Pharmaceutical Up-Front Licensing Fees

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Abstract

A general discussion of up-front licensing fees is presented for market entry and emerging pharmaceuticals, along with a theoretical discussion on why up-front fees should be considered as a part of every license. The same up-front fee discussion applies to other technologies. This paper provides practical advice on how to determine pharmaceutical up-front and milestone fees. A survey of pharmaceutical up-front fees, along with a suggested valuation approach, is provided to aid the licensing officer in valuation and eventual negotiations.

Introduction

Pharmaceutical and biotechnological technologies have consistently been areas in which large licensing fees have been negotiated. However, there is no information in the open literature on how pharmaceutical up-front licensing fees are determined. A number of papers discuss valuation methods, but these are general discussions and no specific models or valuation methods are provided.[1,2,3] Thus, the licensing executive is not only left to "guess" at a value, but also lacks a consistent, repeatable, logical method for determining an appropriate up-front or milestone payment. It is noted by Degnan and Horton[4] from a survey that only 60% of licensors ask for an up-front fee. One may wonder why, but could it be because there are no well documented or referenced methods for determining up-front fees? Because a pharmaceutical has to pass through several Food and Drug Administration (FDA) approvals, milestone payments are often associated with FDA approval for a particular phase. In this paper, milestone payments are discussed and are assumed to be part of the up-front fee valuation, where one may think of the initial up-front fee as being split into several installment (milestone) payments.

Running royalties are another area of interest, and may be used in negotiations as a trade-off for up-front fees. As the focus of this paper is up-front fees, running royalties are mentioned here only for completeness. The 25% rule provides a basis for calculating a first royalty estimate (Note: the 25% rule suggests taking 25% of the product profits as a running royalty). Additional royalty information can also be found in general "industry standards" tables. According to two recent surveys,[5,6] average pharmaceuticals running royalties are calculated to be 5.1% (an average over the years of 1980-2000) and 7.0% (an average over the years of 1986-2002). These recent values are within a wider range suggested in the licensing-out survey of royalties provided by McGavock, et. al[7] where 67% of the pharmaceutical rates are in the 5%-10% range. The McGavock survey is widely quoted and reproduced in a number of sources including the AUTM Handbook.

The purpose of this paper is to present a basis for understanding that an up-front fee should be considered as a part of any license. This paper continues the up-front fee valuation process by providing a suggested valuation approach based on total lifetime market sales, along with a survey of university pharmaceutical up-front licensing fees. It is hoped that this survey will provide a reference and consistent approach for the licensing executive to determine the initial value of these up-front fees.

Why Ask for an Up-front Fee?

There are many reasons one can propose asking for an up-front licensing fee:

- It's standard business practice and we are acting in a business-like manner.
- Our policy requires an up-front fee for licenses (similar to a down payment on a house).
- We need to recoup patent and administrative costs.
- We need to partially recoup R&D expenditures.
- All licensors in the field ask for one!
- We want to maximize institutional income.
- It gives both the institution and the inventors immediate returns.
- It increases licensee commercial commitment.
- The licensee shows more commitment by paying an up-front fee.

1. L. Somogyi, "Determining Royalty Rates in Health Care," *les Nouvelles*, December 1993.
2. M. Yamasaki, "Determining Pharmaceutical Royalties," *les Nouvelles*, September 1996.
3. M. Pohl, "Valuing Pharmaceutical I.P.," *Pharmaceutical News*, Vol. 8., No. 1, 2001, pp. 42-45. Also see "Valuing Pharmaceutical I.P." , available at *http://licensinglaw.net/Library.asp*
4. S. Degnan and C. Horton, "A Survey of Licensed Royalties," *les Nouvelles*, June 1997.
5. R. Goldsheider, J. Jarosz, and C. Mulhern, "Use of the 25 Per Cent Rule in Valuing IP," *les Nouvelles*, December 2002.
6. *Licensing Economics Review*, "Industry Royalty Data Summary," December 2002.
7. D. McGavock et al., "Factors Affecting Royalty Rates," *les Nouvelles*, June 1992.

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• It provides a trade-off mechanism for royalties using a net present value calculation.

• It represents the "current" value (lump sum) of the technology.

One could consider an up-front fee analogous to the down payment on a home mortgage. The larger the down payment, the more the bank is convinced that the home purchaser is seriously committed to buying and paying off the mortgage. Thus, an up-front fee demonstrates the seriousness of the licensee's intent. The larger the up-front payment, the larger the financial commitment to commercialize the technology.

Another viewpoint this author currently favors is to view an up-front fee as the "now" value of a technology, and the running royalties as the "future" value of a technology. Let's consider a pharmaceutical example. As is noted in Table 1, which summarizes FDA approval percentages as a function of clinical trial stage, only about 1 drug in 5,000 will make it through the Federal Drug Administration (FDA) drug approval process from pre-clinical trials to drug approval and commercial release. Specifically, the table indicates that out of 5,000 pre-clinical drug trials, only 5 will make it into the FDA approval process (99.9% failure rate). Of those 5, about 1.3 will fail during each phase, with only one actually making it to market (80% failure rate). These are extremely high failure rates, and conversely it is reasonably safe to conclude that 4,999 of the licensors will never see any running royalties on sales. Thus, if running royalties represent the future value of the technology, 4,999 of the drugs will have no running royalties and the licensor will receive no income other than the up-front or milestone fees. For the one licensee who makes to market it, the future value will be a "big hit" involving running royalty payments. For the licensor, however, the up-front fee, either as an annual option payment or milestone payment, will be the only licensing income seen. Thus, the up-front fee represents the "now" or current value of the technology.

Product Sales and Marketing Cycle

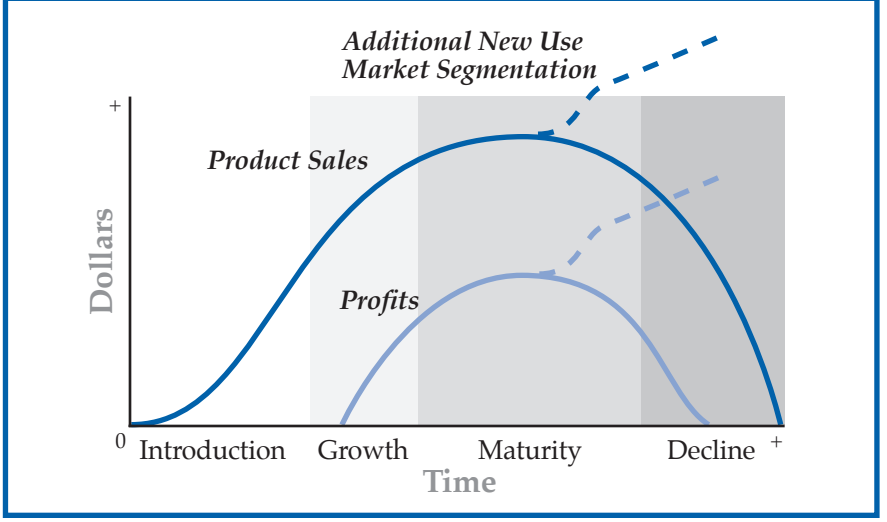
Most people who have taken a marketing course have seen the product sales and marketing curve, and the related profit curve, as shown in Figure 1. This sales curve is generic in shape and applies to products ranging from "hula hoops" to airplanes to nuclear reactors, with only the cost and time coordinates varying with product type. Products are generally considered to have four stages: (1) *Introduction*, where the product is introduced and sales are slow in starting and gaining market acceptance, (2) *Growth*, where the product is started to be accepted by the public and sales grow rapidly, (3) *Maturation*, where the product has reached saturation in the market and additional sales do not occur, and (4) *Decline*, where the product is decreasing in market acceptance, sales decline, and the product is eventually abandoned. Profits from product sales follow a similar behavior; however, there is a time lag after product introduction before profits occur. This lag occurs because initial product startup and marketing costs, as well as other "sunken" costs, must be repaid before profits can occur. Profits also stop in the decline stage of a product because they are directed toward product manufacturing shutdown costs. It is important to note that Figure 1 represents a successful product life cycle.

As will be noted later, only about 1 in 10 of the introduced products will be wildly successful, with the other 9 failing or having only limited market success.

The dream of most product managers is to find another product use in a totally different field of use. This diversification, known as market segmentation, permits a rise in sales and profits because product cost reductions can occur as a result of eliminating or reducing the sales stages of Introduction and Growth, and the sunk costs associated with building the first plant are already returned. Nylon is a typical example of market segmentation in a product in which initial sales were limited to industrial uses, but quickly spread to clothing, tire reinforcement, carpet fibers, automotive components, etc.

Understanding how a technology fits into the product sales cycle is an important factor in determining the up-front licensing fee. That is, the initiation of product profits will depend on the time needed to develop the Introduction and Growth stages. Licensees may be reluctant to commit a large up-front licensing fee if profits are perceived to occur many years in the future. This is especially true for pharmaceuticals and emerging technologies where the product and market are not well defined or there is a substantial time delay before market penetration.

Figure 1. Product Life Cycle Sales and Market Entry Curve



The Total Product Life Cycle

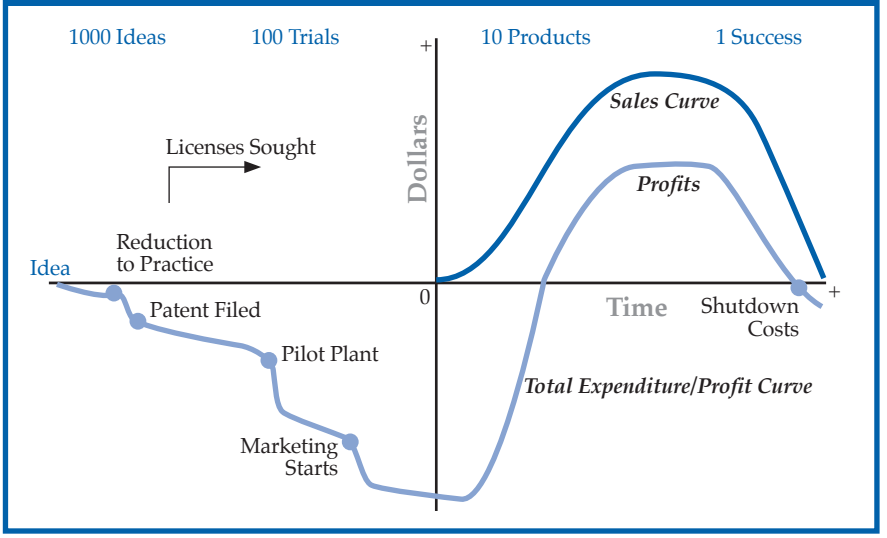
The licensee should be aware of the total product life cycle, as shown in Figure 2, to fully understand the sunken costs in developing a new product and how those costs can impact the up-front licensing fee. Figure 2 represents a generic product curve, as in Figure 1, where time and cost are shown as coordinates. For simplicity, it is assumed in this example that all sunken costs are absorbed by different departments within a single organization. The total product life cycle starts with an inventor having an idea and reducing it to practice, with expenditures being made and covered for by the current project. If the idea is patentable, a patent is filed, and this is denoted by an increase in sunken costs. Patent costs are then covered by another part of the organization, generally the legal or technology transfer department, depending upon the organization's policies. (For universities, licensees may be sought at this time, as well as sponsored research for prototype development and small-scale manufacturing operation. This is also the "valley of death" where R&D funding runs out but no commercial organization is interested in providing funding until pilot plant data are available.) The technology transfer process now starts in earnest and effort proceeds on developing a pilot plant and operational parameters for large-scale manufacturing. Often, the pilot plant production will be used for creating a limited volume of products for market testing or for the Introduction market stage. Sunken costs now become greater as the pilot plant is built and production increases. If all goes well, the organization's marketing department starts advertising seriously to create a product "buzz" so that the public will want the product. This incurs still more sunken costs. Thus, as noted in Figure 2, a substantial sunken cost has been incurred by the company when the product is ready for introduction into the market, yet no sales have occurred. Once sales and market gains occur, profits begin to accrue, and the sunken costs are recovered slowly as sales increase and the transition to the Product Sales and Marketing Cycle (Figure 1) develops. The total expenditures to develop a product, or the sunken costs, are often referred to as the total replacement cost (TRC). The TRC, or more often a certain percentage of it, is often used in technology valuations to estimate the "value" of the technology. How the TRC can be related to up-front fees will be discussed subsequently in this paper.

It is generally stated that for general product development only one product is successful from among 1,000 ideas. That is (as indicated in Figure 2 by the product numbers at the top of the figure), 1,000 ideas develop into 100 trial products that are further reduced to 10 products introduced into the market, but only 1 product will be a success. It is this one success that pays the sunken costs for the 1,000 ideas, 100 trial products, and 10 market introduction products. If a company is skillful, it may be able to provide 2 or 3 market successes out of its 10 market entry products, and that will provide an even bigger return to the company. Similar success statistics occur for venture capitalists' investments in startup companies. Out of 10 startups, a good return is one "home run," perhaps two "doubles" and two "singles," with the rest being "strike outs."[8]

For pharmaceuticals, the total product cycle curve in Figure 2 is applicable; however, more sunken costs occur as the product cycle curve is changed to accommodate additional spending in each of the three phases of the FDA approval process noted in Table 1. Literature indicates that drug research and development (R&D) costs are rising, as is the success rate of drug approvals. In 1993 the FDA[9] reported that $390 million of R&D funds are needed to develop a new drug, and this represents the pharmaceutical's total sunk cost needed to be recovered so that a new drug can become profitable. In 1998, Merck's annual report[10] indicated that it takes $500 million and 10-15 years of effort to develop 1 drug out of 5,000. The following year, the FDA[9] reported new drug costs and success rates as identical to those reported in the Merck report. In 2003, the Pharmaceutical Research

8. AUTM Startup Course, "Investors and Capital Sources," Terry D. Bibbens, Small Business Administration, September 25, 2000, Arlington, Virginia.
9. Food and Drug Administration (FDA), "From Test Tube to Patient: New Drug Development in the United States," 2nd Edition, 1995 (Order code 8307, 017-012-00400-8). Updated in 1999. Also see FDA web page: *http://www.fda.gov/dfac/secial/newdrug/begin.htm*
10. Merck & Company, "*Merck 1998 Annual Report*," p. 6. Also see *http://www.merck.com/overview/98ar/p6.htm.*

Figure 2. Total Product Life Cycle Birth to Death Expenditures



and Manufacturers Association[11] indicated that the total R&D cost for a new drug has risen to an average of $802 million, and that only 3 out of 10 new drugs brought in enough revenue to cover the average development cost[12].

Valuation and Total Replacement Cost

In the physical sciences, two methods have been suggested for determining up-front fees. Heller[13] suggests using the standard industrial classification (SIC) codes to estimate the lifetime net sales in a market, for a specific product and market share, and then using an empirical factor as a multiplier times the total market sales to determine the up-front fee. For sales (a) less than $1 million, Heller suggests a multiplier between 0.5 and 0.9% (0.005-0.009) for a minimum and maximum value, (b) between $1 and $50 million, Heller suggests a multiplier between 0.1 and 0.6% (0.001-0.006) for a minimum and maximum value, and (c) for sales over $50 million, a multiplier of 0.01-0.1%(0.0001-0.001) is suggested. Thus, if total market sales are estimated to be $2 million, and an average factor of 0.3% (0.003) is used, the suggested up-front fee would be $6,000.

In another method, Betten[14] suggests that emerging technologies use a multiplier with the R&D modified replacement cost (MRC) to determine the up-front fee. The logic is that market sales are probably more than three to five years away, and the market is too difficult to estimate. Betten suggests varying the multiplier from about 5% of the MRC for a non-exclusive license, and up to 15% of the MRC for exclusivity. The MRC is generally taken to be about 25-33% of the total replacement cost or, stated another way, "knowing what you now know," how much time and unique instrument costs are needed to recreate the technology? For example, if the TRC is taken to be $1 million, the MRC would be about $250,000 (assuming the 25% factor for ease of calculations), and a non-exclusive license up-front fee would use a 5% multiplier, resulting in a suggested up-front fee of $12,500.

A Pharmaceutical Total Market Valuation Model

In the pharmaceutical area, as noted earlier, some authors[1,2,3] suggest using a multiplier of the total market value of the product; however, no specific factor is provided. In an ad hoc discussion at an AUTM meeting, an emerging pharmaceutical drug rule-of-thumb was provided. The valuation process starts with determining the total lifetime sales market. If there are multiple products possible from this drug, and there is interest in several countries, then the market should be estimated for each product and each country. A multiplier of 0.5% (0.005) times the total market value is used to estimate a "total valuation" for the drug. Surprisingly, this multiplier is within the range suggested by Heller for physical science technologies. The up-front fee is taken to be a percentage of this total valuation number, depending on the FDA phase. In this instance, when the drug is in pre-clinical trials, the up-front fee is taken to be about 10% of the valuation, with the remaining 90% to be split into milestone payments and back-loaded with higher payments in later FDA phases. One may arbitrarily suggest 20, 30, and 40% of the valuation number for milestone payments at the end of Phases 1, 2, and 3, respectively. Alternatively, one could suggest an increase of 30% per phase (i.e., a 30% increase per each of three phases would add up to 90%). For example, if the estimated total sales market is $1,000 million, the drug total valuation would be 0.5% of sales, or $5 million. The up-front fee would be 10% of the total valuation, or $0.5 million. The remaining 90% of the total valuation, $4.5 million, would be arbitrarily split into milestone payments for the completion of each phase at 20, 30, and 40% of the total valuation. This translates into suggested milestone payments of $1 million, $1.5 million, and $2 million for Phases 1, 2, and 3 respec-

Table 1. FDA Drug Approval Rates

FDA Drug Testing in Humans

	Number of Patients	Length	Purpose	Percent of Drugs Successfully Tested
Pre-clinical	Animal tests	1-3 years	Toxicity, how it works	.01% (5000 to 5)
IND Filed	–	30-days	Safety review	–
Phase 1	20-100	Several months	Mainly safety	70% (5 to 3.5)
Phase 2	Up to several hundred	Several months to 2 years	Some short-term safety but mainly effectiveness	33%
Phase 3	Several hundred to several thousand	1-4 years	Safety, dosage, effectiveness	25-30% (1.5 to 1.25)
PLA/NDA Review	–	2 months-7 years	Data review	80% (1.25 to 1)
Post-Market Surveillance	In use	Drug lifetime	Adverse reactions, surveys / samplings, inspections	No data

11. Pharmaceutical Research and Manufacturing Association, "Most Drugs Never Recoup the Average Cost of Development," *http://www.phrma.org/publications/quickfacts/16.04.2003.717.cfm.* Also see: J. A. DiMasi, R. W. Hansen, and H. G. Grabowski, "The Price for Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics* 22 (2003): 151-185.
12. Pharmaceutical Research and Manufacturing Association, "Most Drugs Never Recoup the Average Cost of Development," *http://www.phrma.org/publications/quickfacts/16.04.2003.717.cfm.* Also see: H. G. Grabowski, J. Vernon, and J. DiMasi, "Returns on Research and Development for 1990s New Drug Introductions," *Pharmacoeconomics, Suppl.* 3, 11-29 (2002).
13. P. Heller, Texas A&M University System, College Station, Texas, August 1999 AUTM Central Meeting.
14. P. Betten, "5% Solution to Pricing Software IP,@ *les Nouvelles*, September 1999.

tively. If a drug is already in Phase 1 and licensing occurs, the up-front fee of 10% and the Phase 1 fee of 20% could be combined into a fee of 30% of the total valuation. These up-front and milestone fees are always technology– and market-dependent, with final values left to the skill of the negotiators.

Survey of Pharmaceutical Fees

In late 2001 a survey of 10 universities was made to determine the pharmaceutical licensing fees the universities negotiated in pre-clinical trials and the different FDA phases. About 160 data points were collected; the results are shown in Table 2. The universities asked for business confidentiality on the data so only a range and low and high payments are provided. The survey indicated that pre-clinical payments are in the $10,000-$50,000 range and tend to be annual payments until the drugs enter FDA testing. Once in the testing phase, milestone payments are generally associated with approval in each phase, with the payments increasing as each phase is passed. In some instances a milestone payment is associated with the individual new drug (IND) application. In the later phases, milestone payments may be associated with the new drug application (NDA) or the product license application (PLA). When the NDA/PLA is filed/approved, the universities indicated milestone payments in the range of $500,000 to $2 million. Low and high values are noted in the table, and these can vary greatly depending on the potential market. It is noted that in collecting the data, not all universities collected milestone payments at the end of each FDA phase, with payments at the end of Phase 1 (IND filing) and Phase 3 (NDA/PLA) approval being the common occurrence. In subsequent discussions with the universities, most agreed that one should try to collect milestone payments at the end of each testing phase; however, this is not always possible. It may be that drug technologies, the markets, and the corresponding negotiations are complex, and other factors enter into the negotiations that make milestone payments inapplicable at every phase.

Table 2. University Survey of Pharmaceutical Payments

FDA Stage/Up-Front Fees	Typical Range ($1,000)	Low/High ($1,000)
Pre-clinical	$10-$50	$5/ $100
IND Filed	$50-$250	$50/$500
Phase 1	$20-$50	$200/ $1,000
Phase 2	$50-$500	$50/ $1,000
Phase 3	$200-$1,000	$200/ $2,000
PLA/ NDA filed/ approved	$500-$2,000	$100/$5,000

Conclusions

The ability to determine up-front fees in the pharmaceutical area is more of an art than a science, with high weighting on negotiation skills. There are essentially no open-literature publications on the value of up-front fees, how to determine them, and a strategy for their use. A discussion of the "hows", "whys" and logic of determining up-front fees has been presented. Another purpose of this paper has been to present selected methods or models that can be used to determine such fees. A pharmaceutical model based on taking a percentage of the total lifetime market sales is provided. Surprisingly, this pharmaceutical model is somewhat similar to another model used in the physical sciences. In addition, a survey has been compiled to provide a basis to empirically select such fees based on university-industry standards.

The determination of up-front fees is complex and confusing because of a lack of valuation models and the difficulty in making an accurate but representative assessment. At one end of the spectrum there is hesitancy (by either the licensee or licensor) to reveal what was paid because the fee may be very low and the technology may be perceived as having been given away. At the other end of the spectrum, the ability of licensee or licensor to estimate total lifetime sales is an indeterminable problem. It is only an educated guess, even when consultants are used, and such a number can be documented only at the end of the drug's life. Few can predict their lives several years ahead, let alone accurately predict the total lifetime market sales of a drug over the course of a decade or two. It is, of course, left to the negotiators to sort out these issues and eventually evaluate the drug technology and determine whether it merits the proposed licensing fee. It is hoped that a licensing staff may be able to use the methods provided here to provide consistent, repeatable, and reasonable estimates of up-front fees that will gain the trust of users in additional future valuations. Further, 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.

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