
PAPERS

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What to do when your technology is good but a licence is terminated

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Abstract

One of the biggest challenges in the biotech industry is to secure sufficient funding to support product or technology development. Partnering with companies that have cash and expertise – which, for the most part are larger biotech or pharmaceutical industries – may for many small biotech companies be more appealing than dealing with the financial community – venture capitalists and the like. The risk to the small biotech, however, is enormous because the partner may decide to return the rights to the product. This event usually leaves the product in limbo and the technology used to develop it tainted because of uncertainty regarding the real reasons for the return and the assumption in the world at large that there is something wrong with the product/technology. Thus, the licensor is left in the dark and is faced with ‘what’s next?’ Here our company’s strategy to overcome the terminated licence disaster or alternatively to take advantage of the terminated licence opportunity is described.

INTRODUCTION

This paper provides a case history of the major challenge that biotech companies in today’s world are facing: how to secure funding to progress a technology or product to the next stage, preferably commercialisation, without ‘betting the company’.

Although there are hundreds of venture funds out there shopping for deals, it is very difficult to identify one that shares your vision. Teaming up with a group that almost certainly does not share the biotechnology company’s vision, because they (frankly) do not understand your business, can doom the company. Venture capitalist (VC) funds are not interested in advancing a product to market *per se*. Their stated objective is to secure for their investors the highest possible return on investment. The way most VCs try to accomplish this today is by seeking to reduce the pre-money valuation of the company to compensate for the fact that eight or nine out of ten of their investments lose money and they strive to make their entire return on the one or two that do make money. VCs

thus should, but usually do not, recognise that they have little or no ability to identify which product or technology will be the next blockbuster or stepping-stone technology. Therefore, the prospect of entering into an agreement with a biotech or pharma partner, which is probably more capable of valuing a product or technology, is on its face very attractive and appears to be the focus of most biotech companies to advance their products to market.

Many meetings are organised to facilitate deal-making and *BioWorld Today* is full of partnering announcements almost on a daily basis. Here we will address what are the options when the rights are returned. Are they obvious or not?

PROTEIN SCIENCES BACKGROUND SITUATION

In 2001, after a long and often disharmonious dispute with its former partner Pasteur Mérieux Connaught, which became Aventis and is now sanofi-pasteur, Protein Sciences Corporation was finally able to re-acquire all rights to two

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Partnership: good or bad for your product?

patented, late-stage influenza vaccines. The products at stake were recombinant haemagglutinin (rHA), now called FluBlØk™ (where the 'Ø' appears as an egg with a line through it – no eggs used) and recombinant neuraminidase (rNA).

The FluBlØk vaccine is made using cell culture (insect cells) and is potentially a replacement for the licensed egg-grown influenza vaccines. Its characteristics are such that it is the only new vaccine in development that can address all of the shortcomings of the licensed vaccines. Thus, FluBlØk represented a major opportunity for sanofi-pasteur but also, and unquantifiably, the major potential threat to its influenza vaccine franchise.

Prior to the sanofi-pasteur licence, FluBlØk had completed several Phase I/II human clinical trials conducted by the National Institute of Allergy and Infectious Diseases (NIAID) and academic institutions involving over 600 subjects that demonstrated safety and efficacy as reported in four published studies in the *Journal of Infectious Diseases*. No clinical development of FluBlØk occurred during the six year period the product was licensed to sanofi-pasteur.

rNA, which also is made using cell culture, can potentially be used as an efficacy-enhancing additive to influenza vaccines. Only one clinical trial was conducted during the time the portfolio was licensed, a challenge study of rNA used in combination with a licensed egg-grown influenza vaccine, and even this was sponsored by NIAID.

After years of frustration because the licensor decided to shelve our influenza products, Protein Sciences finally was able to reacquire the rights at the end of 2001 (six years after licensure) and was therefore able to once again actively pursue their full potential either alone or with a partner.

Raising money in 2001 was difficult at best because management had to take a cautious approach to the lead products, FluBlØk and rNA, in its business plan, mentioning only that they had been licensed to sanofi-pasteur and, fortunately

it turned out, not including any value in its financial projections from such products. Thus, it was possible to raise only a modest amount of money primarily from a few previous investors who believed in the company and its technology and knew the real potential of the influenza products. Had the projections included any value from the influenza products, the return of the rights just prior to the closing would certainly have killed the financing and, probably, Protein Sciences.

Management realised that post-return the world at large would view the influenza products as 'damaged goods' since they had been returned by the world leader in influenza vaccines. Furthermore, the underlying technology was at risk if Protein Sciences, the world leader in that technology, were to fail, a result that management was dedicated to avoiding at all cost. It was clear that only new clinical data would rekindle interest in potential partners and investors. However, the hurdle to overcome was how to generate the data with no money and how to stay alive until the data could be generated!

THREE-LEGGED STOOL BUSINESS MODEL

Three avenues were pursued to recover from the terminated licence:

- Pursue government funding for the development of a better influenza vaccine for high-risk populations.
- Develop a service business, which we called GeneXpress[®], to progress development of the platform technology, drive products to market, generate revenues, license the technology platform for multiple applications and by doing so build future value in the form of royalties.
- Sell research reagents to drive revenue and increase recognition of Protein Sciences and the value of its technology.

Impact of returned licence on funding of company

Strategy to survive Returned licence

Government support to generate critical new clinical data

Government funding

Influenza is and has been a major field of interest and concern from a public health perspective as demonstrated not only by the active role that the government takes in increasing annual influenza vaccination but also by the government role and planning for a pandemic and its active sponsoring of new technology development.

FluBlØk was eligible for government funding because it has long recognised that inevitably the egg-based technology will need to be replaced. There are a number of major issues associated with the egg-based manufacturing process, such as egg supply (what happens with the egg supply in case of an avian influenza outbreak that kills the egg-laying chickens?), surge capacity (how can capacity be increased rapidly in case of a pandemic?), yields in manufacturing (what happens if the influenza virus cannot be produced in adequate amounts in the chicken embryos?), inability to stockpile (egg-grown vaccines have a shelf-life of less than one year) and contamination associated with the production process (are there more Chiron disasters waiting to happen?).

NIAID had funded many clinical trials of new influenza vaccines, including Protein Sciences. In the end NIAID generously funded a new clinical trial and also our cost of producing clinical materials, although getting to the top of their priority list required persistence and patience. The support of NIAID enabled Protein Sciences to gather new clinical data in the elderly population using a trivalent rHA formulation that outperformed FluZone[®], a licensed vaccine made, ironically, by sanofi-pasteur.

In addition, Protein Sciences also pursued a licensing partner for FluBlØk as an influenza vaccine for veterinary applications to further validate the technology and generate revenues. The rights to FluBlØk for swine influenza were successfully out-licensed to a major multinational animal health company.

Validation of platform technology through GeneXpress

Product line for research market to generate income

Service business – GeneXpress

The main goals of the GeneXpress service programme were to drive to market products made using the Protein Sciences' proprietary baculovirus expression vector system (BEVS) technology and to generate revenues to stay alive. The secondary objectives were to build a portfolio of potential royalty payments that could generate exponential profit growth in the future and to develop the BEVS technology to a point where Protein Sciences would have total freedom to operate from a patent perspective, strategies management has used successfully in previous companies.

It was felt that by enabling other companies to pursue the development of products using our BEVS technology it would be possible to benefit in a number of ways: multiple products in development would lead to validation of the technology; it would ultimately be possible to justify establishment of our own manufacturing capacity; clarification of the regulatory pathway would be secured; and it would be possible to in-license products that became ancillary to the customer's ever-changing strategy or fallout from the customer's failure or merger or acquisition.

As a result of this service business and pursuing licensing opportunities for non-core applications of our BEVS technology and products we stayed alive, validated our BEVS technology by establishing collaborations with both biotech and pharma companies, advanced several new products into the clinic and secured clear freedom to operate in the insect cell field (and, potentially, the ability to block others).

Research reagents

Initially the company focused on selling protein products, such as HIV and influenza antigens, derived from internal projects to the research markets. Later technology-related reagents such as the serum-free scaleable *expresSF+*[®], linearised baculovirus DNA and transfer vectors were added to our portfolio.

Recently SARS and cancer antigens have been added. This business has enabled us to generate revenue and create awareness and acceptance for our BEVS technology.

Products derived from internal and external projects continue to be added and in addition our customer base is used to explore technology licensing opportunities.

WHERE ARE WE TODAY?

Over the past two years significant progress has been made with the development of FluB1Øk. The aim was to develop a better vaccine for the elderly population, where the licensed vaccine is less effective than in other populations. A clinical study was conducted in 399 elderly subjects (average age 70 years) in 2003–2004 in collaboration with NIAID, which indeed demonstrated the FluB1Øk has the potential to outperform the licensed vaccine and potentially save more than 30,000 lives per year in the US alone! Following these results, sufficient funding was secured to sponsor a field efficacy study. Results of this efficacy study were excellent. The 135 µg dose of FluB1Øk was 100 per cent **efficacious** in preventing culture positive influenza illness, the FDA standard measure of efficacy, compared to placebo (statistically significant: $p=0.0146$) and also met the established measure of vaccine **effectiveness** in that it statistically significantly reduced the occurrence of flu-like symptoms (as defined by CDC) compared to placebo ($p \leq 0.05$). The race is now on once again to either identify a bona-fide licensee or secure money through the capital markets.

The GeneXpress business continues to grow and this business is anticipated to further expand once the first BEVS-produced products reach the market. There has been a relatively slow acceptance of the technology because most companies prefer not to pioneer a new technology that has not yet produced a licensed product. Also, manufacturing capacity for this technology has not developed as rapidly as expected and

therefore we are planning to establish our own product launch-capable facility.

The research reagents business is a steady income business and has enabled us to generate revenue while further developing our technology and proprietary products. New products have been added and the introduction of technology-related reagents has enabled a potential licensing partner for the technology to be identified.

WHAT LESSONS HAVE WE LEARNED?

Establishing a successful partnership

Establishing partnerships is dangerous, especially if the company's success depends on the progress made by the partner. For example, an agreement with clearly defined obligations is not necessarily sufficient to protect the licensor if you have (or more likely the deal morphs into) a 'buy and kill' deal, since the licensee usually has vastly more resources than the licensor. Furthermore, management's experience is that a biotechnology company with a lawsuit ends up with that as its only asset. Contracts with pharma companies perhaps should be seen for practical purposes as a statement of intention that they will respect the spirit of the agreement only if the licensor shows flexibility in adjusting the terms to conform to the licensee's needs at the time.¹

In the process of establishing a partnership the following steps could be key to success:

- Determine what is most important for the success of your company. Is this a product on the market, validating the technology through having a 'major' pay a lot for a product developed using that technology, securing capital for various purposes, eg funding other products in the pipeline or buying out 'tired' investors or directors, teaming up with a major player?
- Identify as many potential partners as

Partnership can be dangerous

Key to success: what do you want; who can provide that; what type of agreement; keeping options open

Dilemma: what information to share at what stage of the deal-making process

possible and perform a thorough analysis of what the partner will gain or can lose when the product makes it to market. For example, a company that does not yet have a product in the market of interest may be more eager to bring a product forward than a company that will be cannibalising an existing product. Once this is done, adjust your thinking and accept that the analysis applies only to today and not to tomorrow. As a seasoned colleague once commented, 'if you think you know what a major pharmaceutical company is thinking today you are almost certainly wrong, and even if you are right, if you think this is what they are thinking tomorrow, you need to be institutionalized.'

- Explore the type of agreement that the partner is willing to enter into and identify whether such agreement would be appropriate for the partnership. For example, if the potential partner already has a product on the market, a fully paid-up licence fee may be more appropriate than a scheme of milestones and royalties that depend on the product reaching the market.
- Do not bet on one horse until the deal is finalised, ie do not put all your eggs in one basket but, once you do, watch that basket! During the process of establishing the final agreement the interactions between partners are often under pressure. It may become clear that philosophies are not aligned and the partnership will terminate before it even started. Watch your partner closely and react quickly and forcefully to any apparent deviation from what you perceive to be the agreed-upon plan. The squeaky wheel gets the oil!

Ensure that deal structure is properly aligned with roles of parties

Managing the partnership

Often partnerships are terminated before the goals set out at the beginning have

been reached. Usually this is not because of failure of the product in the clinic, but more often because of changing priorities, changing philosophies etc. The process of managing a successful partnership starts with the agreement where the partners establish responsibilities of each party and establish the appropriate structure of the deal.

If all responsibilities for bringing the product to market are in the hands of the licensee, the licensor should seek a fully paid up fee. This is the easiest and clearest way to go: the partner can assume full responsibility for product development and because the licensee has received a full payment it will not damage the licensee if the licensor moves slower than anticipated or even decides to shelve the product.

If both parties are equally able to contribute to the success of the product, responsibilities need to be assigned very clearly and each party needs to have the right incentives to make its part of the agreement a success! For example, a deal in which the licensee will receive double-digit royalties, but where the licensee has no influence at all in generating sales may be a *licence to fail*. It would be more appropriate to allocate milestones to those areas where the licensee is able to have an impact.

Competitive information gathering?

Competitive information gathering versus conducting a true 'due diligence' is yet another complicating aspect when trying to identify the right partner. The question of how much information to provide is a difficult one and requires a thorough assessment that most biotech companies lack the resources to undertake. It is best to be cautious and feed an increasing level of information to potential licensees as their true intentions become clearer. For example, insist on seeing a draft term sheet before providing potentially sensitive information such as Food and Drug Administration (FDA) comment letters. This information can be misused

through selective quoting and/or can accelerate development of a competitive product by identifying a path you have pioneered.

There is no clear recommendation possible on what information should or should not be shared because each situation will be different. The licensee should decide ahead of time what information it is willing to share at each stage of the process. It may be beneficial to request an option payment prior to providing the most detailed and sensitive information (although this will normally result in a demand for a period of exclusivity). If the potential partner is willing to make a payment at the 'due diligence' stage, it demonstrates that they are serious about making a deal.

Government funding and how to get it

Government funding can be extraordinarily helpful in providing the resources to establish proof-of-concept data without having to access expensive and potentially company-killing venture capital. Public funding is available for many areas of unmet medical needs or where better treatment would be beneficial. There are many programmes that enable small businesses to secure grants. The Grants.gov website² allows you to electronically find and apply for competitive grants from all Federal grant-making agencies. It is important to adhere closely to the guidelines and required qualifications, otherwise grant writing can become a useless exercise. For example, if the Request for Proposal (RFP) indicates that in order to qualify the offeror has to be a licensed vaccine manufacturer and you are not, you may not want to apply. On the other hand, applying may bring your capabilities to the attention of the authorities and, as has occurred in our case, result in a follow-on RFP for which you will qualify.

It is important that a company does not become dependent on government funding because often government timelines and shifting priorities ('off the

front page, out of mind') are not compatible with your company's goals.

There is only one true champion in advancing a technology to the market. Despite the fact that our GeneXpress service business has brought in revenues, none of our customers' products has advanced as rapidly as we had hoped. You have to be the pioneer of your technology because no surrogate can possibly have the single-minded devotion to your technology as do you, and that once you have achieved licensure for one product many more will follow using the 'validated' technology. We have seen our GeneXpress business increase as FluBlØk has progressed toward licensure.

WHAT SHOULD HAVE BEEN DONE DIFFERENTLY?

It is always important to 'stop and think' about what should have been done differently and there are a few ideas that come to mind. Some important opportunities were definitely missed because Protein Sciences simply was not ready from an organisational standpoint in the early years of new management. In retrospect, we should have paid more attention early on to aligning the organisation with the new goals of the company.

More effort should have been spent on generating grants from the government; for example, for the establishment of manufacturing capacity and the development of our BEVS technology. Recently it was announced that ID BioMedical obtained a US\$10m grant for development of its influenza cell culture vaccine. Also, sanofi-pasteur and Chiron were awarded very large sums by the government for the production of egg-derived H5 vaccine despite the fact that only Protein Sciences has had such a product in the clinic in the USA to date.

On the service and product business end, we worked with a partner, Nosan, only in Japan and we probably could have leveraged our service business more in other continents. There has been a steady

Go to grants.gov to identify opportunities in your field

growth in this business in Japan because of Nosan's tireless efforts to generate more business. We were reluctant to transfer control of our technology to other parties, and this may have limited the acceptance of awareness that we could have created otherwise.

We should have been more aware of changing conditions in the marketplace that in today's world dictate sale or fully paid-up licence of a lead product rather than partnership. Here are some things to think about:

- A sale or paid-up licence validates your technology – not as much as product approval but almost as much – if the price is high enough and the buyer is a respected company.
- There is much lower risk to the surviving company from future events if the product is dropped or fails in the clinic because there is no high-profile product return or disappearance of anticipated milestones and royalties. Your technology already has been validated and there is nothing to remind investors that it is yours. Big companies try to 'bury their dead at midnight', so the event may not gain any publicity at all. You may even be able to reacquire the product advantageously if the reasons for dropping it were changing priorities, which they often are these days.
- If the terms are right, the deal allows for restructuring of surviving company (especially the Board if you have tired investors and/or VCs as directors). Such boards are in the authors' opinion the single greatest reason for company failure.

Compare this with a traditional licence deal with an up-front payment, milestones and royalties. The quoted price is usually completely misleading and only a tiny fraction of the deal value is certain

with the vast majority representing 'BioBucks'.³ The licensee ends up with questionable financial stability, there is no validation of the platform technology, the 'market' ascribes little or not value to the potential milestones or royalties because of the uncertain state of the industry, the licensee retains the risk of significant damage to the company and/or product if the partner cannot secure financing, returns the rights, drops the product for whatever reason or sells the rights to an incompatible third party (eg a company with a competitive product).

CONCLUSIONS

Protein Sciences performed well in focusing on advancing its lead product through clinical development and balancing revenue generating service business with developing technology and its own products. Partnering or licensing requires a clear risk analysis of opportunities. There is a lot at stake and once a partner is chosen for the wrong reasons or that partner changes direction and de-emphasises your product, the recovery process can be long, as exemplified by our company, or not possible at all, as exemplified by the large number of companies that go out of business as a result of terminated partnerships, eg Pharming when Genzyme in-licensed a competing product that it had licensed from Pharming.

One wonders whether this means that the financial market is not such a bad alternative after all.

References and notes

1. When one of the authors was running another company, he remembers confronting a pharma company with a firm 'take or pay' contract it had signed. They responded, 'If you think that is a contract, we will see you in court.'
2. URL: <http://www.grants.gov/>
3. The term was coined by Frederick Frank, now Vice-Chairman of Lehman Brothers, and the acknowledged Dean of biotechnology investment bankers.

Value of biotech deals: BioBucks — how real are they?

Question remains: do the risks of partnerships outweigh the cost of venture funding?