

# Considering Pharmaceutical Royalties

BY HARMEN JOUSMA\*



Deals with pharmaceutical companies constitute a major commercialization route for the biotechnology industry. Likewise, many agreements on IP from universities involve technology in the area of the life sciences, with applications that are ultimately aimed at the development of new pharmaceuticals. With potentially large markets and high profit margins there is much at stake. Consequently, many tech transfer and licensing executives as well as many researchers in the life sciences, will at some point in time get involved in a pharmaceutical licensing deal and need to have a basic understanding of how pharmaceutical royalties can be determined.

Over the years, pharmaceutical royalties have been the subject of various articles in this journal. Most specifically on this subject was the article on determining pharmaceutical royalties by Motohiro Yamasaki of September 1996.<sup>1</sup> Many other articles of a more general nature deal with determining reasonable royalty rates, as for example the article by Goldscheider et al. evaluating and underpinning the empirical value and usefulness of the 25% rule.<sup>2</sup> In his November 2003 article on pharmaceutical up-front licensing fees,<sup>3</sup> Betten stated “it is hoped that this paper will encourage others to report their methods or to develop other models and surveys to further develop a larger database that

future licensing staff may draw on—not only to help determine up-front fees—but to gain new insights into the process of valuation.” This constituted the ultimate inspiration for drafting the present paper.

Most pharmaceutical deals are early stage, that is: before or somewhere in between the start and the middle of the expensive, lengthy and risky process of clinical drug development. Whereas this product development process in itself is not unique for complicated technology, a special feature of drug development is that it is highly regulated and thus a well-defined process. Its statistics in terms of costs and chances of technical success have been researched extensively. This enables relatively detailed calculations as benchmarks for actual deals to be made. Based on such calculations and on the analysis of deal terms in published agreements, various commercial undertakings offer quite expensive information, databases, software programs and consultancy services to help establish what might be reasonable economic terms in a licensing deal.

Not everybody will be able or willing to buy such information and to use such services let alone carry out complex methods like Monte Carlo calculations for simulating deals, particularly not when one only sporadically has to do with a pharmaceutical licensing deal. And even when using such information and services, it is important to have a general idea about what determines the economic terms in pharmaceutical licensing. The objective of this article is to provide a (relatively) simple analytical approach based on the major economic terms underlying pharmaceutical licensing

deals. The aim is to enhance the understanding of the relations between the major factors involved. Details are disregarded, as generally, where the terms of licensing deals depend on prognoses over a considerable length of time, the value of detail is limited anyway.

Some specific issues addressed by the approach are:

- The impact on profits of large investments, high risks and long development times characteristic of drug development;
- The consequent strong impact that the ultimate sales levels and operating margins may have on what might be considered a reasonable royalty rate;
- The relationship between upfront payments and milestone payments (to be) paid during pharmaceutical development and the royalties due once the drug enters the market.

In itself, there is not much new to the approach. In fact, it is implicitly embedded in spreadsheets set up for modeling the licensing deal. An excellent example of a publicly available spreadsheet is the one developed by Martha Luehrmann, which is distributed via the AUTM Website.<sup>4</sup> A more recent example is the spreadsheet supplementing the article “Putting a Price on Biotechnology” in *Nature Biotechnology* of September 2001.<sup>5</sup> These

1. M. Yamasaki, “Determining Pharmaceutical Royalties,” *les Nouvelles*, September 1996.

2. R. Goldscheider, J. Jarosz, and C. Mulhern, “Use of the 25 Per Cent Rule in Valuing IP,” *les Nouvelles*, December 2002.

3. P. Betten, “Pharmaceutical Up-Front Licensing Fees,” *les Nouvelles*, December 2003.

4. [www.autm.net](http://www.autm.net).

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spreadsheets offer the opportunity to calculate pharmaceutical royalty payments based on various assumptions. The disadvantage of these spreadsheets is that they do not as a matter of course provide an intuitive understanding of the relationships between the many factors involved. The following analytical approach hopefully will.

### Expected Profits

The basis for most deals will be that the licensee may expect to generate excess profits from the licensed technology. Excess profits means to say that the return on the capital invested is (significantly) higher than the cost of capital to the licensee.<sup>6</sup> Anticipated sales should clearly exceed the costs and provide sufficient return to cover the investments the licensee has to make prior to market introduction. In most general terms, the expected profit can be expressed as:

$$\text{Profit (P)} = \text{Sales (S)} - \text{Costs (C)} - \text{Investments (I)} \quad (1)$$

Where:

*Profit: profit generated by licensee;*

*Sales: sales generated by licensee;*

*Costs: the sales-related costs incurred by licensee;*

*Investments: the costs incurred by licensee prior to market introduction.*

Limitation of this formula is that it doesn't account for the fact that income (sales), costs and investments occur over a long period of time and are not distributed evenly over time. The so-called time value of money needs to be introduced. The present values of sales, costs and investments have to be calculated at a certain point in time. Which point in time is, in principle, arbitrary. A most convenient point in time, however, is the (anticipated) moment the prod-

uct will be introduced on the market. It has the (subjective) advantage that the sales figures calculated are more realistic as they are not mitigated by discounting over a long period and—in drug development—by the often relatively small chance that development is successful. To express that it is about the present value of the sales, costs and investments at the time of introduction on the market, formula (1) is rewritten as:

$$Ppvm = Spvm - Cpvm - I \quad (2)$$

Where *Ppvm* is the (anticipated) present value of the product at the time the product is introduced on the market, *Spvm* that of the sales, etc.

This formula is, of course, at the heart of the regular spreadsheet applications. The spreadsheet enables calculation of the present value of the cash flows as they may be expected to evolve over the years. In the spreadsheets, all kinds of variations can easily be introduced and thus various scenarios can be worked out in considerable detail. The aim of the subject analytical approach, however, is to disregard the detail and to focus on the major parameters as are set out in the following paragraphs.

### Present Value of Sales

Sales of pharmaceuticals are usually expressed in terms of (hundreds of) millions of dollars per year. E.g., “the expected sales level of this drug in development is about 200 million per year.” In practice, sales levels will vary from year to year, may be expected to rise or decline over the years, and there may be all kinds of scenarios with different average expected sales levels. Disregarding all these details, the average expected sales level can be turned into the present value of sales at market introduction, by applying the so-called Annuity formula:

$$Spvm = S * (1 - 1 / (1 + COC)^N) / COC = S * PVF \quad (3)$$

Where:

*S = expected yearly sales level<sup>7</sup>*

*COC = (real) cost of capital*

*N = number of years*

*PVF = Present Value Factor*

An important feature is that *Spvm*

is directly related to the yearly sales level through the PVF, the value of which is determined by the cost of capital and the period over which the sales are expected to generate excess profits.

Cost of capital is a parameter that reflects the riskiness of the anticipated revenues, the contemporary interest rates and the capital structure of the company. As such, the cost of capital is an attribute of both the subject pharmaceutical market (e.g. oncology, cardiovascular, etc.) and the licensee. But generally, it will suffice to consider the pharmaceutical market and pharmaceutical industry as a whole. In this article the real cost of capital (= cost of capital excluding inflation) is assumed to be 11%, as this can be considered a contemporary standard for pharmaceutical industry (*vide infra*).

The period over which the sales generate a profit obviously depends on the length of time the product is on the market, which in principle might be endless. But licensing as considered here is primarily about granting rights under patent protection. This is a (basically not very good) reason to limit the period to the (expected) number of years of patent protection left at the time of market introduction. A better reason is that once the patent protection expires, competing products (generics) will come on the market and severely reduce profitability. From this moment onwards, the licensee will most often not make excess profits, that is, will not generate a return higher than the cost of capital. In addition, discounting reduces the contribution to the profit more and more as the time from market introduction increases. This is not meant to advocate that there should be no royalty payments following patent

5. Jeffrey J. Stewart c.s., *Nature Biotechnology*, 19, pp 813-817 and [http://biotech.nature.com/web\\_extras](http://biotech.nature.com/web_extras).

6. More correctly, the cost of capital reflecting the business risk embedded in the project, which may differ from the cost of capital to the company. See general textbooks on corporate finance, e.g. S.A. Ross, R.W. Westerfield, and J. Jaffe, *Corporate Finance 7th ed.*, p. 330.

7. It is assumed that there is no information which predicts a specific curve of the sales over time. If there is such information, e.g. that in all scenarios sales will continuously increase over time, one should not use the arithmetic average but calculate *Spvm* by directly discounting the expected sales numbers.

expiry. There may be good reasons to prolong royalty obligations, e.g. when characteristics embedded in licensed production technology prevent generics from entering the market.<sup>8</sup> But in a basic approach for considering pharmaceutical royalties, it will suffice to limit the period the licensee will have a monopoly on the product. Most often, it will take about 10 years from the original patent application to get a product on the market. Consequently, the remaining patent life from the time of introduction on the market usually is also about 10 years.

Table 1 shows PVFs for the number of (profitable) years on the market ranging from 8 to 12 and the COC ranging from 9 to 11%. Also shown (between brackets) is the deviation from the base case: a COC of 11% and 10 years on the market, resulting in a PVF of 5.9. The deviations are relatively small. E.g., considering a percentage point more or less COC is like considering 4 million in yearly sales more or less

at a sales level of 100 million a year. Even when the changes in number of years and COC work in the same direction, the effect is fairly limited, e.g. a reduction of only 20% when simultaneously the COC goes up to 13% and the number of years goes down to 8. Most likely, the uncertainty due to variations in cost of capital and the period over which the drug generates excess profits<sup>9</sup> will in general be small as compared to the uncertainty in the sales levels that may be expected.

### Costs Associated to Sales

Costs associated to sales include numerous items like costs of goods, production costs, costs of sales, depreciation of investments in equipment and facilities, etc. As most licensing deals are entered into many years ahead of market introduction, one will generally not want or be able to calculate the (anticipated) specific costs of the product. Based on experience and proprietary information, the licensee may be inclined to make more specific estimates of the costs involved. Most licensors will not be able to do so. Instead, one may assume that the costs will constitute some reasonable fraction

of the sales value, based on a comparable or industry standard. A most convenient possibility is to use the operating profit margin (OPM) of comparable products or companies. As basically  $OPM = (\text{sales} - \text{costs}) / \text{sales}$ , the equation defining the profit is rewritten as:

$$Ppvm = OPM * Spvm - Ipvm \quad (4)$$

### Operating Profit Margin

Prior to considering the height of the operating profit margins for pharmaceuticals, with regard to OPM two remarks need to be made. Firstly, if the costs embedded in OPM will include depreciation of specific, relatively large investments to be made in connection to setting up the production or the introduction on the market of the product, formula (3) will overestimate the present value of the profits. It might then be necessary to include this part of the costs in the investment in product development. Secondly and more importantly, as the R&D-costs connected to the product will be calculated separately as investment in development, the OPM has to be corrected for the R&D – costs except for those R&D – activities that relate to sustaining products already on the market. (Smith and Parr 317). To clearly distinguish from the regular operating margin as used in annual reports, in the remainder of this paper the operating margin corrected for costs of R&D will be designated as OPM'.

8. E.g., when the production process requires high up-front investments this will reduce the profitability and thus the royalty payable. The need for such an investment may however prevent generic companies to enter the market as when prices fall, it will not be possible to generate sufficient return on investment. This it seems would constitute a good economic reason to continue payments to the licensor.

9. The risk that profits are reduced by unanticipated circumstances like new products competing in the same market should be considered a business risk which risk is (to be) included in the cost of capital.

**Table 1. Present Value Factors (PVFs) and (% deviation from base case).**

Years on Market	Real Cost of Capital				
	9%	10%	11%	12%	13%
8	5,5 (-6%)	5,3 (-9%)	5,1 (-13%)	5 (-16%)	4,8 (-19%)
9	6,0 (2%)	5,8 (-2%)	5,5 (-6%)	5,3 (-10%)	5,1 (-13%)
10	6,4 (9%)	6,1 (4%)	5,9 (0%)	5,7 (-4%)	5,4 (-8%)
11	6,8 (16%)	6,5 (10%)	6,2 (5%)	5,9 (1%)	5,7 (-3%)
12	7,2 (22%)	6,8 (16%)	6,5 (10%)	6,2 (5%)	5,9 (0%)

For an estimate of OPM for pharmaceuticals we can look at the operating margin and the R&D-costs as a percentage of sales reported by pharmaceutical industry. Table 2 lists the operating profit margins realized by 10 major pharmaceutical in 2002. Table 3 lists the percentage of total sales that has been spent on R&D as reported by the PhRMA based on its annual membership surveys. The operating margins vary from 17 to 44% with an average of 29%. R&D expenditure is on average 16.3%. OPM' thus averages around 45%.

These data suggest that pharmaceutical companies manage to make an average profit of about 45% of sales once a product is on the market. Obviously, the actual figures vary from year to year, company to company and product to product. Furthermore, the average may well underestimate the actual figures for patented pharmaceuticals since most reports of the big companies will also include at least some other business like generic drugs, animal health, etc. Illustrative in this respect is the effect of Merck spinning off Medco Health (pharmacy benefit management services) in 2003. Restating the financials for 2002 to reflect the new situation raised the operating margin of the company from 20% to 44%.<sup>10</sup>

But the average gives a general idea of the profits that pharmaceuticals can generate. The average OPM' of about 45% is the average maximum percentage of sales available for royalty payments. That is, when the investments (present value at the time of marketing), here the investments in development of the drug, are insignificant compared to the present value of sales.

Neglected in this calculation is that part of the R&D-expenditure not used for drug development prior to market introduction, but directed at efforts obligatory or helpful for sustaining the marketed product. So, this part should not be considered available for reimbursing prior investments and for payment of royalties. However, instead of deducting this part from the R&D-costs, the subject post-marketing costs will be included in the calculation of the investments in drug development.

### Investments in Drug Development

One of the challenges in pharmaceutical licensing—in particular in the earlier stages of develop-

ment—constitutes the many uncertainties embedded in developing the product and bringing it on the market. The road to the introduction on the market is costly and long, and along the way there is a considerable chance that the development will fail due to adverse effects or lack of clinical efficacy. Fortunately, drug development is a well-researched process. This research includes studies of the costs of the various phases of (clinical) drug development. In January 2003, DiMasi et al. published the most recent estimates of drug development costs.<sup>11</sup> Based on a survey of 10 pharmaceutical firms, the development costs, chances of successful development and the development time were assessed. These data allow for the calculation of the (average) present value of the investments in drug development at the time of market introduction.

Table 4 displays the most important results of this study as well as the way they are calculated. It starts with the mean costs incurred in the subsequent development phases (A). Next, the data on the time it takes to complete a phase (mean

10. Annual Reports 2002 and 2003 of Merck & Co.

11. Joseph A. DiMasi, Ronald W. Hansen and Henry G. Grabowski, "The Price of Innovation, New Estimates of Drug Development costs," *Journal of Health Economics* 22 (2003), pp. 151-185.

**Table 2. Operating profit margins in 2002 reported by ten major pharmaceutical companies.**

Company	Operating Margin
Pfizer	36%
Johnson & Johnson	26%
Merck & Co.	44%
GlaxoSmithKline	34%
Novartis	24%
AstraZeneca	18%
Eli Lilly	29%
Abbott Laboratories	20%
Wyeth	41%
Bristol-Myers Squibb	17%
<b>Average</b>	<b>29%</b>

**Table 3. R&D costs as % of sales.**

Year	%
2002	16.3
2001	16.7
2000	16.2
1999	15.5
1998	16.8
<b>Average</b>	<b>16.3</b>

phase length) and the time between starting one phase and the start of the subsequent phase are used to calculate the mean time to market (B) of the respective phases. In combination with the figure for the (average) cost of capital, this allows the calculation of the “PV-factor.” This PV-factor is the number by which the costs need to be multiplied to find the capitalized mean phase costs, this is the present value of these costs at the time of market introduction. DiMasi et al. found the real cost of capital (this is the cost of capital corrected for inflation) in the period the study covers to be around 11%.

The next factor to take into account is the risk that development fails. In Table 4, the outcome of the inventory of a large number of clinical studies is translated into the chance of entering the next phase, i.e. the chance that the outcome of the trial is positive and merits continuation of drug development. Multiplication of these chances gives the chance that a drug at a certain stage of development will finally be introduced on the market. For example, the chance that a drug entering phase I clinical studies will reach the market is  $0.71 \times 0.44 \times 0.86 \times 0.8 = 0.21 = 21\%$ . In other words, only 1 in 5 drugs entering clinical trials

will finally gain marketing approval. In Table 4, the inverse of this chance is called the risk-adjustment (RA-) factor. This factor tells that on average, phase I has to be done 5 times to get one drug on the market. Which means that the phase I development costs need to be multiplied by 5 to arrive at the risk-adjusted, average phase I costs of drugs obtaining marketing approval. The two factors are combined to adjust the costs for both the costs of capital and the development risks involved. This leads to the so-called risk-adjusted, capitalized mean phase costs as displayed in row G of Table 4. Finally, the costs

**Table 4. Calculation of the (average) present value of the investments in drug development at the time of market introduction.**

All Monetary Values in Millions of US\$.							
Phase		I	II	III	R	Total	
A	Mean out-of-pocket expenses (mln)	15	24	86	2	127	
	Mean phase length (months)	22	26	31	18		
	Mean time from start to next phase(months)	12	26	34	18		
B	Mean time to market (months)	80	65	37	9		
C	PV-factor @ 11%	(1.11 <sup>B/12</sup> )	2.0	1.8	1.4	1.08	
	Capitalized mean phase costs	(A*C)	30	41	119	2	
	Chance of entering into next phase (%)		71	44	86	80	
D	Chance of market introduction (%)		21	30	68	80	
E	RA-factor	(1/D)	4.8	3.3	1.5	1.25	
	Risk-adjusted mean phase costs	(A*E)					
F	RA-PV-factor	(C*D)	9.4	5.7	2.0	1.4	
G	Risk adjusted capitalized mean phase costs	(A*G)	141	137	173	3	
	<b>To Market Introduction From Start Of</b>					Incl. PA - R&D	
	Phase I	141	137	173	3	454	549
	Phase II		137	173	3	313	408
	Phase III			173	3	176	271
	Registration				3	3	98

of the various phases can be added to arrive at the average costs expected to be incurred between the start of a certain phase of clinical development and the anticipated moment of market introduction. As is shown in Table 4, these average costs vary from 454 million for a drug entering clinical studies to 3 million for a drug entering the registration phase.

As mentioned above, the R&D-costs of pharmaceutical companies include costs of research on drugs for which marketing approval already has been obtained. These costs can be accommodated either by correspondingly reducing OPM' or by including the post-approval R&D costs in the investments in drug development. The first approach implicitly assumes that the post-approval R&D-costs are proportional to the level of sales, the second approach that these costs are a fixed amount per marketed drug. In reality, neither will be the case and the post-approval costs will probably depend on regulations and the perceived chance that such R&D will enable discovering additional market opportunities.

Here it has been chosen to include the post-approval R&D-costs in the investments in drug development.<sup>12</sup> DiMasi et al. have calculated that average, out-of-pocket, post-approval R&D-expenses are around 140 million US\$. Taking into consideration the average period after market introduction that these costs are incurred, they estimate the present value of these costs at the time of market introduction to be around 95 million US\$. Adding these costs to those calculated for the pre-approval investments in drug development, we finally find that the expected, average capitalized, risk-adjusted total R&D-costs range from 549 mil-

lion US\$ for a drug entering phase I of clinical drug development to 98 million US\$ for a drug entering the registration phase.

### Royalties and Average-based Profit Margin

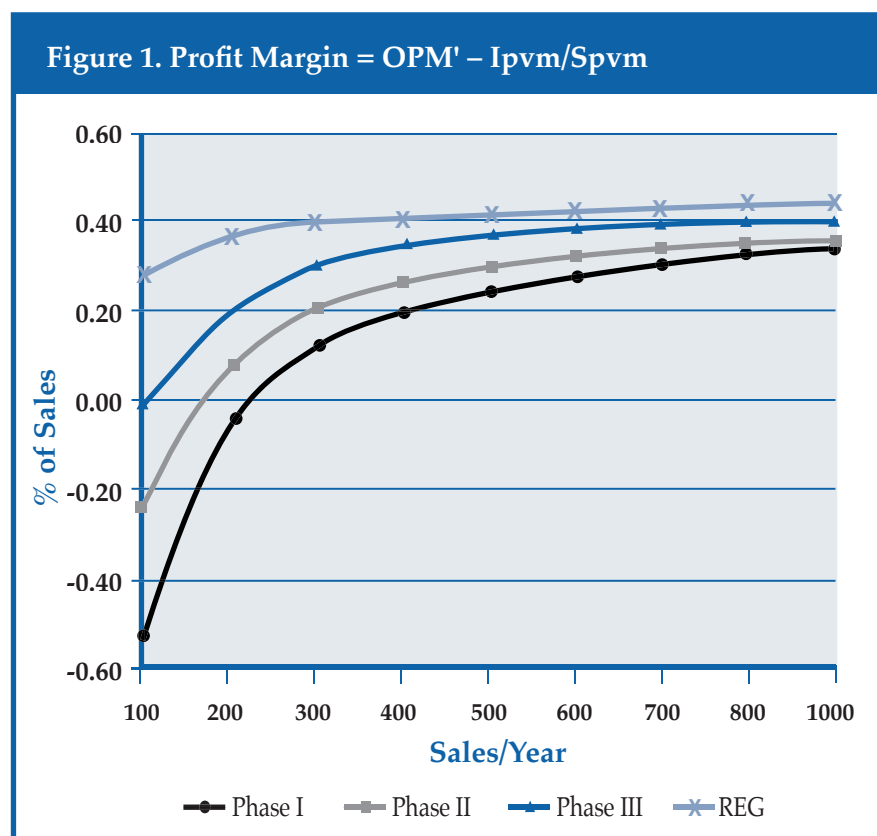
Royalties are usually expressed as a % of sales and meant to cover (part of) the profits generated by the licensee through exploiting the technology. Dividing formula (4) by the present value of sales directly shows how the investments reduce the profit margin (Ppvm/Spvm) available for royalty payments:

$$Ppvm/Spvm = OPM - I_{pvm}/Spvm \quad (5)$$

When there are no investments to be made, the maximum available for royalty payments (that is without the licensee making a loss) is the operating profit margin. The extent to which prior investments reduce the available percentage depends on the sales levels in relation to these investments.

In the preceding paragraphs, the averages have been calculated for the—phase dependent—costs of drug development, the operating

margin corrected for R&D expenditure and the PV-factor linking the present value at market introduction to the yearly sales level. Based on these averages, Figure 1 depicts the relation between the profit margin (Ppvm/Spvm) and the yearly sales level. It shows how the percentage of sales available for royalty payments differs between drugs in early development (start-of-phase I) and those that are close to market introduction (entering the registration phase). The magnitude of the difference very much depends on the sales levels. When the expected sales level near blockbuster status (sales over 1 billion US\$ per year) the difference in profit margin between a start-of-phase I drug and one entering the registration phase is relatively small. In fact, for a drug like Remicade, with a sales level of 1.3 billion US\$ in 2002, the investment in drug development starting phase I would only reduce the profit margin by 7% with respect to the operating margin. At lower sales levels, however, the impact of the investment, and thus the stage of development, is significant. In fact, according to the averages, a



12. Most likely consequence of this choice is that the post-approval costs are overestimated for drugs with smaller and underestimated for drugs with higher sales volumes. Accounting for the post-approval costs by reducing the R&D percentage available for reimbursing prior investments would have the opposite effect.

start-of-phase I (SOPI) licensing opportunity is not expected to generate a profit if the anticipated sales level is below 200 million a year. At the same sales level, an average SOPIII drug—again, based on the average—would make a profit margin of about 20% of sales available for sharing with the licensor.

### Beyond the Averages

An average-based approach may be informative, but real life licensing is not about averages. It would be a mistake to treat the averages as a standard. It can also be learned from the analysis by DiMasi that the costs of development vary significantly from drug to drug. Similarly, the operating margin to be attributed to individual drugs will vary. This is already manifest from the OPM' for individual companies. Considering for example, the annual accounts 2002 of Pfizer and Abbott Laboratories, one finds operating margins of respectively 36 and 20% and R&D expenses of 16 and 9% of sales, resulting in OPM' differing 13% between these two companies. Further taking into account that the OPM' of a company is an average of the operating margins generated by the various drugs on the market, it is likely that on an individual drug basis, OPM' will vary even more. Unique drugs with no competition will generally (also dependent on therapeutic value) have a higher OPM' than those that share the market for a particular indication with other drugs.

It is therefore important not to treat the averages as a standard but as a point of reference. For instance, if the anticipated development costs of a start-of-phase I drug are relatively low and the expected operating margin is relatively high, it may well be profitable. In this context, one might consider an orphan drug. The market in terms of number of patients may be small, but when the price of drug treatment amounts to US\$ 100,000-200,000 per patient per year, the yearly sales can still be significant (e.g. 200 million US\$ per year for Genzyme's Fabrazyme). And at such costs per patient one may reasonably expect that the costs of

sales are far lower than the industry average and correspondingly, the operating margin is higher. At the same time, special regulations with respect to the development of orphan drugs and associated tax credits are likely to reduce the costs of development.

Figure 2 illustrates how variations in operating margin and development costs may affect the anticipated profit margin of drugs entering phase I. In this figure, the anticipated costs of development (present value at market introduction) are assumed to vary between 300 and 750 million US\$. OPM' is considered at three levels, low (20%), average (45%) and high (70%). The numbers are (somewhat) arbitrarily chosen and only serve to help illustrate the large impact the variations may have. Consider for example a start-of-phase I drug that promises to generate sales levels of 500 million per year. Impressive as the anticipated sales levels may be, when at the same time the development is expected to be relatively costly and the market (which 8 years prior to market introduction may be hard to

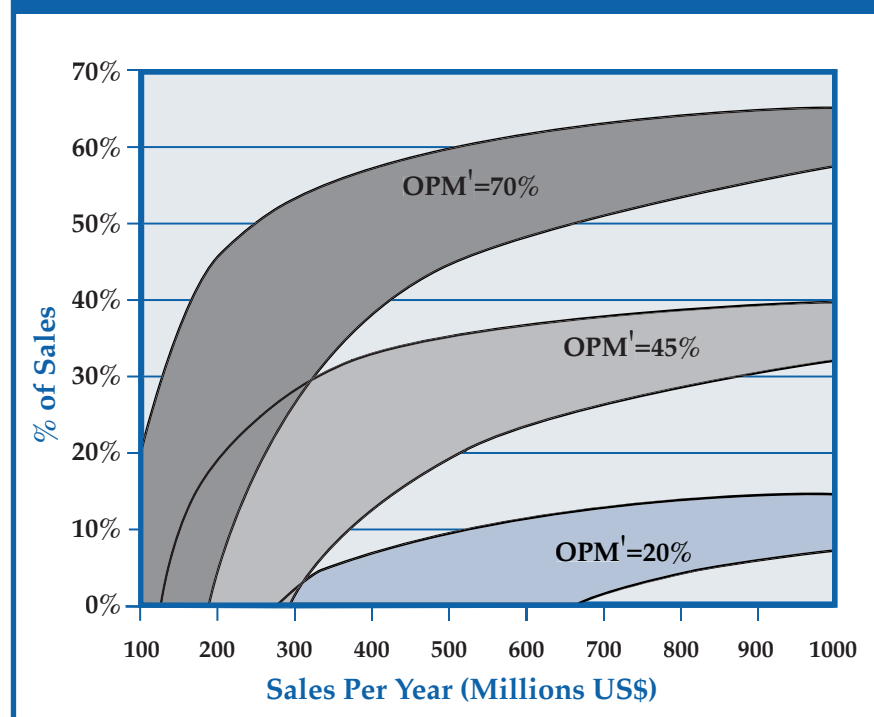
tell) to be competitive, the drug is unlikely to generate a profit. On the other hand, if the drug candidate is expected to behave like an industry standard, then the anticipated profit margin that can be shared with the licensor is about 25%.

### Profit Distribution

The analysis so far only regards the profit margin in relation to investments in drug development, operating margin and sales level. Unfortunately—at least from the perspective of the licensor—this profit needs to be shared with the licensee. Before our calculations can be translated into royalty rates, we have to arrive at an estimate of the profit distribution.

One of the major reasons for the profit distribution is that the calculations of the profit generated by the technology so far do not take into account the contributions by the licensee, such as know how of development, production, marketing, sales, distribution channels, etc. Of the various ways to view and assess the profit distribution (also see the discussion further on), for the

Figure 2. Profit margins at different operating margins investment and levels for drugs entering phase 1.



calculations of royalty rates we here assume a profit distribution factor can be defined which denotes the part of the profit the licensor would be entitled to. The formula for the income of licensor thus becomes:

$$\text{Licensor income} = X * \text{Ppvm} = X * (\text{OPM}' * \text{Spvm} - \text{Ipvm}) \quad (6)$$

where  $X$  = profit distribution factor  
 = present value of licensor income/present value of profit.

$X$  is expected<sup>13</sup> to vary between 0 and 1, and should reflect the relative contribution of licensor and licensee to the profits (not necessarily limited to their contribution to the product generating the profits). Obvious factors that influence  $X$  are: the extent to which know-how is needed to develop the product and introduce it on the market; the status of de-

velopment at the time the licensing deal is made; and the necessity for licensor to acquire or develop other technologies to enable market introduction. With a product close to market that almost “sells itself,” it would foremost be the licensee that deserves the credits and  $X$  may be close to 1. When the product needs further development that includes additional “inventive steps” and requires ingenious and costly marketing strategies to become successful, it may be reasonable that  $X$  is close to 0.

A famous example of a distribution factor is the empirically established 25% rule.<sup>14</sup> This rule of thumb basically states that the licensor is entitled to a royalty equivalent to 25% of the operating profits.<sup>15</sup> Applying the 25% rule is the same as setting  $X$  to 0.25. Deducting the costs of the investments in development from the operating profits is not at odds with the rule as these costs would normally be charged to the profits in the form of the costs of R&D. The major difference is that the subject

13. In principle there may be situations in which the licensee e.g. for strategic reasons is willing to pay more (and  $X > 100\%$ ) for the license than its “intrinsic” value in terms of future cash flows the subject technology is expected to generate.

14. For a recent discussion of the 25% rule see Robert Goldscheider et al, Use of the 25 Percent Rule in Valuing IP, 37 *les Nouvelles* 123 (December 2002).

15. See note 2.

16. - means that the calculated royalty rate is zero or negative.

**Table 5. Implied pharmaceutical royalty rates in relation to expected operating profit margin and sales levels.**

Operating Profit Margin	From Start Phase												Investment in Development
	I	II	III	R	I	II	III	R	I	II	III	R	
High (70%)	5	9	18	31	15	20	26	34	16	22	27	34	Low
	- <sup>16</sup>		4	22	11	17	23	32	14	20	26	34	High
Average (45%)	-	1	8	18	9	12	16	22	10	13	17	22	Low
	-	-	-	10	5	9	13	20	8	12	16	21	High
Low (20%)	-	-	3	6	2	4	6	9	4	5	7	10	Low
	-	-	-	-	-	-	3	7	2	3	6	9	High
	Low (100 million)				Average (500 million)				High (1 billion)				
SALES: discount weighted average per year													

Percentages calculated with the following assumptions:

- Distribution factor  $X$ / at start of phase: 0.25/phase I; 0.33/phase II; 0.4/phase III; 0.5/registration phase.
- Present value of investments (millions) at start of market introduction from start of phase (low/high): phase I: 300/750; phase II: 250/550; phase III: 150/350.
- Present value of sales: assuming constant sales levels for 10 years following market introduction, discounted at 11%.

approach deals more specifically with the costs of development that the licensee is expected to incur considering the timing of the licensing deal.

An explanation or justification of the rule is that the profit should be allocated about equally to the following functions: invention, development, production and sales.<sup>17</sup> And although this explanation is highly speculative and not founded by hard facts, it has the advantage that it allows for an extension of the rule. Such an extension seems in order when considering pharmaceutical royalties, as start-of-phase I licensing means that the licensee needs to do all the development whereas start-of-registration licensing means that virtually all the development has been done by licensor. Assuming the invention is completed when the clinical evaluation starts, X would be 0.25 for a start-of-phase I deal. This probably is on a relatively low level considering that already preclinical development will have to have taken place. A benchmark for the profit distribution in deals at the end of the clinical development is the royalty rate paid in co-marketing and distribution agreements. This ranges reportedly from 40 to 70%.<sup>18</sup> So it seems reasonable to set X at 0.5 for

start-of-registration deals. Based on the proportion of the present value of the costs of the respective phases, the corresponding distribution factors for start-of-phase II, and -phase III deals and are calculated to be about 0.33 and 0.4.

### Royalty Rates

The estimates of the royalty rates can be calculated by dividing the present value of licensor income by the present value of the expected sales which changes formula 6 into:

$$R = \text{Licensor income}/\text{Spvm} = X * [\text{OPM}' - \text{Ipvm}/\text{Spvm}] \quad (7)$$

Royalty rates calculated with this formula are shown in Table 5. The table displays the ranges of royalty rates one might “theoretically” expect, based on variations in operating margins, development costs and sales levels and assuming a distribution between licensor and licensee, as discussed in the preceding paragraphs.

### Up-front and Milestone Payments

Next to royalty payments, the economic terms of a licensing agreement usually also include up-front and milestone (U&M) payments. U&M payments are part of the profit dis-

tributed to the licensor and should be considered in combination with the royalty payments. Inserting the U&M payments and rewriting formula 7 one finds:

$$\text{Licensor income} = \text{U\&Mpvm} + R * \text{Spvm} = X * (\text{OPM}' * \text{Spvm} - \text{Ipvm}). \quad (8)$$

where U&Mpvm is the present value of the up-front and milestone payments at the time of market introduction. To see how the U&M payments affect the royalty payments formula 8 is rewritten as:

$$R = X * (\text{OPM}' - \text{Ipvm}/\text{Spvm}) - \text{U\&Mpvm}/\text{Spvm} \quad (9)$$

Interesting feature of this formula is that the way the U&M-payments decrease the royalty percentage is independent of the distribution factor X. And as with the investments in development, the effect depends on the ratio of the values of the U&M payments and the sales. It is important to note that the present value at market introduction of the U&M payments depends on the applicable risk-adjustment and present value (RA-PV) factors as calculated for the base case in Table 4. E.g., at the start-of-phase I, the RA-PV-factor is 9.4. This indicates that an up-front payment of 5 million at the start-of-phase I has a present value of almost 50 million at market introduction. At a sales level of 500 million US\$ per year and a PVF of around 6, this would be equivalent to a royalty of 1.6%.

17. See e.g. Razgaitis.

18. S. Finch (2001), “Royalty Rates: Current Issues and Trends,” *Journal of Commercial Biotechnology*, 2001, Volume 7, Number 3; and <http://www.mediuspublications.com/articles.html>.

**Table 6. Average up-front and milestone payments and royalty percentages as reported by McKinsey and by Medius Associates.**

Development Phase	Up-front		McKinsey Milestones		Royalty %		Medius Royalty %	
	current	improved	current	improved	current	improved	low	high
Preclinical	2	5	15	37	7	17	0	5
Phase I	5	10	25	50	10	20	5	10
Phase II	10	12	35	42	20	25	8	15
Phase III	15	15	50	50	25	25	10	20

All monetary values are in millions of US\$

## Discussion

The above table of implied royalty rates allows a comparison with royalty rates reported based on surveys and on the analysis of terms in deals that have been published. Two relatively recent sources of such comparables are an article by J. Kalamas et al. of McKinsey & Co.<sup>19</sup> and one by S. Finch of Medius Associates.<sup>20</sup> The numbers reported are shown in Table 6.

The Medius numbers are based on a survey in which 68 pharmaceutical companies took part. The McKinsey numbers are part of a plea that pharmaceutical industry should offer biotech companies better terms in early stage licensing deals. As shown in Table 6, it gives both the numbers for what McKinsey regards the current and suggested improved average deal terms. Monte Carlo analysis has generated the improved terms as an average of deals which one would expect to be established if the circumstances and (improved) deal terms generate a high enough rate of return for the licensee.

Regarding the numbers in Table 6, it is obvious that the current royalty rates reported by McKinsey are considerably higher than the Medius numbers. This is most likely due to 1) the McKinsey numbers being based on a relatively small set of published deal data, and 2) that—also considering SEC-guidelines—the deals with better deal terms stand a bigger chance of being published. Consequently, it is also very likely that the McKinsey numbers reflect pharmaceuticals with relatively high sales potentials. This is certainly the case for the suggested improved deal terms. The basis for these terms is a portfolio approach with focus on the one in 10 in-licensed compounds that is likely to generate annual sales of 500M or more, the profits of which should pay for the failed and less successful compounds.

Comparison with the calculated implied royalty rates is somewhat hampered because the reported numbers refer to preclinical, phase I, etc. compounds. This is less specific than it may seem, for there obviously is a big difference between a compound that has just entered a phase and a compound for which the studies in the respective phase are almost completed. In comparing, we will assume that the reported numbers refer to the end of the subject phase, e.g. a phase I royalty is compared with the implied start-of-phase II (SOPII) royalty rate. A further difference is that the implied royalty rates have been calculated in the absence of U&M-payments, whereas the rates reported by McKinsey and Medius regard situations which include such payments. This has as a consequence that the implied rates should be somewhat higher than the reported rates.

Compared with the average implied royalty rates, when also considering the U&M-payments, the McKinsey numbers for current deals are somewhat higher for SOPI and -II deals. They are substantially higher for SOPIII and start-of-registration (SOR) deals, resp. 20 vs. 13-16% and 25 vs. 20-22%. As this also applies at the billion US\$ sales level, the difference cannot be explained by differences in sales levels. To arrive at similar implied royalties, we have to assume either a higher operating margin or—more likely—a higher distribution factor.

The rates reported by Medius are somewhat lower than the implied royalties. For a good part this is likely due to the value of the U&M payments on which there is no information provided. In addition, as discussed above, the Medius numbers may well be somewhat lower because the survey results better reflect the complete spectrum of deals, including deals at much earlier preclinical stages and deals of less significance because of lower or highly speculative sales potential. But overall the reported numbers seem in reasonable agreement with the average implied royalty rates; this is the calculated rates based on

an anticipated annual sales level of 500M and an operating margin of 45%. This regards both the absolute value as well as the trend when going from SOPI deals to SOR deals.

The calculations show for pharmaceuticals that at higher than average expected sales levels (500 million+/year) and average or better (45%+) expected operating margin, the pre-marketing investments in drug development have only a very limited effect on the royalty rates. At these levels, the difference between SOPI and SOR royalty rates would be mainly caused by differences in the profit distribution factor. E.g., for a drug with 45% OPM' and expected sales levels of 500 million a year, the difference between SOPI and SOR in % of sales available for distribution would be only 8% (36 vs. 44). If for both the same distribution factor of 0.5 were applied, the difference in the royalty percentage would only be 4% (18 vs. 22%) instead of 13% (9 vs. 22%). So, for drugs with high (expected) sales levels it would seem that applying the comparables to SOPI licensing would overemphasize the costs and risks involved in clinical drug development. Put in other words, if the (expected) high sales levels are to be considered an attribute of the invention, then this should be reflected in the distribution factor allocating more to the invention and less to the development process.

This view supports the analysis by McKinsey that pharmaceutical industry should consider licensing-in at earlier stages of development at better deal terms for the licensor. At high sales levels, the (expected) operating margin is the dominant factor next to the (subjective) view of what would be a reasonable distribution of profits between licensor and licensee.

Table 7 shows the distribution factors corresponding to the McKinsey numbers for the current and proposed improved economic deal terms. For the current deal terms, at annual sales levels of both 500 million and 1 billion US\$, the distribution factor increases from respectively 0.33 and 0.22 at SOPI to 0.66

19. J. Kalamas, G.S. Pinkus and K. Sachs, "The New Math of Drug Licensing," *The McKinsey Quarterly* 2002, number 4, pp. 9-12.  
20. See note 17.

and 0.6 at SOR licensing. In accordance with the extended 25% rule, the licensee is rewarded for earlier in-licensing. In comparison with the distribution factors with which Table 5 is created, the figures are relatively high. But as the McKinsey numbers seem geared towards the in-licensing of drugs with high sales potential this is not unexpected.

For the improved economic deal terms at the 1 billion US\$ annual sales level, the distribution factors rise from 0.54 at start-of-phase I to 0.6 at start-of-registration. This seems a reasonable approach if the development phase is to be considered of less importance and the deal terms for earlier licensing are to be improved. However, at the 500M annual sales level, the improved deal terms have the somewhat strange consequence that—taking the costs and risks of drug development into account—the reward for licensor increases with earlier out-licensing.

At lower (expected) sales levels and/or lower operating margins, the percentage of sales available for royalties, and thus the figure that might be considered a reasonable royalty rate, is more sensitive to the various other parameters underlying the financials. The investments in drug development have a significant effect on the percentage of sales available for royalty payments. At such sales levels, the development phase at which the licensing

occurs, variations in the expected sales levels, expectations about the costs and length of development and the chances of the drug reaching the market all can have a significant impact on the royalty rate. The sensitivity to such parameters seems reflected in the spread in the reported royalty rates.

Considering the sensitivity to these parameters, one may question the validity of licensing deals that are made long before market introduction, at a point in time that there are so many uncertainties unresolved. It will take teams of experts in drug development, drug markets and drug reimbursement policy to come to a reasonable estimate of what might be reasonable economic licensing terms considering what the circumstances in the quite distant future might be. This would also seem to undermine the concept of royalties in that they are meant to maintain a fair distribution irrespective of the sales volume. Instead, when a deal is made with high expectations of product sales which do not materialize, the licensee will have to pay unreasonable high royalty rates (and probably use its driver's seat position to renegotiate). When a deal is made with low or moderate expectations and the drug turns out to be a blockbuster, the licensor will not be duly rewarded (and be in no position to renegotiate).

Operating margins and develop-

ment costs are factors that are hard to assess objectively as profit & loss statements usually will not provide sufficient detail and cost allocations within big pharmaceutical companies may be quite cumbersome and arbitrary. So, although there may be good reason to adapt the royalty rates if these factors turn out far different from the assumptions upon which the economic terms have been based, this will mostly not be very practical.<sup>21</sup> But where it concerns the sales which are the basis for the royalty calculations, it seems relatively straightforward to correct for differences by including royalty kickers or inverse wedding cake rates.<sup>22</sup>

Betten has proposed to apply a Pharmaceutical Total Market Valuation Model for setting up-front and milestone payments. He proposes taking 0.5% of the total market value (= total lifetime sales) as the total of up-front and milestone payments. For a preclinical deal, this total would be divided in 10% up-front, 20% at start-of-phase II, 30% at start-of-phase III and 40% at start-of-registration. Applying the RA-PV-factors—this is correcting for the attrition rate and time

21. Although there are various examples of agreements in which parties draw on other than the top lines of the profit & loss to for the calculation of royalty payments.

22. Razgaitis.

**Table 7. Distribution factor X calculated from deal terms as reported and proposed by McKinsey.**

Timing of the deal, assumed investments and economic deal terms							Distribution factor X			
PHASE		Ipvvm	R%		U&Mpvm		@S=500M/year		@S=1000M/year	
Mckinsey	Assume		current	impr	current	impr	current	impr	current	impr
Preclinical	SOPI	549	7%	17%	52	129	0.33	0.81	0.22	0.54
Phase I	SOPII	408	10%	20%	70	139	0.40	0.79	0.29	0.59
Phase II	SOPIII	271	20%	25%	69	73	0.62	0.77	0.52	0.65
Phase III	SOR	98	25%	25%	70	70	0.66	0.66	0.60	0.60

to market—the actual percentage of total market value at market introduction can be calculated. Furthermore, as the present value is calculated with the annuity formula, the total market value is directly related to the present value of sales at time of marketing. In the base case as used in this article, TMV is 10 times the yearly sales level and Spvm is about 6 times the yearly sales level. With the calculations shown in table 8, one finds that the U&M payments at the time of introduction on the market would constitute about 1.6% of the TMV. This is equivalent to about 2.7% of the present value of (expected) sales at market introduction. In other words, the suggested schedule for U&M payments would be a risk- and time-adjusted equivalent of a royalty of 2.7%.

As Betten states: “...the ability of licensee or licensor to estimate total lifetime sales is an indeterminable problem. It is only an educated guess and such a number can be documented only at the end of the drug’s life.” The impact this “problem” may have is best illustrated with an example. Suppose a drug at the start-of-phase I is expected to generate sales of about 1 billion US\$ per year. Assuming average investments in development and profit margins, distribution of 25% of the profits would imply a royalty of 9%. With U&M payments as scheduled above totaling 50 million US\$ (0.5% of TMV of 10 billion US\$) this might

be reduced to 6.3%. 10 years later, the drug is not as successful as hoped and the annual sales are “only” 500 million US\$. All else equal, this would merit a royalty of about 7%. More importantly, the already made U&M payments now constitute a royalty equivalent of 5.4%. Consequently, to keep the distribution factor the same, the royalty payment would have to be reduced to 1.6%. And as often it will probably be the other way around; the product sales are higher than accounted for at the time the licensing deal was made. It seems it would make sense in licensing arrangements to have royalty rates vary with the level of sales.

### Concluding Remarks

First of all, it should be stressed that this is a soup-to-nuts approach. It is meant to illustrate the impact of the major parameters on the economical terms in pharmaceutical licensing. It does not necessarily give a correct answer to the question what the terms in an actual case should be, as will also become clear in the following paragraphs.

One might argue that this approach doesn’t handle correctly the differences in risk characteristics of the investments versus revenues. That the initial investments will be done is certain, whether the revenues will materialise is not. Consequently, in the subject approach, the initial investments should firstly be discounted to the moment of the

deal at the risk-free rate before the present value at market introduction is calculated with the industry average cost of capital. It would result in a somewhat higher value of the investments.

What also may be questioned is whether the industry average cost of capital correctly reflects the riskiness of the revenues. Down the development road, it may be necessary to limit the indication for use of the drug resulting in a smaller market than was anticipated. By the time the drug can be introduced on the market, competitors may have developed alternative therapies that put pressure on the pricing of the drug. Another source of uncertainty forms the control over the pricing by regulatory authorities in many countries. The riskiness will be in some way specific for every drug and may require adjustment of the discount rate.

Furthermore, there are several other ways to view the profit distribution. The extended 25% rule in some ways reflects the fact that the revenues should constitute a return to all of licensee’s (intangible) assets. Assets other than the investments into the subject drug development itself are e.g. the development know how, drug registration know how, manufacturing know-how, distribution channels, sales force, branding, etc. A better estimate of the profit distribution factor requires an assessment of the relative economic

**Table 8. Translating % of TMV into % of Spvm**

Phase	% of TMV	RA-PV Factor	RA-PV adj. % of TMV	% of Spvm
SOPI	0.05	9.4	0.47	0.79
SOPII	0.1	5.7	0.57	0.95
SOPIII	0.15	2.0	0.30	0.50
SOR	0.2	1.3	0.26	0.43
<b>Total</b>	<b>0.5</b>	<b>N/A</b>	<b>1.6</b>	<b>2.7</b>

contribution of all of these assets.<sup>23</sup> Also questionable is what the baseline should be. One might wish to compare the value of the drug under patent with the value which might be realised without patent protection, e.g. by assuming that a number of companies share the development costs and subsequently market the drug in competition. Another benchmark could be the profits generated by a generic drug, which the new drug would replace. Considering the market capitalisation of generic companies, also the value of generic drugs can be substantial and might thus have a considerable negative impact on the value of the licensed product. Another way to deal with the demand for return on other assets is applying a higher discount rate, i.e. by setting the desired internal rate of return substantially

higher than the company's cost of capital. The excess return pays for the other assets applied.<sup>24</sup> For start-of-phase I deals, such a discount rate would be quite a hurdle. At a discount rate of 20%, the total average investment at market introduction would be 740 million and at an OPM' of 45% it would take yearly sales levels of almost 400 million to meet the return requirements of the licensee.

Keeping these comments and alternative views in mind, the subject analytical approach may help consider economic terms in pharmaceutical licensing; especially from the viewpoint that these terms should establish a reasonable sharing of the profits between licensor and licensee. In combination with industry standards or other estimates and present value tables, formula

9 can be used to calculate royalty rates, to assess distribution factors and to look at the bearing up-front and milestone payments might have on the royalty rate. The analysis of deal terms seems to show that a kind of extended 25 percent rule applies in pharmaceutical licensing. More to the point, the increase in royalty percentage with the advancement of the development stage seems to reflect an increase of the distribution factor in favor of the licensor rather than the decrease of risk and need of further investment in development. Finally, and most importantly perhaps, this analytical approach shows the strong impact sales levels may have on the distribution of profits between licensor and licensee. This would support the view of those who favor deals with royalty rates increasing with the level of sales.

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23. E.g., see G.V. Smith and R.L. Parr (2001), *Valuation of Intellectual Property and Intangible Assets*, 3rd ed., John Wiley & Sons Inc., Chapter 8.

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24. It may be interesting to note that for a drug licensed at the time of market introduction (i.e. there are no further investments in product development), such an approach may give similar results. Suppose the required rate of return is 20% and the cost-of-capital is 10%. Assuming perpetuity, the present value at marketing at a discount rate of 20% is half the present value at a discount rate of 10 percent. In other words, this would imply a 50/50 split of the profits. With a horizon of about 10 years, the profit split would be about 2/1 in favor of the licensor.