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Milestone payments in biopharma: negotiating an equitable value allocation

Development and regulatory milestone payments are a key element of many biopharma deals. This article analyses some of the trends involving these payments over the last decade.

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At the core of every biopharma deal is the question of how to assign value fairly to assets whose future success or failure is often very challenging to predict. Consequently, strategies have been adopted that address this challenge by staggering payments based on future outcomes. Deals often involve some combination of an upfront payment that is made immediately, development or regulatory (DR) milestone payments that are paid once defined goals in the development of assets are achieved and royalty payments once a product resulting from a deal is marketed.

DR milestone payments are very important in the allocation of value in biopharma alliances because most alliances do not result in commercial products owing to failure at some point, but do achieve one or more DR milestones. Conceptually, it is useful to think of DR milestone payments as upfront payments that are escrowed by the licensee of the asset such as a research and development (R&D) program for a drug until achievement of the associated milestone event, and are then released to the asset's licensor. This enables risk and value to be shared between each party. For example, although a licensor may be confident that the R&D program will commence phase 3 trials someday, there is often a significant risk of failure. The licensee can mitigate this by holding back a substantial portion of the total agreed payment until phase 3 trials actually commence.

To help understand how DR payments are used, Bioscience Advisors has undertaken a comparative analysis of such payments for biopharma alliances over the past decade, which it presents key findings from here. Details of the dataset and analysis methods are described in **Box 1**.

Historical context of milestone payments

From the early 1980s until the mid-1990s, the most contentious issue in value allocation during biopharma deal negotiations was the cost of capital. Biotechs were small, venture-backed and in constant need of cash infusion, and so their cost of capital was high. By contrast, pharma companies were large, cash-rich and also able to raise funds via debt, and so had a low cost of capital. However, for an R&D alliance between a pharma company and a biotech, the R&D program itself has a cost of capital, raising the question of what this should be in financial projections used in biopharma alliance negotiations. This is important because the higher the cost of capital, the less valuable downstream payments become and, conversely, the lower the cost of capital, the more valuable milestone payments and royalties are in value allocation between the alliance partners.

Until the mid-1990s, pharmas typically argued that a high cost of capital be applied to financial projections during alliance negotiations. This had the effect of minimizing the incentive of biotech companies to negotiate for higher milestones and, especially, royalty payments. In addition, using a high cost of capital for alliance valuation gave credence to the idea that partnering an R&D program was a biotech financing event—like a venture round or public offering, in which biotech's cost of capital was indeed high—and that upfront and sponsored R&D payments for an R&D program partnered 'out' might thereby be made available to support one or more additional R&D programs that remained 'in' the biotech.

However, this negotiation dynamic changed in the late 1990s, as codevelopment and regional alliance structures increased the visibility of substantial profits from successful biopharma products.

Box 1 | Dataset and analysis methods

The dataset encompasses alliances signed at stages from discovery through to phase 3, commencing after January 2009, that have been filed with the US Securities and Exchange Commission with financial terms available on an unredacted basis and that contain one or more development or regulatory (DR) milestone payments. In total, 218 biopharma alliances were classified by stage at signing as well as the type and amount of DR milestone payment. As shown in **Fig. 1**, 42% of the DR alliance dataset were clinical-stage deals at signing, with the following proportions based on the latest development stage of the associated assets: 30 alliances (14%) at phase 3, 43 (20%) at phase 2 and 18 (8%) at phase 1. Preclinical-stage alliances were the largest component of the dataset with 68 deals (31%). 35 alliances (16%) were discovery-stage deals and 24 alliances (11%) involved lead-stage molecules at signing. With respect to deal participants, 47 deals (22%) involved one of the 15 largest pharmas (classified as 15 top pharma) as the licensee or acquirer, 48 deals (22%) involved a mid-sized pharma or big biotech (classified as mid-size pharma) as licensee or acquirer, and 122 deals (56%) involved another biotech (classified as other licensees) as licensee. The financial terms used in this analysis are defined as follows:

- Total development and regulatory milestones (total DR): the total milestone amount to be paid to the licensor through launch in all jurisdictions for the first product indication
- Other development milestones: typically payments on early R&D, toxicology, candidate designation or license option exercise
- Deal size: a summation of all upfront, R&D reimbursement and milestone payments, including total DR milestones, sales milestones and/or milestones for additional products or indications, plus any equity or loan amounts, to be paid to the licensor
- Upfront cash: the license fee plus any annual payments not based on events (upfront equity was not included, as it is typically based on the fair market value of the securities purchased).

For the average amounts shown in the figures and tables, the deal size typically includes additional payment elements, such as sponsored R&D, equity, loans, sales milestones and/or milestones for additional products or indications, and specific DR milestone payments are included in average calculations only in instances involving non-zero dollar amounts for the corresponding milestone. An analogous analysis covering the period 1998–2018 has been published previously (see bioscibd.com/biopharma-milestone-payments), which also provides additional discussion of the financial terms used.

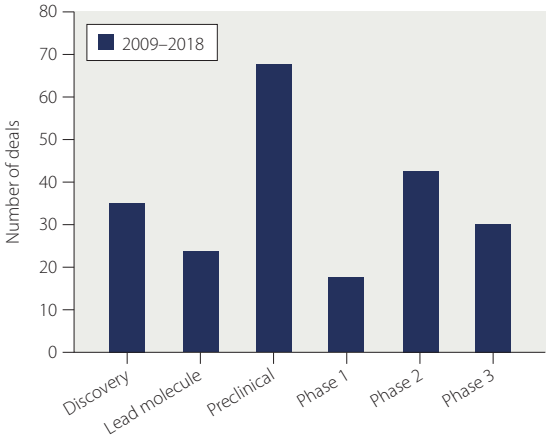

Fig. 1 | Development stage of biopharma alliances analysed. The dataset includes 218 biopharma alliances with development and/or registration milestone payments, classified by the stage of the most advanced asset at signing. See **Box 1** for details.

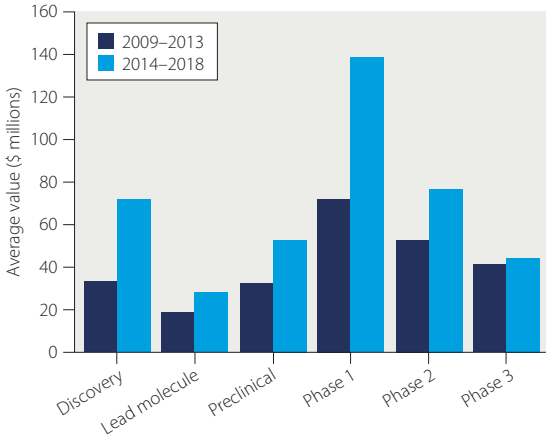

Fig. 2 | Trends in average development or regulatory milestone payments. The 218 deals in the dataset described in **Box 1** were split into two five-year periods, indicating that milestone payments have increased on average over the past decade.

As a result, the cost of capital in alliance financial projections declined substantially from the 30% or higher that had been used to the mid-teens—much closer to the 10–12% typically used by pharma companies internally. This had a dramatic impact on royalty rates and overall deal size—'biobucks'—as pharma companies began to offer more one-off payments such as DR milestones and payments for additional indications instead of greater royalty or profit sharing.

Importantly, such milestone payments are one-off, unlike royalties or profit splits, which are annuities. DR milestones are also second only to upfront payments in timing and are the most likely to be paid of all downstream payments. So, how have deal participants allocated value via DR milestone payments in biopharma alliances in the past decade?

Trends in milestone payments

Average total DR milestone payment terms have increased across all stages of development at signing over time **(Fig. 2)**. Discovery and phase 1 deals in particular saw substantial increases, with average payments almost doubling in value from the 2009–2013 to the 2014–2018 period.

Looking specifically at the subset of deals involving corporate licensors **(Fig. 3)** (defined as for-profit companies, therefore excluding the 50 alliances involving research institutions), average total DR milestone payment terms have increased for selected stage alliances in the 2014–2018 period compared with the 2009–2013 period. (There were few deals in the dataset from the 2014-18 period for each of the other three development stages and so these were not analysed.) Discovery-stage alliances had the largest gains in deal payments: **Table 1** shows that average total deal size increased fivefold, as did the average upfront cash payment. Total DR milestone payments increased by 83% for recent discovery-stage deals, of which the payment for first approval had the largest gain (from $19 million to $48 million). Total DR milestone payments for preclinical-stage deals increased by 49% between the two periods, with the average phase 3 start payment increasing by 55% (from $9 million to $13 million).

In conclusion, DR milestone payments have increased substantially over the past decade in response to a flattening of the cost of capital used in alliance negotiation. Total DR milestone payments have continued to climb the most in recent years for discovery alliances, with the greatest gains coming at first approval.

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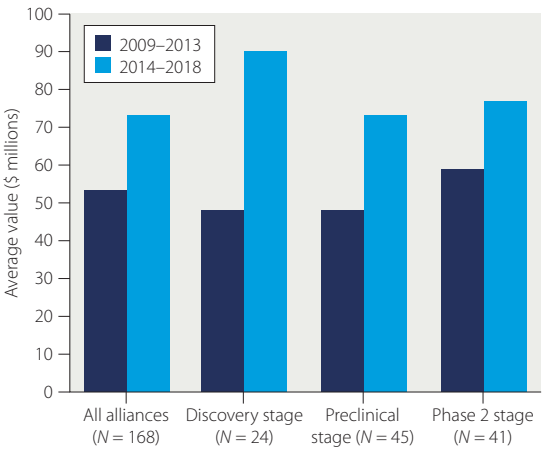

Fig. 3 | Trends in average total development or regulatory milestones for corporate alliances at selected stages. 50 deals involving research institutions were excluded from the full dataset, leaving 168 deals with corporate licensors. Only data for deals at the discovery stage, preclinical stage and phase 2 stage are shown because there were only a few deals at other stages.

Table 1 | Payments in early-stage alliances with corporate licensors

Component	Discovery-stage deals (mean value)		Preclinical-stage deals (mean value)	
	2009–13	2014–18	2009–13	2014–18
Deal size	$139 million	$703 million	$165 million	$144 million
Upfront cash	$11.5 million	$64.4 million	$6.8 million	$6.2 million
Total DR milestones[a]	$49 million	$89.8 million	$49 million	$72.8 million
% of deal size	35%	13%	30%	50%
% of upfront cash	426%	139%	720%	1,177%
Phase 3 start amount	$8 million	$19.6 million	$8.6 million	$13.3 million
% of total DR	16%	22%	18%	20%
First approval amount	$18.9 million	$48.3 million	$17 million	$18.6 million
% of total DR	39%	54%	35%	26%

[a]Total development or regulatory (DR) milestones through first worldwide approval for the first indication.