Funding Clinical Development: More Creativity required?

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While our industry continues to find diverse ways to ensure cash is applied to early-stage R&D – for example venture funding, option-based partnerships, acquisitions, and more recently IPOs again – funding clinical development is becoming tougher, particularly the later and more expensive stages. We are beginning to face a new funding shortage: pharmaceutical companies and their investors appear to be less willing to finance clinical development through their P&L accounts than they are to find cash for deal-making and M&A. How can pharmaceutical companies secure funding for their most important clinical development projects? Alternative funding models have started to emerge in recent years that can provide access to capital with control over the asset and its development. In this paper we classify the available funding options today, and then discuss the key attributes and risk implications of each. We offer our views on how MidPharmas can explore funding arrangements which are best suited to their stability, scale and long-term strategic goals, ensuring the right balance between accessing capital today and giving up value tomorrow.

Introduction

The capital-intensive nature of drug development means that securing adequate funding for R&D remains a central challenge for the pharmaceutical industry. Published average R&D costs per new medicine

indicate an upward trend over the last decade, with the most recent estimate from Mestre-Ferrandiz et al.1 standing at approximately $1.5 billion. While such figures are full of debatable assumptions regarding capital costs and attrition, there is no doubt that the cost trend is upwards. Coupling this trend with the ongoing concerns related to R&D productivity places companies under constant fiscal pressure to justify their R&D expenditures.

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Whether return on investment or NPV or other measures are used to assess the value of clinical projects and prioritise between them, two fundamental issues must now also be considered: the source of funding and how to mitigate the associated risks. Are there sufficient internal funds to support the development activities? Alternatively, what are the additional sources of finance that can help to relieve P&L pressure?

In this paper we classify the various types of available funding for clinical development in the pharmaceutical industry. We also discuss the key attributes and nuances of these options, and what they mean in practical terms for companies in search of capital flexibility and de-risked clinical development.

Alternative ways to fund clinical development

Historically, sources of additional funds for clinical development were limited to debt, sale of equity and/or out-licensing assets through deals that share the value of the innovation with a partner. Alternative models have emerged in recent years that offer more tailored financing and risk management solutions for pharmaceutical companies. There are now five main types of clinical development funding for pharmaceutical companies (Figure 1):

1. Internal budgets.
2. Conventional finance.
3. Revenue-based finance.
4. Asset-centric finance.
5. Asset-centric entity.

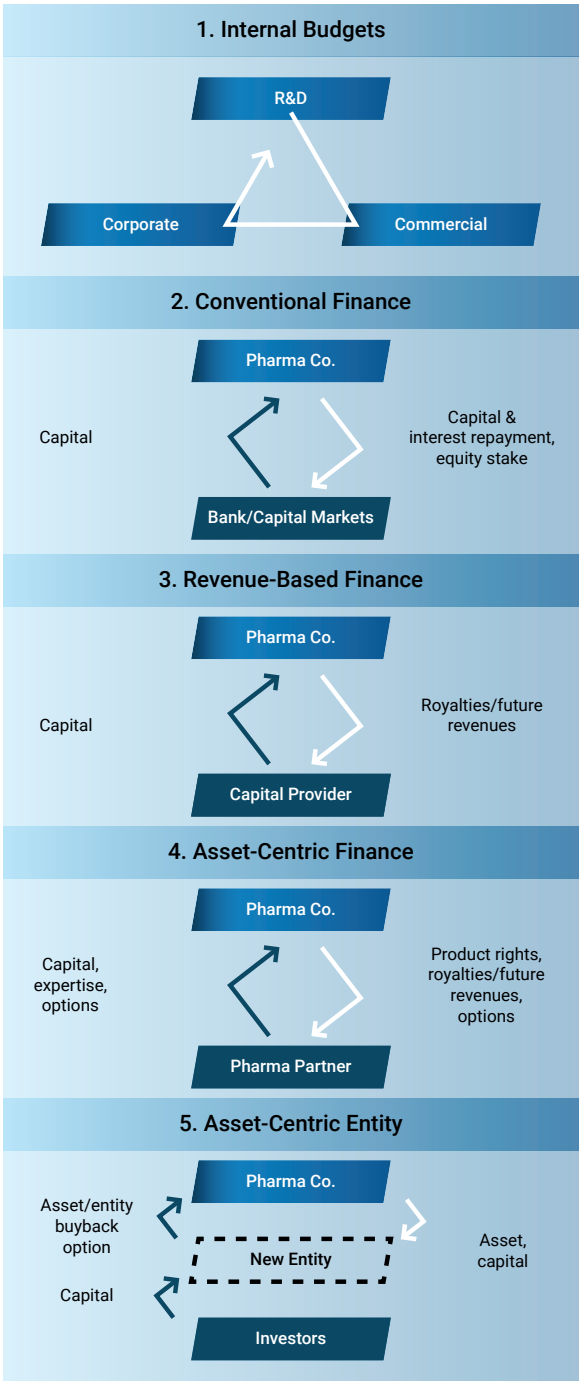

Figure 1. Five types of funding for clinical development.

We describe the characteristics of each funding type in turn:

Internal budgets: Financing from within the organisation is usually preferred in cash-rich companies with a steady profitability stream from marketed products. In this instance, the core functions of R&D, Corporate and Commercial need to be aligned on budget allocation, balancing strategic goals with appropriate use of internal cash, and avoiding excessive burden on the company's P&L.

Conventional finance: This comprises borrowing with potentially high interest costs or raising funds by selling equity. A number of implications arise for both private and public companies including dilution of equity, financial risk spread over the entire organisation, and whether the increased R&D spend that would result is an acceptable rationale for the financiers providing debt or equity.

Revenue-based finance: This involves selling some or all of current or expected product revenues in exchange for capital to invest in either clinical development or other priorities. The most familiar form of this funding is termed 'royalty financing', involving the sale of an existing royalty stream, which would have been created as part of a separate licensing or partnership deal. Another variant includes creating a synthetic royalty where none had previously existed, also known as 'revenue interest financing'. A synthetic royalty is derived from revenues for products that are developed and marketed internally (as opposed to by a licensee or partner), and the revenue interest is sold to the capital provider. In both instances, the capital provider assumes a share of the commercial risk whilst the royalty seller retains full control over the product(s). The products in question are usually near or at commercialisation stage. Although revenue-based finance provides a non-dilutive source of capital, the seller may risk losing substantial upside in cases where the products that create the revenue or royalty streams exceed sales expectations.

While revenue-based financing is technically feasible for companies to use on any product's revenue stream, transactions to date have been most common for supporting well-defined and near-term capital requirements, as exemplified in the AstraZeneca – Royalty Pharma deal2. In 2006 AstraZeneca acquired Cambridge Antibody Technology ('CAT') including its passive royalty interest related to Abbott's Humira. The $1.3 billion transaction triggered mixed reactions from industry analysts and investors, questioning the balance between strategic fit and the seemingly high price premium that was paid. AstraZeneca's subsequent move to sell the Humira royalty stream to Royalty Pharma effectively reduced the net acquisition cost to $300 million (after adjusting for $300 million existing cash in CAT and the $700 million value of the Humira royalty stream).

Asset-centric finance: This encompasses most archetypal licensing and co-development partnerships to further develop specific clinical assets. In addition to securing funds, this enables the licensor to leverage the licensee's expertise and development resources, as both parties have a vested interest to progress the product's development. Although upfront payments provide cash infusions to fund existing operations and defer the need to obtain capital from the equity or debt markets, such transactions also involve giving up all or partial control over product development and downstream financial benefits. Often deals can be designed to incorporate option terms, thereby increasing flexibility in managing risk profiles and providing leeway for unexpected strategic decisions by either partner.

Though the providers of asset-centric finance have traditionally been larger pharma/biotech companies, over time various types of clinical research organisations (CROs) have experimented with this model. Solvay's pioneering risk-sharing deal with NovaQuest (then part of the Quintiles group) in 2004 was one example3. More recently SFJ Pharmaceuticals ('SFJ') has entered the area. With capabilities rooted in both financing and providing CRO services, SFJ provides funds and resources to assist with Phase 3 trials in exchange for future royalties4. However providing finance means taking risk, and SFJ recently announced mixed results from their two partnered Phase 3 trials in oncology. The disappointment and potential loss in investment from its Pfizer trial (dacomitinib) may be offset with the good news from its Eisai partnership (lenvatinib) with anticipated downstream rewards once marketing approvals are achieved. To maintain momentum, SFJ will need to recoup a hefty premium from future successful programmes.

Asset-centric entity: In this model, a company places the rights to an asset in a separate entity that is part or sole funded by other investors. Asset development is carried out in the new entity, and the donor company can have the option to re-acquire the asset and the entity after a pre-determined milestone, usually after achieving proof-of-concept. Each party benefits: the investor can have a pre-determined exit strategy to obtain sufficient returns, and the donor company obtains funding for development that does not hurt its P&L yet retains an option to re-acquire the asset and thereby replenishes its R&D pipeline. The lean and nimble setup of an independent entity can also reinforce objective decision-making in driving asset development.

This type of model is well illustrated by Arteaus Therapeutics ('Arteaus')5. In 2011 Lilly granted rights of its monoclonal antibody drug LY2951742 to Arteaus. Established as a private company with $18 million investment from Atlas Venture and Orbimed, Arteaus' sole purpose was to investigate the drug's potential in preventing migraines. Following promising results from a Phase 2 study, Lilly exercised its option to re-acquire LY2951742 in January 2014. Here the investors successfully exited from their initial investment and Lilly can now accelerate the subsequent development of a promising drug candidate.

Though the concept of asset-centric entity is sound, it is tough to execute. The initial suspicion of external investors is generally that they only get to invest in the projects that pharma/biotech does not want, which increases perceived risk. A strong and credible strategic rationale for creating the entity (rather than own-development or licensing) is therefore essential. This is arguably easier for MidPharmas that have to be commercially focused and by definition create valuable non-core assets than it is for Big Pharmas that can usually fund and commercialise any asset with potential.

MidPharma experiences with new funding models

Despite the almost universal P&L pressure we are hearing from our R&D clients, the number of published examples of more novel alternative clinical development funding activities has been limited to date. We suspect this is simply a matter of time: there is no imminent sign of a return to the days of pharmaceutical companies generating reliably high profits that allow internal funding of a wide variety of promising projects. However there are already interesting examples that provide some pointers to the future (Table 1).

It is interesting to note that in each case the proportion of revenue that was being spent on R&D at the time of the deal was generally higher than conventionally assumed to be the appropriate level in the industry.

The reasons for each of these deals are diverse, just like the companies that are executing them. It is interesting to note that in each case the proportion of revenue that was being spent on R&D at the time of the deal was generally higher than conventionally assumed to be the appropriate level in the industry. This points to more usage of external financing in future as companies increasingly face pressures to reduce R&D spending and move clinical development spending off their P&Ls.

Table 1. Published examples of different financing options.

Company	R&D Spend (as % Total Revenues) at Year of Deal Signing	Nature of Financing
Eisai (Japan)	$1,827m (19%)	• Asset-centric finance: SFJ provided funding for global Phase 3 study of lenvatinib for thyroid cancer (2011)
Exelixis (US)	$257m (218%) $185m (188%)	• Conventional finance: Loan facility from Deerfield Management (2008) • Asset-centric entity: Formed 'Symphony Evolution Inc' with Symphony Capital to develop three Phase 2 products (2006)
Plethora Solutions (UK)	$17m (1438%)	• Revenue-based finance: Sold royalties related to two Phase 3 products and one marketed product for $15m investment from Paul Capital, with the option to invest in equity subscription (2008)

Skyepharma (UK)	$44m (42%)	• Revenue-based finance: $60m investment from Paul Capital in two separate revenue interest financing deals (2002)
		  • $30m proceeds used to develop pipeline product and defer partnering
		  • $30m proceeds used to acquire RTP Pharma and develop the acquired products

UCB (Belgium)	$940m (22%)	• Revenue-based finance: Sold royalties related to non-core products for $100m investment from Paul Capital (2009) • Asset-centric finance: Licensed non-core oncology preclinical portfolio to Wilex with the option to re-acquire (2009)
Vertex (US)	$918m (76%) $516m (294%)	• Revenue-based finance: Sold royalties related to Incivo® (telaprevir) to Janssen for $152m (2013) • Revenue-based finance: Sold royalties to Lexiva® and Agenerase® (under 1993 GSK licensing agreement) to Healthcare Royalty Partners (2008)

Source: Company annual reports and 10-k forms. Currency conversion with annual average exchange rate from www.oanda.com.

How should MidPharmas address funding issues?

In our previous white paper15, we discussed how MidPharmas could benefit from combining their ambition and stability with the mentality of biotechs to achieve R&D efficiency and productivity. Could MidPharmas embrace a biotech-like mentality when it comes to financing? Inherently the funding requirements and long-term strategic goals differ considerably from their biotech counterparts: MidPharmas, often privately held or family owned, can be averse to public markets and corporate acquirers.

For MidPharmas there is a fine balancing act to deliver value from the internal portfolio while satisfying financial budgets. In some instances this can lead to the misallocation of funding between projects due to misalignment of organisational goals. Critical financing decisions must be made to ensure that the most value-generating projects flourish and those that are not are discontinued on a timely basis. To supplement traditional business case analysis, five core drivers must be considered when making financing decisions:

1. Financial resources.
2. Risks.
3. Revenue impact.
4. Control of the asset.
5. Development capabilities.

We describe each of these drivers in turn below:

Financial resources: Each company must constantly assess the best use of all its financial resources, including how these are allocated to R&D projects (linked to portfolio management). From the perspective of a CFO, one concern could entail the best use of surplus cash reserves; retain cash for future acquisitions or expense it in additional R&D efforts? On the other hand, increased borrowing could relieve a lack of sufficient cash reserves in the short-term but could result in the company being vulnerable during a recession or susceptible to takeovers. Transactions for funding clinical development can affect the health of the company's balance sheet and P&L, and such implications should be considered carefully.

Risks: These include (but are not limited to) regulatory risks, financing risks, execution risks and reimbursement risks. Can the most relevant risks associated with a particular business model be identified and mitigated accordingly? How much of these risks can be shared with a partner? Conventional financing (debt and equity) could lead to financial risk being spread over the whole organisation. Revenue-based financing allows a portion of the commercial risk to be transferred to a capital provider. In asset-centric financing, depending on the deal terms, all or part of the development risk can be mitigated to a partner, financial risk can be reduced, and option terms can offer flexibility in terms of risk sharing. In asset-centric entities, financial and development risks can be mitigated by transferring them to a new entity.

Revenue impact: Selling part or all of future sales revenues in exchange for capital today will improve cash reserves in the short-term but at the cost of future upside potential, i.e. reducing future profits once the product is commercialised. This approach is particularly advantageous to cash-starved companies and minimises commercial risk, however corporate sustainability is consequently put at risk.

Control of the asset: In exchange for funding, the loss of ownership of an asset and IP can often occur. The extent of this loss must be considered in the context of several factors, for example whether the asset represents a core or a non-core asset, the company's strategic focus, and the company's culture.

Development capabilities: In addition to gaining funds, it is advantageous to simultaneously gain access to development capabilities that may be lacking in-house. A suitable partner will both provide those capabilities and set a platform for potentially later integrating new capabilities to ensure future commercial success.

A flexible and integrative approach to funding

To date the creativity that has been applied to financing early-stage projects and companies has not been as widespread in the more expensive area of clinical development. Companies should continue to exploit multiple financing models to provide options and flexibility in funding. Assets should be valued using appropriate and rigorous methods to facilitate negotiable deal terms and risk profiles. Creative alternatives should be identified and explored, and the key R&D, Corporate and Commercial functions must align behind clear and justifiable choices. This all represents a significant technical and managerial challenge. And as funds for R&D become tighter, pharmaceutical companies that need to fund their next product breakthroughs must confront this challenge head on.