Edquist (2005), the system of innovation approach focuses on the fact that firms do not innovate in isolation but rather in collaboration and interdependence with other organizations such as other enterprises, universities and government research institutes.

The Innovation Ireland Report (2010) sums up the following elements that make up an innovation ecosystem:

- entrepreneurs and enterprises;
- investment in R&D
- education system, in particular higher education institutions;
- risk capital;
- tax and regulatory environment;
- public policy and institutions;
- international networks.

A successful innovation policy requires all elements of the ecosystem to co-operate and collaborate together. This is in line with the "triple helix"-model by Etzkowitz & Leydesdorff (1997; 2000) which creates constructive and mutually reinforcing activities between academia, government, and industry.

According to Leten et al. (2013), innovation ecosystems generate value for partners by reducing development costs and risks and by combining complementary knowledge, enabling partners to address problems with high complexity. Ecosystem partners can subsequently use the knowledge created within ecosystems to support their own businesses.

Country-specific institutional features support or impede the accumulation and diffusion of knowledge between the scientific and industrial communities.

Clusters, taken as concentrations of "interconnected companies and institutions in a particular field" (Porter, 1998) continue to be of interest to policymakers.

Biotechnology clustering in Belgium is the result of a longitudinal"regional systems of innovation" approach in the Flanders, Brussels and Walloon regions (Segers, 1996). The region-specific technology policy in Belgium (Segers, 1992) has been organized around two focal points:

- the existence of state-of-the-art research potential in the country's universities and

- emerging technology centres, charged with supporting new technology based firms (Segers, 1993).

Over the years, a wide range of incentives have been created for assisting new technology-based firms. The main categories are:

- financial and fiscal incentives (e.g., the Belgian patent income deduction regime)
- employment incentives
- access to seed, venture, and growth capital
- government-supported laboratories and industry-specific collective research centres
- technology clusters and infrastructural incentives
- establishment of incubators in the proximity of universities for stimulating and assisting university spin-offs

The critical success factors are:

- access to key scientific personnel and mobility of researchers
- access to seed and venture capital
- the number of initial public offerings (IPOs)
- operating losses in the early stages of development
- regulatory approval from the Food and Drug Administration (FDA; http://www.fda.gov/) in the United States and from the European Medicines Agency (EMA; http://www.ema.europa.eu/ema/) in the European Union
- patents and intellectual property rights
- dependence on the strategic large partner(s)
- expected revenues derived from the strategic large partner(s) (e.g., milestone payments)
- manufacturing, clinical trial and regulatory compliance capabilities

The life sciences and biotechnology industry have become important regional clusters of new economic development in Belgium, and many new biotechnology firms in Belgium are university spin-offs. Due to strong collaboration between research institutes, universities, venture capitalists, high-risk finance providers, and existing large companies (big pharma), strong biotechnology clusters have developed in the regions of Flanders (e.g. Ghent and Leuven) and Wallonia (e.g. Liège and Louvain-La-Neuve).

The Belgian biotechnology industry is now firmly positioned as a key player in Europe, with a market capitalization of about 30 % in the eurozone.

Results and discussion

Case study results

Within Belgium's strong regional biotechnology clusters, we found a large number of strategic technology partnerships between large, international, and established chemical or (bio)pharmaceutical firms and new biotechnology firms (Segers, 2013).

Table 1 lists a sample of biotechnology firms, along with details on their strategic partnership alliances.

We observed strong collaboration between research institutions, universities, venture capitalists, high-risk finance providers, existing large companies, and new biotechnology firms. The basic innovative activity occurs mainly in university-based new biotechnology firms,(i.e., new, small firms that are spin-offs from university research centres performing state-of-the-art research).

On the other hand, large and international chemical or (bio)pharmaceutical firms participate in or establish joint ventures with university research centres and small, university-based new biotechnology firms. Of the new biotechnology firms in Belgium that were included in this study, most are unlikely to become fully integrated pharmaceutical companies, because they are heavily dependent on their strategic large partners, especially for marketing outlets, for manufacturing resources when they reach the commercialization stage, and for continuing product development efforts. They have to rely heavily on licensing agreements and milestone payments.

While aiming for sustainable growth, most new biotechnology firms in Belgium have not yet reached an independent stage of maturity and are predominantly driven by the takeover alternative, as was the case in recent years for Movetis (takeover by Shire) and Devgen (takeover by Syngenta). Up to this point, only ThromboGenics, Galapagos, and UCB have succeeded in becoming mature, self-sustaining biotechnology/biopharma firms.

ThromboGenics is a biopharmaceutical company focused on the discovery and development of innovative medicines for the treatment of eye diseases. The company was established in the 1980s as a spin-off of the University of Leuven. ThromboGenics developed over the years from a university spin-off to a fully integrated specialty pharmaceutical company. Its lead product, Jetrea (ocriplasmin), was approved by the FDA and the EMA in 2013. The company signed an important strategic partnership with Alcon (Novartis) to commercialize Jetrea outside the United States. Since that time, ThromboGenics experienced difficulties in selling Jetrea and revenues and share value dropped extensively.

Conclusions

Over the past decade, both academics and practitioners have increasingly recognized the need for collaboration and knowledge exchange for successful business development. The challenges are especially large in resource intensive industries, where huge investments are needed to develop new products. The way to overcome these costs and to stay competitive is through embracing open innovation strategies.

Companies are increasingly forced to join forces in complex regional innovation networks or startup/ spinoff ecosystems where they organize open innovation activities. Both emerging companies (startups) and high-growth (technology) firms will have to embrace open innovation to stay relevant. The open innovation approach provides small and large firms and regions new ways and insights to collaborate in order to create regional growth potential and mutual long term benefits. The development of innovation ecosystems is a prerequisite for future sustainable regional growth.

Life sciences and especially the biotechnology industry have become important regional clusters of new and sustainable economic development in Belgium. The implications for the national and regional systems of innovation are numerous. Our case-based analysis of the biotechnology cluster in Belgium shows that strategic technology partnerships

between new biotechnology firms and established, large, and international (bio)pharmaceutical companies have a significant impact on the survival and growth of these new biotechnology firms.

In order to achieve sustainable development, it is advisable that the clusters have good access to scientists, that they employ the new collaborative model or open campus model where open innovation leads to creativity. It implies mobility of researchers between companies or from universities to companies. On the firm level, it is important that firms have multiple projects and product portfolios, high ability to adapt, and solid technology platforms.

Our evidence supports the assertion by Fisken and Rutherford (2002): "while a small number of companies with access to a large supply of capital may be able to complete downstream integration and revert to the [fully integrated pharmaceutical company] model, the majority of biotechnology companies will instead need to further develop sophisticated relationship management skills in order to extract greater value from relationships with customers, collaborators and strategic partners".

The interplay between biotech firms, investors, universities, large and raditional pharmaceutical companies, government regulators may lead to new business models, organisational structures, and financing arrangements that place greater emphasis on integration and open innovation (e.g. cross-industry collaboration, the sharing of knowledge and resources) instead of monetisation of intellectual property.

Our conclusion is that the future of new biotechnology firms in Belgium lies in the effective establishment of strategic partnering alliances. In future studies, the impacts of open innovation and novel business models warrant further attention.

Competing interests
The author declares that he has no competing interests.

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Acknowledgements
An earlier version was published in 2013 in TIM Review : "Strategic Partnerships and Open Innovation in the Biotechnology Industry in Belgium" (http://timreview.ca/article/676) under creative commons - Copyright notice: http://timreview.ca/copyright.

Received: 1 June 2015 Accepted: 24 July 2015
Published online: 05 August 2015

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Paper ④ 2016 Regional systems of innovation: lessons from the biotechnology clusters in Belgium and Germany

Regional systems of innovation: lessons from the biotechnology clusters in Belgium and Germany

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Prior research shows that innovation performance is linked to system, collaboration and networking. There is a growing attention for open innovation. However, the interplay between regional systems of innovation, technology clustering, disruptive business models and open innovation practices is not sufficiently addressed in the global entrepreneurship and technology innovation literature. There is an absence of studies that look at strategic partnerships – and specifically the role of open innovation – in the development of regional technology clusters and novel business models. We observe that biotechnological firms have been engaged in open innovation for a long time by clustering and intensive partnering to innovate with knowledge from inside and outside the firms. In other words, they have been engaging in open innovation. This paper presents a case study of biotechnology clusters in Belgium and Germany. The focus is on the interplay between new biotechnology firms, strategic alliances and open innovation, within a regional system of innovation context. In particular, the article looks at the case-based evidence from biotechnology-related industrial or regional economic cluster policies.

Keywords: regional systems of innovation; biotechnology clusters; strategic alliances; open innovation

Des recherches antérieures montrent que les performances en matière d'innovation sont associées au système, à la collaboration et à la mise en réseau. L'intérêt pour l'innovation ouverte est croissant. Cependant l'interaction entre les systèmes régionaux d'innovation, la formation de grappes technologiques, les modèles économiques disruptifs et les pratiques d'innovation ouverte n'est pas suffisamment traitée dans l'entreprenariat mondial et les publications sur l'innovation en matière de technologie. Il n'existe pas d'études qui explorent les partenariats stratégiques – en particulier le rôle de l'innovation ouverte – dans le développement des grappes technologiques régionales et des nouveaux modèles économiques. Nous observons que les entreprises de biotechnologie sont engagées dans l'innovation ouverte depuis longtemps en se regroupant et en formant des partenariats de manière intensive pour innover à partir des connaissances existant à l'intérieur et en dehors de leur périmètre. En d'autres termes, elles se sont lancées dans l'innovation ouverte. Cet article présente une étude de cas sur les grappes biotechnologiques en Belgique et en Allemagne. L'accent est mis sur l'interaction entre les nouvelles entreprises de biotechnologie, les alliances stratégiques et l'innovation ouverte, dans un contexte de système régional d'innovation. L'article examine plus précisément les cas avérés obtenus des politiques industrielles en lien avec la biotechnologie ou de regroupements économiques régionaux par grappes.

Mots-clés : systèmes régionaux d'innovation; grappes biotechnologiques; alliances stratégiques; innovation ouverte

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Research methodology and theoretical model

The explorative and comparative nature of this paper renders a case study approach most appropriate. A case study requires the description of the dynamics of the sectoral innovation system. The regional systems of innovation (RSI) for the biotechnology clusters in Belgium and Germany are compared, combining both qualitative and quantitative (Organisation for Economic Co-operation and Development (OECD)) data. A qualitative case study design (Yin 2009; 2012) is employed to explain phenomena and to provide description of the facts of each country case.

The theoretical model in Figure 1 captures the interplay between new technology-based firms/new biotechnology firms, strategic partnership alliances, technology clustering and open innovation. The model is derived from earlier country studies for Belgium by Segers (1992; 1993; 1996; 2015) with a specific focus on the regional biotechnological innovation system.

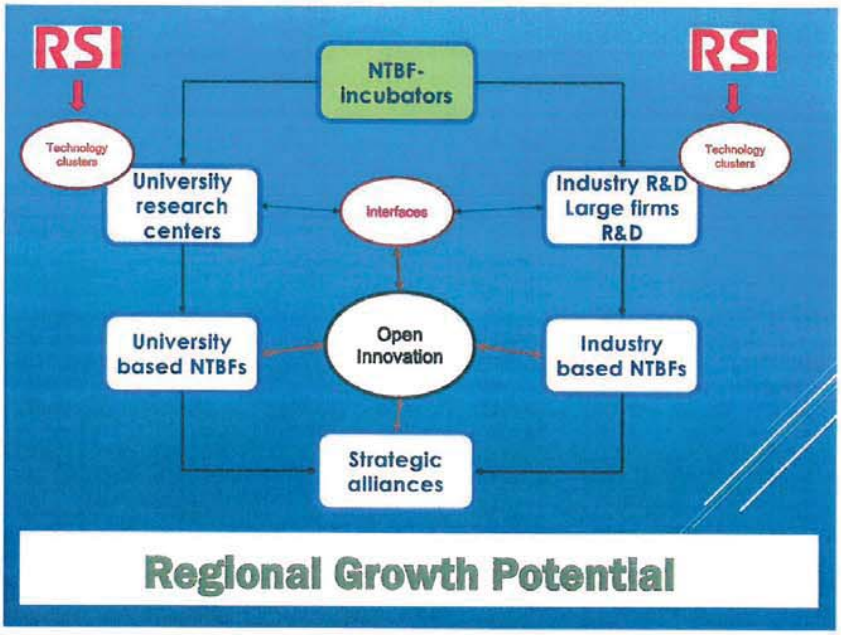

Figure 1. Theoretical model.
Note: RSI: regional system of innovation.

The dynamics of biotechnology

Biotechnology is defined as the application of science and technology to living organisms, as well as parts, products and models thereof, to alter living or non-living materials for the production of knowledge, goods and services. A number of biotechnological fields that have traditionally been distinguished include health, agriculture, food and beverages processing, natural resources, environment, industrial processing and bioinformatics (OECD 2009).

Next generation biotechnology opens new frontiers in personalized medicine, advances in imaging and the use of powerful bioinformatics. The emphasis here is on the valorization of red biotechnology. Red biotechnology brings together all those biotechnology uses connected to medicine. It includes producing vaccines and antibiotics, developing new drugs, molecular diagnostics techniques, regenerative therapies and the development of genetic engineering to cure diseases through genetic manipulation. Some relevant examples of red biotechnology are cell therapy and regenerative medicine, gene therapy, novel scaffolds, genomics, biomarkers, companion diagnostics and medicines based on biological molecules such as therapeutic antibodies.

Biotechnology firms use biotechnology to produce goods or services and/or to perform biotechnology research and development (OECD 2015). Dedicated biotechnology firms are a subgroup of the biotechnology R&D firm. They devote at least 75% of their production of goods and services – or R&D – to biotechnology. A dedicated biotechnology firm is defined as a biotechnology active firm whose predominant activity involves the application of biotechnology techniques to produce goods or services and/or the performance of biotechnology R&D.

The global biotechnology economy is 'a complex network of corporate players, dominated by large firms with strong marketing capabilities and start-up firms that focus on research and development' (Pereira 2006). The biotechnology industry has in recent years undergone major changes associated with waves of mergers, acquisitions and spin-offs (UNCTAD 2001). Typical for biotechnology companies is their heavy dependence on patents and intellectual property rights, the reliance on R&D, heavy regulation of drugs by governments through approval processes and price controls (Rugman 2005).

At the heart of the pharma/biotech business model is the complex process of drug development and/or new diagnostic methods. Challenges such as the expiry of blockbuster patents, competition from generics and biosimilar equivalents, the shift to more personalized medicines, as well as drug pricing pressures have driven pharmaceutical and biotechnology companies to increase their efforts in the hunt for new and smarter approaches to drugs and diagnostics development. Today, companies are frequently putting outsourcing strategies in place to speed up the overall process and to increase the efficiency of drug development (Germany Trade & Invest, 2012).

The large majority of firms working in medically oriented biotechnology are either still in the preclinical stage of therapeutical research or developing technology platforms in modern drug development. In general, biotechnology companies conduct research in the discovery phase I of a new drug and biopharmaceutical companies take the new drug through phases II-III (IV, post-approval) and market it globally.

According to Porter (1998), 'the business model outlines how a company generates revenues with reference to the structure of its value chain and its interaction with the industry value system.' In the biotechnology industry, the business model for a new, small company is necessarily dependent on collaboration with other organizations.

Strategic alliances (i.e. partnerships) and open innovation are commonly leveraged in the biotechnology industry and in the RSI policy framework.

According to Contractor and Lorange (1988; 2002), the term alliances covers several governance modalities ranging from relational contracting to licensing, to logistical supply–chain relationships, to equity joint ventures or to the complete merger of two or more organizations. In most traditional partnerships, smaller firms perform research and development for the larger firms or transfer innovations to them.

Rybka et al. (2015) explored the role of the composition of strategic alliance portfolios for the long-term successful development and growth of new biotechnology firms.

They distinguish between the following modes of pharmaceutical alliances related to biotechnological drugs:

- technology transfer agreements;
- R&D alliances;
- manufacturing agreements;
- marketing agreements;
- licensing agreements;
- exclusive licensing agreements; and
- joint ventures.

In general, these are partnerships that are mostly oriented towards conducting joint research or exchanging technological knowledge (technology transfer agreements, R&D alliances, licensing agreements and joint ventures); and alliances that are predominantly focused on joint commercialization activities (manufacturing and marketing agreements).

According to Mytelka (1999), one of the most significant developments in the structure of the global biotechnology industry is networks involving partnering activities. These networks are the products of complex linkages between a wide range of enterprises, linkages that are designed to reduce the risks associated with the development of new products as well as to facilitate information exchange. More specifically, these partnering arrangements help to provide sources of financing through licensing and upfront fees for R&D expenses; reimbursement of expenses for partnered products and services; royalties; profits and other 'success fees' associated with the achievement of certain milestones.

The collaboration and strategic partnerships between universities and research institutions on the one hand and big pharmaceutical companies and new biotech firms on the other hand opens up opportunities for the translation of innovative (academic) research into potential drugs, new therapies and medical diagnostics (Debackere 2014). This is summarized in Figure 2.

Pharmaceutical companies have changed their business models, consolidated via mergers and acquisitions and increased partnerships (Schuhmacher et al. 2013). Their business model has evolved from a traditional blockbuster approach to a specialty product one (Alcimed 2015). New disruptive business models are introduced faster than the ability to fit these new business models into existing regulatory frameworks and/or the fast-growing competition from generic drugs.

As Fisken and Rutherford (2002) explain: 'for a biotechnology company, the business model serves to secure value from the company's proprietary technology and know-how and is currently often heavily reliant on large (bio)pharmaceutical or established biotechnology company customers, collaborators and partners.' They distinguish between the product-based, platform-based and hybrid business models based on the value chain structure of the biotechnology industry.

1. *Product-based*: this vertical business model has its origins in the 'fully integrated pharmaceutical company', where medicines are developed by the company from the point of discovery up to the end of clinical trials or up to approval. According to Fisken and Rutherford (2002), this business model 'aims to generate value in progressing products along the drug development process and either licensing them out to pharmaceutical and top tier biotechnology companies or taking them straight through to commercialization.'

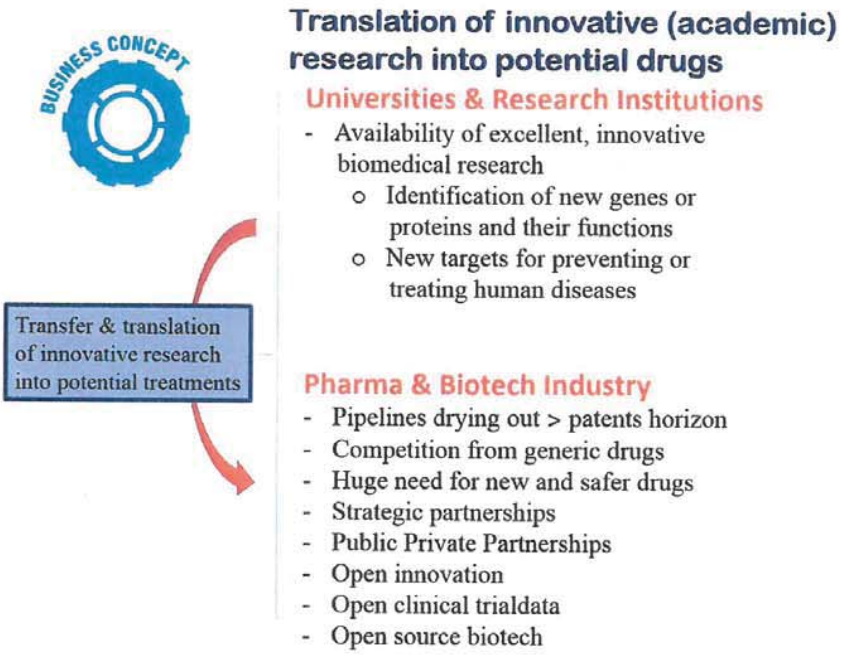

Figure 2. Translation of innovative (academic) research into potential drugs. (Adapted from Debackere (2014)).

2. *Platform-based*: with this business model – also referred to as 'royalty income pharmaceutical company model' - companies develop a set of tools or integrated technologies and license them out. Revenue can be generated relatively quickly through contract research and services. This business model reduces risk and the need for venture capital. New biotechnology firms research and develop new drugs, which they eventually license to a large pharmaceutical company in exchange for a royalty on sales.
3. *Hybrid*: this is the dominant business model in the biotechnology industry. It is a hybrid of the product-based and platform-based business models and focuses on generating a pipeline of products. Investors benefit from reduced risks and the possibility of near-term revenue generation. In the hybrid business model, technology platforms are combined with services and the creation of products.

Pisano (2006) distinguishes between 'types of pharmaceutical innovations which call for vertical integration and which call for alliance-building and R&D outsourcing.' However, for new, small technology companies, the high risk and high cost of developing and commercializing a new product on their own make the platform-based and hybrid business models attractive.

Roth and Cuatrecasas (2010) defined a new paradigm for efficiently advancing new therapeutic products in the value creation chain. In their distributed partnering model for drug discovery and development, product definition companies (PDC) focus solely on

advancing a portfolio of discoveries through the initial definition research phase. PDCs would acquire early stage discoveries from research institutions and invest in defining product applications with a goal of selling the successful ones to pharmaceutical companies for further development and delivery. The PDC business model focuses on identifying and licensing promising discoveries from research institutions.

The virtual R&D-model is another option that has emerged in the biotechnology industry, where small groups of scientists discover and develop a new drug candidate with the help of external resources (Schuhmacher et al. 2013). The basic principle of virtual R&D is essentially to keep the organization trim. Shire has implemented elements of an open, virtual and partnership-oriented concept: an open, collaborative and networked R&D model of 'early alliance' whereby pharmaceutical and biotechnology companies collaborate in early R&D. The biotechnology company provides the innovation, whereas the pharmaceutical partner contributes its capacities to discover and develop jointly an early drug candidate with the purpose of having access to the drug project later. Alternatively, it can use the early alliance to familiarize with a new technology or therapeutic area without investing too many resources.

Companies are increasingly forced to join forces in complex regional innovation networks or startup/spinoff ecosystems where they organize open innovation activities. Open innovation and open business models are two concepts that have been launched by Henry Chesbrough (2003; 2006). They are popular approaches within innovation practice and small business/entrepreneurship literature, in contrast to the traditional closed innovation strategies. Hossain (2015) points out that Oakey (2013) criticizes Chesbrough for exaggerating the applicability of open innovation systems because R&D is often long-term, expensive and always risky and requires necessary protection of outcomes. He argues that closed innovation is still an effective way for R&D investment.

'Open Innovation is a new paradigm that assumes that firms can and should use external ideas as well as internal ideas and internal and external paths to market, as the firms look to advance their technology.' Open innovation is defined as 'the use of purposive inflows and outflows of knowledge to accelerate internal innovation, and extend the markets for external use of innovation, respectively' (Chesbrough, Vanhaverbeke, and West, 2006). It implies collaborating with researchers, customers, suppliers – even competitors – as well as research institutions and universities.

The central idea behind open innovation is that, in our knowledge society or in knowledge ecosystems (Volkokari 2015), companies cannot afford to rely entirely on their own research, but should instead buy or license processes or inventions (e.g. patents) from other companies. In addition, internal inventions not being used in a firm's business should be taken outside the company, through licensing, joint ventures, spin-offs, etc.

Various network forms of cooperation thus come into play to support the value creation process, such as strategic alliances, consortia, ecosystems and business/technology platforms. At the heart of the open innovation model is the recognition that today, competitive advantage often comes from inbound as well as from outbound connections. Leveraging inbound connections means leveraging the discoveries of others, companies should not rely exclusively on their own R&D. Leveraging outbound open innovation means that, rather than relying entirely on internal paths to market, companies can look for external organizations with business models that are better suited to commercialize a given technology (Chesbrough 2002).

The adoption of open innovation may be sequential, starting with customer involvement, followed by employee involvement and external networking, and ending with more 'advanced' practices such as IP licensing, R&D outsourcing, venturing and external participations (Van de Vrande et al. 2009).

With blockbusters running off patent and generics being launched, the paradigm shift in drug discovery is mainly motivated by the pressure on the pharmaceutical R&D-pipeline (Tamoschus, 2014). New opportunities arise in the pharmaceutical innovation ecosystem (Tamoschus, Hienerth, and Lessl, 2015) with external knowledge made available outside a firm through open innovation approaches, open source biotechnology, models of co-development and collaborative innovation.

According to Damani (2013), the need exists for collaborative drug discovery and development as part of the growing attention for open pharmaceutical development. Tamoschus, Hienerth, and Lessl (2015) identified a number of rapidly advancing partnership models and open innovation tools in biopharmaceuticals with newly emerging potential partners, i.e. health innovation stakeholders (lead user innovation) and new technological opportunities such as virtual R&D/open source partnering through powerful bioinformatics.

The open innovation approach is providing new ways for firms of all sizes to collaborate and interact. It is creating opportunities for smaller companies. According to Weverbergh (2013), 'cross pollination between the corporate and the startup world – whether through corporate accelerators, venturing or open innovation – is fast becoming the trend.' In the early stages of R&D, open innovation offers a neutral platform for companies to jointly investigate new and emerging technologies and applications, while sharing risks and costs.

Regional systems of innovation

Widespread research emphasizes the role of RSI (e.g. Cooke 1992; Cooke, Urangab, and Etxebarriab 1997; Cooke et al. 2006) in augmenting the competitiveness and performance of regions and companies. According to Doloreux (2002), the central idea is that the innovative performance of an economy depends on the innovative capabilities of firms and research institutions, and on the ways they interact with each other and public institutions. RSI contains important implications for regional innovative policy. The approach has been widely adopted to highlight policies and measures that increase the innovative capacity of regions. In this sense, the institutional characteristics of the region, its knowledge infrastructures and knowledge transfer systems, as well as the strategies and performance of firms, represent important basic conditions and stimuli for promoting innovation activities (Doloreux 2005). According to Edquist (2005), the system of innovation approach focuses on the fact that firms do not innovate in isolation but rather in collaboration and interdependence with other organizations such as other enterprises, universities and government research institutions.

Asheim (2009) defines RSI as the 'wider setting of organizations and institutions affecting and supporting learning and innovation in a region.' The regional production structure or knowledge exploitation subsystem often displays clustering tendencies (Asheim and Gertler 2005). Clusters, taken as concentrations of 'interconnected companies and institutions in a particular field' (Porter, 1998) continue to be of interest to policymakers (Cooke 2004; Cooke and Leydesdorff 2006; Ketels 2013).

Klepper (2011) points at the valuable agglomeration economies and the Marshall (1920) theory that suggests that firms cluster geographically because it is beneficial in terms of better access to skilled labor (labor market pooling), specialized suppliers (shared inputs) and knowledge spillovers from competing firms. Clustering facilitates learning from other firms, lowers transaction costs for firms and suppliers, and enhances productivity.

A successful innovation policy requires all elements of the ecosystem to cooperate and collaborate together. This is in line with the 'triple helix'-model by Etzkowitz and Leydesdorff (1997; 2000) which creates constructive and mutually reinforcing activities between academia, government and industry.

The biotechnology clusters in Belgium and Germany

Over the last decades, both Belgium and Germany have witnessed the growth of leading bioclusters/bioRegions within a region-specific technology policies context.

In this section, case-based evidence is explored for the regional biotechnology clusters in Belgium and Germany. In both European Union countries, the regional biotechnology clusters are now embracing open innovation. This is opening new windows of opportunity for new biotechnology firms and large pharmaceutical companies working together in a multiplicity of strategic partnerships.

According to the OECD key biotechnology indicators (2011, 2015), a considerable number of firms in Belgium and in Germany are active in biotechnology.

Number of firms active in biotechnology, 2013 or latest available year

OECD, Key Biotechnology Indicators, http://oe.cd/kbi, July 2015.

	Biotechnology firms	Dedicated biotechnology firms	Percentage dedicated	Year	Type of firm
United States	11,367	1165	10.2	2012	Biotech R&D firms
Spain	2831	554	19.6	2013	Biotech firms
France	1950	1284	65.8	2012	Biotech R&D firms
Germany	709	578	81.5	2014	Biotech firms
Belgium	350	127	36.3	2011	Biotech R&D firms

Compared to total of biotechnology firms (production and/or R&D firms)

The percentage of dedicated biotechnology firms in Health is 58.3% for Belgium against 49.4% for Germany.

Percentage of biotechnology R&D expenditure performed by small biotechnology R&D firms

Firms with fewer than 50 employees

OECD, Key Biotechnology Indicators, http://oe.cd/kbi, July 2015.

	Percentage of biotechnology R&D expenditure performed by small biotechnology R&D firms	Percentage of biotechnology R&D expenditure performed by medium and large biotechnology R&D firms		Type of firm
Spain	40.8	59.3	2013	Biotech R&D firms
Germany	34.3	65.7	2014	Dedicated biotech firms
Belgium	17.3	82.7	2011	Biotech R&D firms
France	15.6	84.4	2012	Biotech R&D firms
United States	9.0	91.0	2012	Biotech R&D firms

Compared to total biotechnology R&D expenditure in the business sector

Belgium has a higher biotechnology R&D intensity (R&D expenditures/industry value added) than Germany (0.252 against 0.054). Germany has a higher share in biotechnology patents. On the other hand, Belgium has a higher revealed technological advantage in biotechnology compared to Germany (2.3 against 0.7 for the 2010–2013 period).

Belgium

From the mid-1980s onwards, due to a continued regional policy strategy aimed at developing strong and competitive biotechnology clusters, in both the Flanders and Wallonia regions of Belgium, a growing number of new biotechnology firms emerged (Segers 1992; 1993; 1996). Strong biotechnology clusters (bioRegions) have developed in Flanders (Ghent-Leuven-Mechelen axis) and Wallonia (Liège and Louvain-La-Neuve).

Networked research centers and interuniversity poles of excellence were created to provide a strategic orientation for biotechnology research (OECD 2006). The basic innovative activity occurs mainly in university-based new biotechnology firms, i.e. new small firms that are spin-offs from university research centers performing state-of-the-art research.

Strong collaboration between research institutes, universities, financiers and existing companies has resulted in many university spin-offs. Large, international companies (big pharma) participate in joint ventures with university research centers and small, university based new biotechnology firms (Segers 2013).

The Vlaams Instituut Biotechnologie (VIB) combines a number of universities, research parks, incubators, research institutes, academic hospitals and clinical research organizations. The Flanders bioRegion acts as a regional hub for pre-clinical trials as Figure 3 (Ranger and Lawton 2015) shows.

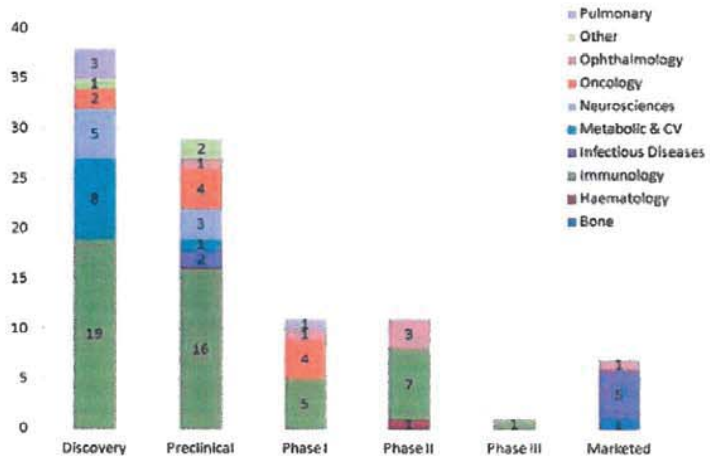

Figure 3. Flanders drug pipeline.
Source: Flanders Bio.

The Wallonia bioRegion is hosting a number of global players in medical research and development, such as GlaxoSmithKline (GSK) and UCB, as well as a network of SMEs and university spin-offs. In 2009, the region implemented the 'Marshall Plan,' a

regional government initiative to encourage further growth in life science/biotechnology entrepreneurship and competitiveness.

BioWin (i.e. BIOtechnologies Wallonie Innovation) is active in the main healthcare biotechnology sectors, namely: (bio)pharmacy, cell therapy, radiopharmacy, diagnostics, biotech products, services, medical devices and equipment. It clusters a number of universities, research centers, higher education institutions and over 100 companies.

Segers (2013; 2015) found a large number of strategic partnerships between large, international chemical and/or (bio)pharmaceutical companies and Belgian new biotechnology firms, the composition of a strategic alliance portfolio being essential in the early years of development of these new biotechnology firms. Table 1 shows the strategic partnership portfolio for a number of biotech IPO's (initial public offering) based in the Flanders and Wallonia bioRegions of Belgium.

Most of the new biotechnology firms in Belgium are unlikely to become fully integrated pharmaceutical companies, because they are heavily dependent on their strategic large partners, especially for marketing outlets, for manufacturing resources when they reach the commercialization stage and for continuing product development efforts. They rely heavily on licensing agreements and milestone payments. Strategic partnerships in the biotechnology industry allow them to gain a foothold in this high-cost, high-risk industry.

This evidence supports the assertion by Fisken and Rutherford (2002) that 'while a small number of companies with access to a large supply of capital may be able to complete downstream integration and revert to the fully integrated pharmaceutical company model, the majority of biotechnology companies will instead need to further develop sophisticated relationship management skills in order to extract greater value from relationships with customers, collaborators and strategic partners.'

Despite their small size and relative immaturity, new biotechnology firms are able to adopt innovative business models by providing R&D and services to larger firms and openly cooperating with them through open innovation. According to Schuhmacher et al. (2013), in view of the stagnating research and development (R&D) productivity, pharmaceutical companies have opened their R&D organizations to external innovation. They are complementing internal project portfolio gaps through licensing and acquisition of drug candidates or acquisition of entire companies, as is also the case for new biotechnology firms in Belgium, as is shown in Table 1.

A number of recent good practices support this assertion:

1. Johnson & Johnson's pharmaceutical division, Janssen (Belgium), opened 'Janssen Labs' (i.e. open collaboration spaces) in San Diego, Boston and Beerse (Belgium). This shared laboratory provides lifescience entrepreneurs with an environment for early-stage research and encourages interaction between startups. It enhances sourcing external innovation.
2. Open source biotechnology in big pharma with open access to data, i.e. sharing of clinical trial data or data on newly approved medicines to researchers. This is already the case for Pfizer, Novartis, Sanofi, GSK, Johnson & Johnson.
3. The Innovative Medicines Initiative is a public-private partnership aiming to boost pharmaceutical innovation in Europe and to speed up the development of better and safer medicines for patients. IMI is a joint undertaking of the European Union and the pharmaceutical industry association EFPIA. Large biopharmaceutical companies and small and medium-sized enterprises are working together with patients' organizations, research institutions, hospitals, regulatory agencies and industrial partners.

Table 1. Belgian new biotechnology firms and strategic partnership portfolio (December 2015).

Firm Name	Technology Platform	Product / Portfolio	Strategic Partnerships/ Alliances	Acquisitions/ Takeovers	Location Region
ThromboGenics*	Ophthalmic medicines	Jetrea	Alcon (Novartis) Novartis		Flanders (Leuven)
Oncurious	Oncology		Bioinvent Int. AB		
Ablynx*	Nanobodies	Alpha-pharmaceuticals Caplacizumab Ozoralizumab	Merck & Co.; AbbVie; Eddingpharm; Novartis; Merck Serono; Algeta Genzyme; Taisho Pharmaceuticals; Boehringer Ingelheim; Novo Nordisk		Flanders (Gent)
Argen-X*	Nanobodies - SIMPLE Antibody Platform		Lonza (GS Xceed); LEO Pharma; Shire Pharmaceuticals, Bayer Pharma; Eli Lilly		Flanders (Gent)
Galàpagos*	Rheumatoid arthritis	Filgotinib	Gilead AbbVie GlaxoSmithKline Eli Lilly Janssen Pharmaceuticals (J&J) Servier Roche Ono Pharmaceuticals	01/2013: acquisition of Cangenix (drug discovery) Biofocus + Argenta: drug discovery divisions (sold)	Flanders (Mechelen)
Tigenix*	Stem cells Cell therapy	ChondroCelect Cx601	Cellerix; Grifols; Lonza; Biolife Solutions	Cellerix (Spain) Coretherapix	Flanders (Leuven)
Movetis	Gastroenterology	Resolor	Shire-Movetis	2010: public takeover by Shire (Ireland)	Flanders (Turnhout)
Genticel*	Vaxiclase Platform - vaccines	ProCervix (HPV)			Paris and Toulouse (France)
Bone Therapeutics*	Stem cells Cell therapy	Preob Allob			Wallonia (Gosselies)

(*continued*)

Table 1. (*Continued*)

Firm Name	Technology Platform	Product / Portfolio	Strategic Partnerships/ Alliances	Acquisitions/ Takeovers	Location Region
Promethera Biosciences	Stem cells Cell therapy	HepaStem H2Sreen; H3Screen	Shire Boehringer Ingelheim		Wallonia (Mont-Saint-Guibert)
Celyad* (Cardio3 BioSciences)	Stem cells Cell therapy	C-Cure		Oncyte (Celdara Medica, USA); Medisun	Wallonia (Mont-Saint-Guibert)
Mithra* Pharmaceuticals	Intrauterine platform	Estelle; Donesta [Estetrol]; Tibelia; Zoreline; MyRing	GlaxoSmithKline	Novalon	Wallonia (Liège)
Uteron Pharma	Intrauterine platform			Actavis (USA) Orgenesis (USA)	Wallonia (Liège)
MastherCell	Stem cells Cell therapy			Orgenesis (USA)	Wallonia (Gosselies)
MDxHealth* (OncoMethy-lome Sciences)	Molecular diagnostics	ConfirmMDx	Exact Sciences; Oncgnostics; Erasmus Medical Center; Labcorp	NovioGendix	Wallonia (Liège)
Biocartis*	Molecular diagnostics	Idylla	Johnson & Johnson (> Janssen Diagnostics) Abbott Molecular Fast-Track Diagnostics Microbiome ETPL (Exploit Technologies; A*STAR) Merck KGaA		Flanders (Mechelen)
UCB*	Neurology/immunology	Zyrtec, Keppra Cimzia, Vimpat, Neupro Brivaracetam (Briviact), Epratuzumab, Romosozumab	AstraZeneca Pfizer Amgen Bayer Neuropore Therapies Oncodesign	Celltech (UK) Schwarz Pharma (GER)	Brussels

*IPO *BEL-Brussels and/or FRA-Paris (double) EURONEXT stock exchange listing*

4. AstraZeneca and Sanofi announced an open innovation model in the search for new small-molecule medicines in several disease areas such as diabetes, cancer and cardiovascular conditions. They will exchange compounds from their respective proprietary compound libraries.
5. The Belgian company Biocartis (molecular diagnostics, rapid cancer and virus tests) is opening up its Idylla-platform for external developers and is working together with Janssen Diagnostics (Johnson & Johnson) and Abbott Molecular.

Given the above findings, the future of new biotechnology firms in Belgium clearly lies in the effective establishment of strategic partnering alliances. The interplay between biotech firms, financiers and investors, university collaborations and academic partnerships, government regulators and big pharmaceutical companies may lead to new business models, organizational structures and financing arrangements that place greater emphasis on integration and open innovation instead of monetization of intellectual property.

Germany

There is a fast-growing need to better manage the translation of innovative ideas into commercial developments. In this role, biotech works as a transmission belt between academia and big pharma (Ernst and Young, 2013). Like Belgium, Germany has firmly established itself as an international medical biotechnology region, characterized by a high number of partnerships of which 70 percent are with research institutions.

Germany has developed a vast number of biotechnology clusters, known as bioRegions, along the entire value chain, from research and development through scale-up and production to sales and marketing. Each bioRegion specializes in particular areas and facilitates the collaboration between universities, R&D institutions, new biotechnology firms and large pharmaceuticals. The bioRegions also include bioparks that offer laboratory space, clean rooms, as well as a range of services for both start-up and established companies.

In the Biotech Cluster Rhine-Neckar (BioRN) bioRegion, new biotechnology firms are well positioned with:

- a mindset for open innovation, including information sharing, knowledge and research tools;
- a strong link to big pharmaceutical companies.

The BioMed X innovation center is a collaboration model at the interface between academia and industry in the Heidelberg Technology Park. Innovations in the fields of biomedicine, molecular biology, cell biology, diagnostics and bioinformatics are explored within a strategic partnership network with biomedical research in an open innovation setting.

Corporate pharmaceuticals like AbbVie, Roche, Boehringer Ingelheim and Merck are key players in this cluster. After a fully funded project term, successful projects are either internalized into the development pipeline of the respective pharma or biotech sponsor or spun off into an independent startup company. Biomed X partners with Roche in an open innovation research alliance in biotechnology, nanotechnology and engineering. The goals are to develop new and faster diagnostic tests, speedier diagnosis and synergies with existing drug treatments.

Bayer HealthCare embraces open innovation approaches with partners from academic and startup environments in its 'Grants4Apps (G4A) Accelerator.' This is part of Bayer HealthCare's open innovation initiatives to advance digital innovation in healthcare.

With its global research incubator concept called 'CoLaborator,' the company offers young life sciences companies access to the Bayer expertize and the global research network, in addition to the ready to use laboratory and office infrastructure in the immediate vicinity of the company's own research facilities in San Francisco and Berlin. The program wants to support the digital health startups in further advancing their projects and business models.

Discussion and conclusions

Over the past decades, governments, academics and companies have increasingly recognized the need for collaboration and knowledge exchange for successful business development. This paper argues that more research is needed with respect to strategic partnerships – and specifically the role of open innovation – in the development of regional technology clusters and novel business models.

The findings for the biotechnology clusters in Belgium and Germany suggest that developing a domestic biotechnology industry and/or hence new biotechnology firms, can be influenced by regional government and company policies that embrace strategic partnership and open innovation strategies in an industry that is characterized as extremely capital, knowledge and infrastructure intensive.

New biotechnology firms in Belgium and Germany have a high degree of integration into global technological networks through strategic alliances. The new collaborative model implies multiple projects and product portfolios, solid technology platforms and the ability of building competencies in all stages of the drug development process. As Rybka et al. (2015) point out, new biotechnology firms need to accumulate skills in production and marketing to bridge the gap between the locus of research and commercialization in the biopharmaceutical industry.

The objective of this paper was to point out a future research agenda. The following research questions should be further addressed:

1a. Is entering into strategic partnership alliances with large established companies beneficial for new biotechnology firms?

1b. To what extent are new biotechnology firms able to become fully integrated pharmaceutical companies?

1c. Is the alliance strategy of new biotechnology firms crucial for their survival and growth?

2. Can regional technology policies (regional systems of innovation) have a significant impact on new technology based firm creation?

3a. Are new biotechnology firms embracing open innovation?

3b. Is open innovation taking strategic partnering to a next level in (Bio)technology clustering?

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