

Modern Biosciences plc

Company analysis

Stewart Adkins, May 2008

Disclaimer

The views and opinions contained herein do not take into account the specific business objectives, investment objectives, financial situation or particular needs of any particular person.

This document is for information purposes only and it should not be regarded as an offer to sell or as a solicitation of an offer to buy the securities or other instruments mentioned in it. This report is based on third party information and current public information that we consider reliable, but we do not represent that this information, is accurate or complete and it should not be relied upon as such. It is provided with the understanding that we are not acting in a fiduciary capacity. Opinions expressed herein reflect our opinions and are subject to change without notice.

Stewart Adkins / Expert Analysis Group Ltd

Analyst certification

The views expressed in this research report accurately reflect the analyst's personal views about the subject companies and their securities and that the analyst has not been, is not, and will not be receiving direct or indirect inducement for expressing the specific recommendations or views expressed in this research report.

Stewart Adkins

Stewart Adkins

Stewart has spent most of his career in the investment banking industry. He was head of pharmaceutical research at Lehman Brothers, a position held for some 23 years, and was one of the most highly regarded analysts in the pharmaceutical sector, consistently ranking number 1 in investor polls such as Institutional Investor Survey for many years. Since leaving Lehman Brothers in 2006 Stewart has been involved in a number of advisory and corporate finance transactions in the pharmaceutical and healthcare services sectors. He is Commercial Director for Marketing Performance Limited, a company specialising in the application of leading edge statistical tools to improve resource allocation in marketing and in sales force effectiveness. He was external adviser to Oxfam in the research and publication of Investing for Life, a briefing paper on Access to Medicines and is current working group member of PharmaFutures 3, a consortium of stakeholders examining different business models within emerging markets. Stewart is also a Non-executive Director of Meldex International, an AIM-listed pharmaceutical company.

Expert Analysis Group Ltd

Expert Analysis Group is a consulting firm that deploys industry experts individually or in teams to undertake client projects; usually detailed analysis of individual companies or sectors. The consultants used by Expert Analysis Group Ltd usually have a long and distinguished career in financial markets either in Research, Corporate Finance or particular product disciplines.

Expert Analysis Group is authorised and regulated by the Financial Services Authority.

www.expertanalysisgroup.com

Table of Contents

Investment Overview	5
Providing modern solutions to a traditional problem	5
Executive Summary	6
Systematic external sourcing of novel products	6
Quickly to Proof-of-Principle in man	6
Monetisation by licensing to the pharmaceutical industry	6
The Pharmaceutical Industry Needs Modern Biosciences	8
25% of drugs entering development are in-licensed	8
Modern Biosciences Business Model	10
There are three key aspects to the Modern Biosciences business model	10
Strong relationships with academic institutions	10
Can the pharmaceutical industry access universities directly?	10
Focus, flexibility and engagement; key factors of Modern Biosciences success	11
How does Modern Biosciences select products?	12
How does Modern Biosciences develop products?	12
Lilly's Chorus - A precedent for rapid/low cost early drug development	13
How can Modern Biosciences sustain competitive advantage?	14
Does Modern Biosciences have limits to its scalability?	14
How will Modern Biosciences create value?	15
Turning Proof-of-Principle into cash via licensing to the pharmaceutical industry	16
Risks to Modern Biosciences business model	17
Financial risks	17
Technical or scientific risks	18
Personnel risks	18
Competition Risk	18
The Financial Model and Valuation	19
Theoretical valuation based on steady state	19
Theoretical valuation based on NPV of product assets	20
Pipeline, Progress and Value	22
Rimcazole for Cancer	23
Rimcazole accumulates in tumour cells, kills them and stops blood vessel growth	23
Rimcazole's mode of action looks intriguing	23
Stopping blood vessel growth (anti-angiogenesis) is a well known phenomenon	23
Toxicology is established, allowing Proof-of-Principle in cancer patients	24
Six patent applications have been filed	24
Does rimcazole have commercial potential?	24
OsteoRx for Rheumatoid Arthritis	25
An oral disease modifying agent for Rheumatoid Arthritis	25

Two activities for the price of one; multiple disease activity from one drug	26
OsteoRx – a lead drug is being optimised	26
Does OsteoRx have commercial potential?	26
Pipeline opportunities	27
Shareholder Structure	28
Management Team	28
Appendix 1: Background to the Pharmaceutical Industry	30
Appendix 2: The R&D Process - Timelines, Attrition Rates and Costs	31
High late phase costs should encourage earlier attrition	31
Attrition is historically due to lack of efficacy and toxicology (side-effects)	32
Development attrition rates vary by therapeutic category and by data source	33
Appendix 3: Traditional Pre-clinical Drug Development is Costly and Time-consuming	36
The exploratory IND is much less onerous in time and costs	37

Investment Overview

Providing modern solutions to a traditional problem

Modern Biosciences (MBS) provides a contemporary solution to the traditional problem of poor R&D productivity in the pharmaceutical industry. The business model is straightforward and the opportunity for value creation is unlimited.

- MBS sources novel and exciting products from British Universities and academic laboratories.
- MBS conducts only those critical experiments needed to get a “go/no-go” decision for Phase II trials, including Proof-of-Principle studies in man and/or animals.
- MBS monetises the value creation through out-licensing to the pharmaceutical industry and pays a percentage to the source university.

Management and the advisory board have a compelling pedigree; Clive Dix, Chairman, was GlaxoWellcome’s UK Research Director before moving to PowderJect, leading the spinout of PowderMed and selling to Pfizer for a significant uplift in value in 2006; Ian Wilding, Chief Scientific Officer, has run over 300 Phase I clinical trials in his previous capacity as a CEO and CSO of a leading UK clinical research organisation; Bruce Campbell, Non-executive Director, was formerly head of R&D at Servier UK and has overseen the development and registration of seven drugs and vaccines while Sam Williams, CEO, brings over 10 years of experience in pharmaceutical and biotechnology finance.

Two assets have already entered the portfolio that address two scourges of humankind – cancer and arthritis. The arthritis product addresses a market that could be worth \$10bn+.

The probability-adjusted NPV analysis of the two products suggests a minimum valuation of £20m. If MBS is successful at sourcing several more products of this calibre over the next two years the valuation could be a multiple of £20m. A more conservative model that ignores milestones and royalties and considers only a theoretical profit stream based on a “steady state” level of deal success (1 in 4) and constant net deal fee of at least £9m supports a valuation of at least £10m. If MBS echoes the deal success with OsteoRx that other companies have had in the rheumatoid arthritis market, the valuation of the OsteoRx programme alone could be a multiple of £10m. Fair value for MBS today may, therefore, be somewhere between £10-20m.

Investors in MBS should consider two likely exit strategies: an IPO perhaps after the model has been validated with an out-license to Big Pharma, or a trade sale should the portfolio of product assets start to look too tempting. One of these events should have a high probability of happening within the next 2-3 years.

Executive Summary

Modern Biosciences (MBS) has created a scalable and potentially valuable business model that addresses one of the major shortcomings of the modern pharmaceutical industry, that of shortage of pipeline product. The key components of the MBS model are systematic external sourcing of novel products from academia and development of these products to a point at which they can be monetised by licensing to the pharmaceutical industry.

Systematic external sourcing of novel products

MBS has no drug discovery of its own but has developed strong relationships with the Life Science departments of British universities and academic laboratories from which it licences novel drug products and intellectual properties. MBS has a strong potential pipeline under review with ten priority projects on the short-list, one project in pre-clinical development and one more in Phase I.

Quickly to Proof-of-Principle in man

MBS pursues a novel approach to drug development that allows it to reach a value inflexion point for any given asset in the shortest possible time and for the lowest possible cost. It pursues only those critical experiments necessary to reach a “go/no-go” decision up to and including Proof-of-Principle; that is, data from studies in man or animal that suggest the drug will have clinical benefit. This is in contrast to the pharmaceutical industry’s conventional approach, which generally follows a success-based model that assumes all drug candidates will reach the market. This necessitates parallel processing of experimentation, requiring additional cost and risk. MBS’s approach is well validated through Eli Lilly’s Chorus model of development.

Monetisation by licensing to the pharmaceutical industry

Big Pharma is desperate for new products and has been paying handsomely even for products at Phase I, with median upfront fees of \$25m. Therefore, sustainable profitability for MBS on the back of licensing early stage product to Big Pharma could be a realistic medium-term goal. The success of this business model will depend critically on five factors:

- **Attrition rate through the transition phase from academic project to drug candidate** with Proof-of-Principle. MBS is hoping to achieve a success rate of 1 in 4 or better, with success defined as a product licensed out at Proof-of-Principle. The industry’s success rate is 1 in 5 but superior project selection and identification of critical experiments should allow MBS to improve on this.
- **Cost of running the transition through Proof-of-Principle.** MBS estimates that on average, each successful project could cost around £1.8m to the attainment of POP, although many unsuccessful projects may be expected to fall before the final hurdle, therefore costing much less than £1.8m.

- **Deal terms upon licensing.** The scalability of the MBS model, where all development work is outsourced and the fixed costs of the small project management team at Modern Biosciences may be amortised over many projects, suggests that break-even could be achieved with deal fees of just £7m upfront and a success rate of 1 in 4. Scaling up the model, with many more projects in the portfolio, would increase the probability of a deal in any one year.
- **Sustainability and competitive advantage.** Although there are some companies whose business models depend upon accessing products from academic sources, these tend to be focused on single therapeutic areas (e.g. Antisoma plc) or do not operate in the UK. Furthermore, Big Pharma's attempts to partner with academia have yet to bear fruit and the likelihood is that the infinitely flexible and personal approach of MBS will triumph over the "one size fits all" mind-set of the industry giants.
- **Minimising business risks** associated with a limited number of key personnel and low barriers of entry to the business area. Modern Biosciences is currently small, in terms of personnel (8 full time employees), and its success is critically dependant on several key employees. These employees are not only responsible for the decisions regarding which products to pursue and which to drop but are also critical in building relationships with academia. Given that MBS does not have exclusive rights with universities for the exploitation of their products the relationship between key personnel at MBS and academia is important in creating a barrier to entry. Clearly, retention of key employees is critical and this is addressed through equity ownership with 32% of the equity owned by the management team and employees. An option scheme is being investigated so that all employees, new and old, can participate in the creation of shareholder value. In such a small company any resignation or loss could be meaningful but some employees are able to substitute for others in time critical roles, such as managing project development. The loss of the CEO or CSO would require some time and effort to address but neither is irreplaceable.

The first phase of this business model, the licensing of product candidates from academic sources, has been validated already - two products, rimcazole for cancer and OsteoRx for rheumatoid arthritis, have been added to the portfolio in the last 12 months. OsteoRx represents an oral alternative to a class of injectable drugs that currently sell in excess of \$10bn. Assuming successful deal outcomes in 2010 for rimcazole and OsteoRx, the first two product cycles of this business model will have been completed within a three-year timeframe.

Modern Biosciences has two sources of value; firstly, the NPV of the probability-adjusted revenue streams from the product assets within the portfolio; and secondly, the intangible value of the relationships and experience that can deliver a flow of new products into the portfolio. A steady-state model in which the NPV of a recurring profit stream is discounted (assuming 1 in 4 success and £9m average net deal fee) suggests MBS is worth at least £10m. A product-based NPV model that includes milestones and royalties suggests MBS could be worth £20m. We estimate the current fair value is between these two figures.

It should be noted that the MBS model is flexible enough to allow the deliberate deferral of monetisation of any particular asset until an additional value inflexion point has been reached, that is, beyond initial POP. MBS could choose to do this on a selected basis where the cost of additional clinical studies can be accommodated within its normal operating budget but is more than justified by the greater returns that could be achieved upon sub-licensing at a later stage.

The Pharmaceutical Industry Needs Modern Biosciences

The stock-market performance of the traditional pharmaceutical industry (Big Pharma) over the last five years and the outlook for the next five years is a clear reflection that the traditional fully-integrated pharmaceutical business model is broken. Appalling R&D productivity lasting at least one product cycle has left the industry over-dependent on a few mega-brands and a handful of blockbusters within each portfolio. Big Pharma is now at the mercy of wholesale cost cutting and reputational damage limitation as it faces a tidal wave of patent expiries over the next five years (see Appendix 1, Figure 17). Realignment of the sales and marketing infrastructure to the new reality of smaller, primary care portfolios and the shift to specialty care is hampered by the simultaneous movement in the balance of power away from individual prescribing physicians and towards the payors. This is manifest in the growing pressure on pricing and reimbursement, the rise of Health Technology Assessment organisations (e.g. NIHCE and IQWIG) and the desperate search within Big Pharma for an answer to the question, “What constitutes an appropriate value proposition?”

25% of drugs entering development are in-licensed

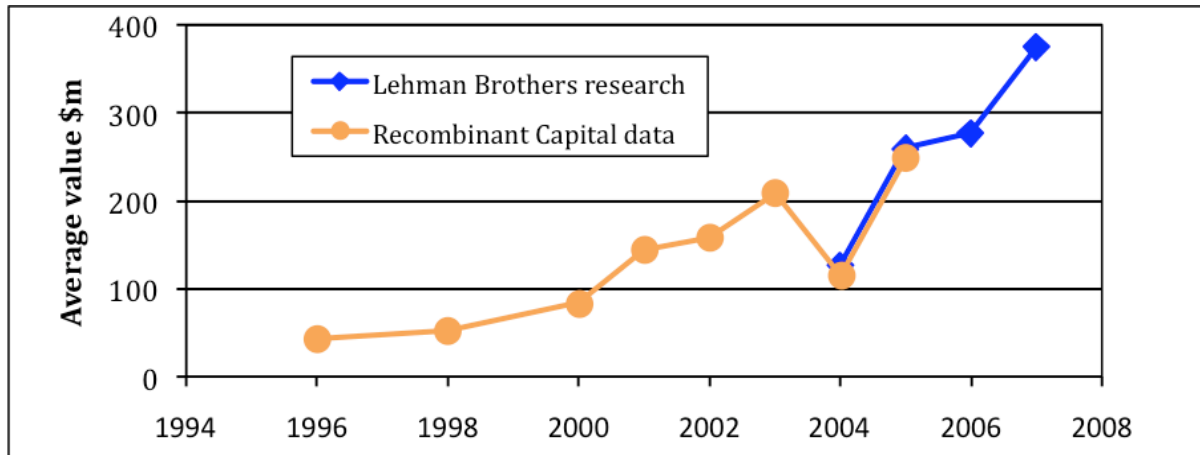
Big Pharma still generates the majority of cash flows in the sector since it controls most of the product assets and their associated downstream sales and marketing activity. Not surprisingly, these cash flows support the majority of R&D expense. Recent estimates suggest Big Pharma spent \$60bn on R&D in 2007 compared with \$19bn by Biotech (Source: Parexel R&D Source Book); a further \$28.6bn was spent by the National Institute for Health but only 10% of this was spent on clinical trials, the rest funded grants to research academics.

If some future model of drug discovery redistributes an even larger proportion of that cash flow to external sources it will not be a surprise. The industry has been supplementing its internal R&D effort for many years with product acquisition and in-licensing, largely from biotech companies. The extent of that demand may be judged in several ways. Lehman Brothers PharmaPipelines data shows the increase in total NPV attributed to in-licensed products as opposed to those created internally has grown from 15% to 23% in the last five years. This is supported by studies from the Tufts Centre showing that in the period 2003-2005, 25% of all drugs entering clinical development were in-licensed, compared with just 15% in the period 1993-97. Clearly, the traditional drug companies do not have a monopoly on good ideas and external companies supplying exciting products should do well. Modern Biosciences is one such company.

Not only is the industry dependence on in-licensed drugs rising but the value attributed to in-licensed products is also rising, shown in figure 1 by the increasing aggregate value of a

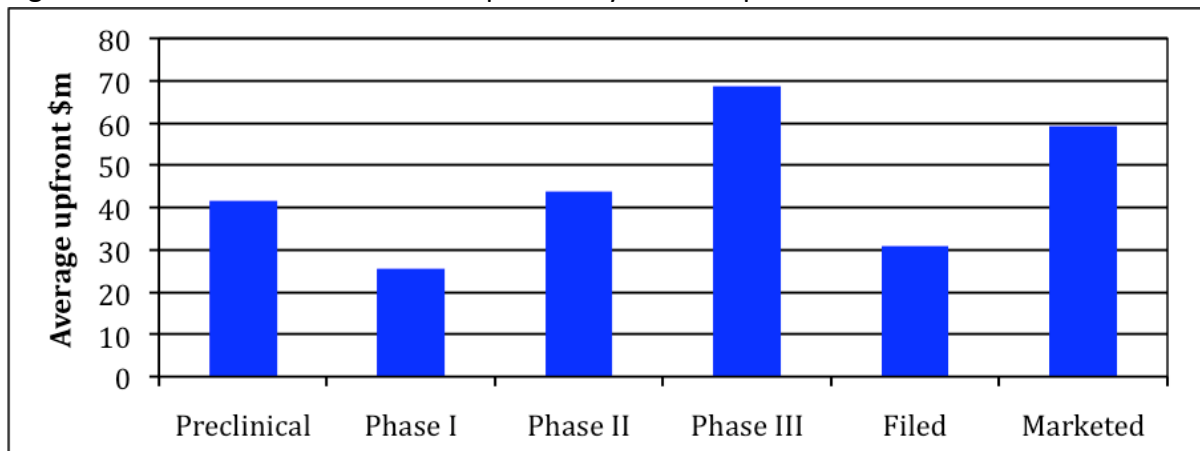
licence deal. Figure 1 shows clearly that, with the exception of the dip in 2004, average deal values for licensed products have been rising rapidly. Furthermore, even pre-clinical and Phase I products can command upfront payments in excess of \$25m (£12.5m) (Figure 2). This partially reflects the availability of valuable new technologies that perhaps were not mature enough to be valued a few years ago (e.g. anti-sense), but undoubtedly recognises that the traditional pharmaceutical industry does not have a monopoly on innovation and needs access to external sources of technology and product.

Figure 1: Average Licence Deal Values Rising Rapidly



Source: Recombinant Capital, Lehman Brothers research. 2007 figures reflect data to 30 August

Figure 2: Even Phase I Licence Deal Upfront Payments Top \$25m



Source: Lehman Brothers research

In conclusion, the pharmaceutical industry is being squeezed at both ends, by lack of new product flow and loss of sales through patent expiry. The search for new products extends beyond each company’s internal discovery efforts and the price of licence deals has created opportunities for those that have product assets to sell. Modern Biosciences is one such company. The question to be answered now is how Modern Biosciences can systematically create product assets valuable to the pharmaceutical industry at a cost that allows for a satisfactory return on investment.

Modern Biosciences Business Model

There are three key aspects to the Modern Biosciences business model

- Strong relationships with academic institutions, such as universities, in the UK that provide the discovery engine for new products, which are licensed by Modern Biosciences
- Selective identification of viable projects and critical experiments, at low cost, that will generate a “go/no-go” signal indicative of Proof-of-Principle of the product. (Proof-of-Principle represents a combination of in vitro and in vivo outcomes that supports the conclusions that the drug has potential for technical success. This could include proof of mode of action, evidence from drug impact on markers of disease and even some limited clinical response in man.)
- Out-licensing of product after Proof-of-Principle with a data package sufficient for pharmaceutical companies to be assured of attrition rates no worse and, preferably, better than other products in the same phase

An experienced management team that has been through this process many times before underpins each of these aspects. The model is explored in more detail below.

Strong relationships with academic institutions

Modern Biosciences has already proven it is able to pick and choose from what has been shown, empirically, to be a very wide range of projects across 30 top tier Universities and selected projects from many more. It is estimated that the number of discovery scientists that Modern Biosciences effectively has access to is around 2,000. Dr Diane Taylor, Director of Business Development at Dundee University, a partner of MBS (through rimcazole) says, *“The Modern formula seems to have the right balance between a strict development orientation and a great relationship with the academics.”* Also *“It works more like a joint venture in which we get good feedback, positive and negative, but always constructive; the academics like that”*

Can the pharmaceutical industry access universities directly?

The answer is that it can and occasionally does but there are several reasons why this does not happen routinely.

- **Cultural barriers** to creating good academic links. The pharmaceutical industry is in a hurry to try and fix its R&D productivity gaps. Working with academia requires understanding of its needs and aspirations. Building relationships to the stage where

mutual trust rather than mutual suspicion exists takes time. Rarely is the pharmaceutical industry that patient, especially since there may be many easier opportunities to exploit.

- **Industry's need for control.** Typically industry will identify a project and then transfer its subsequent pre-clinical and clinical development to its own laboratories. This disenfranchises the academic team responsible for the project's creation and contributes to the cultural barrier.
- **Gaps in the scientific data.** "Big Pharma" will ask the following questions about any new drug candidate:
 - Has the drug target been identified? Pharmaceutical companies are conservative and may reject products with no clear molecular targets.
 - Does the putative drug candidate look like a viable drug? For example is it soluble, bio available and / or active even after first pass metabolism through the liver?
 - Is there *in vivo* (in animals) Proof-of-Principle with the product? That is, does the product demonstrate some impact in animal models of disease?

If Big Pharma cannot answer these questions easily, they tend to move on. In contrast, Modern Biosciences may be able to "tease out" the data they need by doing some simple experiments or going one or two steps beyond what Big Pharma is prepared to do. This only comes from a great understanding of what the academic laboratories are trying to achieve and reinforces the relationship and the competitive advantage of MBS. These "gaps in scientific data" are perhaps the most tangible of the reasons why industry sources few products from academia. Academics rarely have the commercialisation of their discoveries as their main objective. As a consequence they do enough to satisfy intellectual curiosity but often do not do enough to make a decision about whether the product has commercial potential. This leaves significant gaps in the data package, which the pharmaceutical industry is not yet motivated to fill.

Focus, flexibility and engagement; key factors of Modern Biosciences success

The difference in mindset between MBS and the pharmaceutical industry in building relationships with universities may be captured by three words:

- **Focus.** MBS has substantial relationships with academia at all levels of the organisation. For example, there are some relationships that have been forged by the Business Development Manager, others by the CEO and yet others by members of the Advisory Team. The willingness of MBS to provide academics with access to its development expertise is proof of its commitment and focus on its university client's needs.
- **Flexibility.** The ongoing dialogues that suit the culture and mind-set of a small organisation and are reinforced by prompt decision-making. One Assistant Director of Technology Transfer said "*We were struggling with the negotiations over the phone and were about to pull out when Sam (Williams) sensed the tension, stopped the call and said he would visit us the next day. He flew up and we sorted it out in an hour*".

- **Engagement.** Wherever possible and appropriate, MBS will work with academic departments to fill the scientific gaps in the data package, thus empowering the scientists whose projects are being pursued. For example, academic laboratories may have unique biology that allows them to develop product activity assays or they may have unique animal models.

How does Modern Biosciences select products?

Modern Biosciences has a small but experienced full time team of development scientists (see page 20 for list of Management) and access to an advisory board with many years of hands-on drug discovery and development experience. This team has in aggregate developed dozens of drugs including many blockbusters (e.g. Barry Furr discovered Zoladex for cancer, a product that achieve peak sales in excess of \$1bn). Projects within the academic laboratories of universities that are close to technology transfer are discussed with the Business Development team at Modern Biosciences and a portfolio of likely candidates is developed, with priority assigned. Dr Liz Rattray, Deputy Director, Research and Innovation, Aberdeen University, says *“Modern Biosciences offers an attractive model for universities with isolated drug discovery products without bundling or spin-out opportunities.”* And also *“Modern Biosciences had a clear understanding of what the pharmaceutical industry would want and could project manage it. That’s one reason why we will go back to them with other projects.”*

A shortlist of six or seven products is maintained and is the subject of active due diligence. Sometimes an option of £10,000 to £20,000 will be paid to secure exclusive rights to a project while due diligence is being pursued. Whenever a product falls out of the shortlist the next product on the priority list is promoted and due diligence begins.

The key hurdles to clear if products are to be acceptable to MBS are a USP (“me-toos” tend to be avoided) and solid intellectual property with freedom to operate. Sometimes it may be necessary to conduct simple experiments before a licence decision is made. This will depend on the extent of the data already available and the commercial potential of the opportunity. All of the data generated is shared with the academic laboratory and all scientists are kept informed of progress with their product.

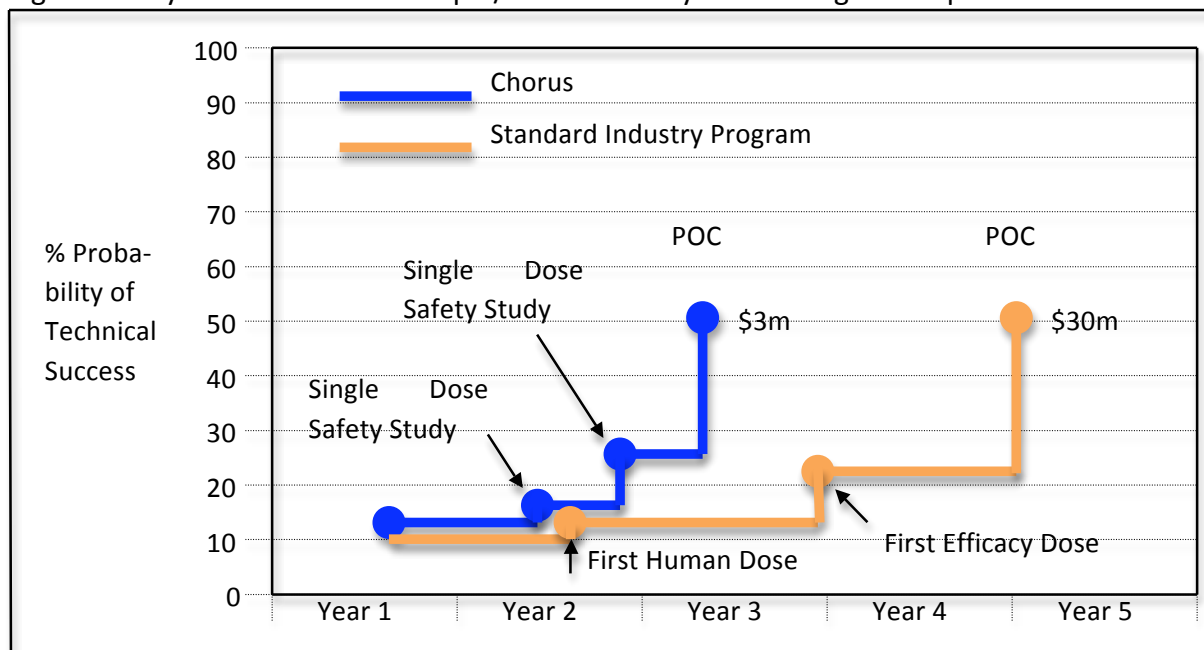
How does Modern Biosciences develop products?

Modern Biosciences pursues an intelligent course of critical experiments that lead quickly and with low cost to a “go/no-go” decision. This is explained in more detail in Appendix 3 but has a precedent in Lilly’s Chorus model, explained below.

Lilly's Chorus - A precedent for rapid/low cost early drug development

The chart below demonstrates exactly what Modern Biosciences is trying to achieve – Proof-of-Principle quickly and at less cost than standard industry procedures. Lilly set up Chorus in 2002 as a sort of “skunkworks”, separate from the mainstream organisation. Its mission was to get Proof of Concept (MBS calls it Proof-of-Principle) quickly and cheaply, doing only those experiments necessary to reach a “go/no-go” decision. If necessary, Lilly would back fill the programme with necessary data after POC had been reached. The point is that without an incentive to succeed there was no emotional attachment to projects and if they did not work they were dropped. This is very different from mainstream development, which pursues several exercises in data gathering in parallel, racking up cost associated with large-scale manufacturing and long-term animal experiments, even before critical experiments were done to check feasibility in terms of safety and efficacy.

Figure 3: Lilly's Chorus Model – Rapid/Low Cost Early Phase Drug Development



Source: In Vivo, May 2007

According to an article in the Harvard Business Review (March 2008, A More Rational Approach to Drug Development), by the end of 2007, Chorus had evaluated 19 drug candidates and completed work on 7. Chorus has recommended that four molecules enter into full-scale clinical development (4/19 = success rate of 1 in 5 and there are still 12 molecules to complete evaluation) and that three go no further. Ian Wilding, MBS's Chief Scientific Officer was one of the first external advisers to Chorus and brings that experience with him.

The HBR article also cites that Chorus absorbs just one tenth of Lilly's investment in early stage development but has recently delivered a much higher proportion of molecules destined for Phase II trials, at almost twice the speed and less than a third of the cost of the standard process.

How can Modern Biosciences sustain competitive advantage?

There are several theoretical sources of competition to Modern Biosciences' business model.

- **Big Pharma.** The traditional industry has a very limited number of academic partnerships or relationships in which it will typically negotiate rights of first refusal in exchange for fees. Were the industry to pursue a land grab approach and "lock out" all potential competitors this would be a worry but so far this has not happened and remains unlikely. Big Pharma does not have the mind-set or patience to develop a systematic way of sourcing new products from academia. It has not been particularly successful so far.
- **Biotech companies.** Many of these companies have been spun out of academia to pursue a particular idea. However, they tend to be single-minded in their focus on that idea and do not benefit from the portfolio effect enjoyed by MBS and do not typically compete for academic product with MBS.
- **Specialty "Search and Development" companies.** These exist in abundance but very few focus on pre-clinical candidates. Those that have sourced pre-clinical candidates tend to be focussed on one therapeutic area such as Antisoma and Eos on cancer, or do not operate in the UK such as Debiopharma and Eclison in Switzerland.

MBS appears to have a unique combination of UK academic relationships, a flexible approach to therapeutic area, commitment to the critical experiment, rather than to the product, and a scalable model. Add in a highly experienced and well-motivated management team and the recipe for sustainability looks secure.

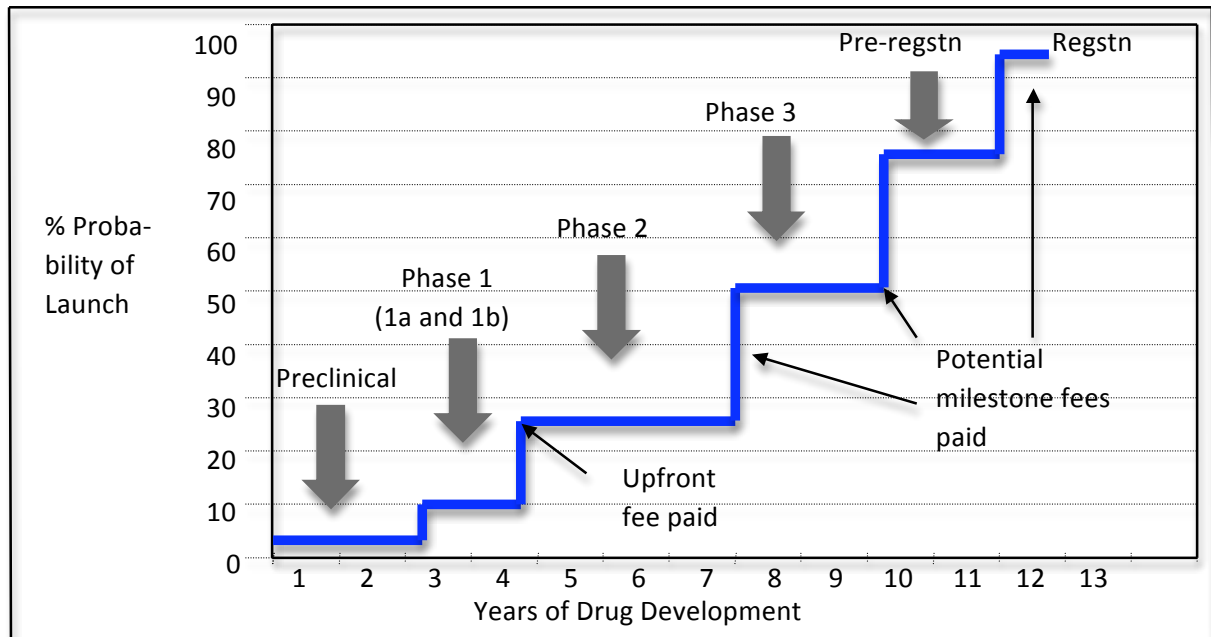
Does Modern Biosciences have limits to its scalability?

The essence of the business model as it currently works is strong relationships with the universities and academic labs and the expertise of the development team. With each asset manager likely to be responsible for a maximum of three projects the business can certainly be scaled up to some degree by adding asset managers and more business development staff. It is also theoretically possible to try and reproduce the model in countries outside the UK, providing more growth opportunities. However, the rate-limiting step is probably going to be the ability of the CEO and his key management team to manage staff recruitment as well as keep a close eye on the academic relationships. These requirements are both a function of time and when time runs out the key managers have to delegate and risk diluting the culture of the company. Realistically, the business model can perhaps accommodate 12-15 projects running at any one time. This suggests 4-5 asset managers to manage the projects and potentially several more Business Development staff to manage relationships. However, at this size with a 1 in 4 success rate then MBS could be agreeing deals at least once a year. MBS would not need to get any bigger to have created a significant growth in value.

How will Modern Biosciences create value?

The graphic below attempts to show that the probability of a drug getting to market increases as the amount of positive clinical data increases. The quantum jumps in probability represent clinical milestones achieved, where critical questions about safety and efficacy in patients are answered in a positive and encouraging way. These milestones, once achieved, allow the product to proceed to the next phase of development.

Figure 4: A Stylised Licence Deal



Source: Expert Analysis Group

Note: The data presented above is not consistent with that presented in figure 23 as the source is different and the definition of preclinical, Phase I, etc. differ.

In a typical licence deal, the owner of the asset receives an “upfront” payment or down payment on signing the licence deal. Then additional payments, called milestones, may be paid as the product makes clinical progress. In this way, payment is staggered and only made in full if the product is successful through the development process. Most licence deals also pay a royalty on sales in the form of a percentage of sales achieved each year. Typically, for a product licensed out at a very early stage the royalty percentage of sales is in the single digit range. A higher royalty percentage is usually paid for products that are in a more advanced stage of clinical development when licensed, since the party acquiring the asset acknowledges that there is less clinical risk.

According to an analysis by Lehman Brothers (Biotechnology; A milestone for PharmaPipelines, 19/9/07) approximately 15% of the total deal value (total cash paid for a successful product) has been paid upfront, although this may include an equity component, with a further 25% paid in milestones. The table below shows the empirical data gathered in 2007 for deal size by clinical phase of drug and the NPV contribution of the cash after

adjusting for probability of success. A typical deal done in Phase I, which is what Modern Biosciences is seeking to do, is worth £16.1m when adjusted for probability of success.

Figure 5: 2007 NPV of Deal Terms Adjusted for \$25m Upfront Payments

	Average deal size (\$m)	NPV (£m)	Probability of launch ⁺	Adjusted NPV (£m)	Adjusted NPV (£m) net of 30%
Pre-clinical	374	62.5	5%	16	11
Phase I	428	105.0	10%	23	16
Phase II	481	133.5	20%	39	27
Phase III	435	137.5	40%	68	47

+ The probabilities shown here are not consistent with those calculated by PharmaPredict and shown elsewhere in this note

Source: Lehman Brothers

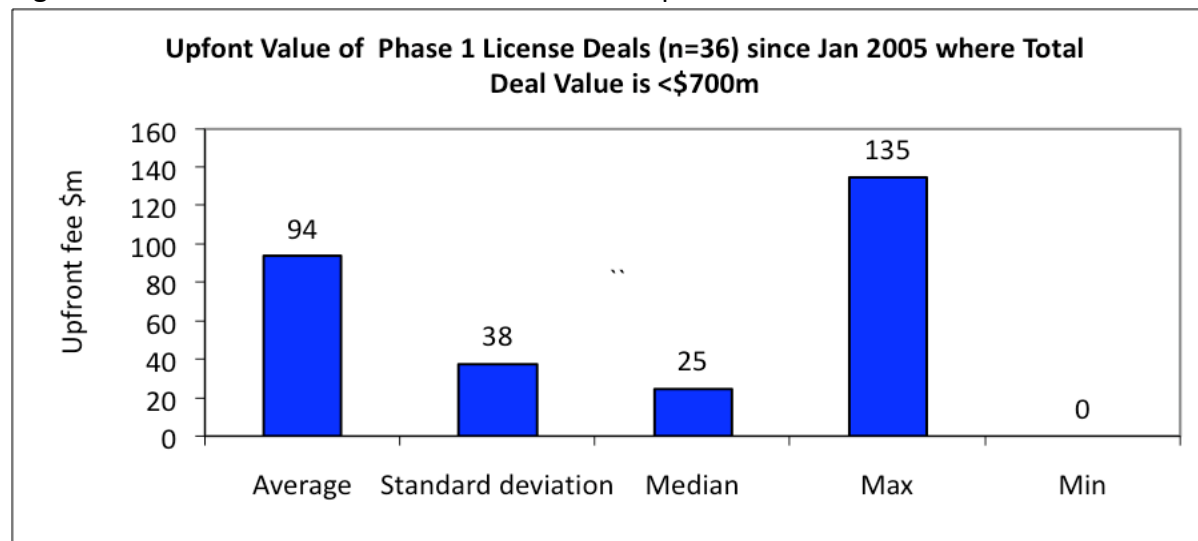
Turning Proof-of-Principle into cash via licensing to the pharmaceutical industry

The desperate need for new products within the industry has been explained earlier. Modern Biosciences' objective is to meet that need by out-licensing of product assets, to which significant value has been added, acquired from academic laboratories. The factors that will determine whether MBS can make a self-sustaining business out of this activity are the following:

- The cost of acquiring the asset and adding sufficient clinical value that it can be licensed to the pharmaceutical industry;
- The net price MBS can achieve from licensing the asset, after passing on the agreed percentage to the academic source, which is typically 20-30% of all payments including the upfront payment; and
- The rate of attrition between acquiring the asset and selling it on.

This financial model is explored later but this chapter seeks to demonstrate that there is significant precedent for out-licensing products with Phase I data or at least with Proof-of-Principle in Phase I. The chart below (Source: Lehman Brothers Biotechnology Research) shows a wide spread between the upfront fees paid for the most valuable and least valuable deals. With the median being some way below the average, it is clear that a few big deals have skewed the data. Suffice to say that at least a \$25m upfront fee can be achieved 50% of the time, based on historical data. It will no doubt be uppermost in the minds of MBS management when they establish their priority list of potential portfolio projects whether there is a high value deal precedent for the therapeutic category they are considering.

Figure 6: Half of Phase I Deals are Worth >\$25m Upfront



Source: Lehman Brothers publication 'Biotechnology A Milestone for Pharma Pipelines. 19 Sept. 2007'

Risks to Modern Biosciences business model

There are four key headings under which risks to the MBS business model should be discussed.

- Financial
- Technical or scientific
- Personnel
- Competition

Financial risks

The main financial risks to the model are twofold;

- Access to capital. MBS needs access to a minimum amount of capital to develop products through to a completed out-license deal with a pharmaceutical company. Undoubtedly a successful outcome from the first deal will validate the approach and encourage further capital investment and, clearly, MBS management will be motivated to sign the first deal that will give an attractive return on investment at the earliest appropriate stage. However, even with a putative success rate of 1 in 4 there can be no guarantees that any of the first four or more products are successful and validate the model; and
- Deal values. Empirical data suggests that the median deal value of upfront payments is \$25m but history may not be a guide to the future. Should MBS run short of capital (and capital markets are fickle) it will not be in good bargaining position to demand top dollar from its licensing counterparties.

Technical or scientific risks

These translate into financial risks but any development project carries technical risk of failure. Failure is part of the game of drug development and “fail early, fail cheap” is the watchword. However, a run of bad luck in which many projects fail towards the end of their development, after most of the money has been spent, could turn this into a “fail too late and expensive” situation, damaging the perceived validity of model. Of course, there are stop loss decisions to be made throughout the development process and it is down to the MBS team to make those judgments.

Personnel risks

There are two issues that could be threatened by staff changes:

- Relationships with academic and tech transfer staff. Since so much of the access to academic and Tech Transfer staff at universities depends on personal relationships it follows that staff turnover can have a very damaging impact on access to future projects. This access is built on trust in staff at many levels, with the CEO, CSO and external advisors all getting involved in addition to the day to day contact with asset managers and the business development function. Furthermore, the progress of each project is very dependent on the individual asset managers. If one of them left it should be possible for the Head of Development to step in but a resignation and a simultaneous leave of absence could be difficult to manage.
- Scientific judgment and expertise. There are key judgments made about project selection and critical experiments by the CSO and the advisors. Loss of that expertise may be difficult although not impossible to replace.

Maintaining staff and their morale is critical to MBS as it is with any small company with rare skills. The management has significant incentives in terms of large equity stakes. Each staff member also has an equity stake and it should be one of the CEO’s main objectives to keep his team motivated and content.

Competition Risk

There will always be competition but at the moment it is certainly not head on, with Big Pharma, Biotech and Search and Development companies all involved in a part of what MBS is trying to achieve. However, as discussed elsewhere, Big Pharma does not have the mind-set, biotech tends to focus on one or two projects as opposed to sourcing multiple projects and most early stage Search & Development companies are either focussed on one disease area or operate outside the UK. The best defence against copying the MBS model is for MBS to execute its strategy well using all of the soft skills (relationship-building, trust and integrity) as well as the hard skills (scientific judgment) available to it.

The Financial Model and Valuation

MBS is a lean organisation that contracts out all pre-clinical and clinical work as well as all biology, chemistry and manufacturing. There are only four functions within the head office.

- Product sourcing, led by the Business Development team. The team is responsible for maintaining active contact with UK universities and academic institutions and bringing forward product ideas. Currently there is just one dedicated person in this role but a second person starts in June, reflecting the importance of this activity.
- Asset management, or project management, led currently by three PhDs with significant experience in the biotech and pharmaceutical industry. These team members will take operational responsibility for the projects assigned to them, ensuring that the experiments needed to get Proof-of-Principle will be conducted reliably and cheaply, often using CROs based in India to ensure good value. The asset managers can draw upon the experience of the Head of Development.
- Out-licensing. MBS has the budget to hire a senior US-based executive to spearhead out-licensing as projects start to come to fruition.
- Central support from the CEO, CFO and secretarial.

Theoretical valuation based on steady state

Modelling the financials is straightforward and can be thought of as consisting of fixed cost overheads (all staff other than asset managers) and variable cost project work. Fixed costs will only rise when new staff join Business Development, Out-licensing or the central support team. Project costs are estimated to be around £1.8m per project, spread over up to 3 years. Each Asset Manager is expected to be able to manage three projects.

Figure 7: Steady State Model in which Total Costs, before Deal Fees, Stabilise at ca £7m pa

	2008	2009	2010	2011	2012
Products entering portfolio	2.0	3.0	4.0	4.0	4.0
Products failing		-1.0	-2.0	-2.0	-3.0
Product deals		0.0	-1.0	0.0	-1.0
Number of projects at year end	4.0	6.0	7.0	9.0	9.0
Cost per project pa	-0.6	-0.6	-0.6	-0.6	-0.6
Project cost £m	-2.4	-3.6	-4.2	-5.4	-5.4
Overhead £m	-1.3	-1.4	-1.6	-1.7	-1.7
Total cost £m	-3.7	-5.0	-5.8	-7.1	-7.1
Deal fee		0.0	9.0	0.0	9.0
PTP	-3.7	-5.0	3.2	-7.1	1.9
Tax @ 20%*	0.0	0.0	0.0	0.0	0.0
Net Income	-3.7	-5.0	3.2	-7.1	1.9

* Tax loss carry forward means tax unlikely to be paid in this timeframe. Source: MBS, Expert Analysis Group

The spreadsheet above is not meant to be a forecast since the rate of product inflow will be adjusted according to the number of eligible products and cash to support their

development. However, this model can be used as the basis for making a valuation, since the steady state is indifferent to two variables that can be changed.

- Success rate through development. The model is funding nine projects each year at £0.6m each per year. If the success rate is better or worse than 1 in 4 this can be reflected in the timing of deal fees; it does not have to impact operating expenses. Note that this model is conservative since in reality many products will fail and no longer incur cost before reaching the end of the three-year period. As a consequence MBS will probably have lower annual operating expenses than shown in this model.
- Deal fees are outside operating expenses.

By varying the success rate and deal fees it is possible to create a matrix of possible valuations, where the NPV of a profit (or loss) stream at steady state can be calculated. The NPV takes account of the losses until 2011, ignores interest payable or receivable and assumes that tax at 20% will be paid on all profits.

Figure 8: NPV of MBS Profits, Varying Upfront Fee and Success Rates

Upfront fee £m	Deal Success Rate		
	1 in 6	1 in 5	1 in 4
6	-5,960	-6,811	-8,514
7	-433	-495	-619
8	3,901	4,458	5,572
9	8,235	9,411	11,764
10	12,569	14,365	17,956
12	21,237	24,271	30,339
15	34,240	39,131	48,914
20	55,911	63,898	79,873

Source: Expert Analysis Group

The matrix above shows that the NPV of the theoretical flow of profits from Modern Biosciences varies with the success rate through the development phase and with the size of the net upfront fee (net means after paying 30% to the academic source). If MBS can achieve success rates close to its goal of 1 in 4 and net deal fees of at least £9m then a valuation today in excess of £10m is easily supportable.

Of course, this valuation approach only takes into account the value of the revenue/profit stream attainable from up-front licensing fees. Clearly, the downstream potential milestone payments and royalties that each licensee will be liable to pay MBS if particular assets make it to market will accumulate as deal number builds, providing significant potential upside for investors.

Theoretical valuation based on NPV of product assets

An alternative way to value Modern Biosciences is to calculate the NPV of the two pipeline products, assuming they are out-licensed after Proof-of-Principle in Phase I. The table below shows a range of NPV valuations for a product, varying according to peak sales. In this model the NPV will rise as the sales rise, since there is a royalty-based component (assumed

just 2%). But if expectations for the product are particularly high, it is not unreasonable to assume in a competitive licensing environment that upfront and milestone payments may also rise. Readers will note that this model differs from the one above in the following ways:

- The NPV considers upfront fees, milestones and royalties on sales. Milestones and royalties are adjusted according to probability of success – 10% in this model.
- Annual running costs are not considered, since these NPV estimates relate only to an individual product. So, for example, if rimcazole is licensed out for £10m upfront and is assumed to reach £250m peak sales while OsteoRx is licensed out for £20m and assumed to reach £2bn peak sales the combined NPV of these deals equates to £48m (£13.1m plus £34.9m). The value of MBS may be estimated as £48m less the NPV of net annual operating expenses. These upfront fees and sales assumptions are justified in the next section, ‘pipeline, progress and value’. Alternatively, if only these two products are considered and assumed to have peak sales of £250m and upfront fees of £10m (top line in Figure 9) each the adjusted NPV of the two deals would be £26.2m. The value of MBS would be £26.2m less the NPV of net annual operating expenses associated with these two products, an estimated £6m, leaving a valuation of £20m. From these comments it can be seen that the valuation of MBS depends on deal success as well as how MBS chooses to spend its cash.

Figure 9: NPV of Theoretical Deal Terms with Peak Sales and Upfront/Milestone Fees

Peak Sales £m	Upfront fee (net of 30%) £m	Milestones (net) £m	Royalties through 20 year cycle (net) £m	Total Deal Size £m	Probability of Launch	Un-adjusted NPV without upfront	Un-adjusted NPV of Deal £m	Adjusted NPV of deal £m
250	10	20	48	78	10%	31	41	13.1
500	10	20	97	127	10%	45	55	14.5
750	10	20	97	127	10%	60	70	16.0
750	20	40	145	205	10%	76	96	27.6
1,000	10	20	195	225	10%	75	85	17.5
1,000	20	40	195	255	10%	91	111	29.1
1,500	20	40	290	350	10%	120	140	32.0
2,000	20	40	386	446	10%	149	169	34.9

Note: The theoretical valuations calculated implicitly assume cash is available to fund the business to the stage when products can be out-licensed. Therefore, they represent equity valuations that would need to be adjusted by cash burn. The discount rate used is 10% representing a long bond rate and equity risk premium. The technical risk of failure is already reflected in the probability of success.

Source: Expert Analysis Group

It should be noted that the MBS model is flexible enough to allow the deliberate deferral of monetisation of any particular asset until an additional value inflexion point has been reached. For example, MBS could choose to conduct a Phase II study if the incremental cost is more than justified by the greater value that could be attained from a subsequent sub-licensing deal. This could hold true for certain inflammatory diseases where the cost of a Phase II trial might be limited to single-digit millions, whereas MBS would always avoid large

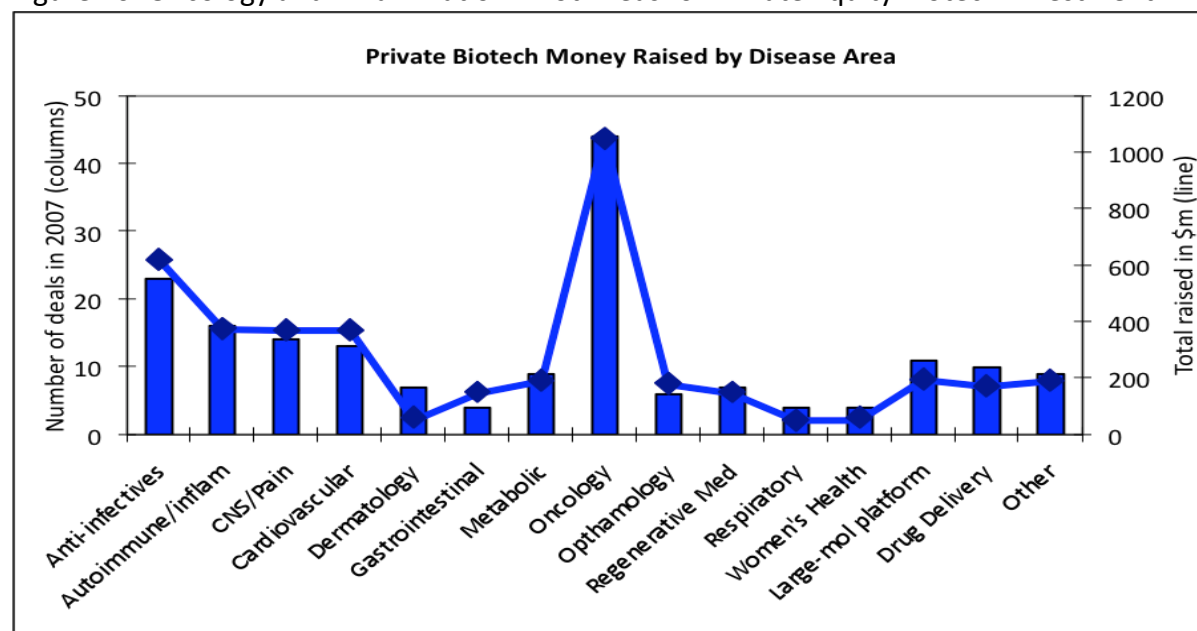
Phase IIs where the costs run into tens of millions (e.g. stroke). This would allow MBS to move up the 'value chain' of drug development on a selected basis, providing for even greater up-front license fees and milestones and providing a greater residual interest in key programmes through higher royalties.

Pipeline, Progress and Value

In the 12 months since Modern Biosciences has established its modus operandi (MBS was constituted as a limited company in 2005 but didn't become a fully functioning entity until it appointed a CEO in April 2007 and started recruiting full time staff), it has in-licensed two projects (a further product was dropped because chemical optimisation of the compound proved extremely difficult) and is reviewing many more which are not yet licensed. In assessing these two and subsequent projects which are, by definition, at an early stage there are just three essential questions for investors to address:

- Is there sufficient medical need in the therapeutic category in which these products lie to be likely to excite the pharmaceutical industry?
- Is there sufficient novelty in mode of action or a sufficiently positive trade-off between safety and efficacy already visible to warrant further development?
- Is the intellectual property position secure, thereby allowing licensees to profit from their efforts?

Figure 10: Oncology and Inflammation - Hot Areas for Private Equity Biotech Investment



Source: Windhover's Strategic Transaction Database

The two products being pursued, rimcazole for cancer and OsteoRx for rheumatoid arthritis, are both in categories where demand for product remains high. The chart above shows, by number of deals and money raised to support private biotech companies, that oncology (cancer) and autoimmune/inflammation (which includes rheumatoid arthritis) are significant

areas of interest. This reflects the high degree of medical need and the knowledge that the right products enter a fast growing market with premium prices and large commercial potential. The other issues are addressed separately below.

Rimcazole for Cancer

Rimcazole accumulates in tumour cells, kills them and stops blood vessel growth

Rimcazole was licensed in June 2007 from the University of Dundee, which had shown that compounds (like rimcazole) that bind a particular receptor in cancer cells can cause those cancer cells to commit suicide (apoptosis). These compounds selectively accumulate in cancer cells and have the further advantage of inhibiting angiogenesis (development of blood vessels) at the site of the tumour.

Figure 11: Rimcazole for Cancer

Characteristic	Key Benefits
Orally available	• Once/twice daily pill versus injectable for standard-of-care
Excellent safety	• Rimcazole has been to Phase II in another indication and toxicology looks good
Multiple targets	• Efficacy in breast, lung, colon and prostate cancers
Patents	<ul style="list-style-type: none"> • Use in cancer – 2 patents expire 2019 and 2021 • Combination for use with other cancer agents– filed 2007 • Process – expires 2027
Double Mode of Action	• Pro-apoptotic (causes cell death) and anti-angiogenic (stops blood vessel growth into cancer tissue)

Source: Modern Biosciences, University of Dundee

Rimcazole's mode of action looks intriguing

Rimcazole is known to be a sigma-1 receptor antagonist and sigma-1 receptor proteins are commonly considered to be tumour biomarkers. Spruce et al (Cancer Research 64, 4875-4886, July 15, 2004) have shown that molecules like rimcazole can inhibit the growth of lung, breast and prostate tumours in mouse models and postulate that inhibition of sigma-1 receptors remove a brake on apoptosis (cell death). Work by Renaudo et al (J. Biol. Chem., Vol. 282, Issue 4, 2259-2267, January 26, 2007) has demonstrated a potential mechanism of modulating "cell destiny" through volume-regulated chloride channels. It may be that MBS will monitor biomarkers of tumour progression as well as tumour shrinkage to assess Proof-of-Principle in a Phase Ib trial, although tumour shrinkage alone would be sufficient to attract pharmaceutical company interest in licensing this product.

Stopping blood vessel growth (anti-angiogenesis) is a well known phenomenon

It is well known that tumour cells need access to oxygen and nutrients in order to grow and tend to stimulate blood vessel growth in order to achieve that. Inhibition of blood vessel

growth is a logical way to stop tumour growth and to reduce the spreading (metastasis) of the primary tumour to secondary sites in the body. Avastin has been successful (2007 global sales of \$3.4bn) partly because of its activity at inhibiting the start of the signalling pathway that leads to angiogenesis and partly because of the huge number of clinical trials that have supported its use across many cancers and in combination with different drugs. But Avastin and other biological agents have the disadvantages of injectable delivery and high price.

Toxicology is established, allowing Proof-of-Principle in cancer patients

What makes rimcazole particularly interesting from the MBS point of view is that toxicology is well known since the compound was developed through Phase II trials in the 1980s by Burroughs Wellcome for schizophrenia. Development was stopped after a portfolio review, but new data shows that rimcazole may have significant utility in cancer. Other sigma 1 receptor antagonist programmes crop up in the literature (Adis Insight) but have focussed on CNS programmes and discontinued for lack of efficacy; toxicity was never a problem. A 28-day toxicology bridging study was completed by MBS to validate the safety of the new drug substance produced using an improved manufacturing process. A Phase Ia pharmacokinetic study in healthy volunteers has begun and a Phase Ib study in patients with cancer is planned to start in early 2009. While it is possible that MBS may look for biomarkers of tumour progression, MBS will also measure tumour volume through in vivo imaging.

Six patent applications have been filed

Although there is no longer a composition of matter patent for rimcazole the intellectual property estate remains strong, with six families of patents. These cover the use of sigma ligands in cancer treatment, the manufacture of rimcazole as well as the use of sigma ligands in combination with other agents. The precedents for re-profiled drugs to achieve solid intellectual property protection are well established. As recently as last year Novartis paid Antisoma \$75m upfront for rights to a vascular disruption agent, AS1404, with milestones on top, despite the fact that the composition of matter patent will expire in 2011 in the US, almost certainly before the drug has been approved. Clearly, lack of composition of matter patents are no barrier to achieving a solid IP position and reaching attractive deal terms.

Does rimcazole have commercial potential?

At this stage it is difficult to know how to classify rimcazole – targeted therapy or general cytotoxic, since MBS has not yet found a cancer cell line in which rimcazole cannot induce cell death. The sales of targeted therapies that could be considered to influence angiogenesis and perhaps apoptosis exceed \$7bn. Oral therapies, such as Nexavar (Bayer/Onyx) and Sutent (Pfizer) have sold well and both have potential in excess of \$1bn. But even these products have severe limitations in terms of safety and efficacy. Some

generalised anti-cancer agents, such as the taxanes and the platinum-based compounds, have also achieved significant sales, with most of these products used in combination with other agents.

Rimcazole appears to have reasonable safety, based on human data in the 1980s, and interesting activity in animal models. Of the 10 small molecule oncology deals done in the industry since 2001 where deal terms have been disclosed the average upfront and equity investment was \$36m. This would translate to £12m after paying an estimated 30% to University of Dundee. This would be consistent with the model.

Figure 12: Sales of Top 10 Cancer Products

Top Ten Cancer Products (excl Gleevec and hormonals/targeted mAbs)	2007 Sales \$m
Avastin (Roche/Genentech)	3,422
Taxotere (Sanofi-Aventis)	1,874
Gemzaar (Lilly)	1,592
Eloxatine (Sanofi-Aventis)	1,521
Camptosar (Pfizer)	969
Xeloda (Roche)	959
Tarceva (Roche/Genentech)	886
Alimta (Lilly)	854
Sutent (Pfizer)	581
Nexavar (BayerSchering/Onyx)	372

Source: Company Accounts

OsteoRx for Rheumatoid Arthritis

An oral disease modifying agent for Rheumatoid Arthritis

The OsteoRx family of small molecules was licensed from the University of Aberdeen in October 2007 and have the potential to alter the progression of rheumatoid disease. Products in the OsteoRx family are oral and not only inhibit the TNF-signalling pathway, but also the RANKL-stimulated pathway. The inhibition of these two pathways leads to reduced inflammation and selective induction of apoptosis (programmed cell death) in osteoclasts, thus preventing the breakdown of bone. This could mean a significant advance on current therapy in terms of clinical efficacy, ease of use and cost.

Figure 13: OsteoRx for Rheumatoid Arthritis

Characteristic	Key Benefits
Orally available	<ul style="list-style-type: none"> Daily pill versus injectable for standard-of-care
Multiple targets	<ul style="list-style-type: none"> Rheumatoid arthritis (RA), Crohn's, psoriasis and osteoporosis
Disease modifying	<ul style="list-style-type: none"> Can stop joint destruction in RA versus non-steroidal drugs which treat only symptom of pain and inflammation
Patents	<ul style="list-style-type: none"> Composition of matter: <ul style="list-style-type: none"> Granted patents expire 2022 and 2024 Various pending patents expire 2025 and 2027
Double Mode of Action	<ul style="list-style-type: none"> Inhibitors of TNF and RANKL pathways could mean reduced inflammation and bone damage

Source: Modern Biosciences, University of Aberdeen

Two activities for the price of one; multiple disease activity from one drug

The inhibition of both TNF and RANKL pathways not only suggests that OsteoRx could be a more attractive disease modifying agent for rheumatoid arthritis but it could also be used for osteoporosis, a therapeutic area dominated by a class of drugs (bisphosphonates) with significant potential to cause gastric discomfort. MBS will not focus on osteoporosis since this is antithetical to the strategy but the potential should be reflected in the upfront payment in the event of a deal. Animal data is convincing that bone can be protected in both the collagen-induced arthritis model (a mouse is sensitised to collagen to induce an arthritic response and OsteoRx is used to prevent joint destruction) and the mouse ovariectomy model (ovaries are removed from a mouse to simulate the loss of oestrogen that normally takes place during the menopause and which stimulates bone loss; OsteoRx is used to prevent bone loss).

OsteoRx – a lead drug is being optimised

A lead candidate drug has yet to be identified from the family of molecules synthesised so far. Lead optimisation is underway and is expected to last through 2008. A lead will be identified, chemistry scale up developed and toxicology will begin. A Proof-of-Principle study should initiate by the end of 2009. The biomarkers for rheumatoid arthritis are well known and the in vivo data so far very impressive. Intellectual property has been granted for some chemical families but ultimate composition of matter patents and chemical synthesis will depend on the lead candidate.

Does OsteoRx have commercial potential?

The treatment of rheumatoid arthritis has undergone a revolution in the last 10 years with the launch of the anti-TNF antibodies that bind TNF, a naturally occurring pro-inflammatory protein in the blood of patients suffering from autoimmune diseases like rheumatoid arthritis, Crohn's Disease and psoriasis. However, these drugs are injectable and very expensive. Second generation products have tended to focus on easier to manufacture and less frequently dosed derivatives of monoclonal antibodies but they are still proteins and have to be injected. Although there are several companies working on oral TNF inhibitors (e.g. Wyeth on TNF alpha converting enzyme inhibitors) and several more on NF Kappa B inhibitors (downstream of the RANKL pathway) they are all at early stage and very few are for rheumatoid arthritis. A search of the ADIS Insight database reveals only three RANKL inhibitors, one of which has been suspended, another is in pre-clinical and delivered by injection; and the most promising, Amgen's denosumab, is in Phase III but delivered subcutaneously and pursued for osteoporosis and bone cancer initially. Lehman Brothers forecast sales in all indications for denosumab to be in excess of \$5bn. Denosumab is deemed to be so attractive that Daiichi Sankyo licensed the Japanese rights alone for \$20m upfront and a further \$150m contribution to development costs. Although this literature

search may not be totally comprehensive there appears to be a gap in the market for an orally acting product with dual mode of action like OsteoRx.

There have been only three Phase I licence deals in this therapeutic category where terms have been disclosed and the average, less an estimated 30% fee to the University of Aberdeen, would be £24m, certainly consistent with a successful business model.

Figure 14: Rheumatoid Arthritis drugs sales

Top Marketed Products	2007 Sales \$m
Enbrel (Amgen + Wyeth)	5,250
Remicade (Johnson & Johnson + Schering Plough)	4,975
Humira (Abbott Labs)	3,000
Orencia (Bristol Myers Squibb)	231
Rituxan/ Mabthera RA (Roche/Genentech)	275 e

Note 'e' denotes estimate Source: Company accounts, Lehman Brothers

Pipeline opportunities

The products shown below have not yet been licensed since they are awaiting a successful funding round with new investors, but they clearly demonstrate the variety of the opportunity that the best academic laboratories in the UK can offer.

Figure 15: Top Ten Pipeline Opportunities

Project	Indication	USP	Licence status	Precedent
Phosphate binders	Dialysis	Convenience, fewer side effects	Under exclusivity	Renagel - \$598m/year; Amgen buys Ilypsa for \$420m in July 07 for ILY101 in Phase II
Vascular disrupting pro-drugs	Cancer	Increased therapeutic index	Terms agreed	Xeloda - \$955m/year
Neuraminidase inhibitors	Influenza	Improved resistance profile	HOT agreed	Tamiflu - \$1,738m/year; Relenza - \$262m/year
CHK Inhibitors	Cancer	Potentiator of exist'g agents	MBS reviewing	All cytotoxics; >\$5bn
3rd generation fusion proteins	Various	Longer acting	MBS reviewing	Related recombinant proteins selling \$18bn+/annum
Inhibitor of angiogenesis	Ophthalmology	Fewer side effects	MBS reviewing	Lucent's - \$1,209m/year
PKB Inhibitor	Cancer	Greater selectivity / safety	MBS reviewing	All targeted cancer therapeutics; >\$5bn
G protein receptor antagonist	Multiple sclerosis	Oral, fewer side effects	MBS reviewing	Interferons/Tysabri - >\$4bn/year; Zantac - \$3,532m/year at peak
Therapeutic protein	Osteoporosis	Fewer side effects	MBS reviewing	Fosamax \$3bn
Immuno-suppressive	Inflammatory diseases	Oral, fewer side effects	MBS reviewing	TNF inhibitors - >\$7bn/year

Source: Modern Biosciences, Company Reports and Accounts, 2007

Several of these projects are very near to signing and will contribute to the 4 new projects a year shown in the Steady State model in figure 7. The projects identified span several therapeutic areas but all have a clear USP and are believed to have strong intellectual property. The precedent column shows that there are existing products in these markets that have achieved significant sales, despite them being less than ideal.

Shareholder Structure

The table above shows that IP Group plc and its nominees own just over 68% of the business; Sam Williams, the CEO, owns 16% and other employees own just over 4%. Clive Dix is Chairman of MBS and Ian Wilding, who is Chief Scientific Officer on a part time basis (2 days per week), is one of the founders. Every one of the employees owns shares in MBS and it is expected that new employees will also be granted shares in order to maintain a spirit of shared enterprise.

Figure 16: Shareholder Structure

Shareholders	Holding
IP Group plc	56.26%
IP2IPO Nominees Ltd	12.15%
Sam Williams	16.00%
Clive Dix	5.00%
Ian Wilding	4.83%
Other employees	4.08%
Modern Biosciences Nominees Ltd*	1.68%
Total	100.00%

* Of which 1.17% held on behalf of Ian Wilding

Source: MBS

Management Team

MBS has a lean organisation but a valuable mix of skills and hands on experience for a company that must survive on pragmatism, flexibility and speed of decision-making. The combined tenure in drug development of the team exceeds 100 years while the external experts upon whom the Executive Team can call adds even more expertise in the areas of chemistry and toxicology.

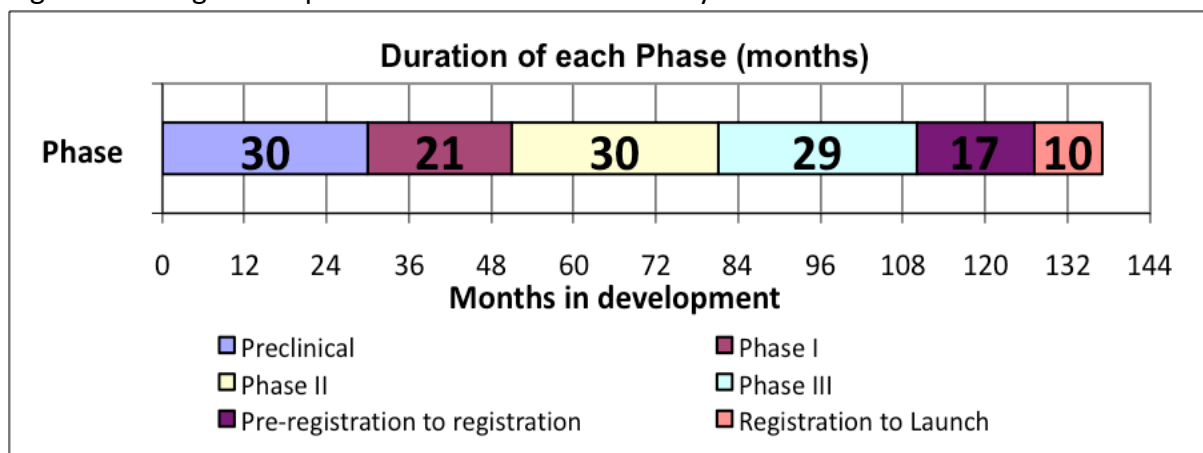
- **Clive Dix, Chairman**, has over 22 years' experience in the pharmaceutical and biotechnology industries, encompassing business leadership, project management and drug development. He was formerly the Chief Executive Officer of PowderMed Ltd and prior to that he was the Senior Vice President, Research and Development of PowderJect Pharmaceuticals plc.. He also held a senior position at Glaxo Wellcome as the UK Research Director where his role included co-chairing the management group that oversaw all of the company's research projects worldwide.

- **Sam Williams, CEO**, was an award-winning biotechnology analyst with over ten years experience in the financial services industry at Lehman Brothers and Robertson Stephens. He also has expert life sciences knowledge, particularly in molecular biology, where he worked in the research group of Sir Gregory Winter FRS, scientific co-founder of Cambridge Antibody Technology (CAT) and Domantis.
- **Will Turner, CFO**, was Group Financial Controller of IP Group plc where he oversaw the finance and operations of the company. Will was actively engaged in board level roles within IP Group's portfolio of biotech company investments and acted as interim Finance Director during the IPOs of Oxford Catalysts Group plc and Modern Water plc.
- **Ian Wilding, Chief Scientific Officer**, has direct experience of 250 phase clinical studies during his tenure as CEO of Pharmaceutical profiles and was the first external adviser to Chorus, in some ways the role model for MBS.
- **Kevin Moulder, Head of Development**, managed 12 discovery programmes while at Domantis, including one project to Phase I on time and on budget.
- **Bruce Campbell, Non-Executive Director**, spent 27 years at Servier (UK) where he left as head of R&D having been responsible for the development and registration of seven drugs and vaccines. At Neuroscience he advanced eight novel drugs into clinical trials for insomnia, depression, anxiety, brain cancer, multiple sclerosis, type 1 diabetes and endometriosis.
- **Alan Aubrey, Non-Executive Director**, is CEO of IP Group Plc. Previously he was founder and CEO of Techtran Group Ltd, which was acquired by IP Group Plc in January 2005, and was formerly a partner in KPMG where he specialised in corporate finance advice to technology-based fast growth businesses.
- **Barry Furr, External Advisor**, has 30 years of experience at AstraZeneca and its predecessors, specialising in oncology. Dr Furr was involved in the discovery and development of Zoladex, Casodex and Tomudex and the direction of AZN's entire cancer strategy in the late 1980s and since then has held senior research positions across all most therapeutic areas.
- **John Dixon, External Advisor**, retires as Head of Drug Discovery at AstraZeneca R&D Charnwood in June, after 36 years at AZN and its predecessor companies, Astra and Fisons. He is the inventor of one cardiovascular drug in the market today and several other compounds that reached advanced stages of development. He has overseen the move of dozens of drugs through pre-clinical into clinical development.
- **Harry Finch, External Advisor**, spent 23 years at Glaxo Wellcome and its predecessor company Allen & Hanbury, leaving as Director of Chemistry. He was a co-inventor of Serevent (blockbuster medicine for asthma) and oversaw the discovery of dozens of drug candidates.

Appendix 2: The R&D Process - Timelines, Attrition Rates and Costs

Research & Development, by its very nature, can be tedious, time-consuming and expensive. Estimates of the cost of bringing a product from discovery to market vary, depending on the source, but the Tufts Centre for the Study of Drug Development estimates around \$1bn in 2005 \$. This includes the cost of failures along the way, or attrition (75% of total costs according to a Pfizer source), which in turn includes out-of-pocket costs and the opportunity cost. Figure 18 shows that successful development of a product from early discovery phase to launch can take 11.5 years, although the clinical phases in man may last only 9 years.

Figure 18: Drug Development can take more than 10 years



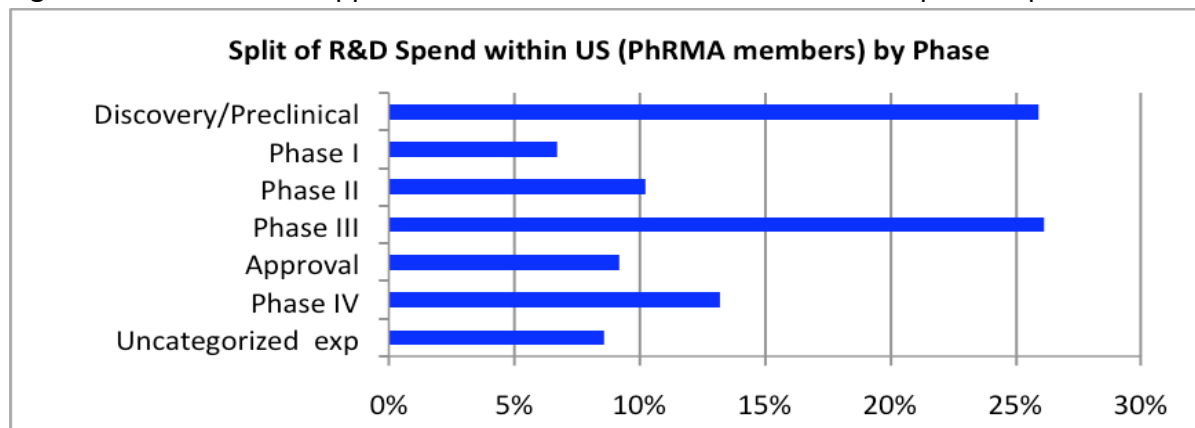
Source: Pharmapredict March 2006

High late phase costs should encourage earlier attrition

The empirical split in R&D costs according to phase of development is shown in Figure 19. Given the significant proportion of total costs spent in Phase III and the approval process, typically 5-7 years after the project begins, any process or activity that can reduce downstream attrition will save a lot of money.

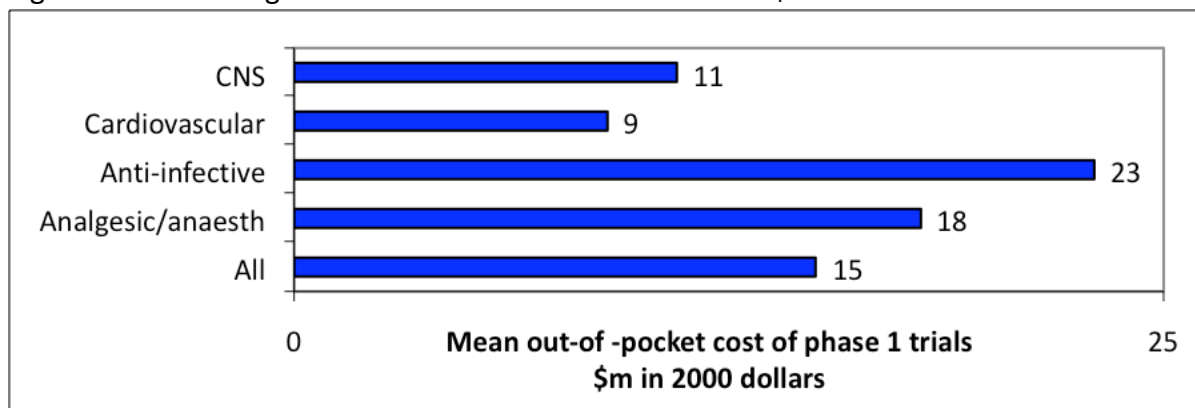
The mean cost of all Phase I trials (in the survey of 68 drugs by Tufts) is estimated at \$15m (Figure 20), but this does vary according to therapeutic category. Phase I is the most expensive phase of trial on a per patient basis, mainly because of the degree of complexity. Studies by Fast Track Systems Inc have shown that the mean number of procedures per patient in a Phase I trial is 135, compared with 113 procedures in Phase II and 109 procedures in Phase III. Once again, Modern Biosciences seeks to cut down complexity by focusing only on what is necessary to achieve Proof-of-Principle, starting with the studies that give the highest probability of yielding “go/no-go” signals.

Figure 19: Phase III and Approval Costs Take One Third of Total Development Spend



Source: PhRMA 2006

Figure 20: On Average Phase I Trials Out-of-Pocket Costs is \$15m



Source: Tufts Centre for the Study of Drug Development

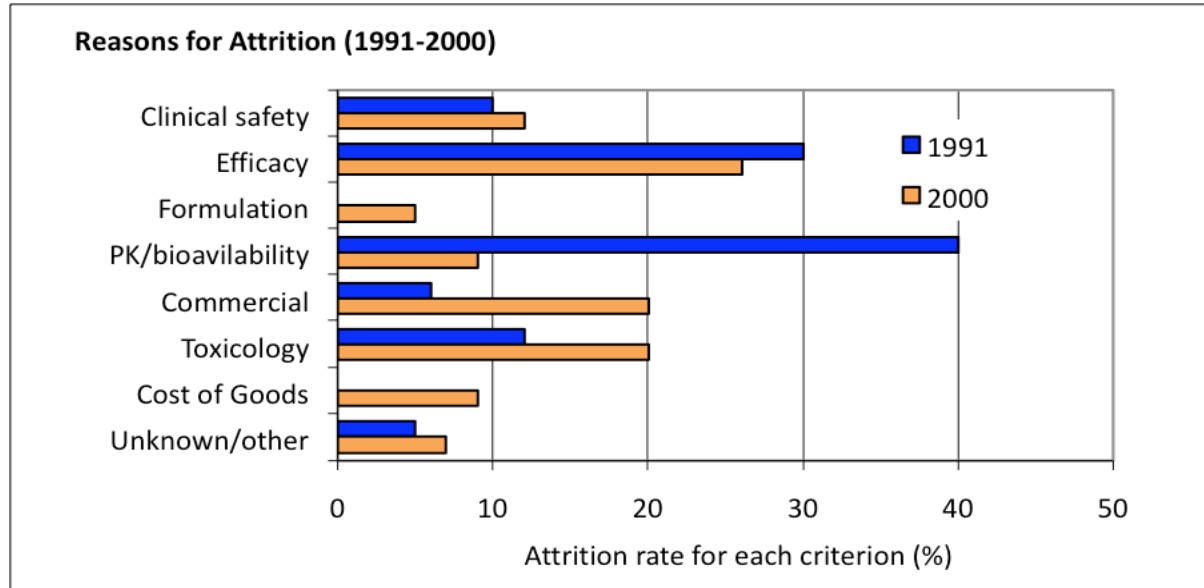
Attrition is historically due to lack of efficacy and toxicology (side-effects)

In 1991, the main reason for attrition during the overall development process was poor bioavailability or pharmacokinetics, followed by poor efficacy. Better drug design and improved pre-clinical testing since then have helped reduce failure through pharmacokinetics or bioavailability. As a consequence, ten years later, the main reasons for attrition are lack of efficacy, followed by toxicology. If the industry is to reduce its attrition in development this mind-set should be in place from the discovery stage, resulting in the following approach:

- Build proof of mechanism into the discovery process
- Use appropriate animal models for efficacy testing
- Eliminate compounds that have mechanism-based toxicology
- Identify and use biomarkers that can signal drug-related activity at the target
- Build Proof or Principle into the earliest human trials

Modern Biosciences sets out to achieve each of the above in the design of its pre-clinical and Phase I trials, thereby cutting its costs of development to less than £2m per project and reaching a Phase II “go/no-go” decision and value-inflection point sooner and less expensively than the industry typically does.

Figure 21: Efficacy and Toxicology Problems Account for Most Drug Development Failures



Source: Parexel R&D Source Book

Development attrition rates vary by therapeutic category and by data source

Beating the industry average attrition rate (a technical term for probability of failure) during the pre-clinical-Phase II transition (i.e. completing pre-clinical and Phase I to Proof-of-Principle) and doing so at low cost are key to the Modern Biosciences model. Henceforth this report refers to probability of success rather than its complement, attrition rate. To be able to compare MBS’s objective success rate of 1 in 4 it is helpful to discuss what industry success rates are. There are two main sources for probability of success in different phases of development, Pharmapredict (based on the Pharmaprojects database) and Centre for Medicines Research (CMR). Unfortunately, the accessible CMR data does not include pre-clinical success rates, only the later phases of development. Figure 22 below shows the range of probabilities of reaching the market depending on therapeutic category and phase of development.

Figure 22: Probability of Reaching the Market Varies with Therapeutic Area and Phase

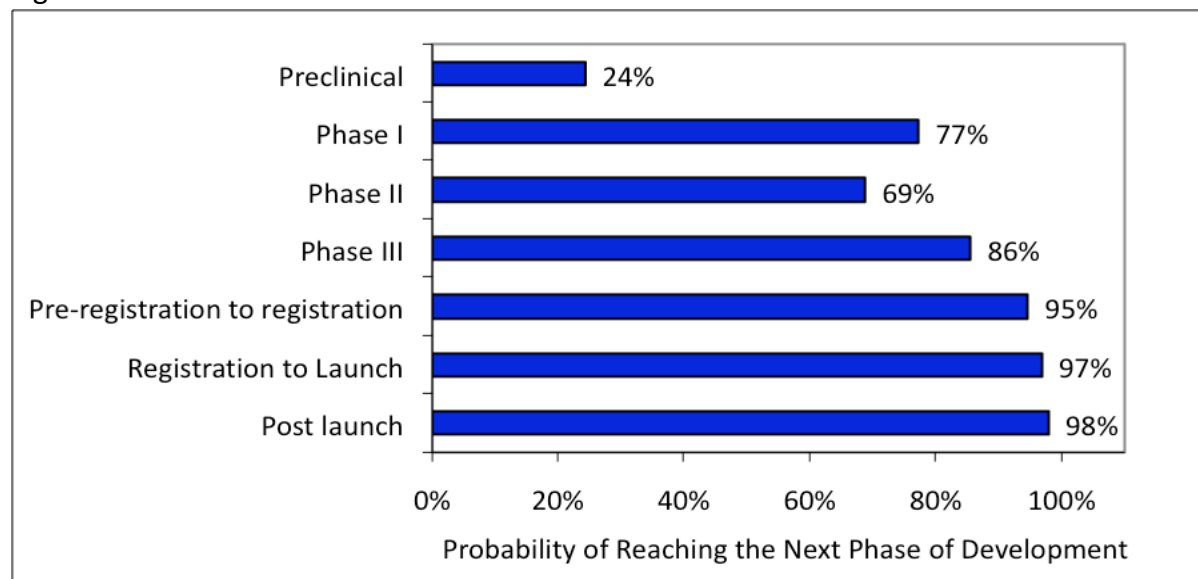
2006 n= 490	Therapeutic area				All drugs	Pharmapredict
	CNS	Cardiovascular	Anti-cancer	Anti-infectives		
Pre-clinical	NA	NA	NA	NA	NA	10%
Phase I	8%	9%	8%	28%	10%	41%
Phase II	12%	13%	12%	38%	18%	53%
Phase III	39%	44%	32%	70%	69%	77%
Filing	92%	79%	71%	85%	97%	95%

Source: CMR data compared with Pharmapredict

It can be calculated from the data for all drugs above that the probability of moving successfully through Phase I to Phase II is 55% or approximately 1 in 2.

With success in pre-clinical of 10% (i.e. 10% of drugs in pre-clinical get to market) and success in Phase I of 41% (i.e. 41% of drugs in Phase I reach the market) it can be deduced that the success rate from Pre-clinical through to Phase I is around 24% or 1 in 4. Furthermore the success rate from Phase I to Phase II is 78% or approx 4 in 5. It follows that the success rate from pre-clinical through to Phase II is 24% of 78% or 19%, approximately 1 in 5.

Figure 23: Success Rate from One Phase to the next



Source: Pharmapredict

Note that the success rate in Phase I varies enormously between Pharmapredict and CMR data. It is impossible to reconcile two databases where the data has been gathered and probably classified differently. However, the success rate in the Pharmapredict database is an “all-comers” success rate including products from both pharmaceutical and biotechnology sources. It is generally acknowledged that many of the smaller biotechnology companies with very few assets tend to be reluctant to kill off those assets early since the raison d’être of the company can suddenly cease. As a consequence, the success rate may

have been increased by products reported as progressing to the next phase when in reality they should have been terminated. It is easy to see why the industry-accepted attrition rate through pre-clinical to a positive Phase I outcome is more like 1 in 5 or worse. Modern Biosciences should be able to beat the standard industry attrition rates through judicious choice of experiments and projects. Some of these experiments may even be conducted during the due diligence phase, before they are licensed. MBS will have no hesitation in terminating products that do not meet critical benchmarks, even before they are licensed.

Appendix 3: Traditional Pre-clinical Drug Development is Costly and Time-consuming

The traditional way of preparing a product candidate for a “go/no-go” decision into Phase Ib or Phase II clinical trials is a two-part process.

- The Investigational New Drug application (IND) represents a checklist of requirements that must be submitted to the FDA and other regulatory bodies showing that the drug is reasonably safe for use in small-scale clinical studies in man. During this pre-clinical phase a drug company sponsor is typically asked for
 - a pharmacological profile of the drug,
 - the acute toxicity of the drug in at least two animal species and
 - short-term toxicity studies ranging from 2 weeks to 3 months depending on the proposed duration of use of the drug in the proposed clinical studies.

If these requirements meet the regulatory agency standards then the drug proceeds into Phase I testing i.e. the first human clinical trials. Phase I may be broken down into Phase Ia, where healthy volunteers are involved and Phase Ib, where patients with relevant clinical disease are involved.

- Chemistry, Manufacturing and Controls Information (CMC) is required at each phase of clinical trial and should include sufficient information to ensure the proper identity, strength or potency, quality and purity of the drug being studied. This includes data on the manufacturer, the manufacturing process, starting materials, physical characterisation of the product, the analytical procedures used during processing, stability data and much more. Some of this is required before Phase I testing but the size of clinical trial at Phase II necessitates a significant step up in data submitted.

The traditional pharmaceutical industry approach has been to embrace the many requirements of the IND and CMC assuming that their products are going to succeed, despite the fact that at this stage of development (Phase I) perhaps 80-90% of product candidates will fail. This success-based behaviour can lead to manufacturing scale-up and long term animal testing before critical experiments have determined whether the drug will proceed to Phase II.

According to Neil Bodick, a development scientist at Lilly and the author of the Chorus concept (see box on page 10), most companies “think they’re doing proof-of-concept (testing) but they’re not. They’re planning on success without any evidence for it. This mindset has been described as “success-seeking behaviour” and is even incentivised in many organisations with bonuses paid on the basis of the number of products pushed through to the next stage. However, a moment’s reflection should reveal that this can be counter-

productive, since products where an experimental outcome is marginal will always be pushed forward.”.

A more cost-effective way forward is to pursue only those experiments and supply only enough data that is the bare minimum to meet regulatory requirements but which will get a “go/no-go” decision quickly and cheaply. This is what Modern Biosciences is doing under rules of the new Exploratory IND.

The exploratory IND is much less onerous in time and costs

One of the outcomes of the FDA’s Critical Path Initiative was the Guidance for Industry, Investigators and Reviewers: Exploratory IND Studies. This aims to facilitate drug development without compromising safety. The upshot is that the amount of supporting data required in an IND is reduced and depends on the design of the clinical study and the expected risk to the patients involved. There are two main headings under which the benefits of an Exploratory IND can be categorised:

- A reduced toxicology burden. It is permissible to study pharmacokinetic effects of a new drug in man using microdose studies (a dose less than 1/100th of the dose calculated to yield a pharmacologic effect). It is also permissible to use pharmacologically effective doses in man, provided they do not reach maximum tolerated dose. Both of these types of study can yield valuable information but do not require the same level of toxicological testing as for traditional IND. For example, it may be that only one species of animal is needed for toxicology instead of two.
- Earlier Proof-of-Principle studies. It is permissible to pursue confirmatory clinical studies on mode of action, provided that a safe starting dose has been selected based on appropriate pre-clinical studies. This means that it may be possible to get a clear signal of Proof-of-Principle even though the product is being used at sub-optimal dosing and almost certainly below dosages pursued under traditional IND.

Modern Biosciences not only exploits the advantages of Exploratory IND but also is seeking to exploit biomarkers as a proxy for clinical impact. In this way it should be possible to demonstrate clear Proof-of-Principle in man, complete with sufficient information about the drug to excite the interest of the pharmaceutical industry.■