How Do We Recognise the End of the Road for a Partnering Campaign?

The pharmaceutical business development (BD) world tends to be a positive and constructive environment where, within reason, all things are possible and the overriding theory is that if the partnering strategy and valuation are right then all assets are, in principle, partnerable. Therefore the concept of "non-partnerability" is a difficult one to recognise. This is particularly the case for a biotech company that has been extolling the virtues of its technology to its investors for many years during early development.

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Closing deals is a skilled and demanding activity. With the best will in the world even the most carefully planned partnering campaigns that have been properly resourced and managed with appropriate timelines do not always end with success in securing a partner. Unfortunately, the BD person is often first in line of fire from the Board and investors when partnering campaigns go awry.

It is appropriate, therefore, to consider the early identification and management of assets that are proving challenging to partner. In this article we will review some of the early indicators for damage to partnering prospects and consider some of the tactics to adopt to manage stakeholders' expectations.

The Deal is the Goal

For many companies signing a deal and securing a partner is the end point for the commercialisation strategy for the product or technology asset. Depending on the point in its life cycle, the opportunity will consist of either selling future promise (an early-stage deal) or selling reality in the form of turnover / profit (a late-stage deal).

One of the key issues for a biotech company is its ability to recognise the limitations for a project when the target product profile is emerging as sub-optimal. Because biotechs generally have limited project portfolios, most of the value is ascribed to the most advanced programme. Consequently the impact of a damaged lead asset is hugely significant and requires careful PR management.

In the case of a biotech or a small / medium-sized enterprise (SME), the commercialisation strategy will most likely have been developed very early and stated publicly; this firmly sets the expectations within the Board, investors and stakeholders. Early promises of multi-million dollar deals are not easily forgotten and delivering anything less inevitably results in disappointment. Consequently, real danger looms in a BD strategy devoid of flexibility to adapt to changing circumstances.

There also has to be a degree of realism within the licensor as to deal valuation, which may necessitate some modification in the light of responses to the opportunity; we all want to achieve as much value as possible but do not expect, or worse still, hold out for clinical or even pre-registration values for an unproven preclinical asset.

Beauty is in the Eye of the Beholder

It is important for a perspective licensor not to be blinded by internal enthusiasm for an asset and to remember that the task in hand is to convince those with a less rosy view that the opportunity is a "must have". A compelling case will be critical in captivating that "all too ready to doubt" audience. For example, for a very early-stage asset with a novel untested approach, ensuring that there is well worked out biology and a convincing, clear

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understanding of the proposed mechanism of action will be key to grabbing attention.

If the project is at the lead-molecule stage, being honest at the outset as to its ability to develop into a drug product is essential. Do not forget the Lipinski rule! The potential partner will need to be convinced that the molecule will make a viable drug. Is it sufficiently potent and selective? Is there sufficient target engagement? Are there predictable pharmacokinetics allowing a reasonable prediction of dose selection? Do you have an idea of tolerability / toxicology? For a small molecule, is it orally bioavailable and does it lend itself to daily dosing? For a biologic, do you have a dosing strategy and is the half-life appropriate? Have you considered biomarkers and patient stratification?

Timing is All Important – Think Strategically

An aggressive "big sell" at a too early stage, particularly in the absence of compelling data to back extravagant claims, can at best damage and at worst render an asset "unpartnerable". It is essential to resist the temptation, even if under pressure from investors, to over sell. Once dismissed for lack of data, it becomes far harder to recoup favour and overturn a negative view embedded within a potential licensee company. By the time there are new data available, the window of opportunity may have closed as the potential partner may have lost interest or moved on to alternative options.

The Lipinski Rule

Lipinski's Rule is a rule of thumb to evaluate drug-likeness or assess if a new molecular entity would make a likely orally active drug. The rule describes molecular properties important for a drug's pharmacokinetics, including ADME but does not predict if a compound is pharmacologically active.

The rule states that, in general, an orally active drug does not violate more than one of the following criteria:

- Not more than five hydrogen bond donors
- Not more than 10 hydrogen bond acceptors
- A molecular mass less than 500 daltons
- An octanol-water partition coefficient log P not greater than five

This does not negate a more measured approach, i.e. a gentle introduction with regular progress updates. Care should be taken to avoid saturation and "information fatigue" setting in, and reach out only when real progress has been made. Such an approach will allow an interested party to move quickly once the appropriate inflexion point has been reached.

It is important to be aware of the strategy of the target audience and question if the offering is ever likely to fit. For instance, Abraxane as a reformulated paclitaxel cytotoxic was generally recognised as active, with a promising commercial future. However, it was not perceived to be consistent with the image of many "novel, high science, targeted therapeutics" companies. Only time will tell if the acquisition of Abraxis BioScience by Celgene will demonstrate a painful lack of vision by some of the bigger players.

Licensors need to consider that today's flavour of the month may well have lost its sparkle tomorrow. For example RNAi and Hsp90 inhibitor opportunities are not as eagerly sought after as they once were, largely due to the intractable issues that have come to light since the early halcyon days of interest.

Reaching phase 3 guarantees no safe harbours either as exemplified by the failures of many an Alzheimer's Disease approach. As we discuss later, the shine can be lost at an even later stage: the many regulatory hurdles in the obesity arena have suppressed the appetite for what was once high on the wish list of many large pharma.

On reaching the deal negotiation stage, striking while the iron is hot is to be recommended, never allowing a minor point of principle to interfere with the race to the finishing line. There may be unknown and unfavourable forces afoot which may well be unrelated to the deal to be done but nevertheless could derail the whole transaction.

A Day Lost During Development is a Loss of One Day's Peak Sales

With increasing pressures to show clinical proof of concept, it is understandable that some biotech companies rush the early clinical trial stages taking the most expedient, not necessarily most informative path. Other factors that can impact the quality of the preclinical and early development include limited funds or, for a first-in-class asset, uncertainty as to precisely what the development path should be.

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Therefore it is not uncommon to find that in later clinical development, certain aspects may need to be repeated, often by the acquiring company. This in turn impacts on the launch date and given the restricted patent life, the number of years patent coverage post launch are reduced. It is a perennial issue in negotiations as to where exactly a product is in its development, as clearly stage influences the valuation.

The importance of delays in the development programme is perhaps best illustrated by the willingness of major companies to make all necessary resources available to drive through clinical studies – often at the expense of earlier stage programmes. The cost per day of a delayed launch translates to a day’s peak sales lost.

In the extreme case, significantly delayed early-stage development may result in the product failing to reach launch ahead of patent expiry. In this scenario, it would not then be possible to file for any Supplementary Patent Certificates, and, with no patent protection post launch, few companies would be willing to invest in such an opportunity, as the ability to recover the investment is at much increased risk.

So has the asset reached the end of the partnering road or is it even “unpartnerable”? Possibly the latter, if the development investment is significant. But, if the value in the opportunity is perceived to be high, it may be possible to convince investors to pursue the high risk, high investment phase to the market based on the data and market exclusivity that would be available on registration. The possibility of developing a new formulation, or incorporating a novel drug delivery technology to create a “new or improved product” with its own patent protection, may help rejuvenate an opportunity with no or limited patent coverage.

Clinical Efficacy is the First Hurdle; Then Comes the Real Obstacle - Regulatory Approval

The aborted potential deal between BMS and Merck & Co for the co-development and co-marketing of the anti-diabetic Muraglitazar illustrates this issue. This programme was in phase 3 clinical development when the FDA required additional safety data. These additional clinical studies, with the consequent impact on development costs and timelines, were sufficient to result in both parties electing to terminate the deal.

More recently Abbott, SkyePharma’s US partner for Flutiform, returned the rights to the product following the FDA’s request for additional safety data prior to achieving registration. SkyePharma has subsequently indicated that no further development work will be undertaken in the US in the absence of a partner to provide funding (Press Release, November 14, 2011). It will be interesting to see how Flutiform sales take off in Europe following its 2012 launch by SkyePharma’s European partner, Mundipharma. Will a positive sales outcome in Europe stimulate interest from potential partners for the US?

The issuance of Complete Response Letters by the FDA to communicate that an NDA or ANDA is not approvable in its current form are not at all uncommon these days. During the early months of 2013, a range of pharma and biotech companies have received Complete Response Letters, e.g. Gilead for its anti-HIV drugs elvitegravir and cobicistat as monotherapies; Valeant for efinaconazole for the treatment of onychomycosis; Aveo Oncology for tivozanib for advanced renal cell carcinoma; and Depomed for gabapentin to treat vasomotor symptoms in menopause.

Whereas a large pharma can decide whether to absorb the delays and costs resulting from a Complete Response Letter for one of its own products (depending on the issues cited), this is not so easy for a smaller company, where cash flow and funding may be critically linked to the specific product’s success. For a biotech, probably the worst outcome is for an existing partner to terminate its agreement as a result of a failure to secure marketing approval. The chances of securing an alternative partner for the asset when the regulators have pushed back will most likely be very slim, or only possible with a significantly depressed valuation.

Aveo Oncology may be fortunate as, although its partner for tivozanib, Astellas, has no plans to fund any future clinical trials in renal cell carcinoma, the companies are still evaluating tivozanib in phase 2 studies in advanced breast and colorectal cancer.

Reimbursement, Reimbursement, Reimbursement

Following the payer barriers, reimbursement, reimbursement, reimbursement must be uppermost in the thinking of all drug hunters.

Not all BD opportunities are new molecular entities; many companies are focusing on improved formulations or altered drug delivery characteristics to provide the necessary improved market profile, which may provide market share advantage.

The timing of the development of such assets, however, remains key. Even if the product per se offers tangible advantage, it is the degree of advantage that is imperative. A simple improved side-effect profile, ease of manufacture or more convenient dosing regimens may not always be sufficient to persuade increasingly stringent payer bodies. In addition, if the gold standard product is well established and cheaper, e.g. methotrexate in rheumatoid arthritis, then even a superior product may find it difficult to supplant the original.

Novel developments, although patentable, may not always confer commercial advantage. For example, if a market has switched over to a predominance of generics for a given indication, it will be difficult to generate sufficient data to convince payers to cover a higher priced product over an acceptable and effective generic.

Also if a product is too far behind the first-in-class molecule, for example fifth or sixth, with no clear advantage or market differentiation, then finding a partner will be particularly difficult. An exception to the gloom for later entrants to a class is the potential for local development of individual markets – a new statin may well have potential in a less developed market, for example Russia, but find little opportunity in the UK.

You May Find You Are a Lone Trailblazer

In some cases a product or technology may simply be too innovative for the naturally cautious big players, as may have been the situation for Dendreon with Provenge, an autologous cellular immunotherapeutic preparation for the treatment of metastatic prostate cancer. Under these circumstances, the only option may be for the company to keep going with its development to be able to reach any return on its investment.

IP is All Important

Lack of or questionable IP coverage can be a real block to partnering. One key difficulty is that opinions on the strength of IP can be very subjective. Even after patent grant, the freedom to operate under a patent may remain an uncertainty as it is not until the IP has been used to protect the asset in the market place, and upheld, that the strength can be truly determined.

There may be many a due diligence exercise that on detailed probing into the IP the potential partner has taken fright and decided not to progress for various reasons. However, it may be that the potential issues are manageable but it really depends on the risk that the partner is prepared to take.

What are the Signs That Your Partnering Campaign is Going Nowhere?

Possibly when the asset has been walked around the pharmaceutical world and no one 'takes up the offer'! Close monitoring of the shifts within the industry will reveal valuable pointers allowing a realistic assessment of the likely future take-up of an opportunity by a chosen partner audience. The key is to stay abreast of developments and to closely monitor all press releases relevant to the asset of interest.

Examples of early serious lack of interest indicators for an asset are:

- Sighs when the product is mentioned
- Calls are no longer returned
- Being avoided / inability to secure any meetings at partnering conferences
- Christmas cards stop coming!

It's Not a Problem with the Asset – We Just Need to Re-Assess & Adjust the Strategy

It is not uncommon in companies for the lone BD person or BD team to be held to account for the inability to partner an asset. The key questions here should include:

- Was the partnering campaign run properly?
- Is the issue the asset itself?
- Do we have the option to refocus?

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It is important to do an audit to cover whether the right contacts were made and at the right level, and also to check that full and complete feedback was received from all potential partners, i.e. that no stone was left unturned. There may be a consensus of opinion coming back from your BD contacts, such as:

- The technology is not competitive
- Too much competition
- The IP position is unclear
- Too early in development / too late to market
- The data package is deficient or inappropriate
- The inherent risk is too high
- The investment required is not supported by the commercial prospects i.e. the projected market numbers do not stack up.

Of course not all prospective licensees provide informative feedback rather merely a "no thank you". This can be frustrating and may require a charm offensive to obtain a more detailed and helpful response.

Once all the relevant feedback has been collated, it is important to review and challenge the original premise. A transparent, full post mortem will allow the identification of the causes of the failure, not only for the benefit of the investors but also to facilitate the planning of a productive way forward.

So How to Deal with the "Unpartnerable" Asset and the Consequent Fallout?

Managing an unsuccessful partnering campaign is difficult especially if this is the key programme upon which major shareholder expectation rests. Clearly it is not always possible to undo potentially years of positive spin on how a specific asset will command a "multimillion dollar" deal.

So if in the final analysis the conclusion is that the asset is "unpartnerable", what are the options? Management of expectations is key and there are essentially two choices: to continue the development or to allow the project to slip into hibernation.

Carry On or Hibernate?

Taking the development forwards requires the confidence of the investors that derisking the asset will open up a commercial path either by partnering at a later date or using distributors to access the markets. A detailed review of the feedback gained during the partnering campaign, supported with key opinion leaders' advice or commercial assessments, will allow this decision to be taken. An unbiased assessment of the factors that prevented the asset from being partnered must be made and a realistic evaluation regarding their resolution e.g. if poor solubility of a drug was the big concern, a phase 1 study on the original formulation will not address the partnering block.

The default position will be to allow the project to slip into development hibernation whereby no active investment in future progress is made. The project will of course incur some cost even in hibernation, such as patent maintenance fees. It will also represent a diminishing return as competitors will be progressing and the patent clock will be ticking.

This approach will have the benefit of allowing undiluted focus on earlier stage assets, which in terms of partnering activity, being further back in the development pipeline, may offer a better commercial prospect. Additional revenues generated in this way can then be deployed to the development of the original asset. One approach that will most likely have a low chance of success is to continue to try and partner an asset when it has been hibernated. It is always difficult to respond to an obvious question from potential partners, i.e. "If this asset is so good, why are you are not progressing it?"

Final Thoughts

As BD people, we face the challenges of an apparent increase in reported project failures and at later stages of development. The knock-on effect of this is that due diligence is increasingly becoming a higher focus activity; assets that may have partnered under less stringent due diligence previously, may not now be taken up. For licensors, it is important to recognise the early signs of what could be a very challenging partnering campaign and to confront the issues, and importantly, manage stakeholders' expectations.

Unfortunately there are no instant solutions to securing a partner for a challenging asset. The most important aspect of managing this situation is to have realistic expectations and to develop a flexible strategy reflecting the feedback from the partnering campaign. ■

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