Determining Pharmaceutical Royalties

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Initial payments and royalty increasing for numerous reasons; here are formulas for determining rates

In pharmaceutical licensing deals, an initial payment was traditionally recognized to secure any one or a combination of the following: a fee for disclosure of know-how, an advance payment for patentable improvements to be granted during the agreement period, and settlement for a patent dispute. Linked to the initial payment are royalties, which the licensor considers as the "rent"— which includes a profit for the sales of the drug. Recently, the initial payment has become a key part of contracts of ever-increasing complexity and magnitude. A single licensing deal for a new drug might involve an initial payment ranging from a few millions to several tens of millions of dollars. Also a part of a deal will be royalties that could be as high as 20% on net sales.

Initial payments and royalty rates have tended to increase in the pharmaceutical industry. There are several reasons for this trend.

1. New drug discovery has become increasingly difficult.

2. Because it takes more than 10 years and at least a few hundred million dollars to put a new drug on the market, pharmaceutical companies must continually discover and/or obtain new compounds that show promise of becoming important new drugs

3. The internal R&D efforts at pharmaceutical companies have not been completely successful, resulting in an insufficient pipeline of new products.

4. Pharmaceutical companies must supplement their R&D deficiencies with licensing activities.

In aggregate, these factors have created intense competition for key licensing opportunities. Thus, it is not surprising that initial payments and royalty rates have escalated sharply in pharmaceutical licensing deals. Nevertheless, there should be rational and objective basis for determining the magnitude and relationship between initial payments and royalty rates in the deal. In this article, an attempt is made to develop a theory on how to reasonably determine the amount of initial payments and royalty rates in licensing of drug candidate compounds at different stages of research and development.

INITIAL PAYMENT

The mean research and development (R&D) times for new drugs and the mean attrition rates of drug candidate compounds at each stage of R&D, which can be estimated from statistics gathered from leading pharmaceutical companies, are shown in Table 1. It also shows a theoretical example of the number of compounds required in each stage to bring one new drug on the market.

As seen from Table 1, if a company could generate 10 preclinical drug candidates every year, it could conceivably launch one new drug every year.

As is generally recognized in the pharmaceutical industry, the R&D cost of one new drug is approximately $200 million. (This sum is calculated by dividing the sum of the R&D expenditures at the leading pharmaceutical companies for the past 10-year period by the number of new drugs launched during the same 10-year period.). From this information the cumulative cost of a drug candidate at each stage of R&D can be determined as follows:

If one assumes that a compound that completes its Phase 3 clinical study eventually reaches the market without failure, the cumulative cost of this one new drug after Phase 3 clinical study could be considered to be $200 million. On this assumption, the cost of one compound having

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R&D TIMES AND ATTRITION RATES

Stage	R&D Stage	Time year (cumulative years)	Attrition rate (%)after each stage	No. of compounds remaining after each stage
1	From start of research to selection of preclinical drug candidates	3.5		10
2	Selection of clinical drug candidates	1.5 (5)	70	7
3	Phase 1 clinical study	1.5 (6.5)	70	5
4	Phase 2 clinical study	1.5 (8)	50	2-3
5	Phase 3 clinical study	2 (10)	50	1-2
6	NDA approval and launch	2 (12)	80	1

Table 1

(Note: Phase 1 clinical study starts when the new drug is first introduced into man to determine human toxicity, metabolism, absorption, elimination and other pharmacological action. Phase 2 clinical study is conducted to determine the safety and utility of performing further and more extensive human investigations. Phase 3 clinical study is expanded controlled and uncontrolled trials to gather additional information about effectiveness and safety. NDA stands for New Drug Approval for marketing.)

completed Phase 2 clinical study is calculated by the following equation:

$$(\$200M - \text{Phase 3 clinical study cost} \times 2) \div 2$$

where an attrition rate is assumed to be 1/2(50%). For example, if the cost of Phase 3 clinical study is assumed to be $10 million, the cumulative cost per compound after Phase 2 clinical study (Stage 4) is $90 million. Likewise, the cumulative cost of one compound having completed Phase 1 clinical study is calculated by the following equation:

$$(\$90 M - \text{Phase 2 clinical study cost} \times 2) \div 2$$

where an attrition rate is assumed to be 1/2(50%). When the cost of Phase 2 clinical study is assumed to be $5 million, the cumulative cost per compound after Phase 1 clinical study is $40 million.

pound that has completed Phase 3 clinical study. This means that the value of a compound can increase substantially with progress of R&D.

If a compound is licensed at the cost, shown in Table 2, it means that the licensee obtains the compound at cost, and that the licensor recovers the expenses spent for the compound, provided that money rates are neglected. Therefore, these figures could be used as standards to determine a justifiable amount for an initial payment to a compound at each stage of R&D. Of course, the amount can go up and down from the standard among compounds even at the same stage of R&D, depending upon (1) probability of success in developing a compound to be licensed, (2) sales potential of the compound, (3) the cost of development, (4) marketing

payment is recovered from future profits from the compound's sales.

ROYALTY RATES

For the licensing professional, it is always exciting and challenging to negotiate mutually acceptable royalty rates. In the pharmaceutical industry, royalty rates have ranged from a few percent to over 10% on sales. As to how to determine the rates, a concept employed is that the minimum royalty should be at a rate to recover the money invested in licensing patent and know-how. The most commonly observed ratio of research and development expenditures for sales is between 7 and 15% at research-oriented pharmaceutical companies.

For new drugs ready to be marketed, the minimum royalty rates could be within this range. How then can we determine royalty rates for compounds at pre-marketing stages?

Table 3 shows an approximate breakdown of R&D expenditures in percentage according to "Annual Survey Report 1989-1991" from the PMA (U.S. Pharmaceutical Manufacturer's Association). If a company is spending 10% of its sales to generate a new drug ready for marketing, a compound having completed Level 1 is worth a 3% (10% × 0.3) royalty rate at cost, a compound having completed Level 2 is worth 4%, and a compound having completed Level 3 is worth 6%.

The average royalty rates on sales by R&D Stage at signing of agreements were reported by Mark G.

CUMULATIVE COST PER COMPOUND

R&D Progress	R&D Stage No. (from Table 1)	Cumulative cost ($M)	Assumption
Before Phase 1 clinical study	2	26	Phase 1 clinical study cost: $0.5 M
After Phase 1 clinical study	3	40	Phase 2 clinical study cost: $5M
After Phase 2 clinical study	4	90	Phase 3 clinical study cost: $10 M
After Phase 3 clinical study	5	200	

Table 2

(Note: The cumulative costs estimated from mean attrition rates and average study costs can be validated at individual companies by cost-tracking the record of R&D. "Before Phase 1 clinical study" means completion of all preclinical studies required for Phase 1 clinical study, and "after" means completion of the corresponding phase of clinical study.)

The cost of one clinical candidate compound having completed all preclinical studies is calculated by the following equation:

$$(\$40 M - \text{Phase 1 clinical study cost} \times 3/2) \div 2/3$$

where an attrition rate is assumed to be 2/3 (about 70%). When the cost of Phase 1 clinical study is assumed to be $0.5 million, the cumulative cost per compound before Phase 1 clinical study is about $26 million.

Cumulative costs per compound in each stage of R&D are summarized in Table 2.

Table 2 shows that the cumulative costs of a compound escalate from $26 million for a preclinical compound to $200 million for a com-

expenses, and among others, (5) profit/loss estimates after initial

BREAKDOWN (%) OF R&D COSTS BY LEVEL AND THEORETICAL ROYALTIES

R&D Level	Breakdown of R&D costs	Theoretical royalty rates (%) on sales	
		Example 1	Example 2
1. Synthesis, extraction, for hints	30%	3%	4.5%
2. Toxicity, ADME*	10%	4%	6%
3. Pharmaceutics, quality assurance, pilot production	20%	6%	9%
4. Phase 1,2 & 3 clinical studies, government registratration, approval for marketing	40%	10%	15%

Table 3

Example 1: R&D expenditure is 10% of sales.
Example 2: R&D expenditure is 15% of sales.
*: ADME = Absorption, Distribution, Metabolism, Excretion in animals.

AVERAGE ROYALTY RATES (ROUND FIGURES) ON SALES BY R&D STAGE AT SIGNING AGREEMENTS

R&D Stage	Royalty rates	
	Biotechnology ►University company	Major ►Biotechnology pharmaceutical company company
Discovery	3%	7%
Lead molecule	4-5%	9%
Pre-clinical	6-7%	10%
Phase 2-3 clinical	-	15%

Table 4

Edwards of Recombinant Capital at the 1995 LES (USA & Canada) Annual Meeting in Orlando. These figures are averaged rates of many deals and are shown in Table 4.

Average royalty rates of past deals between biotechnology companies and major pharmaceutical partners appear to exceed theoretical royalty rates. It is interesting to see how a biotechnology company, as a middleman, licenses technology from a university, adds value to it, and then re-licenses it to a pharmaceutical partner.

INITIAL PAYMENTS AND ROYALTIES IN COMBINATION

In most deals, initial payments and running royalties are negotiated in combination as part of a complex package deal. How does one theoretically combine these two elements into a single deal?

As shown in Table 2, if a company spending $200 million for a new drug licensed a compound that completed Phase 3 clinical study for an initial payment of $200 million, it means that the company succeeded in acquiring the new product at the cost of its R&D. In this case, the amount of payable running royalty should be within the company's operating profit to be obtained from sales of the product. How can one logically allocate the profit to royalty?

For example, suppose if at the licensee company, R&D expenditures, marketing and administrative expenses, and operating profits are 15%, 45% and 20% (production costs are assumed to be 20%), respectively, in percentage of sales, the ratio of R&D expenditures to marketing and administrative expenses is 1 to 3. When the same operating profit (20%) can be expected by sales of the product and is fairly shared between the licensor and the licensee, the licensor could get one fourth of it, 5%, and the licensee three fourths, 15%. So, a fair royalty rate in this instance would be 5% on sales. If the licensee company acquired the product for an initial payment of $100 million, which is supposed to be one half of the R&D expenditures, a percentage corresponding to one half of R&D expenditures (15% of sales) could be added to the royalty rate. As a result, the royalty rate will be increased to 12.5%. This same calculation can also be applied to compounds having completed the Phase 2 or Phase 1 clinical study.

In another example where R&D expenditures, marketing and ad-

ministrative expenses, and operating profits are 10%, 30% and 10% (production costs are assumed to be 50%), respectively, a fair royalty rate calculated in the same manner is 2.5% when the full amount of R&D cost is paid as an initial payment, and 7.5% when one half of the R&D cost is paid as an initial payment.

Please note, however, that in these instances the probability of success (or failure) in and the amount of investment for R&D, manufacturing and marketing of the product are not taken into account. A big question for the company (licensee) is as to whether the initial payment can be offset by sales of the product during lifetime of the product, while a reasonable amount of profit is secured after payment of the royalty. Indeed, a profit and loss analysis of the product is the determining factor for a licensee company in deciding affordable amounts of initial payment and royalty.

On the other hand, the licensor should try to find a partner who will buy a compound at a higher initial payment than the licensor's R&D cost and will generate the highest operating profit that shall be fairly shared.

As mentioned above, the reasonable amount of initial payment to pay (or to require) can be determined by statistically analysing amounts of money spent at each stage of R&D to generate one new product at each pharmaceutical company. A theoretical royalty rate can be calculated from percentages in sales of the company's R&D expenditures, marketing and administrative expenses, and operating profits in combination with the initial payment.