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Valuations using royalty data in the life sciences area—focused on anticancer and cardiovascular therapies

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Abstract

Purpose: This research seeks to answer the basic question, "How can we build up the formula to estimate the proper royalty rate and up-front payment using the data I can get simply as input?" This paper suggests a way to estimate the proper royalty rate and up-front payment using a formula derived from the regression of historical royalty dataset.

Design/methodology/approach: This research analyzes the dataset, including the royalty-related data like running royalty rate (back-end payments) and up-front payment (up-front fee + milestones), regarding drug candidates for specific drug classes, like anticancer or cardiovascular, by regression analysis. Then, the formula to predict royalty-related data is derived using the attrition rate for the corresponding development phase of the drug candidate for the license deal and the revenue data of the license buyer (licensee). Lastly, the relationship between the formula to predict royalty-related data and the expected net present value is investigated.

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Findings: For the anticancer (antineoplastics) and cardiovascular drug classes, the formula to predict the royalty rate and up-front payment is as follows.

$$\mathrm{X} = (\mathrm{Attrition\ Rate} * \mathrm{Licensee\ Revenue})/100$$

$$< \mathrm{Drug\ Class:\ Anticancer\ activity\ candidates} >$$

$$\begin{aligned}\mathrm{Royalty\ Rate} &= (1 + \mathrm{a} * \mathrm{X})/(\mathrm{b} + \mathrm{c} * \mathrm{X}) \\ &= (1 + -5.14147\mathrm{E}\text{-}09{*}\mathrm{X})/(0.128436559 + -6.37\mathrm{E}{-}10 * \mathrm{X})\end{aligned} \quad (1)$$

$$\begin{aligned}\mathrm{Upfront\ payment\ (Up\text{-}front + Milestones)} &= (\mathrm{a} + \mathrm{X})/(\mathrm{b} + \mathrm{c} * \mathrm{X}) \\ &= (-133620928.7 + \mathrm{X})/(-3.990489631 + 2.04191\mathrm{E}{-}08 * \mathrm{X})\end{aligned} \quad (2)$$

$$\mathrm{X} = (\mathrm{Attrition\ Rate} * \mathrm{Licensee\ Revenue})/100$$

$$< \mathrm{Drug\ Class:\ Cardiovascular\ activity\ drug\ candidates} >$$

$$\begin{aligned}\mathrm{Royalty\ Rate} &= \mathrm{y0} + \mathrm{a}/\mathrm{X} + \mathrm{b}/\mathrm{X}^2 \\ &= 9.26\mathrm{e} + 0 + (-8.528 + 5)/\mathrm{X} + 1.744\mathrm{e} + 10/\mathrm{X}^2\end{aligned} \quad (3)$$

$$\begin{aligned}\mathrm{Upfront\ payment\ (Up\text{-}front + Milestone)} &= \mathrm{y0} + \mathrm{ax} + \mathrm{bx}^2 \\ &= 7.103\mathrm{e} + 6 + (-3.990489631) * \mathrm{X} + (-1.536\mathrm{e}{-}12) * \mathrm{X}^2\end{aligned} \quad (4)$$

In the case of Equations Equation 2 and Equation 4, it is statistically meaningful (R2: 039–0.41); however, in the case of Equations Equation 1 and Equation 3, it has a weak relationship (R2: 022–0.28), thus requiring further study.

Research limitations/implications (if applicable): This research is limited to the relationship between two drug classes—anticancer (antineoplastics) and cardiovascular—and royalty-related data.

Practical implications (if applicable): Valuation for the drug candidate within a specific drug class can be possible, and the royalty rate can be a variable according to drug class and licensee revenue.

Keywords: Valuation, Licensing deal, Drug, Royalty data, Royalty rate, Up-front fee, Milestones, Regression, Drug class, Anticancer, Antineoplastics, Attrition rate, Development phase, Licensee, Life sciences, rNPV, eNPV (expected NPV), DCF, QSAR, Computational chemistry

Introduction

The existing valuation methodologies used in the life sciences area and their strengths and weaknesses

As shown in Fig. 1, the R & D process of medicine requires a lengthy long-term development period between 12 to 15 years and a development cost that can reach about USD 13 billion. However, among the number of drug candidates that ranges from 5000 to 10,000, only 1 can be finalized as the approved drug. Because of this, the attrition rate of medicine is extremely small. With this, the drug development process is categorized by the following development stages: drug discovery; preclinical testing; phase I, II, and III clinical trials; submission for approval; and phase IV. To sum up, drug development is expensive, time-consuming, complex, and risky.

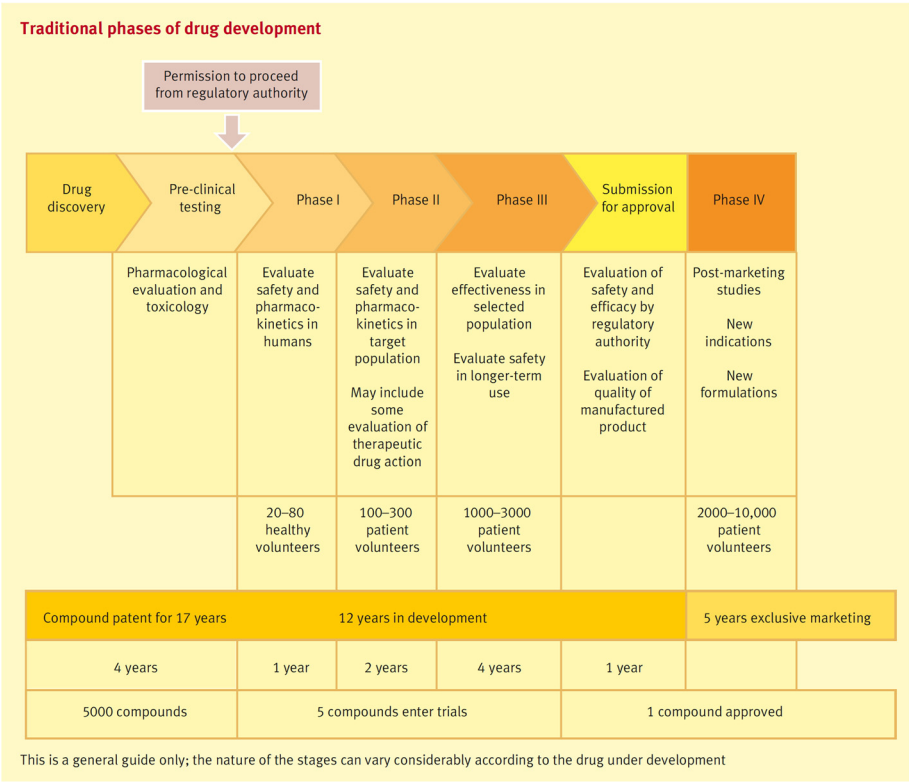


Fig. 1 R & D process of medicine (Richards 2003)

As shown in Tables 1 and 2, drug development requires a great amount of time and money for each development phase. In particular, the phase 3 clinical trial requires a huge amount, from 10 M$(Million dollar) to 60 M$(Million dollar), and about three years to complete. For this reason, the phase 3 clinical trial is regarded as the Death Valley that is necessary to overcome.

As shown in Fig. 2, the total number of pharmaceutical candidates in clinical development by the year 2005 exceeds more than 3000; here, the most number of candidates can be found in the phase 1 clinical trial while the least can be found in phase 3.

The prediction of the future value of the asset is useful and important to determine economical action (Lee and Lee 2015). Also, licensing deals between

Table 1 Drug development costs (Bogdan and Villiger 2010)

Phase	Cost
Lead optimisation	US$ 2–3 mn
Preclinical phase	US$ 2–3 mn
Clinical phase 1	US$ 1–5 mn
Clinical phase 2	US$ 3–11 mn
Clinical phase 3	US$ 10–60 mn
Approval	US$ 2–4 mn

Table 2 Drug development duration (Bogdan and Villiger 2010)

Phase	Length
Lead optimisation	20–40 months
Preclinical	10–12 months
Clinical phase 1	18–22 months
Clinical phase 2	24–28 months
Clinical phase 3	28–32 months
Approval	16–20 months

pharmaceutical companies and biotech/academia are popular in the life sciences area because drug development is expensive, time-consuming, complex, and risky.

As shown in Fig. 3, the total number of licensing deals for 1 year by the year 2006 reached almost 700 cases, and the total value of deals in the same year is lively enough to reach 77 B$(Billion dollar). Licensing deals, as you can see from the other paper, were increased from about 50 cases in 1993 to more than 400 cases in 2001—about an 8-fold increase as shown in Fig. 4.

In Fig. 5, the number of back-end payments (running royalties) is higher than that of up-front payments (up-front fee + milestones) in a normal license deal condition in all development stages.

Determining a reasonable royalty rate for a licensing deal is highly difficult, and proper valuation is essential to make a reasonable determination. There are two major valuation approaches used in the life sciences area: discounted cash flow (DCF) and real options. According to a preceding paper (Puran 2005), the risk-adjusted net present value (rNPV), DCF, scenario analysis, and decision-tree method achieved the highest scores as the valuation methods used by biotech and pharma companies, analysts, and venture capital (VC) firms on value part-developed projects, as shown in Fig. 6. The DCF method is based on the knowledge that a dollar today will be worth less in the future; here, the most common DCF metric used in biotechnology is the net present value (NPV). The NPV

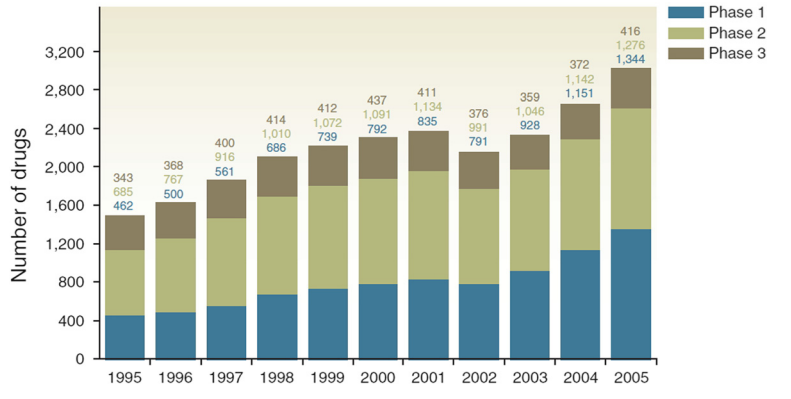


Fig. 2 Clinical stage development candidates (Kessel and Frank 2007)

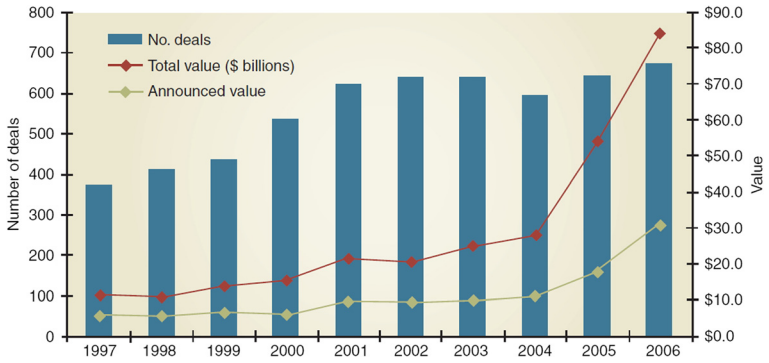


Fig. 3 Value of biotech out-licensing deals (Kessel and Frank 2007)

evaluates situations by looking at investments in a product made today and comparing this with the future predicted stream of cash flow. That future value is then discounted back to its present value using a discount factor, which takes into account the time that it will take to realize product sales, the risk of getting the product into the market, and the "cost of money" invested (i.e., what the initial investment might be worth if invested elsewhere). The real options method evaluates investments and returns by increments. In this way, investments can be done slowly, giving enough time for one to learn more about the investment and defer the decision for further investments until uncertainty is reduced (Arnold et al. 2002). The valuation methodology for new drug pipelines includes rNPV or eNPV (expected NPV) or the probability-adjusted NPV method in which technical risk is reflected on the cash flow, the scenario-implemented decision tree method, which calculates the weighted average NPV according to the probability of specific scenarios, and real options, which is often used by financial professionals but are not preferred by drug experts. The rNPV method is most frequently used in practical work in the life sciences area (Lee 2010).

Figure 7 shows a screenshot of the Excel application to apply the rNPV methodology developed by Dr. Jeffrey J. Stewart of the Milken Institute.

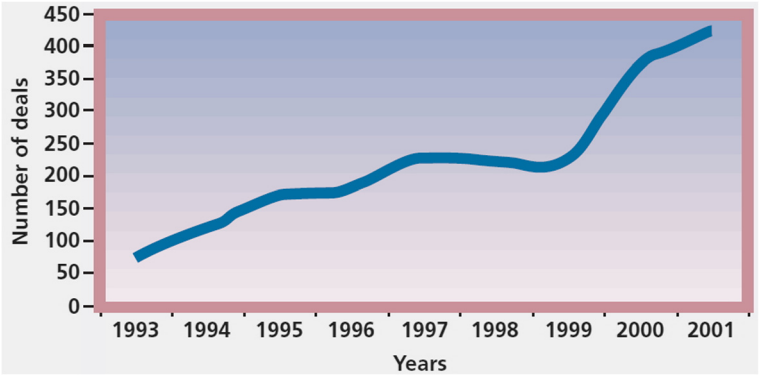


Fig. 4 Total number of deals in the period 1992–2001 (Arnold et al. 2002)

PARAMETERS

COMPANY NAME		Neklim Biotech Co.		**PROJECT TITLE**		Neklimed	
Orphan Drug (y/n)?		N	Orphan if <200,000 U.S. patients	**Financials**	Annual Market	$1,000,000,000	
					Peak Market Penetration	35%	
Preclinical	Duration	1			Market Growth Rate	3%	
	Annual Cost	$2,000,000	8 Scientists at $250,000 per scientist			OR	
	Likelihood of Reaching Revenue	10%			Patient Population		
					Annual Revenue Per Patient		
Clinical Phase 1	Duration	1			Peak Market Penetration		
	Number of Subjects	60	20-80		Patient Polpulation Growth Rate		
	Cost Per Patient	$12,000	$8,000-15,000			AND	
	Animal Studies Phase 1	$500,000			Ramp to Market Peak	2	Maximum 4 Years
	Annual Overhead (Other Costs)				Discount Rate	15%	
	Likelihood of Reaching Revenue	25%	20% for a chemical pharmaceutical		In-licensing Royalty Rate	5%	
					Manufacturing and Marketing Offset	60%	
Clinical Phase 2	Duration	2			Year Patent Protection and Revenues End	21	
	Number of Subjects	200	100-300		Annual Ramp Overhead (Other Costs)		
	Cost Per Patient	$12,000	$8,000-15,000		Annual Peak Revenue Overhead (Other Costs)		
	Animal Studies Phase 2	$1,000,000					
	Annual Overhead (Other Costs)						
	Likelihood of Reaching Revenue	35%	30% for a chemical pharmaceutical				
Clinical Phase 3	Duration	3					
	Number of Subjects	2000	1,000-5,000				
	Cost Per Patient	$6,000	$4,000-7,500				
	Animal Studies Phase 3	$1,500,000					
	Annual Overhead (Other Costs)						

Figure 8 shows an example of the application of the decision alternative and tree methodology on the valuation for a licensing deal by Merck & Co.

Table 3 shows the pros and cons of the two main valuation methodologies: DCF and real options. While DCF has been the gold standard for years, real options valuation is gaining grounds and is regarded as a possible alternative in life sciences. Both methods have their advantages and drawbacks. DCF, when applied to early stage projects, generally yields negative values; nevertheless, the industry remains profitable. Consequently, managers do not trust their valuations and disregard the recommendation retrieved from the valuations. Projects in early development are continued despite their negative DCF values. This often translates into a general refusal of quantitative methods. As soon as it comes to licensing and M&A, companies are in urgent need of a valuation method that displays the correct value of early stage projects. Real options valuation, on the other hand, has been developed to overcome the shortfalls

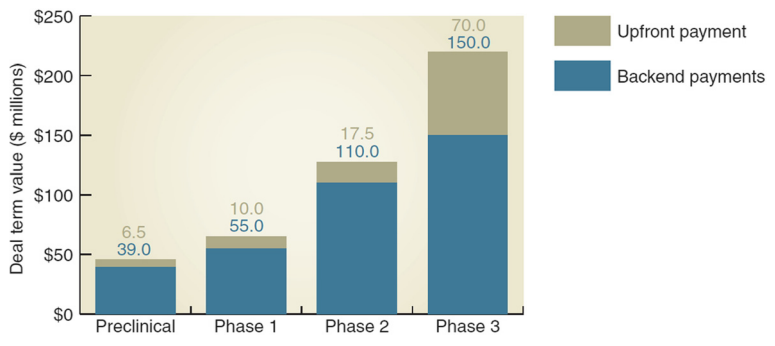


Fig. 5 Common deal terms by development stage (Source: Adapted Recombinant Capital) (Kessel and Frank 2007)

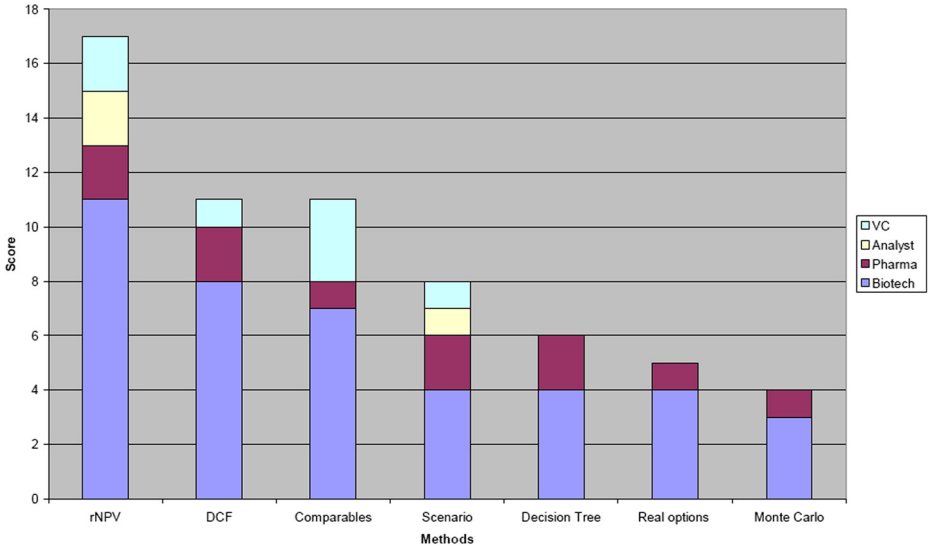


Fig. 6 Valuation methods used by biotech, pharma companies, analysts, and VC firms (Puran 2005)

of DCF; however, it is still regarded as too complex and highly theoretic, compared to the easy-to-use DCF method. Today, there is no standard on how to apply the method to life sciences valuation.

Table 4 shows the main pros and cons of the four methods of the real options valuation methodology. All four methods of the real options methodology yield the same result, but the ways to achieve it are different. In case of the formula and finite difference methods, the calculation process is similar to a black box,

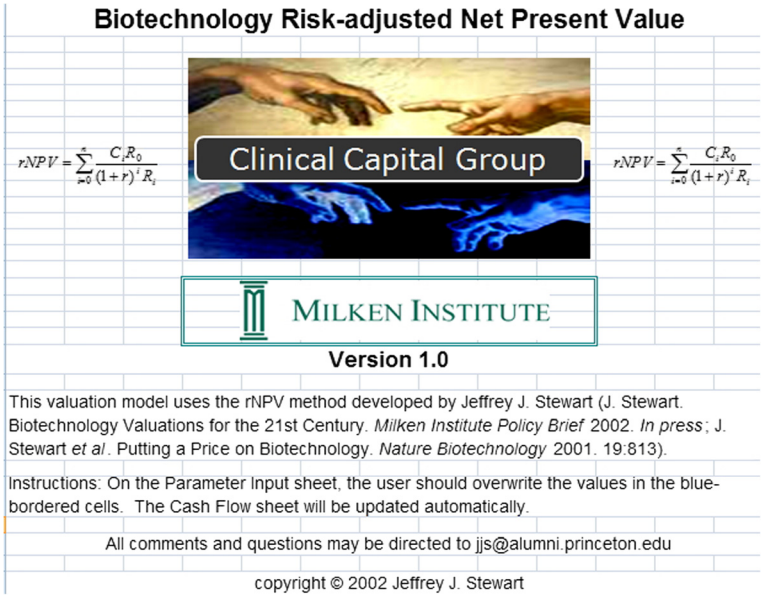


Fig. 7 Excel application to apply the rNPV methodology developed by Dr. Jeffrey J. Stewart of the Milken Institute (Stewart et al. 2001)

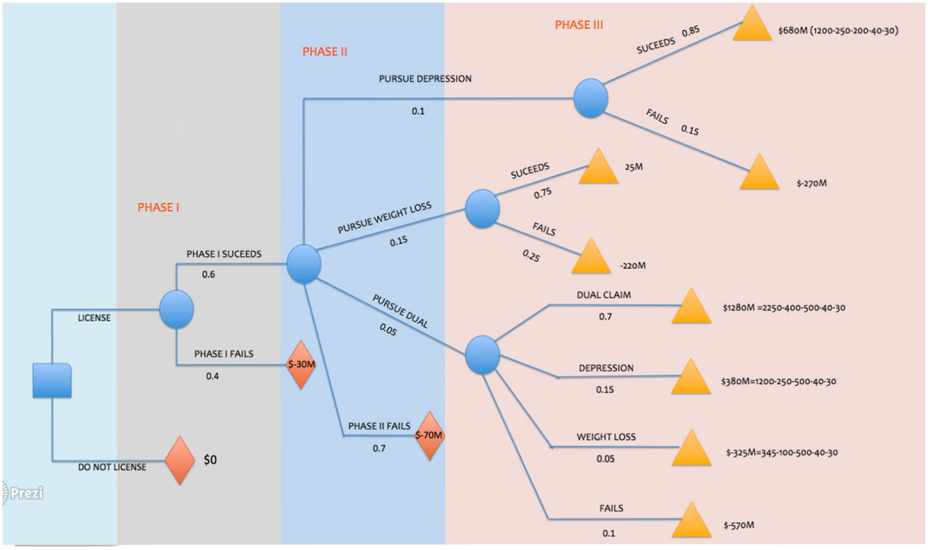


Fig. 8 An example of the application of the decision alternative and tree methodology (Cho 2004)

as it is not visible, and here, it is not helpful to use a formula. In case of the simulations method, it gives a good impression about the uncertainty of the value and is, therefore, an excellent risk measurement too1. However, the process of the simulations method is time-consuming and carries a path-dependency problem. In case of the trees method, it is easy to understand and visualize what can happen to the market, but the link to the value drivers continues to be missing.

Review of preceding research

The prevailing wisdom in the biotech industry is that the main factor driving the size of a deal is the development phase—whether preclinical, clinical, or approval. Because of this, the attrition rate of each development phase is used in the eNPV valuation in the life sciences area. Table 5 shows an example of the process to derive the risk-adjusted added-value pharmaceutical NPV from the attrition rate (Blair 2008). The eNPV (rNPV) value can be derived by multiplying the attrition rate of each development phase of the drug to the NPV in the table.

Table 3 Main pros and cons of the two main valuation methodologies (Bogdan and Villiger 2010)

	Advantages	Disadvantages
DCF	Easy to implement and to understand	Misses the value of flexibility and market uncertainty
	Standard in all sectors of the economy	Not suitable for risk management
Real Options	Captures market uncertainty and the management's ability to react	Relies on more hypothesis and requires more data
	Suitable for risk management	Technical
	Improves strategic thinking if properly understood	

Table 4 Main pros and cons of the four methods of real options valuation methodologies (Bogdan and Villiger 2010)

Method	Advantages	Disadvantages
Formula	Easy to use	Calculation process not visible
	Fast	Only for simple option structures
	Sensitivities	Simple assumptions
Trees	Easy to understand	Rigid
	Visualisation	
	can deal with more complicated options	
Simulations	Easy to understand	Time consuming
	Visualisation	Problems with path dependency
	Can deal with more complicated assumptions	
Finite differences	Can deal with more complicated assumptions	Calculation process not visible, hard to understand
	Can deal with more complicated options	Technically demanding

$$\mathrm{eNPV} = \mathrm{Risk} \times \mathrm{NPV} = (\mathrm{Attrition\ \ Rate}/100) \times \mathrm{NPV}$$

The valuation is required to proceed the licensing agreement, and the latest attrition rate mainly used for the valuation in the life sciences area is that of Dr. Joseph A. DiMasi, as shown in Table 6 (DiMasi et al. 2010).

There is a preceding research work on the main factor driving the size of the licensing deal in the life sciences area that fully evaluated 105 biotechnology drug deals signed over the past 10 years, identifying the factors that influenced the size of the deal in a statistically significant manner and then comparing these results with the opinions of a panel of industry leaders actively involved in the out-licensing of products and technologies (Arnold et al. 2002). According to the paper, there are 6 factors that influence the value of a licensing deal, and the ranking of factors from the manager panel of 16 biotechnology leaders is available, as shown in Table 7. Here, the ranking of the factors for influencing the deal size follows this order: development phase, drug class, contract type, contract scope, licensee, and molecular structure. These factors can be the candidates for the input to estimate the size of a licensing deal in the life sciences area. In the same paper, other value drivers, like the market, strategies, competition, intellectual property (IP), novelty, and so on, can also be found, as shown in Table 8. This study considers the

Table 5 Risk-adjusted added-value pharmaceutical net present value (NPV) (Blair 2008)

Trial phase				Cumulative risk	NPV ($US million)		Risk adjusted eNPV ($US million)
II	III	Pre-registration	Registration		Base-case	CDx enhanced	
Baseline attrition rates[a]							
0.52	0.76	0.89	0.94	0.331	892		295
CDx adjusted attrition rates[b]							
0.57	0.81	0.4	0.99	0.429		2694	1157

[a] Data on file at PJB PharmaPredict (http://www.pjbpubs.com/pharmaprojects_plus/predict.htm) and EvaluatePharma® (http://www.evaluatepharma.com/)
[b] Primary research with industry experts
CDx = companion diagnostic test; eNVP = expected NPV

Table 6 Attrition rate (DiMasi et al. 2010)

♦ Preclinical to IND: 70 %	Start	End	Probability
♦ Phase I to Phase 2: 71 %	PC	Approval	13.3 %
♦ Phase 2 to Phase 3: 45 %	P1	Approval	19.0 %
♦ Phase 3 to NDA/BLA: 64 %	P2	Approval	26.8 %
♦ NDA/BLA to approval: 93 %	P3	Approval	59.5 %
	NDA/BLA	Approval	93.0 %

likely candidates for the input to estimate the size of a licensing deal in the life sciences area as the development phase, drug class, market size, IP, and molecular structure, taking data availability and the ease of quantification into consideration.

As a likely candidate for the input to estimate the size of a licensing deal in the life sciences area, there is a drug classification of over 300 kinds according to Drugs.com, which is the largest, most widely visited, independent medicine information Web site available on the Internet (Drugs.com 2015). However, such a detailed drug classification is not available in the licensing deal data; thus, a simpler drug classification like that in Table 9 is needed for this study. Table 9 shows the main drug classification by Drugs.com, and there are 21 main drug classes.

There is only one case to perform the regression analysis on the work on evaluating pharmaceutical licensing agreements (Arnold et al. 2002; Rogers and Maranas 2005), but the analysis for historical licensing data was for identifying the factors that most affect a deal's financial terms (Arnold et al. 2002; Rogers and Maranas 2005). In reviewing the preceding research, there have been no cases where a regression analysis could be performed to estimate the proper royalty rate and up-front payment using the formula derived from the regression of the dataset of historical licensing data.

This study is believed to be the first case to estimate the royalty rate and up-front payment using the formula derived from the regression of the dataset of historical licensing data, and can therefore be used as a simple tool to answer the basic question, "How can we find the formula to estimate the proper royalty rate and up-front payment using the data I can get simply as input?" It can also be a good starting point to be referred to by a manager in case of negotiations in pharmaceutical licensing deals for a specific drug class.

Table 7 Manager panel's ranking of factors that influence the value of a licensing deal (Arnold et al. 2002)

Rank	Driver	Score[a]
1	Phase of molecule	1.13
2	Therapeutic area	1.56
3	Type of agreement	1.94
4	Scope of agreement	1.94
5	Type and reputation of buyer	1.94
6	Type of molecule	2.19

[a]Scores are ranked from 1 (most important) to 3 (least important)

Table 8 Manager panel's perceptions about the importance of value drivers (Arnold et al. 2002)

Value driver	Percentage of respondents mentioning it as important
Market, including market size for the licensing agreement, market potential, or patient population	88 %
Stage-phase or stage in the development of the product	69 %
Strategy, including issues of "fit" of the product in the company's pipeline and franchises, impact on the current business, and synergies	44 %
Competition-competitive markets, competition from other partners for the product, and competitive products	38 %
Reputation of the licensee or licensor, including inventor and management talent	31 %
Investment-financial needs to develop the product	25 %
Intellectual property-gaining key patents or trade secrets	25 %
Novelty-innovative merit of the product (revolutionary or evolutionary)	19 %
Control of the development and commercialization of a product	6 %
Comparable deal valuations for similar products/technologies	6 %
Reimbursement–ability or willingness of customers (payers or patients) to pay for the product	6 %

Research design and scope and limitation

Research design

The purpose of this research is to derive the formula to predict royalty-related data, such as running royalty rate (back-end payments) and up-front payment (up-front fee + milestones), using the attrition rate for the corresponding development

Table 9 Main drug classification (Drugs.com 2015)

Drug class- Tre view	
1	Allergenics
2	Alternative medicines
3	Anti-infectives
4	Antineoplastics
5	Biologicals
6	Cardiovascular agents
7	Central nervous system agents
8	Coagulation modifiers
9	Gastrointestinal agents
10	Genitourinary tract agents
11	Hormones
12	Immunologic agents
13	Medical gas
14	Metabolic agents
15	Miscellaneous agents
16	Nutritional products
17	Plasma expanders
18	Psychotherapeutic agents
19	Radiologic agents
20	Respiratory agents
21	Topical agents

phase of the drug candidate within a specific drug class, such as anticancer (antineoplastics) or cardiovascular, and the revenue data of the license buyer (licensee) using regression analysis. Another purpose is to find the relationship between the formula to predict royalty-related data and eNPV.

According to the preceding research, the main factors to drive the size of licensing deals in the life sciences area are development phase, drug class, contract type, contract scope, licensee, molecular structure, market, strategies, competition, IP, and novelty (Arnold et al. 2002). Market size, licensee revenue, molecular structure, and IP can be converted to numerical value and can be used for the input for prediction for royalty-related data such as running royalty rate (back-end payments) and up-front payment (up-front fee + milestones). In the case of market size, it requires a great amount of time to estimate the proper market size for the subclass of a drug class (e.g., epidermal growth factor, anticancer immunity, ovarian cancer, alpha interferon as a subclass of the anticancer drug class). In the case of molecular structure, it requires professional chemical software to convert chemical structure into numeric code and requires the collection of molecular structure information for the drug candidate. In the case of IP, identifying what could be the unique descriptor for the drug-related patents for input for the X-axis of regression requires more thought (e.g., the technology cycle time median value for the International Patent Classification (IPC) code can be the descriptor candidate). This study selected drug class, licensee revenue, and attrition rate for the development phase as descriptors for the input for the X-axis of regression.

The main research procedure is divided into three steps as shown in Fig. 9: data collection, data normalization, and regression analysis.

Step 1. Collection of data such as the running royalty rate, up-front fee, milestones, licensor, licensee, the revenue of licensee, the corresponding drug class, and the development phase in drug licensing deals

This study collected the data for two drug classes in the format of Table 10: anticancer and cardiovascular. Data collection is based on the following resources: ① Book: Royalty Rates for Pharmaceuticals and Biotechnology, 8th Edition Published by IPRA Inc (2012);

② Book: Intellectual Property: Valuation, Exploitation, and Infringement Damages, written by Russell L. Parr and Smith (2005); ③ Site for checking the deal condition: http://www.sec.gov/ (U.S. Securities and Exchange Commission);

④ Site for checking the development phase: https://clinicaltrials.gov; ⑤ Site for

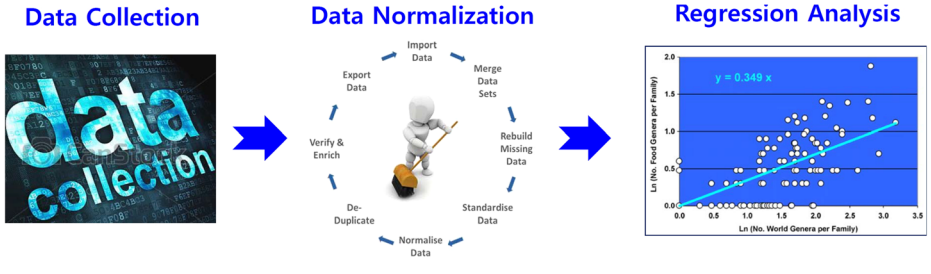


Fig. 9 Procedure and steps to carry out research

checking the revenue of Licensee: http://www.google.com/finance and http://finance.yahoo.com/; ⑥ Site to retrieve the needed data: http://www.google.com.

Step 2. Preparation of dataset ready for regression analysis via data normalization like in Figs. 10 and 11

Step 3. Regression analysis to investigate the relationship between (attrition rate * licensee revenue) and up-front payment (up-front fee + milestones) and the relationship between attrition rate * licensee revenue and back-end payment (running royalty rate)

Used software: ① Preliminary analysis for checking rough type: Microsoft Office Excel 2007

② Main analysis: open-source statistical software

Regression 1: X-axis = (attrition rate * licensee revenue)/100

Y-axis = up-front payment (up-front fee + milestones) [Unit: USD]

Regression 2: X-axis = (attrition rate * licensee revenue)/100

Y-axis = back-end payment (running royalty rate) [Unit: USD]

Scope and limitation of research

The scope of this research is to derive the formula to predict royalty-related data, such as running royalty rate (back-end payments) and up-front payment (up-front fee + milestones), using the attrition rate for the corresponding development phase of the drug candidate for the anticancer (antineoplastics) or cardiovascular drug class and the revenue data of the license buyer (licensee), and to investigate the relationship between the formula to predict royalty-related data and eNPV. Statistically speaking, this research derives the formula to predict royalty-related data using a single independent variable like royalty rate and up-front payment, (attrition rate * licensee revenue)/100]. Also, this research selected drug class, licensee revenue, and attrition rate for the development phase as descriptors for the input for the X-axis of regression. This study is limited to the relationship between the two drug classes of anticancer (antineoplastics) and cardiovascular and royalty-related data. For further studies, it is advised that the relationship be analyzed in more detail to involve more drug classes and royalty-related data using several independent variables through software like SPSS or SAS.

Table 10 Example of data collection (IPRA Inc 2012)

#	Development stage	Upfront fee	Milestones	Royalty rate	Contract year	SubClass
1	Pre-Clinical or Phase I	$500,000		4 % of sales	2006	Lyophilized docetaxel
2	Phase I/II	35 M$	372 M$	Low double digit	2009	MEK inhibitors
3	Pre-Clinical	$30,000	$155,000	1 %~2 % of sales	2005	Immunotherapy
4	Pre-Clinical	$100,000		8.5 % of sales	2001	Platinum complex
5	Pre-Clinical			3.5 % of sales	2006	Pseudomonas exotoxin
6	Pre-Clinical			1.5 % of sales	2002	Lm-LLO cancer
7	Phase II	$3,000,000	10 M$	0	1997	Immune system cancer product
8	Phase II	25 M$	400 M$	35 % of sales	2005	VEGF Trap

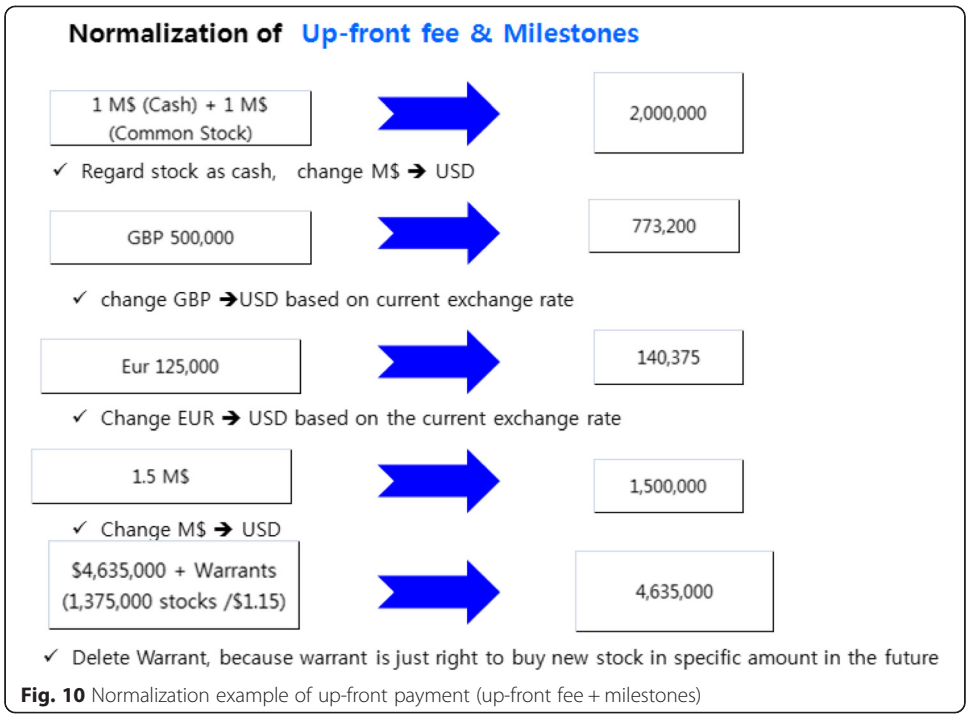


Fig. 10 Normalization example of up-front payment (up-front fee + milestones)

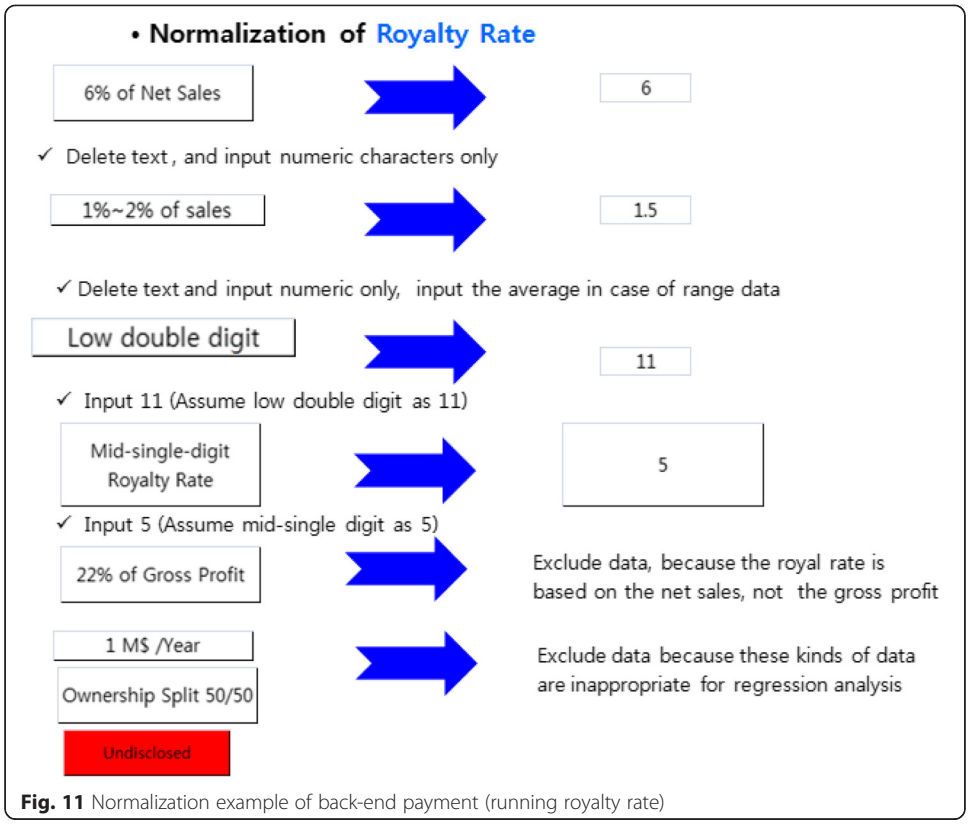


Fig. 11 Normalization example of back-end payment (running royalty rate)

Table 11 Distribution of the development phase in the anticancer (antineoplastics) dataset

Development phase	No. of hit	%
in vitro activity	4	5.56
Preclinical	9	12.50
Phase I	11	15.28
Phase I/II	10	13.89
Phase II	19	26.39
Phase II/III	2	2.78
Phase III	14	19.44
NDA/BLA	3	4.17
Total deal number	72	100.00

Analysis of dataset

Analysis of anticancer (Antineoplastics) dataset

As shown in Table 11 and Fig. 12, the number of the phase II-related stage deals (phase I/II, phase II, phase II/III) is dominant (over 43 %) in the anticancer (antineoplastics) dataset collected.

The average of the up-front fees in the anticancer (antineoplastics) dataset collected is USD 6,123,474, and the average of the milestones in the anticancer dataset is USD 30,088,181. With this, the average royalty rate in the anticancer dataset is 8 % and is slightly higher than average royalty in pharma/biotech license deals in Table 13 and lower than the average royalty rate (11.5 %) of phase II in Table 14.

Tables 12, 13, 14, and 15 show several industry guidelines for royalty rates published by several groups.

Analysis of cardiovascular dataset

As shown in Table 16 and Fig. 13, the number of the phase III stage deals and NDA/BLA stage deals is dominant (over 61 %) in the cardiovascular dataset collected.

The average of the up-front fees in the cardiovascular dataset collected is USD 10,886,596, and the average of the milestones in the anticancer dataset is USD 10,167,742.

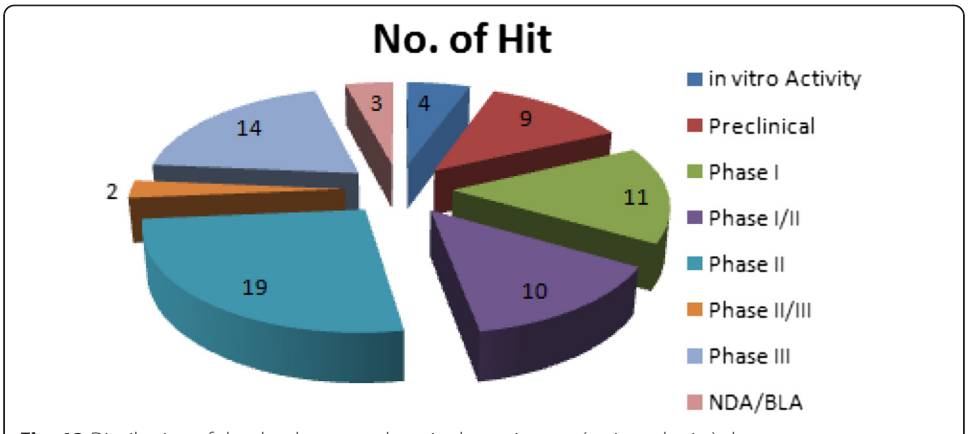


Fig. 12 Distribution of the development phase in the anticancer (antineoplastics) dataset

Table 12 Industry guideline for royalty rates (Source: 1998, Dr. Michael, CASRIP Newsletter) (IPRA Inc 2012)

Industry	Royalty rate
Electronics	0.5–5 %
Machinery	0.33–10 %
Chemical	2–5 %
Pharmaceutical	2–10 %

The average royalty rate in the anticancer dataset is 10 % and is slightly higher than the average royalty in pharma/biotech license deals in Table 13 and slightly lower than the average royalty rate (15 %) of Phase III; it is much lower than the average royalty rate (20 %+) of launched products in Table 16.

Regression analysis

Preliminary regression analysis of anticancer (Antineoplastics) dataset

To detect and exclude outliers (an observation point that is distant from other observations in statistics) and to find proper regression models for a specific dataset, a preliminary regression analysis using Microsoft Excel is needed. Figures 18 and 19 show some outliers, and a linear regression model does not fit the anticancer dataset.

The following items are the X-axis and Y-axis input information in the regression analysis in Figs. 14 and 15.

Figure 14: X-axis = (attrition rate * licensee revenue)/100
Y-axis = up-front payment (up-front fee + milestones) [Unit: USD]
Figure 15: X-axis = (attrition rate * licensee revenue)/100
Y-axis = back-end payment (running royalty rate) [Unit: USD]

The deal data from the preliminary regression was excluded if the normalization of the "royalty rate" data is not possible (a total six sets of deal data).

This study selected outliers in the following cases according to the result from the preliminary regression analysis of the anticancer (antineoplastics) dataset; such outliers from the main regression analysis in section Main regression analysis of anticancer dataset by open-source statistical software were excluded.

① If "up-front payment" has a value of 0 (zero), it is selected as an outlier (a total of 15 outliers).

Table 13 David Weiler's royalty rate based on 458 deals in the pharma/biotech license agreement (Source: www.royaltysource.com) (IPRA Inc 2012)

485 deals	Rate
Average royalty	7 %
Median royalty	5 %
Maximum royalty	50 %
Minimum royalty	0 %

Table 14 Medius Associates' royalty rate by development stage (Source: www.medius-associate.com) (IPRA Inc 2012)

Development stage	Royalty rate
Pre-clinical	0–5 %
Phase I	5–10 %
Phase II	8–15 %
Phase III	10–20 %
Launched product	20 % +

② If "(attrition rate * licensee revenue)/100" has a value of more than 5,000,000,000, it is selected as an outlier (a total of 3 outliers),

Thus, the number of deal data used for the main regression analysis to develop the model for prediction is 48.

The deal data from the preliminary regression was excluded if the normalization of the "royalty rate" data is not possible (a total of seven sets of deal data).

Outliers were selected in the following cases according to the result from the preliminary regression analysis of the anticancer (antineoplastics) dataset, and such outliers from the main regression analysis in section Main regression analysis of anticancer dataset by open-source statistical software were excluded.

① If "(attrition rate * licensee revenue)/100" has a value of more than 1,000,000,000, it is selected as an outlier (a total of eight outliers).

Thus, the number of deal data used for the main regression analysis to develop the model for prediction is 57.

Main regression analysis of anticancer dataset by open-source statistical software

The used regression model for investigating the relationship between (attrition rate * licensee revenue)/100 and up-front payment (up-front fee + milestones) is "Rational Model, 3 Parameter Type 4 Regression", having the following formula type and curve type in a statistical software; its graph is as shown in Fig. 16, and its prediction formula follows Equation 1.

$$[\text{Formula type}] \qquad y = \frac{a + x}{b + cx}$$

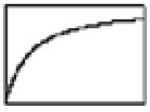
[Curve type] 

Table 15 Mark G. Edwards' royalty rate guideline (Source: www.recap.com) (IPRA Inc 2012)

Average royalty by R&D stage	
R&D Stage	Rate
Discovery	6.4 %
Lead Molecule	8.1 %
Pre-Clinical	11.3 %

Table 16 Distribution of the development phase in the cardiovascular dataset

Development	No. of hit	%
in vitro activity	3	9.68
Preclinical	3	9.68
Phase I	4	12.90
Phase II	2	6.45
Phase III	7	22.58
NDA/BLA	12	38.71
Total deal number	31	100.00

Equation 1

$$Y = (a + X)/(b + c * X) = (-133620928.7 + X)/(-3.990489631 + 2.04191E{-}08 * X)$$

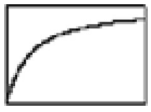
$R^2 = 0.384618$

X = (attrition rate * licensee revenue)/100

Y = up-front payment (up-front fee + milestones) [Unit: USD]

The used regression model for investigating the relationship between (attrition rate * licensee revenue)/100 and royalty rates is "Rational Model, 3 Parameter Type 2 Regression" having the following formula type and curve type in a statistical software; its graph is as shown in Fig. 17, and its prediction formula follows Equation 2.

[Formula type] $y = \frac{1 + ax}{b + cx}$

[Curve type] 

Equation 2

$$Y = (1 + a * X)/(b + c * X) = (1 + (-5.14147E{-}09) * X)/(0.128436559 + -6.37E{-}10 * X)$$

$R^2 = 0.223928$

X = (attrition rate * licensee revenue)/100

Y = royalty rates [Unit: %]

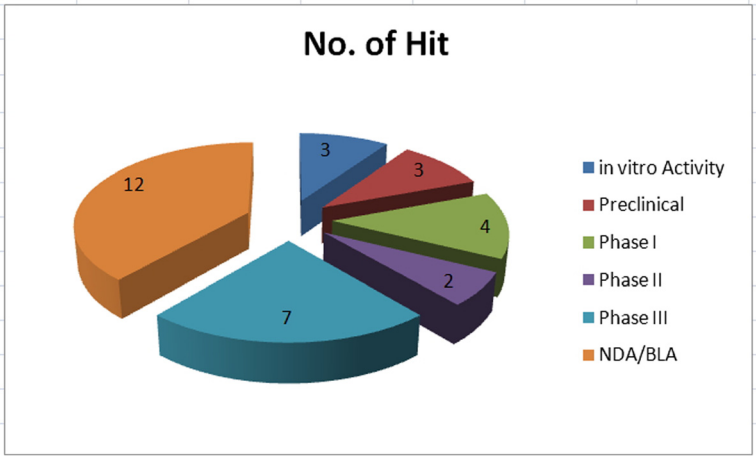


Fig. 13 Distribution of the development phase in the cardiovascular dataset

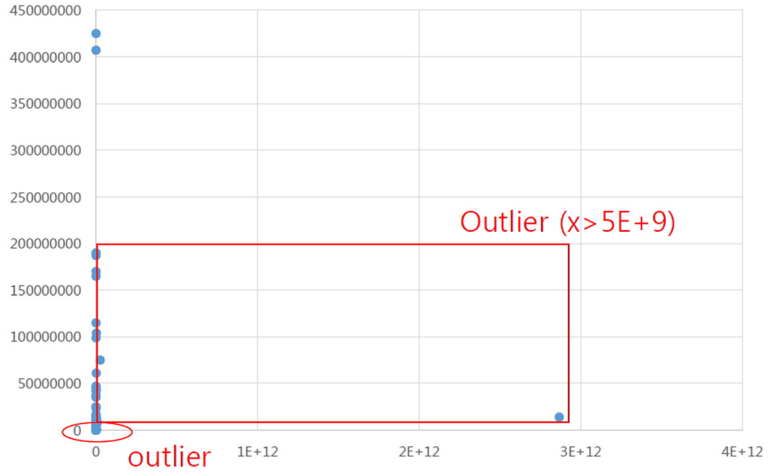


Fig. 14 Preliminary regression analysis of the anticancer (antineoplastics) dataset for up-front payment (up-front fee + milestones)

Preliminary regression analysis of cardiovascular dataset

To detect and exclude outliers (an observation point that is distant from other observations in statistics) and to find proper regression models for a specific dataset, a preliminary analysis using Microsoft Excel is needed. Figures 22 and 23 show some outliers, and a linear regression model does not fit the cardiovascular dataset.

The following items are the X-axis and Y-axis input information in the analysis in Figs. 18 and 19.

Figure 18: X-axis = (attrition rate * licensee revenue)/100
Y-axis = up-front payment (up-front fee + milestones) [Unit: USD]

Figure 19: X-axis = (attrition rate * licensee revenue)/100
Y-axis = back-end payment (running royalty rate) [Unit: USD]

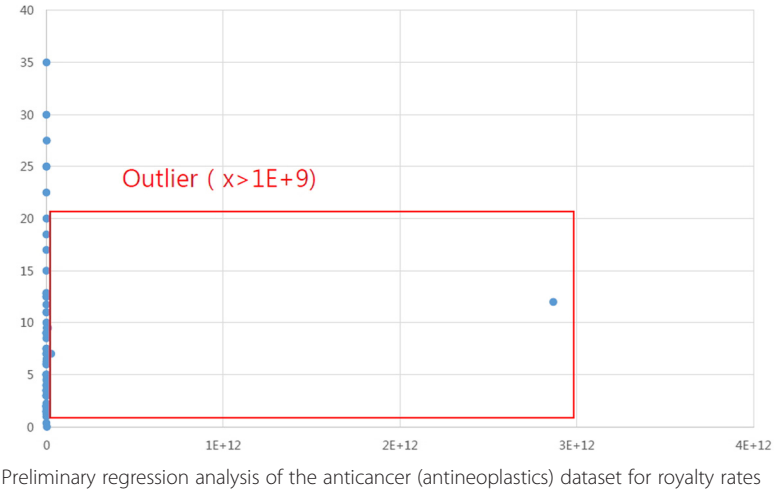


Fig. 15 Preliminary regression analysis of the anticancer (antineoplastics) dataset for royalty rates

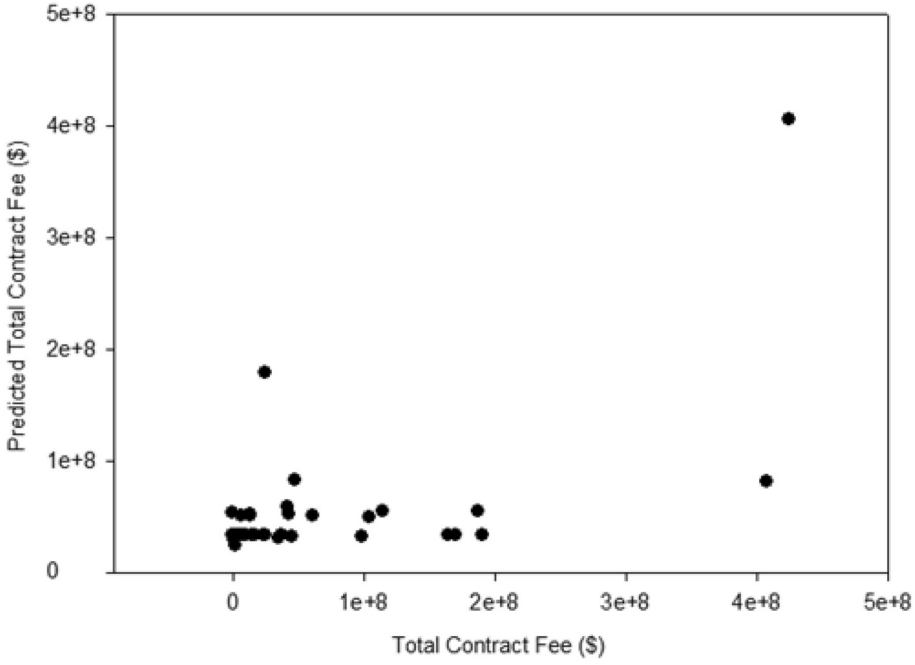


Fig. 16 Main regression analysis of the anticancer dataset by statistical software for up-front payment (up-front fee + milestones): X-axis (real up-front payment) vs. Y-axis (predicted up-front payment)

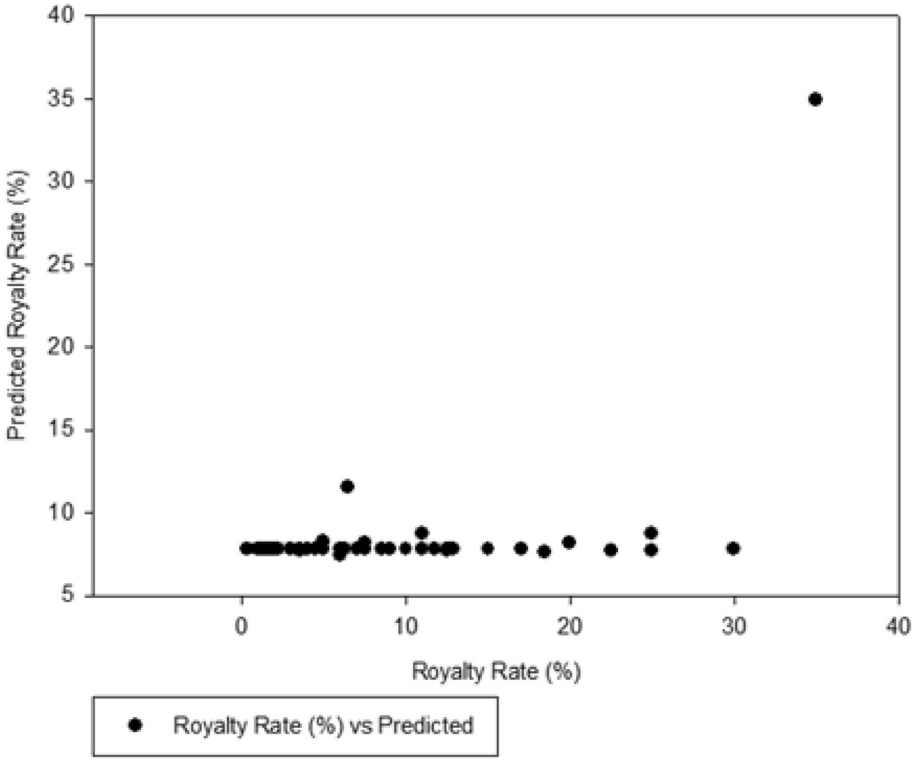


Fig. 17 Main regression analysis of the anticancer dataset by statistical software for royalty rates: X-axis (real royalty rate) vs. Y-axis (predicted royalty rate)

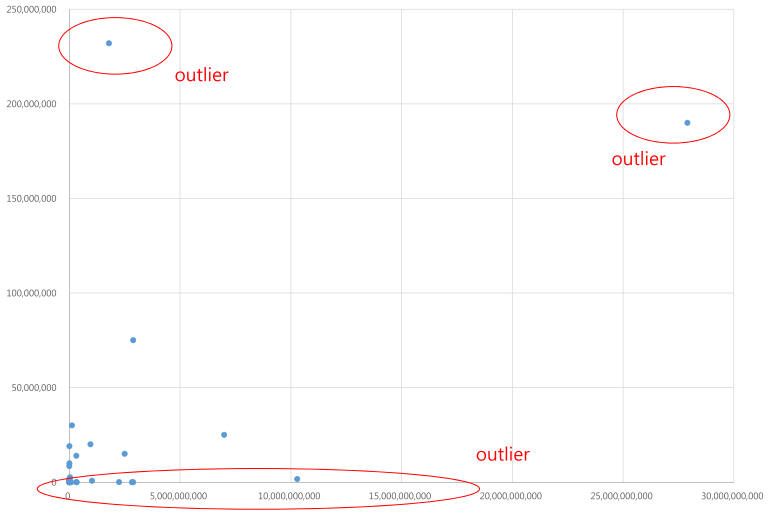


Fig. 18 Preliminary regression analysis of the cardiovascular dataset for up-front payment (up-front fee + milestones)

The deal data from the preliminary regression was excluded if the normalization of the "royalty rate" data is not possible (a total of one set of deal data).

Outliers were selected in the following cases according to the result from the preliminary regression analysis of the cardiovascular dataset, and such outliers from the main regression analysis in section Main regression analysis of cardiovascular dataset by open-source statistical software were excluded.

① If the "up-front payment" has a value under 50,000, it is selected as an outlier (a total of 12 outliers).
② If the "up-front payment" has a value of more than 190,000,000, it is selected as an outlier (a total of 2 outliers).

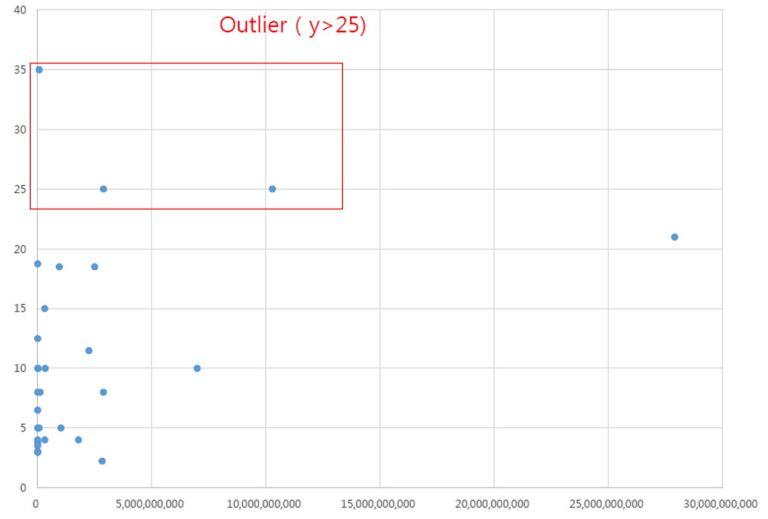


Fig. 19 Preliminary regression analysis of the cardiovascular dataset for royalty rates

Thus, the number of deal data used for the main regression analysis to develop the model for prediction is 16.

The deal data from the preliminary regression was excluded if the normalization of the "royalty rate" data is not possible (a total of one set of deal data).

Outliers were selected in the following cases according to the result from the preliminary regression analysis of the cardiovascular dataset, and such outliers from the main regression analysis in section Main regression analysis of cardiovascular dataset by open-source statistical software were excluded.

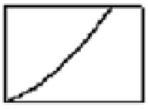
① If the "royalty rate" has a value of more than 25, it is selected as an outlier (a total of 3 outliers).

Thus, the number of deal data used for the main regression analysis to develop the model for prediction is 27.

Main regression analysis of cardiovascular dataset by open-source statistical software

The used regression model for investigating the relationship between (attrition rate * licensee revenue)/100 and up-front payment (up-front fee + milestones) is the "Polynomial Model, Quadratic-type Regression" having the following formula type and curve type in a statistical software; its graph is as shown in Fig. 20, and its prediction formula follows Equation 3.

[Formula type] $Y = y0 + ax + bx^2$

[Curve type] 

Equation 3

$$Y = y0 + ax + bx^2 = 7.103e + 6 + (-3.990489631) * X + (-1.536e-12) * X^2$$

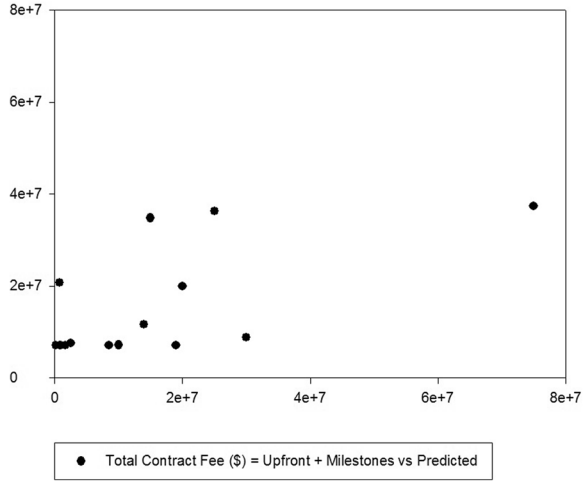


Fig. 20 Main regression analysis of the cardiovascular dataset by statistical software for up-front payment (up-front fee + milestones): X-axis (real up-front payment) vs. Y-axis (predicted up-front payment)

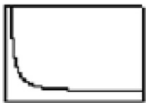
$R^2 = 0.413879$

X = (attrition rate * licensee revenue)/100

Y = up-front payment (up-front fee + milestones) [Unit: USD]

The used regression model for investigating the relationship between (attrition rate * licensee revenue)/100 and royalty rates is "Polynomial Model, Inverse Second Order-type Regression" having the following formula type and curve type in a statistical software; its graph is as shown in Fig. 21, and its prediction formula follows Equation 4.

[Formula type] $y = y0 + a/x + b/x^2$

[Curve type] 

Equation 4

$$Y = y0 + a/X + b/X^2 = 9.262e + 0 + (-8.528 + 5)/X + 1.744e + 10/X^2$$

$R^2 = 0.287886$

X = (attrition rate * licensee revenue)/100

Y = royalty rates [Unit: %]

Discussion

A regression analysis was carried out to estimate up-front payments and royalty rates for two datasets of anticancer (antineoplastics) and cardiovascular drug classes. In the case of the prediction of up-front payments, the models for predicting having an R^2 value of 0.384618 for the anticancer (antineoplastics) dataset and an R^2 value of 0.413879 for the cardiovascular dataset were obtained through statistical analyses. In case of the prediction of royalty rates, the models for predicting having an R^2 value of 0.223928 for the anticancer (antineoplastics) dataset and an R^2 value of 0.287886 for

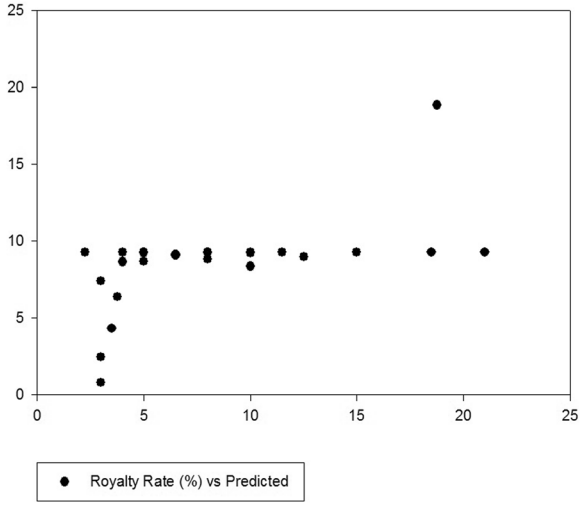


Fig. 21 Main regression analysis of the cardiovascular dataset by statistical software for royalty rates: X-axis (real royalty rate) vs. Y-axis (predicted royalty rate)

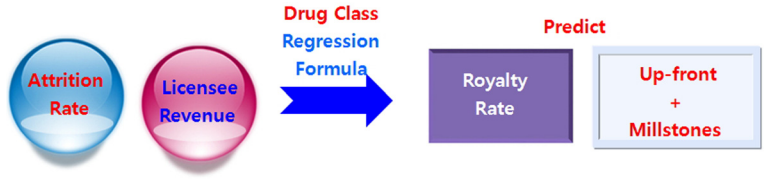


Fig. 22 Overview of the study's process

the cardiovascular dataset were obtained through statistical analyses. Figure 22 shows the overview of the process of this study.

This study was presented with many limitations to reasonably determine the variables for prediction because up-front payments and royalty rates are determined by various environmental variables in the field. However, this study developed a prediction model having an R^2 value of about 0.4 if the variables of "attrition rate * licensee revenue" are used. This is a "statistically significant" finding, and it shows the importance of the variables of "attrition rate * licensee revenue" for determining up-front payments. Thus, the said variables can be used as the solid basis for evaluating up-front payments in the future.

In the case of the prediction of royalty rates, this study achieved a low R^2 value of about 0.25 in the statistical analysis using the variables of "attrition rate * licensee revenue". This means that it is not possible to perform the analysis reasonably using the said variables only. Because of this, the introduction of other variables is necessary for the analysis of royalty rates.

It is possible to identify the relationship between the eNPV and input for the regression formula as shown in Fig. 23. This can be used for predicting rough eNPV using the licensee's revenue and the licensee's maximum reserve for the project according to the development phase and drug class.

Conclusion

Summary

This study yielded meaningful results as it aimed to create a tool to predict royalty rate and up-front payment (up-front fee + milestones) only using knowledge on the development phase and its attrition rate, drug class, and licensee's revenue, which can easily be known.

It is possible to predict rough eNPV using the licensee's revenue and the licensee's maximum reserve for the project according to the development phase instead of the attrition rate for the development phase.

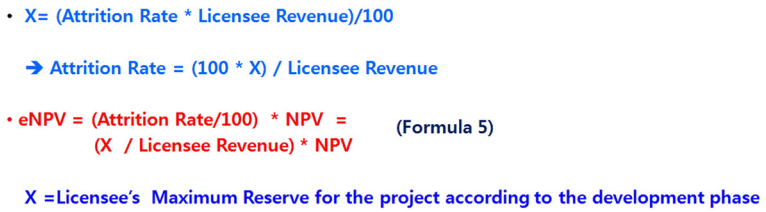


Fig. 23 The relationship between the eNPV and input for the regression formula

Implications

This study allowed valuation of a drug specific to a drug class and proved that the royalty rate can be a variable according to drug class and licensee.

Topics for further research

Further in-depth research is necessary for the following topics in the future.

① The relationship to involve more drug classes and royalty-related data.
② Regression analysis using several independent variables through software such as SPSS or SAS.
③ Regression analysis to investigate the relationship between royalty-related data and more input descriptors such as market size, molecular structure (numerical code for sub-structure/fragment), and IP (technology cycle time median value for the IPC code).

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