Money for nothing? Risks in biopharmaceutical companies from the perspective of public financiers

Laura Heinonen and Birgitta Sandberg

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Laura Heinonen
is Research Associate in International Business at the Turku School of Economics. She holds a Master of Science degree in Economics and Business Administration. Previously she worked in the business-development division of a Finnish biopharmaceutical company and is currently working on her doctoral thesis, the aim of which is to assess the role of public funding in the development and performance of biopharmaceutical companies.

Birgitta Sandberg
is Assistant Professor in International Business and coordinator of the Global Innovation Management Master's Degree Programme at the Turku School of Economics. She holds a Doctor of Science degree in Economics and Business Administration. Her recent publications include articles in the *European Journal of Innovation Management* and *Creativity and Innovation Management,* and a book titled *Managing and Marketing Radical Innovation; Marketing new technology* (2008, Routledge).

Abstract

The risks faced by biopharmaceutical companies during the process of drug development are multifaceted and complicated. Furthermore, resource intensiveness and the long time perspective force them to rely on external finance. This study describes the risks in the industry along the biopharmaceutical development process and evaluates how public investors take these risks into account in their investment decisions. The empirical study focuses on Finnish public investors. The data consists of both interviews and secondary sources. Biopharmaceutical development is divided into three stages (discovery, development and commercialisation), and the main risks at each stage are identified. The results show that the risk the investors are willing to take is reflected in the stage of the product development process they invest in. Finnish public investors tend to avoid taking commercial risks and thus invest in the early stages of development where there are mainly technical risks involved. They are increasingly emphasising risk management, and they are also keener to emphasise the importance of commercialisation. Paradoxically, however, commercialisation efforts are generally not supported financially.

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INTRODUCTION

Biopharmaceutical companies are extremely research-intensive, developing innovations that are more radical than in many other industries. The product-development process differs significantly from that in other industries, especially in terms of its length and the risks and costs involved.[1,2] It involves several stages, including research, development, commercialisation and regulatory approval, and on average takes approximately 14 years.[3]

Correspondence: Laura Heinonen, Turku School of Economics, Department of Marketing, Rehtorinpellonkatu 3, Turku 20500, Finland.
Tel: +358 2 481 4485
Fax: +358 2 481 4299
E-mail: laura.h.heinonen@tse.fi

There is a vast amount of risk involved in biopharmaceutical development. Developing new drugs is inherently highly risky given the profound uncertainties related to the limited knowledge about human biological systems and processes, and thus companies lack predictive models to mitigate risk.[4] Although it has been acknowledged that risk plays a major role in the development of biopharmaceutical products, past research has paid surprisingly little attention to its characteristics. The literature provides lists of risks faced by the industry, but does not emphasise the financial risks related to drug-development projects.[5,6] In fact, the financial risks are among the most serious that biopharmaceutical companies face.[7]

R&D costs in the industry in general are rising, and competition is becoming keener. Companies tend to lack the resources to survive in this dynamic environment.[8] The development costs of a successful drug may on average extend up to USD 800 million or even up to USD 1 billion including the costs of drugs that fail to during the development.[4,9] Young biopharmaceutical companies usually carry out these expensive development projects without generating any revenue from marketable products, which means that the need for outside finance is critical.[4] It is therefore worth considering how public financiers take the risks into consideration when they decide to which companies the money is allocated, what type of money is invested, and when the investment is made in terms of the lifecycle of the company and of the biopharmaceutical development process. Consequently, the purpose of this study is *to describe the risks along the biopharmaceutical development process, and to evaluate how public investors take these risks into account in their investment decisions*.

The focus of the study is on Finnish public investors, which are independent agencies working under the supervision of the Finnish parliament. The main focus is on Tekes (The National Technology Agency), which is the largest public financier and the most important financial supporter of private companies in Finland. Biotechnology is an important and growing sector in Finnish society and in the economy, the strongest areas being pharmaceuticals, biomaterials, diagnostics and industrial enzymes.[10]

RISK IN BIOPHARMACEUTICAL DEVELOPMENT

Risk has been defined as 'the extent to which there is uncertainty about whether the potentially significant and/or disappointing outcomes of decisions will be realised'.[11] There is a vast array of risks that is inherent in biotechnology development, and various researchers have presented different risk listings, classified as technical, commercial and regulatory, depending on the stage of the process.[12,13] The discovery and development phases mainly involve technical risks regarding the safety and efficacy of the potential product, for example, whereas in the commercialisation phase they are related more to competition, financial return and marketing.[5,6] Regulatory risk, related to patent legislation, for example, is present at each stage of the process.[13]

The aim during the *discovery stage* is to identify new promising chemical and biological properties of either previously known or newly synthesised substances.[14] Patent searches and evaluations are carried out, and the first patent applications are filed.[15,3] The most promising compounds are developed further. The proliferation of new research areas such as molecular biology, cell biology, assay development and combinatorial chemistry has enabled researchers to discover specific disease-causing targets for drug treatment. Hence, the focus at this stage has turned from the treatment of symptoms to the curing of diseases.[16]

Often, decisions have to be made even though all the relevant information is not available, and this obviously involves a high degree of uncertainty.[17] Even now the risks

are not only technical, but also commercial. Companies should already be concerned about the commercial and competitive characteristics of the product, in particular with its clinical advantage over the current market offerings.[18] This clearly reduces uncertainty and risks related to the development and helps companies allocate resources to most potential products.[19]

According to Loch, DeMeyer and Pich, under these circumstances an exploratory approach (ie improvisation and experimenting) would be beneficial.[20] According to Baker, the most successful biotechnology companies develop multiple products at the same time, thereby spreading the risk and also supporting their capability to deliver innovations repeatedly.[21] Hence, a considerable number of investments are needed at the very early stages of the process in order to ensure success later on.[22]

Pass and Postle suggest that too many biopharmaceutical companies engage in this 'betting exercise' at this stage, leading to a 'fatalistic belief that risk cannot be managed'. They further argue that the so-called funnel-shaped pipeline is better suited to bigger firms that can afford to undertake multiple trials, whereas small firms would need outside funding for these experiments.[5] Nevertheless, even though big firms have the resources to conduct multiple trials, their prevalent structures and practices may discourage the most risky (and most radical) discovery projects.[23] Hence, large established firms may need outside financing specifically in the early stages of product development to stimulate divergent thinking and new discovery attempts.

The *development stage* in biopharmaceutical companies consists of preclinical and clinical development (Phases I, II and III). The risks at this stage are mainly related to the technical characteristics of the compound, that is, whether it is safe for the patients to use (toxicological risk) and whether it is efficacious in treating the disease in question (pharmacological risk). Its safety and effectiveness are tested in different kinds of animal models during the preclinical phase.[24] If there is evidence of efficacy as well as safety, an investigational new drug application is filed, and if the regulatory authorities approve the application, the process continues to the clinical-development phase.[8,3] The safety and dosage are tested on healthy individuals in Phase I of the clinical assessment, the efficacy and side effects are tested on real patients in Phase II, and finally in Phase III the adverse reactions to long-term use are evaluated, also on real patients.[24] This stage also involves commercial risks, because once again there is a need to consider the competitive characteristics of the compound.[18]

The costs of running parallel trials during the development stage may become prohibitive, particularly for smaller firms. Thus, it is often necessary to select one or a few development streams and improve them in a process of sequential learning.[20] It is often, however, challenging to choose from a number of projects, given the difficulties involved in interpreting the results of clinical trials. The conclusions reached on whether to continue to the next stage of development vary from company to company,[4] which may well prove challenging to investors. The probability of success increases, the further advanced the development process becomes. There are, however, still risks involved during the regulatory processes, and even after the product has reached the market. According to a study conducted by DiMasi,[7] 39 per cent of later-stage drug-development projects are terminated for commercial reasons such as limited market potential or insufficient return on investment. Fewer projects were terminated for technical reasons connected to efficacy (32 per cent) and safety (16 per cent).[7] Thus, over time the commercial factors become more important and also the primary reason for abandoning a development project.

If these clinical trials are successful and tests show that the compound will potentially serve the medical needs of the market, the

regulatory process begins. A New Drug Application is filed and the company now waits for market approval. If this is forthcoming, the market launch process can begin.[8,3] In general, the definition of *commercialisation* in the literature relates to bringing technical inventions into markets in order to generate profit.[25] Many researchers have emphasised the critical role of this stage.[26] Marketing expenses in the biopharmaceutical sector are more extensive than in many other industries.[12] The commercial risks are also high and difficult to predict due to the time it takes to develop a new drug. These risks relate to issues such as the actions of competitors, therapeutic recommendations and advances, financial returns and patent expiry.[5,6] Commercial risks were realised for example in Pfizer, which withdrew its much-anticipated inhaled insulin product from the market after disappointing sales results.[27]

Post-launch modification based on market feedback, that is, 'probing and learning', is often recommended in situations involving high uncertainty.[28] This kind of behaviour is, however, not applicable in the highly regulated field of biopharmaceuticals.[20] Hence, biopharmaceutical firms need to approach markets proactively and to anticipate and influence competitors, customers and other actors in the business environment.[29] Proactiveness is expensive, however, and the costs may be prohibitive for small companies. Long-range market scanning and extensive lobbying normally require a significant sacrifice of scarce resources.[30]

Biopharmaceutical development is extremely costly. The estimated total average cost of drug development varies from USD 800 million to USD 1 billion.[4] The average proportion of the finance required at the different stages increases as the process advances: between one and three per cent for discovery, 40–50 per cent for development and the rest for commercialisation and post-marketing development.[30,8]

Figure 1 summarises the *a priori* framework, formulated on the basis of previous studies. It shows the different stages of development, the risks involved and the finance needed in a biopharmaceutical drug-discovery project. It could be used to guide and focus the investigation, but as a preliminary attempt to combine the findings of past studies, it does not provide a good enough basis for hypothesis testing. On the contrary, it is left open for modification based on what emerges from the empirical data.

RESEARCH METHODOLOGY

The empirical data for the study was collected from both interviews and secondary sources. The interviewees included one representative each from three biopharmaceutical companies and Tekes, and three other public-sector representatives (Finnish Bioindustries, Turku Science Park, Ministry of Employment and the Economy). Publications and presentations given by public financiers were used as secondary data sources.

The aim of the interviews with Tekes and other public-sector representatives was to clarify the current investment strategies of the public investors and to evaluate how the risks faced specifically by biopharmaceutical companies are taken into account when investment decisions are made. The company interviews made it possible to evaluate these issues from the perspective of private firms receiving financial support. Three management-level persons, each with at least 20 years of experience in the industry, were interviewed. At the time of the interviews, these companies had been operating for approximately ten years and were in the stage of at least initiating the commercialisation efforts. The representatives from Finnish Bioindustries, Turku Science Park and Ministry of Employment and the Economy gave their varying opinions on the current situation in the industry in Finland. Semi-structured interviews were the main data collection method, in which the themes of the interview were planned beforehand but the interview was conducted without precise form and structure.

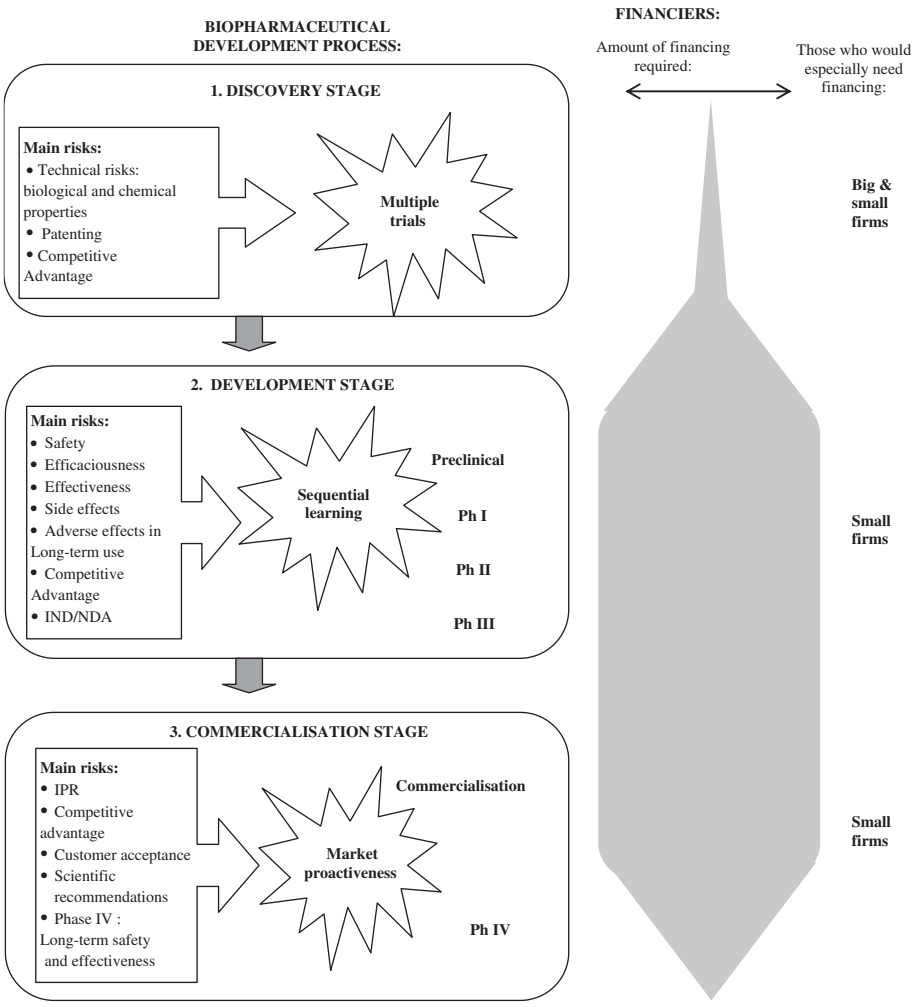

Figure 1: The need for financing in biopharmaceutical development (preliminary framework)

During the analysis stage, the data were organised thematically, according to the preliminary framework. Pattern-matching logic was then used to link the theoretical framework to the empirical findings.[31] The data analysis was a continuous process that required repeated reading of the interview text files, the notes and the secondary data. It involved returning to the theory and to the interviewees with additional questions. This constant comparison between theory and empirical reality resulted in the creation of a modified framework. In order to eliminate possible errors, the interview data were crosschecked and, in case of contradictory evidence, the interviewees were contacted by telephone or e-mail to clarify the points in dispute.

RISK AND FINANCING IN THE FINNISH BIOPHARMACEUTICAL INDUSTRY

In recent years Tekes has invested EUR 40–60 million annually in biotechnological research: in 2005, investments in private companies amounted to approximately EUR 23 million.[32] Other major public financiers include Sitra (The Finnish National Fund for Research and Development) and Finnish

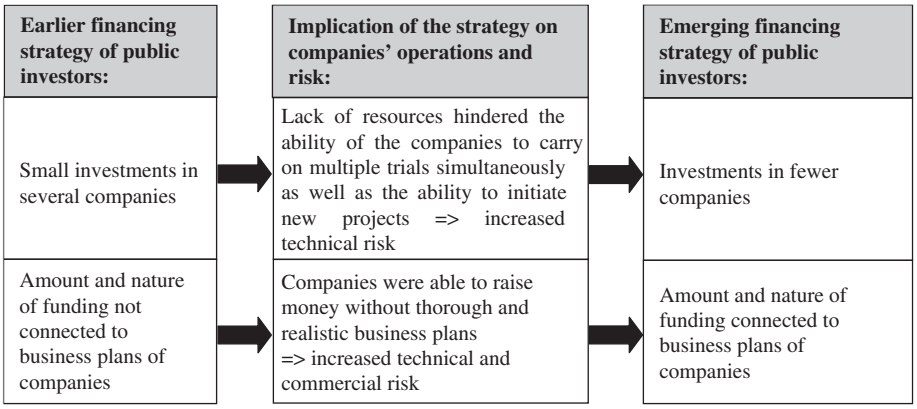

Figure 2: Financing strategies of public investors at the discovery stage

Industry Investment Ltd. Sitra invested EUR 10.4 million in biotechnological companies in 2005.[33] According to Finnish Industry Investment Ltd,[34] the overall investment liabilities for biotechnology companies were EUR 18 million. Finnish public financiers have since 2005 started to change their financing criteria. In the following sections, it is evaluated how well the old and new criteria take the risks into account.

Risk and financing at the discovery stage

In general, the probability of new-product success in the biotechnology industry is low: it has been estimated that one in about 5,000 compounds synthesised ever reaches the market.[3] The risks of financing early-stage companies are taken into account in that the grants awarded to them are smaller. The risk could be spread by developing multiple products simultaneously,[21] but, however, due to lack of financial resources the companies have not been able to carry out several projects at the same time nor have they been able to initiate new projects.

Consequently, many companies have been built around just a few flagships projects. As the risks in biopharmaceutical product development are high, companies would definitely have better ability to bear the risks if they had a stronger and wider portfolio of projects in the development pipeline. One interviewee stated that '*if a public investor such as Sitra has tens of biopharmaceutical companies in the portfolio, it's clear that they haven't considered how these companies will be taken further in the coming years, nobody has the resources needed for that*'. Hence, lack of finance at the discovery stage increases technical risks (see Figure 2). Nowadays public financiers are, however, increasingly paying attention to this issue and focusing their investments on fewer companies. For instance, Sitra is, no longer making new investments in biopharmaceutical companies but it is supporting the ones currently in its portfolio.

The interviewees from the companies felt that it was easy to raise some funding at first but that there was not enough of it available, and that its allocation did not always meet their needs: '*We had business plans but looking back now, I think that they weren't probably realistic enough*'. Inadequate finance based on unrealistic business plans increased technical and commercial risks even further. The criteria are now being tightened and companies are expected to provide a proper and realistic business plan in order to receive financial support. This indicates that public financiers are willing to decrease the risks related to their investments. Results indicate that public financiers were probably not fully aware of the risks involved in biopharmaceutical product development in

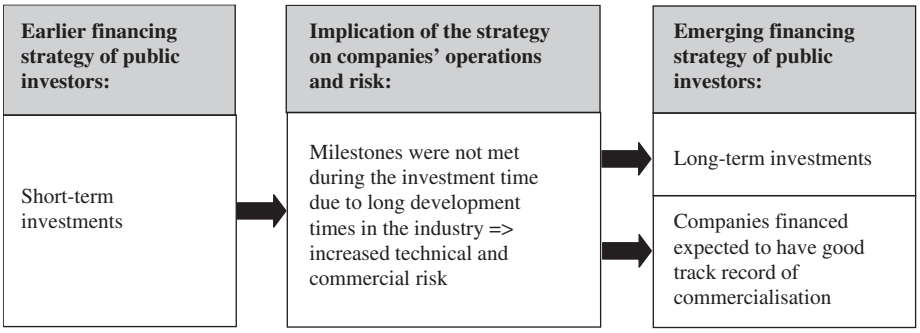

Figure 3: Financing strategies of public investors at the development stage

the beginning . As the financiers have become more aware of the risks involved, they have tightened the investment criteria.

Risk and financing at the development stage

In the development stage, the costs of running parallel trials may become too high, especially for smaller firms. Thus, these companies focus on certain development streams and improve them through sequential learning.[20] Sequential learning takes time and requires long-term commitment from financiers. Companies have not been satisfied with the commitment of public financiers: '*Investment decisions haven't been considered in depth and the amount of resources and commitment needed to build up a biopharmaceutical company haven't been understood thoroughly*'.

The lack of patience seems to have come as a surprise for many companies: '*Financiers are inexperienced in this industry but we realised that only when they suddenly stopped believing in this industry. We would definitely need more "patient money" as the development times are so long in pharmaceuticals*'. The interviewees from the public-sector organisations, Finnish Bioindustries, Turku Science Park and Ministry of Employment and the Economy, supported the views of the company representatives: '*This industry is relatively young in our country, financiers are still rather inexperienced and the needs of the companies are not totally recognised*'.

Recently, however, the time perspective of the investors has become longer (see Figure 3); nowadays Tekes usually commits to supporting the project for between three and five years. The funding is mainly in the form of R&D grants, but also includes low-interest loans. The operations of the companies are followed more carefully, their objectives are clearly defined and they are required to submit regular reports.

It was also stated that in order for the companies to be able to decrease the risks involved, they would need to be big enough and have enough resources to carry through several development projects simultaneously. They are also expected to have a proven track record in the commercialisation of innovations, and to have several development projects in the pipeline at the same time. Companies with several parallel development projects are preferred because it is felt that this reduces the risks related to technical failure. This requirement, however, limits the chances of small start-ups receiving long-term financing.

Risk and financing at the commercialisation stage

In general, most of the financing is allocated to the early developmental stages, as the representative of Tekes stated: '*We support technology development, not business. Commercialisation efforts, such as marketing, are regarded as business.[…] We are willing to take*

technology risks but not risks related to commercialisation, financing or human resources'. This kind of allocation was criticised by the companies: '*Tekes supports our technical operations but we don't get any support for commercialisation. We would really need this support for hiring skilful marketing people*'.

Even though the emerging financing strategy recognises the importance of commercialisation, there are still very few financial instruments available: in principle it is not supported financially. Hence, the companies are not able to proactively approach their future markets. This leads to an increased level of commercial risk (Figure 4).

Figure 4: Financing strategies of public investors at the commercialisation stage

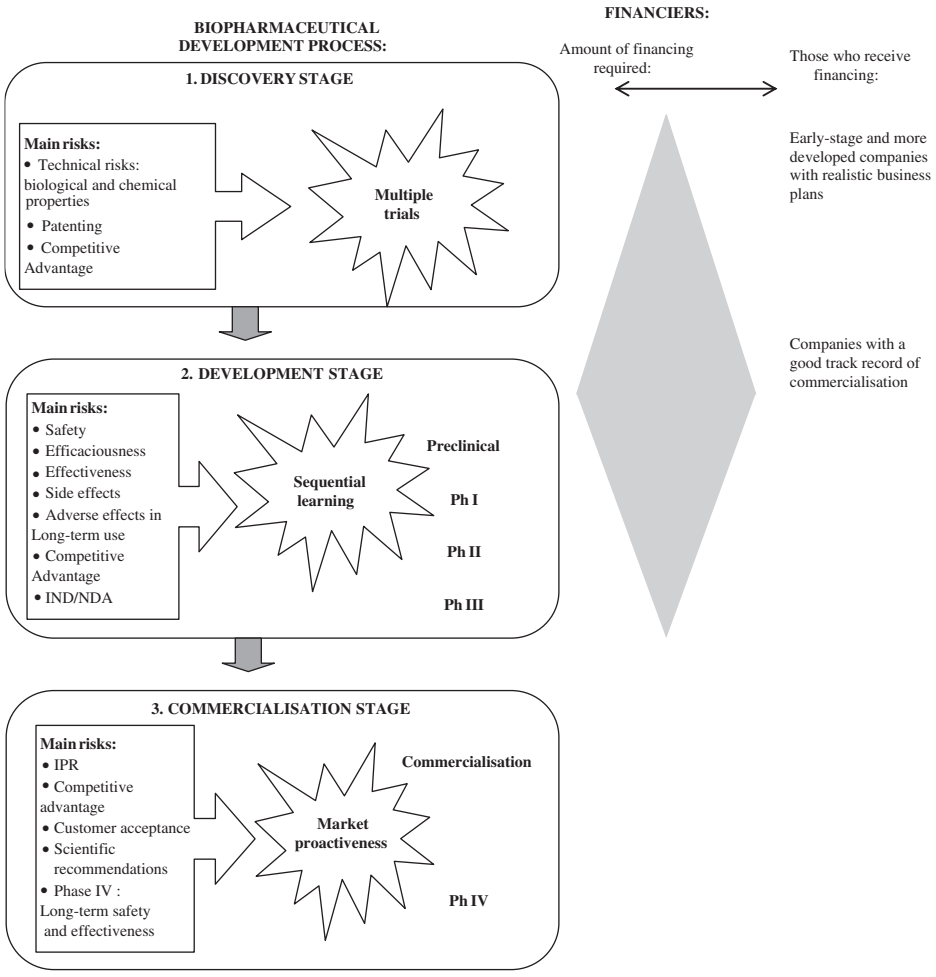

Figure 5: Amount of financing granted in biopharmaceutical development (modified framework)

Synthesis

Figure 5 presents the modified framework of the study, based on the findings from the interviews. In general, the findings from the company interviews seemed to support the preliminary framework: the need for financing is critical and increases during the development process. It, however, also seems that public investors are nowadays giving more thought to decreasing the risks related to the financing of biopharmaceutical companies than previously. Nevertheless, the financing seems to end just on the edge of the critical commercialisation stage, which has a bias towards development of later-stage companies.

A good track record on commercialisation is becoming an important financing criterion of the public financiers. Thus, even though at the discovery stage the support is allocated to both early-stage companies as well as those that are a little further advanced in their lifecycle, the financing prospects of smaller firms seem to decrease drastically as the development proceeds.

CONCLUSIONS AND IMPLICATIONS

Developing new drugs is extremely challenging. The process involves various risks, the development times are long and extensive resources are needed. Most biopharmaceutical companies earn no profit, thus the operations have to be funded through external investors. Public financiers provide critical support to European biopharmaceutical companies. The aim of this paper was to evaluate the risks involved in investing in biopharmaceutical companies from the perspective of public financiers. The results show that public financiers take the risks into account by trying to avoid them (by allocating finance to fewer companies that have a good track record on commercialisation) instead of supporting the companies to manage the risk.

The study focused on the multifaceted relationship between risks and finance: on the one hand the amount of perceived risk influences the finance granted, and on the other hand the financing may help the firm to cope with the risk. For example, overcoming the risks inherent in the commercialisation of biopharmaceuticals seems to require proactive behaviour towards the market, which in turn demands financial resources. The previous literature indicates that multiple trials, sequential learning and market proactiveness influence the financing needs of firms during the process of pharmaceutical development.

As almost all industrialised countries, Finland has set high hopes on biotechnology as a source of new high-tech growth. The history of Finnish biotechnology is, however, rather short compared with many other countries.[10] In Finland, the government model was traditionally built up to serve the ICT industry. Whereas the model worked well in fast-to-market industry, it has however proven to be inadequate for biotechnology firms facing different kinds of risks.[35]

It can be concluded from the empirical findings that public investors increasingly emphasise the risk management of their biotechnological investments. Financial support is allocated only to certain types of companies, at certain stages of the development process. For example, the most important public supporter of Finnish companies, Tekes, specifically focuses on the financing of technology development. It is not willing to take any risks other than technology risks, and thus avoids commercial, financial and human-resource risks.

On the other hand, Tekes emphasises the importance of commercial aspects in their financing decisions, expecting companies to have a track record of successful commercialisation. It is notable, however, that most of the support is still allocated for the early stages of the drug-development process, and not to product commercialisation, for instance. From the perspective of the companies this raises the question of the

rationality of such a strategy. The development times in the biopharmaceutical industry are long and it takes 14 years on average to develop a marketable new drug. Currently, companies generally do not receive any support for their commercialisation efforts, but they are still expected to succeed in commercialising their innovations.

Resolution of this contradiction would require either that public financiers change their criteria for evaluating potential target companies, or that new financing instruments be developed to cover the commercialisation stage. In fact, it may be that the identified contradiction between words and actions indicates that public financiers are in a transitional phase: they have recently changed their decision-making criteria, which may be the first step towards changing their actions. Due to the long development process, the short history of the biotechnology industry and consequent lack of commercialised products, commercial performance in biotechnology companies has often been measured through such indicators as patent applications, number of biotechnology firms, venture capital investment and initial public offerings.[36] These measures, however, tell us more about the commercial potential than the actual performance. Therefore, along with the maturation of the industry, it would be necessary to re-evaluate the measures for commercial success.

Comparing these findings to the findings of previous studies gives us an impression that the situation in Finland is by no means unique. For more than two decades, many European governments have put biotechnology as a priority on their innovation policy agenda and most European countries support the industry by providing public finance, especially during the early stages of a company's operations.[37] Nevertheless, the inability of European firms to turn scientific knowledge into commercial success, called the European Paradox, has been acknowledged in many previous studies. A study by Enzing, van der Giessen and Kern shows that small European biotechnology firms regard the lack of financial support for their later growth stages as a considerable hindrance. In particular, firms in Sweden, Finland, the Netherlands, Belgium and Ireland see it as a very serious problem.[36] According to the EPOHITE report it seems to be a big problem for French, Austrian and Irish firms as well.[38]

This paper reported an exploratory study, which was limited to Finland, where venture capital is very scarce and public investors are of critical importance: in future it would be interesting to compare the behaviour of public investors in various countries. As the European biotechnology industry is moving towards more mature development stages, it becomes increasingly important to reconsider how the public sector could better support commercialisation. Without a support that would better meet the needs of the companies, the large amount of public investment targeted to scientific development could be wasted along with the failure of the companies.[39] On the other hand, the financial support requires careful consideration and timing in order to avoid the interference with market mechanisms.

The development of biotechnology in Europe – and increasingly also in Asia – has become largely policy-dependent. Therefore, it is crucial for national governments to understand what measures to take in order to increase the competitiveness of their biotechnology industries.[38] This study analysed some of these measures and consequently brought practical viewpoints to the issue. Theoretically, the study contributed to the current literature by describing the risks involved in a particularly challenging industry, and assessing these risks from the perspective of public investors. Public financiers seemed far more disposed to tolerate technical rather than commercial risks. Future research could help them in terms of developing tools that permit them to estimate and anticipate commercial risks more accurately.

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