Designing Optionality in Biopharma Licensing Agreements

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ABSTRACT

The article provides new insights into how licensing-based strategic alliances between firms in the biopharmaceutical industry really work illustrating the main deal-making business practices concerning the therapy areas most frequently encompassed, the timing of negotiations at distinct R&D stages, the financial terms and the typical value splits among the parties. In light of the above, it deals with optionality in sequential innovation and its interaction with licensing design, thus modeling R&D development where a licensor licenses a technology to a licensee and analyzing embedded real options across different types of licensing contracts. It addresses how to structure and value biopharmaceutical licensing agreements focusing on which party controls R&D drug development and hence interim continuation/abandonment decisions. Standard contractual licensing schemes are classified along these dimensions and valued as multistage options. The article reexamines the fairness of the value appropriation split between the parties after accounting for optionality and uncertainty and considers tradeoffs between fixed payments and royalties. Finally, extending the idea to a portfolio level, a R&D portfolio strategy framework is developed to help a pharma company analyze internal drug development opportunities and flexibly manage related investment/divestment decisions so as to enhance shareholder value.

Keywords: finance; real options; drug development; licensing; value appropriation.
JEL codes: O32, L24, G30

When GlaxoSmithKline (GSK) entered a strategic alliance with Actelion in Europe in 2008, it agreed to co-develop Almorexant for the treatment of insomnia, committing to pay almost half the R&D development costs. In 2011 GSK partnered with Epizyme, a U.S. biotech firm pioneering epigenetic drug development for several cancer indications. It was agreed Epizyme would be primarily responsible for conducting discovery research, while GSK would take over in the subsequent development and commercialization stages. Teva Pharmaceutical in 2009 signed a licensing agreement with OncoGenex to co-develop a compound related to chemotherapy resistance for prostate and lung cancers, securing control over the execution of the R&D program at Phase III by making a $30m prepayment of OncoGenex's development expenditures.

As shown in the above illustrations of business practices, licensing contracts in the biopharmaceutical ("biopharma") industry commonly differ based on the degree of cooperation and control exerted among the parties involved in drug (co)development. In some cases, the innovator/biotechnology ("biotech") firm controls the drug development process by incurring the related expenditures, while in other cases the pharmaceutical ("pharma") company may be the one to pay the development costs securing control over the continuation or abandonment of the R&D process. Alternatively, the parties may opt for co-development sharing related costs or for other hybrid contractual schemes like starting with one licensing scheme and along the way switching to another.

Licensing deals that are typically signed in the biopharma sector may also differ based on the mix of fixed upfront and milestone payments vs. royalties. For example, a licensing deal between Genzyme and ISIS gave most weight to a large up-front fixed payment of $325m paid for licensing the technology. Celgene's license deal with Acceleron Pharmaceuticals gave more weight to contingent (milestone) payments. Bayer and Ortho-McNeil (a Johnson & Johnson company) reached a fairly balanced agreement involving co-development and co-marketing of a Phase II stage inhibitor for the prevention of thrombosis after orthopedic surgery, with the latter company paying $290m in development milestones plus up to 30% in royalties. The economic terms of the previous GlaxoSmithKline-Actelion deal consisted of a fixed upfront fee of $139m, milestone payments of up to $384m, plus sales-tied royalties up to $3 billion. The optimal mix of fixed vs. use-based payments and the form of collaboration or maintenance of development control are inter-dependent and there may be alternative combinations equally preferable and fair to the parties.

Following years of depleting R&D pipelines, pharma firms have become more receptive to insourcing strategies involving the licensing-in of new drugs from biotechs at various stages of

drug development to supplement their in-house innovation activities.[1] Rising costs of drug production and commercialization limit the capacity of smaller biotechs to manufacture and distribute compounds on their own, making it necessary to license out many new drug opportunities to large pharma incumbents. As a result of these trends, biopharma experienced unprecedented growth in product innovation via collaborations involving licensing deals.[2] In 2016, biotechs and pharmas signed 160 deals worth $57.7 billion, an all-time high.

In light of this growing collaboration activity, our article presents an interesting application of real options theory to the product innovation and licensing setting, with a specific focus on the biotech industry. It considers a model of R&D development and licensing whereby a licensor (biotech) licenses a technology that needs further development to a licensee (pharma), with either party (individually or jointly) potentially controlling the R&D process at different stages. Specifically, it deals with structuring the innovation process and subsequent licensing deal considering the real options associated with the sequential nature of the product innovation process and licensing features agreed between the biotech/licensor (LR) and pharma/licensee (LE). Although it is known in the literature that licensing agreements involve option-like decisions[3], much of this literature has focused on university technology licensing or rationalizing the choice between fixed-fee and royalty licensing payments, and examining related empirical implications.[4] The specific aspects of licensing agreements addressed herein (those related to the sequential nature of the innovation process and the sharing consequences of who controls the decision rights) have not been adequately considered in extant literature, though they are important for our understanding of product innovation management and associated transactions in markets for technology.

A main and unique contribution of our study is our attempt to analyze real options (especially who controls the option to continue or abandon product development) across different types of licensing contracts or alternative contractual structures, namely our specific focus on the interaction between real options theory, the sequential nature of product innovation, and contractual licensing arrangements. This is particularly important as the parties to a licensing agreement may have conflicting incentives, e.g., to discontinue a failing product development effort or not. To facilitate this, we first provide a comprehensive overview of licensing deal-making practices in the biopharma sector based on a dataset of 257 transactions recently conducted in the market for drug development technology. This enables us to shed light on the therapy areas most frequently encompassed by licensing activities, the timing of negotiations (relative to R&D stages), the financial terms and the typical value splits among the parties. Our study then provides the number crunching behind the innovation efforts leading to the

development and the follow-on market commercialization of a novel (representative) drug. In doing so, two approaches for assessing the value creation potential of a drug R&D program and the related licensing-based partnership – (i) conventional vs. (ii) strategic net present value based on real options thinking – are discussed and compared. We then catalogue and subsequently analyze common contractual schemes in licensing deals in the biopharma sector based on specific key option driver characteristics. Our findings corroborate the wide variety of contractual arrangements used in licensing business practice. The real options logic, proposed herein for designing and valuing a licensing-based alliance, is illustrated using an actual inter-company application involving structuring a licensing deal surrounding sequential product innovation. We thus take a new look (from a real options perspective) at fair value appropriation from the viewpoint of licensor vs. licensee (accounting for the option value of development or discontinuation) examining alternative combinations of financial terms resulting in the same sharing split. Finally, extending our idea to the portfolio level, we provide guidance to a pharma company on how to strategically analyze and flexibly manage its R&D pipeline (and associated budgets) so as to enhance shareholder value.

Licensing deal-making in the biopharma industry: evidence from the field

This study aims at shedding light on business practices followed to arrange and design terms, conditions and value split among parties in licensing deal-making in the biopharma sector. To this end, we have collected a dataset of 257 licensing transactions completed in more than a decade (2003-2013) drawing upon two top professional and academic sources of drug intelligence/analytics, Medtrack® and Recap IQ. Licensing deals of our sample are evenly distributed across the period considered, with an average number of 23 transactions per year, displaying peaks in 2006-2007 (40 and 36 deals, respectively).

Our sample includes small-sized biotechs, such as the Nasdaq-listed Cti BioPharma (formerly known as Cell Therapeutics) with expertise in developing drugs to cure blood cancers, large-sized biotechs, such as Amgen, or big pharmaceutical companies, such as Pfizer, Merck, GlaxoSmithKline or Novartis. The majority of deals are biotech/pharma (or pharma/biotech) agreements (53%), 100 are biotech/biotech (39%), and only a few (8%) are pharma/pharma. The geographical origins of the parties are varied, though slightly concentrated in North America (70% of licensors and 56% of licensees), with 21% of licensors and 28% of licensees operating in Europe, 7% of licensors and 13% of licensees in Asia & Middle East, 0,4% in Australia.

Our research reveals that licensing activity in the biopharma industry encompasses all important therapy areas that nowadays are central to medical research aimed at enabling increasingly impactful cures for patients suffering from rare or common diseases. More specifically, licensing contracts are fairly distributed across 10 therapy areas (from cardiovascular to gastroenterology or immunology), with oncology being the most targeted category (75 deals) and central nervous system the second most sought-after one (42 deals) (Table 1, first column).

The timing at which negotiation of licensing deals (included in our data) leads to an agreement among parties and related signing is executed spans all main phases of a novel drug's R&D development, from preclinical to clinical trials (Phase I, Phase II, Phase III) and (domestic) drug authority approval (NDA) up to market commercialization (only the early discovery stage is absent). Most transactions are signed at the preclinical (77) or Phase II stage (66). The more advanced the stage of development reached by the candidate drug (e.g., Phase III, NDA), the less likely the attainment of an agreement to collaborate on R&D activities and/or subsequent commercialization via sharing risks, investment costs and rewards in the form of in-cash flow payments. Deal-making is thus very limited when the new molecule faces pending approval or after it has been successfully approved and is ready for launch in the marketplace (27 deals) (Table 2, first column).

Licensing deals enable collaborative joint exploitation of patentable drug development among a licensor and licensee with complementary capabilities. Control of early-stage development is typically retained by the innovator/licensor (biotech). Advanced clinical trials, commercialization and distribution are typically retained by the licensee (big pharma). Commonly, the LE (pharma) obtains use to the patented drug by agreeing to pay a set of fixed payments (an upfront fee and milestone payments) as well as specified percentage royalties to the LR (biotech) for successfully carrying out drug development. More specifically, at the start of the collaboration LE pays an upfront fee to provide LR with a monetary incentive for initiating or continuing the R&D program. Milestone payments can be of two types: R&D milestones, progressively paid by LE to reward LR for successful completion of development phases, and Sales milestones (less frequent), paid by LE at the end of the R&D program to compensate LR for taking the candidate drug to approval and making it ready for commercialization. After market launch, LR also receives royalties on drug sales from LE.

Table 1 provides empirical evidence on the financial terms of licensing agreements recently completed in the biopharma sector across therapy areas showing that the median upfront fee is $ 10 m, median R&D milestones are $ 57.5 m and median Sales milestones are $ 92.5 m.

Median upfront fees and R&D/Sales milestones are also available based on the actual phase at which licensing deals are signed by the parties (Table 2). It can be noted that the more advanced the phase at which the agreement is reached, the higher the amount of the upfront fee received by LR. For instance, the upfront fee paid from LE when parties agree to collaborate at Phase III is higher ($ 15 m) than that paid when starting to cooperate at Phase I ($ 8.5 m) implying that LR demands for a greater compensation for its more long-lasting, successful development efforts. R&D milestones also increase as the candidate drug moves forward in the program due to the fact that later clinical trials (Phase II), Phase III) are more costly requiring higher capital expenditures from the innovator. Such investments are thus compensated for by higher R&D milestone payments. Median R&D milestones received by LR at Phase II or Phase III ($ 101 m and $ 111.8 m respectively) are halved compared to those obtained at the Preclinical stage ($ 54.5 m). Median royalty rates negotiated among the parties across phases at deal signing are also available (Table 2, last column). The later the stage at which the deal is signed, the higher the royalty rate set in the contract (5% at Preclinical vs. 14.5% at Phase III) as LR will try to profit from the impending drug market launch choosing to be compensated by LE via a higher amount of sales-tied payments. Such empirical evidence is further validated looking at the increasing pattern of median royalty rates across therapy areas (Table 3).

[INSERT TABLE 1, TABLE 2 AND TABLE 3 ABOUT HERE]

Economics of a representative R&D drug development valuation

The innovation efforts of a biotech (or pharma) leading to origination and sale of a novel drug are typically carried out through two main stages: product development (R&D) and market launch/commercialization. Development of a representative drug may take up to 10 years with the first 4 years being mostly concentrated on early stage research-driven and preclinical activities (Discovery, Preclinical, Phase I) and the subsequent 6 years devoted to more advanced clinical trials on an increasing number of patients (Phase II, Phase III), filing for approval of indications by the NDA (National Drug Authority) and market launch. Total development expenditures typically amount to $ 145 m with such costs being about a half for biotech compared to pharma companies. Phase III is the longest (3 years) and most costly clinical trial ($ 45 m). Implementation of drug market launch costs $ 75 m. Each R&D stage is characterized by its own typical success probability. Table 4 displays duration, development costs and success probabilities by stage for a representative drug development. Success probabilities by stage also

differ based on therapy areas (see Table 5). Starting from Phase II, the more advanced the clinical trial, the more likely the transition to the subsequent phase. For instance, successful completion of Phase III (70%) is more likely than that of Phase II (50%) and approval is obtained with 90% probability. The cumulative probability of successfully terminating a drug's R&D program is 21.9% (see Table 5, last column).[5]

Market launch of the novel drug typically occurs at year 11 with peak sales being reached after six years (year 16) and amounting to $ 446 m. Based on industry data on mean and median peak sales by therapy area, average peak sales of Table 5 (column 5) are used to draw the sales curve of a representative drug until patent expiration enabling entry of the generic product (year 20) (Figure 1). The drug sales (and parallel cash flow) curve rises from market launch to the attainment of peak sales with revenues' growth pace slowing down between year 14 and year 16 due to "me-too" product competition and it then declines as the market life cycle approaches patent expiration, after which sales revenues rapidly collapse. Figure 1 also shows the above articulate R&D stage (and its related costs) preceding drug commercialization. A novel molecule can be discovered and/or developed internally by (partially or entirely) conducting the above R&D activity or acquired from a third party. The cost of discovery or acquisition of related right typically amounts to $ 4 m.

[INSERT TABLE 4, TABLE 5 AND FIGURE 1 ABOUT HERE]

Appraisal of a R&D program of a molecule (potentially leading to a novel representative drug) at the discovery stage from preclinical to market launch carried out using the *probability*-adjusted net present value (NPV) (where after-tax costs are multiplied by associated success probabilities by stage and sum of total after-tax cash flows by cumulative probability of reaching market launch) yields a value of $ 2.7 m, which becomes - $ 1.3 m after deducting the cost of discovery (or acquisition of related right from a third party) of $ 4 m.[6] The same R&D program can also be valued using real options analysis. Figure 2 provides a visual representation of the above R&D program valued as an option on a option (compound option) using real options analysis. Decision points for option exercise are symbolized as hexagons with development costs and timing (at which each option may be exercised) shown below each option/hexagon, probabilities of successfully completing the current stage (or abandoning the program) displayed in the boxes preceding each option and values of the drug accounting for the optimal exercise of subsequent options (associated with the residual R&D stages of the program) displayed in bold on the top of each hexagon. Real option valuation of the

representative drug's R&D program yields the so called *expanded* (or *strategic*) net present value (*E*-NPV), that is the value of investing in the R&D program including the compound option value, amounting to $ 13.3 m, which becomes $ 9.3 m after deducting the cost of discovery (or acquisition of related right from a third party) of $ 4 m. Hence, a pharma company recognizing the optionality embedded in drug R&D and thus using a real options approach to valuing an internal or acquired program for developing a novel drug at discovery would be better positioned to capture the value of flexibility arising from active R&D management (whether to continue or abandon the program based on optimal option exercise conditions) compared to use of the naïve (static) NPV rule.

Consider now a licensing situation, whereby the pharma (LE) obtains access to the R&D program at discovery by agreeing to collaborate with a biotech (LR), which would continue carrying out the latter, in exchange for paying an upfront fee and milestones as well as royalties on future drug sales to LR. Upfront fee is $ 10 m, milestone payments are set proportionally to such fee and royalty rate (on sales) is 2.5%.[7] *Probability*-adjusted NPV of the R&D program is - $ 18.9 m implying that the pharma should not proceed to license in use of the patented molecule.[8] A real options approach to valuing the same licensing transaction instead provides a different advice. A *strategic* NPV of $ 1.0 m suggests that the pharma can create value by partnering with a biotech through a licensing agreement.

[INSERT FIGURE 2 ABOUT HERE]

Our sample includes a licensing transaction signed in June 2007 between Skyepharma (LR) and Somnus Therapeutics ("Somnus") (LE) to share the risks and rewards of a new molecule in the broad therapy area of central nervous system at the Preclinical stage. Skyepharma (part of Vectura Group, a London Stock Exchange listed company) is a biotech firm specialized in complex oral solid dosage forms offering to pharmas a wide range of premium services (e.g., small-scale programs, manufacturing) at any stage of the product development lifecycle through its Lyon-based facility. Somnus is a US-based, VC-backed, private pharma engaged in developing therapeutic solutions for insomnia patients.

More specifically, this exclusive agreement provides for the fact that Skyepharma will develop and manufacture SKP-1041, a new controlled release formulation of a non-benzodiazepine hypnotic agent usable as a sleep therapy which relies on a proprietary technology, while Somnus will be responsible for marketing it. Based on the terms of the agreement, the LR would conduct the R&D activities at the standard (development and clinical

trial) costs (shown in Table 4, row 4 – Cost) financed by the LE, thus undertaking the technical risk of making the molecule ready for market commercialization with a cumulative success probability of 18.5% (see Table 5, Central Nervous System). This situation enables the LE to control the R&D program by agreeing to reward the biotech with the payment of an upfront fee of $ 4 m and milestones of $ 31 m (R&D milestones of $ 11 m and Sales milestones of $ 20 m) plus a 6% royalty rate on future drug sales. The first milestone payment will be triggered by the successful completion of the Phase I clinical study of the product. As better explained in a later section, the pharma's upkeep of control over the biotech's R&D efforts corresponds to a contractual scheme frequently applied in the practice of licensing deal-making.

Compare now the results associated with the appraisal of such a licensing situation using the *probability*-adjusted NPV and the real options approach. The R&D program underlying the licensing agreement takes 8 (rather than 10) years to complete (market launch) as the latter is signed at Preclinical (2 years after discovery). The *probability*-adjusted NPV accruing to Skyepharma (LR), based on fixed payments (upfront fee and milestones) and sales-tied royalties, is $ 8 m. Operating cash flows mainly accruing to Somnus (LE) at launch and thereafter are driven by drug sales (net of royalties payable to LR), with a peak of $ 584 m being reached 6 years later (see Table 5, column 5, row 2 for Central Nervous System). This yields a *probability*-adjusted NPV of - $ 2 m, which creates no incentive for Somnus to proceed to the licensing situation. The parties may apply real options analysis to value the same potential transaction obtaining a different answer. A *strategic* NPV of $ 8.6 m suggests that Somnus can create value by agreeing to fund (and thus control) the development of Skyepharma' sleep therapy technology being responsible for its future commercialization. Skyepharma would capture more than half (52%) of the licensing deal value (*strategic* NPV of $ 9.3 m). Based on a real options view of the transaction, the two parties should proceed to engage in such a strategic alliance.

Conventional Framework and Structuring Challenges

A biotech and a pharma striking a licensing deal commit to leveraging their distinct know-how to jointly take a new molecule to market.[9] The biotech (LR) is rewarded for conducting early-stage innovation activities based a three-part tariff contract (upfront fee, milestone payments, royalties) with commercialization and distribution risks being transferred to the pharma (LE).[10] However, the way the terms of licensing transactions are designed often embeds significant optionality. We therefore address several related issues: How should LR and LE

optimally design the licensing agreement accounting for embedded optionalities and contingencies involved in (co)development? Which menu or mix of payments is preferable? How to share the value created?

Value appropriation in licensing negotiations in the sector is usually based on how much of the net present value (NPV) of the R&D activity is appropriated by the licensee (LE) vs. the licensor (LR), called the profit split ratio (PSR). Figure 3 provides a summary of all cash flows being exchanged among the two parties under a standard licensing agreement showing the interconnections among the various payments. The biotech (LR) agrees to license its patented drug compound to a pharma or another biotech firm (LE) giving up, partially or fully, the project's value (-NPV) in exchange for obtaining a compensating amount of fixed and use-based payments, namely an upfront fee (F_0), the present value of milestone payments [PV(M)], and the value of royalties estimated as R% of cash-flow value V (R^*V). The cash flows accruing to the biotech (LR), including the project's value (-NPV) that is given up to the benefit of the other party, are shown on the left-hand side of Figure 3. As such cash flows are also payments made by the LE to the LR, the related symbols with negative sign are shown on the LE' side and the same ones with positive sign on the LR' side (with the interconnection represented by grey arrows from LE to LR). Conversely, the pharma agrees to enter the licensing agreement provided the (gross) cash flow value received ($+V$) exceeds the present value of associated R&D development [PV(D)] and commercialization costs [PV(C)] under the agreement. The cash flow payments due by the pharma (LE) for developing and/or commercializing the novel drug and those accruing to the pharma (LE) from the biotech (LR), including the (gross) cash flow value received ($+V$) by the other party, are shown on the right-hand side of Figure 3.

Based on conventional theory, the *passive* NPV of the R&D program underlying the contractual licensing arrangement is the gross value (upon R&D completion) of cash inflows expected from drug sales (V) net of all R&D development [PV(D)] and commercialization costs [PV(C)]. Such NPV and its elementary components are highlighted with the bold dotted arrows in Figure 3. The NPV that normally would go to R&D owner, if it pursued development and commercialization on its own, is now divided among licensor (LR) and licensee (LE) if they reach a licensing deal.[11] The biotech (LR) fully gives up the NPV of its R&D activity if development expenditures are paid by the pharma (LE) in addition to those needed for drug commercialization. The NPV is only partially foregone if R&D development is fully undertaken by the LR or shared with the LE (so called co-development). Hence, the standard NPV (conditional on R&D completion) of a licensing agreement is apportioned among the two parties in different ways based on the relative bargaining power and the contractual terms

actually negotiated: $NPV = V_{LR} + V_{LE}$. Licensing negotiations are carried out using the profit split ratio (PSR), V_{LE} / V_{LR}, as a practical benchmark, where V_{LE} is the value to the licensee (LE) and V_{LR} is the value to the licensor (LR).[12]

Correct assessment of the value of a patented drug and more accurate determination of the profit split ratio is key in negotiations and reaching agreement. Nonetheless, the full value of a drug development deal that involves a sequential multi-stage R&D process with multiple (market and technical) risks and, eventually, remote and contingent cash flows cannot be adequately captured by standard NPV.[13] Given the contingent development and/or sharing decisions involved under conditions of technical and market uncertainty, standard PSR based on NPV (rather than Expanded NPV that also accounts for option value) cannot give the correct value.

In line with the above intuition, recent scholarly research has challenged the use of NPV analysis in the context of R&D licensing recognizing its main deficiencies and proposing alternative real options-based methods. Yet, a recent academic survey[14] finds limited use of real option methodologies in the pharma industry noting practitioners' reluctance arising from lack of validation through real-life applications.[15] Moreover, despite the rising importance of licensing agreements between biotech and pharma, little attention has been given to analyzing the intra-alliance value appropriation in biotech R&D alliances. More specifically, the issue of partners' heterogeneous capabilities to arrive at efficient contracts and to appropriate the options knowledge embedded in R&D operations is yet to be addressed. From a real options lens, conventional licensing valuation approaches are static in that they assess LR and LE's decisions as to whether to enter agreement and develop the drug by focusing on committed or expected payoff effects based on static revenues and cost-driven assumptions, ignoring the contingent multistage nature of the underlying R&D process and the optionality in the licensing deal itself. A real options analysis of licensing deals in the biopharma industry would encompass the main drivers of the R&D process (uncertainty, exclusivity, irreversibility, flexibility and staging) as well as any optionality features in the licensing contract itself. Our proposed framework enables IP managers of biotech and pharma firms to optimally and fairly design licensing contracts with embedded optionality features, thus taking a step toward closing the gap between theoretical developments and practical implementation of the real option method in R&D licensing.

[INSERT FIGURE 3 ABOUT HERE]

Licensing Schemes and a Contract Taxonomy

In an innovation-driven industry such as biopharma, whereby some firms have innovative ideas but lack the funding to develop and launch needed R&D projects whereas other big players who do have the financial resources are short on discovery, licensing has become a valuable business model. To account for different risk allocation and financial preferences of potential counterparties, a variety of licensing contract structures and provisions have been considered in the industry. Table 6 illustrates real-world examples of such licensing transactions recently conducted in biopharma. From the perspective of which party controls R&D development and hence the continuation or abandonment option[16], we catalogue prevailing licensing contract schemes as follows:

I) LE (big pharma) pays the development costs and controls R&D development;

II) LR (innovator/biotech firm) pays the development costs and controls R&D development;

III) LR and LE agree on co-development and share/control R&D costs.

For each of the above schemes we consider variations (a, b) to account for the execution of different modalities under the same contractual framework. These contract typologies, discussed in the next section in the context of the BioCryst/Mundipharma case application, are:

Scheme Ia: LE (pharma) maintains from the outset control of the R&D program, whose execution is carried out by the LR (biotech) until its completion, with full disbursement of related expenditures. Since the LR is relieved from the responsibility of incurring any drug development costs, it agrees to receive a lower % of royalties.

Scheme Ib: in this variant, LR (biotech) at first controls the R&D operations and incurs related costs in the early stage, but control is later taken over by the LE (pharma) upon exercise of a specified option granted to the latter. The licensing situation resulting from this option exercise eventually resorts back to scheme Ia.

Scheme IIa: LR (biotech) retains control over drug development, incurring all related costs, until completion of the R&D program. In exchange for fully bearing this technical development risk, the LR is compensated by receiving a specified amount of royalty payments tied to the commercial success of the drug.

Scheme IIb: in this variant, the LR pays the R&D expenditures and the LE (pharma) *refunds* related costs to the LR via milestone payments linked to the successful attainment of specified results.[17] Such a contract is beneficial to the LR as it can devote reimbursed financial resources to build up further research capabilities while still controlling the R&D operations, while the LE ensures the R&D program progresses on target with appropriate incentives. Because the LE funds part of the LR's costs for the development of the drug, it can negotiate a lower rate of

royalty payments.

Scheme IIIa: LR (biotech) and LE (pharma) agree to jointly conduct drug development from the outset and share related expenditures (co-development) until termination of the R&D program. In this way the LR preserves cash resources for other R&D initiatives, while the LE can reduce its costs of discovering new drugs while gaining access to broader innovation competencies.

Scheme IIIb: in this variant the LR starts to develop the candidate drug on its own and at some stage the LE exercises an (exclusively granted) option to switch to co-development.

It can be noted that schemes Ib and IIIb are hybrid licensing situations in-between scheme IIa (where LR controls development and pays related R&D costs) and scheme Ia (LE controls development and pays related R&D costs) and between scheme IIa and IIIa (LR and LE agree to co-develop), respectively. Table 7 (left part) provides a summary of this taxonomy according to the above-discussed schemes.

Our findings also shed light on how assorted the contractual framework for licensing activity has become so far in biopharma. Table 7 shows that contract scheme Ia prevails (180 deals; 70%); use of scheme IIa is very limited (3 deals; 1%) with parties being more inclined to apply its variation IIb (with the pharma making reimbursements of R&D costs to the biotech) (33 deals; 13%); co-development is still narrowly spread (scheme IIIa is applied in 23 transactions – 9% and only in 5 deals the licensee/pharma has an option to switch to co-developing the candidate drug with the biotech at a certain stage).

[INSERT TABLE 6 AND TABLE 7 ABOUT HERE]

Illustrating the Approach via the BioCryst/Mundipharma licensing transaction

We illustrate our proposed approach to designing and valuing a licensing deal involving product innovation in the case of Mundipharma International, a global network of independent pharma companies leading the fields of pain medicine, respiratory and oncology headquartered in Cambridge (UK). Founded in the U.S. by two physicians in 1952 and still privately owned, the network has a presence in over 120 countries, employing over 8,600 people and generating annual revenues in excess of $ 3.4 b. Mundipharma has a strong track record of building successful alliances to license, develop and market medicines that improve patients' lives. Its alliances are long-term licensing arrangements (typically 10 years or more) based on high levels of interaction and transparency in the way information is shared with the other party to identify potential of new drugs and work collaboratively to accelerate their market releases. In February

2006, Mundipharma signed a licensing agreement with BioCryst Pharmaceuticals, a U.S.-based publicly listed (Nasdaq, 1994) biotech company committed to strategically partnering with the pharma industry in drug discovery, to develop and commercialize BioCryst's lead compound at Phase II, Fodosine, in markets across Europe, Asia and Australasia for use in oncology. The contractual arrangement applied by the two parties is that of licensing scheme Ia, whereby Mundipharma (LE) retains the responsibility to incur the development costs thereby controlling the drug development process with the actual R&D work being carried out by BioCryst (LR).

We next illustrate the appraisal of such a licensing agreement involving BioCryst's oncology R&D program using a real options logic and contrast it with standard NPV analysis. To license-out its cancer molecule to Mundipharma (LE), BioCryst needed to engage in a negotiation based on the following terms. BioCryst would develop the candidate drug until completion of the remaining stages (Phase II, Phase III), taking 2 and 3 years respectively, and then apply for FDA approval (obtainable after one year). The probabilities of successful completion of each of the three remaining stages are 47%, 65% and 95%, respectively (see Table 5, row 7, Oncology & Hematology). The development expenditures in the various stages of the R&D program, expected to be incurred by Mundipharma, are as follows: $ 10 m (Phase II); $ 45 m (Phase III); $ 3 m (NDA filing) (see Table 4, row 4). The LR (BioCryst) would receive an upfront fee of €10 m. Total milestones of $ 155 m would be paid by the LE (Mundipharma) to BioCryst as a reward for the successful completion of Phase II, Phase III and NDA approval stages. The LE (Mundipharma) would also take the responsibility of launching, commercializing and distributing the new drug, assuming all R&D stages are successfully completed. The present value of launch, commercialization and distribution costs the LE is expected to incur amounts to $ 75 m (see Table 4, row 4, Market Launch). The royalty rate for use-based payments to be made by the LE to BioCryst (after drug market launch) is 6.5% of sales (which corresponds to 13% of V). The (gross) present value (V) of cash inflows expected from selling the drug in the marketplace is estimated to be $ 419 m.

To estimate the PSR and negotiate the remuneration structure of the deal according to industry norms, BioCryst and its pharma partner would apply a standard (static or passive) NPV analysis of the licensing contract, obtaining the *probability-adjusted* NPV. *Probability-adjusted* NPV involves multiplying the value of net cash flows accruable to the R&D owner (conditional on successful R&D completion) by the cumulative probability associated with successful completion of all remaining R&D stages (13.4%). The *probability-adjusted* NPV for Mundipharma is - $ 44.6 m, a value destruction advising against the licensing transaction, and $ 32.5 m for BioCryst. The negative NPV potentially accruing to the LE yields a negative PSR,

which clearly inhibits the application of PSR as a benchmark for licensing negotiations with value destruction for either of the (or both) parties.

A real option valuation of the same deal recognizes that the process of discovering, testing and marketing a new drug is very much alike a sequential multistage (compound) option, with each stage having a different probability of technical success (p), where stage options are economically and chronologically interconnected.[18] At each stage, the R&D owner pays a development (investment) cost (D) to acquire the option to proceed to the next stage of the R&D program. The program can be discontinued if any of the staged options to proceed is deemed unworthy of being exercised. Drug commercialization is successfully reached only if all intermediate R&D development options are exercised. The value of the R&D program depends on the future growth opportunities that such earlier contingent investments may open up via subsequent drug commercialization. The eventual underlying (gross) project value (V) is the present value of a *real* claim the R&D owner has on the cash flows expected from drug sales. Option maturities correspond to the timing of each development phase. Technical risk gets reduced as the drug proceeds from early stages toward completion.

The financing arrangement of a licensing deal analogously typically involves staging a series of contingent milestone "installments" with earlier payments giving the right to make further investments in the execution of clinical trials, filing for drug approval, and proceeding with market launch. Whether it is the LR or LE (or both) who will effectively act as the R&D program owner, controlling the embedded optionality to continue or abandon drug development, depends on which one of the three types of licensing agreements (I, II, III) (with their respective variants a and b) will be selected. Furthermore, the parties may engage in the licensing deal *actively* or *passively*. If both parties ignore the option-like features of the underlying R&D program and engage in the transaction passively, they would share the static (*probability*-adjusted) NPV of the licensed drug (as described above). Active management of the licensing opportunity, by contrast, implies keeping control over the decision to exercise the compound (real) option implicit in drug discovery, or to discontinue it, through commanding the disbursement of the associated development costs.

Appraisal of the value of the licensing contract to the LR (V_{LR}) or the LE (V_{LE}), accounting for the R&D-related options, is conducted applying a standard real options analysis based on a discrete-time binomial numerical procedure (as exemplified in the Supplementary Appendix). Six types of input parameters are required: 1) the terms of the licensing contract (e.g., the amount of the upfront fee, milestone payments, royalty rate); 2) the characteristics of the

candidate drug development program (e.g., the stages remaining, the costs per stage, and the success probabilities associated with remaining R&D phases); 3) the stochastic evolution of the underlying drug (asset) value and of the embedded options (in the form of binomial trees); 4) the sequential nature and interdependence among the staged options; 5) the sources of business uncertainty driving the value of embedded options (e.g., drug market demand volatility); 6) other general parameters (e.g., the risk-free interest rate).

Following options thinking, the above licensing valuation problem can be structured and illustrated by an option map, a collection of nodes (options, graphically represented by "exploding" stars as in Figure 4, or committed decisions, represented by rectangles), probabilistic decision operators and connecting branches. Each discretionary (optional) decision is characterized by its payoff [present value of expected cash flows from drug sales minus development cost or V – D] and its timing (maturity), so the option node actually takes the maximum of the NPV or V – D (if the firm invests to further develop the candidate drug) and zero (if it chooses not to invest further and abandon the R&D effort). The probabilistic operator permits to average across alternative courses of action (i.e., proceed to the next R&D phase or abandon) in the presence of technical uncertainty, accounting for the specified discrete probability of success (p) or failure (1-p) in each stage.

In the illustration of Figure 4, the Phase II and Phase III staged options are linked by a branch, with the exercise of the first option on the left (Phase II) being a prerequisite for the exercise of the second option that follows on the right (Phase III). This implies that the value of the underlying asset (licensed drug) for the earlier option (Phase II) includes the value of the follow-on option (Phase III). The value of the licensing contract accruing to the LR (V_{LR}) or the LE (V_{LE}), under each of the three contractual schemes presented above, is thereby obtained as a multi-stage or *compound* option working backward in time through the various stages of the binomial tree shown in Figure A.1 (see the Supplementary Appendix for details). Licensing values are determined based on the notion of *expanded* (or *strategic*) NPV (*E*-NPV) that includes the value of embedded (real) options.[19]

We next appraise the value of the licensing contract signed by BioCryst and Mundipharma under the contractual scheme I in its variant a, analyzing how the *E*-NPV of the R&D program underlying the licensing agreement will be apportioned among the parties.

Under scheme Ia, the LE (Mundipharma) is fully responsible for incurring the development costs thereby *actively* controlling the drug development process and embedded optionality -- even when the actual R&D work is carried out by the LR (BioCryst). Option-based valuation

of the current licensing contract replicates the one shown in Figure 2 with the only differences that the candidate drug underlying the contract is at Phase II at deal signing and the contract's financial terms are also considered. The Phase II-value of the licensing contract (as of time 0) to an *active* LE (contingent on successful completion of all subsequent R&D stages) under scheme Ia is determined by working backward the underlying drug values in a binomial tree (similar but shorter than that of Figure 2) across the entire R&D program within a compound real option valuation framework.

Licensee's perspective

The *active* LE (Mundipharma) keeps control of the R&D program incurring related expenditures ($ 10, 45 and 3 m in years 0, 3 and 6, respectively). It remunerates the LR for its R&D efforts by making an upfront fee payment of $ 10 m at t = 0 and subsequent milestone payments of $ 28, 56, 28 and 42 m at t = 2, 5 and 6, respectively. As the R&D program progresses successfully and optional decisions ("exploding stars" denoting options) to enter the next stages are exercised sequentially by the LE, the value of the licensed molecule increases (from $ 20.56 m at t = 0 to $ 233.75 m upon market launch at the end of t = 6). [Figure A.1 in the Supplementary Appendix shows the evolution of the value of the licensing contract to the *active* LE].

More specifically, the decision to exercise the option to control completion of Phase II requires the LE to incur development costs (- D_{II}) of $ 10 m. The Phase II-related option has the following payoff: max ($+F_0 - D_{II} + p_{II}*C$, 0), where C is the value of the continuation option received with probability of success p_{II} = 47%. If the R&D program carried out by the LR does not prove successful over the 3-year duration of Phase II, the LE can exercise the option to abandon it with probability 1 - p_{II}. Exercise of this first option opens up for the LE a follow-on option (at t = 3) to proceed to the next R&D stage (Phase III). Analogously, the LE will optimally exercise the option to control management and completion of Phase III if the current (*continuation*) value of the licensed candidate drug (including the value of all follow-on options) exceeds the sum of development costs (-D_{III} = $ 45 m) that the LE will incur to continue engaging in the supervision/management of R&D operations and the milestone payment (+ M_{II} = $ 28 m) that the LE makes to reward the LR for successful completion of Phase II. The probability of successfully completing Phase III by year t = 5 is 65%. If technical uncertainties associated with Phase III clinical trials do not resolve favorably, the LR will exercise the implied abandonment option (with probability 1 - p_{III} = 35%).

If the R&D program progresses successfully, the LE will exercise the option to file to the

National Drug Authority (NDA) for drug approval if the value of the licensed candidate drug (including the value of the next market launch option) is greater than the sum of expenditures incurred by the LE for the NDA application (- D_{NDA} = € 3 m) and the milestone payment (+ M_{III} = $ 56 m) due by the LE as compensation for successful completion of Phase III. Obtaining drug approval (with probability p_{NDA} = 95%) will lead both parties to proceed to drug commercialization (with probability p_m = 100%). The chance of abandoning the project at the FDA approval stage is only 10% (= 1 - p_{NDA}). Upon drug market launch, the LE compensates the LR for obtaining FDA approval of the molecule by making an additional fixed milestone payment (+ M_{NDA} = $ 28 m) and exercises the option to commercialize the new drug by incurring related marketing and distribution costs (I_{mkt} = $ 75 m). Such a market launch option is worth € 233.75 m at the end of t = 6. At this stage, a sales milestone payment may be made by the LE as a bonus to further reward the LR for successfully bringing the novel drug to market launch.

The value of the licensing contract to an *active* LE under scheme Ia is determined by working backward the underlying drug values in the binomial tree of Figure 4 Panel A across the entire R&D program within a compound real option valuation framework. The value of the licensing opportunity to the LE (assuming successful completion of all R&D phases) as of the beginning of Phase II or time 0 is the present value of future cash flows arising from new drug sales [(1-R)*V], net of the fixed (upfront, F_0 and milestone, M) and royalty payments (R*V) paid to the LR and the drug launch/ commercialization investment expenditures (I_{MKT}) incurred by the LE. The licensing contract at time 0 is worth $ 20.56 m to the LE.

The LR and LE share the total licensing value pie of about $ 62 m with an E-NPV-based PSR of 0.5. As the LR merely *passively* conducts (but does not sponsor or control) the R&D operations, whereas the LE *actively* controls embedded optionality by making development and remuneration payments, the licensing value apportionment between LR and LE is asymmetric (PSR of 0.5). At time 0, the LR receives more value (67% of *strategic* NPV; $ 41.48 m) as it is fully relieved of decision responsibilities and costs involving drug development while getting compensated for its passive R&D work. The LE obtains 33% of *strategic* NPV ($ 20.56 m). Such portion of value accruing to the LE is substantial considering that the licensing transaction would not take place if appraised using a conventional analysis based on the *probability*-adjusted NPV. From a real options (E-NPV) angle, the licensing situation becomes viable for the LE, thus leading it to opt to control the optionality embedded in the R&D program. Illustration of the valuation of this licensing scheme in Excel is shown in the Supplementary Appendix.

Licensor's perspective

In Figure 4 Panel B, BioCryst (LR) faces a specified probability of successfully completing the current Phase II (p_{II} = 47%) and bringing the candidate drug to the subsequent stage (Phase III). The LR receives an upfront fee (+ F_0) of € 10 m from the LE as a signing bonus and remuneration for committing to conduct the R&D operations. More in general, the biotech (BioCryst) acts as a *passive* LR as it merely carries out drug development without controlling the decision process and related costs, relinquishing the continuation/abandonment option exercise decisions underlying the R&D program to the LE (Mundipharma). The LR receives the present value of the stream of fixed and royalty payments ($ 41.48 m) paid by the *active* LE (Mundipharma) as compensation for its R&D efforts. In Figure 4 Panel B, several rectangular boxes (rather than "exploding stars" denoting options) are linked together by branches to represent (each) a committed decision yielding a specified *cash flow* (upfront fee, milestone payment, % royalty payment) that must be made to the LR in the course of the R&D program. The royalty rate is kept at a relatively low level (6.5%) as drug development is not sponsored by the LR. No optionality is involved on the side or for the benefit of the LR under this scheme.

[INSERT FIGURE 4 ABOUT HERE]

We next propose the appraisal of the above licensing transaction between BioCryst and Mundipharma simulating the application of the alternative main contract schemes (II and III) that the parties could have adopted following the common business practices.

Under scheme II in its variant a, the LR controls the candidate drug development from the outset by managing the underlying R&D program, and thus commanding embedded optionality to (dis)continue the project (options as "exploding" stars). The LE, on its part, commits to undertaking the drug market launch and related distribution activities once the R&D program underlying the licensing agreement is successfully completed by the LR. To accomplish this, the LE also commits to make the contractual remuneration payments to LR at each stage (rectangular boxes). LE's net value consists of the present value of expected cash flows from drug sales net of fixed (upfront fee and milestone) and use-based payments (royalties). This type IIa licensing contract is worth $ 30.97 m to the LE. LR and LE share a total licensing value pie of $ 57.86 m, with an *E*-NPV-based PSR of 1.2. Under scheme IIa value capture is more balanced among the parties as the LR, who controls the continuation or abandonment option, pays all development costs and the LE saves such costs. The LE appropriates more than half

(54%) the value of the licensed molecule, while the residual value ($ 26.89 m; 46%) accrues to the *active* LR.

Under scheme IIIa, LR and LE agree to co-develop the candidate drug sharing control and the related R&D expenditures from the start. Both the LR and its pharma partner are *actively* and jointly carrying out the R&D program. Co-development no longer requires that the LE rewards the LR through milestone payments due to their joint involvement in R&D operations. Compared to previous schemes, the LR only obtains (from LE) the upfront fee (+ F_0 = € 10 m) as compensation for its previous efforts to take the licensed molecule up to Phase II and its willingness to continue joint development. The LR is also allotted a share of the value of future revenues from drug sales in the form of royalty payments (r*sales). The value of the licensing contract to the LR (at time 0) is € 11.61 m. The value of the licensing agreement accruing to the LE is $ 52.93 m. LR and LE share a combined licensing value pie of $ 64.55 m with an *E*-NPV-based PSR of 4.6. This is an asymmetric licensing situation with LR facing a value dissipation for its licensed-out molecule. Because the LE (pharma) pays only half of development costs and no longer makes fixed milestone payments to LR, it captures most of the licensing contract value (82%).

Licensing contract III in its variant b is a hybrid scheme where the start of the agreement is like above scheme IIa but along the way it converts to scheme IIIa. The LR begins to develop the candidate drug alone paying all related costs and receiving fixed cash payments (from LE) as reward for its R&D efforts (plus royalty payments at market launch). At a certain stage, the LE can exercise its (exclusively granted) option to convert to co-development, which involves sharing subsequent R&D expenditures with the LR while ceasing payment of milestones.[20] In the case of BioCryst-Mundipharma, co-development starts at Phase III. From this stage onwards, R&D expenditures are equally shared among LR and LE (1/2*D_{III}, 1/2*D_{FDA}), with the former no longer receiving milestone payments (only M_{II} is paid to compensate LR for successful completion of Phase II).[21] The values of the licensing contract apportioned among LR and LE are $ 21.74 m (32%) and $ 45.71 m (68%), respectively. LR and LE share a licensing value pie of $ 67.46 m with an *E*-NPV-based PSR of 2.1. Although the total value of the licensing contract is similar to the one obtained under scheme IIIa ($ 67.46 m vs. $ 64.55 m), the value split among the parties is significantly different becoming more symmetric to the benefit of the LR (a PSR of 2.1 vs. 4.6 under scheme IIIa).Value dissipation for the LR is lower compared to scheme IIIa as the LR takes full responsibility for the R&D program paying related R&D costs and thereby commanding the embedded optionality until successful completion of Phase II. From this stage onwards, the LR relinquishes part (half) of its control of optionality

to the LE, who gains additional value from a real options (*E*-NPV) angle. Figure 5 shows the option map for the LR under scheme IIIb.

Our assessment on how the *E*-NPV of the licensing contract is split between BioCryst and Mundipharma under the most commonly used licensing contract typologies (and some of their variants a and b) yields asymmetric outcomes under schemes I and III, and a more symmetric split under scheme II depending on who pays and controls the drug development expenditures (and hence the embedded continuation/abandonment options). These asymmetric outcomes may often favor the LE (pharma) at the expense of the LR (biotech). Our findings also shed light on how the *strategic* NPV (*E*-NPV) of licensing transactions in biopharma is typically apportioned between LR and LE across common contract typologies depending upon the specific stage at which the deal is signed. Table 8 shows that, as the R&D stage progresses, the LR (biotech) tends to capture more value (on average 35% at Phase I, 45% at Phase II, 60% at Phase III) because of its increasing contribution to drug development.

[INSERT FIGURE 5 AND TABLE 8 ABOUT HERE]

Tradeoffs and Implications for Licensing Contract Design, Negotiation and Portfolio Management

We next highlight certain tradeoffs and discuss managerial implications on how the *expanded* NPV of the R&D program should be divided among LR and LE under the various licensing schemes that differ in the extent of embedded optionality and control of the R&D process. Under licensing scheme I, the partition of the R&D project value tends to favor the LR (at the expense of the LE) due to the liability of LE to incur all R&D expenditures associated with control of embedded optionality. However, such a liability creates an incentive for the LE to engage in the licensing situation and be apportioned a portion of the value created when applying a real option valuation (*strategic* NPV) framework. In scheme II, the value of the underlying R&D program accrues almost equally to LR and LE (assuming symmetric market power). Under scheme III, the split favors the LE as milestone payments otherwise due to the LR are foregone due to co-development. A higher royalty rate may instead be used to readjust the split. Co-development under the variant b of scheme III enables a more balanced value spit among the parties as the LR commands optionality until completion of Phase II and shares control of the underlying R&D program with the LE from midway (Phase III) onwards.

What would be of interest, in particular, is identifying menus consisting of a different mix of fixed payments and royalties that result in the same split (PSR) for each party and induces the parties to engage in optimal and fair license deal-making. Understanding the degree to

which fixed payments and royalties are equivalent in terms of *E*-NPV and hence can substitute for each other would enable (i) tailoring the agreement to individual preferences from among the menu of equivalent alternatives, and (ii) facilitating deal making itself.[22] For example, the LR can accept to enter the licensing scheme Ia and attain the same *strategic* NPV while negotiating a different mix of fixed payments (upfront fee and milestones) vs. royalty payments agreeable to the LE. The LR might relinquish the continuation/abandonment option exercise decisions underlying the R&D program (associated with choice of licensing scheme IIa) to the LE only undertaking the technical risks of drug development (and avoiding payment of related R&D expenditures) by negotiating a higher rate of royalty payments after drug market launch.

As seen in Figure 6, the LR can obtain the same *E*-NPV value ($ 41.48 m) shown on the solid line, while achieving a remuneration scheme with its preferred mix as to fixed vs. royalty payments. As an illustration, the LR can attain the same *E*-NPV with the following three combinations: (i) fixed payments of $ 195 m and a royalty rate of 4%; (ii) fixed payments of $ 165 m and a royalty rate of 6.5%; (iii) fixed payments of $ 135 m and a royalty rate of 9%. As the royalty percent on sales rises, the sum of upfront fees and milestone payments needed is lower. Through presenting an equivalent *E*-NPV menu of choices to the respective parties, their particular fixed vs. variable compensation preferences, risk appetites and financial constraints can be met while achieving a fair and jointly value-enhancing licensing deal that accounts for the staging optionality embedded in the R&D process and the licensing contract terms.

[INSERT FIGURE 6 AND 7 ABOUT HERE]

We also provide the means for quantifying the notion that an investment decision undertaken by a pharma firm, such as Mundipharma, should consider both its immediate cash payoff and future growth potential. At any stage of development (from molecule to marketable drug) the total value of the R&D program can be viewed as the sum of the present value of the cash inflows from expected drug sales net of development and commercialization costs (*static* NPV) plus the present value of follow-on options embedded in the staged R&D process. Extending this idea to the portfolio level, we should envision a growth options (GO) matrix where existing (patented) and new (patentable) drug development opportunities are categorized into four regions in option-value space based on their current "cash flow" (NPV) versus "growth option" (GO) potential (Figure 7). The horizontal axis measures the *static* NPV of R&D projects (currently in place or realizable in the future) capturing current expected profitability from immediate, passive investing. The vertical axis measures the extra strategic value resulting from

exploiting these (existing or new) projects as a growth platform. Hence it captures the value of the staged (or compound) development of drug-related growth opportunities as technical and market uncertainties are resolved (Present Value of Growth Opportunities, PVGO).

The bottom-left region of the GO matrix (region I) accommodates molecules that are currently unprofitable but have high growth option potential. As the pharma company identifies R&D programs conducted externally by third parties as belonging to this region of the option-value space, it might *acquire* or *license* them *in* to be able to capture (not only the immediate value of direct cash inflows but also) the extra strategic value of their follow-on growth opportunities such as those connected to the "market for technology" (e.g., licensing). The same logic applies when the pharma company identifies one or some of its R&D projects as belonging to region I. It may decide to invest *more* resources into their full *development* to turn them into "licensable out" drugs in deals to be negotiated with biotech firms in the course of (or upon) R&D completion and authority approval. The strategic path to follow is then to move these projects from region I to region II. Region II is the portion of the option-value space where molecules for which staged development has been successfully completed may be *commercialized* or *licensed out* in the form of novel, "ready-for-market" drugs in order to obtain both the immediate value of direct cash inflows from sales and the extra strategic value of their follow-on growth opportunities (e.g., long-term licensing transactions with biotechs to split distribution rights across different geographical regions).

The top-right of the GO matrix (region III) comprises molecules whose further development can be rapidly accomplished under low uncertainty and related new drugs brought to market with a prospective commercial success. Their strategic growth option potential is rather modest but their NPV is high. As these molecules are "cash cows", prescribed managerial action is to complete development and *commercialize* them. Alternatively, such molecules can be *licensed out* to biotech firms so as to complete the related R&D program and exploit them in a short-term fashion via market commercialization or *sold* off to other competitors for their immediate use in the marketplace. In the top-left region of the GO matrix (region IV) there are molecules with both low current commercial value and growth option potential that should be *divested* or *abandoned* now. By recognizing early in the R&D process that these molecules may be hampered by high technical uncertainty that, if developed, may lead to low-prospect drugs under current and future market conditions, divesting (for salvage value, if any) or abandonment is the most appropriate strategy.

Drug development programs in regions III and IV might be less risky as there might be a low degree of technical and market uncertainty involved, while those falling in regions I and II

are riskier but present more potential upside opportunity that can be exploited by committing to invest more at subsequent stages. R&D portfolio risk can be mitigated by controlling the option not to advance development if conditions turn out to be unfavorable (divestiture in region IV). The GO matrix can provide guidance to a pharma company on how to strategically analyze the impact of its R&D portfolio composition on shareholder value, prioritize internal R&D budgets and flexibly manage its R&D pipeline based on *real option* exploration and exploitation potential.

Conclusions

This study gives new insights into how the activity of engaging in licensing-based strategic alliances between firms really works focusing on the interaction between real options theory, the sequential nature of the product innovation process, and contractual licensing arrangements. Based on our proposed classification of common contractual schemes for licensing in the biopharma industry, we used the BioCryst/Mundipharma case to exemplify the application of real options theory to: (a) accessing licensing deals accounting for the sequential nature of product innovation viewed as multistage compound options with success probabilities; (b) prescribing how deal making among licensor and licensee can be conducted in uncertain conditions to attain a more fair split given the sequential nature of product innovation; (c) offering a framework for reaching an optimal and fair remuneration of the deal for both parties; (d) providing the parties with equivalent deal structuring solutions tailored to their specific conditions, funding or control needs and preferences; (e) providing a pharma company with a R&D portfolio strategy framework for carrying out a strategic analysis of its internal drug development programs (e.g., license-in vs. license-out), undertaking flexible project investment/divestment decisions and managing the allotment of associated budgets with the aim of ultimately improving shareholder value. Uncertainty is a key driver of the option to discontinue sequential product innovation and hence can affect the relative attractiveness of alternative contractual schemes, with different implications for licensing negotiation than traditional analyses of license contracting.[23] That is because different degrees of uncertainty and optionality can change optimal decisions about the contractual structure of a license deal and change the true sharing allocation among the parties. License deal-making critically depends on who controls the development option and on the degree of the underlying uncertainty. The above can lead to quite asymmetric or biased R&D value capture.

Our study adds value in several respects. It illustrates the key business practices followed by biotech and pharma companies to design financial terms and value split when engaging in

licensing-based strategic alliances. It supplements the innovation and alliance literatures by extending licensing value appraisal and appropriation to account for embedded optionality. Relatedly, it re-examines how the value split between licensor and licensee must be adjusted in light of uncertainty and optionality conditions. It is our hope to contribute toward combining real options theory with alternative biopharma licensing contractual structures offering an insightful, fair and effective way of designing and negotiating the terms of licensing deals under uncertainty.

The approach to designing optionality in licensing proposed herein can be extended to other industries and business contexts, such as franchising, where two parties (franchisor and franchisee) aim to reach a deal through which one party grants the other the right of representation to sell its product or service using its business format (brand name or process) in a given location for a specified period in return for fixed (franchise fee) and use (sales)-based payments (royalties). Our methodology is likely of use also in an entrepreneurial setting where remuneration, funding and exit are typically conditioned on staged or interim success.

FIGURE 1. Drug development life cycle and sales curve for representative drug

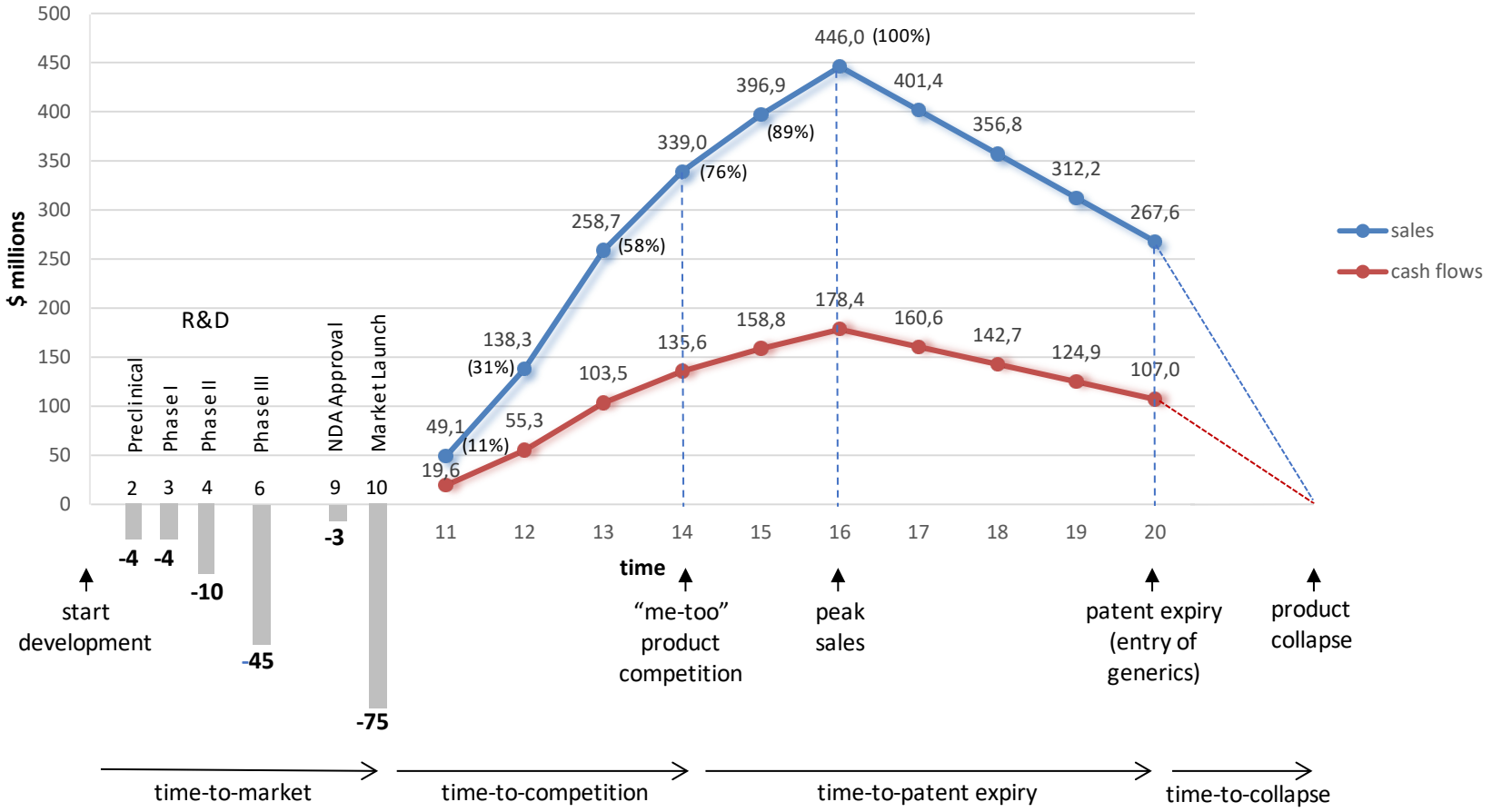


FIGURE 2. *Strategic* net present value of a representative drug's R&D program using real options analysis

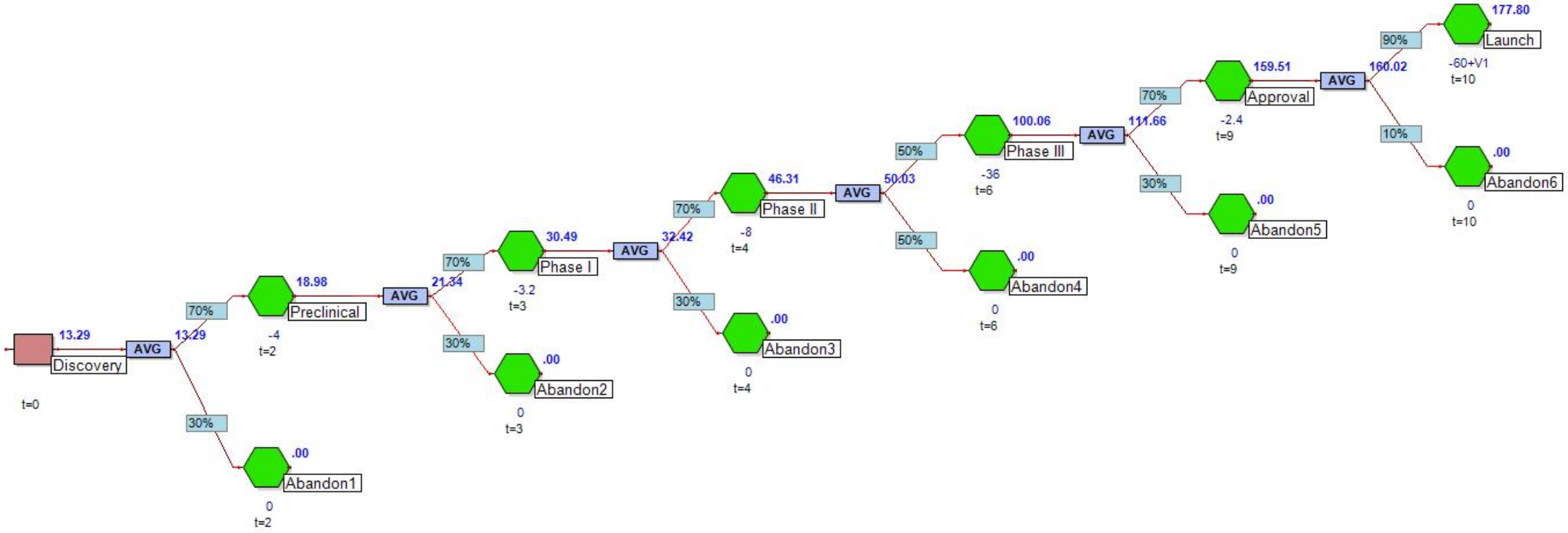


FIGURE 3. Licensing-related cash flows

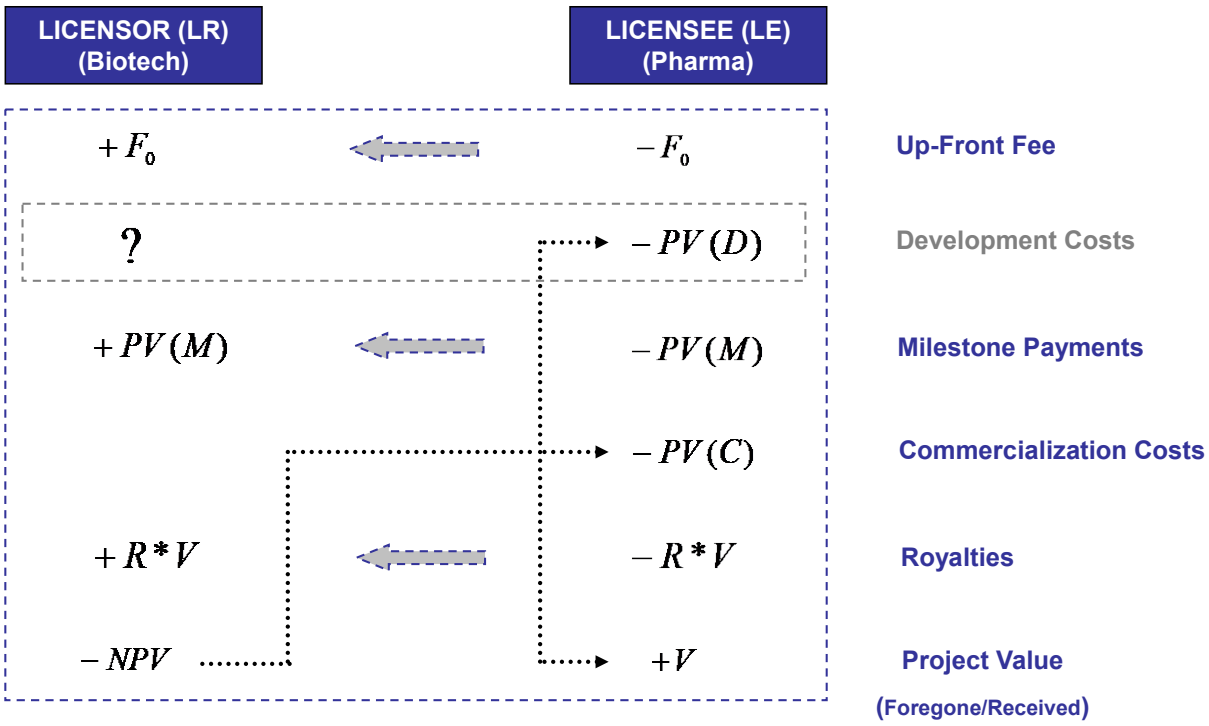
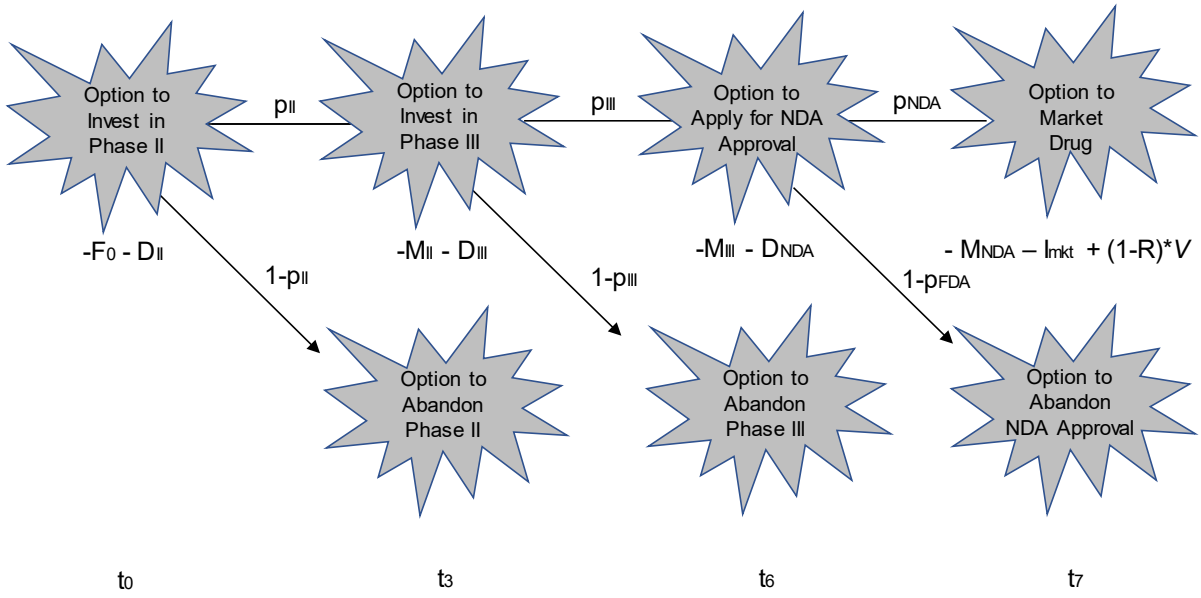
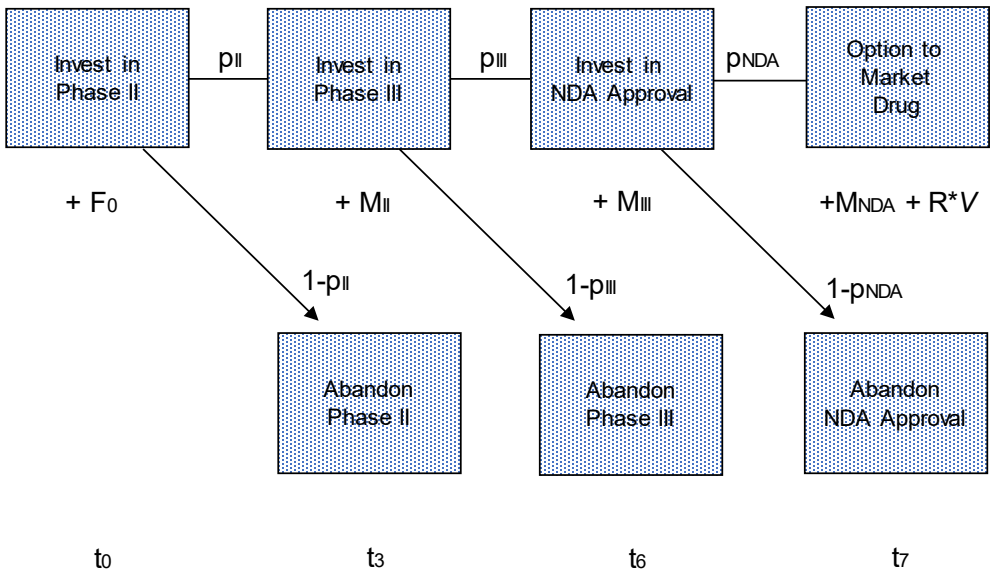


FIGURE 4. Illustrating R&D licensing as a multistage option based on BioCryst/Mundipharma R&D program case. Scheme Ia: active Licensee (LE) pays development costs and controls optionality.

Panel A. active Licensee (LE)



Panel B. passive Licensor (LR)



Legend:
F = upfront fee
M = milestone payment
D = development cost
I_{mkt} = investment for drug market launch
R = royalty rate
V = underlying drug value
p = probability of technical success

FIGURE 5. Scheme IIIb: Licensor (LR) starts development (active) but Licensee (LE) has option to switch to co-development from Phase III.

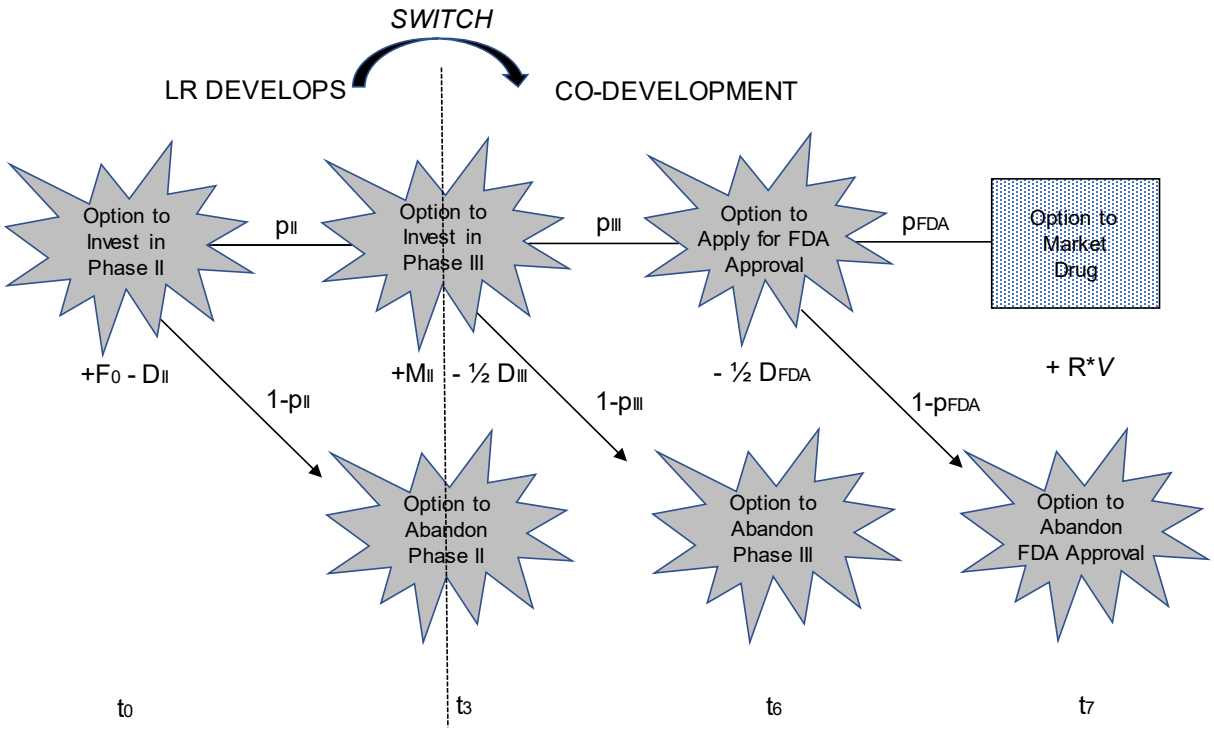


FIGURE 6. Equivalent E-NPV choices for Licensor (LR) for contract scheme Ia.

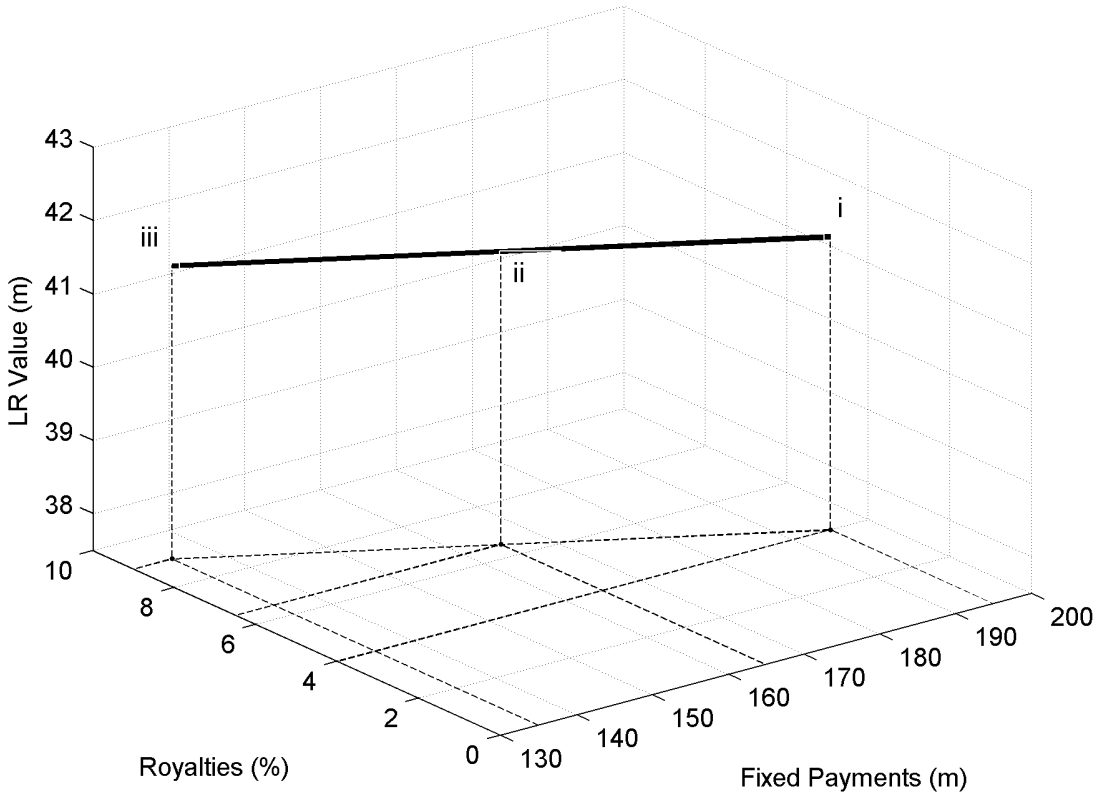


FIGURE 7. Growth option matrix for R&D portfolio management

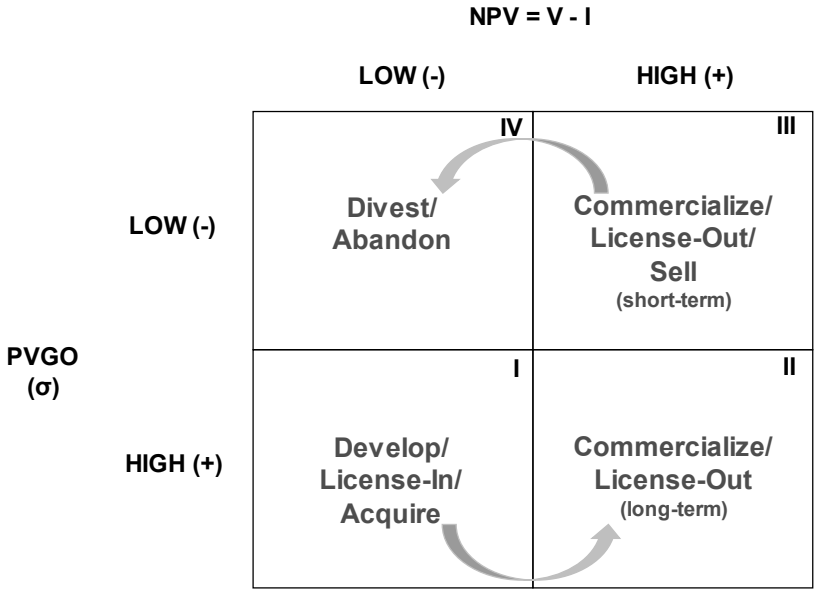


TABLE 1. Number of licensing deals, median upfront fee and milestones by therapy area (based on available deal data).

Therapy Area	# Deals	Upfront Fee ($m) (**)	R&D Milestones ($m) (***)	Sales Milestones ($m) (****)
Cardiovascular	17	2.0	42.5	43.5
Central Nervous System	42	6.3	35.0	55.0
Endocrine, Metabolic and Genetic Disorders	24	22.7	30.0	120.0
Gastroenterology	16	10.0	65.0	78.8
Immunology and Inflammation	17	13.5	74.0	100.0
Infectious Deseases	28	14.0	151.5	747.5
Oncology and Hematology	75	6.7	138.0	87.8
Osteo-arthritis & Musculoskeletal	9	10.0	60.0	200.0
Respiratory	8	10.0	24.5	
Urology & Women's Health	6	7.5		
Other (*)	15	6.8	40.0	135.0
Overall	**257**	**10.0**	**57.5**	**92.5**

(*) Other include dermatology, ophthalmology and miscellaneous.
(**) Based on 190 deals with available upfront fee data.
(***) Based on 88 deals with available breakdown data on R&D milestones.
(****) Based on 24 deals with available sales milestone data.

TABLE 2. Median upfront fee, milestones and royalty rates by stage.

Phase at deal signing	Number of Deals	Upfront Fee ($m)	R&D Milestones ($m)	Sales Milestones ($m)	Royalty Rate
Preclinical	77	9.5	54.5	110.0	5.0%
Phase I	48	8.5	70.0	95.0	8.0%
Phase II	66	10.0	101.0	100.0	10.0%
Phase III	39	15.0	111.8	103.8	14.5%
Approval	27	9.8	20.4	75.0	13.0%
Total	**257**	**10.0**	**57.5**	**100.0**	**10.0%**

TABLE 3. Representative royalty rates by therapy area and stage of deal signing.

Therapy Area	Preclinical	Phase I	Phase II	Phase III	Approval
Cardiovascular	4.5%	7.5%	7.7%	10.0%	12.5%
Central Nervous System	5.0%	8.0%	9.3%	11.3%	11.2%
Endocrine, Metabolic and Genetic Disorders	5.0%	7.0%	10.0%	10.8%	15.0%
Gastroenterology	5.0%	8.6%	10.3%	14.0%	
Immunology and Inflammation	5.7%	7.5%	11.5%	14.5%	14.0%
Infectious Deseases	8.0%	10.0%	13.1%	14.0%	14.0%
Oncology and Hematology	5.0%	8.0%	10.0%	12.1%	13.4%
Osteo-arthritis & Musculoskeletal	5.6%	8.0%	10.0%	12.1%	13.4%
Respiratory	6.3%	11.5%	10.4%	10.0%	13.8%
Urology & Women's Health	5.6%	8.8%	7.5%	12.1%	13.4%
Other/Avg	5.6%	8.5%	10.0%	12.1%	13.4%
Overall (based on 256 deals)	**5.0%**	**8.0%**	**10.0%**	**14.5%**	**13.0%**

TABLE 4. Representative (typical) drug development parameters: duration, development costs and success probabilities by R&D stage.

	Discovery	Preclinical	Phase I	Phase II	Phase III	NDA Approval	Market Launch	*Total/ Cumul.*
Time (year)	0	2	3	4	6	9	10	
Duration (years)	2	1	1	2	3	1		*10*
Cost (US $ mln)	-4	-4	-4	-10	-45	-3	-75	*-145*
Biotech	*-3*	*-3*	*-3*	*-7*	*-30*	*-3*		
Pharma	*-6*	*-7*	*-5*	*-12*	*-68*	*-3*		
Success Prob.	70%	70%	70%	50%	70%	90%	100%	*11%*

Source: DiMasi et al. (2003, 2016), Bogdan and Villiger (2010).

TABLE 5. Peak sales by therapy area and probabilities of success by therapy area and stage.

#	Therapy Area	Mean Peak Sales (US $ mln)	Median Peak Sales (US $ mln)	Peak Sales Used (US $ mln)	Success Probabilities by Stage				
					Phase I	Phase II	Phase III	Approval	*Cumulative*
1	Cardiovascular	466	145	306	68%	48%	76%	89%	*22.3%*
2	Central Nervous System	746	422	584	71%	51%	62%	83%	*18.5%*
3	Endocrine, Metabolic & Genetic Disorders	803	371	587	53%	57%	79%	98%	*23.2%*
4	Gastroenterology	792	299	546	72%	54%	71%	91%	*25.1%*
5	Immunology & Inflammation	571	349	460	70%	50%	65%	87%	*19.5%*
6	Infectious Diseases	385	265	325	76%	56%	80%	102%	*34.7%*
7	Oncology & Hematology	735	323	529	69%	47%	65%	95%	*20.1%*
8	Respiratory	646	213	430	68%	46%	60%	82%	*15.5%*
9	Osteo-arthritis & Musculoskeletal	127	127	127	82%	43%	78%	94%	*25.9%*
10	Urology & Women's Health	602	535	569	50%	45%	58%	74%	*9.5%*
11	*Average/Other* (*)	***587***	***305***	***446***	***70%***	***50%***	***70%***	***90%***	***21.9%***

(*) Other includes dermatology, ophthalmology and miscellaneous.
Main Source: Bogdan and Villiger (2010), pp. 75, 78.

TABLE 6

Real-world illustrations of some licensing contract schemes.

Licensing Contract	**Licensor (LR) (biotech)**	**Licensee (LE) (pharma)**	**Date of transaction**	**Description of the licensing deal**
Scheme Ia LE pays development costs (D)	Ra Pharmaceuticals	Merck & Co	01/04/2013	Ra Pharmaceuticals signs an agreement with Merck to develop Cyclomimetic™. Ra will use its Extreme Diversity™ platform to develop Cyclomimetic™ candidates for protein targets in multiple therapeutic areas. Ra will receive up to $200 m including upfront fee, discovery, development and commercialisation milestones.
Scheme Ib LR starts development (D) and LE has option to take over midstream	BIND Therapeutics	Pfizer	06/04/2013	BIND Therapeutics enters into global collaboration with Pfizer to develop and commercialise multiple Accurins™. Pfizer is granted the exclusive option to develop and commercialize Accurins™ selected by its team after preclinical stage. Both companies will share preclinical research, and if Pfizer exercises its option, it will take over. BIND will receive a $50 m upfront fee and development milestones amounting to $160 m for each Accurins™ commercialised plus royalties on future sales.
Scheme IIa LR pays development costs (D)	Chiasma	Roche	18/02/2013	Roche receives a worldwide exclusive license to Octreolin® assuming responsibility for its commercialisation. Chiasma will continue development until completion of Phase III clinical trial for acromegaly receiving an upfront fee of $65 m, development and commercial milestones of $530 m and double-digit royalties.
Scheme IIb LR pays development costs (D) but gets reimbursed by licensee	Acura Pharmaceuticals	King Pharmaceuticals	12/10/2007	Acura Pharmaceuticals grants King Pharmaceuticals rights to use its Aversion® technology platform for release of 4 opioid analgesic products (including ACUROX tablets). Acura will conduct full development of ACUROX tablets until NDA approval receiving an upfront fee of $30 m, R&D milestones of $28 m (plus similar amounts for each subsequent Aversion® Technology product) and royalties (5%-25% on sales). King will reimburse Acura for all R&D expenses incurred.

Scheme IIIa Co-development (LE agrees to co-develop by sharing development costs)	Ultragenyx	Kyowa Hakko Kirin (KHK)	03/09/2013	Ultragenyx enters into a license agreement with KHK to develop and commercialise KRN23 for X-linked Hypophosphatemia (XLH) for US, Canada and EU sharing development costs. The parties will share commercial responsibilities and profits in US and Canada. KHK has completed Phase I and II trials in adults with XLH in US and Canada. The two partners will also collaborate on a paediatric XLH program.
Scheme IIIb LR starts development paying related costs (D) but licensee has option to switch to co-development	Genmab	GlaxoSmithKline (GSK)	19/12/2006	Genmab and GSK enter a worldwide agreement to co-develop and commercialize HuMax-CD20. Genmab will be responsible for development (including related costs, e.g. of 2 ongoing late stage oncology studies) for 2 years, after which GSK will have an option to start co-developing by equally sharing R&D costs with Genmab.

TABLE 7. Taxonomy of alternative licensing contract schemes

	Licensing contract scheme	Who controls development	# Deals	%
I	a) Licensee controls development and pays development costs (D)	LR	180	70%
	b) Licensor starts development (D) but Licensee has option to take over midstream		13	5%
II	a) Licensor controls development and pays development costs (D)	LE	3	1%
	b) Licensor pays development costs (D) but gets reimbursed by Licensee		33	13%
III	a) Licensor & Licensee co-develop (share development costs, D) from start	LR/LE	23	9%
	b) Licensor starts development (D) but Licensee has option to switch to co-development		5	2%
		Total	***257***	***100%***

TABLE 8. Value share for Licensor (E-NPV LR) as % of total value (with range).

Stage at deal signing	Based on	
	% E-NPV LR *	**% NPV/Practice ****
Preclinical	40% (20-50%)	15% (10-20%)
Phase I (IND)	35% (25-45%)	30% (20-40%)
Phase II	45% (35-55%)	50% (40-60%)
Phase III	60% (50-70%)	
Approval	55% (40-80%)	70% (60-80%)

Sources:

(*) Authors' option-based estimates using Medtrack & RECAP IQ databases.
(**) Bogdan and Villiger (20

Supplementary Appendix: Option valuation of Scheme Ia: Licensee (LE) controls development and pays development costs

This Appendix illustrates the real option valuation (using binomial trees in Excel) for the case of licensing contract scheme Ia where the LE (pharma) incurs the development costs and controls the optionality embedded in the underlying R&D program (exercise of the compound option). The licensor counterparty (LR) here passively receives the committed cash-flow payments (upfront fee, milestones, royalties).

The evolution of uncertainty is modeled by a standard binomial lattice tree where the underlying (asset) value of the R&D program (V) can either move up ($u = e^{\sigma\sqrt{t}} = e^{0.6*1} = 2.7$) or down ($d = 1/u = 0.4$) in each period ($t$ = 1) depending on the candidate drug market demand fluctuation, with an estimated volatility (σ) of 100%. The resulting binomial tree (top tree shown in the Excel spreadsheet in Figure A.1 below) represents the evolution of the candidate drug value (V) across the subsequent R&D stages until commercial launch in the market at the end of t = 6.

The licensing contract value (E-NPV or V') based on the *strategic* or *expanded* NPV criterion (see also Smit and Trigeorgis, 2017) is derived by dividing the compound valuation process into 4 steps (or stages) corresponding to the 4 remaining stages of the R&D program (clinical Phases II and III, NDA approval, commercial launch) before the molecule can become a marketable drug. Each step must account for the probability of successfully completing the relevant stage (clinical, NDA approval or market launch) taking the candidate drug forward in the R&D process (p_s being the probability of technical success in stage s). Compound option valuation is carried out by working backward the drug investment opportunity values in the binomial tree across the various up and down states. At each stage (clinical Phase II and III, NDA approval, commercial launch), the payoff structure of the option that would be exercised by the LE is: $V_t' = \max\left[\mathrm{p} * \ V - \mathrm{I}\right]$.

At the launch/commercialization stage (t = 6), the associated option payoff is $V_t' = -\mathrm{M}_{\mathrm{NDA}} + \max\left[\mathrm{p}_{\mathrm{mkt}} * V_6(1-\mathrm{R}) - \mathrm{I}_{\mathrm{mkt}} - \mathrm{M}_{\mathrm{mkt}}, 0\right]$, where $\mathrm{M}_{\mathrm{NDA}}$ (= \$ 28 m) is the milestone payment due to the LR for successfully achieving the national drug authority approval, $\mathrm{p}_{\mathrm{mkt}}$ (=1) is the probability of commercializing the drug following NDA approval, V_6 is the value of the molecule at year 6 (contingent on the up/down state), R is the royalty rate (6.5% or 0.065), $\mathrm{I}_{\mathrm{mkt}}$ (= \$ 75 m) is the total investment cost to be incurred for launching the drug into the marketplace and is $\mathrm{M}_{\mathrm{mkt}}$ (= \$ 42 m) is the milestone payment due to the LR for successfully

taking molecule to a ready-for-market drug. Upon successful NDA approval the LE here will commercialize the drug (with probability 1) appropriating the value of future cash inflows from sales net of royalty payments (due to LR) and marketing/milestone costs. By proceeding backward along the binomial tree, the preceding values are obtained as the continuation value (discounted expected payoff) based on $C_t = \left[\mathrm{p} V_{t+1}^{u} + (1-\mathrm{p}) V_{t+1}^{d} \right] e^{-rdt}$. Here V_{t+1}^{u} and V_{t+1}^{d} are the future option payoffs (under the up and down states) at the subsequent node at time t+1; p (=0.3) and 1-p (=0.7) are the risk-neutral probabilities of up and down moves; e^{-rdt} (=0.97) is the discount factor (at risk-free rate interest rate r = 0.035). If the LE were to appraise the licensed molecule at time 0 (embedding the option to launch it in the marketplace at end of t = 6), its value today would be $ 233.75 m.

A similar backward induction procedure is applied to precedent stages. At the NDA approval stage (t = 6), the associated option payoff is $V_t^{'} = -\mathrm{M}_{\mathrm{III}} + \max\left[\mathrm{p}_{\mathrm{NDA}} * C_6 - \mathrm{D}_{\mathrm{NDA}}, 0 \right]$ and the value at time 0 reflecting the prospects of successful completion of this stage is $ 185.92 m. At Phase III (t = 3), the associated option payoff is $V_t^{'} = -\mathrm{M}_{\mathrm{II}} + \max\left[\mathrm{p}_{\mathrm{III}} * C_3 - \mathrm{D}_{\mathrm{III}}, 0 \right]$ and the licensed molecule value at time 0 is $ 86.67 m. At Phase II (t = 0), the option payoff is $V_t^{'} = -\mathrm{F}_{\mathrm{II}} + \max\left[\mathrm{p}_{\mathrm{II}} * C_{\mathrm{II}} - \mathrm{D}_{\mathrm{II}}, 0 \right]$ and the licensed molecule value at time 0 is $ 20.56 m. The Phase II (t = 0) value of the licensed molecule thus represents the licensing deal value accruing to the LE if contract scheme Ia is chosen by the parties.

FIGURE A.1 – Inputs and multistage option valuation in Excel - Scheme Ia: Licensee (LE) controls development and pays development costs (D)

Panel A – Inputs

	Phase II			Phase III			NDA	Launch
Year	0	1	2	3	4	5	6	7
Prob	*0,47*		*0,65*			*0,95*	*1*	
Fee (F)	10							
Devel (D)	10		45			3		
Milest (M)			28			56	28	42
Launch (C)								75
Inv (I)			73			59	28	117

Panel B – Excel-based real option valuation

Launch/Commercialization (t = 6)

Year	0	1	2	3	4	5	6
0	233,75	737,83	2.202,27	6.398,92	18.309,17	51.960,11	147.021,74
1		61,03	238,91	776,79	2.360,61	6.910,59	19.771,46
2			-0,96	54,10	236,18	813,80	2.550,01
3				-21,11	-9,76	36,72	219,34
4					-26,28	-27,21	-28,18
5						-27,21	-28,18
6							-28,18

$- M_{NDA} + \max(P_{mkt} * V_6(1-R) - I_{mkt} - M_{mkt}, 0$

NDA Stage (t = 5)

Year	0	1	2	3	4	5
0	185,92	654,32	2.032,10	6.004,43	17.281,46	49.146,86
1		23,91	182,98	680,27	2.178,18	6.484,97
2			-33,02	10,28	166,34	711,31
3				-50,43	-46,22	-24,59
4					-54,43	-56,36
5						-56,36

$- M_{III} + \max(P_{NDA} * C_{NDA} - D_{NDA}, 0)$

Phase III (t = 2)

Year	0	1	2
0	86,67	357,26	1.255,81
1		-7,93	46,49
2			-28,18

$- M_{II} + \max(P_{III} * C_{III} - D_{III}, 0)$

Phase II (t = 0)

Year	0
	20,56

$- F_{II} + \max(P_{II} * C_{II} - D_{II}, 0)$

[1] See H. Chesbrough and Eric L. Chen, "Recovering abandoned compounds through expanded external IP licensing," *California Management Review*, 55/4 (2013): 83-101.

[2] The rapid pace of product innovation fostered an increase in US and European biotech firms' revenues. In 2016, 47 IPOs were completed raising $2 billion. In recent years, heightened competition and availability of cash created a more positive license deal-making climate. In 2016 pharma-biotech licensing in Europe increased by 6% to 68 deals worth $19 billion (See Ernst & Young, *Beyond Borders. Global Biotechnology Industry Report*, 2017).

[3] A. Ziedonis, "Real options in technology licensing," *Management Science*, 53/10 (2007): 1618-1633; E. Dechenaux, M. Thursby, and J. Thursby, "Shirking, sharing risk and shelving: The role of university license contracts," *International Journal of Industrial Organization*, 27/1 (2009): 80-91; B. Bodgan and R. Villiger, *Valuation in Life Sciences: A Practical Guide* (Springer, 2010).

[4] Ziedonis, op. cit. examines the use of option contracts by firms acquiring rights to commercialize university technologies. By combining information about the sequence of licensing decisions with characteristics of the firms and technologies involved, he examines empirically factors that shape decisions to purchase and exercise option contracts for early-stage technologies.

[5] Cumulative probability of completing the drug R&D program becomes 10.8% if discovery is also considered.

[6] NPV appraisal is based on the following assumptions: operating margin (50%), tax rate (20%), risk-adjusted discount rate (RADR) (12%), risk-free rate (3.5%).

[7] Milestone payments for successful completion of Phase I, Phase II and approval are 1x the amount of upfront fee ($ 10 m); milestone payments rewarding completion of Phase III are 2x the amount of upfront fee ($ 20 m); sales milestone payments are 1.5x the amount of upfront fee ($ 15 m).

[8] Under a licensing situation the pharma/licensee does not pay the cost of discovery as it has already been incurred by the biotech/licensor.

[9] See C. Taylor and Z. Silbertson, *The Economic Impact of the Patent System: A Study of the British Experience*, (Cambridge University Press: New York, 1973); E. Caves, H. Crookell, and J.P. Killing, "The imperfect market for technology licenses," *Oxford Bulletin of Economics and Statistics*, 45/3 (1983): 249-267; see also A. Arora and A. Fosfuri, "Licensing the market for technology," *Journal of Economic Behavior and Organization*, 52/2, (2003): 277-295; H. Chesbrough, "The logic of open innovation: managing intellectual property," *California Management Review*, 45/3, (2003): 33-58; A. Arora and M. Ceccagnoli, "Patent protection, complementary assets and firm's incentives for technology licensing," *Management Science*, 52/2, (2006): 535-554.

[10] Prospect evaluation of licensing activities and related deal making are challenging given the existence of asymmetric information among the parties [N.T. Gallini and B.D. Wright, "Technology transfer under asymmetric information," *RAND Journal of Economics*, 21 (1990): 147-160; A.W. Beggs, "The licensing of patents under asymmetric information," *International Journal of Industrial Organization*, 10, (1992): 171-194; A. Bousquet, H. Cremer, M. Ivaldi, and M. Wolkowicz, "Risk sharing in licensing," *International Journal of Industrial Organization*, 16/5 (1998): 535-554; R. Hernandez-Murillo and G. Llobet, "Patent licensing revisited: heterogeneous firms and product differentiation," *International Journal of Industrial Organization*, 24/1 (2006): 149-175] and common remuneration schemes used in the sector [B.N. Ananda and T. Khanna, "The structure of licensing contracts," *Journal of Industrial Economics*, 48/1 (2000): 103-135; R.S. Ruback and D.B. Krieger, "Merck & Co.: evaluating a drug licensing opportunity," *Case 9-201-023*, (Harvard Business School Publishing, Boston, MA, 2000); P. Crama, B. De Reyck, Z. Degraeve, and W. Chong, "R&D project valuation and licensing negotiations at Phytopharm plc," *Interfaces*, 37/5 (2007): 472-487]. Licensing legal structures have evolved from earlier contracts involving a single term, e.g., an upfront fee [M.I. Kamien and Y. Tauman, "Fees versus royalties and the private value of a patent," *Quarterly Journal of Economics*, 101 (1986): 471-493; M.I. Kamien, S. Oren, and Y. Tauman, "Optimal licensing of cost-reducing innovation," *Journal of Mathematical Economics*, 21 (1992): 483-508] or a royalty rate [M.L. Katz and C. Shapiro, "On the licensing of innovations," *RAND Journal of Economics*, 16 (1985): 504-520; M.L. Katz and C. Shapiro, "How to license intangible property," *Quarterly Journal of Economics*, 101/3 (1986): 567-590] to two-part tariff contracts involving both upfront fee and royalties [C. Shapiro, "Patent licensing and R&D rivalry," *American Economic Review*, 75/2: (1985): 25-30; I. Macho-Stadler, X. Martinez-Giralt, and J.D. Perez-Castrillo, "The role of information in licensing contract design," *Research Policy*, 25/1 (1996): 43-57; R. Jensen and M. Thursby, "Proofs and prototypes for sale: the licensing of university inventions," *American Economic Review*, 91/1 (2001): 240-259], to three-part tariff contracts with milestone payments, besides an upfront fee and royalty rate (E. Dechenaux, M. Thursby, and J. Thursby, op. cit.) that are superior to two-tier structures [P. Crama, B. De Reyck, and Z. Degraeve, "Milestone payments or royalties? Contract design for R&D licensing," *Operations Research*, 56/6 (2008): 1539-1552] and most preferred in deal negotiations [C. Hall, "Renting ideas," *Journal of Business*, 64/1 (1991): 21-48; D.W. Elfenbein, "Patents, publications, and the market for university inventions," *Journal of Economic Behavior and Organization*, 63/4 (2007): 688-715]. E. Dechenaux, M. Thursby, and J. Thursby (op. cit.) suggest that milestone payments should complement royalties to enable a risk-averse LR to hedge against the risk of completing a technology that has no commercialization potential. Milestone and royalty payments ensure that the LR collaborates with the LE in

developing the technology from the early stage through the provision of proper incentives (tying remuneration to successful completion of subsequent R&D phases and potential market success of the drug) (I. Macho-Stadler, X. Martinez-Giralt, and J.D. Perez-Castrillo, op. cit.), while allowing a small biotech to access cash reserves via payment of upfront fees, milestones and royalties from its pharma partner to finance further R&D operations and share technical and commercial risks (Bodgan and Villiger, op. cit.).

[11] See also F. Baldi and L. Trigeorgis, "IP Licensing," *Sinergie Italian Journal of Management*, 93, (January-April 2014): 55-78.

[12] Above, no optionality is involved on the part of the LR. The LE receives V_{LE}, which corresponds to the value of the licensing contract net of the value share accruing to the LR (V_{LR}).

[13] We assume here NPV is suitable for valuing the license to a *passive* investor. NPV assumes committed decisions under an expected (mean) scenario and is unable to properly quantify the value of contingent decisions and options embedded in the sequential nature of the R&D process and the structure of the licensing deal itself.

[14] M. Hartmann and A. Hassan, "Application of real option analysis for pharmaceutical R&D project evaluation," *Research Policy*, 35/3 (2006): 343-354.

[15] Early work on real option valuation in R&D employed option pricing formulas [D. Newton and A. Pearson, "Application of option pricing theory to R&D," *R&D Management*, 24/1 (1994): 83-89; E. Pennings and O. Lint, "The option value of advanced R&D," *European Journal of Operational Research*, 103/1 (1997): 83-94], binomial lattices [D. Kellogg and J.M. Charnes, "Real-options valuation for a biotechnology company", *Financial Analysts Journal*, 56 (2000): 76-84; R. Shockley, S. Curtis, J. Jafari, and K. Tibbs, "The option value of an early-stage biotechnology investment," *Journal of Applied Corporate Finance*, 15 (2003): 44-55] or Monte Carlo simulation [e.g., E.S. Schwartz, "Patents and R&D as real options," *Economic Notes*, 33/1 (2004): 23-54]. E. Pennings and L. Sereno (2011) develop a compound R&D option model accounting for the technical risk of failure (by R&D stage), viewing drug development as a Poisson jump process. See E. Pennings and L. Sereno, "Evaluating pharmaceutical R&D under technical and economic uncertainty," *European Journal of Operational Research*, 212/2 (2011): 374-385. Viewing multi-stage pharma R&D as a chain of options, D. Cassimon, M. De Backer, P.J. Engelen, M. Van Wouwe, and V. Yordanov (2011) extend the n-fold compound option model of D. Cassimon, P.J. Engelen, L. Thomassen, and M. Van Wouwe (2004) to handle technical risk in addition to commercial risk [see D. Cassimon, M. De Backer, P.J. Engelen, M. Van Wouwe, and V. Yordanov "Incorporating technical risk in compound real option models to value a pharmaceutical R&D licensing opportunity," *Research Policy*, 4 (2011): 1200-1216; D. Cassimon, P.J. Engelen, L. Thomassen, and M. Van Wouwe, "The valuation of a NDA using a 6-fold compound option," *Research Policy*, 33/1 (2004): 41-51]. They also apply their model to a real-life project of a pharma firm. D. Cassimon, M. De Backer, P.J. Engelen, M. Van Wouwe, and V. Yordanov (op. cit.) consider a licensed-in molecule in the discovery phase viewing the upfront fee as the cost paid by the licensee (pharma) to acquire the option to enter the preclinical phase. However, their study does not offer an analysis of the effects of real options valuation of the R&D project on the licensing deal-making, such as contract design and structuring or negotiation of key remuneration terms. Taking a portfolio analysis perspective, S. Van Bekkum, E. Pennings, and H. Smit (2009) show that the presence of conditional financing in R&D might invalidate standard diversification strategies for portfolio construction due to the option characteristics of R&D projects. They conclude that, when evaluating the risk of a portfolio of R&D opportunities, it is not sufficient to merely examine the risk-return properties of various projects but it is also important to consider the presence of conditional investment decisions. See S. Van Bekkum, E. Pennings, and H. Smit, "A real options perspective on R&D portfolio diversification," *Research Policy*, 38/7 (2009): 1150-1158.

[16] We assume here that the parties' investment incentives to continue or discontinue the R&D effort are different. For example, the innovator may have incentives to continue with the R&D effort even if there are signs it is failing if it can utilize the experience or capabilities gained from continuance for some other future innovation. This would be prevented if the pharma controls the innovation decision. See P. Aghion and J. Tirole, "The management of innovation," *Quarterly Journal of Economics*, 109/4 (1994): 1185-1209.

[17] Redemption is similar to R&D expense reimbursement with the difference that it is typically linked to the achievement of a milestone. Redemption is analogous to milestone payments but the amount is not known in advance.

[18] See L. Trigeorgis, *Real Options. Managerial Flexibility and Strategy in Resource Allocation*, (The MIT Press: Cambridge, MA, 1996). Other researchers using real options logic in the context of R&D valuation include R. Pindyck, "Investments of uncertain cost," *Journal of Financial Economics*, 34/1 (1993): 53-76; P.D. Childs and A.J. Triantis, "Dynamic R&D investment policies," *Management Science*, 45/10 (1999): 1359-1377; M. Perlitz, T. Peske, and R. Schrank, "Real options valuation: the new frontier in R&D project evaluation?" *R&D Management*, 29/3 (1999): 255-269; H.S.B. Herath and C.S. Park, "Economic analysis of R&D projects: an options approach," *The Engineering Economist*, 44/1 (1999): 1-32; E.S. Schwartz and Mark Moon, "Evaluating research and development investments," in: Michael J. Brennan and Lenos Trigeorgis (Eds), *Innovation, Infrastructure and Strategic Options*, (Oxford University Press, 2000): 85-106; D.A. Paxson, "Introduction to real R&D options," *R&D Management*, 31/2 (2001): 109-113; H.T.J. Smit and L. Trigeorgis, *Strategic Investment*, (Princeton

University Press: Princeton, 2004); K.R. Miltersen and E.S. Schwartz, "R&D investments with competitive interactions," *Review of Finance*, 8/3 (2004): 355-401; J.B. Berk, R.C. Green, and V. Naik, "Valuation and return dynamics of new ventures," *Review of Financial Studies*, 17/1 (2004): 1-35; N. Lewis, D. Enke, and D. Spurlock, "Valuation for the strategic management of research and development projects: the deferral option," *Engineering Management Journal*, 16/4 (2004): 36-48.

[19] H. Smit and L. Trigeorgis, "Strategic NPV: real options and strategic games under different information structures," *Strategic Management Journal*, (2017), 38/13: pp. 2555-2578.

[20] The royalty rate applied under scheme IIIb is 6.5% (same as in scheme Ia).

[21] Only the first milestone of $ 28 m is made by the LE to the LR for successfully completing Phase II.

[22] The result that the same outcome can be achieved by different combinations of fixed fees and royalties relies on the assumption of symmetric information. If there is moral hazard (e.g., the parties make unobservable investments in the technology) or adverse selection problems, the result may not hold.

[23] See A. Bousquet, H. Cremer, M. Ivaldi, and M. Wolkowicz, op. cit..