All companies — large and small, biotech included — have felt the pinch of the current (or recent, depending on your point of view) recession. From huge multinational companies to virtual start-ups, all are taking a good hard look at the way they do business. And as it does every year, the 2010 BIO International Convention will offer something for every company and every situation. Business-oriented sessions range from hard-earned experience to provocative new ideas.

“In these difficult times, early stage companies need to look at creative types of financing and collaboration structures to progress their company’s product to the next level of development,” says Arthur Pappas (managing partner of Pappas Ventures). “In my view,” he continued, “this is the only way they’re going to become viable and financially self-sufficient enterprises able to attract the larger financing that may be required as they get into the clinic.”

Pappas’ session at the convention will address clinical risk-sharing models and approaches that can help early stage biotechnology and pharmaceutical companies access capital and develop their growth plans. Contract research organizations (CROs) already have a well-established relationship with large pharmaceutical and biotechnology companies. But in recent years, CROs have been developing more sophisticated models that enable them to do business with smaller, emerging companies. This panel will discuss the structure of these types of new deals and define the pros and cons for CROs, investors, and the companies involved.

Critical to any deal-making process, according to Christopher Merrill (director of business development at Tolerx, Inc.) are soft skills. Merrill defines those as “intangible traits that can enhance a business development professional’s overall effectiveness. These traits include being an effective communicator and team builder, being friendly and flexible, and having integrity.” Such skills are difficult to measure, but Merrill points out, “they can play an equally if not more important role in deal making than more measurable traits like intelligence, education, and a lengthy deal sheet.”

For example, Merrill said, “a simple mistake often encountered in business interactions is neglecting the common courtesy of a returned phone call (or perhaps more relevant these days, an email response). Yes, we are all busy and buried by multiple communication sources, but a simple reply can go a long way to building a potential relationship, even if the answer is, ‘No thank you.’”

In today’s global marketplace, that phone call or email response may come in any number of languages and from almost any continent. Richard Brown (partner and head of the Tokyo office of Plexus Ventures LLC) described some scenarios a company may face in deciding how to structure its deal making. “There have been some recent regional deals,” he said. “For example, Kyowa Hakko Kirin Co., Ltd. (a Japanese company) in-licensed a chronic kidney disease drug from a Texas company called Reata. Kyowa Hakko licensed the drug for the Asian region while Reata retained rights to all other territories. This is a good example of a company licensing a product to a market it would not otherwise reach — in this case the Asian market.”

Brown continued, “An example of a multinational deal (a global deal) would be the one between Daiichi Sankyo and Eli Lilly for the Prasugrel
compound for coronary use involving blood clots. Because it has a presence in most every country in the world, Eli Lilly licensed the global right. Daiichi Sankyo is expanding, but it was not in a position at that time to take over the drug or to launch it in as many countries as it wanted. Daiichi Sankyo needed a partner that could commercialize Prasugrel in countries it couldn’t reach. Since that time, Daiichi Sankyo purchased Ranbaxy, the Indian generics company. So in addition to having Eli Lilly as a multinational commercializing partner, they also picked up a company that can get them into India and Africa; places with less multinational presence.”

“In any negotiation there are trade-offs,” Brown added. “And the challenge is to craft a deal so that it addresses the primary needs of each party. If you’re the licensor, you have the asset and you’re going through the list of possible licensees and picking the ones with which you think your needs will best be addressed. During the negotiation process you try to define exactly what you need. So the challenge is that you have two different companies, neither one being fully open with what it wants. You’re trying to figure out what the other party really needs and what they can sacrifice. You’re also asking your own company, ‘What do we really need? What can we sacrifice?’ So the challenge is making sure that the dominant needs of each party are satisfied. A reasonable deal can collapse because the parties find some issue that they just can’t resolve.”

**Technology Transfer**

One of the most important deals a company will make is its first one. Whether the licensor is an individual, a small (or large) company, or a university tech transfer office; whether the deal is a sale, a joint venture, hiring a CMO, or something entirely unique, tech transfer is going to be an essential part of it.

According to Cheryl Reicin (practice leader in the technology and life sciences group at Torys, LLP), “tech transfer, particularly in universities, has changed a great deal during the past 30 years or so.” Thirty years ago, she says, universities were not thought of as commercialization centers. “In fact, I think there was a bias against commercialization among academics. And basically, the tech transfer offices were there to serve professors or students that came up with an invention and wanted help getting a patent.

“So it was a very discreet type of service — not very proactive, more passive — and the focus was on patents. As university tech transfer offices developed, there was a real premium on how many patents an office could produce. But they weren’t concerned with how much money a tech transfer office could make or how well the commercialization opportunities were doing. Eventually, though, the focus went to licensing out technology and getting some commercial benefit from it.”

That change of focus didn’t happen overnight, nor did it happen universally. Reicin continued, “I would say that over the past 20 years Stanford and MIT and Harvard were ahead of the curve — and some universities are not there yet. But some of these tech transfer offices started not only licensing out technologies, but also spinning out and building companies because they realized that sometimes when you license out technology too early you give up a lot of the value.

“So that was a next step. Now a few tech transfer offices have even gone beyond that by pulling IP [intellectual property], taking it public in a vehicle, or pulling spin-out companies and taking them public.”

**Creative Business Models**

Traditionally, small biotech companies have counted on either an IPO or partnering with a larger pharmaceutical (or biotech) company to launch their products. Wendy Pan of Morgan Lewis & Bockius pointed out “people realize the IPO market may not be a realistic source of financing, so they’re looking for creative strategies. From a US biotech company’s point of view, collaborating with a Chinese partner (for example) can provide a source of financing.”

One of Pan’s industrial colleagues, James Hattersley (Vice President, Business Development, Sun Pharmaceutical Industries) said, “When talking about crossing borders, we’re primarily talking about international commerce and having a presence in countries different from regions where we’ve operated in the past; going into regions different from our headquarters, having a presence in different countries. When we talk about going beyond boundaries, we’re talking about a change of perspective or a change in the business culture as it relates to our operations. So the boundary speaks more to therapeutics; the border speaks more physically to regions.

“There are companies that historically have been innovative, new-
chemical-entity, new-molecule type companies that have not only transitioned toward being in the off-patent or specialty or generics business, but they're also acquiring companies. So they’re moving in a different direction from the past. And then there are companies that historically have been in APIs [active pharmaceutical ingredients], which have moved into generics and are now moving further into specialty products and new chemical entities (cross boundary).”

Pan provided an example: “Simcere is a Chinese-branded generics company and one of the top Chinese pharmaceutical companies. Although it's been a successful generics company, now it's looking for innovative medicine in the Western world. There are a couple of reasons for this movement. One reason it has become the leader in the Chinese market is because its product is proprietary. And the banks have given it a competitive edge in China's drug market. I think they have realized the value of the IP of innovation.”

Louise Sarup (senior business development manager of IP at Pragmatics Ltd.) talked about bundling of intellectual property. “There are two basic ways of doing IP bundling,” Sarup said. “I can speak about InterAct projects, which will be discussed in the session. We use comarketing as one strategy. To do that, we offer companies a group of patents that relate to separate technologies — all in a similar field but with no overlap. In these cases, the synergy makes an attractive bundle. It may contain patents from academic institutions or government funded research agencies. Such a deal is advantageous for the company because it reduces the time it has to spend marketing and licensing its technologies.

“An example of that type of bundle is one we’re working on now. We have a whole series of molecular diagnostic tests from multiple institutions, all of interest to similar sets of companies. We’re presenting them as a bundle to companies that might be interested in licensing them.”

The other method Sarup described “is actually combining patents. In this model, institutions we’re working with can obtain patents covering different aspects of the same technology. When those are grouped together and combined, they give the licensor extensive coverage of that particular area.”

She explained that IP “could take the form of know-how as well as the more traditional type of patent. The InterAct project came out of the institutions we work with. The institutions involved in the entire project are six UK government research agencies: the equivalent of the US federal laboratories. Those particular agencies are under increasing pressure at the moment regarding costs and the funding they get from the UK government. They’re encouraged to commercialize their IP and their patent portfolios more. So they came up with this idea as they started working together — each looking at what the other had — and coming through their know-how, their technologies, their patents.

“If you look in both trade papers and academic papers, you can see more evidence of patent pooling in industry as well as academia. I think it’s perhaps harder to do between companies than between academic institutions or government research agencies, but it is starting to happen more.”

David Anderson (deputy director and head of the business development office at Burnet Institute) shared insights about global challenges in health diagnostics, many of which apply as well to therapeutics. “There are two closely linked challenges,” he explained. “The first is that many health conditions predominant in developing countries offer very small profit margins. They are often large markets, but because of low unit costs in developing countries, they are not seen as being particularly attractive. That makes it hard for companies to commit the major resources for early stage R&D and really figure out how best to diagnose these infections.

“The second problem is that if a company — or an academic institution for that matter — has developed a test, how do they then do the clinical and field trials to show that it works? Unfortunately the global market is full of rapid point-of-care diagnostic tests against different diseases, but no one has any idea how good or bad they are because no one has ever rigorously tested them. Typically a company might develop a new test, get hold of a dozen serum samples, and that’s as much testing as they do before they put it on the market (particularly in countries with fairly limited regulatory processes). Therefore, you have a preponderance of poor-quality or unknown-quality tests, which reduces people’s faith in using diagnostic tests generally. You end up not having the high level of faith in the diagnostic system that we would expect in Western countries.”
Anderson continued, “A very good example is the Program for Appropriate Technology in Health in Seattle, which is largely funded by the Bill & Melinda Gates Foundation. The PATH plays two major roles, as I see it. One is a technology developer. But more important, they have been very instrumental in leading validation studies of the diagnostics already out there.”

One big success stories for the PATH has been in diagnosis of hepatitis B. “In Western countries,” Anderson said, “we have good-quality laboratory blood tests to strain individual patients or blood donations for hepatitis B. But in countries like India and China, which have the highest rates of hepatitis B, they don’t have the laboratory infrastructure. Most tests are very simple point-of-care blood tests with good-quality records that have been around for many years. But it’s also easy to make a bad-quality test. And tests play a very important role. We’ve had good success with studies that showed how to make a good test and then transferring that technology to different manufacturers in India, then doing ongoing quality control with those companies and making sure the final product worked well.”

“In an example closer to home for me,” Anderson went on, “we at the Burnet Institute developed technology around another form of hepatitis, hepatitis B virus. It is very uncommon in developed countries — but very common in developing countries — being spread by water and food. Along with academic and clinical collaborators in a number of developing countries, we developed a test. We were able to work with a company called MP Biomedicals in Singapore that licensed the technology, produced the tests on a commercial scale, and then worked with us on the validation studies to show that those tests did indeed work well. Prior to our collaboration, the company had been selling a substandard hep-B test for about 15 years because it never had access to academic collaborators for the proper studies. Through this collaboration they could develop and validate an improved test. As a result, they have now taken our technology and produced three different laboratory-based tests and a point-of-care test, which we have been very pleased to see used in many parts of the world.”

“If you can get a CLIA [1988 Clinical Laboratory Improvement Amendments act] waiver for a diagnostic,” Anderson said, “meaning that it’s simple enough for doctors to perform in their offices, that’s a much better market proposition than if it’s only a laboratory-based test. By making things suitable for field use in the developing world, you’re making a good affordable test that can also be used in the developed world. So when you sell it in the developed world, you have high margins.”

A second example Anderson shared was the CD4 initiative. “The funding originally came from a Gates Foundation grant to Imperial College London.” CD4 refers to the T cells that are attacked by human immunodeficiency virus (HIV) in acquired immune deficiency syndrome (AIDS). “In managing HIV/AIDS infection, you need to measure patients’ T cells to determine when to start giving them antiviral drugs. This is the standard of care in all of the developed world. But in the developing world, measuring the T cells is now the biggest problem in getting HIV-infected people on the appropriate medications. The drugs are now available, and there is enough money through the Clinton Foundation and other bodies to pay for them.” But using those drugs properly requires a laboratory test, which is often unavailable.

“One main issue is that currently we need to use flow cytometry to measure the T-cell counts. Flow cytometry requires an instrument that costs anywhere between [US]$20,000 and half a million as well as highly trained technicians and high maintenance costs. It’s very hard to maintain that sort of technology in Africa, for example. What’s needed is something that’s more like a pregnancy test that can be done in the field. Although our test was not the one chosen for the CD4 initiative, the Burnet Institute has since developed a simple test. We are now going ahead with clinical tests in the field with a number of partners and trying to find someone to license it for manufacture and distribution worldwide.”

Finding the Right Partner
David Charrap (special counsel for Foley & Lardner, LLP) talked with me about preparing for commercialization while simultaneously talking to potential partners. “The concept for this panel,” he said, “involves a dynamic
that has been becoming more and more prevalent over the last few years. Companies — either because they were unable to partner earlier or preferred to increase the value of their asset by continuing to develop it — have increasingly had products in late-stage development without partners. That situation creates an interesting dynamics that the panel will explore.”

Such business is complicated, Charrap said, “because the biotech company has to continue clinical development and the regulatory process without knowing for sure whether what it’s doing is going to match up with what a (potential partner) pharmaceutical company would have done if it was calling the shots.”

A biotech company that finds itself in such a situation, Charrap said, “really has to go in two different directions at the same time. It needs to pursue those partnering discussions, but it also needs to prepare for the potential of having to commercialize the product itself.” And that reality can be both complex and expensive. “The biotech may need to start building an entire commercial team, hiring people for that purpose, only to potentially share those rights or give them up entirely to a partner.”

Charrup pointed out that his session is not just for companies currently in late-stage development without a partner. “This topic is important for companies at an earlier stage or for investors, such as venture capitalists, who sit on boards and are involved in deciding the direction of companies,” he said. “Earlier-stage companies often go through the process of deciding whether or not they want to hold onto their compound and pass up potential early licensing opportunities to try to enhance value and get a better partnering deal down the line. And if they hold out long enough and end up in this category, this could be important information for them to consider in making those earlier-stage determinations.”

**The Challenges of Biotech Business**

Among the many issues a biotechnology company must keep in mind, one of the most critical and potentially catastrophic is drug counterfeiting. Rainuka Gupta (principal engineer with Cambridge Consultants) talked with me about practical anticybersecurity efforts.

“A number of biologic and general pharma products are subject to counterfeiting,” she said. “Aside from the obvious lifestyle drugs that you hear about all the time, biologics are particularly attractive because of their extremely high value.”

Companies are responding in a variety of ways, as Gupta explained. “Generally, the approaches they take are a combination of technologies. There are the obvious things like holograms and trademark-protected labeling. But those measures are one piece of the process. To successfully protect against counterfeiting, you need to have a layered system that continuously evolves because counterfeiting is evolving right behind any steps a company takes.”

The key to protection against counterfeiting, she explained, is to be dynamic and have a layered, systematic solution to attack it on multiple fronts.

“What we’re trying to do is take a pragmatic approach with respect to what things a company can think about early on that might help later on. Also, we will look at the lessons that some more established companies have learned that could be incorporated earlier in development. We’ll also flip that around and have some of the more established companies talk about what challenges they face, what would help them along, and what can they also learn in the process because it’s not anything anyone has mastered at this point.”

Gupta continued, “It’s easier to counterfeiting a biologic than, say, a pharmaceutical. The reason is that a lot of times the way counterfeit oral drugs are detected is because a consumer notices.” An oral drug may not taste right or look right or feel right in the mouth of someone taking it, she explained. But most biologics are injectibles. “Consumers don’t actually interact with the drug directly, so they can’t say it smells or tastes funny. You don’t know whether the powder you’re reconstituting is talcum powder or an actual drug.”

She went on to explain, “The profit margins are incredibly high, and small outfitters to organized crime are getting involved with counterfeiting. They’re willing to do anything from taking discarded vials and refilling them to taking legitimate products and diverting them. So if you take a low-concentration drug that sells for $200–300 for a single dose, they can bleach the label off it and then reprint and market it as the high-concentration drug that sells for thousands of dollars. Thus, with a little investment into some sort of printing and labeling technology they’ve just created a huge profit for themselves. There are lots of different angles they take, and that’s one of the
reasons why counterfeiting is so problematic, because it’s not just counterfeiting: It’s also diversion, relabeling, taking legitimate product that was exposed to incorrect environmental and shipping conditions and therefore needs to be destroyed, but it’s been diverted instead.”

It’s a worldwide problem, and there are people all over trying to figure out how best to address it, she said. As for enforcement, counterfeiting has been handled differently in different jurisdictions. “There are organizations and global efforts to try to approach things more systematically. One of the big challenges right now is that often counterfeiting is seen as a relatively minor crime. You could counterfeit a drug or biologic and end up killing hundreds of thousands of people, but the punishment is going to be less than the punishment a drug dealer pushing on the streets is going to get. In some cases, it’s not even punishable by jail, but by a fine. Say a counterfeiter has to pay a $10,000 fine. How much counterfeit product do they have to sell to repay that?"

**The Bankruptcy Problem**

Tamsen Valoir (a partner at Baker & McKenzie LLP) spoke with me about licensing and bankruptcy. “You always have the risk that a licensee will go bankrupt,” she said. “If the technology is still good, and the company went bankrupt for reasons of poor management or bad luck — and you think you can sell it again — then that could be a good thing.” It might also be a bad thing, however, and that depends on who the buyer is.

“Typically bankruptcy is an area of law that’s handled by specialists, and the rest of us don’t know anything about it. So here we are drafting clauses related to bankruptcy, which have no effect. I think that if you learn the basics, you can at least know what risks you are taking on — and to some extent you may be able to mitigate with those risks.”

Valoir explained that boilerplate contracts often used for customizing contracts contain clauses that spell out what happens if a licensee goes bankrupt. They are not binding in court, however, so the outcome for a licensor can be uncertain at best.

“I’m not convinced that we can eliminate the risks,” she said, “but if we know about the basics of bankruptcy, we can mitigate those risks and at least know what we’re getting into.”

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