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OUT-LICENSING IN MARKETS WITH ASYMMETRIC INFORMATION: THE CASE OF THE PHARMACEUTICAL INDUSTRY

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Few large pharmaceutical companies have recently discovered out-licensing of terminated R&D results as a way to recoup some of the significant investments made in R&D and to improve R&D productivity. Our empirical investigation reveals that the licensing partners are preferably young, small and highly specialized companies. This reverses the traditional logic of out-licensing. While out-licensing is usually done because of downstream concerns, our analysis shows that the company which owns the necessary assets for further development (the large pharmaceutical company) sells the license to a firm (the small partner company) which has — at the time of deal closure — no track record to prove its ability to successfully develop the compound.

As the lack of a track record does not allow the pharmaceutical company to distinguish between the partner firms based on their development capabilities, these out-licensing deals are characterized by an asymmetric distribution of information. The application of the theory of adverse selection allows deriving managerial recommendations along three dimensions of the out-licensing deal: product coverage, price setting and performance presumption. By making changes along these dimensions, R&D managers are able to reduce the information asymmetry and approximate an equilibrium in the out-licensing market.

Keywords: Out-licensing; research & development; pharmaceutical industry; asymmetric information; adverse selection.

Introduction

The R&D productivity at major pharmaceutical companies is deteriorating for years (see PhRMA, 2004; Reuters, 2003). R&D spending has arrived at a record level of US$ 33 billion in 2003 while the number of new drugs introduced to the market has declined from 53 in 1996 to only 35 (see Fig. 1). The plunge in R&D

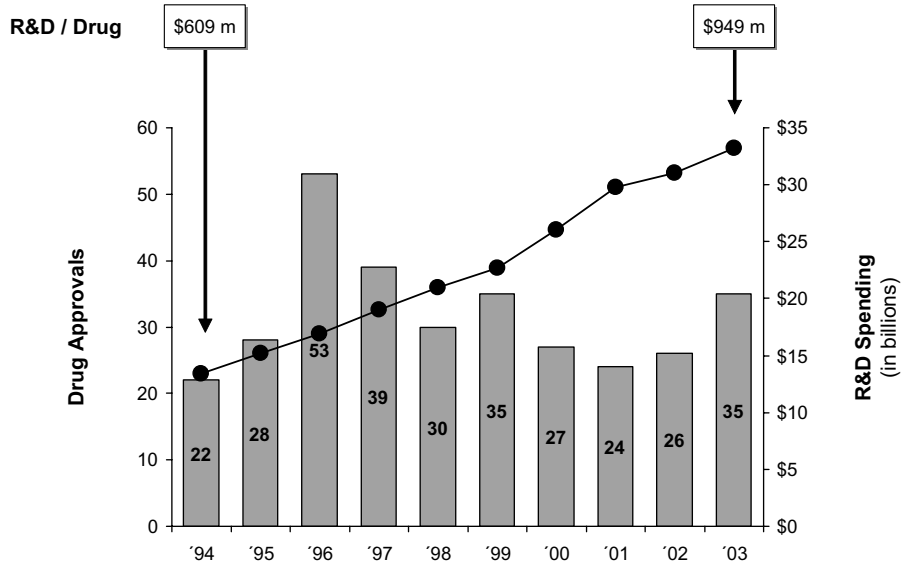


Fig. 1. Declining productivity in pharmaceutical R&D.
Source: PhRMA (2004).

output constitutes that many R&D projects are terminated at some point during the R&D process although pharmaceutical companies are heavily investing into R&D. However, Gambardella (1992) already figured out years ago that the more a pharmaceutical firm invests in basic research the more patents it typically produces. Also, drug discovery firms with a strong research orientation generally produce a greater number of important patents (Cockburn and Henderson, 1998). As a consequence of the rise in R&D input and the decline in R&D output, most pharmaceutical firms have built up large portfolios of patents, technologies and other forms of intellectual property which effectively decay in the companies' archives see also (Longman, 2004).

While much idle intellectual property has little value, others could provide significant economic benefits if they were brought to a respective market. Atun (2007) came to the conclusion that not only investment in R&D and IP generation is necessary to gain competitive advantage but also the commercialization of its results. In fact, some pharmaceutical companies have recently turned to external partners and licensed out some of their terminated R&D projects for further development and commercialization. For example, Eli Lilly generated approximately US$2 billion in additional revenues due to out-licensing over the last five years (Longman, 2004). Schering announced to set an increasing strategic focus on out-licensing activities, and in 2004 out-licensing has become — for the first time ever — an own item in the company's budget calculations. While it

might seem unreasonable to assume that a partner company would be interested in developing a substance that has been terminated by an established pharmaceutical company, it should be considered that many R&D projects are not stopped because of failures in the underlying substances. In many cases, the reason for termination is simply a misfit with the overall strategy or portfolio of the pharmaceutical company (Kollmer and Dowling, 2004). Also, a medical advance that results from an initial discovery may not be obvious (Sheridan, 2007), and therefore its value might not be judged accurately at early stages of discovery. By out-licensing terminated substances which did not make it into the firms' top-priority list but still have a certain value for other companies or patients, the pharmaceutical company could recoup some of the already incurred R&D investments which could amount up to a few hundred US$ million depending on the stage of termination see (BCG, 2001). Thus, out-licensing represents a promising approach to improve the declining R&D productivity by commercializing terminated R&D results.

In our paper, we illustrate the novel phenomenon of out-licensing at established pharmaceutical companies by using a cross-case analysis. We highlight the special characteristics of these collaborations and illustrate main issues faced by the licensing firms. By applying the economic theory of adverse selection, we derive recommendations for managing these out-licensing deals.

Literature Review

Literature on pharmaceutical R&D management is quite extensive. Several publications discuss success factors and strategies for producing new chemical entities see (Boerner, 2002; Needleman, 2001; Teoh, 1994). While the generation of IP appears to be pivotal in biopharmaceuticals, key to success is that innovation is only sustained if it is appropriately rewarded. Investments in the science base alone without appropriate reward systems are unlikely to promote competitiveness (Attridge, 2007). Other publications analyze the origins and drivers for competitive advantage (Cockburn *et al.*, 2000; Henderson, 2000; Yeoh and Roth, 1999). Another stream of literature on pharmaceutical R&D covers issues related to resource allocation and portfolio management decisions (Blau *et al.*, 2004; Cockburn and Henderson, 1998; Gittins, 1997; Halliday *et al.*, 1997). In addition, different allocation models and valuation tools for pharmaceutical R&D projects have been widely discussed see (Bunch and Schacht, 2002), whereas most scholars focus on the real option valuation (see McGrath and Nerkar, 2004; Cassimon *et al.*, 2004; Brach and Paxson, 2001; Loch and Bode-Greuel, 2001). A general point of interest in the literature on pharmaceutical R&D management has also been the organizational structure of R&D departments (Cardinal and Hatfield,

2000; Cockburn *et al.*, 1999; Pisano, 1997; Drews, 1989). A relatively small number of publications cover internationalization aspects and international comparisons among pharmaceutical R&D activities see (Kuemmerle, 1999; Albertini and Butler, 1995).

By far, most research on pharmaceutical R&D management deals with the emergence of the biotechnology industry over the last two decades and the subsequently increasing interaction of pharmaceutical companies with external partners. At the end of the 1990s, R&D partnerships in the pharmaceutical industry accounted for about 30% of all R&D partnerships across all industries (Hagedoorn, 2002). Lin (2001) as well as Albertini and Butler (1995) analyzed the nature of these agreements highlighting that the pharmaceutical companies usually form the nodes in large-scale scientific networks with biotech firms and universities, whereas the biotech firms play a mediating role to transform scientific knowledge into patented technologies. Mangematin *et al.* (2003), Tapon *et al.* (2001) and Pisano (1991) found out that the partners in novel biotechnology areas are usually small and mid-sized companies which continue to remain small, even those set-up several years ago. As new entrants in the pharmaceutical industry typically co-exist in a 'symbiotic' relationship with mature companies rather than replacing them, it may not even be realistic to expect the small biotech firms to become fully integrated in the foreseeable future. Reasons that motivate pharmaceutical firms to enter into alliances have been analyzed by Jones *et al.* (2000), Greis *et al.* (1995) and Pisano (1990). While collaboration reasoning generally follows a shift away from upstream R&D to downstream manufacturing and marketing, the major reasons for collaboration include market access, speed to market, flexibility, complementary assets, shared risks, the firms' R&D experience, their dependence on the pharmaceutical business, and the companies' national origin.

Several publications discuss the different organizational types of R&D partnership agreements in the pharmaceutical industry (see Herrling, 1998). While all forms of cooperation seem to be increasing, there seems to be a growing tendency towards looser forms, such as project-based and non-equity partnerships (see Hagedoorn, 1996; Narula and Hagedoorn, 1999; Osborn and Baughn, 1990). The share of equity-based R&D joint ventures in all newly established technology alliances decreased from around 80% in the early 1970s to less than 10% in 1998 while contractual arrangements, such as licensing, radically increased both in number and share over the same period (Hagedoorn, 2002).

Licensing deals from biotech to pharmaceutical companies (i.e., in-licensing from the perspective of the pharmaceutical company) have received a lot of attention in management research. For example, Lerner and Merges (1998) focused on the allocation of control rights of these agreements, whereas Roberts

and Mizouchi (1989) described licensing as a means of technology sourcing via inter-firm collaboration. However, literature on licensing from pharmaceutical to biotech companies (i.e., out-licensing from the perspective of the pharmaceutical company) is very scarce. Only one publication by Kollmer and Dowling (2004) compares licensing strategies at both fully and not-fully integrated firms in the biopharmaceutical industry. The authors figured out that out-licensing brings comparable compensation in both cases although there are differences in the licensing strategies of the two types of firms. However, the research does not analyze the manageability of out-licensing at established pharmaceutical companies. Thus, research on out-licensing from the perspective of an integrated pharmaceutical company seems to be fairly underrepresented in management research so far.

Research Methodology

Due to the novelty out-licensing as an empirical phenomenon in the pharmaceutical industry, this research applies an exploratory research approach. It follows the concept of qualitative research in accordance with Eisenhardt (1989). The research uses a multiple-case design with the out-licensing deal as the single unit of analysis (Yin, 1994). Validity and reliability during this research is ensured by combining the data from semi-structured interviews with the results of thoroughly conducted desk research, internal R&D documentation as well as presentations by R&D personnel. The interpretations are then confirmed in follow-up interviews.

The research is based upon 86 semi-structured interviews with 35 different companies primarily from the pharmaceutical/biotech industry. It can subsequently be assumed that R&D management at all analyzed companies is subject to the same industry conditions. As the environment for all companies is considered similar, the firms' actions and performance solely depend on firm-specific characteristics. Although most of the analyzed companies are domiciled in three different countries (Switzerland, Germany and the USA), all companies are located in Western economies. According to von Zedtwitz, Gassmann and Reepmeyer (2003) as well as Gassmann and von Zedtwitz (1998), the pharmaceutical industry is considered to be highly internationalized for several years. Thus, it can reasonably be assumed that R&D management at these companies follows related principles and shares similar values and beliefs. In addition to the interviews, a survey among 60 companies has provided further input during the research investigation.

The empirical analysis covers three in-depth case studies of Novartis (out-licensing to Speedel), Schering (out-licensing to Intarcia) and Roche (out-licensing to Actelion) as well as several smaller case examples including companies such as

Eli Lilly, Merck KGaA, Bayer or Aventis among others. The goal of the case study analysis is to identify patterns and schemes regarding the management of out-licensing collaborations from the perspective of a large and integrated pharmaceutical company. All cases pursued the following research question: How should established pharmaceutical companies manage out-licensing deals in order to improve their R&D productivity?

Out-Licensing at Large Pharmaceutical Companies

Characteristics of the deals

Out-licensing deals in the pharmaceutical industry are generally done because of downstream concerns (Cockburn, 2004). This means that the out-licensing company usually has limited development capabilities and the in-licensing firm possesses the necessary capabilities to develop the licensed compound, such as (i) the expertise to deal with regulatory bodies, (ii) the competence to develop timely clinical testing, (iii) the ability to scale up manufacturing of a product for large quantities, and (iv) established marketing and distribution capabilities (see McCutchen and Swamidass, 2004).

Our empirical investigation, however, has led to contrary results. The case study analysis revealed that the out-licensing pharmaceutical firms are fully integrated companies that possess the necessary assets and capabilities to successfully develop the licensed compounds (compare Table 1). Each of the out-licensing pharmaceutical companies serves several therapy areas and employs more than 38000 people on average. By contrast, their in-licensing counterparts are all comparatively small companies that focus on some selected therapy areas and have only a few lead compounds in development. The licensees have on average around 185 employees, which makes them more than 200-times smaller than the licensors. The number of these small and focused companies which pursue the business model of in-licensing unwanted and underappreciated drugs in the portfolio of discovery-based large pharmaceutical companies has grown significantly over the recent past. On average, the licensees in Table 1 have only been founded in early 2000. However, some of them have already experienced great success on the capital markets. The best performing IPO in 2003 in any industry has been the company Pharmion that operates exactly under this business model. Out of 28 therapeutics companies which made their IPO since 2003, nine have cleaved closely to the same business model and at least two more such firms were on deck at the time of writing (Thiel, 2004). The importance of these specialty pharma companies has grown so much that these firms have even received their own classification as NRDO (no-research-development-only) firms.

Table 1. Out-licensing deals of major pharmaceutical companies: Characteristics of the licensing partners.

NRDO Partner company (licensee)					Major pharma company (licensor)		Comparison (licensor/ licensee)
Name	Strategy or focus	Lead compound(s) or product(s)	Year founded	Number of employees	Name	Number of employees	Employee multiple
Actelion	Endothelin	Tracleer®	1997. IPO in 2000	840	Roche	65,000	80x
Advancis Pharmaceuticals	Anti-infective, including preclinical assets	Keflex	2000. IPO in October 2003	88	Eli Lilly	44,500	505x
Aspreva Pharmaceuticals	New indications for existing drugs	Certain rights to CellCept	2001	N/A	Roche	65,000	N/M
CoTherix	Pulmonary hypertension	Ventavis (NDA pending)	2000. IPO in registration	39	Schering	26,000	666x
ESP Pharma (acquired by PDL in 2005)	Approved or late-stage products	Cardene IV (hypertension) among others	2002	N/A	Wyeth	51,400	N/M
Intarcia	Oncology, Infectious diseases	Atamestane	1997	35	Schering	26,000	740x
InterMune	Pulmonary fibrosis	Infergen (for hepatitis C); Amphotec (for fungal infections)	1999 (spin-off of Connetics)	326	Genentech	9,500	29x

Table 1. (*Continued*)

NRDO Partner company (licensee)					Major pharma company (licensor)		Comparison (licensor/ licensee)
Name	Strategy or focus	Lead compound(s) or product(s)	Year founded	Number of employees	Name	Number of employees	Employee multiple
Novacardia	In-licensing	Adenosine A1 receptor antagonist(s)	2003	N/A	Kyowa Hakko	6,000	N/M
Peninsula Pharmaceuticals (acquired by J&J in 2005)	In-licensing	Several antibiotic compounds	2001	N/A	Takeda	14,500	N/M
Rejuvenon	Oncology	Cachexia (Phase I)	2000	N/A	Novo-Nordisk	20,300	N/M
Speedel	Cardiovascular, metabolic diseases	Aliskiren	1998	60	Novartis	81 000	1 350x
Tercica	Insulin-like growth factor	Endocrine (Phase III)	2002. IPO in March 2004	60	Genentech	9,500	160x
Vanda Pharmaceuticals	Schizophrenia	Iloperidone (Phase III)	2003	30	Novartis	81,000	2 700x
Average			20001/4	185		38,438	208x

Despite of their small size, the partner companies seem to be motivated to take an R&D project under development which initially had been terminated by the large pharmaceutical company. While this seems to be counterintuitive, the partner firms have various reasons to get involved in those deals. In Schering's deal with Intarcia, the licensee Intarcia saw a higher value potential in Schering's substance Atamestane than Schering was able to see itself, although the substance was identical for both partners. While Schering decided to terminate the development of Atamestane, Intarcia's business strategy deliberately allowed the firm to alternate the clinical application and/or the development pathway of the in-licensed compound. After closing the deal, Intarcia changed the substance's indication from prostate cancer in men to the treatment of hormone-dependent breast cancer in women. According to Intarcia, re-directed substances face less competition because the originator(s) disregarded the respective development opportunities. Consequently, the relative licensing costs and future financial obligations seemed to be less expensive for Intarcia than for Schering. The discrepancy in the perception of the substance's relative costs and benefits translated into the fact that Intarcia assigned a higher value to Atamestane than Schering did. This enabled Intarcia to acquire and develop a substance which had initially been terminated by a major pharmaceutical firm.

The out-licensing deals of Novartis (with Speedel) and Roche (with Actelion) have been characterized by slightly different circumstances. The management of the in-licensing partner firms previously worked with Novartis and Roche respectively. Soon after Novartis and Roche decided to stop the development of their substances Aliskiren and Bosentan, the responsible R&D managers — who still believed in the substances' potential — left the firms. They set up their own companies (Speedel and Actelion respectively) and in-licensed the compounds from their previous employers. In both cases, Novartis and Roche retained a call-back option to license the substances back at later stages of development. Novartis exercised the call-back option in 2002. Aliskiren was approved by the FDA in 2007. In the US, it generates revenues for Novartis and Speedel under the brand name Tekturna®. In Europe Aliskiren is marketed under the brand name Rasilez®. By contrast, Roche did not exercise its call-back option. After in-licensing Bosentan, Actelion changed the substance's indication from congestive heart failure to pulmonary arterial hypertension and was able to receive FDA approval for Bosentan in 2001. Today, Bosentan is marketed under the brand name Tracleer® and posted revenues of around US$1.4 billion in 2009.

The sold licenses of the out-licensing deals of Novartis (with Speedel), Roche (with Actelion) and Schering (with Intarcia) were all straight licenses under a highly royalty-based contract. Under a straight license, the licensee becomes the full owner of all intellectual property covered by the license. Under a highly

royalty-based contract, the partner firm pays only a small fraction of the entire price as an upfront payment immediately upon closing the deal, and in return it will receive all of the intellectual property related to the license. The majority of the price is paid in terms of royalty revenues which accrue only if the partner firm successfully executes the compound's development and brings the drug to the market. Due to the limited financial resources of Speedel, Actelion and Intarcia, the licensing deals were all characterized by highly success-based compensation structures including comparatively small upfront payments and correspondingly significant contributions of royalty revenues.

Sometimes, the marketing strategy of smaller partner companies allows them to effectively bring a new drug to a market which doesn't seem attractive to a big pharma company. Prometheus, a small specialty pharmaceutical company based in San Diego, has built a unique commercialization platform from which it launches its specialty pharmaceuticals based on providing a continuum of care in gastroenterology. Prometheus offers other technologically sophisticated diagnostic services, all geared to help gastroenterologists deliver optimal therapies for inflammatory disease (which includes Crohn's disease and ulcerative colitis). Prometheus' then Chairman Michael Walsh is quoted by saying "ultimately, this technology is part of a strategy for differentiating the sales and commercialization process. We have a field sales force of 50, calling on the 4,500 high-prescribing, high patient volume physicians. Our people end up with 20–30 minutes in the clinician's office, instead of the 2 minutes that reps in other specialties spend near the sample cabinet." Prometheus' sales representatives lead a consultative sale that doctors welcome, because they help physicians provide a continuum of care from early detection and diagnosis to drug therapy. This commercialization strategy is rarely applied by big pharmaceutical companies which solely rely on mass-marketing of high volume drugs. As a result, Prometheus positioned itself as an attractive partner in this specialty niche.

Different cost/benefit perceptions, changes in the compound's initial indications, smaller and more specialized target markets as well as a strong entrepreneurial setting enabled the smaller partner companies to see a commercialization potential in substances that large pharmaceutical companies had decided to terminate. However, because of the distribution of resources and experience, it may be assumed that the out-licensing pharmaceutical companies should ideally be the ones that develop the drug and not the smaller partner firms. By contrast, the newly founded NRDOs are conducting the further development of the licensed products although they do not have a track record that proves their ability to successfully develop a compound. Without a track record, the pharmaceutical companies have only little information about the operational or financial capacities, the development efficiency, the project management skills, the financial discipline, the expertise in

regulatory affairs, the experiences in sales or marketing, or the manpower resources of a potential partner company. All these characteristics influence heavily the ability to successfully execute the compound's development. Subsequently, the pharmaceutical companies sell their licensing contracts to external partners even though they do not seem to be able to ascertain the licensees' ability to successfully execute the compound's development. As the licensees usually have more information about their own development capabilities than the licensors, out-licensing at established pharmaceutical companies is thus characterized by an asymmetric distribution of information regarding the capabilities of executing the licensed compound's further development. Especially if the partner companies are small and not publicly traded yet, they are not subject to rigid reporting regulations. This even increases the information asymmetry between the pharmaceutical companies and their out-licensing partners regarding the necessary development capabilities.

Out-licensing as a market with asymmetric information

Markets which are characterized by asymmetric information are defined as all markets where the characteristics of the commodities exchanged are not fully known to at least one of the parties to the transaction. Rothschild and Stiglitz (1976) were among the first scholars who discussed markets with asymmetric information showing that these markets might lead to a process of sorting or "adverse selection". The authors conducted their research by looking at competitive insurance markets, and they described how these markets would behave when the buyers of insurance policies differ by risk levels (i.e., the likelihood of them being involved in an accident) but the sellers of the insurance policies are unable to distinguish among these risks. They show that, if potential insurance buyers know their risk levels — and if they can keep that information from insurers — and if insurers are willing to offer any potentially profitable contracts, a process of sorting or self-selection might follow. As a consequence, the authors conclude that not only may a competitive equilibrium not exist, but when equilibria do exist, they may have strange properties. Rothschild and Stiglitz (1976) refer to this process of sorting as "adverse selection".

The market for out-licensing at large pharmaceutical companies shows many similarities to the insurance markets described by Rothschild and Stiglitz (1976). The pharmaceutical company is about to offer a licensing contract to a potential partner firm (equivalent to an insurance company offering an insurance contract to a potential buyer). However, as the licensees are usually small companies which do not have a track record of successful drug development, the pharmaceutical company cannot differentiate among the potential licensees based on their ability

to execute the compound's further development (equivalent to the different risk levels of the buyers of insurance contracts which are unknown to the insurance company). Especially if the pharmaceutical company sells the license to the partner firm as a straight license under a highly royalty-based contract, the nature of the out-licensing contract is similar to the nature of the insurance contracts as illustrated by Rothschild and Stiglitz (1976). If the partner company is now unable to execute the compound's development (equivalent to "the accident" in the insurance case), it is entitled to retain all intellectual property related to the license (equivalent to the "insurance pay-out after the accident") although it has paid only a comparatively small amount to the pharmaceutical company (equivalent to "the insurance premium").

An example of the case described above would be the Japanese pharmaceutical company Kyowa Hakko Kirin, a Top 50 pharma company in the world, and NovaCardia, a US-based, privately held company focusing on clinical-stage drug development that was founded in 2001. In 2003, Kyowa Hakko offered NovaCardia its adenosine A1 receptor antagonist KW-3902 which NovaCardia subsequently in-licensed. In return for rights outside Asia, NovaCardia paid only US$2.4 million in up-front fees. The deal included US$19.5 million in potential milestone payments and royalties on resulting sales. Given its young operating history, NovaCardia did not have any track record of successful drug development projects. In 2009, the development of KW-3902 was terminated because the results of a large clinical trial indicated that the drug is not superior to placebo for patients with acute heart failure. In this case the partner company NovaCardia was unable to execute the compound's development (equivalent to "the accident" in the insurance case), however, it retained the intellectual property related to the license (equivalent to the "insurance pay-out after the accident") although it has paid only a comparatively small amount to Kyowa Hakko (equivalent to "the insurance premium").

Due to the similarities between the insurance market and the out-licensing market, transferring the theory of adverse selection to the case of out-licensing allows for the utilization of the theory's insights in order to deduce recommendations for locating equilibria in out-licensing markets. For a detailed explanation of the applicability of the theory of adverse selection to the case of out-licensing, refer to Table 2.

Adverse Selection in the Out-Licensing Market

When applying the theory of adverse selection to the case of out-licensing, most of the argumentation will be made by the analysis of a simple out-licensing example

Table 2. Applicability of the theory of adverse selection to the case of out-licensing.

Assumption of the theory of adverse selection	Denotation	Explanation of the theory's applicability to the case of out-licensing
There are only two kinds of participants in the out-licensing market.	1. licensees who buy licensing contracts 2. licensors who sell licensing contracts	Licensing deals in the pharmaceutical industry are usually closed directly between the licensor and the licensee. It can reasonably be assumed that no third party intervenes in the deal.
No trade constraints of the licensing contracts.	The out-licensing market allows free trade of the licensing contracts (the α's)	Licensing contracts are generally free of any trade constraints. Only generally accepted rules, such as anti-trust regulations, apply.
The market begins with a single policy offered.	If providers of a good cannot distinguish well among risk levels, the premium for the policy will be approximately "community rated" (i.e., it will be similar for all potential buyers).	Each licensing contract in pharmaceutical R&D is individually negotiated between the licensor and licensee. Thus, it can reasonably be assumed that the market might begin trading the licensing contracts with just one single policy offered.
The partner firms (licensees) are risk-averse.	The second derivation of their utility function is negative ($U'' < 0$).	While the licensees are taking over the risks of the compound's further development, it can be assumed that they are rather risk-taking than risk-averse. This becomes particularly eminent as most licensees are significantly venture capital funded which is a strong sign for a higher risk exposure of the firms' business. However, the risk-aversion in the context of this model does not relate to the licensees' business model but refers to the licensees' willingness to achieve their projected revenues W (a closer explanation of this argument is provided in chapter "adverse selection in the out-licensing market"). As all licensees want to avoid failing to achieve their projected revenues, it is reasonable to assume that they are risk-averse.

Table 2. (*Continued*)

Assumption of the theory of adverse selection	Denotation	Explanation of the theory's applicability to the case of out-licensing
The partner firms (licensees) are identical in all respects.	The licensees all try to avoid that their projected revenues do not meet expectations.	General business practice.
	In addition, the risk-aversion of all licensees is expected to be identical.	The licensees' level of risk-aversion is not affected by their differing probabilities of not being able to execute the compound's development.
The pharmaceutical companies (licensors) are risk-neutral.	The licensors are concerned only with expected profits.	Commonly applied assumption in business practice.
The return from a licensing contract is a random variable.		Commonly applied assumption in business practice.
Pharmaceutical companies are willing and able to sell any number of licensing contracts that they think will make an expected profit; and the market is competitive in a sense that there is free entry.	Together, these two assumptions guarantee that any contract that is demanded and that is expected to be profitable will be supplied. Free market entry and perfect competition will ensure that policies bought in competitive equilibrium make zero expected profits.	Due to the existence of several potential sellers (big pharmaceutical companies) and the surge in new companies that could serve as potential buyers (e.g., specialty pharma and/or NRDO companies), it can be assumed that the out-licensing market is competitive in a sense that there are no monopolistic or oligopolistic market structures in demand or supply.

Table 2. (*Continued*)

Assumption of the theory of adverse selection	Denotation	Explanation of the theory's applicability to the case of out-licensing
The partner firms know the probability that they are unable to execute a compound's development, while the pharma firms do not.	The pharmaceutical companies cannot discriminate among the potential buyers of their licenses on the basis of their characteristics.	Due to the high complexity in pharmaceutical R&D it might be difficult for a pharmaceutical firm to judge the partner's probability of not being able to execute certain development activities. This is particularly true if the partner firm is a small company that is not listed on the stock market and is therefore not subject to certain reporting rules. Without track record, pharmaceutical companies have only little information about the operational or financial capacities, the development efficiency, the project management skills, the financial discipline, the expertise in regulatory affairs, the experiences in sales or marketing, or the manpower resources of a potential partner firms. Therefore, the partner firm has more information about its own development capabilities. This assumption represents the basis of the underlying information asymmetry.
The partner firms (licensees) can buy only one licensing contract.	The pharmaceutical firm can determine both: price and quantity of the licensing contracts.	Each licensing contract typically involves a fairly long due diligence and negotiation process. Thus, it seems to be reasonable to assume that the pharmaceutical company has control over both the price and quantity of the licenses.

Table 2. (*Continued*)

Assumption of the theory of adverse selection	Denotation	Explanation of the theory's applicability to the case of out-licensing
Equilibrium in a competitive licensing market is a set of contracts such that, when customers choose contracts to maximize expected utility, (i) no contract in the equilibrium set makes negative expected profits, and (ii) there is no contract outside the equilibrium set that, if offered, will make a non-negative profit.	This definition of an equilibrium is comparable to the Cournot-Nash equilibrium.	The Cournot-Nash equilibrium applied to the case of out-licensing means that each pharmaceutical company assumes that the contracts its competitors offer are independent of its own actions. It can be reasonably assumed that this complies with general business practice.

describing the behavior of a comparatively small company that might become a potential buyer of a license ("the partner firm" or "licensee"), whereas the license is sold by an established pharmaceutical company ("the licensor").

Consider a partner company which projects its total revenues to be W. In order to meet its revenue projection, the firm has to come up with a sufficient number of new drug candidates that leave its R&D department and enter the market. Usually, the partner firm has only a limited number of R&D projects to reach the projected sales of W, especially if the partner company is a small firm. If the partner firm's R&D department is — for any reason — not able to deliver the required number of compounds because the company cannot successfully execute the development of some projects, the partner firm experiences a decline in projected revenues of d. This would leave the partner company with total revenues of $(W - d)$. However, the partner firm can 'insure' itself against this potential revenue decrease by purchasing a straight license from another company (in this case: the pharmaceutical company) under a highly royalty-based contract. Thereby, the partner firm only pays a small fraction of the entire price as an upfront payment immediately upon closing the deal (assumed to be α_1), and in return it will receive all of the intellectual property related to the license which is assumed to have the value $\acute{\alpha}_2$. The majority of the price is paid in terms of royalty revenues which only accrue if the partner firm successfully executes the compound's development and brings the drug to the market. This assumption is reasonable because of two reasons. Firstly, pharmaceutical companies normally out-license only compounds that they have already terminated. Therefore, they do not believe that these compounds have a high value any more, and they are more likely to sell them for low upfront payments. Particularly if the partner firm is a smaller firm, the upfront payments are limited due to the partner's financial constraints. Secondly, the pharmaceutical companies are afraid to out-license a compound which might turn out to become a blockbuster later on. Therefore, pharmaceutical companies typically prefer large revenue participation over upfront payments.

The partner firm is a small but highly specialized company. It focuses on some selected therapy areas. Due to its experiences and specialization in the selected areas, the partner firm is able to assess its own ability to execute the compound's further development without significant investments. Furthermore, many employees of the partner firm are former employees of the out-licensing pharmaceutical firm. This employment situation reduces also potential investments which could be necessary to assess own development capabilities. Thus, the partner firm's total revenues are not reduced by costs arising from gathering information about their own development capabilities.

Now assume that the partner company cannot successfully execute the licensed compound's development. This leaves the partner firm with the following situation.

It only pays the pharmaceutical company the comparatively low upfront payment α_1, and is allowed to retain all intellectual assets inherent to the license valued at $\acute{\alpha}_2$. The remaining and comparatively large royalty revenue payments to the pharmaceutical company which are still outstanding do not have to be paid by the partner company any more because the compound's development has failed. While this situation seems to be a bargain for the partner company because it acquired a license for a relatively low amount, it has to be considered that the value of the compound's intellectual property rights usually drops to a certain extent in case the compound's development fails. However, the intellectual property rights that the partner firm is allowed to retain might lead to additional synergies, such as learning-effects, spill-overs, process know-how or other forms of knowledge transfer to the partner company which have not been monetized in the upfront payment made to the pharmaceutical company. Especially if the partner firm is a small and young company, this additional inflow of intellectual capital might have a comparatively high value for the firm. In this argumentation, it is assumed that the value of these synergies — particularly for a small partner company — helps raise the value of the in-licensed product to approximately its initial value of $\acute{\alpha}_2$. Therefore, the partner firm's situation in this case would be $(W - d - \alpha_1 + \acute{\alpha}_2)$.

By contrast, if the partner company is able to execute the compound's development, the pharmaceutical company would most likely re-license the compound including its underlying intellectual property ($\acute{\alpha}_2$), as has been done by Novartis in 2002 after it had out-licensed the substance Aliskiren to Speedel in 1998. However, it is assumed that a fair licensing deal is usually structured in a way that the payments by the pharmaceutical company for re-licensing the compound will allow the partner company to compensate for the decline in projected revenues (d) as well as potentially occurring milestone payments that had to be made by the partner firm. This would leave the partner company with the situation $(W - \alpha_1)$. If the deal terms of the licensing agreement would allow the partner company to retain the license (or if the pharmaceutical company would not execute its re-licensing rights), the partner company would usually have to reimburse the pharmaceutical company with royalty revenues or milestone payments. As the scope of these payments towards the licensor typically relates to the advancements of the compound, they usually compensate for the value of $\acute{\alpha}_2$ which would leave the partner firm in the same position as if it had to return the intellectual assets of the compound to the pharmaceutical company.

Figure 2 summarizes the partner firm's situation for the different states 'can execute the compound's development' and 'cannot execute the compound's development' for both cases: without having acquired a license and with having acquired a straight license under a highly royalty-based contract. Reflecting that the term $\alpha_2 = \acute{\alpha}_2 - \alpha_1$ describes the value of the license for the partner firm, the

	Partner firm can execute	Partner firm cannot execute
without license	W	$W - d$
with license*	$W - \alpha_1$	$W - d - \alpha_1 + \alpha_2$ = $W - d + \alpha_2$

* assumes a straight license under a highly royalty-based licensing contract.

Fig. 2. The partner firm's projected revenues in the case of out-licensing.
*assumes a straight license under a highly royalty-based licensing contract.

vector $\alpha = (\alpha_1, \alpha_2)$ completely describes the licensing contract. Actual licensing contracts are more complicated but in the scope of this model, however, it is assumed that the vector $\alpha = (\alpha_1, \alpha_2)$ sufficiently describes the entire licensing contract (compare Rothschild and Stiglitz (1976: 630) for a more detailed explanation why the vector α can be used to portray the licensing contract).

On the out-licensing market, the licensing contracts (the α's) are now traded. To describe how the market works, it is necessary to describe the supply and demand functions of the participants in the market.

Demand for licensing contracts

Determining a partner firm's demand for licensing contracts is straightforward. The partner firm purchases a license to modify its pattern of projected revenues across different states of nature. Assume that W_1 denotes the projected revenues if the partner successfully executed the development, and W_2 describes the projected revenues if it could not execute. The expected utility theorem states that under relatively mild assumptions the partner firm's preferences for revenues in these two states of nature are described by a function of the form,

$$\hat{Y}(p, W_1, W_2) = (1 - p)U(W_1) + pU(W_2) \tag{1}$$

where $U()$ represents the utility of projected revenues and p the probability that the partner firm cannot execute. The licensee's demand for licensing contracts may be derived from (1). A contract α is worth $Y(p, \alpha) = \hat{Y}(p, W - \alpha_1, W - d + \alpha_2)$. From all the contracts that are offered to the partner firm, the partner chooses the one that maximizes $Y(p, \alpha)$. As the partner firm always has the option of buying no license, the partner will purchase a license α only if $Y(p, \alpha) > Y(p, 0) = \hat{Y}(p, W, W - d)$. Reflecting the case of licensing in the pharmaceutical industry, it is

assumed that all licensees are identical in all respects trying to avoid that their projected revenues do not meet expectations which means that they are generally risk-averse (i.e., the second derivation of their utility function is negative, $U''< 0$); thus $Y(p, \alpha)$ is a quasi-concave curve.

Supply of licensing contracts

In contrast to explaining the demand for licensing contracts, it is less straightforward to describe how pharmaceutical companies decide which licensing contracts they should offer and to which potential partners. Thereby, it should be reflected that the return from a licensing contract is a random variable and it is assumed that the pharmaceutical companies are risk-neutral. After the pharmaceutical company has decided on the general strategy to sell its research results via licenses to external partner firms, they are concerned only with expected profits, so that the licensing contract α (when sold to a licensee who has a probability that it cannot execute the development of p), is worth

$$\pi(p, \alpha) = (1 - p)\alpha_1 - p\alpha_2 = \alpha_1 - p(\alpha_1 + \alpha_2). \tag{2}$$

Even if the pharmaceutical companies are not expected to be profit maximizers, on a well-organized competitive market they are likely to behave as if they maximized Eq. (2). A more detailed derivation is available in Rothschild and Stiglitz (1976, 631). Pharmaceutical companies have financial resources such that they are willing and able to sell any number of licensing contracts that they think will make an expected profit. The market is competitive in a sense that there is free entry. Together, these assumptions guarantee that any contract that is demanded and that is expected to be profitable will be supplied.

Probability that the licensee cannot execute

Both formulas (1) and (2) rely on the parameter p which describes the probability of the partner firm not being able to execute the license's further development. As mentioned earlier, the theory of adverse selection implies that the partner firms know the probability that they are unable to execute the development tasks, while the pharmaceutical companies do not know the parameter p. This assumption represents the basic requirement of the underlying information asymmetry. As the partner firms are identical in all respects and try to avoid that their revenues do not meet expectations, the result of this assumption is that the pharmaceutical companies cannot discriminate among the potential buyers of their licenses on the basis of their characteristics.

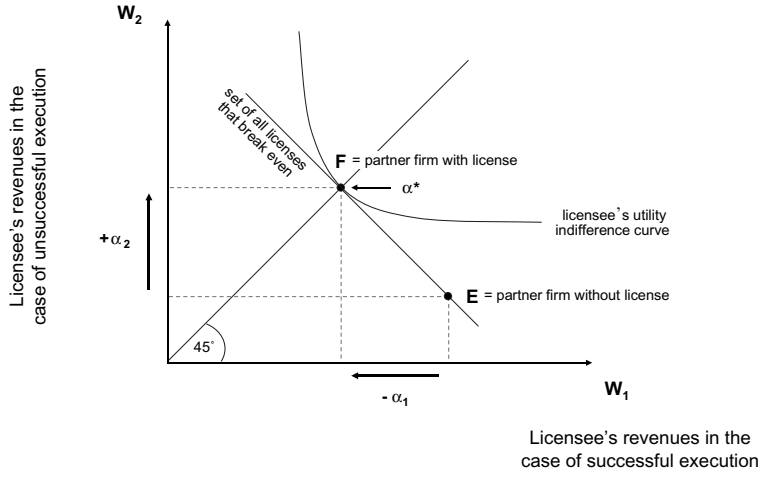
However, a pharmaceutical company may use its partner's market behavior to draw some conclusions about their probabilities of not being able to execute. Other

things being equal, those partners with high probabilities of not being able to execute will demand licensing contracts with a higher coverage than those who are less prone to fail on the respective development tasks. Although possibly accurate, this is not a profitable way of finding out about buyer characteristics. Pharmaceutical companies want to know their license's characteristics upfront in order to decide on what terms they should offer to let them buy licenses. Information that accrues after the deal has closed may be used only for follow-on licensing deals but has no value for the current licensing deal. However, it is often possible to force the partner firms to make market choices in such a way that they both reveal their characteristics and make the choices the pharmaceutical firm would have wanted them to make had their characteristics been publicly known (this process is also known as the mechanism of self-selection). In order to force the partner firms to make market choices, the pharmaceutical company has to have at least some information about the potential partner's preferences to get involved in the licensing deal (i.e., their need to in-license a compound from the pharmaceutical company). The pool of potential partner companies that might feel the desire to in-license a compound is generally very large, given the challenges in R&D productivity as described in the introduction. The parameters that distinguish the potential partners among each other are usually related to the constitution of their R&D departments which in turn includes information about their resources, competencies and capabilities that enable them to successfully conduct the compound's development. Since smaller companies cannot serve all therapy areas due to resource constraints, they are consequently specialized on certain areas. The attractiveness of the therapy areas that also indicates information on resources, competencies and capabilities subsequently leads to a self-selection of the partner firms.

Finding an equilibrium in the out-licensing market

In order to find an equilibrium in the out-licensing market, demand and supply have to meet reflecting the side condition of the parameter p. Finding an equilibrium can be illustrated by a mainly graphical procedure (see Fig. 3). In Fig. 3, the horizontal and vertical axes represent the partner firms' projected revenues for the two states: can execute, and cannot execute. The point E with the coordinates $(\hat{W}_1, \hat{W}_2)$ is the typical state of a partner firm which did not acquire a license. Indifference curves are level sets of the function of Eq. (1). Purchasing the licensing contract $\alpha = (\alpha_1, \alpha_2)$ moves the partner firm from E to the point F $(\hat{W}_1 - \alpha_1, \hat{W}_2 + \alpha_2)$. Free entry and perfect competition will ensure that policies bought in competitive equilibrium make zero expected profits, so that if α is purchased,

$$\alpha_1(1-p) - \alpha_2 p = 0 \tag{3}$$



* equilibrium license (it maximizes the licensee's expected utility and breaks even)

Fig. 3. Equilibrium in the out-licensing market.

The set of all policies that break even is given analytically by Eq. (3) and graphically by the line *EF* in Fig. 3 which is sometimes referred to as the 'fair-odds line'. The equilibrium policy α* maximizes the partner firm's (expected) utility and just breaks even. Purchasing α* locates the licensee at the tangency of the indifference curve with the fair-odds line. The license α* also satisfies the two conditions of the equilibrium: (i) it breaks even, and (ii) selling any contract preferred to it will bring pharmaceutical companies expected losses.

As licensees are risk-averse, the point α* is located at the intersection of the 45°-line (representing equal revenues in both states 'can execute' and 'cannot execute') and the fair-odds line. In equilibrium, each licensee buys complete licensing contracts at actuarial odds. In order to see this, it can be observed that the slope of the fair-odds line is equal to the ratio of the probability of being able to execute the compound's development to the probability of not being able to execute $((1-p)/p)$, while the slope of the indifference curve (the marginal rate of substitution between revenues in the case that the partner could execute to revenues in the case that the partner could not execute) is $[U'(W_1)(1-p)]/[U'(W_2)p]$, which, when revenues in the two states are equal, is $((1-p)/p)$, and therefore independent of U.

If the partner firms now differ in risk-levels (i.e., they have different probabilities p of not being able to execute), Fig. 3 has to be adjusted in a way that there are different utility indifference curves for each licensee. For licensees with a higher probability of not being able to execute, the indifference curve will shift to

the upper-left corner in Fig. 3 compared to the initial situation. The initial situation implies that licensees are identical regarding the parameter p. Licenses sold under this assumption are therefore considered to be "community rated". This has the reason that high-risk licensees are usually more willing to buy a licensing contract with a larger coverage in order to compensate for their higher exposure to the risk of not being able to execute the compound's development. In an efficient licensing market, the high-risk licensees (i.e., the licensees with a higher p) have to pay a higher price for these licenses. As a result of receiving a higher coverage $\acute{\alpha}_2$ and paying a higher price (it is assumed that all price elements increase pro-rata, and therefore also the upfront payment α_1), their utility indifference curve moves to the left and upwards in the coordinate system. The indifference curve of licensees with a lower probability p will subsequently be located in the lower right hand corner compared to the "community rated" situation. The slopes of the indifference curves, however, remain the same as the licensees' risk-aversion is assumed to remain unchanged for both scenarios.

Now, pharmaceutical R&D managers (after they have made the decision to out-license a certain product) have to structure the licensing deal in a way that they will reach an equilibrium in the out-licensing market. Reflecting that an equilibrium can only exist at the intersection of the licensee's utility curve with the fair-odds line which represents the set of licenses that break even (the line EF), the pharmaceutical company has to structure the licensing arrangement in a way that the license is placed exactly at this intersection. Subsequently, obtaining an equilibrium in the out-licensing market depends on the features of the licensing-contract (α_1 and α_2, whereas $\alpha_2 = \acute{\alpha}_2 - \alpha_1$) as well as the partner firm's probability of not being able to execute the compound's development (p). Thus, there are in total three parameters which have a direct impact on finding an equilibrium in the out-licensing market:

- $\acute{\alpha}_2$ Value of the intellectual property rights that are subject to the license.
- α_1 Upfront payment to be paid by the licensee for obtaining the license.
- p Probability that the licensee will not be able to execute the compound's development.

Based on these parameters, the following managerial dimensions emerge which can proactively be managed by the pharmaceutical company in order to reach an equilibrium in the out-licensing market:

- *Product coverage*: structuring the "right" scope of the license by aggregating intellectual property rights to bundles;
- *Price setting*: determining the "right" price structure for the license;
- *Performance presumption*: assuming the "right" probability that the licensee can execute the compound's development.

In other words, these parameters answer the question: "*what* should we out-license for *how much* and to *whom*?" Pharmaceutical R&D managers now only need to know how they should adjust these managerial dimensions in order to find the equilibrium.

Managerial Recommendations

The starting situation for deriving recommendations regarding the manageability of out-licensing collaborations shall be as follows. The pharmaceutical company has decided to out-license a respective product but does not know about the potential licensees' capability to execute the compound's development ("the asymmetric information"). In order to approximate a potential (temporary) equilibrium, the following discussion uses a "community rated" license as a starting point (as mentioned earlier, a "community rated" license is a license that will be similar for all potential buyers). Compared to the "community rated" license, the pharmaceutical company can make adjustments along the three dimensions product coverage, price setting and performance presumption. The explanation can be done analytically as well as graphically (see Fig. 4). In Fig. 4, no licensee has acquired a license yet and the potential licensee is thus located at point *E*. At the time when the licensee purchases the license $\alpha = (\alpha_1, \alpha_2)$ from the pharmaceutical company, the licensee's position shifts from point *E* to *F*. Because the

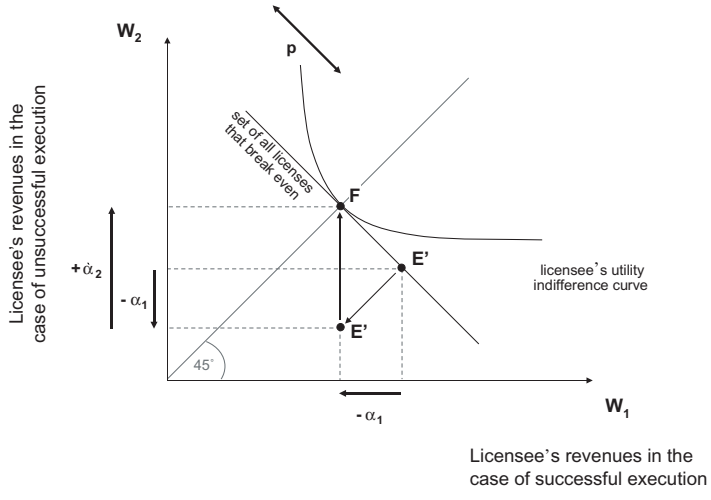


Fig. 4. Parameters for finding an equilibrium in the out-licensing market.
α_1: size of the upfront payment; $\acute{\alpha}_2$: license's coverage; p: risk exposure of the licensee.

licensing contract consists of two parts α_1 and α_2 (whereas $\alpha_2 = \acute{\alpha}_2 - \alpha_1$), this transition is graphically illustrated in the figure as a two-step process $E \rightarrow E'$, and $E' \rightarrow F$. The first transition $E \rightarrow E'$ describes the impact of the license's price in terms of the upfront payment α_1 on the transition process. As the upfront payment α_1 is plotted on both axes as an amount that the licensee has to pay, this transition moves the licensee's state parallel to the bisecting line towards the origin. The second transition $E' \rightarrow F$ describes the impact of the license's coverage $\acute{\alpha}_2$ on the transition process. As the license's coverage $\acute{\alpha}_2$ represents the amount of intellectual property rights that the licensee is expected to receive, this transition moves the licensee's state straight upwards.

As it is still assumed that the licensee is risk-averse, this argumentation locates the licensee's new state F after having purchased the licensing contract, on the 45°-line. In order for an equilibrium to exist, the new state F must as well be located at the tangency of the fair-odds line with the licensee's utility indifference curve, whose shape and location are characterized by the partner firm's probability of not being able to execute the compound's development which is described by the parameter p. At the point where the licensee's new state F and the licensee's utility indifference curve meet, the equilibrium emerges. The changes by the pharmaceutical company regarding the product coverage, price setting or performance presumption cover increasing or reducing the respective parameters. The managerial impact of these changes is discussed in the following paragraphs.

Product coverage

The product coverage describes all aspects which characterize the scope of the commodity exchanged during the out-licensing agreement (i.e., the bundle of intellectual property rights that constitutes the license). The patents exchanged in a licensing deal generally cover certain biotechnological processes (platform-technologies), exclusive know-how, or compounds (i.e., new molecular entities). The licenses then mostly comprise databases or software modules, which contain the research results of the company that is selling the license. The stages of the licensing deals usually vary. While Eli Lilly out-licenses any compound, no matter at which phase of the pre-clinical or clinical stages of the R&D process, Bayer considers the grant of the IND (Investigational New Drug) approval to be an important milestone before a substance can be effectively licensed out. The IND approval is filed with the FDA prior to the clinical trials of a new drug (i.e., before the substance enters the human body and after it has completed the pre-clinical studies). It already gives a full and comprehensive description of the new drug. The IND is followed by the NDA (New Drug Application). As development is responsible for filing INDs at Bayer, most out-licensing agreements at

Bayer are done by the development department which means that the majority of substances are out-licensed at relatively late stages of the R&D process. However, Bayer also recently started to out-license early-stage substances of its research department. Novartis out-licensed the substance Aliskiren before the compound was about to enter clinical phase I. Schering out-licensed Atamestane after the IND approval and Roche out-licensed Bosentan right before clinical phase II. The commercial scope of a compound generally increases in later stages of the R&D process. However, the pharmaceutical company has to bear significant investments and related risks to bring that compound to a later stage in the R&D process. Besides the stage of the compound in the R&D process, the compound's indication is another important parameter. In this context, it should be considered that one compound can have multiple indications. A good example that illustrates the breadth of a single substance's application is the case of thalidomide which — at one point in time — became known for tragic reasons (compare Thiel, 2004). The German pharmaceutical company Chemie Grünenthal initially studied the substance as a potential anticonvulsant, and later found that thalidomide acted as an effective sedative. Thalidomide hit the West German market in 1957 under the name Contergan, marketed as a sleep aid and eventually as a treatment for morning sickness. In 1961, a sudden spike in infant phocomelia — malformations of the limbs, hands, and feet — caused Grünenthal to stop the production of Contergan. In 1965, however, an Israeli doctor prescribed it as a sedative to a patient with leprosy, hoping to alleviate some of the discomfort caused by a painful skin condition known as erythema nodosum leprosum (ENL). Instead, the drug appeared to actually help the symptoms. Thus, thalidomide was still quietly used for decades to help this tiny patient population. In 1991, a study at Rockefeller University in New York showed that thalidomide selectively inhibits tumor necrosis factor-alpha, giving it a potential role as an anti-inflammatory. Although thalidomide itself had long been off patent, the US-based company Celgene licensed the new patents from Rockefeller University in 1992. In subsequent years, evidence indicated that thalidomide even helped AIDS-related complications such as cachexia (wasting syndrome). Faced with "buyer clubs" of AIDS patients importing thalidomide from South American and other manufacturers, the FDA decided to work with Celgene to get the drug approved and manufactured in the US, where prescribing and distribution could be better controlled. After various clinical studies, the FDA approved thalidomide for ENL in 1998. As better AIDS drugs made cachexia a less frequent complaint among patients with HIV, however, the market for thalidomide once again changed. After a study in 1999 showed an impressive positive response rate in people with multiple myeloma, the drug became widely used to treat this rare blood cancer. Sold under the brand name Thalomid, thalidomide reached sales of

around US$290 million in 2004 in the US. The specialty pharma company Pharmion licensed most non-US rights from Celgene and is now selling the respective drug. The total sales of thalidomide in 2004 are remarkably high when it is considered that the substance's indication had to change several times before it reached today's status, and the discovery of the initial drug was more than 50 years ago. As illustrated by the case of thalidomide, renewing a compound's indication (also called repurposing, reprofiling or redirecting) might increase the commercialization potential of a drug candidate and therefore has a strong importance for defining the product coverage in an out-licensing deal.

Giving a compound a new spin might also affect its delivery system or formulation chemistries which improve bioavailability or reduce side-effects. Further parameters which describe the intellectual property bundle include the compound's efficacy, safety, compliance or administration. Oftentimes, these parameters interdepend with each other. Drug candidates offering only marginal improvements in efficacy in a certain target market may need to enhance their commercial prospects by other differentiating aspects, such as a better compliance.

In summary, the empirical investigation reveals that the most important parameters constituting the scope and coverage of the license include:

- Position (stage) of the substance in the R&D process;
- Indication(s) of the substance;
- Formulation of the underlying chemical entity;
- Efficacy;
- Safety;
- Side effects;
- Delivery system;
- Compliance;
- Administration;
- Dosage;
- Changes in regulation or managed care;
- Possible spill-over effects.

As changes in a drug's profile (i.e., the product coverage) can create multiple medical opportunities, a pharmaceutical company can either increase or reduce the coverage of the bundle of intellectual property rights that it is about to out-license compared to the "community rated" situation. It simply has to extend/scale down existing intellectual property rights or add/subtract additional rights to adjust the product coverage. As the product coverage $\acute{\alpha}_2$ is plotted on the vertical axis, changes in this parameter move (ceteris paribus) the equilibrium straight upwards or downwards respectively. As any change in this parameter represents a move away from the

initial equilibrium, the pharmaceutical company has to make adjustments to the other two parameters (price setting and performance presumption) as well in order to reach an equilibrium again. The necessary managerial actions can be derived by Eq. (3) which constitutes the requirement for the equilibrium. An algebraic transformation of Eq. (3) leads to the following relation between the three parameters and provides the basis for deriving managerial actions:

$$\acute{\alpha}_2 = \alpha_1 / p \tag{4}$$

In order to find an equilibrium, the pharmaceutical company can only change the product coverage ($\acute{\alpha}_2$) if it simultaneously adjusts the other two parameters as well. To fulfill the equilibrium condition, the following economically useful actions can be taken.

If management *increases the product coverage*, it also has to.

- raise the upfront payment and target the same licensee or a lower-risk licensee (the upfront payment α_1 goes up and the licensee's probability of not being able to execute p remains constant or decreases);
- raise the upfront payment and target a higher-risk licensee (however, the upfront payment α_1 has to grow proportionally more than the licensee's probability of not being able to execute p);

If management *reduces the product coverage*, it also has to.

- lower the upfront payment and target the same licensee or a higher-risk licensee (the upfront payment α_1 goes down and the licensee's probability of not being able to execute p remains constant or increases);
- lower the upfront payment and target a lower-risk licensee (however, the upfront payment α_1 has to decrease proportionally more than the license's probability of not being able to execute p);
- leave the upfront payment constant and target a higher-risk licensee (the upfront payment α_1 remains constant and the license's probability of not being able to execute p goes up);
- raise the upfront payment and target a higher-risk licensee (however, the licensee's probability of not being able to execute p has to increase proportionally more than the upfront payment α_1).

When modifying the product coverage, pharmaceutical R&D management should also keep in mind the following caveats. On the one hand, pharmaceutical R&D managers might be tempted to provide a rather generous offer (i.e., offering a product that has a higher coverage than the "community rated" offer) in order to increase the probability that the partner company will be successful in executing

the compound's development. On the other hand, the pharmaceutical company might be tempted to provide a fairly humble offer (i.e., offering a product that has a lower coverage than the "community rated" offer) because it could be exposed to giving up too much intellectual assets. While the more generous offer will increase the chances of finding a partner, the less generous offer will reduce the downside risk of the collaboration but might also impede the closing of the out-licensing deal.

Price setting

While the parameter α_1 describes the upfront payment that the licensee has to pay to the pharmaceutical company immediately after closing the deal, the price setting describes all aspects which relate to the entire price of the license. This could include payment elements which go beyond the upfront payment α_1 and are considered to have an indirect influence on the size of the upfront payment. The compensation structure of today's licensing deals is highly complex. When GlaxoSmithKline licensed a couple of Phase II products from Exelixis in 2002, the deal was structured into an upfront payment of US$30 million, milestone payments of up to US$350 million, additional R&D funding of US$90 million, an equity investment of US$14 million and a loan facility of US$85 million. When Aventis licensed the Phase III compound Genasense from Genta, the overall deal included an upfront payment of US$10 million, milestone payments of up to US$280 million, an equity investment of US$72 million and a loan facility of US$75 million. Eli Lilly (licensing the Phase III product AC 2993 from Amylin) and Pfizer (licensing the Phase III product Indipplon from Nerocrine) reported similarly complex licensing deals in 2002.

One of the most important parameters with a strong impact on the price setting in the out-licensing deal includes the re-licensing rights, particularly the call-back options. In case a call-back option is included into the licensing contract, the value of the license typically experiences a substantial discount from the perspective of the partner firm because the licensee will not be able to fully utilize the outcome of its R&D efforts. This might have a strong impact on the partner firm's willingness to pay upfront payments.

Besides re-licensing rights, royalty revenues represent another important price parameter. By agreeing on royalty revenue payments, the licensor might expect future cash-flows from the drug's market launch and is usually willing to sell the license for a lower upfront payment α_1. If the product does not reach the market, no royalties will incur. Therefore, pharmaceutical companies could be tempted to demand higher upfront payments in order to make up for this risk.

Other compensation elements include milestone payments. Milestone payments have to be made after specifically defined goals throughout the development process have been reached. While the licensee is consequently able to defer the payments to later stages of the development process, the pharmaceutical company would prefer to receive a higher proportion of upfront versus milestone payments.

Another group of parameters that influence the price setting includes additional resources which the pharmaceutical company might contribute to the collaboration but which are not directly monetized in the deal terms. This could include co-promotion/co-marketing arrangements or manufacturing agreements. As the pharmaceutical company is providing these resources to the collaboration, the price for the licensee will rise because the pharmaceutical company expects to be compensated for these resources.

In summary, the most common payment elements that affect the size of the upfront payment in licensing deals usually include the following:

- Call-back options;
- Royalty revenues;
- Milestone payments;
- Co-promotion/co-marketing arrangements;
- Manufacturing agreements;
- Non-compete clauses;
- Regional split-of-rights;
- Sharing of R&D costs;
- Loan facilities;
- Equity stakes.

The configuration of all price parameters defines the price setting. Compared to the "community rated" license, the pharmaceutical company can now either increase or reduce the amount of the upfront payment. These modifications could include adding/dropping call-back options or lowering the relative contribution of royalty revenues or milestone payments. As α_1 is plotted on both axes W_1 and W_2, increasing and/or reducing the upfront payment moves the equilibrium along the bisecting line in Fig. 4 either towards or away from the origin. As this change represents a move away from the initial equilibrium, the pharmaceutical company has to take some managerial actions in order to reach an equilibrium again. Derived from Eq. (3), the necessary managerial actions can be deduced from the following relation:

$$\alpha_1 = \acute{\alpha}_2 * p \tag{5}$$

If management *increases the upfront payment*, it also has to:

- raise the product coverage and target the same licensee or a higher-risk licensee (the product coverage $\acute{\alpha}_2$ goes up and the licensee's probability of not being able to execute p goes up as well or remains constant);
- raise the product coverage and target a lower-risk licensee (however, the product coverage $\acute{\alpha}_2$ has to grow proportionally more than the licensee's probability of not being able to execute p decreases);
- leave the product coverage constant and target a higher-risk licensee (the product coverage $\acute{\alpha}_2$ remains constant and the licensee's probability of not being able to execute p goes up);
- lower the product coverage and target a higher-risk licensee (however, the licensee's probability of not being able to execute p has to increase proportionally more than the product coverage $\acute{\alpha}_2$ decreases).

If management *reduces the upfront payment*, it also has to:

- lower the product coverage and target the same licensee or a lower-risk licensee (the product coverage $\acute{\alpha}_2$ goes down and the licensee's probability of not being able to execute p goes down as well or remains constant);
- lower the product coverage and target a higher-risk licensee (however, the product coverage $\acute{\alpha}_2$ has to decrease proportionally more than the licensee's probability of not being able to execute p increases);

However, modifications in the price setting also bear some caveats which should be considered by pharmaceutical R&D management. The upfront payment represents only the first payment of the entire collaboration agreement. Most of the remaining payments are tied to the compound's successful development. If the partner firm is unable to successfully execute the compound's development, the pharmaceutical company will end up with only a small fraction of the overall payments. Only if the partner firm can execute the compound's development, the pharmaceutical company could expect additional payments or might be tempted to exercise the call-back option. Therefore, the payments other than the upfront payment are all exposed to the risk that the partner cannot execute. An increase in upfront payments (compared to the "community rated" terms) would result in a more immediate cash flow. However, the partner firm might most likely not be willing to get involved in the licensing deal at these terms. In addition, the pharmaceutical company would have to give up some part of the potential to receive large royalty revenues in case the drug turns out to be a blockbuster. By contrast, a reduction in upfront payments (compared to the "community rated" terms) would most likely increase the willingness of the partner to accept the deal,

but would expose the pharmaceutical company to the risk to receive only a small fraction of the license's entire value if the partner firm cannot successfully execute the compound's development.

Performance presumption

When out-licensing a certain bundle of intellectual property rights, pharmaceutical R&D management is not only able to decide about the product coverage and price setting but also about the risk/benefit profile of the out-licensing deal. Assuming perfect competition in the out-licensing market, the pharmaceutical company has generally the choice to enter either into a collaboration which is more likely to succeed but would generate lower returns for the pharmaceutical company or a collaboration which is less likely to succeed but would generate higher returns for the pharmaceutical company if the collaboration turns out to be successful. An example of the first alternative is the following out-licensing deal of Altana Pharma. In 2001, Altana Pharma (then known as Byk Gulden) was developing the substance Alvesco®, a corticosteroid which delivers a new approach to treat asthma. As Altana Pharma didn't possess the appropriate presence in the US market to introduce the product, the company out-licensed the development rights of Alvesco® to Aventis Pharmaceuticals (the US subsidiary of Aventis) to ensure a proper market introduction of the drug in the US market. In 2004, Aventis received market approval for Alvesco® in the US and has started since then to market the product. Aventis will compensate Altana Pharma in return for providing the substance by conveying a certain percentage of the drug's revenues incurred in the US. Altana Pharma recognized that Aventis was much more likely to successfully introduce Alvesco® in the US market. Therefore, Altana gave up the prospects of retaining 100% of Alvesco's® US revenues in return for raising the substance's probability of success in the US market.

While presuming a potential partner's ability to successfully develop a compound, there are several parameters that might help a pharmaceutical company get an idea of the probability that the collaboration turns out to be successful. One of the most relevant parameters that determine the partner's likelihood to conduct the required development tasks includes the firm's experience with the R&D tasks that have to be completed. If the partner has already conducted several similar projects it will be more likely that the out-licensing collaboration might become a success than if the partner firm has never done any related job.

Another important parameter includes the expertise of the people working in the partner's R&D department. If the partner firm's employees are highly skilled in the respective therapy areas or technology platforms, the collaboration has a higher probability to be successful. Besides expertise, employees' commitment towards

the project as well as teamworking and management skills are important parameters. In general, human resources and the company's infrastructure represent other factors that describe a company's ability to successfully develop a new drug candidate. Moreover, networking and breaking down barriers between corporations are considered to be further important success factor which are related to the partner firm's ability to bring a compound successfully through the development stages.

Last but not least, the constitution of the partner's R&D portfolio also allows drawing conclusions about the presumed likelihood of a collaboration's success. Parameters related to the R&D portfolio usually include the number and stages of R&D projects under development, the therapy areas served, the number and types of technology platforms applied, the number of issued and pending patents, the scope of conducted activities that describe which R&D stages/phase are covered, or the depth of activities highlighting the ratio of the firm's own activities vs. outsourced activities. If a partner deploys a rather large portfolio, applies several technology platforms and has already secured several patents in the respective area of development, this is usually a strong indicator for the company's ability to execute a compound's development.

Results of our empirical investigation show that these parameters usually relate to the partner's development capabilities and include the following aspects:

- Experience with respective R&D tasks;
- Strength of presence in target market;
- Technology familiarity;
- Clinical capabilities;
- Commitment;
- Management skills;
- Human resources;
- Infrastructure;
- Networking;
- Constitution of R&D portfolio (number and stages of the R&D project, therapy areas served, technology platforms applied, patents).

The specifications of all these parameters allow the pharmaceutical company to draw conclusions about the potential partners' likelihood of being able to execute the development of the licensed compound which allows for presuming the performance potential of the collaboration. While the firms which are more likely able to execute are usually larger and more established firms, the firms that are less likely are usually rather small and newly incepted companies that do not have a solid track record of successful development programs yet. Compared to the "community rated" situation, the pharmaceutical company can now either target a

Table 3. Summary of managerial actions to approximate an equilibrium in out-licensing markets with asymmetric information.

Change in the product coverage (moves the equilibrium straight upwards or downwards)	
Increasing the product coverage requires one of the following actions:	***Reducing the product coverage*** requires one of the following actions:
Raising upfront payment **and** targeting same licensee or lower-risk licensee	Lowering upfront payment **and** targeting same licensee or higher-risk licensee
Raising upfront payment **and** targeting higher-risk licensee (upfront payment has to grow proportionally more than licensee's probability of not being able to execute)	Lowering upfront payment **and** targeting lower-risk licensee (upfront payment has to decrease proportionally more than licensee's probability of not being able to execute)
	Leaving upfront payment constant **and** targeting higher-risk licensee
	Raising upfront payment **and** targeting higher-risk licensee (licensee's probability of not being able to execute has to increase proportionally more than upfront payment)
Change in the price setting (moves the equilibrium along the 45°-line)	
Increasing the upfront payment requires one of the following actions:	***Reducing the upfront payment*** requires one of the following actions:
Raising product coverage **and** targeting same licensee or higher-risk licensee	Lowering product coverage **and** targeting same licensee or lower-risk licensee
Raising product coverage **and** targeting lower-risk licensee (product coverage has to grow proportionally more than licensee's probability of not being able to execute decreases)	Lowering product coverage **and** targeting higher-risk licensee (product coverage has to decrease proportionally more than licensee's probability of not being able to execute increases)
Leaving product coverage constant **and** targeting higher-risk licensee	
Lowering product coverage **and** targeting higher-risk licensee (licensee's probability of not being able to execute has to increase proportionally more than product coverage decreases)	
Change in the performance presumption (moves the equilibrium in the upper left-hand corner or lower right-hand corner)	
Targeting a high-risk licensee requires one of the following actions:	***Targeting a low-risk licensee*** requires one of the following actions:
Raising upfront payment **and** lowering the product coverage or leaving product coverage constant	No economically useful adjustments of product coverage and prices setting.

Table 3. (*Continued*)

Raising upfront payment **and** raising product coverage (upfront payment has to grow proportionally more than product coverage)
Leaving upfront payment constant **and** lowering product coverage
Lowering upfront payment **and** lowering product coverage (product coverage has to decrease proportionally more than upfront payment)

partner who has a higher or lower probability of not being able to execute. As deduced in the chapter "adverse selection in the out-licensing market", partner companies with a higher p are located in the upper left-hand corner compared to the "community rated" situation, whereas partners with a lower p are found in the lower right-hand corner. As targeting partners with different $p's$ represents a shift away from the equilibrium, an algebraic transformation of Eq. (3) exhibits the managerial actions to reach an equilibrium again:

$$p = \alpha_1/\acute{\alpha}_2 \tag{6}$$

If management *targets a high-risk licensee*, it also has to:

- raise the upfront payment and lower the product coverage or leave the product coverage constant (the upfront payment α_1 goes up and the product coverage $\acute{\alpha}_2$ remains constant or goes down);
- raise the upfront payment and raise the product coverage (however, the upfront payment α_1 has to grow proportionally more than the product coverage $\acute{\alpha}_2$);
- leave the upfront payment constant and lower the product coverage (the upfront payment α_1 remains unchanged and the product coverage $\acute{\alpha}_2$ goes down);
- lower the upfront payment and lower the product coverage (however, the product coverage $\acute{\alpha}_2$ has to decrease proportionally more than the upfront payment α_1).

If management *targets a low-risk licensee*, there are no economically useful adjustments of the product coverage and price setting to make. From an economic perspective, it can easily be argued that all activities related to targeting a firm with a lower probability of not being able to execute are counterproductive because the product coverage always has to be raised more in relative terms than the upfront payment.

As illustrated above, an equilibrium in the out-licensing market can be approached by making adjustments to the three managerial dimensions product coverage, price setting and performance presumption. Table 3 summarizes the managerial recommendations for making adjustments in the respective parameters.

Conclusions

This paper has analyzed out-licensing at established pharmaceutical companies as a means to improve R&D productivity by commercializing terminated R&D results. Pharmaceutical companies prefer to sign out-licensing deals with young, small and highly specialized partner companies. While out-licensing deals are usually done because of downstream concerns, this observation reverses the traditional logic of out-licensing. The companies that own all necessary assets to develop the licensed products sell the license to firms which have — at the time of deal closure — no track record that proves their ability to successfully develop the licensed compounds. Because the pharmaceutical companies can not distinguish between these small partner companies based on their development capabilities, the out-licensing deals are characterized by a high degree of asymmetric information. The application of the theory of adverse selection to the case of out-licensing allows deriving managerial recommendations for finding an equilibrium in markets with asymmetric information. The strategies to reduce the information asymmetry center around three managerial dimensions: (i) product coverage, (ii) price setting and (iii) performance presumption. Pharmaceutical R&D managers can take different actions along these dimensions in order to approximate an equilibrium in the out-licensing market. However, all changes bear some caveats and require a trade-off between different scenarios:

(i) When modifying the *product coverage*, the pharmaceutical company can offer a license to the partner firm that has either a higher or lower coverage than the "community rated" offer. While the more generous offer will increase the chances of finding a partner, the less generous offer will reduce the downside risk of giving up too much intellectual capital but might also impede the closing of the out-licensing deal. Thus, the "right" product coverage always requires a trade-off between maximizing the likelihood that the partner firm agrees to in-license the product and minimizing the outflow of too much intellectual capital. In the cases of Novartis and Roche, the companies' previous employees had set up the in-licensing partner firms Speedel and Actelion. Thus, they transferred a significant amount of knowledge associated with the substances' development to the in-licensing partner firms simply by moving the people involved in the development process to the new firms. The implicit spill-over effects consequently enlarged the overall product coverage of the deal even if that hasn't been constituted explicitly in the licensing contracts.

(ii) When modifying the *price setting*, the pharmaceutical company can increase or reduce the required upfront payment as compared to the "community rated" terms. An increase in the upfront payment would result in a more immediate cash flow towards the pharmaceutical company. By contrast, a reduction in the

upfront payment would most likely increase the willingness of the partner to accept the deal, but would expose the pharmaceutical company to the risk to receive only a small fraction of the license's entire value if the partner firm cannot successfully execute the compound's development. Therefore, the "right" upfront payment always requires a trade-off between maximizing the potential payoff expected from the out-licensing deal and minimizing the risk of losing almost the entire value of the license. In all analyzed deals, the partner firms were small and highly venture capital funded which restrained their ability to pay large upfront payments. Thus, the observed out-licensing deals have been characterized by comparatively low upfront payments but call-back options and/or a rather high royalty revenue participation instead. The pharmaceutical companies' fear to give up a potential blockbuster drug seemed to weigh more than the financial rewards of immediate cash inflows from out-licensing.

(iii) Regarding the *performance presumption*, it seems to be self-explanatory that the pharmaceutical company should try to approach a partner firm with a lower probability of not being able to execute the compound's development compared to the "community rated" situation (which equates to a higher probability of success for the project). This research, however, has shown that it only makes sense for the pharmaceutical company to target a partner firm with a higher probability of not being able to execute. The lower probability of success seems to be overcompensated by the potentially occurring revenues and profits that the pharmaceutical might be able to expect if the compound turns out to be a success. The pharmaceutical company's risk-adjusted gains seem to be higher than its costs regarding the out-licensing deal. Even more, targeting a partner with a lower probability of not being able to execute compared to the "community rated" situation would be counterproductive. The pharmaceutical company would be required to always accrete the product coverage more in relative terms than the upfront payment. Thus, the theory of adverse selection confirms that out-licensing deals are preferably closed with smaller partner companies as could have been observed in the case study analysis centering around the deals of Novartis/Speedel, Schering/Intarcia and Roche/Actelion. The "right" performance presumption always requires a trade-off between maximizing the probability that the partner firm is able to execute the compound's development and minimizing the risk that the partner firm retains too much of the joint project's benefits.

In summary, changes in one of the three dimensions always require changes in the other two parameters as well in order to reach an equilibrium in the out-licensing market. Therefore, finding an equilibrium always requires R&D managers to come up with a hybrid construct of adjustments in the product coverage, price setting and performance presumption. While the managerial recommendations cannot straightforward show how to find an equilibrium, our work has

illustrated avenues to overcome the asymmetric information existent in out-licensing deals at large pharmaceutical companies. Future research might pay closer attention to the out-licensing process itself as well as the actions necessary for negotiating and managing the respective collaborations. In addition, the existence of the negative externalities caused by the existence of adverse selection in the out-licensing market — which seem to be completely dissipative — offers further potential for research on this highly relevant topic.

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