Headwinds into opportunity

Prabhavathi Fernandes

Numerous challenges face any emerging company developing a biopharmaceutical. How you anticipate hurdles, plan for contingencies and communicate with stakeholders will play a big part in determining your success.

It would be nice if all the stars aligned to benefit your business and product development plans, but that is almost never the case. There is usually some kind of hurdle: a difficult regulatory path, a challenging pharmaceutical company buy-in, investor skepticism, risk aversion toward your lead candidate, market exclusivity and so on. At some time in their careers, most life science entrepreneurs have faced at least one of these challenges.

My experience at Cempra Pharmaceuticals (Chapel Hill, North Carolina) is a case in point. Following its founding in 2006, my antibiotics startup faced several obstacles. Even so, taking the time up front to address each issue and develop and communicate rational, achievable solutions enabled the company to overcome challenges with regulators and investors as well as skepticism from pharmaceutical companies. We even managed to change US law so one of our compounds received market exclusivity. Although I do not envisage many other emerging biopharmaceutical companies taking on the US legislature, I believe my experience in building Cempra as a company can be instructive to others who aspire to build a life science business.

Opportunity, but challenges

When starting Cempra, I was determined to focus the company on the development of differentiated antibiotics, because despite a decrease in industry investment in the therapeutic area, the need for new antibiotics was only growing. Also, because of my experience, I knew I could recruit veteran executives in the space. Together, we would determine the best approaches in this increasingly neglected area.

Yet we faced several tests. First, over the prior few years big pharma had significantly reduced its investment in the discovery of new antibiotics, resulting in a decline in the number of new antibiotic launches despite the increased need for new drugs. On the one hand, this provided an opportunity for small companies like Cempra to exploit the vacuum in a field in which efficacy in clinical trials is highly correlated with preclinical efficacy and development times are relatively short. On the other hand, the apparent lack of interest in new antibiotics by big pharma meant that validation of new products for investors would be more challenging and private investors’ end games (either an initial public offering (IPO) or an acquisition) would be more difficult to accomplish. What’s more, the flight of experienced scientists with antibiotics expertise from major pharmaceutical companies precluded their detailed and conceptual due diligence on specific products and also on R&D collaboration on early stage candidates.

Second was the serious side effects that emerged with the general use of Ketek (telithromycin) resulted in a more conservative regulatory stance by the US Food and Drug Administration (FDA). As a result, the FDA initiated a prolonged review of the regulatory pathway for many classes of antibiotics, producing regulatory uncertainty. Companies had no guidance on the regulatory path going forward as the FDA worked to change the guidelines.

Third, because Cempra’s lead candidate, solithromycin, was related to telithromycin, there was concern by investors that similar adverse events could emerge. This would make it challenging for Cempra to raise additional funds at a reasonable valuation unless a way was found to reduce the risk profile of the company.

All this was known going in. Understanding the multiple challenges you may face as you start a biopharmaceutical company gives you the advantage of being able to plan ahead so you will not be taken off guard. Cempra was able to develop a corporate strategy that addressed these issues and several others that emerged as the company progressed.

Overcoming regulatory uncertainty

A lack of regulatory certainty can be a significant problem for many biopharmaceutical companies, as FDA guidance can evolve and potential therapeutics for previously untreatable diseases may not have an established regulatory path at all. Understanding your path to approval is critical to avoid wasting time and capital.

In Cempra’s case, as the regulatory environment for antibiotics changed, many larger pharmaceutical companies working on antibiotics began to discontinue their R&D after concluding the return on investment was not worth the effort. But the Cempra team realized that very few established companies were developing antibiotics, and we understood the continuous selection pressure toward resistance development, so it was clear there would be an increasing demand for new, effective antibiotics in the years ahead. Our next challenge was to understand the direction the FDA was heading regarding the regulatory path for antibiotics.

Up until about ten years ago, the path for new antibiotics was relatively straightforward; however, the serious adverse events that emerged with telithromycin changed that. The FDA engaged in a long process of reviewing and revising guidelines for developing future antibiotics. Few antibiotics were approved after telithromycin’s toxicity became known, as the FDA was revising guidelines.

Thus, when Cempra was being set up, the management team was in the dark as to what direction the FDA would take, as were executives at many other antibiotics companies. This was a major hurdle to overcome as the team tried to design clinical trials appropriately and
Continued to move product programs and the company forward.

Because the regulatory path was in flux, keeping in close and constant communication with the FDA was critical. Cempra made a point to attend every meeting and conference, including advisory committee meetings, in which the FDA discussed proposed changes to the regulatory pathway for antibiotic approval. The company also actively reached out to FDA staff to obtain clarifications on announcements and to get answers for its regulatory staff. Cempra's perspective was to view the FDA not as an adversary but as a drug development expert that could advise it on clinical trial design. In addition, several consultants and FDA advisory committee members were utilized who understood the current thinking at the agency and who could project the direction of future guidance. This allowed Cempra's management to prepare trials with the FDA's thinking in mind, thereby minimizing the risk that clinical trial design would stray from the FDA guidelines that were in progress.

The key point here is if you face an uncertain regulatory environment, communication with regulators is essential. Don't wait—reach out.

Reducing the risk profile

As Cempra only had one product in its pipeline—what's more, a compound related to a drug that has known safety issues—the company had a raised risk profile. However, accumulating evidence suggested that the adverse events associated with telithromycin would not be observed with Cempra's compound, solithromycin; nevertheless, Cempra's management faced negative perception regarding the compound's safety. Cempra's investors, management and board were concerned. Would the risk profile generate problems as the company engaged in future capital-raising activities?

If your compound is perceived as risky and you are intent on pursuing it, you'll need to change that perception for both the FDA and potential partners or investors. This can be done in several ways. The most convincing but time-consuming approach is to generate more data. In the case of solithromycin, the problem regarding perceived safety issues was something that would change over time as the company conducted trials and then published the results. The aim was to conduct, and continue to conduct, preclinical and clinical studies that went beyond FDA requirements for demonstrating safety. For example, toxicology studies over a three-month period were undertaken, even though the FDA requires only a one-month toxicology study before starting a phase 2 trial. It was critical to show solithromycin was safe and that it only shared membership in the telithromycin subclass while belonging to the macrolide class.

Another approach is to conduct nonclinical experiments to demonstrate that your molecule does not have safety characteristics attributed to related molecules that are of concern. In the case of solithromycin, a research collaboration with an outside expert who had an assay based on human cloned acetylcholine receptors expressed in Xenopus oocytes showed that telithromycin was a potent inhibitor of certain nicotinic acetylcholine receptors, whereas Cempra's compound, solithromycin, and other macrolides were not.

Unfortunately, both of these approaches took time and raised costs, so to decrease the company's risk profile quickly, Cempra management added a second low-risk and clinical-stage product to the pipeline: an exclusive supply of fusidic acid, an antibiotic with a long history of safety and efficacy outside the US, was obtained from a contract manufacturer.

At this point, it is important to highlight that decreasing your company's risk can sometimes generate other challenges. This was the case for fusidic acid. It was an off-patent, oral antibiotic that had been in use for about 40 years in Europe, Canada and several other countries but not in the US. Although pharmaceutical companies are not interested in compounds lacking patent protection, Cempra's management deduced that the compound could be positioned to have several years of exclusivity combined with a low-risk development profile. Furthermore, such a product could be a valuable addition to a partner's pipeline.

On the plus side, activities to reduce your company's risk profile can generate opportunities, too. For example, Cempra's management team initiated development work expecting to receive five-year Hatch-Waxman exclusivity plus a six-month pediatric extension. The FDA informed the company that hundreds of old publications would not be considered as data and that new preclinical data, using modern scientific methods, would be required to gain approval. While conducting these studies, it became apparent that established clinical practice dosed the antibiotic suboptimally, resulting in resistance development in some cases. Thus, Cempra filed a patent based on dose optimization, determined through its own pharmacokinetic and pharmacodynamic work, to transform fusidic acid into a proprietary and important drug for the US market, providing Cempra with up to 18 years of patent protection.

However, an issue facing fusidic acid was its lack of market exclusivity because it fell into the category of 'old antibiotics', of which most had been marketed and were not eligible for the exclusivity provisions afforded by section 505(c). Here again, Cempra management decided exclusivity was possible, albeit through a rather daunting, but doable, undertaking—amending US law.

Cempra, with the assistance of its scientific advisory board, worked with government consultants and the Infectious Disease Society of America (IDSA; Arlington, Virginia) to recommend an amendment to US law, enabling the compound to obtain Hatch-Waxman exclusivity. It was the company's view that because the compound had never received marketing approval in the US, it should not have been refused exclusivity. In addition, fusidic acid is an oral antibiotic active against multidrug resistant Staphylococcus aureus (MRSA), for which there is an urgent need for safe and effective compounds. After two years of hard work and lobbying, Cempra was able to get an amendment added to a supplemental Medicare bill that was signed into law (Public Law 110-379) in October 2008. Fusidic acid was then in position to be a proprietary drug for Cempra and any future pharmaceutical partner. Looking back, this was a high-risk venture, as the probability of passing the amendment was low, but the risk was worth taking as Cempra had a backup plan—the dosing patent—that would also provide exclusivity.

With the amendment supporting market exclusivity and the loading dose patent in hand, the company transformed what many considered a nonprofitable drug into one that could have substantial value. What's more, the road to approval was shorter and less costly than a truly new chemical entity, thereby decreasing Cempra's risk profile and making the company a more attractive investment opportunity. Although the specifics may differ for your company, the core premise of identifying an in-license opportunity and making it viable are the same. If your company faces such a scenario, prepare a backup plan, as the Cempra team did for fusidic acid. Without a backup plan, we would not recommend starting the company on one product that carries substantial risk.

Costs, your board and investors

To help keep costs low Cempra followed a virtual company model. Contracting out lab work...
enabled the company to keep staffing and R&D costs down. Because Cempra is not a technology-based company and had acquired the rights to the compound that became the lead candidate, there was little sense in investing in labs and drug discovery scientists, especially if the work could be assigned to well-equipped contract research facilities and academic laboratories with the requisite expertise. This is a viable approach for other companies with acquired assets working in well-established therapeutic areas, in which the preclinical and clinical protocols are well understood and there is available expertise in your target area. Conversely, it would not work if you are a discovery-focused organization or if your target therapeutic area is not well understood and you need significant in-house expertise.

Ultimately, the board of directors is the final arbiter of the company’s plans. As solithromycin had an unclear risk profile, it was obvious that considerable effort would be needed to prove the lead compound was safe. Fortunately, solithromycin has both oral and intravenous availability as well as a broad spectrum of activity. This suggested a larger market potential if the company could find a path to approval. As founders, we were able to convince the board by carefully formulating a logical and well-reasoned development plan for solithromycin, involving a plan to work closely with the FDA to facilitate and guide development strategy. With fusidic acid, the founders needed to convince the board that acquiring the compound was a feasible approach to further reduce the company’s risk profile and that its specific challenges could be overcome.

Our management team focused on communicating in detail our plans for accomplishing these goals. This included both the advantages and the risks of our plans, as well as an estimate of the capital required. Regarding solithromycin’s safety profile, we explained why allocating additional capital to conduct longer toxicology studies and developing an intravenous dosage form was important in light of the telithromycin issues and the new FDA guidance documents. Acquiring fusidic acid was more complicated because it required the commitment of more capital and it included the uncertainty of gaining US market exclusivity. Again, the key was communicating our detailed plans and its risks and benefits as well as executing those plans. We were fairly confident about developing an optimized dosing regimen to eliminate the resistance issue because of our internal expertise and feedback from our research collaborators.

Getting the amendment passed was a more uncertain prospect. But here again, the management team laid out a detailed plan to the board and, in part because of their own deep understanding of the antibiotic space, they agreed with the plan, and we moved forward with acquiring fusidic acid.

Cempra’s team laid out the details and demonstrated the value of fusidic acid as well as the lower risk and shorter time for development in both informal discussions with board members and formal board presentations. We also included thought leaders and people who had participated in relevant FDA advisory committee meetings in these discussions who could provide an independent third-party perspective. Management was able to convince the board of its strategy because of our open lines of communication, persistence and innovative approach.

But Cempra also needed to convince current and future investors of the potential of our pipeline and the soundness of our strategy. Thus, company management was very proactive in reaching out to selected investors who fit in with our business culture and members of the team. We conducted market research to provide a more quantitative and third-party review on each candidate molecule’s market size, and we connected possible investors to experts in the field and coordinated meetings with the Cempra management team so they would know who was handling their investment.

In all of these discussions, the Cempra team tried to understand the investor perspective. What would you want to see if you were investing? Would you invest up front or through tranches as the company met milestones? Through constant dialog, we aimed to increase investors’ comfort level. We provided as much information as we could about the company, the pipeline and the market potential for the product candidates, and we were honest about obstacles or potential issues. In some ways, it is not much different than material disclosure for quoted companies. We wanted investors to be fully informed about their investment.

When the company did receive funding, we preferred to receive it in tranches, and we think this reflects well on a company’s capital management. Besides, if Cempra’s drug candidates had failed during development, we would not have needed the money anyway. There’s no sense in collecting what you might never spend.

Parting words
Opportunities in the biopharmaceutical industry can be masked by what appears to be a collection of insurmountable challenges. But just because potential partners or suppliers of capital have shied away from a sector does not mean that there is no opportunity. Be sure to develop specific solutions to each of the challenges. In the case of Cempra, it was about communication, not only of our ideas but also of our constituents’ perspectives and concerns. The Cempra team also wanted our constituents, particularly investors, to share in our excitement concerning the programs and to be involved in problem solving.

Remember to constantly communicate with regulatory authorities so that you understand what is required for approval. Also, talk with your investors and board, meet with them on a regular basis and be available to answer their questions. Make sure your communication tools (for example, your website) are clear and up to date. Look at your company from the perspective of investors—listen to their concerns and demonstrate value.

Understand that some solutions to challenges will create new challenges. We faced that with our second clinical candidate, but part of our due diligence was to identify these new hurdles and determine if they could be overcome, and to then develop the plans to tackle them.

Finally, treat capital like gold! Be clear about your total funding needs and receive capital in tranches. Create a strategy that is realistic and has some flexibility built into it, because there will always be unforeseen obstacles.
Corrigendum: Headwinds into opportunity

Prabhavathi Fernandes

Nat. Biotechnol.; doi:10.1038/bioe.2011.8; corrected online 22 September 2011

In the version of this article initially published online, the author wrote, “This suggested a market potential in the billions of dollars…” The sentence should have read “This suggested a larger market potential….” The error has been corrected for the print, PDF and HTML versions of this article.