A formula for drug licensing deals

Could a mathematical model predict the total value of licensing deals?

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Licensing deal transactions are confidential, and there can be long waits before royalties from market sales are realized, so it can be difficult to make generalizations about their total value and distribution structure. Conversely, details of upfront payments are a little more readily available and display sensitivity to the development phase of the drug[1,2].

So, could a mathematical model using upfront payments be developed to predict the total value of licensing deals?

To address this question, we collected data from in-licensing deals where the upfront payments, milestones—investigational new drug (IND), phase 1, phase 2, phase 3, approval, registration and sales—and royalties from market sales were recorded in US dollars. The data were collected from the global Biotechgate database (www.biotechgate.com), which at the time of analysis had information on 94,885 assets (including 54,946 therapeutics and 8,411 technologies), 63,460 companies, 30,826 out-licensing opportunities, 23,902 financing rounds, and 22,684 licensing agreements.

Overall, 2,942 licensing deals totaling $905.3 billion were analyzed—all of which were agreed in 2010 or thereafter. Of those deals, 86.6% included upfront payments, 85.8% included milestone payments, and 65.5% included royalties from sales (Fig. 1a). The specific amounts were disclosed for 80.0% of upfront payments, 75.1% of milestone payments, and 9.7% of royalties from sales. Interestingly, 59.1% were listed as having exclusive agreements.

From the 2,942 deals analyzed, three sets of formulae were generated and then united to create a 'licensing deal formula'.

Initially, we calculated the average values for the upfront payments (y, $58.6 million, $n = 2{,}353$) and the milestone payments comprising IND, (a_1, $4.6 million, $n = 45$), phase 1 (a_2, $5.6 million, $n = 40$), phase 2 (a_3, $5.0 million, $n = 66$), phase 3 (a_4, $20.3 million, $n = 89$), approval (a_5, $41.4 million, $n = 127$), registration (a_6, $120.4 million,

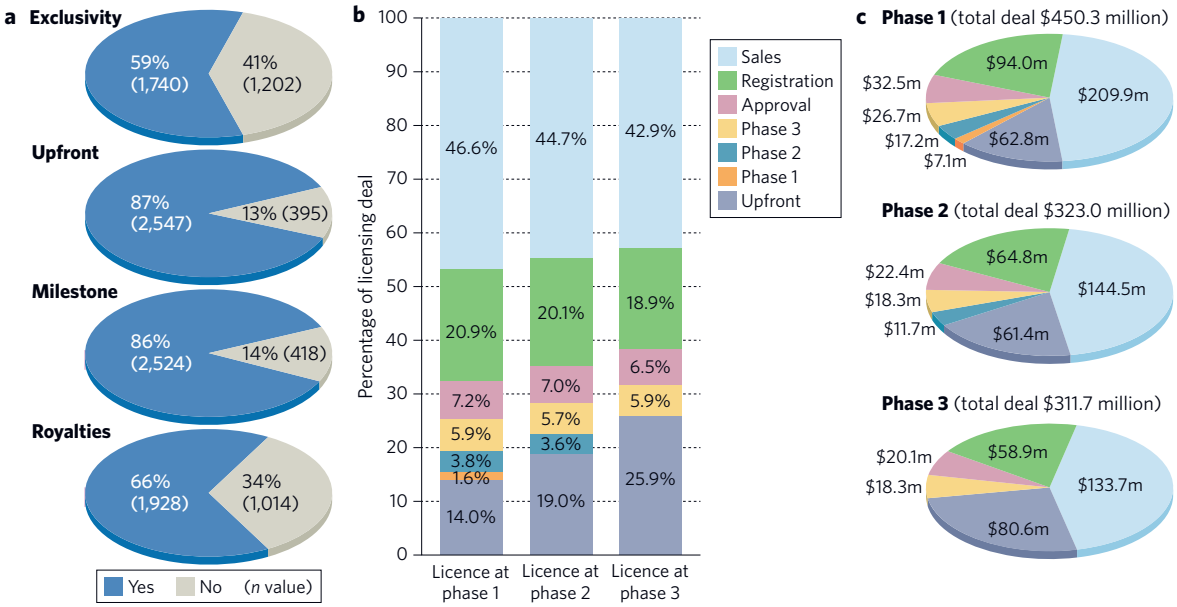

Fig. 1 | Demographics, structures, and sizes of deals analyzed. a, Deals with 'Yes' or without 'No' exclusive agreements, upfront payments, milestone payments, and royalties on sales are shown both as percentages (%) and as exact numbers (indicated in parentheses). The total number of deals analyzed was 2,942. **b**, Based on the average upfront payments for phases 1 ($62.8 million), 2 ($61.4 million), and 3 ($80.6 million), the respective deal structure values for licensing were calculated using the licensing deal formula. **c**, Using the average upfront payments for phases 1, 2, and 3, the individual payments and total deal sizes were calculated as $450.3 million, $323.0 million, and $311.7 million, respectively.

$n = 482$), and sales (a_7, $275.2 million, $n = 301$), which summed (Σ) to give a total of $531.1 million. The relationship between the average upfront payments and the average milestone payments was then formulated (see the *a* values in Fig. 2).

Next, linear regressions between upfront payments and development milestone payments or sales milestone payments were calculated. The correlation coefficients for the slopes ($b_{1–7}$) with their intercepts ($c_{1–7}$) were recorded for each linear regression. Here, one regression for each milestone stage, *i*, was calculated. These coefficients were then formulated (see the *b* and *c* values in Fig. 2). Our analysis revealed a moderate correlation (R^2) between upfront payments and milestone payments for the earlier development phases (i.e., IND and phases 1–3). As expected, the correlation between upfront payments and later stages of development (i.e., approval, registration, and sales payments) was weaker (Fig. 2a). In all cases, the probability values for these correlations were <0.01 or better.

The total milestone size per deal stage (w_j) was forecast by an additional regression between upfront payments and total milestone payments. Here, one regression across all deal stages, *j*, was calculated. This analysis used the upfront coefficient, *d*, and the deal-stage coefficients, $e_{1–5}$, for stages 1–5 (i.e., IND, phase 1, phase 2, phase 3, and sales) (Fig. 2b). In this case, the probability values for these correlations were <0.001 or better.

Lastly, using the calculated average payments ($a_{1–7}$) and the coefficient values ($b_{1–7}$, $c_{1–7}$, *d*, $e_{1–5}$) (Fig. 2), we devised a licensing deal formula that, using upfront payments, predicted the percentage (%) split of payments for milestones and upfront, as well as the total deal size. The licensing deal formula calculated the size of payments for all development milestones and sales milestones across all stages (see the full equation in Fig. 2c).

To test the model, we took the calculated averages of upfront payments for drugs licensed at phase 1, phase 2, and phase 3. In our previous studies, these payments had the following ranges[1,2]: early research/preclinical ($9.3–15.6 million) < phase 1 ($20.1–30.3 million) < phase 2 ($18.6–$33.7 million) < phase 3 ($23.6–$39.1 million) > drug filed ($13.5–24.9 million). The average values were as follows: phase 1 = $24.4 million; phase 2 = $25.8 million; and phase 3 = $32.7 million.

Analysis of the recent data used here gave higher average values for phase 1 ($62.8 million), phase 2 ($61.4 million), and phase 3 ($80.6 million), with a similar trend observed between the phases.

Using these average upfront payments within the licensing deal formula, the percentages of all upfront and milestone payments across all the milestone stages were calculated for deals in phases 1–3, representing typical deal structures for these deal stages (Fig. 1b). In addition to the individual payments, total deal sizes were also calculated as follows: phase 1 = $450.3 million; phase 2 = 323.0 million; and phase 3 = $311.7 million (Fig. 1c).

a

		Average (*n*)	Slope (*n*)	Intercept	R^2
		a	*b*	*c*	
IND	1	4.6 (45)	0.33 (28)	2.9	0.57
Phase 1	2	5.6 (40)	0.17 (27)	3.5	0.31
Phase 2	3	5.0 (66)	0.68 (42)	3.1	0.58
Phase 3	4	20.3 (89)	0.76 (58)	8.2	0.41
Approval	5	41.4 (127)	0.09 (94)	41.2	0.13
Registration	6	120.4 (482)	0.49 (372)	103.5	0.15
Sales	7	275.2 (301)	1.67 (247)	186.2	0.22
		y			
Upfront		58.6 (2,353)			

b

		Coefficients
		d
Upfront		0.72
		e
IND	1	272.8
Phase 1	2	342.3
Phase 2	3	217.5
Phase 3	4	173.2
Sales	5	90.2
R^2		0.42
(*n*)		(2,880)

c

$$payment\ at\ each\ stage = \left(w_j = upfront \times d + [e_j]_1^5\right) \times \left(z_i = \left(\left(\frac{[a_i]_1^7}{\sum_{i=1}^{7} a_i}\right) + \left(\frac{v_i = upfront \times [b_i]_1^7 + [c_i]_1^7}{\sum_{i=1}^{7} v_i}\right)\right) \div 2\right)$$

Fig. 2 | The licensing deal formula. a, Correlations between upfront payments and individual milestone payments. The symbols denote the following: *a* = average value of deals analyzed at each milestone stage ($ million); *b* = slope coefficients; *c* = intercept coefficients ($ million); *y* = average value of upfront deals analyzed ($ million). **b**, Linear regression between upfront payments and total milestone payments. *w* = total milestone size at each deal stage ($ million), forecast by an additional regression analysis using the upfront coefficient *d* and the deal-stage coefficient *e* for stages 1–5 (i.e., IND, phase 1, phase 2, phase 3, and sales). In this case, the intercept was set to 0 and there was a stage unknown category that is not displayed. *n* = number of deals averaged or used for linear regressions; R^2 = fit of linear regression; Ave, average. **c**, Final formula. The licensing deal formula created from correlations between upfronts, individual milestone payments and total milestone payments is shown. The *a* and *v* values for the stages reached were set to 0, such that for a compound in phase 2, the investigational new drug (IND) (a_1 and v_1) and the phase 1 (a_2 and v_2) values were set to 0. The percentages for upfront and milestone payments and the total deal size were calculated by the formula shown.

Summary of results

Taken together, our data showed that more than half of licensing deals could expect to arbitrate exclusive arrangements with a mix of upfront payments, milestone payments, and/or royalty payments on sales. There was a clear preponderance of back-loaded deals, with more than 60% of milestone payments scheduled to take place after approval.

Our findings showed that the developed formula was a reasonable tool to calculate the total size of licensing deals and the distribution of payments from upfront and deal stages. In simple terms, the model predicted the total size of a licensing deal to be about 7× that of the upfront size for a phase 1 deal, 5× for a phase 2 deal, and 4× for a phase 3 deal, which appeared realistic.

Resolving dependencies in deal making

This licensing deal formula highlights the triangle of dependencies that decision makers need to solve during deal negotiations. Every deal is defined by its value in a risk-adjusted net present value (rNPV) sense, its size (in bio-dollars), and its distribution (front versus backloaded). In order to derive deal terms in a rigorous way, the rNPV value, together with risk and development structures of the asset in question, usually have to be determined. This is commonly combined with—or in cases where rNPV information is not available, replaced by—personal experience and benchmarking against comparable deals.

A formula to supplement current approaches

The licensing deal formula derived here can serve as an additional heuristic to find deal terms that are in line with industry standards. For this, an agreed upfront payment can be plugged into the licensing deal formula to determine milestone payments at each stage. Alternatively, the licensing deal formula can be combined with deal sizing via rNPV calculation or benchmarking. The total deal value (from the rNPV) or the total deal size (from benchmarking) can be distributed across the upfront payment and various milestones according to the typical distribution implied by the licensing deal formula at that stage. Under both methods of using the licensing deal formula, business partners can then negotiate to shift the distribution of payments towards a more front-loaded or back-loaded design than typical. Thus, the licensing deal formula may act as a tool to assist in deal making and create an industry-standard starting point for negotiations between partners. Considering the relatively low disclosure rate of royalties, we have not included them in this analysis, and they need to be addressed separately.

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