In-licensing Pharmaceutical Product Opportunities in Early Development: How Can Project Appraisal and Decision Making Be Optimised ?

by

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Abstract

In-licensing is the activity whereby pharmaceutical companies acquire rights on compounds from other companies, and it complements own research and development.
The process of in-licensing is similar to that of preparing own project appraisal and decision-making. Its practice has, however, so far not been researched much.

This dissertation examines the question how in-licensing decision preparation and decision making can be optimised. It will do so by analysing the type of decision preparation that is needed, with particular reference to quantifying relevant variables. It will look into the usefulness of capital investment appraisal techniques and decision analysis tools. Those will be examined regarding their relevance for in-licensing decisions.

In-licensing, in this context, is investment under uncertainty. Here, capital investment appraisal has close links to tools and techniques of decision analysis, and to the theory of games. The behavioural aspects of decision-making will also be covered as far as this is important to put the above techniques into their context. Concepts such as the limited rational choice and the value of information will be covered.
Among the capital investment appraisal techniques, pay-back period, internal rate of return, net present value, and options pricing will be discussed. As for decision analysis tools, influence diagrams, decision trees, and utility functions will be examined as to their usefulness.

There is little historical data regarding documentation and efficiency of in-licensing. Also, little, apart from informal presentations, information exists on this process as seen from decision makers.
Therefore, the fieldwork for this dissertation set out to examine two key areas of in-licensing at Boehringer Ingelheim (BI), an international pharmaceutical company:

- the history of 1990-1995 decision making at Boehringer Ingelheim and the results in retrospect (through a systematic documentation in the pharmaceutical licensing document, PLD)

- the current (1996/1997) process of decision-making in in-licensing prescription drugs (through a decision maker questionnaire to the members of the two main decision making bodies, the business area conference (BAC) and the international steering committee (ISC), DMQ)

The PLD showed that while decisions at BI were frequently „correct“ in in-licensing successful compounds, this also resulted in a high percentage of rejections of - as it later turned out - favourable projects. Most often projects were rejected or accepted for medical reasons.
The DMQ showed that BI decision-makers are certain that most of such decisions have been correct. The criteria for acceptance or rejection do not differ in general, but in their relative weights: strategic fit, likelihood of success and commercial value. They rate the decision preparing assessment papers as acceptable but not excellent, and find that not infrequently decisions should better have been postponed because of that. BI decision makers agree that more quantitative evaluation methods should be used. In general, they would prefer more and better in-licensing.

These findings have been extended into hypothetical case studies where capital investment appraisal techniques have been used. The influence of assumptions that go into the calculations will be discussed, for instance the expected market share. In addition, influence diagrams and decision trees and their advantage over „conventional“ descriptions of problems will be shown.
The close relationship between capital investment appraisal and the behavioural side of decision making, for instance, the perception of commercial value, has been highlighted, especially regarding the type of financial analysis that will be acceptable to decision makers.
The dissertation also seeks to integrate the concept of options pricing technique, decision analysis, and game theory, in their application to in-licensing, for instance with information asymmetry and risk sharing.

In its conclusions and recommendations, it takes up the fieldwork, integrates it into the context described above, and focuses on four areas: the documentation of in-licensing decisions, the use of decision support tools by decision makers, the translation of decisions into (options)

contracts, and the creation of in-licensing audits to increase efficiency. In detail, the following is recommended:

(1) documentation of in-licensing decisions

- decisions should be minuted, including rejection decisions that do not reach the level of top decision-making bodies (Business Area Conference, BAC; International Steering Committee, ISC)
- for all in-licensing opportunities, a logbook should be kept, with a format similar to the PLD

(2) use of decision support tool by decision makers

- options pricing techniques should be used in all in-licensing compounds with a high level of technical uncertainty
- decision makers should be presented a set of appraisal data, including net present value, options pricing, pay-back period
- decision makers should be presented several possible contract designs derived from the structure and uncertainty of the opportunity

(3) translating in-licensing decisions into contracts

- option contracts and sequential option contracts should be the method of choice
- the payment structure and schedule should be adapted to the opportunity

(4) in-licensing audits to increase efficiency

- in-licensing audits should look into the adequacy of decision preparation at least once a year
- the results of in-licensing audits should also serve as a feedback, especially as the outcome of rejected opportunities will be included

The dissertation, in its final chapter, briefly touches areas for further research, for instance the analysis of the cost of information for drugs in development, the value of time to licensors, and the use of vague („fuzzy“) decision criteria.

Preface

The field work for my dissertation originated from my work as a member of the Corporate Medical Division in the Project Ethical Pharmaceuticals (PEP) at BI which aimed at speeding up sales growth by a systematic search for business opportunities, in particular in-licensing.

Having gone through discussions on „lost opportunities“ and having seen some of the problems on the side of the decision making bodies when such business opportunities were presented, I decided to look deeper into the subject.

It was obvious that it was difficult to estimate the correctness of decisions given the long development process of drugs. Therefore it was necessary to go several years back in history where documentation was not as advanced as it is nowadays at BI. Due to little fluctuation in the Business Development (BD) Division in past years, much could be supplemented by interviews with its members if it was not comprehensively minuted somewhere.

To investigate decision processes it turned out that this information could not come from minutes, but only from interviews or from questionnaires. I chose the questionnaire as it allows the decision maker to complete it without external interference or bias. There was no precedent to this, and in some cases, the procedure had to be explained and argued for.

I should like to thank the sponsors of this work, Dr. Peter Gieseler, Head of Corporate Division Business Development, and Dr. Dr. Andreas Barner, Head of Corporate Division Medicine, for their constant support, suggestions and the openness regarding information. In particular, I am obliged to the members of Dr. Gieseler`s Division for sharing information and „opening the books“ as well as telling me where some information could be obtained from.

I thank the members of the BAC and ISC at BI who gave open, clear answers to a demanding questionnaire.

Finally I thank my Henley tutor, Ms. Edwina Byass for constructive criticism and help during the preparation of this dissertation.

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APV	Adjusted present value
BAC	Business Area Conference
BD	Business Development
BI	Boehringer Ingelheim
BOT	Business Opportunity Team
DCF	Discounted cash flow
DMQ	Decision maker questionnaire
GmbH	Gesellschaft mit beschränkter Haftung (equivalent of plc in Great Britain)
HBR	Harvard Business Review
IMS	Institute of Medical Statistics
ISC	International Steering Committee
NPV	Net present value
PLD	Pharmaceutical Licensing Document
R&D	Research and Development
Rx	Prescription (business)
RD Focus	(Pharmaceutical magazine on drugs under research and development)
S.D.	Standard deviation
SBU	Strategic business unit
SCRIP	(Pharmaceutical Weekly)
WACC	Weighted-average cost of capital

1 Introduction

1.1 In-licensing in the pharmaceutical industry

The pharmaceutical industry finds new chemical entities or other biological principles that work as drugs, develops and tests them, and distributes them either via prescriptions or a non-prescription drugs. [1]

The process of finding new compounds is fraught with uncertainty: in contrast to situations in engineering the biological behaviour of chemical molecules is difficult to predict.[2] Thus, even in large companies, own research may not bring compounds into clinical testing for several years, what is called an "empty pipeline".[3] The consequences are not only discontinuity in sales, but also parts of the workforce, for instance in clinical development are not being used to their full potential. Therefore, compounds from other companies or research institutions are bought or in-licensed, i.e. the in-licensing company acquires rights to develop, produce or market the compound. The licensor is usually driven by different motives:

a) he may be a company unable to develop the compound for lack of know-how or resources
b) he may be a company not present in all major markets and need a distribution partner
c) he may have too many compounds in the pipeline and prefers to earn cash by licensing out one.
d) he may wish to exchange an own compound for one of the other company ("quid pro quo"), for instance because of the better „strategic fit". Such situations can also occur when a company finds several drug candidates for a given indication but decides to develop only one.
e) he may have stopped or may plan to stop the development, and earn some royalties by out-licensing it

[1] Allary and Sully (1996)
[2] Baker et al. (1994)
[3] Duelli et al. (1991)

The valuation of compounds is dependent on several uncertainties which are in part inter-related:

a) the compound is truly novel, and no comparable drugs are on the market, thus the principle of action has not yet been established
b) non-clinical data, especially animal data, are difficult to interpret and extrapolate to the human, often no databases on such extrapolations occur, but could be constructed from knowledge in the public domain combined with proprietary research data
c) the indication is difficult to test or may be a disease process not yet well understood
d) the activities and likelihood of success of competing compounds are difficult to judge
e) the regulatory climate may favour or discourage the development of such drugs , e.g. stimulants
f) the effort needed to market the drug is not known
g) the market depends on the magnitude of the effect of the drug vs. competitors (which is often known only by the end of development

These areas of uncertainty mentioned in the preceding paragraph can be classified into research and development, medicine, regulatory, and marketing. In research and development, a chance finding in toxicology may mean the end of a development. In medicine, the crucial („pivotal“) clinical trials may not be able to substantiate earlier findings of efficacy in small phase II trials. For the first two, new experimental data reduce uncertainty, but have a price. The Regulatory Affairs Department sets a framework for the size and complexity of preclinical and clinical studies. The Marketing Department depends on previous experience and market research to arrive at figures, but will most likely come up with scenarios, optimistic, pessimistic, and „realistic“ ones.

In addition, these products - like all others in the pharmaceutical industry - have a limited value over time as the expiry of patent protection of a profitable product causes generic companies to develop their versions and enter the market with a low price strategy.

While those situations are germane to both in-house and in-licensed compounds, there are notable differences between those two groups, as viewed from the potential licensee.

	In-house compounds	*In-licensed compounds*
History	Completely known	May never know entire story
Reliability of data	Usually high	Should be high
Trust	Rather high	Depends on size and standing of licensor
Cost structure	Often little known	Partly known (value of compound, down-payment)
Project exit hurdle	Low to medium	Medium to high

Table 1. Comparison of in-house and in-licensed development compounds

In-licensing is a typical example of „investment under uncertainty" with the known features irreversibility and deferability, and their opposites. [4] This can be shown by two examples:

a) irreversibility: when a company has decided to produce clinical trial supplies for phase III, (where large trials on patients are conducted) such supplies usually cannot be used elsewhere if the development is stopped
b) deferability: by postponing the talks the company may get into a better situation for negotiations, as for instance results from their own, possibly competing developments may be known by then.

1.2 The in-licensing process and its phases

1.2.1 Searching / receiving an offer

In-licensing starts either by a purposeful search for certain drug groups (in Pharmaprojects, RD Focus, or other databases), or when a licensing offer is received. At this stage, often little is known about the compound, especially in early stages of development. Frequently, little information is in the public domain, and this information is biased towards "good news".

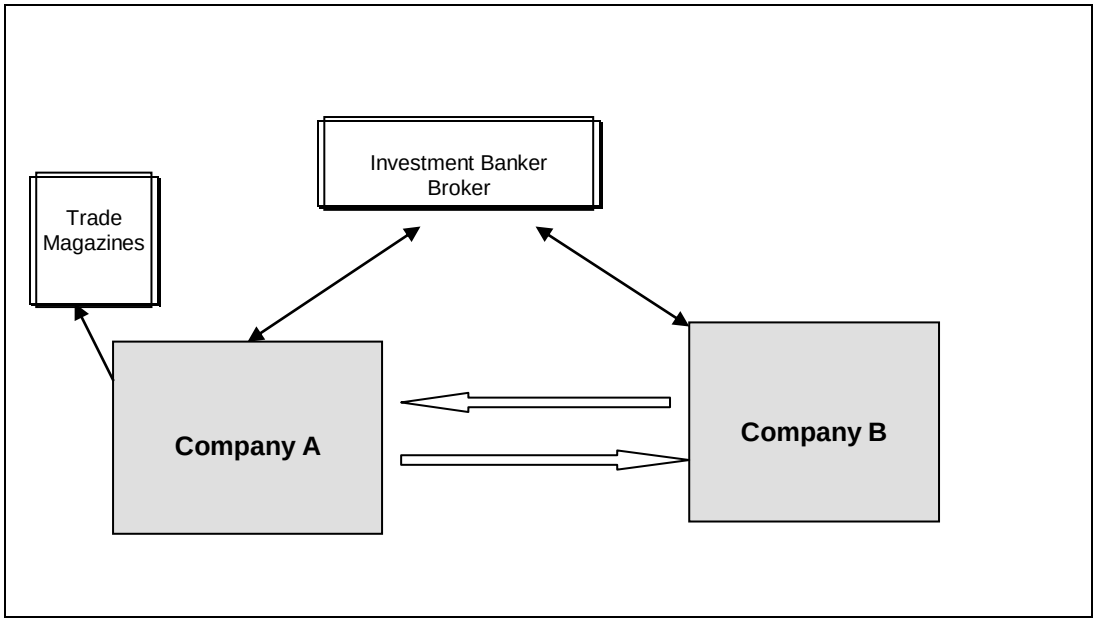


Figure 1: Licensing interactions

1.2.2 Selecting (first filter)

The information is usually insufficient to make a decision for in-licensing, although sometimes it is sufficient to decline such an offer immediately. Sometimes, a first filter in a company may be minimum expected sales in a given territory, or even stage of development.

Frequently, at such a stage, the potential licensor opens with a list of financial requests that are far beyond the value of the compound.

1.2.3 Evaluation and determining negotiating interests/strategy

With the preliminary analysis at hand, the in-licensing company will determine their counter-offer or first offer, based on a scenario with a “base case”. At that stage, crude financial modelling should be possible, at least for sensitivity analysis. The company must then determine the extremes of their negotiating position, and it should already have several options at hand.

[4] Dixit and Pindyck (1994)

1.2.4 Negotiation

Negotiations ensue, where the type of deal is outlined that may be acceptable to both sides. The licensor is usually interested to place as much risk sharing on to the potential licensee. It is the negotiations where game theory can be a valuable tool (see in later chapters).

1.2.5 Due diligence (second filter)

In the „due diligence“ examination, further sources of information previously not disclosed are used. Such disclosure only occurs when the potential licensor gets the impression that the licensee wishes to seriously enter a next round of negotiations. The licensor may ask for a fee, and he may limit this stage to a certain period. This is understood under the premises of considering out-licensing as an option the value of which may change over time. In pharmaceuticals, the likelihood of a negative outcome surpasses that of a positive outcome by a factor of 5:1, depending on the clinical phase of testing and the indication area.

Also, an options agreement to test the compound directly in one’s own laboratories or in patients may be concluded at this stage.

1.2.6 Decision on commitment to negotiations

If the general agreement is likely, the in-licensing team asks its commissioning bodies to be allowed to offer a binding proposal. This will provide the team with a framework and minimum requirements for the contract, best specified as the in-licensing company’s basic interests.

1.2.7 Final negotiations and closing of deal

The last stage is usually on technicalities, but may go back to the negotiation stage. Frequently, once the company is at such a stage, new information may also have come in, either on the compound, the competitors, or the regulatory environment.

This stage of development determines the risk involved and the type of contract.

1.2.7.1 In-licensing a product „as is“

Such a product can be at different stages of development. At late stages, such products carry little risk regarding the likelihood of success at the approval stage.

In earlier stages, the risks are high, and the contracts do tend to award less money for the work already invested by the licensor.

The licensee intends to shift most of the payments to the phase during which the product will be marketed. The risk sharing can be modelled using game theory.[5] In principle, the interests of licensor and licensee are contrary, but an equilibrium can be achieved. This is, however, only true, if a two-player game is still possible, and if no subsequent games are possible for the licensor - an assumption that is unrealistic at least for potential blockbuster drugs where several potential licensees may be queuing up.

1.2.7.2 In-licensing product to be developed by licensor

The analysis of cash flows in such a case, seen from the licensee, reflects his view of what efforts are needed to make the compound an approved drug. The financial analysis will put in values based on the cost that would be incurred.

The analysis becomes difficult again when it means financing the other company developing the product as in such a case, the entire risk is carried by the licensee. While a simplistic assumption could be to accept options pricing here as well, the exercise price of the option for the licensee becomes a problem if he has little or no influence on the development program and objectives, and the staff of the licensor may not have the expertise for drug development.

[5] Hirshleifer and Reilly (1992)

2 Objective of the dissertation

The problems described in the preceding chapter often need decision support tools which are mostly derived from financial management (accounting)[6],[7],[8], and from formal decision analysis.[9],[10]

Most of those tools are not mutually exclusive, but complement each other. While some are obviously easy to grasp, some others (like options pricing) require more understanding from the decision maker, but have advantages, especially with high-risk projects. [11]

This dissertation will examine the suitability of different methods of capital investment appraisal and decision analysis tools to aid the in-licensing process. In particular, their underlying assumptions and the type of data needed to use them in the first place will be discussed. In consequence, their applicability for in-licensing decisions in the pharmaceutical industry will be discussed, with some emphasis on the behavioural side and related limitations.

Practical investigations into decision processes at Boehringer Ingelheim (see section 4.2) showed that such methods have been and may still be underused when substances or products are to be in-licensed.

Different tools that are in use will be compared as to their theoretical validity and practicality. In addition to the findings of the investigations at BI, hypothetical examples will be used as well as examples from other international companies. The dissertation will make conclusions using both the fieldwork (part 1 of the dissertation) and the theoretical concepts available, regarding their impact on contract design, the preparation of decisions, in-licensing efficiency, the documentation of in-licensing decisions, and the structure and function of an in-licensing audit. Applications will be given focusing on the construction of contracts and option agreements. [12]

[6] Hirshleifer and Reilly (1992)
[7] March (1994)
[8] Kirkwood (1997)
[9] Brealey and Myers (1996)
[10] Clemen (1996)
[11] Baldwin (1991)
[12] Brandenburger and Nalebuff (1996)

Thus, the dissertation will examine what practical value such methods can have for decision makers. It will define what makes a „correct“ decision in in-licensing, and it will try to find out parameters that on one hand are likely to lead to catastrophic decisions, and, on the other hand, those that are likely to aid in making the correct decision. It will also look which variability the different parameters contribute at the different stages of uncertainty, with different impact on the subsequent calculation of the NPV.

The dissertation will also connect ideas from capital investment, decision analysis, and the theory of games, in an attempt to provide a theoretical framework for the in-licensing decision.

The dissertation sets out, as a final goal, to arrive at a set of tools for assessing in-licensing opportunities, both from capital investment appraisal and decision analysis. The aim is to help develop a comprehensive structure for decision papers that presents all reasonable available options including the option of not taking the opportunity. Also, it aims at providing concrete recommendations to decision makers, within the framework described above.

Finally, it will describe areas where further research is warranted.

3 In-licensing as investment under uncertainty

3.1 Concepts

3.1.1 In-licensing as project appraisal

The project appraisal for compounds to be in-licensed is a special case of project appraisal in pharmaceuticals. Anticipated costs and revenues must be described, if possible using different scenarios. Still, at Boehringer Ingelheim (BI) own developments are frequently not subjected to rigid financial analysis as the cost side is not assessed on a project or substance basis. It is, however, regularly done with in-licensing opportunities as in such cases the costs are defined by the potential licensor and need not be collected over years in-house. With an in-licensing opportunity, the requirement of cost transparency is given which is frequently not the case with own developments where the cost in early stages of research and development are not budgeted on a specific project.

3.1.2 In-licensing and the theory of games

In-licensing can be seen as a game of two or more players, the licensor and the licensee, or, rather, several potential licensees or even licensors. [13]

At the very simple level, licensors and their products face potential licensees. The information is usually limited on the side of the licensee, and may be increased after signing a confidentiality agreement. By simultaneously negotiating with several potential licensors offering essentially competing products, the optimal deal is made more likely at least as long as there is not a correspondingly larger number of potential licensees.

As the players can make simultaneous moves, too, the situation can be uncertain and thus impact on the price of the opportunity. Potential licensees may, in a classical pay-off matrix,

[13] Binmore (1992)

display their strategies and those of the potential licensor and their bidding competitors and thus determine their optimal moves.[14]

To arrive at such a pay-off matrix for several comparable opportunities, the risks and benefits have to be converted into (monetary) units.

3.1.3 In-licensing and the behaviour of decision makers

Pharmaceutical companies have a differing predilection for in-licensing products. While some are still close to the „NIH-syndrome“ (Not Invented Here) and prefer compounds from their own laboratories, a recent survey found that among the 10 largest drug companies, 22-51% of drugs between phase II (small trials in patients to obtain proof of concept) and registration have been in-licensed.[15] It appears that once financial goals are clear, the decision makers use these tools and choose projects accordingly.

There may be differing opinions of decision makers regarding the validity of such tools. As no data are publicly available, one cannot speculate about the correlation between the use of such tools and the likelihood of picking “winners”.

3.1.4 In-licensing and the time factor

The development of the value of an in-licensing compound can be described by a discontinuous risk („jump“) function. While the perceived price may be independent of results, the price for potential licensees follows the appearance of new information. In figure 2, an example is given where poor early results resulted in a relatively low value of the opportunity. The later excellent phase III results boost the value of this compound, sometimes overnight.

[14] Binmore (1992)

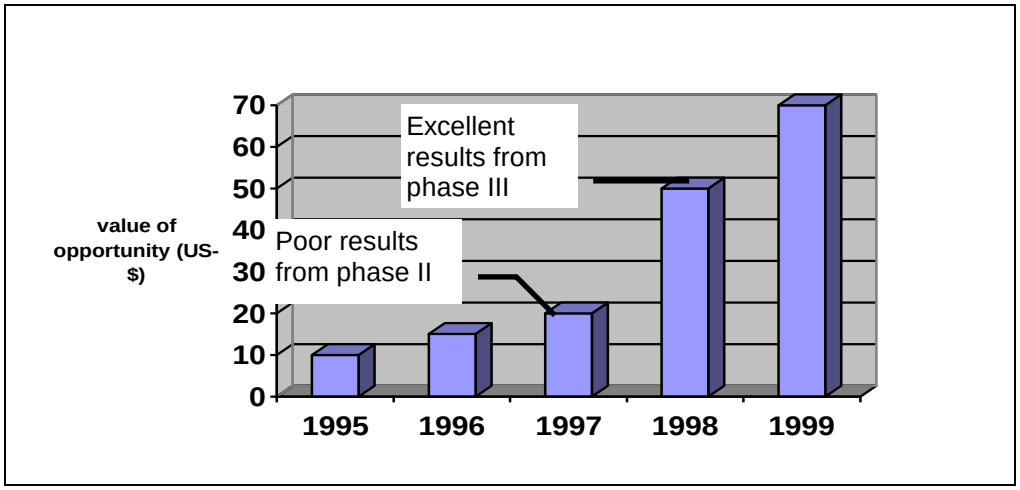


Figure 2. Value of an opportunity is dependent on stage and results

3.1.5 Limited rational choice

In-licensing is here defined under the constraints of the theory of limited rational choice. It means that decision makers do not exclusively use rational thinking, but they may even fill information gaps by analogous experience or suppress discrepant information altogether. It is assumed that decision makers see themselves as responsible, rationally acting persons. [16] Therefore, appropriate economic analyses and concepts will be used. No investigation into their decision motives or even „hidden agendas“ will be attempted.

3.1.6 Value of information

The value of information can be described by utility functions.[17] Expected losses should be minimised in high risk ventures. On the other hand, the cost of perfect information, i.e. waiting until the results of the pivotal phase III trials are available, can be enormous, and this is even disregarding the fact that other companies may be less risk-aversive and conclude a deal with

[15] SCRIP (1997)
[16] March (1996)
[17] Lindley (1971), pp. 119 ff.

the licensor based on less than perfect information already. Therefore, the cost of information could be much larger considering several competitors all striving to obtain the same license.

3.2 Potential tools for decision-making in in-licensing

This discussion does not deal with the ability of individuals to estimate technical risks or predict commercial benefits. Such depends on the knowledge and experience of experts in the first place. Still, decision analysis has, besides providing concrete tools such as decision trees, made major contributions by finding out about biases, for instance the apparent independence of judgement regarding sample size of data, anchoring, and availability of information.[18] The combination of decision analysis with capital investment appraisal techniques will be discussed within the framework of options pricing.

3.2.1 Capital investment appraisal techniques

The value of an investment under uncertainty may be estimated by different methods. Most of these, however, have been made for classical investment decisions with a relatively clear and predictable outcome. Also, these theories do not account for the irreversibility of (some) investment decisions and the possibility of deferring a decision. [19]

3.2.1.1 Pay-back period

The pay-back period is the number of years it takes before cumulated forecast cash flows equal the initial investment. The pay-back method depends on several assumptions:

a) there is a reasonable cut-off date
b) the project eventually produces rather homogenous cash flows and is much devoid of discontinuities such as down-payments or milestone payments

Frequently, the duration of the pay-back period (cut-off date) is chosen on the basis of the remaining patent life or other protection of intellectual property, or the assumed entry of a major

[18] Tversky and Kahnemann (1974)
[19] Luehrman (1997a)

competitor with features that are advanced compared to the product. Pay-back periods beyond five years are not popular as the prediction of sales rarely is accurate beyond this period. However, with relatively large markets and few serious competitors, this often changes, such as in Alzheimer's Disease (see fig. 3).

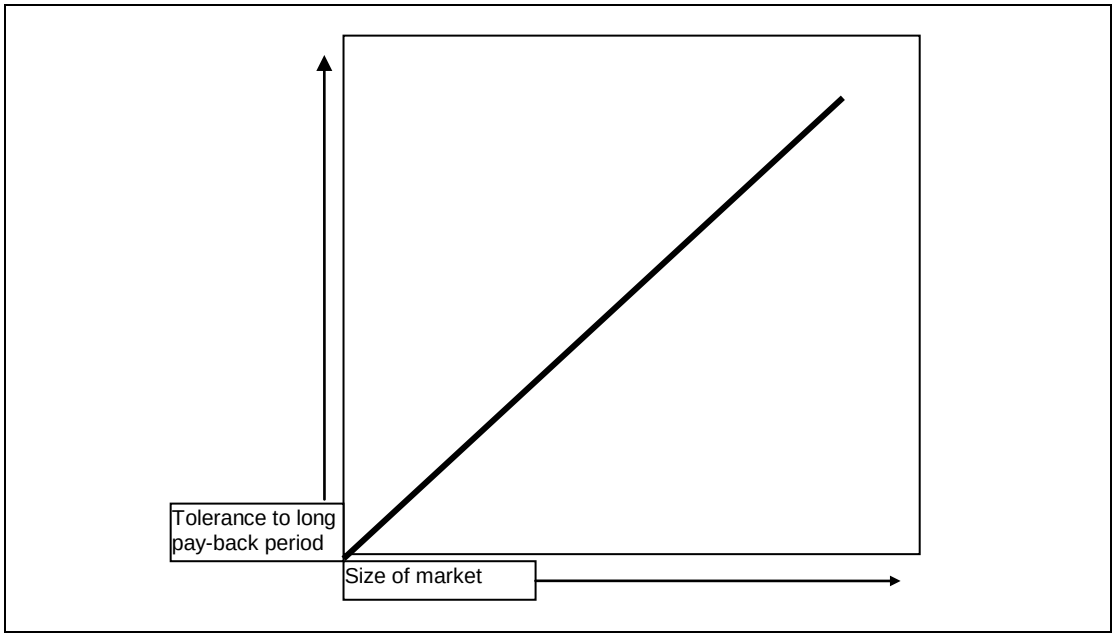


Figure 3. Decision makers weigh both pay-back period and market size

Some companies do use discounted pay-back periods. While this accounts for the time value of money, it does, however, not eliminate the basic flaws in the concept.

3.2.1.2 Internal rate of return

The internal rate of return (IRR) or discounted cash-flow (DCF) rate of return is the rate of discount where the net present value (NPV) equals zero. The rule is usually to accept a project if the IRR is higher than the opportunity cost of capital.

This method has several pitfalls:

a) With alternating negative and positive cash flows, the IRR may conflict with the NPV and give an erroneous value. With a pharmaceutical product, there may be a change in the sign for cash flow when high milestone payments are due during the marketing phase or when

life-cycle planning needs additional input to develop a new indication, or when a re-launch needs high marketing expenses.

b) If there are multiple rates of return, the criterion fails such as in a project where cash flows first increase and then decrease.

c) With mutually exclusive projects, the IRR may give a less "objective" answer than the NPV. This is frequently the case where an in-house project is measured against an in-licensing opportunity. In the latter, the outflow of costs, for instance the advance and/or the milestone payments occur comparatively late in the development.

d) The cost of capital in the pharmaceutical industry may vary over time or contain uncertainties itself. In such cases, it is questionable against which interest rate to compare the DCF. Given the long development times of drugs, this may be particularly true for the cost of capital which increases in the later stages of the clinical development phase.

3.2.1.3 Net present value

The net present value (NPV) is the difference between the discounted revenues minus the discounted costs in a given period, summed up. For discounting cash flows, several caveats are given. [20] All apply for in-licensing decisions. They will be explained by practical examples, and implications will be discussed.

a) Average and incremental payoffs must not be confused

The additional cost of conducting a phase III trial which could eventually pave the way to drug approval may be comparably small (especially when the phase II results have been promising) compared to the lack of any revenues if this is not undertaken.

b) All incidental effects must be included

Certain projects, for instance diagnostics, may have a borderline NPV. If a company that manufactures an agent which dissolves blood clots in myocardial infarction when given soon after the symptoms is able to provide a reliable and fast blood test on such a diagnosis, this will

[20] Brealey and Myers (1996), pp. 114-116

have a positive impact on their therapeutic agent business. Such influences must be factored into the NPV for the in-licensing offer of the diagnostic kit.

c) Working capital requirements must not be omitted

Conducting clinical trials on an in-licensed product that has not been completely developed, ties up working capital. These resources will likely be idle again when the development is complete.

d) Sunk cost must not be considered

Sunk costs in drug development have to be carefully set against the incremental payoffs mentioned above. A company faced to in-license a product that will surely have a clinical advantage over one developed internally, will have to leave sunk cost of internal development out of the basis for calculation.

e) Opportunity cost must be included

The opportunity cost of in-licensing a product must be seen and calculated considering several parameters: the use of internal resources to develop or market other products, the cost of increasing working capital, or the delay of other developments as a consequence. At the same time, the opportunity cost of *not* in-licensing a product must be calculated, based on the knowledge of potential moves of the licensor, e.g. to other potential licensees that are the firm's competitors. As major companies develop dozens of compounds simultaneously, the technical and practical difficulties to obtain such data are enormous.

f) Allocated overhead cost can distort the entire calculation

It is commonplace to distribute the „normal" overhead cost also onto in-licensing projects-to-be, which, in large companies may place a high financial burden on such. However, only truly additional expenses, such as additional personnel to administer the project, or cost of additional facilities may be charged against the new project.

More recently, the concept of adjusted present value (APV) has been put forward.[21] It adds the impact of „financing side effects“ such as interest tax shields, cost of financial distress, subsidies, hedges, issue and other costs. Thus, exit hurdles for R&D ventures that have partly been subsidised by the state can, for instance, be calculated using APV. On the other hand, because of its limitations and exclusive reliance on DCF methodology it is less suited to evaluate projects that carry substantial chance risks.

3.2.1.4 Weighted-average cost of capital (WACC)

The weighted average cost of capital is still frequently used. In principle it is a special case of the DCF method. As it takes up the impact of taxes and debt capacity, it picks up the value of interest tax shields. This figure may change on a yearly basis, and it must be computed especially if the project depends on different sources for funding.

Its main disadvantage is that is it most suited for static capital structures, but not dynamic ones, such as hedging, subsidies, or derivatives.

For project appraisal, it offers little advantage over DCF, with the possible exceptions of mergers and acquisitions where for instance taxation issues become important and where an entire portfolio is considered. Also, for a pharmaceutical company, the WACC gives an appropriate estimate for the aggregate cost of capital, however, this figure could also be reached by using APV (see above) and weighting and adding up the individual values.

3.2.1.5 Options pricing

Options pricing is a technique derived from the stock exchange. In principle, the value of an option is determined by the value of the stock and vice versa. Stock options are there to secure a profit if the value of the stock is „volatile“, and the more volatile, the higher the price of such options. A second parameter is the length of time the project may be deferred.[22]

This has many analogies to in-licensing. Take, for instance, the case of a company that tries to out-license a compound, but asks for too high a price. It may loose a year until it finds a second

[21] Luehrman (1997b)
[22] Faulkner (1996)

negotiations partner, however, by then, the factors mentioned above, may have been changing. In the optimistic case, the project may have generated new data that increase its value, and it may be in a therapeutic indication that is meanwhile more recognised by the medical community. In the pessimistic case, new data reduced the medical value, and now, one year later, other competing compounds are being offered to potential licensees.

A call option is equivalent to the money paid by a potential licensee to have the right of first refusal or the right to review a potential product for a given time exclusively.

Black and Scholes[23] defined a formula whereby the price of a call option is determined by the price of the stock now, the exercise price of the option, the standard deviation of the rate of return on stock in a given period, and the bank loan. One major advantage is that subjective risk tolerance is not part of the formula.

Applied to in-licensing as a special form of project appraisal [24], the "formula" would contain the following analogue parameters:

a) the exercise price: the capital investment that would have to be made at some time in the future
b) the stock price: the present value of the cash flows from the project, excluding capital investment as above, the present value of the „down-payment", and the development cost until the time the exercise price has to be paid
c) the time to expiration (which can be constructed considering patent expiration date or the entry of significant competitors
d) a parameter for the project volatility, which may differ from project to project. It may be specific for the general area, such as biotechnology product developments, or for certain indications. Most difficult is the calculation of such a parameter in indications where no drug exists and many have failed to obtain approval.
e) a risk-free rate of interest can be obtained according to the current and future lending rates for companies

[23] Black and Scholes (1973)
[24] Nichols (1994)

One might sketch the relationship between the price and the risk of a project as a partly linear relationship. It can also be expressed by a binomial distribution, where the probabilities can be derived from a decision tree.[25] If one increases „project volatility“, the price for the option may increase, however, in contrast to fig. 4, the volatility is frequently less than one standard deviation (S.D.), except for high technology stocks.

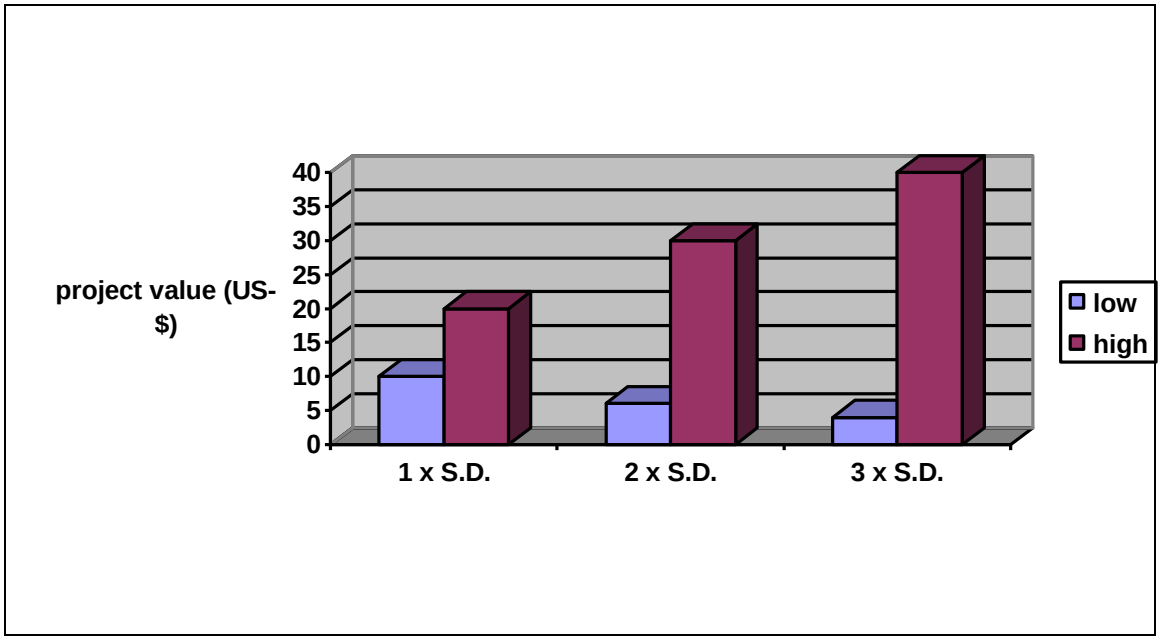


Figure 4. Variability of a project value of US-$ 15 million depending on assumptions of project „volatility“ *(S.D. = standard deviation of project value)*

There are, though, significant differences between stocks and stock options on one side and pharmaceutical in-licensing opportunities on the other side.

a) pharmaceuticals have a different time scale. The „options price“ may not change much for more than a year, while stock options are dependent on many more variables. Thus, the negotiation and agreement times can be more extended and are not comparable to the hectic behaviour at the stock exchange.

b) pharmaceuticals have a rather well defined period of expiration which is clearly determined by the patent life or other intellectual property rights. The competition through generic versions of the drug is fierce and can lead to rapid price erosion.

[25] Hodges and D'Ambrosio (1996), 209-211

c) pharmaceuticals may take „quantum leaps“ as to their valuation. When, for instance, phase III data become available, the project volatility is greatly reduced. As those clinical trials are usually long-term and blinded to the outside until the end, no interim changes of project value are expected. Such changes can be expresses mathematically by „jump functions“.
d) for pharmaceuticals, the exercise price is frequently not absolutely fixed. The license fee is coupled to the proposed net sales price which may not be certain. Thus, the margin can still float depending on how much price limitations, through the state or insurance companies, come into existence.

It is clear that there are prerequisites for such quantitative approaches. Not only must cost and revenues be given, but all must be given in monetary values, over time, and with a probability for both.

At Merck, the system uses software employing Monte Carlo simulation methods. Thus project NPVs can be obtained including a probability distribution. Whether such a probability distribution reflects the frequent yes/no situations is debatable. As the results are rarely “continuous”, a bimodal distribution with narrow peaks better reflects the decision situation.

There are no disadvantages to the use of options pricing, however, the method is very „vulnerable“ to flaws in the construction of the decision tree.

3.2.2 Decision analysis techniques

There are several techniques available. They will be described below, using examples from in-licensing decisions.

3.2.2.1 Influence diagrams

Influence diagrams show graphical representations of decision situations. They are a qualitative model of the decision tree and represent the fundamental objectives hierarchy. [26] Rectangles represent decisions, ovals represent chance events. Rectangles with rounded

[26] Clemen (1997), pp. 50-63

corners show consequences. The following influence diagram shows a decision to in-license a phase II compound.

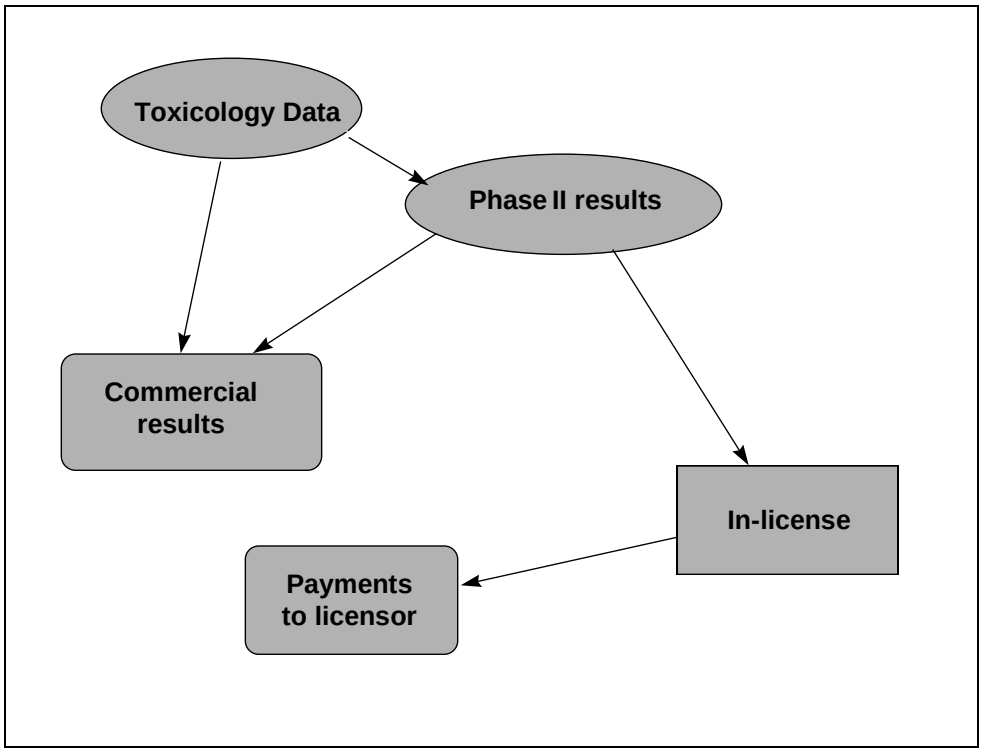


Figure 5. Influence diagram for a simple phase II in-licensing decision

3.2.2.2 Decision trees

Decision trees show the ramification of possible decisions. On a decision tree, the branches contain both probabilities and values. Decision trees can be used to calculate potential outcomes and do sensitivity analyses on them.

For instance, in an in-licensing project, the results of different phases of clinical trials could have a probability and a money value attached. Thus one could calculate whether certain results are worth the money, i.e. if and what impact they could have on future decisions. Or, in a market analysis, different scenarios for indications could be connected to different market values of the compound.

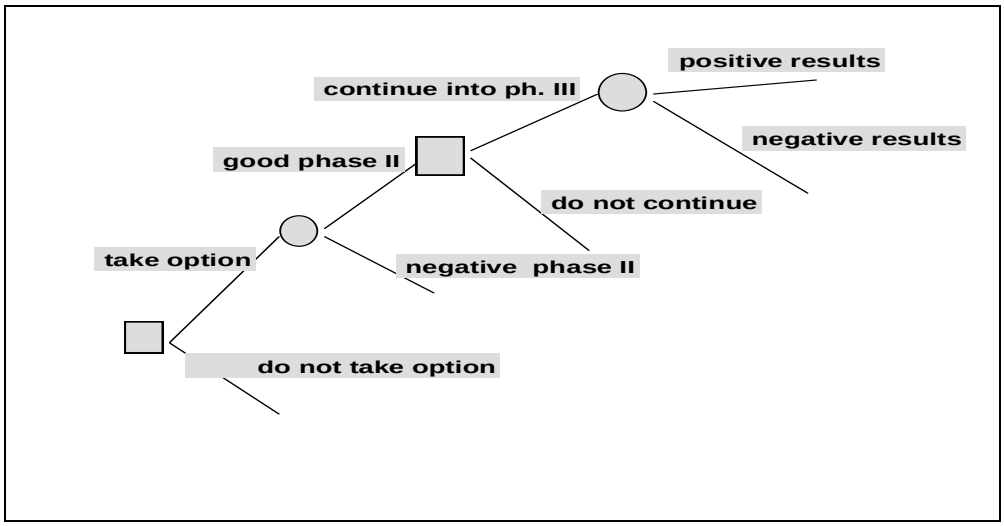


Figure 6. Decision tree for in-licensing an option on a compound in phase II

3.2.2.3 Utility functions and conflicting objectives

Utility is a number that measures the attractiveness (or opposite) of a consequence [27]. As in-licensing may conflict with the development of own product development, conflict is built in when decisions involve postponing or abandoning an own research or development project in favour of one from outside. Utility functions can be constructed for individuals and groups (companies).

Usually, no utility functions are constructed for in-licensing situations, however, this dissertation will attempt to show whether such functions could be constructed.

There are several steps to be undertaken for each competing project:

a) Probabilities have to be assigned, e.g. to the likelihood of success

b) Weights have to be given to the projects, e.g. by the commercial value of them

c) Decision makers must be asked to construct their own function

It appears that this is possible in theory, but it requires not only full cost and other transparency on the projects, but also simultaneity for the decision. This latter criterion will be violated the moment new information may be available on either project, but possibly only after having made an irreversible decision.

In the case of in-licensing a compound, the following parameters would have to be when constructing the utility function:

a) Likelihood of success for the competing projects
b) Market potential for each of the products
c) Remaining value of own product if in-licensing is done
d) Opportunity cost for not developing own product
e) Loss of research know-how
f) Research area “re-focusing” cost
g) Main decision maker utility function (considering whether he is risk-averse or risk-prone)

There are, however, no data in the literature where such a risk function would have been documented. According to Kirkwood [28] , such functions are difficult to determine especially when there are multiple objectives. While this has been covered by several authors, its application would be subject for further scientific work. [29], [30]

[27] Lindley (1971)
[28] Kirkwood (1997), pp. 162-164
[29] Fishburn (1970)
[30] Keeney and Railffa (1990)

4 The use and value of quantitative tools

The working hypotheses of this dissertation are:

a) the process of in-licensing compounds lacks the proper quantitative tools and techniques to estimate the value and risk of an opportunity
b) therefore, in-licensing, in this case seen from the potential licensee, is sub-optimal by not choosing the correct opportunities more frequently, and, in the case of chosen ones, sub-optimal contracts are being made
c) the choice of proper decision preparation instruments would enhance the quality of in-licensing considerably (if they are accepted as such by decision makers)
d) options pricing, alone or combined with tools from decision analysis, and game theoretical approaches (negotiation strategies) could serve this purpose

4.1 Historical data

No data on the efficiency of in-licensing were available in the public domain. Though one side – the in-licensed products in other companies could be found out through annual reports or Pharmaprojects or SCRIP, this would not account for the –likely higher- number of opportunities that were rejected. On the long run, due to better documentation, it will, however, be possible to estimate the percentage of a company's in-licensed compounds brought to the market as a ratio vs. the total number of those in-licensed.

Though such processes have not been systematically researched. Hans Mohr, the former Head of Licensing at Ciba, described the Ciba approach as pro-active, by determining the profile, the criteria for licensing candidates, and their desired stage of development. He emphasised both numerical value (NPV, probability of registration) and strategic value which requires „qualitative assessment" .[31]

[31] Mohr , in: IIR Seminar (1996)

R.D. Nolan , at the same seminar, only flatly mentioned that „the financial group will be assembling an appropriate model..“ and he recommended an „automatic stop loss position“.[32]

4.2 Empirical data on decision making for pharmaceutical in-licensing

The project (fieldwork) done at BI had two parts:

a) it looked into the 1990-1995 projects that were up for in-licensing at the BAC or ISC or both. All such projects were listed by means of a pharmaceutical licensing document (PLD) which is given in the appendix.
b) it looked at actual (1996-1997) decision making at the two committees relevant for in-licensing using a questionnaire that was given to the decision makers. As these represented 50% of the Corporate Board members and 100% of the next level executives in the pharma division, this reflected well the decision making styles at BI.

4.2.1 BI Pharmaceutical Licensing Document (PLD)

During the work done at BI, several pieces of evidence were found regarding the efficiency of such in-licensing.

BI has, more so in recent years, collected and standardised the data leading to decisions. They are contained in different documents such as

- minutes of the BAC or ISC
- overviews to ISC of licensing department
- personal files and notes of licensing project leaders

Only in the last two years, formal documents (as mentioned in the Questionnaire) have been in use. No uniform document has been available throughout. It turned out that the evaluations were not collected at a central place, but had to be reconstructed asking the relevant persons. In many cases, only hand-written notes were available. In many cases, only personal interviews with present or previous members of the licensing department could determine the reason why a project was abandoned by BI.

[32] Nolan, in: IIR Seminar (1996)

Compounds can only be compared when they are evaluated according to the same set of parameters. The PLD has been collected on all such drugs. It is anticipated that for some substances very limited data will be available.

To see the outcomes, databases and magazines, such as Pharmaprojects, SCRIP, RD Focus, and IMS were searched. Pharmaprojects is a database that allows to look into the fate of a compound. It allows to judge where the development stands and what can be expected in the near future. Not infrequently, the database keeps drugs as „under development“ whereas their development has been stopped already. Therefore, in all cases, independent information via SCRIP or RD Focus was sought. Of marketed products, sales can be obtained via the IMS, the Institute of Medical Statistics. They are usually correct within 10%.

The PLD will (as the fields on the time intervals, evaluation tools and primary contact at BI could frequently not be filled out) be analysed for the following parameters only:

- substance
- indication
- type of data available
- offering company
- decisive reasons
- evaluation tools
- outcome

In a 2x2 table, the decisions and the outcomes will, if they are known, be analysed and decisions categorised as correct positive, false-positive, correct negative, and false-negative.

Opportunities declined or accepted will be analysed as percentage depending on the stage of the clinical development.

The frequency of the use of quantitative tools will be given. Where details are available, individual tools will be given.

4.2.1.1 Results

Decisions and outcomes

During the period surveyed, there were 34 decisions made on offers for compounds in phases I-III with more than local relevance and for which documentation was available. In 12 cases only phase I data were available, in 5 cases early, mostly uncontrolled phase IIa data were available while in the rest controlled clinical trials of smaller or larger size were done.

In 24 cases, the fate of the compound was identified and could be defined as „success“ or „failure“, in the remaining cases no further entries were found in Pharmaprojects suggesting that no activities were going on any more. In table 2, „successes“ are defined as compounds which at least had to be pre-registration, „failures“ were compounds the development of which was stopped and this was documented.

	SUCCESS	***FAILURE***	***TOTAL***
BI ACCEPTANCE	6	1	**7**
BI REJECTION	13	4	**17**

Table 2. 2x2 table of BI decision performance in in-licensing

The table shows that BI is good at avoiding compounds that fail in development, however, it does also reject projects that, at least in development, live up to their expectations. Thus the table reflects a company that creates high hurdles for in-licensing products. It should be noted that many compounds may never have reached the level of the BAC or ISC as they had been rejected at lower levels.

Reject ratings and reject reasons

In table 3, the data describing the reasons for BI rejecting an opportunity are given. The data must be taken with some caution. Frequently, when a project is rejected for toxicological reasons, no further evaluation is attempted. Similar is true when it is rejected for medical

reasons where no commercial assessment is usually attempted. Therefore, a hierarchical decision making process seems to be followed implicitly, with most rejections at the level of medicine. In many cases, some opinions were never given as a low (<< 10%) likelihood of success did lead to rejection by itself. The results become interesting when the correct and incorrect rejections with regard to the fate of those opportunities are taken into account:

Main rejection reason	*correct*	*incorrect*	*total*
R&D	1		**1**
Medical	4	4	**8**
Marketing	1	5	**6**
Commercial		1	**1**
Not specified	2	2	**4**
Total	8	12	**20**

Table 3. Origin of main rejection reason by discipline.

It can be seen that the medical opinion was most frequently obtained, that it was well balanced and correct in 50% of cases. Overall, in many cases, formal opinions were not available, but had to be extracted from the BAC and ISC minutes. In many cases, the reasons were not given explicitly or had not been documented. For marketing and commercial the category „correct“ was given only if the product turned out not be a major success in the marketplace.

Acceptance depending on stage of development

There was little correlation between the stage of development and the likelihood of rejection as seen in the following table. In the earlier stages, rejections were based on the medical opinion most of the cases, later marketing played a dominant role.

Stage of clinical development	*rejected/ offered*	*% rejection*
I	6/8	75
IIa	3/5	60
IIb	14/16	84
III (pivotal)	3/5	60

Table 4. Rejections by stage of development

Use of quantitative tools

Quantitative tools such as pay-back periods, net present value or other systematic approaches were used but their impact on the decision rarely documented. A mentioning was given in at least one project-specific document for about 30% of all cases. In some cases, the cost of preclinical or clinical development were mentioned. For compounds accepted for in-licensing, the following data were consistently available:

pay-back period, contribution margin III (Deckungsbeitrag III), discounted cash flow (DCF), and net present value (NPV).

Trends during the period

During the period, the documentation system changed. From 1993 on, lists from Business Development became available. Before, the information had to be extracted from ISC minutes. Still, the in-licensing search seemed to have intensified since 1993, however, not accompanied by a surge in in-licensed products which were 0, 1 or 2 per year. There was no trend to projects in earlier or later phases of development during these years. Also, the only trend was in terms of indication areas where more oncology products were discussed in later years.

4.2.1.2 Preliminary conclusions from the PLD

Documentation of decisions during 1990-1995

The documentation of decisions is rather incomplete for these years. The minutes do not always allow to find the main reason for rejection or acceptance, and in most cases the assessment documents were not retrievable. The quality of these documents ranges between a note of less than one page and a detailed and well-referenced document. One may note that there must have been compounds that were rejected at lower levels in the hierarchy, and that other projects that were considered promising initially never reached the contract stage as the licensor insisted on commercially unacceptable conditions.

There are no standards or checklist for these assessment documents nor for the process and responsibilities.

It appears that the software used for commercial assessment is not described in a standard operating procedure and that standard assumptions not given. Marketing data, in particular, consistently give high marketing expenses (up to 50% of gross price) thus decreasing the commercial value of an offer.

Accepted vs. rejected opportunities

BI tended to reject many projects. On the other hand, projects accepted by BI had a good chance of being completed. It is noteworthy that medicine was right in half of the cases which is much higher than expected given the paucity of data available.

The value of rejected opportunities is difficult to estimate. Roughly, sales between 50 and 100 mio DM/year would be expected per product. Given that in 5 years, 10 projects were rejected that could have contributed to sales, this accounts to 500 - 1,000 mio DM/ year for the lifetime of these products.

This policy reflects prudence rather than gambling, but may also reflect a lack of calculated risk taking, e.g. by making options agreements (this has been done more frequently in 1996/1997).

4.2.2 Experience with the BI decision maker questionnaire (DMQ)

At BI, in-licensing for global or major regional products is a task of the Business Development Division at Boehringer Ingelheim GmbH (Headquarters). They propose in-licensing opportunities to the Business Area Conference (BAC) which consists of the Heads of the Divisions within Pharma and the Regional Responsibles for Europe, America, and AAA (Asia, Australia, Africa), and is chaired by the Head of Corporate Pharma. Decisions by the BAC are taken up again at the International Steering Committee (ISC) if internal resources for development are needed (which has been the case for all offerings covered in this project). The ISC which consists of the Heads of the Pharma Divisions and the Marketing Directors of Germany, the USA, and Japan, may overturn or modify a decision of the BAC. As it is chaired by the Head of Corporate Pharma, too, this usually does not happen.

Therefore, the members of these two committees (which greatly overlap) were sought for questionnaire interviews. This method was chosen over direct interviews as it avoids vague statements and allows the participant to take time to answer the questions. The choice of questions was guided by learning more about the decision behaviour of the individual. Compromises had to be made as full anonymity was not possible, so direct questions as to the degree of preparation for decisions were left out. As the meeting minutes do not contain dissenting opinions, the basis for decision making as well as judgement on the quality of decision preparation were most important to know. Therefore, the questionnaire concentrated on

- the criteria for taking or leaving an opportunity
- the certainty of having taken correct decisions, and at the right time
- the satisfaction with the preparation of the decision (by area of expert opinion)
- the reliance on quantitative tools
- the opinion on the in-licensing process

The questionnaires will be analysed by what decision makers have in common, and where a wide range of opinions may be seen.

The number of returned questionnaires will be given as a percentage, with reasons for not completing.

The reasons leading to positive or negative decisions will be summarised into appropriate categories or headings and the main five categories rated 5,4,3,2, and 1 points according to the rank in the listing. Points will be added to give a composite score for the two separate sets of criteria; if criteria are essentially similar but use different wording, they will be grouped and the scores added to that group.. An extra analysis will be undertaken for members who are members of the BAC or ISC only, and for members of both committees..

The percentage of inadequate decisions, i.e. decisions that should have been delayed, will be plotted as a histogram table and as a scatter plot against the individual certainty of a right decision.

Mean scores and deviations will be given for the ratings of the four different assessments.

The use of quantitative tools will be classified as follows:

- ignorance
- does not see relevance (relative to other means of judgement)
- sees relevance
- prefers more such tools

Allowance will be made if particular tools are mentioned.

Regarding in-licensing activity, the type of responses will be classified and described as such:

- current status sufficient
- current status to be improved quantitatively
- current status to be improved qualitatively
- current status needs qualitative and qualitative improvement

Individual responses will be cited where appropriate.

4.2.2.1 Results

Return rate and completeness of questionnaires

Of 16 questionnaires sent out to members of BAC and ISC, 15 were returned completed. The Head of SBU Self-Medication did not return the questionnaire as he was not informed in in-licensing processes outside his group of over-the-counter medicines.

In some questionnaires, not all questions were answered. In particular, only two or three decision criteria were given in some cases.

Individual certainty of decision making

Most members of these committees rated their percentage of correct in-licensing decisions as very high, around 80-100%. Only one member went as far down as 50%. One person did not give an answer.

Correct decisions in % of decisions	*Number of questionnaires*
90-100	3
80-89	3
70-79	6
<70	2

Table 5. Individual certainty in decisions.

Given the results of the PLD, these figures appear rather high. A critical appraisal of one`s own decisions may be difficult for decision makers, or they may indeed have improved compared to the 1990-1995 period.

Criteria for positive decisions

The questionnaire set out deliberately to ask for criteria for accepting or rejecting separately. Normally one would assume that the two are just two sides of one coin, however, the obvious difference in most questionnaires probably reflects additional decision strategies. According to

the rating, the following list was constructed (sum of ratings for all respondents; any parameter listed as no. 6 or lower was not given a point.) If criteria were by content related, they were grouped under one single heading.

Ratings (group)	*BAC*	*ISC*	*BAC/ ISC*	*Total*
strategic fit	16	15	27	**58**
NPV/cost of goods/financial/profitability	14	8	15	**37**
likelihood of success	3	8	19	**30**
time to market/earlier than own	4	6	10	**20**
sales volume	13	2		**15**
good clinical data/stage of development	2	8	4	**14**

Table 6. Sum of ratings for positive decisions

Strategy and profitability seem to be top on the agenda for taking on a project. This high rank for strategy surprises as it is very broadly defined at BI. Ratings not mentioned here were thoroughness of evaluation, internal resources, preclinical rationale, improvement of business, technology in house, take option, no own product, global availability. Most of them never were mentioned among the top five in anybody`s list. BAC „only" members seem to place a high emphasis on sales volume which may be an expression of the need to obtain large market shares.

The ranking could also be interpreted as a consequence of the type of in-licensing offers received.

Criteria for negative decisions

Those criteria are displayed in the same way. In the questionnaires, these were given as frequent as for positive decisions. There is a different pattern compared to the criteria applied for positive decisions. Economic arguments dominate rejections, but also competition with in-house projects appears as important. This stresses the relevance of the commercial

assessment, but as in the criteria for positive decisions, the technical issues (likelihood of success, quality of technical data) follow next. Strategic fit is not an argument which, conversely, could mean that the absence of this criterion will not exclude an opportunity. Criteria like quality of evaluation, patents, limited scope/territory, technology in-house or early stage product were rarely mentioned.

Ratings (group)	*BAC*	*ISC*	*BAC/ ISC*	*Total*
economic less/cost of goods/sales/cost	30	10	17	**57**
validity of data/efficacy/safety/preclin.rationale,	2		29	**31**
likelihood of success/feasibility of approach	4	11	12	**27**
contribution to medical field/competitive advantage	5	9	9	**23**
strategic fit	8	12	2	**22**
compete with own products		5	14	**19**

Table 7. Sum of ratings for negative decisions.

Decisions perceived as not adequately prepared

13 of 15 respondents answered this explicitly.

Percent decisions better postponed	*Number of respondents*
0	1
1-19	2
20-40	7
>40	3

Table 8. Post-decisional regret.

The results show that decisions may have been made in up to 30% where clearly the preparation of the decision had been deficient.

As this may be inversely related to decision certainty, the two percentages are related to each other to some degree. The respondents giving high values in this question often scored low on their own decision certainty.

Ratings of decision preparation papers

The decision papers had to be rated retrospectively and are an overall impression of such papers in the past 12 months. This does not allow objective judgement, but the „gut feeling“ is asked for. The data are given as means and standard deviations, and as a percentage of „good“ (=2) and „very good“ (=1) grades. They are given for the total group of respondents to this question (n=13).

Expert opinion	*Rating mean*	*Rating variation*	*% grades „very good“ or „good“*
R&D	2,46	1,05	62
Medicine	2,38	0,87	54
Marketing	3,00	0,82	23
Commercial	2,62	0,77	54

Table 9. Rating of expert opinions by committee members

The ratings may partly reflect a good status of the quality of decision preparation. Medicine and R&D fare quite well although with a large spread (standard deviation). The rating for the marketing opinion is poor, especially taking into account that the commercial decision is much based on the marketing assessment.

Use of quantitative tools

In general, the use of quantitative tools seems to be encouraged, but some members may have little experience actually using them taking from the scarce comments received.

Comment	*Number of respondents*
ignorance	1
do not see relevance	2
see relevance	10
prefer more of such tools	2

Table 10. Relevance of quantitative tools

The answers were usually positive. No special suggestions on specific instruments were given, but they had not been requested. Among the techniques, NPV was mentioned several times. Still, three members do not know or see the relevance of such tools. All in all, the results are what should have been expected from members of top management committees.

Opinion on in-licensing activity

The opinions on in-licensing activity were clear-cut. There was little consensus as to the performance.

Comment	*Number of respondents*
current status sufficient	3
needs more quantity	3
needs more quality	3
needs both more quality and more quantity	5

Table 11. Satisfaction with in-licensing function

Overall, most respondents saw room for improvement qualitatively and/or quantitatively. Taking results from responses further above, this may have to do with decision preparation.

4.2.2.2 Preliminary conclusions from the DMQ

Reliance on quantitative tools

The assessments usually contained figures such as cost or time of development, estimated market share or likely price acceptable to the market. When it came to likelihood of success, rarely did R&D or Medicine give a probability figure, or a series of probabilities (in the case of a stepwise approach). Such would, however, be needed for more sophisticated decision analysis.

Tools for capital investment appraisal were in general found relevant. The most frequent comments were on net present value and pay-back period. Options pricing was never mentioned. While net present value was mentioned, almost none of the decision makers stated its relative impact when accepting or rejecting the proposal. The same was true for the pay-back period.

Sensitivity analysis was partly employed giving a pessimistic, realistic, and optimistic version of sales expectations. More frequently, scenarios were used.

Criteria for decision

BI decision makers are very sure of their decision quality given the known likelihood of taking a wrong decision. It is not clear whether this is a justification process or simply is based on insufficient feedback on decisions made in the past.

The decision criteria are rather homogeneous although they purportedly did not communicate to each other about the questionnaire. There were some remarkable findings:

a) BAC members had a preference for business criteria while likelihood of success or validity of data played a higher role for members of both committees (of whom 6 are medically trained).
b) While positive decisions were much determined by strategic fit, financial, marketing and scientific aspects, negative decisions were mostly driven by business (economics) and/or scientific and medical validity and likelihood of success.

This discrepancy could be explained by the fact that there exists a hierarchy of criteria. A positive decision may only be reached once the likelihood of success and commercial criteria are fulfilled, and in such cases the next criterion will be „strategic fit“ .When, on the other hand, a project is rejected, it does not even reach the level where the „strategic fit“ question is posed.

Quality of decision preparation

Decision makers had major problems with the quality of decision preparation. In particular, marketing assessments were seen as critical. It should be said that the opinions were mostly „benevolent“ given some of the criticisms that are voiced at the committees themselves.

The mean percentage of 30% of decisions that should rather have been postponed surprises as this is not reflected in the minutes of those meetings. This contrasts with the decision certainty mentioned above, and it points to a potential lack of candid communication during meetings. Also it appears that appeals to better decision preparation have not been followed and that poor assessment papers are still tolerated, even if just by inaction.

4.3 Hypothetical case studies

In the following sections, examples will be given that underscore the relevance of precise decision preparation, including the consideration of probabilities in a project. During drug development, there are some stages where the relative importance of medical vs. economical uncertainty may vary. For an average project in a therapeutic indication with several competitors, the reductions of such uncertainties does not go in parallel. Please note that in figure 7 the Y axis has arbitrary units of „uncertainty“.

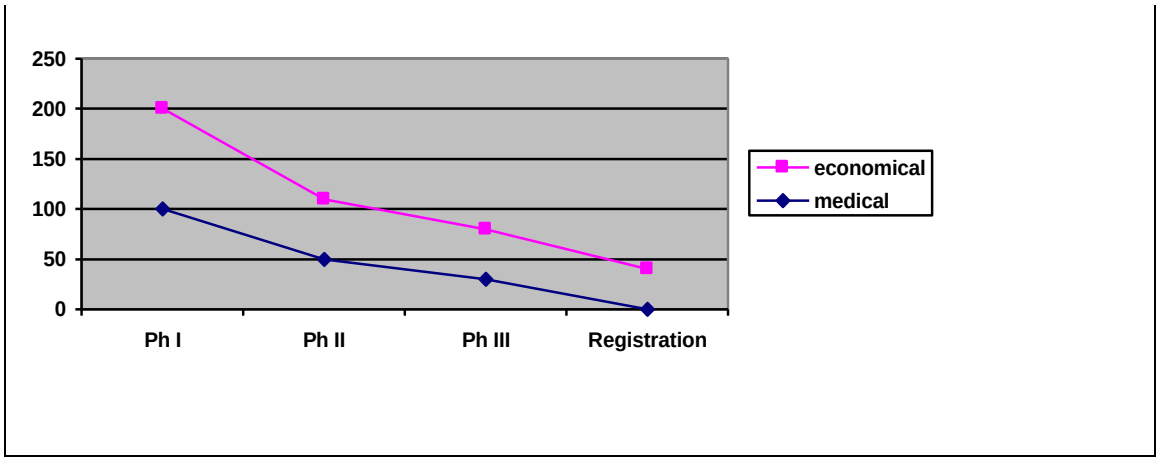


Figure 7. Uncertainty (arbitrary units) over the development period

The following examples will be used to illustrate the concepts in capital appraisal and decision making. While they are not fully representative of in-licensing opportunities for each and every company, they are modelled by different stages of development, and reflect international in-licensing opportunities.

Cases A, B, and C are strictly hypothetical. In addition, two recent examples at BI have been calculated, cases D and E. Case D is the in-licensing opportunity of an end of phase III passive vaccine, and case E is a novel anti-cancer agent of which some phase II data are available.
While the „base case“ was used here, marketing uncertainties gave rise to differences of estimated market sizes of more than two times, and a potential price range that was more than a factor of three. In case D, this meant a pay-back period between 5 and 10, and in case E, between 4 and 10 years.
BI was turned down by the licensor of case D following its counter-offer, and obtained the compound in case E.

As in the entire dissertation, merely national in-licensing opportunities are not considered as they usually do not happen with early stage products. They are taken from the matrix described by the following parameters (for details on parameters see appendix G).

a) SDEV: stage of development of in-licensing opportunity (phase I, IIa, IIb/III, registered)

b) PLE: patent license expiration (number of years, by the time of launch)

c) ESVOL: estimated sales potential (volume daily doses, x 1,000), from year 3 after launch; for year 1 and 2, 20 and 50% of this value are estimated

d) EAP: estimated average price per daily dose (US-$)

e) LDA: likelihood of obtaining drug approval (%)

f) PRS: payment and royalty structure of in-licensed product (DP = down-payment, million US-$; MSP= milestone payments, million US-$; RP = royalty payments, incl. cost of goods as percent of sales)

g) IHP: availability of an in-house product (yes, same development stage; yes, earlier development stage; no)

Case	***SDEV***	***PLE*** years	***ESVOL*** x 1,000 patients	***EAP*** US-$ per day	***LDA*** (%)	***PRS*** million US-$	***IHP***
A	I	15	1000	2	20	DP=100 MSP=20 RP=40	no
B	IIb/III	10	500	5	70	DP=100 MSP=50 RP=30	no
C	IIa	12	200	10	30	DP=50 MSP=50 RP=30	yes, same stage
D	III	10	50	15	100	DP=80 MSP=50 RP=50	no
E	IIa	10	200	5	40	DP=50 MSP=50 RP=50	no

Table 12. Examples for in-licensing opportunities with parameters for applying capital appraisal techniques

4.3.1 Comparative use of investment appraisal techniques

Investment appraisal techniques can be seen as (mutually exclusive) alternatives, but also as complementary techniques that show different facets of the decision at stake.

As they partly logically build upon each other, a set of them may suffice.

It is important to know that all of them are unable to reduce the marketing uncertainties by themselves. It will be shown later that it is this uncertainty that accounts for a large part of the variance of the future of some drugs in development.

In the following table, IRR and NPV have been calculated. Also, a simple options pricing approach has been calculated using the data available above and making no further assumptions. The maximal loss is the one that occurs when both down payments and milestone payments have been made, and the development is then stopped.

Case	*pay-back period (years)*	*IRR (%)*	*NPV cumulated (million US-$)*	*NPV (option) (million US-$)*	*maximal loss (million US-$)*
A	6	47	644	129	120
B	6	39	253	177	150
C	6	40	67	20	100
D	8	20	92	92	130
E	6	35	231	177	100

Table 13. Comparison of financial appraisal parameters in different projects

For the calculation, an EXCEL spreadsheet program (Microsoft Office 95) was used that is the standard at BI to provide data for the commercial assessment of in-licensing opportunities. The NPV option value was calculated assuming a one-step binomial probability (likelihood of success).

It appears that

- the pay-back period is beyond 5 years in each case which may not be acceptable to cautious decision makers

- the IRR gives even high figures when the NPV is relatively small, for instance in case C.
- the difference between the NPV option value and the maximal loss (added down-payment and milestone payments) may be a good parameter for estimating risk. Only options A, B, and E fulfil this criterion. If it is negative, taking this compound is clearly a bold move.

The data show clearly that reliance on one parameter is not prudent. Except for the NPV option, none of them takes the technical risk into consideration. For case C, as there is an in-house competing project, opportunity cost should be calculated.

One major question regarding the assumptions is whether to assume point estimates for the parameters rather than taking a probability distribution. While the point estimates may in addition need several scenarios, the probability distribution would, due to its characteristics - broadness, skewedness, and individual values allow the construction of systems that can be used for Monte-Carlo simulation which may still not exclude the use of the scenario technique. In practice, the respective person would be asked to give the 10%, 25%, 50%, 75% and 90% percentile for the value, for instance, sales revenues. This is, admittedly, a cumbersome procedure, and it has not been proven to avoid the pitfalls of point estimates. Also it is not sure how stable, even for a given rater, such estimates are over time.

4.3.2 Applicability of decision analysis techniques

Of the decision analysis techniques of potential use, the following will be discussed:

a) influence diagrams

Influence diagrams use a „notation“ that is not familiar to decision makers. While this is considered a disadvantage influence diagrams are better at demonstrating interrelationships between variables than do the frequently used simple listings of „critical issues“ or „criteria for decision“. For instance, note the difference of presentation for the case of an in-licensing opportunity (=Innomood) that competes with an in-house development (BIMT-17) that is about 3 years behind in development but essentially serves the same indication field.

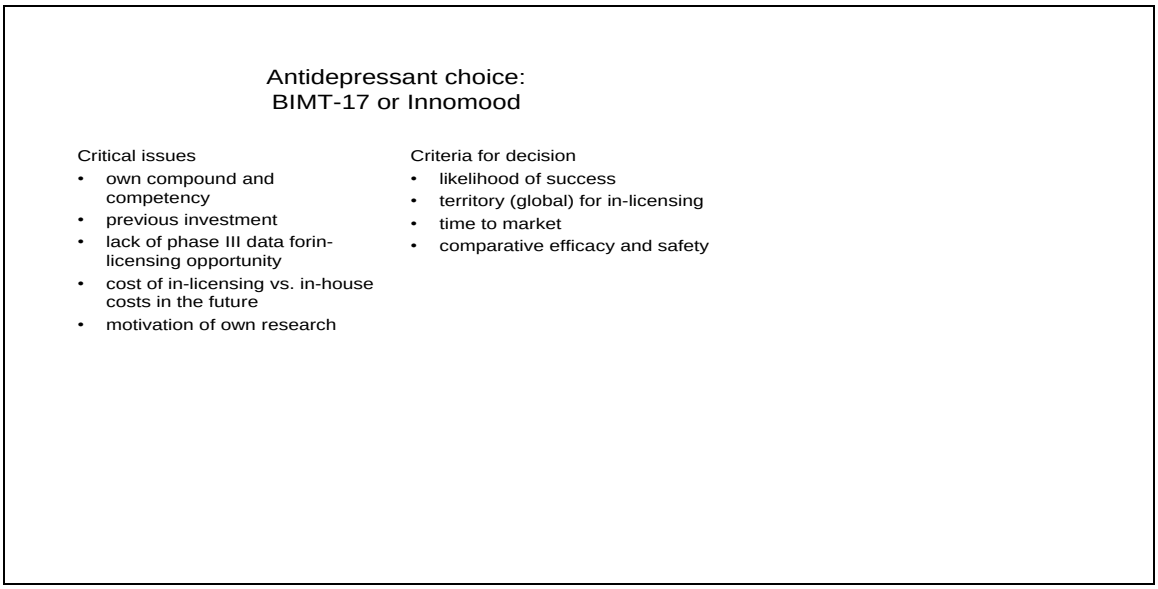


Figure 8. Conventional presentation for showing critical issues

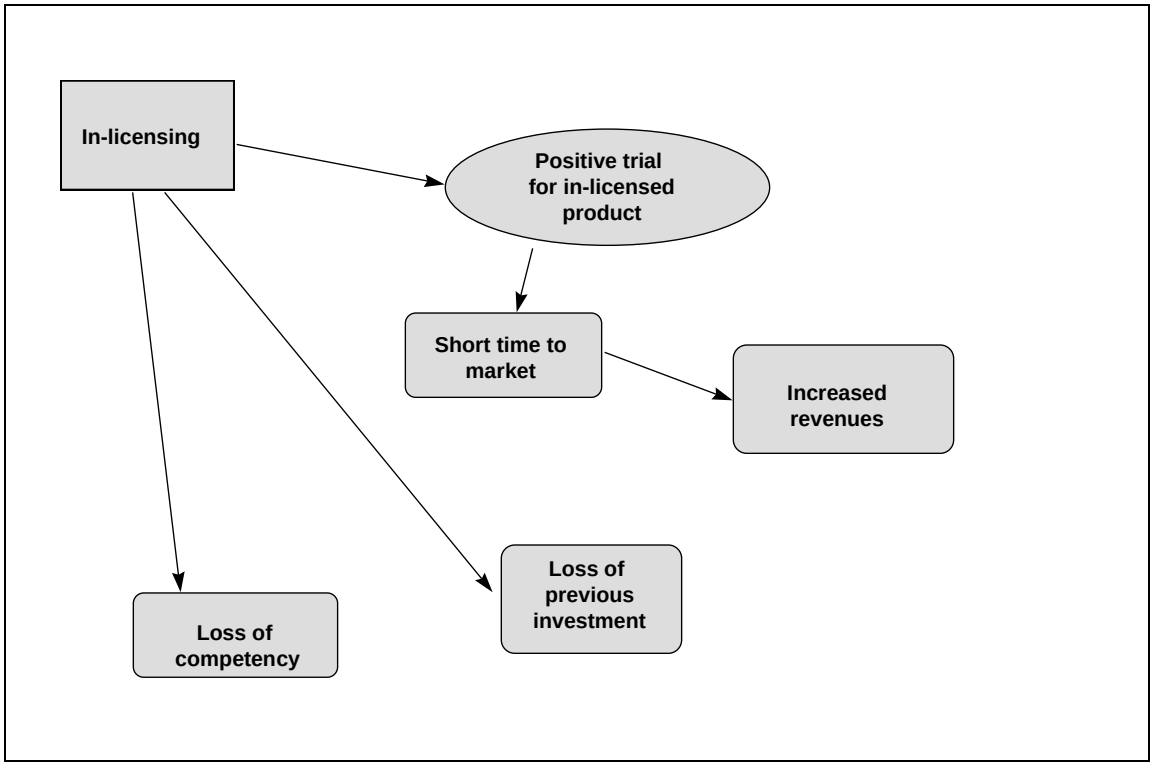


Figure 9. Influence diagram for in-licensing for the same case

b) decision trees

For the main decisions, a decision tree is a reasonable tool. If hierarchical decision making is not possible or if there are more than 20 branches at the end, the decision tree must be condensed into the above mentioned influence diagram. In principle, the decision tree is the influence diagram, with probabilities and (monetary) outcomes. In the case above, the likelihood of success for the own and the in-licensing compound would have to be given as a fraction of 1.

c) utility functions

Utility functions come in two ways: they can be expressed in utility units if one works with expected utility (EU), while certainty equivalents (CE) or risk premiums are given in currency units. Another approach is to use probability equivalents (PE). Utility functions are based on subjective assessment of risk.

As a basis for either, the decision tree must have been constructed, with various different probabilities attached to the decision nodes.

It is questionable whether the individual utility functions in a committee such as the BAC or ISC would have any bearing on the final decision. Neither are they easy to elicit, nor are they in any way computable to allow for a decision. They seem to lend themselves better to clarify one's real beliefs or concerns than to guide a company.

4.4 Company strategy and the choice of technique

The techniques used may be dependent on the general strategy a company has determined for itself. This section assumes that certain techniques will suit decision styles and overall strategic goals better than others. Apart from the individual risk-seeking or risk-aversive profiles of decision makers, this may be subject to the following parameters which may be not exhaustive but are based on information from the literature and personal communications during the field work.

a) previous experience: having used a technique without major pitfalls would support staying with this technique in the future. This requires adequate feedback mechanisms on the performance of the technique and the adequacy of the decisions based on it. Below, one possible feedback mechanisms, the audit, will be described. Feedback on decisions will be of lesser help when decision makers change frequently and when they do not stay in a job long enough to see the consequences of their actions. In addition, decision makers may be differently sensitive to such feedback, and some may simply suppress such information as it could assault their self-image. With the very positive assurance of BI decision makers (very few think they are right less than 70% of the time) such feedback may not reach the addressee.

   Conversely, a technique that clearly failed may not be used again. More often, the commercial analysis is considered the „icing on the cake“ as the technical assessment of the potential product prevails and determines largely the outcome of such analyses.

b) ability to tolerate major failures: if this is given, a more conservative technique like pay-back period may not be applicable as it leads to the exclusion of many possibilities. In the later stages of negotiation, companies that can tolerate such major failures may be tempted to outsmart their competitors in the bidding process and in-license a compound as a high down-payment looks more attractive to many licensor companies than a sophisticated agreement with sequential options.

c) emphasis on fast growth: is such a case, the opportunity is seen more frequently than the risk side. In addition, fast growth requires that in-licensed compounds are in later stages of development where the technical risks are usually smaller. Techniques like simple NPV may prevail. On the other hand, short pay-back periods can also be seen as essential, but longer ones could be easily tolerated if the competition need not be feared.

d) application of financial analysis to in-house projects: in the absence of such an attitude, in-licensing projects may be subjected more to likelihood of success approaches than to financial modelling. If in-house projects are subject to financial analysis, the same pattern is likely to be used for in-licensing.

4.4.1 Conscious decision and integration of in-licensing into overall strategy

In-licensing, if seen as additional product opportunities, should be fully integrated into the evaluation process. Moreover, entering a new therapeutic area, the strategy should consider in-licensing as an opening move even. It must be noted that the type of decision concern varies somewhat between in-licensing projects and the decision to move into or go ahead in an area with an own compound. The perceived uncertainties determine, sometimes unconsciously, the behaviour of decision makers towards an in-licensing opportunity.

Type of uncertainty	*own product*	*in-licensed product*
professionalism of staff	low	high
cost of product	low	high
time to market	medium - high	high
reliability of data	medium	high

Table 14. Uncertainties differ for licensed vs. own compounds

In-licensing into a new area could mean not to have to build up expertise, to save resources for other areas, and to have a rather simple exit strategy available. This is to be weighed against the cost of such opportunities. Licensors, however, prefer licensees that have shown that they are experienced in the area at stake, at least regarding marketing the compounds. Contracts may be written in such a way as to allow for minimum sales in addition to best effort clauses.

4.4.2 Strategy types and the type of decision support

In a recent paper on strategy under uncertainty, several „futures“ were presented: clear enough vs. alternative future vs. range of futures vs. true ambiguity. The alternative futures, where decision trees dominate, are the closest to in-licensing. By the same authors, typical approaches were classified as “shapers”, “adapters”, or “reserving the right to play”. [33]

[33] Courtney et al.(1997)

The latter approach is closely connected to the philosophy of options pricing, while the other two may be served by other techniques, for instance, scenario building. All of these strategies may, however, co-exist in one company, for instance dependent on the therapeutic area. Therefore, no “pure” strategy is envisioned.

In any case, the type of tools needed for in-licensing situations should derive from several sources:

a) net present value: provides the value of the project and contains all information needed for sensitivity analyses
b) simple options pricing: on the basis of the values obtained by NPV, subjective parameters, and parameters analogous to stock options pricing (modified Black-Scholes formula)
c) influence diagrams (more as a heuristic instrument)
d) decision trees
e) utility functions, only in selected cases, for instance when (external) experts are involved, in order to clarify their risk tolerance, however, the construction of such functions is difficult and may not add too much value, especially in committee decisions.

For details see also 5.2.2 .

The different strategies could also be grouped according to likelihood of success. In principle, there are two hurdles to take: the approval by regulatory (health) authorities, and the success in the market itself. Both are related, in particular as the official “claims”, i.e. the wording of the indications, precautions or contraindications and risks when using the drug, determine the position relative to competitors. The decision tree for an angiotensin-2-antagonist, a compound used for the treatment of high blood pressure, can be drawn as such:

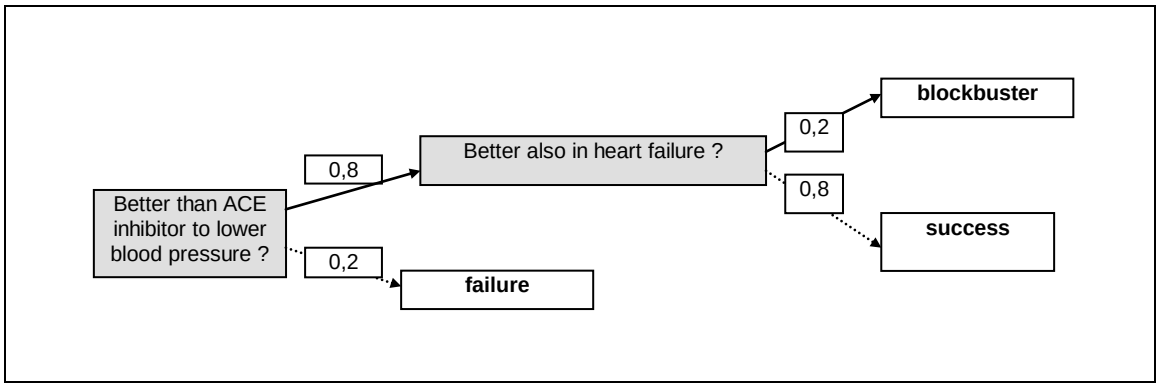


Figure 10. Decision tree for angiotensin-2-antagonist. *Solid arrows are positive results, broken arrows are negative results. Probabilities are given in rectangles.*

From this it can be seen that the drug approval may be described by three scenarios, with different probabilities. For each of these branches, there is a probability distribution for average price, and following this, by sales revenues. The search for the optimum price can be supported by conjoint analysis, except that in such a case the price/sales volume diagram is not giving a single line but a series of lines.

Modelling probabilities above 80% is comparatively easy as this reflects traditional risks of projects, such as in engineering, and additional risks can be accounted for by adjusting the "interest rate", the opportunity cost of capital which historically is 15-20% within the pharmaceutical industry.[34] This approach is risky as it is an average and may have to be estimated for different types of products.

Even for probabilities between 50 and 80%, this is fairly simple. For probabilities of success below 50% - and in some indications and novel therapeutic principles like Alzheimer's disease or cancer this may be below 20%, such adjustments are difficult to do. Using traditional accounting, e.g. the IRR, incredibly high returns would have to be postulated to justify these outlays. This can be shown by another example:

A proposed product has an estimated remaining patent life of 10 years by the time of launch, the estimated average sales is 500 million US-$ per year, of which 80% are cost of goods and royalties, and a likelihood of success of 10%. Down-payments are 50 million US-$, and milestone payments at the end of phase III are 100 million US-$ for this product which will be fully developed by the licensor. The IRR is calculated to be 25% (which is only little above the

cost of capital), and the pay-back period is 7 years. Thus this product is not seen as acceptable, although its cumulated NPV is positive with slightly less than 100 million US-$.

In other words, traditional accounting does not give sufficient answers when high-risk projects are to be evaluated, as is the case now with many projects of major pharmaceutical companies. This is particularly true of co-operations with small biotechnology companies where the risk of complete financial breakdown has to be factored in as well, and where, even in preclinical disease models, comparisons to the appropriate gold standard are often lacking. However, the pay-back period may be a useful screening instrument if pay-back periods of 5 years or less are an established criterion in the in-licensing company.

4.4.3 Large companies vs. small companies

The major difference between larger and smaller companies today is the degree of risk-taking they can afford. [35] The financial resources and possibilities of a small company are limited, therefore, it may have to be more conservative regarding projects with a low probability of success.

While this is particularly true of companies that are privately owned, the situation is different if the company is traded at the stock exchange and thus has an additional source of funds given the financial community agrees with the evaluation.

It should not be forgotten that small companies often lack the expertise for doing sophisticated financial modelling, and that their internal expertise to quantify risks and rewards may also be limited. This is partly counterbalanced by their use of investment bankers that know these tools.

A closely associated question is whether the link to the overall strategy of the company can be subjected to such quantitative simplification. [36] It is not given that companies can determine beforehand, if they go for a therapeutic area strategy, the level of engagement. The comparison of different alternatives, taking the entire development portfolio, is almost impossible given the usual development strategy of postponing most evidence into the final

[34] Brealey and Myers (1996), p. 212
[35] Walker and Zinssli (1996)
[36] Matheson and Menke (1994)

phases of clinical testing. Therefore, such a strategy makes little sense even in large companies, although it helps to focus the search for opportunities.

4.5 Capital investment and behavioural issues

4.5.1 Perception of commercial value

The perception of commercial value is, contrary to beliefs of decision makers themselves, likely to be influenced by „more objective“ and „less objective“ parameters.

4.5.1.1 More objective parameters

Major indications

Indications such as hypertension or acute myocardial infarction are per se seen as large enough to accommodate many competitors. Thus, such indications receive a bonus from decision makers as the range of potential market share allows a high upside potential. In particular when the company is already known in this field, the subjective likelihood to gain a sizable market share is usually high. Also, there is the perception that even a small market share would mean significant income. This belief has lured several companies to take on in-licensing candidates for hypertension or rheumatic diseases while in the asthma area, in-licensing usually occurs between the three major companies that have 80% of market shares combined.

Large obvious medical need

Medical need is voiced differently by indication. In some, cure is requested, in others, the level of achievement is down-scaled to controlling symptoms. In any case, such indications sometimes force themselves upon pharmaceutical companies and obfuscate financial considerations, such in the case of the treatment of HIV infection.

Interestingly, often major medical breakthroughs were, neither by the originating company nor by its competitors, considered as such:

a) histamine H2 antagonists for the treatment of gastric/duodenal ulcers: development was done without agreement of corporate R&D, at a small laboratory as market research did not discover a medical need
b) fluoxetine and other new antidepressants were not in high regard when they were developed; in some companies, in-licensing considered them a minor, incremental improvements over existing treatment

4.5.1.2 Less objective parameters

Biotechnology

Such products, based on the experience of erythropoietin (sales 1996: 2 billion US-$) or tissue plasminogen activator (sales 1996: 1,4 billion US-$), have a bonus also as their manufacture requires special know-how and resources. In principle, such compounds also have high prices on a weight basis.

Experience

Executives that have, in their own career, made the experience of such a product, are more likely to express that they have the „gut feeling“ to sense such an opportunity. [37]

Blockbusters

The perception of having a blockbuster (a compound that „transforms“ an entire field, such as the histamine antagonists did with duodenal ulcer) opportunity also falls into the subjective realm. Most known blockbusters were only late recognised as such. It is clear that the absence of such qualitative estimates implies the same for any quantitative approaches.

4.5.2 Cognitive abilities and multi-project decisions

Decision making for in-licensing happens on a semi-continuous scale: the decision-makers are confronted with an opportunity, and while the competitor analysis allows them to judge the competitive environment, they do not have the chance to evaluate projects against each other. Furthermore, the projects are usually represented more than one time. At one situation recently at BI, a project was judged by the licensor to have a market of potential of at least 100 million US-$, while BI estimated 40-60 million US-$. A BI-sponsored primary market research arrived at 80-120 million US-$, which was heavily doubted internally.

One major reason for this is that information is often not complete. By the time the decision needs to be made, a full appraisal is not possible, often because of incompetence within the company where the opportunity is seen in too narrow a context. One major reason is that the available information is indeed not captured by the experts assessing the opportunity for likelihood of success.

Another reason is the absence of the complete project picture. There is little available regarding the risk portfolio of projects when such decisions are made, or a map specifying when a new important information will come up (influence diagram could serve as such mental maps). And it is not possible at such a stage to foresee future opportunities that may be impossible to realise as previous decisions have consumed all available resources.
This, as well as the confidence data of the DMQ, supports earlier results that overconfidence is frequently found among other cognitive biases. [38]

4.5.3 Personality type and decision making behaviour

Very little is known about personality types and risk-taking behaviour. Even less is known about decision-making in groups where opinions may not be openly discussed. The examination at BI did not aim at elucidating such parameters as first discussions revealed resistance to such

[37] Brenner et al. (1996)
[38] Kirkwood (1997), pp. 112-116

potential questions which was underscored by some respondents even not commenting on some less direct questions regarding subjective decision certainty and post-decisional regret.

4.5.4 The appeal of simple parameters

Decision makers who are not experts in finance tend to like simple and „obvious“ parameters.[39] They use “rules of thumb”, among which the pay-back period is a frequently used one. The BI questionnaire results support this statement. Many respondents pointed to the overriding issues of likelihood of success that should, in their view, make sophisticated financial calculations a secondary consideration. Also, the fact that only Merck seems to use option pricing models (in addition to more conventional tools) shows that such tools are often not evaluated in detail, or at least such information is not in the public domain.

Such behaviour can be understood under the concept of „bounded rationality“ when decision makers behave as though they were using a rational way. Repetition - or rather, using the results of similar experiences- is one way of coping with uncertainty, and it occurs that even seasoned decision-makers do not see this „heuristic trap“. Adaptation, adjustment, and learning by doing are often quoted here.

The special attention which the pay-back period receives may have to do with the inherent belief that predicting the future in the drug business is almost impossible. It is not clear where that assumption comes from. There have been no systematic studies showing a surprising increase of „project volatility“ after 5 years. A time horizon of more than five years is therefore considered by some as very daring, and five years is usually the time by which results of a new compound are seen when it leaves the preclinical phase of development. There is evidence that the life cycle of a drug does not correspond to such simplistic assumptions. In the case of diclofenac, the life cycle could very much be stretched, and the majority of sales of the stomach ulcer drug ranitidine were reached in the years after the pay-back was complete. It is estimated that more than 80% of the ranitidine net income came after the „pay-back period“. It must be noted here that the other „rule of thumb“, equating the pay-back period with the remaining patent life of a compound, has been supported by the (in the USA) more than 80% price

reductions of ranitidine generics. However, the contrary has also been shown for several compounds, such as the combination of levodopa with another compound for the treatment of Parkinson`s Disease.

An additional inherent assumption is that income during a pay-back period of five years or less is a “base case”, and that any additional income can be considered upside potential. This also reflects the belief that the money today is more worth than the money in some years from now, however, forgets that DCF and other methods are available to account for this.

4.6 The integration of options pricing, decision analysis, and game theory

The decision analytic techniques should include tools of game theory, taking the potential moves of the licensor into consideration.

In the more general case, the interests of a licensor vs. a licensee are shown to be quite antagonistic.

Area	*Licensor*	*Licensee*
Openness	may hide weak points	wants to detect weak points
Price	high price	low price
Down-payment	as high as possible	none
Royalties	progressive with sales (%)	decreasing with sales (%)
Follow-up compounds	not included	must be included
Development	minimal effort	broad effort
Share price	keep constant by all means	not much interested
Options	variable	favourable

Table 15. Interests of licensor vs. licensee are different and can be modeled by game theory

[39] Gigerenzer and Goldstein (1996)

4.6.1 Information asymmetry

Despite confidentiality agreements and the disclosure of proprietary information, the licensor has an advantage over the licensee as he may have more information, especially regarding the risks. He is likely to retain such information as it lowers the bargaining value of the compound.

On the other hand, licensees, through obtaining confidential information from several potential licensors, may have a better overview over the field and a good position to check the value. As they may not disclose the sources of this information, this may be of limited value for them in the bargaining process.

Information theory differentiates between produced and emergent information. The former is intentionally done and will be available to some price, the latter will occur without contribution from either side, for instance, data from emerging competitors.

4.6.2 Risk taking as a zero-sum game

The distribution of risk between licensor and licensee is a zero sum game for a given strategy of development. It can be shown that, like a price in a complete or incomplete market, a risk-bearing equilibrium can form.[40] Taking more risk at the beginning can, however, be rewarded later through lower royalties.

4.6.3 Practical example

For each of the main moves, the change of the value of the project should be considered (sensitivity analysis). For instance, strategic considerations may require that a company „invades" the territory of a partner firm with which it is doing business in the same area. For BI, which is a licensor for Genentech (GTE) but has no rights to their territory, the USA, one potential strategy as a global player is to enter their licensor's territory with another compound. The pay-off matrix must then contain the net sales for the two cases of „invade" or „do not invade". The pay-off matrix below gives arbitrary units, and, by itself does not indicate that some of the moves may be irreversible: when BI has started to invade it is difficult to formally retreat again.

	Genentech	
Boehringer Ing.	**no fight**	**fight**
invade	**200/600**	**50/750**
do not invade	**0/800**	**0/800**

Table 16. Boehringer Ingelheim (BI) and its licensor, Genentech (GTE)

[40] Hirshleifer and Reilly (1992), pp. 91-96

5 Conclusions and recommendations

5.1 Documentation of in-licensing decisions

A simple survey or a collection of minutes is not sufficient. Licensing decisions should be documented using a form comparable to the PLD. Reference should be made to background assessment papers, and the document made be retrievable in an electronic file..

5.2 Use of decision support tools by decision makers

5.2.1 Inclusion of options pricing techniques

Options pricing in the form described can, without major difficulties, be introduced into the tool kit for decision makers. The necessary variables are more than with simple NPV calculations, such as revenue, variable cost, fixed cost, depreciation, pre-tax profit, tax, net profit, and operating cash flow as they include the construction of a decision tree, and, possibly, the elicitation of probability assumptions.

The following situations should be considered:

a) the option to enter a full agreement when the results during the option period appear to justify such an investment
b) the option to wait and not react to the other companies offer (here thoughts and techniques of game theory come in as the development of options is a process that can occur both as simultaneous or consecutive moves)
c) the option to abandon a project
d) the option not to take on a project

With the exception of situation c) which may occur when losses accumulate and there is no high chance of ever arriving at a product, all those options occur with in-licensing. In particular,

the situation d) should always be calculated as companies can only take up a number of projects. So at least decision makers should be made aware of this option.

Practically, the option to wait must be seen with much care as the volatility of the NPV may not decrease but increase, for instance in the case of more competitors coming to the market making significant market shares for the own product all the more unsure.

5.2.2 Presentation of capital investment appraisal data

The conventional separate assessment of in-licensing opportunities frequently leads to seemingly controversial recommendations. To avoid this, a framework of assessing risks and benefits can be introduced that allows for the consideration of decision trees, cost, time, and probability. As utility functions are driven by subjective risk behaviour, such functions may not contribute too much to the decision.

For instance, the medical assessment could contain information on what steps could be done next at which cost and within which time frame to allow a better evaluation or positioning. Thus, the relative costs and benefits that could go into an options agreement are more precisely described. This can be seen in the following hypothetical table:

Activity	*Cost of activity (US-$, x 1,000)*	*Time needed*	*Go-result*	*Proba-bility of go result*	*No-go result*	*Proba-bility of no-go result*	*Next step if „go“*
Phase I single dose study	400	6 m	no safety concern	0,70	major safety concern	0,30	phase I multiple dose
Phase I multiple dose study	600	6 m	no safety concern and no kinetic problems	0,70	major safety concern	0,30	phase II a trial
Phase IIa trial	2,000	18 m	effective over placebo	0,50	no difference to placebo	0,50	phase IIb trial

Table 17. Cost of information in clinical development

It should be noted that the probability in subsequent steps may change upon learning in a previous step. Frequently, when single dose experiments in humans show no problems, the likelihood of a problematic result in the multiple dose trial is much reduced to prior assumption. In such cases, Bayesian statistics should be introduced, however, in such a case, the outcome of the event leading to the next decision node needs to be described precisely. The quantitative information could be arranged as to maximise the amount of information, minimise the amount of time and the cost involved to get it.

This system can be used to also demonstrate the benefits and risks of not deciding immediately. Again, cost and event probabilities have to be set in.

In addition, the way commercial information is presented to decision makers deserves further elaboration. A minimum set of information should contain:

a) Net present value, for the “base case” and for one option with more optimistic features (upside potential)
b) Definition of contract designs that minimise risk and/or maximise gains, considering the maximum down-payment, and the net present value for the likely lifetime of the project. Here, sensitivity analyses should be done.
c) Pay-back period under above mentioned conditions, as well as the upside potential after the end of the pay-back period
d) A failure prevention analysis which gives the areas of potential problems, their likelihood (as a probability figure), and their consequence (as a weight from 1 to 10)[41]
e) What-if analysis in case the agreement is not reached. Here, a detailed analysis of the potential moves should occur, especially regarding one`s own business in the therapeutic area. For instance, one may consider in-licensing a nebuliser technology which can be used for anti-asthma drugs. The value of the option can be calculated taking into account the potential negative impact on the NPV of existing company business should a major competitor lay his hand on this technology. At least, the best alternative (BATNA) approach should be used.

[41] Barker (1996)

5.3 Translating in-licensing decisions into contracts

5.3.1 Option contract and sequential contracts

Option contracts follow logically from the options pricing model. As with the option on stocks, they secure rights without having to pay extremely high sums, and their price can be calculated and is little dependent on personal risk-aversiveness or other personality traits. Given the high sums at stake in in-licensing, such a policy is desirable from the point of the licensee. It reduces the risk for him by cutting it into pieces.

However, such a policy must have attraction also to the licensor in case he has an offer from a different potential licensee that goes for straight in-licensing - without an options agreement - and carries a larger part of the risk.

Also, such contracts must be carried right through the end, i.e. the financial analysis must have considered all ramifications of the decision tree, and already described the final contract if and only if the event of drug approval will have occurred. If this would not be the case, the licensee may be faced with hard negotiations should at the end of the options period, the result look much better than anticipated.

Frequently, the one-stage option is still too simple, for instance in the case of a compound of which only some animal data are known. Then, a sequence of option contracts should be planned. For such sequential contracts, Dixit and Pyndyck have laid some theoretical groundwork.[42] They also gave an example which is close to developing a drug, namely that of an underdeveloped oil reserve. The following table is taken from their book.

[42] Dixit and Pindyck (1994)

Call option	*Undeveloped reserve*
Stock price	Value of developed reserve
Exercise price	Cost of development
Time to expiration	Relinquishment requirement
Volatility of stock price	Volatility of value of developed reserve
Dividend on stock	Net production revenue from developed reserve less depletion

Table 18. Example of analogy of call option to undeveloped oil reserve *(from Dixit and Pindyck, 1994)*

Multi-stage projects or sequential contracts - can be worked out backwards, by defining the value of the product at the end, and the value at each of the different stages.

In the case of an options contract for a drug that is currently still in the preclinical phase this could mean the following sequential contracts:

a) the option to show that the drug is tolerated well in healthy volunteers (phase I)
b) the option to show that the drug works better than placebo and the „gold standard“ of treatment using a surrogate endpoint (phase II)
c) the option to show that the drug is safe and efficacious in major pivotal studies (phase III)
d) the option to market the drug in the territories determined

In principle, these options must in principle have been constructed alongside the first option contract, or safeguards must be built in that make alternative partners undesirable for the licensor in later stages.

Another approach seeing the same problem is that of the value of information. Here, the expected value of information can be calculated backwards, e.g. when the investment needed to answer a crucial efficacy or safety question is known. Such information changes the assumption on the eventual success of the project, thus the probability and the utility curve.

The calculation of such formal values help to determine again the value of an option on a compound if the time until expiry of the option is defined by the respective activities that lead to valuable information.

5.3.2 Types of payments

The payment schedule for in-licensing drugs differs on the philosophy of the company. Frequently, European companies ask for more on royalty income, while venture capital-financed US companies request major down or milestone payments as a signal to their investors that the licensee „believes in the compound“. While this is not proven, it is frequently given as a reason by experienced investment bankers.

5.3.2.1 Down-payments (advance payments)

Such advance payments have a high influence on the cost of investment. Taking that the likelihood of success for pharmaceutical compounds is usually substantially lower than 50% even for drug approval, not to speak of marketing, such cost frequently are the potential loss of the licensee. They also constitute the „maximum loss“ that will be incurred if the drug does not work if no further use of money or resource of the licensee on the way to registration is required.

As the licensor uses them for financing his operations, they are nevertheless important, but can sometimes be replaced for by allowing a favourable credit line.

Negotiating down these upfront payments is the major task for the in-licensing party.

5.3.2.2 Milestone payments

Milestone payments occur at time points related to progress of development, such as the completion of the clinical phase, the filing of a registration dossier, or upon drug approval (in a given territory). Milestone payments are usually negative cash flows, and, if no options agreement is done, constitute the cost to obtain a drug that can then be marketed.

Milestone payment can, however, also be seen as phase-wise options, with the potential of terminating the contract after each phase if such is foreseen in the contract. As such, they must be discounted.

Deferring decisions within a project can also be obtained by specifying different “entry prices” depending on stage, for instance when more than one indication is tested for the same drug, and the licensee is reluctant to commit to all indications from the beginning on.

5.3.2.3 Royalties (usually related to turnover)

Royalties, in this case compounded with the cost of goods (as a fixed price) are usually determined as a percentage of net sales. In some cases, agreements have been made that increase the percentage with increasing sales, usually to satisfy a licensor that has more optimistic sales expectations than the licensee.

5.4 In-licensing audits to increase efficiency

If one describes „in-licensing efficiency“ as maximising number of in-licensed compounds with high net present value by, and, at the same time, reducing the risks of accepting non-viable compounds, the question is how to assure the quality of decision preparation. A licensing group is rarely stable over many years, so personal learning can only occur to some extent. Therefore, organisational learning must be introduced. [43] I suggest to review the quality and timeliness of decision preparation and execution once a year. Such an audit could be conducted by an internal or an external group. This group would use the PLDs and the follow-up to decisions, the questionnaire to decision makers, determine the net present value and risk structure of in-licensed compounds, and give a quantitative view on lost opportunities.

[43] Senge (1992)

5.4.1 Decision preparation

The quality of the technical assessments should, at the stage of due diligence (and, if resources are available, earlier) be counterchecked by a second reviewer blinded to the opinion of the first. All reviewers should give probabilities for crucial outcomes and provide realistic cost estimates.

For marketing, data on prices and market share should be substantiated by primary research. Only with such preparation, the aggregation at the financial/commercial level using sophisticated techniques makes sense.

The calculations of the capital investment appraisal should be filed, and, when appropriate, the underlying assumptions be compared to the evolving reality if the opportunity was not taken by the company.

The deviations should be given quantitatively and to possibly reveal a pattern (e.g. overestimating marketing cost, underestimating likelihood of success).

5.4.2 Decision making

For decision makers, the audit should provide them with a feedback on the correctness of their decisions, but also on the process, especially the time consumed reaching one which is not justified by „strategic waiting“.

In-licensing audits should be a learning experience not only for those working in the respective departments, but in particular for the decision makers. Though due to the time delay between rejecting an early development opportunity and its eventual success or failure as a drug some learning occurs quite late, this will ensure a continuous improvement process.

Such learning could be as a workshop of half a day or one day for the management committee.

5.4.3 Decision implementation

All business opportunities are to be entered into a logbook, preferably in electronic form. Thus it can be seen how much time is spent during the implementation phase. In addition, the financial management tools used previously should be continued. During most „implementation

phases“, unexpected events may happen that need be analysed. The occurrence of a new competitor may drastically alter the value of the in-licensed compound, even to the degree of re-thinking its continuation.

The commitment and precision with which decisions are executed must also be audited against the performance of the business opportunities teams. In addition, the cost of the licensee in the implementation phase should be monitored as own experience tells that it may be unexpectedly high in the co-operation with small companies.

6 Perspectives

The dissertation and the preceding field work have shown that the basis on which in-licensing decisions are made, remains rather unclear. Besides the work here, there is no published information on the decision quality of other pharmaceutical firms. Even more, there is no known feedback mechanism by which executives may learn how to improve such quality. Such an instrument is, however, necessary, as the time somebody is in such a position is decreasing and the „know-how transfer“ hardly exists.

Therefore, in my view, the following fields should be researched with priority.

6.1 Interaction of assessments for in-licensing of different disciplines

There are no integrated scientific/medical/marketing models described in the literature. Assessments are most often set against each other. Nor has research been done on how to unify these, say, in a spreadsheet approach.

No systematic view has been made on the help of scenarios as they are often not developed systematically, and little is said about the likelihood of any of them to occur. Whether techniques used in futurology, such as Delphi methods, method 3-6-5, or morphological box would help quantification, is interesting both theoretically or practically.

6.2 Analysis of the cost of information in drug development

As the cost of information for in-licensing products is often reflected in down-payment or options fees, one can estimate the value of the work done previously. The same instrument could be used for project development where internal „buyers“ could offer prices for certain stages or information in development. No such tests have been done. In principle, the determination of the optimal path of obtaining necessary information (early) is another wording for effective development.

6.3 Use of Bayesian statistics for estimating „prices“ of compounds to be in-licensed

There are no data on the use of Bayesian statistics in combination with such approaches. In short, any drug development makes assumptions about the likelihood of success based on some sort of prior information. That is why it is said that constant „opponents“ are right 80-90% of the time.

6.4 Value of time to licensors

The value of time has usually not been accounted for. There are no subjective data on how to modify the price if the licensee requests waiting periods. While for a positive result in mind, waiting would increase the value, the frequently more probable negative result could be an incentive for the licensor to get a deal done fast.

The value of an option to experiment with the compound on one's own may be extremely valuable as it may signal to the licensee what the compound could be „really“ good for. Therefore, such option periods should be priced according to the expected value of the information - and not time.

6.5 Quantitation of market share

While market share partly depends on the quality of the product, no formal algorithm exists to predict it. There are no data in the literature - not even for large indication areas with gold standards - which compared to different predictions of market share before registration and the reality afterwards. Still, it is with exactly these market shares where small deviations by a couple of percent make a project fail. As with in-licensing decisions in general, there exists no formal feedback loop at Boehringer Ingelheim, and , as far as I know, elsewhere.

6.6 Vague decision criteria

Within the field work, decision criteria such as „strategic fit“ surfaced as top criteria. It is not sure how high these really rank in the hierarchy of values, and because of psychological

reasons - no desire to expose oneself - people may uphold them although they consider them as truly unimportant. How much such criteria contribute to negative decisions should be researched, also in project development of own compounds. It remains to be seen whether concepts of „fuzzy logic“ can be introduced into those processes.

7 List of Appendices

A) Pharmaceutical Licensing Document

B) Decision Maker Questionnaire

C) Members of BAC and ISC

D) BI Organisational Chart

E) In-licensing checklist /Business Development

F) In-licensing checklist /Medicine

G) Glossary of terms for in-licensing

Appendix

A) Pharmaceutical Licensing Document, PLD(sample)

Substance
Indication
Type of data available
phase I
phase II, not controlled
phase II, controlled
Offering company
Sales of offering company (<10 mio, 10-100 mio; >100 mio, <500 mio, 500 mio - <2,000 mio; > 2,000 mio)
primary contact at BI
time of first contact
time to internal evaluation complete
time to BI decision
decision maker
time to contract (if applicable)
If rejected, opinions (1=excellent; 6=absolutely insufficient)
medicine
R&D
marketing
commercial
decisive reasons (specify)
evaluations tools for commercial assessment (e.g. NPV)
outcome
approved

when
not filed
development stopped
unknown
still under development (likelihood of success <u>now</u> ?)

Appendix

B) Questionnaire for members of BAC, ISC /decision maker questionnaire (sample)

As someone deciding on in-licensing projects or contributing to such decisions, you may have a special opinion on how this decision went, or, how it could have prepared for the better.
In order to become ever better in making decisions you could help us in answering the questions below.

1. Which of the two committees are you a member of (BAC; ISC) ?
2. How often have you, as such a member been part of such decisions in the past 12 months?
3. How sure have you been, on average that you made the right decision (0 to 100%) ?
4. If you made a positive recommendation or decision, what features were most frequently important, such as high likelihood of success, strategic fit, or others (please name at least five on descending order of priority) ?
5. If you made a negative recommendation or decision, what features were most often relevant or decisive for you (also name five in descending order) ?
6. In what percentage the decision had not been adequately been prepared for and should have been postponed (give %) ?
7. If you were to give marks (1=very good; 6=miserable) on average, how would you rate the
   marketing assessment
   R&D assessment
   medical assessment
   commercial assessment
   for the proposals in the past 12 months ?

8. How much do you rely on quantitative measures such as NPV ?
9. Do you think BI does adequate in-licensing (yes; rather more; rather less)

Appendix

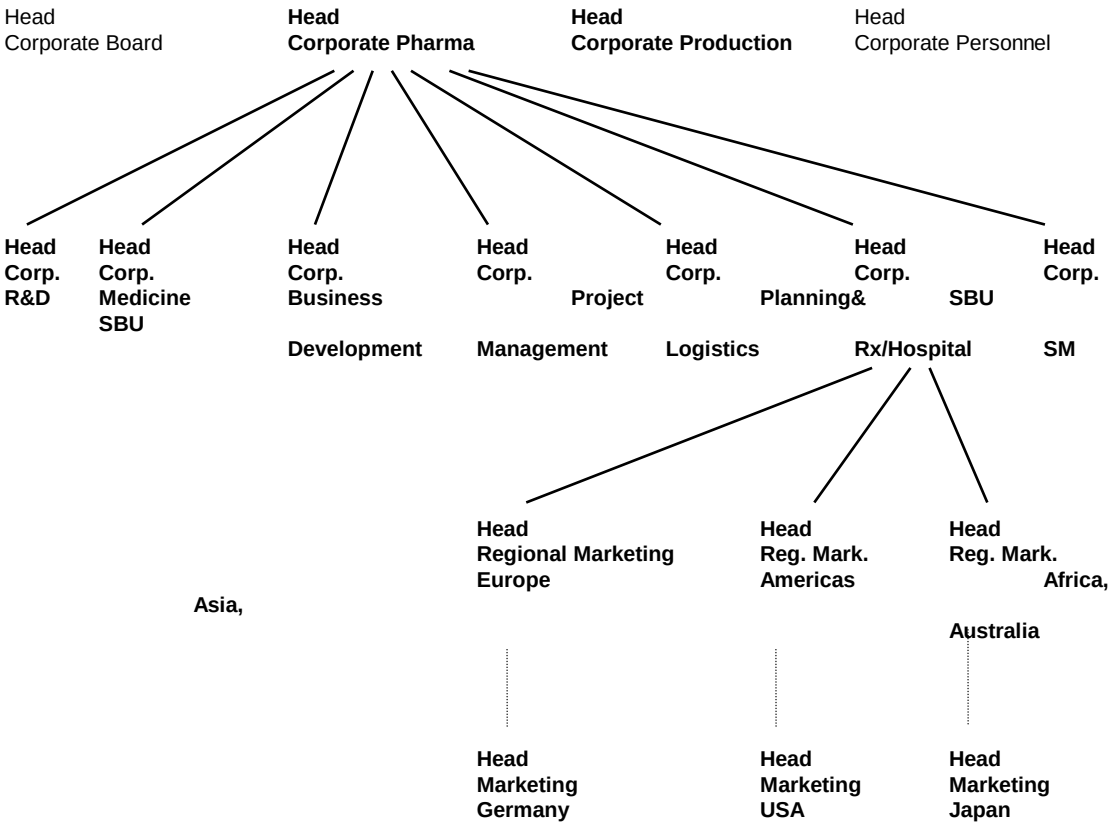
C) List of BAC, ISC members

Function	BAC	ISC
Head of Corporate Pharma (Board)	+	+
Head of Corporate Division Medicine	+	+
Head of Corporate Division R&D	+	+
Head of CorporateTechnics/Production (Board)		+
Head of Corporate Division Business Development	+	+
Head of Corporate Department Project Management	+	+
Head of Corporate Division Pharma Planning	+	
Head of Corporate Division Self Medication	+	
Head of Corporate Division Rx/Hospital	+	+
Marketing Director USA		+
Marketing Director Germany		+
Marketing Director Japan		+
Head Regional Marketing Europe	+	
Head Regional Marketing Americas	+	
Head Regional Marketing Australia/Asia (AAA)	+	

Appendix

D) Organisational Chart, Boehringer Ingelheim

Organisational Chart, Boehringer Ingelheim
(Committee members in bold letters)



functional reporting line; direct reporting line goes to local managing director

Appendix

E) Draft In-licensing Checklist/Business Development

#	Main Questions	done	Remarks
1.	**Strategy**		
1.1	**Is the project in line with the pharma strategy?**		
1.2	**How does the project fit into the R&D strategy?**		
1.3	**When could the product reach the main markets?**		
1.4	**Is the product a potential breakthrough – and why?**		
2.	**Availability of information**		
2.1	**What data can be seen under confidentiality agreement?**		
2.2	**Will important data become available during the negotiation process- and which ones?**		
2.3	**Does the documentation give an orderly impression?**		
2.4	**What negative data are available on the project? Has it been rejected by other parties?**		
2.5	**Which additional information is seen necessary to give a sound recommendation?**		
3.	**Evaluation**		
3.1	**R&D assessment: when and by whom?**		
3.2	**Medical assessment: when and by whom?**		
3.3	**Marketing assessment: when, which scenarios, and by whom?**		
3.4	**Commercial assessment: which method, when, and by whom?**		
3.5	**Who will do the due diligence (names)?**		
4.	**Negotiation**		
4.1	**Is a BI negotiation strategy determined?**		
4.2	**Which negotiation weaknesses has the partner?**		
4.3	**What are the time constraints?**		
4.4	**What is the BI preferred deal structure?**		
4.5	**What is the worst case loss?**		
5.	**BI internal commitment**		
5.1	**Is there a positive opinion from committees (BAC, IMC)?**		
5.2	**What critical issues are known from relevant Division Heads?**		
5.3	**What critical commitment is still outstanding?**		
6.	**Partner**		
6.1	**How trustworthy is the partner?**		
6.2	**How (financially and other) stable is the partner?**		
6.3	**What kind of BI support for drug development is needed/desired?**		
7.	**Contract**		
7.1	**What kind of contract is envisaged and when?**		
7.2	**How will BI control the contents of the contract?**		
7.3	**How is decision mkaing foreseen in the contract?**		
7.4	**What happens if partner gets in trouble/bankruptcy/other events?**		
7.5	**Under which conditions can BI cancel the contract?**		

Appendix

F) Draft In-licensing Checklist /Medicine

#	Main Questions	done	Remarks
1.	**Rationale**		
1.1	**What preclinical data support it/speak against it?**		
1.2	**What clinical/pathophysiology data support it/speak against it?**		
1.3	**What clinical trial data are available and do they support the hypothesis?**		
2.	**Efficacy**		
2.1	**Which efficcay data are available?**		
2.2	**Do they support a claim? Are they a biological signal?**		
2.3	**Are there data which speak against efficacy?**		
2.4	**Are the data exploratory/confirmatory?**		
2.5	**What is the likely advantage over existing treatments? Has it been shown?**		
2.6	**Is there a dose-response-relationship?**		
3.	**Therapeutic Need**		
3.1	**Patient population (potential)**		
3.2	**Treatment gap, e.g. %responders, incomplete response**		
3.3	**Could there be a pharmaco-economic basis?**		
4.	**Safety**		
4.1	**What safety problems are expected from the preclinical data?**		
4.2	**What is the safety pattern from the clinical data so far?**		
4.3	**Which advantage has this pattern over available treatment?**		
4.4	**Is there a chance to optimise the dose?**		
5.	**Convenience**		
5.1	**Are there problems with administration or handling?**		
6.	**Competitive position by the time of launch?**		
6.1	**What are the likely competitors by the time of launch?**		
6.2	**Which early developments must be observed?**		
6.3	**What is the likely gold standard by the time of launch?**		
6.4	**Why would prescribers choice our drug over those, and when?**		
7.	**Risks**		
7.1	**What are the main development risks?**		
7.2	**Are there problems with the material supplied by potential licensor?**		
7.3	**Is there competition with BI own development compounds?**		
8.	**BI resources needed**		
8.1	**What is the cost of non-clinical development from now on?**		
8.2	**What is the cost of clinical development from now on?**		
8.3	**What is the minimum of BI medicine personnel needed (FTE years)?**		
8.4	**If BI would do the entire clinical development, what resources would be needed?**		

Appendix

G) Glossary of terms for in-licensing used in this dissertation

SDEV Stage of development of the in-licensing compound. This is usually described preclinical, or one of the clinical phases, registered, or marketed.

PLE This is the remaining patent life after launch. For compounds at different stages, this should be different, but it also depends on the speed the company developed it Remaining patent lives of less than 5 years are not unusual although they become less

ESVOL The estimated sales potential is the actually expected sales, not the patient potential (i.e. the patients that have the disease to be treated) or the market share. It is usually given as the volume of average daily doses

EAP The average price per day is estimated on the basis of price/volume relationships, through primary market research. It is multiplied by **ESVOL** to give the annual revenues.

LDA This is a probability (in %, or as fraction of 1) to give the likelihood the drug will be approved by health authorities.

PRS This is the payment and royalty structure, with the advance (down) payment DP, the milestone payments at significant achievements, for instance end of phase III (=MSP), and the royalty itself. For simple calculations it was assumed that the RP also includes the cost of goods as a percentage of net sales.

IHP This indicates whether an in-house product from the company's own research is available

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