Monoclonal antibody (mAb) deals notable in size have made headlines recently. While deals with over US$ 1 bio in milestones were highly unusual in the past, even preclinical agreements, including some with very attractive co-promotion or profit-sharing clauses for the licensor, now reach this mark. This article presents an analysis of the structure of high-value mAb deals and the impact of increasingly sophisticated terms. Strategies of licensees and the impact of strategy on a deal’s size and structure are also examined.

Recent Deals and Deal Value

Although numerous mAb deals of more than US$ 1 bio value have been reported, usually very limited information is available about the deal structures and the precise motives of the partners. Nevertheless, we can closely examine some deals, analyze their structures and determine how they might fit hypothetical strategies of the participating companies. The two cases selected for analysis were the Regeneron Sanofi-Aventis deal and the agreement between PDL BioPharma and Bristol-Myers Squibb.

Five recent mAb deals have exceeded US$ 1 bio in value (Table 1). The deal value is usually the sum of all mentioned milestones of the agreement. These agreements often include many indications, and even back-up programs. The scenario where all milestones will be paid out is highly improbable, but not impossible. For example, Genmab is likely to receive a number of the agreed upon milestones because the partnered project, HuMax-CD20 (ofatumumab), is currently being tested in at least nine indications.

So, the reported deal value is likely an exaggeration of the actual value of the deal and provides only limited insight into the deal. The milestones are neither risk-adjusted, i.e., reduced by the likelihood that they actually occur, nor are they discounted. Sales milestones, in the case of the Regeneron Sanofi-Aventis deal of $250 Mio, will only be triggered in ten years or more, and only if the project reaches the market. Using a discount rate of 12% and standard success rates for a new investigational humanized mAb drug (Reichert) of 32% (success rates for fully human mAb are not available) this means that the $250 Mio only represent $25 Mio in actual value. Furthermore, some milestones might never be triggered because they relate to an indication that will never be developed or to sales targets that are too high. The reported $400 Mio milestones in the MorphoSys-Novartis deal are an exception because they are risk-adjusted.

Another misleading feature of the notion of “deal value” is that it does not include royalties. Royalties can make up more than half of the complete actual deal value if calculated with standard risk-adjusting valuation methods, but this depends on whether the deal is front or back-loaded. The same is true for co-development and profit sharing agreements. These clauses, which can be very valuable for the licensor, are also not considered in the deal value. We will demonstrate that these clauses can be of much greater importance than the sum of potential milestones.

Structure of Deals: Regeneron and Sanofi-Aventis

The Regeneron Sanofi-Aventis deal as displayed in Box 1 provides an excellent illustration of the different components of the modern mAb mega-deal. The deal exhibits most clauses that have become increasingly popular:

- Equity investments
- Inclusion of several compounds (technology deals)
- Earlier development undertaken by biotech linked to R&D funding
- Later redemption of funding
- Inclusion of sales milestones
- Co-promotion and profit sharing

All of these terms suggest that biotechnology companies have a strong position when negotiating deals with big pharmaceutical firms. However, the analysis is strongly biased when we only look at the high-value deals.

Equity investments. Many deals include an equity investment of the pharma partner in the biotech company. The infused cash liberates the biotech company from the time-consuming, and attention diverting, process of fund raising rounds. The equity investment, which is often substantial, also ties the two companies closer together. An equity investment does not increase the value of a deal; it is an exchange of shares against cash. Nevertheless, the pharmaceutical industry often perceives equity as another form of upfront payment and writes it off.
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Technology deals. Regeneron has closed a technology deal that includes projects generated over several years (similar to OncoMed and MorphoSys). The terms depend on sales performance, i.e., sales milestones and profit sharing, relating to aggregated sales stemming from all products included in the deal. Usually, these terms depend only on project-by-project sales. Such terms are favourable to the biotech company because it is easier to reach milestones if these sales stem from a variety of products rather than from just one. In general, tiered royalties, tiered profit sharing and sales milestones are reached faster if they depend on portfolio performance rather than project performance. Valuation of deals with tiered royalties (or tiered profit share schemes) and sales milestones on a portfolio level (several projects or also several indications) are quite difficult because we cannot simply value each project and add up all project values. With one project alone, some sales milestones might never be triggered or some royalty tiers might not be reached; we therefore also have to consider scenarios where projects jointly reach the market.

Co-development and profit sharing. Regeneron and Sanofi-Aventis have agreed to co-develop the program and to share profits. The PDL BioPharma and Bristol-Myers Squibb deal also has a similar structure. Sanofi-Aventis will pay all development costs upfront. If marketing approval is achieved, then Regeneron will pay its share of the development costs from the first profits. This repayment schedule is very favourable to Regeneron’s deal value because the development costs will be paid later, and only in the case of marketing approval. We can assume that Sanofi-Aventis cushioned this effect somewhat with a formula for repayments that was mentioned, but not shown. However, the risk reducing effect for Regeneron remains—it only has to pay for the trials once it is clear that they are successful. Profits will be shared 50%–50% in the US, and according to a sliding scale outside of the US. Sanofi-Aventis receives 65% of profits for ex-US sales up to $750 Mio and 55% above. This can be seen as compensation for the unbalanced risk position with respect to clinical trial costs.

Deal mechanism. The mechanism of the deal is illustrated by examination of the various deal components (Fig. 1). Upfront or milestone payments and R&D funding are exactly the opposite for Sanofi-Aventis and Regeneron (assuming that both use the same discount and success rates). These terms basically correspond to the price Sanofi-Aventis has to pay in order to participate in the project; in the beginning Regeneron owns the project and Sanofi-Aventis must compensate Regeneron for the share it claims in future profits. Furthermore, the clinical costs differ as discussed, and this is compensated by a higher profit share outside the US. Sanofi-Aventis’ value increases relative to Regeneron’s value if ex-US sales increase. The tiered profit sharing for ex-US sales suggests that the deal is probably intended to represent a 50%–50% partnership between the two companies, once Sanofi-Aventis compensated Regeneron’s value creation up to deal closing with upfront, R&D funding, and milestones. The difference between Regeneron’s and Sanofi-Aventis’ value can be interpreted as the initial value of the project prior to the agreement, and the remainder of the value (i.e., twice Sanofi-Aventis’ value) stems from the partnership (Fig. 2).

Table 1 Recent mega-deals with monoclonal antibodies

| Licensor      | Licensee        | Year | Deal value | Phase | Comment                                                                 |
|---------------|-----------------|------|------------|-------|-------------------------------------------------------------------------|
| Genmab        | GlaxoSmithKline | 2006 | $2,059 Mio | III   | Genmab receives double-digit royalties and a $357 Mio equity investment. |
| OncoMed       | GlaxoSmithKline | 2007 | $1,400 Mio | Pre-IND | Deal value excludes upfront payment, but includes milestones of several projects. |
| PDL BioPharma | Bristol-Myers Squibb | 2008 | $1,155 Mio | I     | Deal includes option and milestones on second product.                  |
| Regeneron     | Sanofi-Aventis  | 2007 | $1,122 Mio | Pre-IND | Deal includes projects generated over the next five years.              |
| MorphoSys     | Novartis        | 2007 | $1,000 Mio | Pre-IND/I | $600 Mio in committed payments over the next ten years. The remaining $400 Mio are probability adjusted milestones |

(Source: BioCentury, press releases).

Box 1 Regeneron Sanofi-Aventis deal

Regeneron and Sanofi-Aventis, November 29, 2007

- $312 Mio equity investment. Sanofi-Aventis increases its stake to approximately 19%.
- $35 million upfront payment.
- Sanofi-Aventis funds up to $475 million of research over the next five years.
- Sanofi-Aventis will have an option to extend the research agreement for up to an additional three years.
- Sanofi-Aventis will have the exclusive option to co-develop with Regeneron each drug candidate in the collaboration portfolio.
- Development costs will be shared between the two companies, with Sanofi-Aventis funding drug candidate development costs up front (phase I and II 100% by Sanofi-Aventis, Phase III 80%) and Regeneron reimbursing half of the development costs from its share of future profits.
- Sanofi-Aventis will take the lead in commercialization activities and will consolidate the sales.
- Regeneron will have the right to co-promote any and all collaboration products worldwide.
- In the United States, profits will be shared equally.
- Outside the United States, profits will be split on a pre-determined sliding scale with Sanofi-Aventis' share ranging from 65% to 55%.
- Regeneron will be entitled to receive up to a total of $250 million of sales milestone payments when the collaboration achieves certain aggregate annual ex-U.S. sales levels, starting at $1 billion.
- Regeneron responsible for manufacture of clinical supply.
- If Sanofi-Aventis does not exercise option, Regeneron retains global rights and Sanofi-Aventis entitled to royalties.
- Standstill agreement: Sanofi-aventis restricted from increasing ownership of Regeneron common stock to more than specified percentages that increase over time. Maximum of 30% ownership beginning four years after the stock purchase.

Source: Press release on www.regeneron.com, and presentation by Sanofi-Aventis.

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The deal rationale illustrated in Figure 2 is only valid as long as we apply the same discount rate to Regeneron and Sanofi-Aventis. In reality, Sanofi-Aventis will probably experience a lower cost of capital. This implies that Sanofi-Aventis’ value will increase and Regeneron’s value will decrease. So, Sanofi-Aventis’ actual deal value might be greater than Regeneron’s, although Regeneron started ahead with the initial project value. Nevertheless, the 50%–50% partnership might remain a viable deal rationale given the disclosed terms.

**Deal Analysis: PDL BioPharma and Bristol-Myers Squibb**

The PDL BioPharma and Bristol-Myers Squibb deal was also dissected to determine the benefits to each party. This deal was similar to the Regeneron-SanofiAventis deal, but was less complex because there was no equity investment and no R&D funding, the deal related to only two products, and it did not include profit sharing in non-US countries (cf. Box 2). For simplicity, we included only one candidate, elotuzumab, in the analysis of the deal (PDL241 will not be considered).

The goal was to analyze the deal so that the analysis could be used for deals that refer to other compounds. The typical parameters of interest are value share, internal rate of return (IRR) for
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We assumed operating expenses of 35% once the project is on the market, which is in line with reported financials from companies that market mAb therapeutic products.

The companies have communicated only fragments of the license terms. The upfront payment of $30 Mio and the total of milestones of $480 Mio and $200 Mio of sales milestones were disclosed. Furthermore, we know that the development costs were to be split 80%–20% between Bristol-Myers Squibb and PDL BioPharma. The exact distribution of the milestones over phases and indications, and also the royalty rates for ex-EU sales remain undisclosed. Thus, milestones and royalties have to be estimated. For this, metrics previously developed (Bogdan, Villiger)\(^1\) by analysing other license contracts were used. Milestones are usually up-stepped, i.e., they increase with ongoing progress of the project. Analysis of discovery and preclinical datasets suggest increasing milestones (Table 3). The weights indicate that milestones belonging to that phase are a multiple of the upfront payment. The milestones can be split over several indications, and approval milestones include sales milestones that follow later.

In this case, we have $30 Mio upfront payment and a total deal value of $710 Mio (= 30 + 480 + 200). These numbers do not exactly fit into the datasets, because $710 Mio is only 23.7 times $30 Mio. But we remember that the upfront payment also included an option payment for a second compound, PDL241. If we assume this option payment to be about $7.5 Mio the upfront payment for elotuzumab amounts to $22.5 Mio, which is the 31.5\(^{\text{th}}\) part of $710 Mio. With this in mind, the milestones could be as in Table 4.

We can also expect that the milestones are distributed over several indications, with the first being the most important one. Typically such deals include milestones for several cancer indications and also one non-cancer indication. The actual milestones could be as in Table 5.

The exact trigger points of sales milestones and royalties are unknown. We can assume that royalties will range from 15%–20%, and might perhaps be higher. The sales milestones amount suggests that the peak sales expectation is rather elevated. We can assume a first milestone of $100 Mio after having sold $1,000 Mio ex-US, and a second milestone of $100 Mio after having sold another $1,000 Mio ex-US.

Given the 50%–50% profit sharing and the high milestone terms, we expect PDL BioPharma to keep a large portion of the value. Running a valuation with several indications at a 12% cost of capital and a preliminary royalty structure of 15% up to $500 Mio and 20% above, we get the results shown in Table 6.

The valuation results indicate that, under these assumptions, PDL BioPharma negotiated an excellent deal. Usually, the licensee is expected to get about 75% of a phase I deal. In this case, Bristol-Myers Squibb reaches a 50% share if elotuzumab reaches $2.5 bio in sales.

Although the calculations are based on various estimations, they still provide insight into how these deals create value for

| Table 2 | R&D valuation assumptions |
|---------|---------------------------|
| Success Rates | Phase I | Phase II | Phase III | Review |
| 77% | 60% | 81% | 100% | Reichert et al.\(^4\) |
| Costs ($ Mio, per indication) | 5.2 | 15.9 | 43.1 | 3.5 | Avance |
| Duration (months) | 25.4 | 38.2 | 42.9 | 18 | DiMasi et al.,\(^2\) Reichert,\(^5\) |

| Table 3 | Milestones usually keep increasing with progress of project |
|---------|----------------------------------------------------------|
| 1\(^{\text{st}}\) Dataset (Discovery) | Phase I | Phase II | Phase III | Review | Launch | Sum |
| 1 | 2.2 | 3.3 | 4.4 | 20.7 | 31.5 |
| 2\(^{\text{nd}}\) Dataset (Preclinical) | Phase I | Phase II | Phase III | Review | Launch | Sum |
| 1 | 1.9 | 3.3 | 5.7 | 26.3 | 38.1 |

The table reveals the relative amounts of milestones extracted from two datasets.

| Table 4 | Possible milestones for elotuzumab |
|---------|----------------------------------|
| Milestones | $ Mio |
| Upfront | 22.5 |
| Phase II | 49 |
| Phase III | 73 |
| Filing | 98 |
| Approval | 260 |
| Sales Milestones | 200 |
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Table 5  Possible milestone structure for elotuzumab

| Milestones | 1st indication | 2nd indication | 3rd indication | Non-cancer | Total |
|------------|----------------|----------------|----------------|------------|-------|
| Upfront    | 22.5           |                |                |            | 22.5  |
| Phase II   | 25             | 15             | 10             |            | 50    |
| Phase III  | 40             | 20             | 10             |            | 70    |
| Filing     | 50             | 25             | 25             |            | 100   |
| Approval   | 100            | 60             | 60             | 40         | 260   |
| Sales      | 200            |                |                |            | 200   |

Table 6  Results for various sales scenarios, calculated with rival

| Scenario          | Value BMS| IRR BMS | Value PDL | Value share |
|-------------------|----------|---------|-----------|-------------|
| Peak Sales 1,000/1,000/500 | $469 Mio | 25.2%   | $446 Mio | 51–49%      |
| Peak Sales 1,000/500/500    | $188 Mio | 19.8%   | $269 Mio | 41–59%      |
| Peak Sales 500/250/250      | $34 Mio  | 15.6%   | $165 Mio | 17–83%      |

Regeneron included a standstill clause in the agreement with Sanofi-Aventis that prevented Sanofi-Aventis from taking over Regeneron completely. This clause counters the generally prevailing opinion that the pharma companies are going to take over their licensors sooner or later. On the other hand, Regeneron might have wanted to ensure that, in the case of a take-over, their investors are only bought out once the full value potential is evident.

Investors appreciated the deal with Sanofi-Aventis; the share price rose 35% upon announcement. However, PDL BioPharma's deal with Bristol-Myers Squibb only led to a 3% increase. Sometimes a deal is already included in the valuation, or investors don't necessarily see a licensing deal as the better alternative to continuing the development within the company. It has been claimed that license deals could also be value destructive, as they make a take-over by a company other than the licensee much less likely (Longman). The approval effect of a license deal with a big pharmaceutical company player has recently lost importance, and investors seem to care more about the lost potential upside. However, this is more important for private companies, where a trade sale represents an important potential exit scenario for investors. A public company has to care less about exit scenarios, as investors can simply sell their stakes. In any case,
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Figure 3. Value development for Bristol-Myers Squibb, calculated with ri:val.

Figure 4. Value development for PDL BioPharma, calculated with ri:val.

a biotechnology company must compare the term sheet it has on the table with the alternatives, i.e., moving the product forward with its own means and diluting its investors. Closure of a license deal by a public company might also be an indication that the company feels undervalued by the public markets.

It is difficult to judge exactly how investors react to these deals in the mid-term because several effects overlay each other. An immediate share price reaction indicates investors approved the deal, but we have to wait until a few years have passed before we can judge what will come of these recent mega-deals. Only then we can see whether biotech, pharma, or potentially both, were the winners.

**Conclusion**

Our analysis of two large mAb deals has shown that biotechnology companies are able to negotiate much better deal terms, even for early stage projects, than usually assumed in the industry—the exhibited value shares of more than 50% for the licensor exceeded the standard 25% for IND deals by far. The projects obviously exhibit a huge potential. MAbs exhibit a better investment profile compared to other drug classes because several commercialised mAbs have blockbuster status (annual global sales exceeding US$1 billion), and mAbs cannot be easily replaced by generics. As a sign of biotech’s improved bargaining position the pharmaceutical partners have to concede profit sharing models to the presumed junior partners. Nevertheless, our analysis has shown that big pharma still has leverage. Even if profit sharing clauses suggest an approximate 50%–50% value share, as in the two analyzed deals, pharmaceutical companies still profit from a much lower cost of capital. Therefore, pharmaceutical partners probably still receive a larger piece of the pie than biotech. While the US$1 bio milestone figures are certainly notable, they flatter biotech.

www.landesbioscience.com mAbs
The biotechnology company’s value is much lower due to risk adjustments and high costs of capital, even though the so-called deal values do not include royalties and profit share clauses. Venture capital investors have recently been resistant to premature license deals as these impede very attractive trade as exits. Public companies face the same situation, but they might close a mega-deal to signal that they feel undervalued by the market.

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