# Business Development Basics

## A guide for early-stage life science companies

# Introduction

Besides death and taxes, one of the few certainties in life is that the commercialisation of life sciences assets is never simple or quick. Commercialisation can be particularly challenging for early-stage companies, whose assets, regardless of the quality or sophistication of the underlying science, are largely "diamonds in the rough", requiring the polish of proof of concept data or clear competitive advantage. Effective licensing and divestment requires substantial management resources, something often in short supply within a fledgling enterprise.

The inescapable pressures of escalating R&D burn rate and investor expectation mean that few companies have the luxury of postponing the first steps towards commercialisation. Pharmaceutical and medical device companies, the main acquirers of early-stage assets, are under pressure to innovate more rapidly while containing R&D expenditure. The consequent demand for early-stage life science assets has arguably never been greater, but turning passing interest into deals demands clarity of purpose and preparedness. Agreements can be derailed due to a number of factors, but the commonest deal breakers of unrealistic financial expectation, misrepresentation of market data, lack of trust and slow progress can all be largely avoided through early adoption of effective business development practices and processes.[1]

This guide began as attempt to provide concise (and hopefully useful) answers to the commonest business development questions asked by early-stage companies: "when do we start?", "who do we talk to?" and "how much is it worth?" From conversations with fellow licensing professionals and would-be clients, it became clear that the role and mechanics of business development within early-stage companies may not always be understood.

In response, the scope of this guide has been broadened to give an introduction to the main activities and processes which, from experience, are needed by early-stage life science enterprises and to serve as a rough and ready overview for those contemplating first steps towards commercialisation. It is written from a licensing perspective, but it is hoped that those working with service or sales based business models will find something of interest.

This guide is a work in progress; it is greatly oversimplified in parts and with several glaring omissions. In defence, the intention is not to provide a state of the art business development manual, but to help in demystifying the commercialisation process (and besides, you can't beat the price). I welcome all feedback and encourage suggestions for expanded or additional content, including case studies, for possible use in an expanded revision.

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## The business development function

While the day to day conduct of business development varies with the nature of the company's business (whether discovery, development or service based), the objective is the same: the effective selling of expertise and know-how and the buying of complementary intellectual property or other assets.

Along with this goes responsibility for defining and communicating the unique selling points and inherent value of the asset ("the value proposition") and for developing and honing an appropriate commercialisation strategy, a function dependent on building and maintaining detailed and reliable business intelligence on prospects, competitors and market dynamics.

Whether the responsibility for business development is shared across the management team or resides with a single individual, it's important to recognise that the personal and collective skills required for effective commercialisation will change as a company and its value proposition evolve. A good management team needs to ensure that the right mix of technical and commercial awareness is represented in the business development function and that the commercialisation process can be fully executed and supported.

Early-stage value propositions are generally "science heavy". Support from the Chief Science Officer, senior scientists and project team leaders is essential, both in communicating the science behind the proposition and ensuring that the technical components of the selling message remain accurate and up to date. Establishing an effective commercial interface need not be time consuming but does need regular internal communication between the science and business development teams where development progress, anticipated key data and intellectual property generation can be communicated and subsequently factored into the business development plan.

Natural bias aside, external advisors can make an effective contribution to business development, through both mentoring and in support of specific projects or objectives. However, the responsibility for defining and executing commercial strategy should always reside with the management team and should not be dictated by advisors, regardless of their experience. Getting the best value from advisors starts with the drawing up of a well-defined and realistic brief. The establishment of clear objectives and agreed deliverables will minimise "mission creep" and maximise the value of the relationship. Schedule regular communication with your chosen advisor, continually review their activities and be prepared to revise or terminate the assignment if necessary.

## The value proposition

No two life science businesses are the same and it is the unique combination of intellectual property, know how, collective expertise and vision which makes early-stage companies attractive licensing partners or technology providers. Early-stage assets might comprise only limited data and a handful of patent filings, but even this modest package can be perceived to have significant value when the competitive advantage it confers- "the value proposition"- is clearly and credibly communicated.

Even the most astute prospective partner may not immediately comprehend the value of your proposition and should a tangible degree of interest be established, no prospective counterparty will define fair value for you. A fundamental prerequisite for successful commercialisation is to accept that the responsibility for defining, communicating and quantifying the value that a product or technology can offer lies with you, the seller.

In having a clear grasp of where value truly lies and how that value can be increased through focused effort, a company can avoid the internal indecision and misdirected development effort that too often handicaps the commercialisation process.

In selling, credibility and confidence are everything. Jeff Stewart and Ben Bonifant[2] have likened this to the "high ground" in warfare- a position of "offensive flexibility and defensive strength." In other words, when your proposition is based on a thorough, objective and above all defensible consideration of the how, where and why your technology or product creates value, you can defend that value and its basis and negotiate with confidence. The meek might be destined to inherit the Earth, but it's unlikely that they will conclude many licensing deals.

***"Luck is what happens when preparation meets opportunity"***
*Attributed to Lucius Annaeus Seneca (Roman philosopher and dramatist)*

## Positioning your asset

Establishing a credible value proposition is dependent on knowing how your product candidate or technology is positioned in relation to established products, against competing approaches in development and ultimately, where it will fit within the portfolio and strategic objectives of a potential licensing partner.

As in all navigational problems, an accurate estimate of position requires multiple points of reference. Focus on defining and understanding the unmet need that you believe your product or technology will address, whether your offering is "evolutionary or revolutionary", who the current players are, their historical efforts and strategic alliances, the breadth and scope of relevant intellectual property and the strengths and shortcomings of your competitors. Always look at the view from the other side of the table: what would a prospective licensee or buyer make of your professed advantages?

The classic SWOT analysis (Strengths, Weaknesses, Opportunities and Threats) remains an excellent tool for assisting in sharper definition of a value proposition, providing sufficient effort is put into identifying the key internal and external factors which impact on commercialisation.

SWOT analysis is also useful when comparing different in-house projects for the purposes of portfolio management and in evaluating licensing or buying opportunities. Comparison of several internal or external projects can be made easier by applying weighting (on a scale of 1 to 5, for example) to positive and negative attributes and comparing the cumulative score attained by each projects.

In the context of defining a value proposition, the SWOT terms can be broadly defined as:

**"Strengths"** – *the factors and capabilities that make your technology or product candidate competitive or superior to those marketed or in development, such as*:

- broad patent claims and comprehensive filings
- in-house expertise and know-how
- product or technology meets a clearly recognised unmet need
- cost or performance advantages

**"Weaknesses"** – *identified limitations that may prevent your technology or product candidate in succeeding, such as:*

- limited intellectual property
- shortfalls in resource or expertise
- complicated design or manufacturing requirements,
- high cost of goods

**"Opportunities"-** *changes or anticipated changes in the commercial environment which are likely to prove favourable to the technology or product candidate, such as:*

- emergence of new diseases
- changes in healthcare practices
- a product vacuum left by withdrawal of an established drug
- patent expiry of a potentially competing product

**"Threats"-** *current or future unfavourable changes in the commercial regulatory or competitive environments, such as:*

- change in the efficacy criteria required for approval
- increased safety requirements for approval
- imminent approval of a rival product with cost or dosing advantages

Let us consider MossTech Limited, an early-stage company which has identified a series of novel antibiotic substances produced by mosses. They are keen to commercialise their lead candidate, MT-001. The management team has assembled the key laboratory data generated by the company and collated intelligence on the current antibiotics market, investigational agents in clinical development and on competitor activities.

| Strengths | Weaknesses |
|---|---|
| • MT001 more potent than any existing antibiotic against certain bacteria including methicillin resistant *Staphylococcus aureus* (MRSA)<br>• Novel mechanism of action with no evidence of resistance<br>• Long half life *in vivo* | • Manufacture requires multi-stage synthesis which is costly and gives low yields<br>• Limited bioavailability on oral dosing<br>• Spectrum of activity identical to existing antibiotics |
| **Opportunities** | **Threats** |
| • Increasing prevalence and incidence of antibiotic resistance in hospital and community acquired infections<br>• A leading marketed product is close to patent expiry<br>• Entrance of new players has lead to an increased demand for early-stage antibiotic leads | • Key label indication (MRSA) is also claimed by numerous approved antibiotics<br>• Marketing applications have been submitted for four more antibiotics active against MRSA<br>• Clinical management guidelines recommend that narrow spectrum agents be restricted to second or third line treatment |

**Figure 1. SWOT analysis for MossTech's antibiotic product candidate, MT-001.**

MossTech's management conclude that, while a demand for novel antibiotics clearly exists, MT-001's spectrum of activity does not sufficiently differentiate it from current agents or from those known to be close to market approval. Even if approved as a treatment for MRSA, MT-100 would likely be restricted to being a second or third-line choice and be used in a relatively small patient population. Moreover, MT-100 looks expensive to manufacture.

MossTech's Chief Science Officer notes that MT-001 has significantly better activity against organisms which cause infection after orthopaedic surgery than currently used classes of antibiotics. He realises that the longer half-life of MT-100 might reduce or eliminate the need for repeated intra-operative dosing and that it could prove safer for use in individuals allergic to standard antibiotics.

A little desk research indicates that: there are few competing antibiotics in clinical development specifically for prevention of orthopaedic infection; that the prevalence of orthopaedic infection is high and that each episode is very costly to treat, so a product offering more effective prevention and easier dosing might justify a higher product price. MossTech's management team agrees that it will build the MT-001 value proposition around the identified advantages of potency, longer half-life and more convenient dosing in the prevention of orthopaedic infection.

# Two The Partnering Process

## Building a prospects list

The mechanics of prospect identification and network building have been made easier by the Internet, through social media networks and the multitude of annual regional and international partnering events, but the objective in developing a truly useful list of prospective licensees or buyers remains quality over quantity.

It's important to start the prospect identification process with a very clear view of what you intend to offer and what you need in return. For example, a co-development deal where the licensee will be responsible for the bulk of clinical development needs a partner with deep pockets and resources, whereas a straightforward divestment of intellectual property may attract interest from prospects with cash but modest development capacity.

Research your prospects before making that first approach. A number of major and mid-sized companies post comprehensive lists of their licensing requirements on their websites, often accompanied by an outline of their licensing process and key contacts. As an early-stage company, your licensing offering is likely to be fairly narrow or specialised and you are less likely to benefit from comprehensive subscription licensing databases or services than a focused search based on your own intelligence gathering[3].

Apply simple weighting criteria to your preliminary hit list which take account of a prospect's market presence and sales, licensing history, cash and development resources, track record in regulatory approvals and territorial presence. Learn something of their internal structure: is the licensing function centralised or are there designated licensing executives for different therapeutic categories?

Early-stage licensing deals often start through scientific curiosity on the part of a prospect's R&D team and it's always worth polling your own science team for possible contacts. Refine your shortlist through discussion with your industry network and advisors. Canvass your immediate network of Board members and advisors for opinions and insight.

## Getting the best out of partnering meetings

Partnering meetings are the biotech version of "speed dating" and with preparation, they can prove a time and cost effective means of gaining that first introduction to a number of prospective partners. Registration generally gives you access to an online partnering service with keyword-searchable company profiles and licensing objectives with which to begin building your list. Your online profile should be concise and written around appropriate keywords so that your particular offering is easy for others to identify

### Partnering meeting basics:

***DO:***

- Resist the temptation to fill every single slot in your meetings diary. It's important to leave time to organise notes, file business cards and for "*ad hoc*" meetings over a cup of coffee.
- Leave that 40 slide presentation at home. Time will be tight (generally less than 30 minutes per meeting) so forget the laptop and use a couple of printed slides in a binder if you need visual reinforcement of your proposition.
- Have the courtesy to allow your counterpart enough time to tell you about their company and licensing requirements. Listening and learning is part of the process.

***AVOID:***

- Weighing your opposite number down with marketing materials. A two page flyer is usually sufficient for a first meeting, to be followed up with more detailed collateral if there is a continued interest.

- Chasing only "big pharma". While large companies will field large business development teams, they also tend to be inundated by meeting requests. Select and rank your prospects by how well they are aligned with your licensing objectives, their licensing history and whether they have the cash and other resources needed to move your assets along.

- Switching to "autopilot" after the first ten meetings. Stay focused on communicating the specific points which you believe might matter to each different potential prospect you meet.

- Feeling obliged to accept every offer of a meeting. Politely refuse those which serve no strategic value, unless you are desperate for the company of service providers.

It's good practice to organise your collated notes and corresponding contact details as soon as you are back in the office. Review and rank those prospects which you consider worth a follow up with specific information, send a courteous email to everyone you met with and prepare a short memo for your management team and project team leaders. It's always possible that someone else in your organization has met with one or more of your prospects and can provide useful insight.

## Marketing collateral

A good communications company, capable of getting you industry press coverage and meetings with the right journalists can be worth the retainer, but Communication (with a capital "C") should not be confused with marketing, which needs its own strategy and supporting collateral, both printed and electronic.

The company website is an integral part of the marketing collateral package and it's worth investing in the services of a professional designer who understands that the website must broadcast and reinforce the marketing message. Keep the content fresh and provide links to downloadable collateral in PDF format. Use site tracking to monitor interest: who visits, how often, how long do they stay and what do they read?

Don't just rely on electronic media. Printed collateral has value as a "drop off" at both planned and *ad hoc* meetings. Commission a professionally designed and printed high quality folder which can hold a business card and several information sheets outlining the company and its key technologies or product candidates. Scientific publications can be included (copyright permitting) but avoid unnecessary bulk through stuffing the folder with company press releases.

Attractive information sheets can be produced in-house using a good quality office printer. Look at literature produced by companies with bigger design budgets to garner style tips. Avoid cramming a complicated piece of science onto one or two pages: pick out the key selling points, with a line or two detailing development status and a commercial "hook" describing market positioning and perceived value. Include specific contact details for a real live person, not the general company mailbox.

Take a modular approach. Not everything you do will be of interest to all audiences so have a selection of information sheets to hand. Update the sheets regularly to reflect progress and convert to PDF for attachment to emails and uploading to the website. Include version numbers for easy tracking. Establish an effective in-house review and sign-off process to ensure that content is accurate and current.

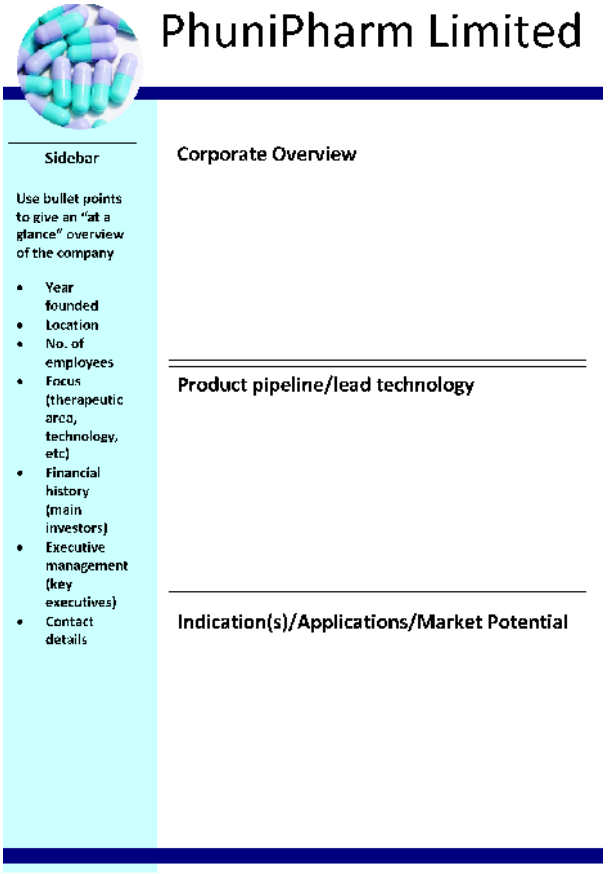


**Figure 2. Example of a simple layout for the first page of a non-confidential company information sheet**

## The licensing pitch

Once you have the attention of a potential counterparty, further information will be needed to support your licensing proposal. An inevitable question at this point is "do I need a confidentiality agreement"? The drafting and reviewing of a CDA can slow the discussion process and is pointless if you are only disclosing public domain information. If you reasonably expect to make more comprehensive disclosure, open discussion under CDA will expedite the initial evaluation process and assist in moving your prospective counterparty towards full diligence. Use a simple and concise template with an unambiguous definition of the purpose of the exchange (the "field" definition).

The second stage of evaluation generally involves scrutiny from a mix of individuals representing business development, licensing, technical, and possibly clinical and regulatory personnel and commonly begins with a group presentation. Ensure that you know who is going to be present on the counterparty's side well before the meeting or teleconference and shape your presentation to the audience.

Have an experienced colleague (and ideally someone outside of the company) review the presentation and listen to their suggestions. Rehearse. Have the right colleagues to hand to field detailed questions and agree which member of your presenting team will respond to questions on specific topics. Prepare a short summary of key facts and figures as an *aide-mémoire*. Avoid having to say "I'll need to get back to you on that one".

Presenting by teleconference is time and cost effective but bear in mind that your standard PowerPoint® presentation might not have the same impact without a live presenter in the room. There are a number of dedicated web conferencing services but it's hard to beat a simple teleconference where the receiving party is sitting with a printed (and therefore easily annotated) copy of the presentation in front of them. Numbered slides are needed to make this work! Group your slides into headed sections and take a modular approach: complicated technical slides which are not needed to give your audience a good general understanding of your proposition should be omitted or provided as an appendix to the main presentation.

Don't become the unwitting victim of your own "killer presentation". Keep it short and allow plenty of time for questions from the counterparty or for expansion of key points. As an early-stage company, strong science may be all you have but resist the temptation to walk your audience through your "journey of discovery"[4]. Forget the dramatic build-up and get the key selling points - market opportunity and the unique attributes of your proposition- upfront.

# Three License structure & basic valuation

## Eyes wide open

While licensing is predominantly viewed as a means of revenue generation, its strategic value is equally important. "Buy in" by a third party serves to validate your value proposition and even a modest deal can be of crucial in securing that second round of investment and to open up additional licensing prospects.

Chasing that first "real deal" brings its own particular excitement but needs a cool head, a clear notion of what you wish to achieve and of the obligations that different deal structures will impose. Signing up to a poorly-structured licensing deal will have lasting consequences. Ambiguous definition of ownership, of remaining rights on termination or change of control provisions or restrictions imposed by regional deals can complicate later licensing opportunities or impact on value in a future trade sale.

Is the partner right for you? Larger companies are well resourced but if your technology is one of a dozen that they have licensed in the last six months, it might not get the attention necessary to reach a point where you can realise its value. Big company strategy and budgets are not immune to internal review and shifts in priority. Gaining an understanding of a potential partner's internal process, long term commitment and commercial intent is critical before getting down to serious negotiation. Would a smaller but more agile partner be better, if they can give your project the degree of attention and nurture required to reach that first significant milestone?

Pay attention to environmental factors. For example, your partner may be in the process of engaging in a significant M&A transaction which at the very least might delay the negotiation process or could result in a strategic shift that will impact on future development of your asset. While licensing is regularly done across borders, unfamiliarity with cultural differences and the logistics of travel or working across different time zones can conspire to slow the licensing process.

## The license structure

Any license needs to be mutually beneficial but has also to satisfy the immediate and longer term strategic objectives of your business. For example, entering into a co-development agreement might significantly enhance your anticipated share of future revenues but brings resource implications which could impact on the development and commercialisation of other assets in your portfolio.

The proposed license structure needs to take reflect the strategic requirements and intentions of the counterparty: do they intend to commercialise the asset themselves or develop it to a point where they can secure a larger development or marketing partner, is their interest confined to a specific use for the asset, such as a single disease indication and will exploitation be confined to a defined territory?

Early-stage data may be too sparse for a potential partner to immediately commit to a licensing deal. An option agreement, where the counterparty commits to entering into a licensing arrangement on successful conclusion of either an ongoing study or jointly-designed new study, or otherwise undertakes its own evaluation of the technology can serve to keep the counterparty engaged.

Option agreements formally establish an interest in commercialisation but can be two-edged since no significant revenue is usually received until the option is exercised. A signature fee is difficult to justify where the option is non-exclusive and even in an exclusive arrangement, the counterparty may be reluctant to risk an upfront payment if it has committed to meeting all study costs. The opportunity cost of an option deal can be mitigated by tight definition of the criteria for exercise and to minimise the exclusive option period. License terms should be in place long before the end of the option period, not negotiated after exercise.

Not all option agreements will be exercised. The agreement needs to make clear provision for ownership of data generated by the parties during the option period and for its commercial exploitation. If the counterparty has incurred significant cost, it may argue for some retention of downstream rights, for example a modest share in revenues from any future deal which involves disclosure of data developed during the option period to another party. Other counterparties may be more benign in that they will allow commercial exploitation of data providing their identity is not disclosed to other parties.

Early-stage companies often hold particular expertise which the counterparty might wish to access under a license and co-development agreement. As “shared endeavour”, co-development deals afford the licensor a larger share of future value, scope for negotiating development funding and possibly equity investment. The requirement to service and manage a co-development arrangement can place a strain on the resources of a small company and reduce the ability to progress other assets and secure deals with other parties. This can lead to actual or perceived overreliance on a single key relationship.

Risk may be mitigated by ensuring that the deal terms are sufficient to secure extra personnel or facilities needed to meet your co-development obligations, through effective management by joint technical committee or other mechanism and by retaining the flexibility and resource to pursue deals with other parties. Even the most amicable co-development agreement can be terminated due to either technical failure or through strategic shift and again, clear definition of the rights to exploit jointly-developed intellectual property is a crucial part of the license.

Other aspects of licence structure for consideration include sublicensing and territorial restrictions. A licensee may be attractive because it holds particular expertise or complementary technology but may not have sufficient breadth or resource to complete commercialisation. The licensee needs the freedom to sublicense to a suitable partner at commercially acceptable terms, while you as licensor can rightly expect a share of revenues accruing to the licensee based on the actual value split negotiated between your licensee and the sublicensee.

The decision to geographically limit license rights may be appropriate when the counterparty is a strong regional player, where the potential market is specific to a certain region or where there is only territorial intellectual property protection. A regional deal can have implications for securing subsequent deals in other territories and it is important to define the obligations of a regional partner with respect to data sharing, branding and trademarks, marketing collateral and pharmacovigilance.

## Placing a value on early-stage assets

Early-stage valuation presents an interesting paradox. No consensus exists as to the most appropriate means of valuing early-stage life science projects and yet the licensing process requires that both parties negotiate a fair price based on a shared perception of value. Since deals are done on a daily basis, the absence of a universally accepted valuation method clearly does not present an insurmountable obstacle.

Like beauty, value is in the eye of the beholder. While all licensing deals involve some element of quantitative analysis, the decision to proceed with a negotiation is often directed by other factors, not least the counterparty's confidence that the seller has the skills and professionalism to participate in a meaningful negotiation process and will be able to support that process through the timely provision of a term sheet, response to any counterproposal and in satisfying due diligence questions. Deals are not won solely by the numbers on a spreadsheet but through convincing the counterparty that the transaction represents fair value and that, you the seller, can deliver that value without undue delay or complication.

All valuation methods have flaws and limitations. Given the degree of risk associated with early-stage assets, any derived value can only serve as a broad indication of what the asset could be worth under defined conditions. Provided the limitations of valuation are recognised and that credible inputs are used, a simple valuation model can at least serve to determine the impact of different deal terms and structure on the relative return to you and the licensee.

For example, a generally accepted value split for early-stage licensing deals is in the range 10-20% to the licensor and 80-90% to the licensee. Opening with terms which give a value split in this range will make for smoother negotiations and increased credibility, even if the overall opportunity value is debatable.

At their simplest, valuation methods capture the estimated spend necessary to take an asset to market together with the value of forecast revenues to generate future annual cash flows. A discount, reflecting the cost of capital is applied to the sum of future cash flows, yielding the current value of the asset (NPV, the net present value). Since value depends on the successful transition of an asset through the development and approval process, a more realistic approach is to apply a further discount which reflects the probability of reaching market to give a "risk-adjusted" NPV (rNPV).

More sophisticated modelling techniques such as Monte Carlo analysis simultaneously consider thousands of scenarios where a range of values is assigned to each risk factor to generate a distribution of project NPVs together with their associated probabilities. Decision tree analysis and real options valuation consider the impact that real world development project decisions (proceed/abandon/repeat the study) have on overall value and on the value at each key decision point[5].

Valuation through reference to similar stage deals has little practical worth for determining early-stage deal terms. Headline "bioworld" deal values give little indication of the true potential return to a licensor and the fine detail of early-stage deals involving privately-held companies is rarely available in the public domain.

***"All models are wrong. Some are useful"***
*Attributed to George Box, chemist turned industrial statistician*

## Estimating market potential and revenue streams

Since you may need share your valuation model or at least the underlying assumptions with a prospective counterparty during negotiation, it is crucial that your grasp of market potential be credible, defensible and reflects your stated value proposition with regard to positioning and market advantage.

Estimates of market potential may be "top-down", where potential market share is estimated as a share of the existing market ("the market is worth $5 billion and we're going to take 10 %") or "bottom-up", where the potential treatment population, treatment uptake and cost are estimated from first principles derived from desk research. A top-down approach is appropriate where the asset will compete with and displace existing products. However, the appeal of innovative products is that they serve unmet needs and consequently create new market opportunities. Provision of a quantitative description of these future untapped markets can only strengthen your business case

A well constructed bottom-up model also allows consideration of different scenarios, for example, differences in market potential if a drug is approved as either a first-line or second-line treatment. The information necessary to construct a market forecast can be collated through consideration of the sales and market development history of approved products used in a comparable indication, from national and international healthcare statistics, epidemiological data, health technology assessments and from a variety of other public domain sources.

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## Constructing a "bottom up" forecasting model

Agitans Limited is working on AGIT-8, a new treatment for Parkinson's disease. From the results obtained in preclinical studies, the management believes this drug will be particularly effective in sufferers with severe symptoms which cannot be adequately controlled by available medications. Agitans has been approached by a major European pharmaceutical company interested in licensing AGIT-8 and has requested opening terms.

As a first step, the company constructs a simple bottom up forecast to provide an estimate of the available treatment population (the number of Parkinson's disease sufferers who experience severe symptoms) in the prospective licensee's target market (the EU15 Member States) and the market potential of the drug should it be approved as either a second-line or first-line treatment.

Desk research indicates that that there are almost 700,000 people living with Parkinson's disease in the EU15 Member States. Over a quarter of these individuals have severe symptoms, of which the majority (85%) don't obtain adequate benefit from current medication, giving a potential treatment population of about 152,490 sufferers.

Parkinson's disease is expensive to treat. Taking a conservative approach of assuming that the price of AGIT-8 will be competitive with the current annual cost of conventional treatment gives the drug a market potential of €762 million. Agitans knows is not alone in this field and anticipates competition from other new treatments. Assuming AGIT-8 can eventually capture one third of the market, the drug could have potential annual sales annual sales of €252 million if approved as a first-line treatment.

A small percentage of Parkinson's disease patients with severe uncontrolled symptoms receive treatments such subcutaneous or gastric bypass drug administration or deep brain stimulation via implanted electrodes at a cost of €40,000 per patient per year. Conservatively pricing the annual treatment cost of AGIT-8 at half of this figure gives a total market potential of around €396 million. There is a high unmet need in this smaller patient population and Agitans anticipates a peak penetration of 50%, giving potential annual sales of €198 million should AGIT-8 receive approval only as a second-line treatment for severe Parkinson's disease refractory to non-oral therapy.

| | |
|---|---|
| EU15 population at 2010 | 324,247,781 |
| Proportion of population aged 65-79 years | 13.30% |
| Prevalence of diagnosed Parkinson's Disease in those aged >65 years | 1.60% |
| Number of patients with Parkinson's disease | 689,999 |
| Proportion of patients with severe symptoms | 26% |
| Proportion with inadequately controlled symptoms | 85% |
| **Target patient population** | **152,490** |
| **1. Market potential as a first line treatment:** | |
| Annual treatment cost per patient (€) | 5,000 |
| Total market potential (€) | 762,450,000 |
| Peak penetration | 33% |
| **Peak sales (€)** | **251,608,500** |
| **2. Market potential as a second line treatment:** | |
| Current uptake of alternative treatments in target patient population | 13% |
| Number of patients opting for alternative treatments | 19,824 |
| Annual treatment cost per patient (€) | 20,000 |
| Total market potential market (€) | 396,474,000 |
| Peak penetration | 50% |
| **Peak sales (€)** | **198,240,000** |

**Table 1. A simple "bottom up" model for use in estimating target patient populations and the market potential of AGIT-8, a candidate treatment for severe Parkinson's disease[6]**

## Development costs & success rates

In early-stage licensing, the majority of the development burden will be borne by the licensee and this expenditure (along with the associated degree of risk) will shape the counterparty's perception of value. Clinical trial size and complexity will of course vary with the therapeutic category and the proposed label indication.

Commonly used estimates of drug development costs for each stage of development are available from the literature.[7] More tailored estimates can be made through consideration of past or ongoing studies of similar drugs. Clinical trial design is often disclosed in press releases or can be found in the invaluable NIH database, ClinTrials.gov[8], which lists clinical studies from around the world.

For example, a search of studies of investigational agents currently in development for Parkinson's disease indicate that a typical Phase II study involves around 80-100 subjects, while a Phase III requires around 350-400 subjects. The cost per subject will depend on the type of clinical or laboratory measurements required and the number of study sites required but again, estimates can be made from information in the public domain[9].

Drug development is a risky business. Drugs in development fail for a number of reasons, with early failure being commonly due to toxicity or poor bioavailability, while late stage failure results from insufficient efficacy or tolerability and increasingly, economic reasons. Any fair valuation needs to take account of the probability of success at each future step in the development process. The most commonly used values have their provenance in analyses undertaken by the Tufts Center for the Study of Drug Development[10] by Joseph Dimasi and colleagues and by Ismail Kola and John Landis[11].

The applicability of these success rates to early–stage valuation models is contentious but they at least provide a recognized and credible starting point. Ralph Villiger and Boris Bogdan have more recently undertaken analyses of the success rates specific to biotech drug and biologics development. A summary of their findings can be found on the Avance website (see Endnote 5).

## Building a simple risk-adjusted NPV (rNPV) valuation model

From your sales forecast and the estimates of development cost and success rates gathered through desk research, it's possible to construct a simple risk-adjusted valuation model to assist in developing opening terms.

The range of values for the key inputs of royalty rate and discount rate for cost of capital are widely debated. The reality is that early-stage royalty rates fall into a relatively narrow range, typically 5-10% for preclinical pharmaceutical deals (and generally below 5% for drug delivery, diagnostic and agricultural biotech deals). If the licensee will require additional royalty-bearing licenses from another party in order to commercialise your technology, the modelled royalty rate will need to be adjusted down to a fixed minimum to compensate for royalty stacking. If product sales exceed a forecast level, it's not unusual to increase the royalty rate on any sales achieved above an agreed level.

Discount rates commonly fall into the range 10-15% for larger companies and 15-20% for small companies. The impact of varying royalty and discount rates and the size and timing of milestone payments or other variables on overall value and value share can be tested in your model in a sensitivity analysis.

Agitan's forecast for its new treatment for severe Parkinson's disease indicated potential peak annual sales of €450 million (Table 1) if successful in gaining approval for both first-line and second-line indications. Taking literature values for average drug development cost and success ("transition probability", that is the chance of entering the next stage of clinical development) and a small company discount rate of 15%, we can build a simple rNPV model to examine the impact of different deal terms on the share of a project's present value on the accruing to the parties[12].

| **Transition probability** | **Ph I** | **Ph II** | **Ph III** | **Submission** |
|---|---|---|---|---|
| | 65% | 45% | 65% | 85% |
| **Discount rate licensee** | 10% | | | |
| **Discount rate licensor** | 15% | | | |
| **COGS & Marketing** | 35% | | | |
| **Peak sales €m** | 450 | | | |

| **Opening Terms** | **€m** | | **€m** | |
|---|---|---|---|---|
| Upfront | 3.5 | Submission | 10.0 | |
| Ph II milestone | 2.0 | Approval | 10.0 | |
| Ph III milestone | 3.0 | Sales milestones | 12.5 | >400m annual sales achieved |
| | | | 12.5 | >1200m cumulative sales achieved |
| | | Royalty on net sales | 7.5% | |

**Tables 2 and Table 3.** Inputs used in the illustrative rNPV model below and summary of opening terms used to achieve a 20% share of the estimated project value for the licensor

| Project cashflow | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| | Preclin | Phase I | Phase II | Phase II | Phase III | Phase III | Phase III | Submission | Market | Market |
| Transition probability | 100% | 65% | 100% | 45% | 100% | 100% | 65% | 85% | 100% | 100% |
| Probability | 100% | 100.00% | 65.00% | 65.00% | 29.25% | 29.25% | 29.25% | 19.01% | 16.16% | 16.16% |
| R&D Costs | -1.0 | -6.0 | -10.0 | -10.0 | -25.0 | -25.0 | -25.0 | -5.0 | | |
| Sales | | | | | | | | | 45.0 | 67.5 |
| COGS, Marketing | | | | | | | | | -15.8 | -23.6 |
| Cashflow | -1.0 | -6.0 | -10.0 | -10.0 | -25.0 | -25.0 | -25.0 | -5.0 | 28.6 | 42.9 |

| | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|---|---|---|---|---|---|---|---|---|---|---|
| | Market | Market | Market | Market | Market | Market | Market | Market | Market | Market |
| Transition probability | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% |
| Probability | 16.16% | 16.16% | 16.16% | 16.16% | 16.16% | 16.16% | 16.16% | 16.16% | 16.16% | 16.16% |
| Sales | 112.5 | 225.0 | 450.0 | 450.0 | 450.0 | 450.0 | 450.0 | 450.0 | 450.0 | 450.0 |
| COGS and marketing | -39.4 | -78.8 | -157.5 | -157.5 | -157.5 | -157.5 | -157.5 | -157.5 | -157.5 | -157.5 |
| Cashflow | 73.1 | 146.3 | 292.5 | 292.5 | 292.5 | 292.5 | 292.5 | 292.5 | 292.5 | 292.5 |

| Licensee | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| | Preclin | Phase I | Phase II | Phase II | Phase III | Phase III | Phase III | Submission | Market | Market |
| Upfront | -3.5 | | | | | | | | | |
| Milestones | | | -2.0 | -3.0 | | | | -10.0 | -10.0 | |
| Royalties | | | | | | | | | -3.4 | -5.1 |
| Risk Adjusted Cashflow | -4.5 | -6.0 | -7.8 | -8.5 | -7.3 | -7.3 | -7.3 | -2.9 | 2.6 | 6.3 |

| | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|---|---|---|---|---|---|---|---|---|---|---|
| | Market | Market | Market | Market | Market | Market | Market | Market | Market | Market |
| Milestones | | | -12.5 | | -12.5 | | | | | |
| Royalties | -8.4 | -16.9 | -33.8 | -33.8 | -33.8 | -33.8 | -33.8 | -33.8 | -33.8 | -33.8 |
| Risk Adjusted Cashflow | 10.5 | 20.9 | 39.8 | 41.8 | 39.8 | 41.8 | 41.8 | 41.8 | 41.8 | 41.8 |
| | | | | | | | | | Licensee rNPV | 49.41 |

| Licensor | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| | Preclin | Phase I | Phase II | Phase II | Phase III | Phase III | Phase III | Submission | Market | Market |
| Upfront | 3.5 | | | | | | | | | |
| Milestones | | | 2.0 | 3.0 | | | | 10.0 | 10.0 | |
| Royalties | | | | | | | | | 3.4 | 5.1 |
| Risk Adjusted Cashflow | 3.5 | 0.0 | 1.3 | 2.0 | 0.0 | 0.0 | 0.0 | 1.9 | 2.2 | 0.8 |

| | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|---|---|---|---|---|---|---|---|---|---|---|
| | Market | Market | Market | Market | Market | Market | Market | Market | Market | Market |
| Milestones | | | 12.5 | | 12.5 | | | | | |
| Royalties | 8.4 | 16.9 | 33.8 | 33.8 | 33.8 | 33.8 | 33.8 | 33.8 | 33.8 | 33.8 |
| Risk Adjusted Cashflow | 1.4 | 2.7 | 7.5 | 5.5 | 7.5 | 5.5 | 5.5 | 5.5 | 5.5 | 5.5 |
| | | | | | | | | | Licensor rNPV | 12.41 |
| | | | | | | | | | Value share | 20.1% |

**Figure 3.** Illustrative rNPV model showing the project cashflow and value to the licensee and the licensor and the licensor's share of project value.

The illustrative rNPV model (Figure 3) lays out the expected project cash flow from the present until 20 years in the future based on the estimated peak sales of AGIT-8, rate of market penetration ("ramp up"), time and cost of development and registration, cost of goods sold (COGS) and marketing expenses. Below this are the licensor and licensee future cash flows, discounted for the probability of success at each stage and the respective costs of capital. The discounted sum of these cash flows gives the corresponding risk-adjusted net present values.

As a small private company, cash is important to Agitans and the most desirable deal would bring a substantial upfront payment. With limited resources and clinical trial experience, the company's preference is for a simple license rather than committing to a co-development agreement, even if this would mean a more favourable value split.

Plugging initial terms into the rNPV model, it becomes apparent that the desired €10 million upfront payment, with €10 million in development milestones and a 10% royalty would give Agitans almost 34% of the project value. The management appreciates that, despite AGIT-8's potential, this value split is unlikely to prove acceptable to the counterparty, given the inherent risk in a preclinical deal.

By adjusting terms, the company find that a more modest €3.5 million upfront, together with €5.0 million in development milestones, €20 million on regulatory success and a 7.5% royalty rate returns a 20% value split, which is likely to prove more acceptable. The potential pre-launch deal value is a respectable €27.5 million and the value split is barely altered by the inclusion of €25 million in sales related milestones.

Agitans's management now have opening terms which give something close to the expected value split for a preclinical licensing deal and which associate reward with downstream success, indicating their willingness to share risk with the counterparty.

# Four The term sheet and beyond

## The term sheet

The purpose of the term sheet is to lay out, in a concise and plain fashion, opening (non-binding) financial terms and the respective rights, obligations and responsibilities of the parties. The term sheet is generally the first formal summary of the deal structure and terms to be seen by the counterparty. As such, the term sheet will dictate the counterparty's initial responses and counterproposal, and hence shape the negotiation process.

While there is a natural enthusiasm to "get the deal moving", time spent crafting the term sheet is never wasted. A term sheet should not be offered until you are confident that you have a clear and defensible proposition with respect to financial terms, deal structure and conditions. Few opening term sheets are immediately acceptable but the need for multiple iterations resulting from lack of clarity or indecision on the part of the licensor is an unnecessary cause of delay and frustration.

Broadly, the term sheet should define the technology or product offered for licensing and the corresponding intellectual property, the field of use and any exclusions (for example, diagnostic and therapeutic, human or veterinary use), the territory (whether global or regional), the type of licence (for example, exclusive and sublicensable), the duration of the licence, the respective responsibilities of the parties (for example, clinical programme management), financial terms (signature fee, milestone payments and royalties). Keep the layout simple and save the legal language for the draft agreement.

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## Negotiation

Negotiation is the process through which you and the counterparty reach accord over terms. Negotiation also offers the opportunity to further develop your relationship with the counterparty. Courtesy and professionalism at all times will expedite negotiations and serve you well even after the agreement is concluded.

Effective negotiation requires a team approach, with the team representing commercial, scientific and legal skills. It's imperative that each team member is clear on their individual role, on the objectives of the process and where and when their required input begins and ends. Role-playing exercises can be a useful way of developing a sharper awareness of, and responses to, the dynamics of the negotiation process. There may be some value in not having the CEO or an individual with signing authority on the team, as this gives a legitimate reason for to pause for broader consultation with executive management before assenting to any binding condition or revision.

The first counterproposal may be short of your expectation, but do not automatically assume that the motivation is just to get a cheaper license. The counterparty, generally with the benefit of more experience, may have a different perception of the risk involved.

Request clarification of the thinking behind any proposed change in terms or structure and ensure that your own counterproposal both acknowledges and specifically responds to any concerns raised during negotiation. Assuming that there is no fundamental disagreement over the quantum of the deal, the perception of risk may be reduced by aligning milestones against mutually recognised achievements or reducing an early milestone in return for a larger, later milestone payment.

Be open when explaining your own perspective. Intransigence is not a negotiating tactic and you should communicate to the counterparty when and why you have reached the limit of your tolerance on proposed changes in deal value or responsibilities. Licensing discussions develop their own momentum and are burdened with natural expectation from colleagues and other stakeholders. The decision to terminate is never easy; hence the need to clearly establish your acceptable limits and degree of compromise well in advance

An extensive publishing industry has grown up offering advice on how to negotiate successfully (from seating the counterparty so that they have the sun in their eyes to always dressing in a blue suit.). The reality is that deals are closed because each party believes that its respective reward is acceptable in the face of mutually acknowledged risk. If you need the comfort of a mantra during negotiation, then “shared risk, shared reward” is no bad choice.

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## Due diligence

Due diligence is the process of evaluating a prospective business decision through review of financial, material, and legal information. The diligence process allows the counterparty to better define the risk inherent in a transaction. Being able to respond to diligence questions in a timely and effective manner with considered, unambiguous, verifiable and concise answers will expedite the licensing process and enhance your credibility with the counterparty.

Take control of the diligence process well before it begins. Nominate one individual (usually on the business development team) to co-ordinate liaison with the counterparty so that diligence questions are relayed to the most appropriate individual and that responses are reviewed for completeness and recorded before forwarding. Ensure that you have sufficient administrative support to manage the collation and supply of needed documents and information.

A virtual data room (VDR) is a secure online repository of scanned and electronic documents. A VDR can greatly expedite the diligence process as it provides a centralised source which is easily updated and eliminates the need for multiple physical copies or email attachments when responding to diligence requests. More importantly, the counterparty’s diligence process is not constrained by the need to travel to consult documents and their diligence team can be expanded or its composition altered as required to address specific issues.

It's possible to electronically manage the diligence process using low cost or even free secure online repositories such as Huddle and DropBox[13] when only a single counterparty is involved. The cost and sophistication of dedicated VDR services varies and it is worth requesting a demonstration or trial before committing to a service contract. It's critical that your VDR be intuitive to use: your counterparty should not be expected to spend time in learning how to navigate the system. An easy log-on procedure, onscreen viewing, printing and downloading are essential, as is automatic alerting by email to advise the counterparty when documents are added or changed in the VDR. Reporting functions which allow monitoring of document access can be valuable if a diligence transaction involves multiple counterparties or advisors.

Early-stage assets are largely defined by their corresponding intellectual property, whether granted or at application stage. A key objective of the counterparty's diligence is to ensure that there are no hindrances to the exploitation of intellectual property or conflicting third party claims and that the intellectual property and any improvements are exclusively owned and controlled by the licensor.

Besides copies of granted patents and applications, the counterparty will wish to see employee, consultant or advisor agreements to confirm that they address intellectual ownership and assignment of rights, any licenses or assignments from third parties such as a university technology transfer office or academic inventor, commercial or academic collaboration agreements, grants or research sponsorship and any correspondence relating to litigation or disputes over intellectual property rights. A third-party review and summary of your intellectual property prepared by your patent attorney and stating the main scope and claims of patents or applications, their status in major territories, anticipated expiry dates can greatly assist the counterparty.

Prepare detailed summaries of key technical data and provide third party reports from any service providers which have undertaken preclinical testing or other pertinent analyses on your behalf. In-house technical reports and development plans should be collated into a professional format with sign-off from the appropriate manager or section head.

Even if a VDR is used, the counterparty's diligence team may still wish to visit your offices. Ensure that all documentation is at hand in labelled and tabbed folders and provide convenient online access with printing capability should the counterparty need to revisit the VDR. Offer to provide a short overview presentation, if the counterparty feels that this will assist them. Have key colleagues on hand to clarify or expand on responses to technical or other questions. Provide the counterparty's diligence team with space to work in privacy and without interruption.

Members of counterparty's diligence team may also be involved in license negotiations but avoid the temptation to pre-empt the negotiation process by interrogation of the diligence team. It is however, a good opportunity to begin developing the relationship with the counterparty through exhibiting professionalism and courtesy to the diligence team.

## Beyond the term sheet

The effort put into building your value proposition, offering realistic terms and deal structure and in satisfying the counterparty's diligence questions has paid off. You have reached a binding accord and your Board is satisfied that you have made the right deal. What now?

The immediate actions necessary to move to final agreement will depend on which party assumes responsibility for drafting. Your partner might have the benefit of in-house counsel but multiple demands on their time can mean that it may be faster for you to manage the drafting process. If so, your own legal advisor will require a comprehensive briefing to be able to package your negotiated terms in an acceptable document. This is also an opportunity to ensure that your agreement recognises and addresses conditions imposed by third party agreements, with academic inventors or technology transfer offices for example.

Avoid creating tension in the early days of the relationship by ensuring that you and the counterparty have a clear understanding of your respective review and sign off processes and of the expected time to execution. If you and your counterparty have agreed for a public announcement of the deal, agree responsibility for drafting of the press release and communicate your respective review and sign-off procedures well ahead of the execution date.

Resist the temptation to kick off the alliance while the ink is still drying on the agreement. Review your responsibilities and obligations and focus on the effective delivery of any agreed materials and data. Ensure that your alliance management team is aware of their expected function on any joint steering or development committee, of any associated reporting obligations and of the limits of their role.

Even with good communication and an excellent relationship, agreements remain vulnerable to the impact of R&D failure or delay, competitor success and strategic shifts in focus. Be open to renegotiation if you and the counterparty still share the belief that value can be preserved through a change in objective or scheduling. Termination is never welcome, but providing you have adequately addressed post-termination data ownership and the right to exploit, it may be a less traumatic option than drawn-out litigation and the frustration of having a valuable commercial asset stuck in limbo.

Alexander Yule Consulting works with businesses at all stages of their commercial and corporate development, and particularly in the provision of cost effective business development support and interim leadership to early-stage enterprises.

The principal has over 20 years experience in commercial and corporate support, working at senior level on behalf of life science and pharmaceutical companies (UK, Scandinavia and North America) across a range of product categories including oncology, CNS, urology, vaccines, infectious disease, medical devices and OTC/consumer healthcare

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## Endnotes

[1] Along with having a poor intellectual property position, unrealistic financial expectations, misrepresentation of market data, mistrust and slow progress were cited as the key deal breakers identified in an analysis conducted by Fabian Schmidt and Christian Sculer "Evaluating licensing opportunities" Business Development & Licensing Journal (9)2009, Business Development & Licensing Journal (PLGeurope.com).

[2] The valuation high ground. Jeffrey J Stewart & Ben Bonifant, Nature Biotechnology 27(11) 2009 980-983.

[3] Innovaro Pharmalicensing (http://pharmalicensing.com/) offers a "pay per click" partnering service which might provide a cost-effective solution for some companies. I have no personal experience of this system.

[4] Designated "Business Development Sin 1" by Jeff Stewart and Ben Bonifant in "The seven deadly sins of business development" Nature Biotechnology 26(4) 2008 1-3. The other six sins listed are: assuming the market is static; product blindness; failing to account for physician's financial motivation; ignoring reimbursement; speaking the wrong valuation language and pitching the "perfect product".

[5] For anyone wishing to dive deeply into the mechanics of valuation, I strongly recommend "Valuation in Life Sciences. A Practical Guide" (2nd Edition, Springer 2008) by Ralph Villiger and Boris Bogdan. Their company website (http://www.avance.ch) hosts a wealth of informative articles.

[6] The numbers used in the example forecasting table are for illustration only although they are drawn from legitimate public domain sources. For simplicity, I have not extrapolated the target patient populations through to the anticipated year of launch and beyond.

[7] The price of innovation: new estimates of drug development costs. Joseph A. DiMasi, Ronald W. Hansen and Henry G. Grabowski, Journal of Health Economics 22 (2003) 151–185, also R&D costs and returns by therapeutic category. Henry G. Grabowski, Joseph A. DiMasi and John Vernon, Drug Information Journal, 38 (2004) 211–223.

[8] ClinTrials.gov is a service provided by the US National Institute of Health http://clinicaltrials.gov/

[9] The Clinical Trial Magnifier website (http://www.clinicaltrialmagnifer.com) offers some useful analyses of clinical trials being conducted in selected therapeutic categories.

[10] Tufts Center for the Study of Drug Development http://csdd.tufts.edu/index.php

[11] Can the pharmaceutical industry reduce attrition rates? Ismail Kola and John Landis, Nature Reviews Drug Discovery (3) 2004 711-716.

[12] Several surveys undertaken on the preferred valuation method indicate that rNPV and benchmarking are the most commonly used methods, with option based methods being only rarely used. This is not to say that rNPV is always the "best" valuation method but I have found it to be a pragmatic choice when developing terms for uncomplicated licensing transactions.

[13] Huddle and DropBox accounts are available at http://www.huddle.net and http://www.dropbox.com, respectively. There are a number of similar providers offering low cost secure data access and while these are not true VDR services, they can assist in expediting the bulk provision of electronic documents needed to support due diligence involving a single party. I've found the usability of dedicated VDR services to vary greatly and strongly recommend requesting a trial or extensive demonstration before commitment.

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