S-CUBED

Optimising the path to commercialisation; Who can help and when?

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This is case study for a joint project S-cubed worked on for a new drug for IBS – PharmaVentures was the lead company and they were providing market valuation expertise, Apex Healthcare were providing the reimbursement expertise and S-cubed provided the regulatory expertise.

With thanks to PharmaVentures and Apex Healthcare for allowing us to republish it here.

At PharmaVentures we have been providing commercialisation advice for 25 years for pharmaceutical, biotech, diagnostics and device companies. The nature of that advice stretches from commercialisation strategy to valuation, licensing and M&A execution. We are frequently asked by companies with drugs in the early stages of development (preclinical or phase 1) what the value of their assets are currently and how this will increase as they move through development. For most companies, there is a monetisation event in their minds and they are seeking to balance how far they take an asset through development to a point where they can license it, sell it or the business, or perhaps embark on an IPO. Clearly, they want to pick the optimum timing where risk and reward are favourable and an attractive market of partners or acquirers will be available. Conducting a valuation in such circumstances is usually relatively straight forward but there are many other considerations that companies should consider.

What do I need to know and when do I need to know it?

For many companies, and in particular smaller and emerging biotechs, the strategy seems pretty clear. Develop my asset to proof of concept and then seek a large partner to complete the expensive late stage clinical development and use their established sales and marketing infrastructure to maximise the returns. It is a tried, tested and successful model. The devil is in the detail, however, and decisions taken very early on often have a major impact upon the value and even commercial viability of an asset at the point at which it's time to do a deal.

When we are approached by a client for help in this area we undertake a thorough audit of the data and information the company has in hand already. It's not an absolute requirement to have all the boxes ticked but the more that remains for the commercialisation partner to do the greater the impact on the potential returns to the current owner. In times past one of the most important areas was to have a clear understanding of the regulatory path through development to approval. Larger companies were less concerned about areas such as pricing and reimbursement. Whilst the importance of regulatory considerations has not diminished, and if anything has increased in complexity, it is certainly true that an appreciation of the pricing and reimbursement position has become very important.

In expressing these views to younger biotech companies, we often hear agreement on the importance of these areas followed by the view that it makes sense to seriously consider them at or after Phase II when there is a much clearer picture of the safety and efficacy of the drug etc. and therefore how it stacks up against the competition. It is true that modelling the value of an asset can be done with a greater degree of certainty at this time but if the preclinical and clinical work up to point has been done without regulatory, payer and prescribing practices taken into consideration you may find repeat work is

required or the asset positioning is sub-optimal to deliver the best returns to both current owner and commercial partner. There are many assets competing for the attention and dollars of the big pharma companies, doing the right things at the right time is key to generating a compelling partnering proposition.

A Recent Case Study

PharmaVentures was approached by Biotech Company A who was developing a novel therapeutic for the treatment of Inflammatory Bowel Syndrome (IBS). The drug was at Phase I with excellent preclinical data including animal models and some limited clinical data on safety and efficacy. IBS is a complex condition, but a significant problem for a very large number of people of which the majority self-medicate and the rest seek medical intervention. Company A was keen to understand what the value of the asset would be at the end of Phase I (where they expected to have clear efficacy signals) and ready for Phase II and also at the end of Phase II. The outputs would help them make decisions around when to partner the asset.

IBS can take different forms featuring either constipation, diarrhoea or both, pain discomfort and bloating. Company A had data indicating they could impact upon all of these features which was ideal from a valuation perspective as it would potentially capture all patient sub-groups and thus maximise the value of the drug. In order for PharmaVentures to build an appropriate valuation model it was important to understand physician prescribing practices. This was accomplished by interviewing Key Opinion Leaders in the field. From the KOL studies it was clear that patients present with varying, and often multiple, IBS features but the physician will use the best treatment option available to resolve the most troublesome aspect in the first instance. The drugs available to the physician is dictated by those that are reimbursed and approved. In order to gain this status, the clinical trials that were undertaken needed to address endpoints that regulators could approve against and payers would be willing to reimburse. In the case of IBS, there are clinical guidelines developed by experts (Rome III and recently released Rome IV) for the treatment of the various forms of IBS. The guidelines are of extreme importance in clinical development and gaining regulatory approval, but less so in everyday clinical practice where the physician will seek the best option for the patient in front of them. We now start to see some of the issues emerging.

Start at the end and work back

As Company A knew their drug could impact on all aspects of IBS they were keen to include all patient types in their clinical development plan to maximise the asset value. An excellent strategy, but what, ultimately will be the label claim for the drug? One could envisage it involving “The treatment of IBS symptoms including diarrhoea, constipation, pain and bloating”. But would the regulators allow such a claim? Furthermore, would the label claim influence how physicians prescribed the drug? Assuming these points can be addressed, what price could the drug command and would it be supported by the payers and reimbursers? It’s clear that in order to develop a robust valuation model now, and have the right clinical development plans in place, the regulatory and payer considerations were important. All of the component parts are connected and influence each other. Knowledge of regulation, payers and prescriber practices all inform the development plan and valuation models which drive toward decisions and deal points. Making informed decisions based upon all the inputs even at this early development stage would give Company A the best chance of returning the highest value for their asset

whilst spending their precious development dollars in the most efficient and effective way.

Who can help?

PharmaVentures has deep experience in commercialisation of assets and a good adviser knows what they don't know and where to access other expertise to complete the picture. In this instance we engaged with Tony Mitchell of the regulatory consultancy S-Cubed and David Cotterell and Stephanie Bewick of Apex Healthcare Consulting for pricing and reimbursement expertise. Companies with early stage assets often delay seeking advice from both of these areas and then incur delays and additional cost later on when they find the clinical development they have conducted will not support regulatory approvals or a pricing and reimbursement strategy that delivers optimal value.

Expert regulatory input early in development is vital to ensure a product will meet regulatory requirements at all stages along the development pathway, from early proof of concept through to product registration. There are many regulatory guidelines which provide guidance along the way, but there are occasions when either a guideline does not exist, or it is simply not applicable to the product in question and cannot be followed. It is in this latter scenario that early engagement with a regulatory expert is critical to define the development plan and route to registration. This was exactly the situation facing Company A and their innovative product for IBS.

The regulatory guidelines for IBS categorise potential new therapies by subtype, which in turn defines the clinical trial patient population, study design features, and expected outcomes for registration of a new therapy. Recent regulatory approvals in the field of IBS have adhered to the guidance both in terms of patient population (Rome III criteria), disease sub-type (IBS-Constipation or IBS-Diarrhoea) and clinical study design features, including utilisation of pain and defecation abnormalities as primary endpoints.

The unique properties of Company A's drug, whilst potentially providing life-enhancing treatment for patients with the condition, were such that the standard IBS clinical development pathway as per the guidance and recent approval precedent, was not applicable. This was particularly evident for the patient population in which all IBS sub-types could potentially benefit, and should therefore comprise the clinical trial population. In addition, efficacy for this innovative treatment would most effectively be demonstrated using a primary endpoint for which there was no precedent or guideline rather than the conventional abdominal pain and defecation abnormalities endpoints.

Hence, the guideline could not be strictly followed and deviation would be necessary. This is generally permitted, as the purpose of any guidance is to assist with, rather than mandate, the development pathway for a product in a particular disease area. However, regulators do expect guidance to be followed unless there is a very good justification for not doing so. This is where regulatory advice is critical to assist Company A with their development plans, clinical study designs, justifications for deviation from the guidance, and subsequent consultations with the regulators in order to maximise the likelihood of regulatory acceptance and approval. Heading off down a path that deviates from guidelines and practice which is familiar to regulators could result in adverse regulatory responses and for the company, wasted time and additional costs to repeat clinical studies.

While it is obviously critical to gain regulatory approval, reimbursement coverage by healthcare payers is the final key hurdle. National, and in some cases, regional payers (in

Europe) and the Managed Care Organisations (in the US) assess new products using a range of approaches often different to the regulatory authorities. Payers are focused on getting value for money and particularly in Europe, ensuring that new entrant product demonstrates improvements over existing treatment.

- In order to assess cost effectiveness and constrain free pricing, the G-BA in Germany conducts an early benefit assessment of new drugs. This allows the evaluation team to weigh up the product's benefits against a range of criteria, including quality of life. If a drug's only benefit is to improve quality of life, it is excluded from reimbursement, whereas innovative products for serious diseases with high unmet need are fully reimbursed. All other products are grouped into therapeutic categories which are allocated a group reference price. If the marketed price exceeds this reference price, the patient has to cover the outstanding amount as a co-payment.
- In France, in order for a drug to be reimbursed, it is evaluated by the Transparency Commission (Commission de la transparence (CT)) to assess its perceived medical benefit (SMR) as well as its improvement in medical benefit rating (ASMR), and given an SMR rating as well as a therapeutic value rating (ASMR 1-V). ASMR1 accounts for drugs which demonstrate a major improvement over standard of care and are reimbursed 100%; ASMR 2 is given to drugs showing a significant improvement over standard of care and is reimbursed 65%, and this continues on down to ASMR 5, which are not reimbursed as they show no improvement. So although the French system does not control the price band, it controls the level of reimbursement, once a product is allocated a reimbursement band, the company then starts a price negotiation with the Comité Economique des Produits de Santé (CEPS)
- In the UK, NICE conducts a Health Technology Appraisal of products expected to have a significant health benefit, make a significant impact on other health-related government policies or have a significant impact on NHS resources.

An example of how a recent entrant of an IBS treatment was considered by payers is a useful yardstick for how Company A's product may be assessed.

- Linaclotide was the most recent entrant for IBS in 2013 and NICE did not consider it necessary to conduct a HTA based on the stated criteria, but the product was approved for reimbursement in refractory patients who have failed prior treatment, thus restricting its use on the NHS to this patient group.
- The G-BA in Germany conducted an early benefit assessment of linaclotide, but concluded that added benefit could not be demonstrated because comparator data as dietary advice in the trials was not tightly controlled.
- It is unclear if France has assessed linaclotide, but older anti-spasmodic products, when assessed where given a reimbursement level of 15% as standard of care is low priced.

A new product such as Company A's product, will have to demonstrate in comparative studies a clinically significant benefit over the comparator standard of care. The dietary advice in the trials will have to be very tightly controlled to ensure that the study arms are

comparative. If a primary endpoint deviates from the accepted endpoints i.e. bloating, it is likely that payers will require more than one primary endpoint to carry out their clinical and economic evaluation.

It will be important to engage with national payers early to understand the extent of the cost effectiveness data package requirement vs. standard of care. Early insight will give Company A the opportunity to marry this advice with the regulatory feedback to design appropriate clinical trials.