Bloomberg BNA

Life Sciences Law & Industry Report™

Venture Capital

Life Sciences Financing Takes Much Longer, Exits More Difficult, Conference Panelists Say

It takes three times as long to get financing for life sciences companies than it did two years ago and it is more difficult to plan exits, venture capital representatives agreed during a Sept. 28 panel session at the 2012 Mid-Atlantic Bio meeting in Bethesda, Md.

The panelists were of different opinions as to whether things had grown better, worse, or stayed the same in certain areas, however.

The recent reduction in the number of VC firms may have been a good thing, allowing the firms to reflect, build life sciences companies for sale, and address knowledgeable investors' questions, they said at the session titled ''New Developments in Traditional and Corporate Venture Capital.''

Panelists were Nina Kjellson of the VC firm InterWest Partners, who also moderated the session; Dr. David Berry of Flagship Ventures; Art Pappas of Pappas Ventures; Brian Gallagher of SR One; and Robert Weisskoff of Fidelity Biosciences.

To provide an overview of the VC challenges for the life sciences, Kjellson said she asked the panelists in advance to rate three areas—financing, exit capacity, and two-year outlook—as better, worse, or the same since the last Mid-Atlantic Bio meeting in 2010.

Berry and Kjellson felt that financing was worse; Gallagher and Weisskoff, better; and Pappas, the same. Gallagher. Weisskoff, and Kjellson said exit ability was the same, Gallagher, worse, and Pappas, better. And Weisskoff and Kjellson said the two year-outlook was better; Pappas, much better; and Berry and Gallagher, the same.

Having acknowledged the differences of opinion, Kjellson pointed to ''positive'' news. ''There's the . . . reauthorization of PDUFA [Prescription Drug User Fee Act], the new patients that will be brought into the system as a result of Obamacare [the Affordable Care Act], and emerging markets that bring new opportunities.''

Culling Not a Bad Thing. Assessing the current capital environment, Fidelity's Weisskoff said, ''There are a bunch of risks out there, especially concerning exits [ways VC firms get return on their investment by mergers and acquisitions, initial public offerings, or redemption of VC-owned stock by the company]. It's harder to plan and time your exits.'' He said he sees bigger syndicates, where a group of lenders works together to provide funds for a single borrower, in the future, which may mean fewer deals.

Berry said that his firm is trying to build a new model for innovation through a partnership with Merck in which the drugmaker's top people will talk to Flagship's staff about ideas of interest to Merck now and in the future.

According to SR One's Gallagher, ''Syndication is tough. In the past, it may have taken three months to get financing. Now it takes a year.''

Pappas said that he has seen important, fundamental changes in raising funds for life sciences. ''The culling in venture capital I don't think is that bad. It gives us all time for reflection and for building companies for sale. We have to make changes because we have more knowledgeable investors who don't just give you the money but ask, 'Will the drug be such that someone wants to buy it or that it will be possible to build a company around it?' ''

Centers of Excellence Dubbed Shortcuts. The panelists saw changes at the Food and Drug Administration, especially when a company goes into a meeting concerning phase II clinical drug trials. ''We had an experience with a drug in the migraine area,'' Pappas said. ''We were concerned that we'd get a good dialogue, but the meeting was reasonably constructive.''

Berry said, ''When we've looked at big platform ideas, FDA has asked for ways we can reduce regulatory costs. Sometimes we have partnered with pharma companies so that we're very well prepared for what FDA brings to the table.''

Two panelists had reservations about the creation by large pharmaceutical companies of intellectual centers of excellence, including public-private collaborations such as Pfizer's Centers for Therapeutic Innovation (see 6 LSLR 239, 3/9/12; 6 LSLR 595, 6/1/12) and GlaxoSmithKline's Center of Excellence for External Drug Discovery.

Gallagher said that these efforts were experiments, trying out different structures of collaboration. ''I'm skeptical it will play out. It's always good to get the involvement of the different parties in life sciences. But pharma is thinking it can cut out the middle man—the small biotech—and it won't work,'' he said.

Berry said, ''Big Pharma doesn't have ideas, entrepreneurs do. These centers are an interesting trend, but they are just trying to do a shortcut. What these centers

 ISSN 1935-7257

attract are not the best ideas and not the best entrepeneurs.''

SR One is one of GSK's independent corporate health care venture capital funds. Gallagher said, ''GSK is aware of the issues, and it is trying to find different ways of meeting with and engaging VCs, to explain what GSK wants to see before a transaction, opening up a dialogue. From GSK's perspective, true innovation is what they pay for.''

Panelists Pick Imagined Early-Stage Co. Kjellson ended the session by asking the panelists, ''If you could run a biotech company, what type of company would it be?''

Berry said, ''An early-stage, broad therapeutics company structured as a semi-vertical, offshore limited liability company. There's a lot of money in China and India that they want to get out of the country. It's easier to raise money for such a company because there's not a lot of substance there but an awful lot of promise.''

Gallagher added, ''With such a company, you hope you can form the strategy to make it successful if you can get into it early on as opposed to coming in when all the big decisions have already been made by somebody else and you're stuck with it.''

The others tended to agree that the company they would like to run would focus on early-stage drug development; only Pappas's would focus on the primary care market and Weisskoff's on cancer.

For her part, Kjellson said she would choose a fully-integrated, start-up product or service company focused on elder care.

BY JOHN T. AQUINO

Drug Development

Panel's Focus on Challenges Puts Damper On Session on Life Sciences' 'Bright Future'

A panel discussion on the ''bright future'' of life sciences turned ''bleak'' Sept. 27 at a biotech conference, with panelists noting the continued problems of balancing the risk and benefit of drugs, the high cost of development, and an overburdened Food and Drug Administration.

Panelists finally allowed they were optimistic about the future—suggesting that there had been more innovation in the last 10 years than in all the rest of human history—but noted the difficulty of achieving the potential of this innovation quickly enough.

The session at the 2012 Mid-Atlantic Bio conference in Bethesda, Md., was titled ''Seeing a Bright Future through the Dense Fog—What's Ahead for an Ever-Changing Life Sciences Industry.''

Vicki L. Seyfert-Margolis, FDA's senior adviser to the chief scientist, was asked what has changed for life sciences since the previous Mid-Atlantic Bio in 2011. She noted great advances—''we're not looking at me-too drugs so much''—and higher drug efficacy rates. ''This is likely the result of increased communication with the agency and a better understanding of the ways to collaborate.''

Need Major Risk-Benefit Conversation. M. James Barrett of the venture capital firm New Enterprise Associates was less enthusiastic about any improvements in areas Seyfert-Margolis noted. ''Two years ago,'' he said, ''we didn't think that FDA was striking a balance between efficacy and safety. Today, I can't say we're seeing a broader swing of the pendulum.''

Dr. Ron Cohen, president and chief executive officer of Acorda Therapeutics, indicated that some thought FDA had become too risk-averse and that there had been some moderation in the balance, although he was not sure that the science had improved that much in the last two years.

He added, ''The larger issue is, what are we willing to accept as the price of innovation? The terminology we use to describe the positive results of the risk-benefit process is that a drug has been approved because it has been shown to be 'safe and effective.' Not 'relatively safe,' but without qualification, 'safe and effective.' This mitigates against the public's understanding of risk-benefit.''

Seyfert-Margolis responded, ''As Janet Woodcock [director of FDA's Center for Drug Evaluation and Research] has repeatedly said, we need to have an important conversation about benefit and risk.''

She brought up Tysabri. FDA first approved it in November 2004 to treat multiple sclerosis, and manufacturer Biogen Idec removed it from the market in February 2005 after people taking it in clinical trials developed a rare, serious brain infection called progressive multifocal leukoencephalopathy (PML), which proved fatal for two individuals.

In 2006, FDA allowed the product to return to market, rolling out a risk-minimization plan designed to inform patients, doctors, pharmacists, and infusion centers about Tysabri's risks and to quickly flag PML cases in patients taking Tysabri.

''MS patient groups became part of the dialogue and of the development of the plan, which basically said that a patient needs to understand that Tysabri is the best drug for MS but that some people who take it could die,'' Seyfert-Margolis said. ''It's a wonderful example of how it should work, with decisions being made by patients and their doctors.''

FDA Already Overburdened. In addressing the high cost of drug development, Barrett said, ''I tell people that if they want to bring down drug costs, then they will have to accept that the medicine they have today won't get better. If you want it to get better, then you have to reward the innovator, and there's a cost for that.''

Seyfert-Margolis said, ''There is a systems problem all the way around, including on the regulatory side, and we need to do an adjustment. There are items in PDUFA [Prescription Drug User Fee Act] V that could have a positive effect on drug development costs.''

  LSLR ISSN 1935-7257

Cohen countered that the execution will determine whether items under PDUFA V such as the independent audit provision and expanding the accelerated approval pathway will make a difference on cost. ''They look good on paper. But you have to remember that all of this is against a background of an agency that is already overburdened and that has limited resources.''

''People ask how to get FDA to be more accommodating to industry,'' Seyfert-Margolis said. ''But on the other side, you have people who are saying that FDA is not standing up enough to industry.''

Achieving Potential Quickly Enough. A member of the audience complained that the session was to be a look at life sciences' ''bright future'' and yet everything said had been relatively ''bleak.''

Asked if he was then pessimistic about the future, Cohen said he was ''quite optimistic'' about the potential for human innovation in the long run. ''We've had more innovation in the last 10 years than in all of human history, and soon we will have a $1,000 genome [referring to the cost of mapping an individual human genome] which will be able to be done in a few hours,'' Cohen said.

''What we have been discussing today are self-inflicted impediments to our getting to the potential of this innovation quickly enough,'' he added.

Seyfert-Margolis said, ''We are seeing consortia and partnerships and advances in health information technology. We're seeing each other coming out of a slump, looking at challenges, and soon we will see some very innovative products come out.''

Acknowledging that he had been, perhaps, the curmudgeon of the group, Barrett asked, ''When was the last time you saw an innovative drug come out of Russia? The answer is, never. The United States leads in drug innovation, but things like Obamacare [the Affordable Care Act] and other stuff going on are acting as an impediment to innovation.''

Barrett concluded, ''The moral is, don't take what we have for granted.''

BY JOHN T. AQUINO

Partnerships

Use of Public-Private Partnerships Growing To Avert 'Unsustainable' Development Model

Universities and life science companies are collaborating to move bioscience discoveries to market more quickly and sidestep the current ''unsustainable'' drug development model, panelists Sept. 27 told a biotech conference.

The panelists at a 2012 Mid-Atlantic Bio session described a number of university-industry partnerships, including centers for innovation, that work to combine the best of academia with entrepreneurial culture.

Addressing a concern about whether such partnerships ''bypass'' small biotechs in favor of research institutions, a Big Pharma representative and an official with the National Institutes of Health's National Center for Advancing Translational Sciences (NCATS) both said that they partner with biotechs as well.

Working Toward Shared Common Goal. Dr. Christopher P. Austin, director of NCATS' Division of Pre-Clinical Innovation, said NCATS is a technology developer and adapter. ''Universities make enormous contributions to NCATS on both the science and clinical sides,'' he said.

Austin noted NCATS provides grant funding to support research projects, core facilities, and scientific resources and tools and has open funding opportunities for a wide range of health care projects and for finding new therapeutic uses for existing molecules. ''We learn by doing. We look for projects that have a deliverable and have it teach us how to do the whole process better. The deliverable is not only a tool, but it is knowledge.''

Anthony Coyle, vice president and chief scientific officer of Pfizer's Centers for Therapeutic Innovation (CTI), stated that $40 billion is spent on pharmaceutical research a year, and yet fewer than 20 molecular entities are approved each year. ''This is unsustainable,'' he said.

It is necessary to combine the best of academia with entrepreneurial culture, Coyle said. ''The challenge is to bridge the culture gap. To be successful, we have to identify a shared common goal.''

Coyle said Pfizer's first CTI facility was created with the University of California-San Francisco (UCSF) in November 2010, and provided up to $85 million in research support and milestones over five years. Pfizer established a CTI lab facility onsite at UCSF for Pfizer and UCSF scientists to collocate and collaborate.

In 2011, Pfizer established CTIs with seven New York academic medical centers—Albert Einstein College of Medicine of Yeshiva University, Columbia University Medical Center, Memorial Sloan-Kettering Cancer Center, Mount Sinai Medical Center, New York University Langone Medical Center, Rockefeller University, and Weill Cornell Medical College—and with Harvard University, Beth Israel Deaconess Medical Center, and Children's Hospital Boston.

''If we decide not to exercise an option, the assets revert to the institution,'' Coyle said.

Mark Crowell, executive director of UVa Innovation and associate vice president for research at the University of Virginia, discussed the university's Wallace H. Coulter Translational Partnership Program, which began in 2005 with nine university recipients.

''It builds industry-like discipline into a project,'' Crowell said. ''The development team is split 50/50, half university personnel, including business development and technology transfer staff, and half from industry. They collect rigorous metrics, which are monitored by experts. They look not just toward publishing results in scholarly publications but toward the licensing of products.''

After seven years, out of 200 projects at participating universities, the return on investment so far has been seven to one, Crowell said. ''The University of Virginia's Coulter project has changed the way we look at partnering. We have a whole new partnering IQ at UVa.''

'A Big Fan of Biotechs.' A member of the audience observed what he called a common theme for the session, which was ''for Big Pharma to pay academia to do what small biotechs have been doing, to bypass small biotechs.''

Coyle responded that a partnering program between industry and universities is not the only way to approach the issue of moving discoveries more quickly to

the marketplace. He noted that Pfizer initiated the Pfizer Global Incubator, a seed-stage investment fund available to support collaborations with start-up companies founded by experienced entrepreneurs who foresee the commercialization of their inventions for the benefit of patients.

Austin said, ''NCATS represents equal opportunity for thinkers. If you look at the TRND [Therapeutics for Rare and Neglected Diseases] Program, you'll see half of the projects are with small biotechs. We participate in the Small Business Innovation Research/Small Business Technology Transfer [SBIR/STTR] programs [which are used extensively by start-up life sciences companies] and are looking to use our SBIR/STTR money better. Also, we do licensing with biotechs.''

He concluded, ''NCATS is a big fan of small biotech companies. What we do is a version of the 'bucket brigade model' [where an idea that originates in research and development is passed from group to group] and try to get projects up to where biotechs might be interested.''

BY JOHN T. AQUINO

Patents

New Patent Law Will Bring Predictability To Life Sciences Over Time, Panelists Say

The America Invents Act, the first changes in patent law in 60 years, will completely change the way university transfer offices and small biotech companies handle filing patents, panelists Sept. 28 told a biotech conference.

The change from ''first to invent'' to establish patent priority to ''first inventor to file an enabled patent'' (FTF) means that small biotechs will no longer be able to file provisional applications with ideas sketched out on napkins and transfer offices will have to work with faculty to contain pre-filing disclosures, panelists said at the Mid-Atlantic Bio conference in Bethesda, Md.

But overall and over time, they said, those working in life sciences should find the law brings more predictability.

Old Law Hard on Life Sciences. Bruce Artim, director of federal affairs for Eli Lilly and Co., described how Congress has a history of bipartisan cooperation when it comes to intellectual property and said the AIA demonstrates that with its general goal of protecting U.S. international IP interests.

''A 2004 report Congress commissioned from the National Academy of Sciences recommended that the patent law be more objective in contrast to the prior law, which had its subjective elements. For example, it's hard to describe 'best mode' in a life sciences patent because you may never know the best way to practice the invention,'' Artim said.

''At the end of the day, Congress ended up with a new system that was supported by every sector of the economy, with what was often called a 'secret prior art area' replaced with procedures where information is more readily available,'' Artim said. ''For life sciences, the system will over time allow for more predictability.''

First-to-File Means Big Change for Universities. Louis D. Lieto of Wilson Sonsini Goodrich & Rosati, Washington, said that the most fundamental change the AIA brings is the switch from first to invent to FTF for patent priority, ''which brings us in line with the rest of the world and reinforces the need to file early rather than later.'' FTF becomes effective for applications with an effective filing date on or after March 16, 2013.

Wes Blakeslee, executive director of Johns Hopkins Technology Transfer, said that the switch presents a ''fundamental change'' for university technology transfer offices. ''Your faculty wants to publish the research results so that they can get that promotion or tenure. They also are in communication with other researchers and basically disclose all aspects of the invention to someone else. In the FTF environment, the university needs to receive the invention early in order to protect the patent and to be on record about it before anyone else publishes on the idea and establishes prior art.''

Blakeslee also noted that, while under the FTF default rule the first to file gets the patent, the AIA has provisions for derivation proceedings to determine whether the inventor named in an earlier-filed application derived the claimed invention from the inventor of an application filed later.

Artim said that FTF is sometimes misunderstood as making it easier for an interloper to get a patent. ''We say 'first to file' but it's really 'first inventor to file.' Anyone who signs a false inventor's oath is subject to criminal proceedings.''

Changes to Make Patent Challenges Go Faster. Another substantial change the AIA brings is the alternatives to litigation to challenge a patent. Erik B. Milch of Cooley LLP, Reston, Va., said eliminating ''inter partes reexamination'' and instituting ''inter partes review'' is a ''pretty drastic change. The problem with inter partes examination is that it took so long. Of the 1,400 that were granted by the Patent and Trademark Office, 1,000 are still pending. The reexamination was eliminated by the AIA effective Sept. 16, 2012, and the inter partes review is now handled by the new Patent Trials and Appeals Board.''

The goal, Milch said, is to have the new IPRs handled within one year rather than the average of 36 months for reexaminations. ''The PTO has hired a good number of administrative law judges, so it's possible the one-year goal will be met.''

Effect on Universities. Blakeslee elaborated on the effect of AIA on university technology offices.

''As I said, researchers are eager to publish and have likely disclosed all aspects of the invention to someone else. Under the old law, we used to file provisional applications to get something on file before publication. But just as Bruce [Artim] clarified that the exact wording for FTF is 'first inventor to file,'' it's really the first inventor to file an enabled claim. Published articles seldom have enabled claims. Now our attorneys are working to have enabled claims in provisional applications, and you can't always'' do that.

He said his office also has become more active with nondisclosure agreements for collaborators.

Effect on Industry. Asked how the AIA's changes will affect Big Pharma, Artim said that because Pfizer is a multinational company, it has been active with the FTF approach. ''We've been living in both worlds—the U.S.

  LSLR ISSN 1935-7257

patent world and the patent world for most other countries—so we don't see major changes for us as a result of the new law.''

Lieto said that the new law increases the need for small biotechs to file early and to file again as more data become available.

Milch said, ''A small biotech company will have to carry the burden of initial drafting. They can no longer file provisional applications with ideas sketched out on a napkin. They will also have to weigh the risk of not filing.''

He called the fees for some of the new proceedings under the AIA ''outrageous. The current total fees for IPRs is almost $28,000. That's difficult for small firms.''

Asked if the change to FTF affects the need for due diligence in acquisitions, Milch said, ''No, it doesn't. You really need good records for derivation proceedings—meeting notes, records of conference attendance. And you still need inventor's notebooks for derivation proceedings and for older patents.''

In final words of advice, Lieto said, ''If you have provisional applications sitting around, get them in before FTF becomes effective March 16, 2013.''

Artim said, ''We're in a transitional period between the old law and the new. Don't get caught in the middle so you get the worst of both worlds.''

BY JOHN T. AQUINO

Drug Development

Clovis CEO Describes Advances, Challenges in Oncology Therapies

Targeted therapies are turning some cancers from a death sentence to a chronically manageable disease, the head of an oncology therapy company told a biotech conference Sept. 27.

But these therapies also are producing challenges in that the smaller target populations for testing are hard to find and there is limited tissue availability, according to Patrick Mahaffy, president and chief executive officer of Boulder, Colo.-based Clovis Oncology.

Addressing the 2012 Mid-Atlantic Bio meeting in Bethesda, Md., Mahaffy began by noting that profound scientific discoveries are driving changes in cancer research, leading to better and smarter oncology drug development with improved trial design and better quality-of-life outcomes.

Benefits, Challenges of Targeted Therapies. In 1999, Mahaffy said, non-small cell lung cancer (NSCLC) was treatable only with platinum doublet chemotherapy and small cell lung cancer with platinum chemotherapy and etoposide. But today, he said, oncology treatments are shifting away from the classical approach of uniform treatment for a given organ, which generally has involved dosing until toxicity becomes intolerable with benefits that are modest overall.

Mahaffy traced the improvement of options for the treatment of chronic myeloid leukemia from chemotherapy to Interferon to Gleevec. ''It's phenomenal what industry can do now to turn cancer from a death sentence to a chronically-manageable disease. We have shifted to targeted therapies for an improved value proposition for patients, physicians, and payers,'' he said.

He described how researchers have been working on a gene sequencing treatment for leukemia that will be tailored to an individual tumor's mutations, with drugs that will hit several key aberrant genes at once.

Mahaffy pointed to the speed of FDA approval of Pfizer's NSCLC drug Xalkori as a possible trend for targeted therapies. In the clinical trials for the drug, the study design required patients' tumors to prospectively test positive for the ALK fusion gene biomarker, increasing the likelihood of response to the treatment. This method allowed researchers to observe a strong efficacy signal in a selected patient population. Preliminary epidemiology suggests that approximately 3 percent to 5 percent of NSCLC tumors are ALK-positive.

''The good news is that the approval of Xalkori in August 2011 took just four years from the discovery of the ALK fusion gene in NSCLC to FDA approval, and we expect to see these fast approval rates for other targeted therapies,'' Mahaffy said. ''We've also been seeing relatively cost-effective trials and a path to positive reimbursements.''

But these changes are happening in a difficult fundraising environment, as the Food and Drug Administration struggles to keep up with technology and difficulties increase in managing clinical trial population shrinkage and dispersion, he said.

''Cancer's Balkanization [breaking down into smaller units] leads to small populations that can be hard to find and that may limit commercial opportunities,'' Mahaffy said.

''There is also limited tissue availability for smaller populations.'' As a result, he said, ''We must move from single-target diagnostics to multiplexing,'' where tests are developed that simultaneously measure multiple analytes in a single run or cycle.

Update Regs for Companion Diagnostics. While companion molecular diagnostics are fast becoming the standard for cancer therapies, Mahaffy noted that drug and diagnostics developers have different perspectives that must be acknowledged as they collaborate.

''Drug developers do prospective studies, while diagnostics do retrospective analyses. The timeline and cost for a drug's development is five to 10 years and $100 million. It takes two years and $2 [million] to $3 million to develop a diagnostic.''

Mahaffy said that the regulatory framework for companion diagnostics must be updated. ''It is based on older technologies. A single test for a single target is not always viable. The need for multiplexing is critical given the limited tissue availability.''

He advised companion diagnostics developers to:

- do it early in clinical development,
- aggressively collect tissue samples,
- engage with regulators early, and
- accept the fact that drug developers will end up paying for everything as the cost of doing business.

Quick Failure Better Than Ambiguity. Addressing the issue of funding, Mahaffy, co-founder of Clovis, which had received $65.6 million in financing from a large syndicate of top-tier life science venture capital firms (4 LSLR 271, 3/26/10), suggested building a syndicate with staying power, pre-financing multiple rounds, reserving committed capital for an initial public offering, and

marrying the financing strategy with the development time line. ''You may find the need to go public earlier than you might normally plan and accept a lower valuation,'' he said.

Mahaffy outlined some ideas and recommendations for developing a successful product:

- discovery and development are completely different skill sets;
- it is important to own the function that is critical to the product strategy and to consider outsourcing or partnering on other activities;
- a company must provide a clear path to value creation for its investors;
- trials should be about data and not milestones and should eliminate ambiguous outcomes;
- a quick failure is better than ambiguity; and
- any phase II clinical trial should set the stage for a phase III that proceeds easily and without incident.

Mahaffy concluded, ''You can really only have one lead product that gets the majority of your attention and resources. This doesn't mean that it's your best. And leads can fail. So you need to have some lifeboat products around as well.''

BY JOHN T. AQUINO

  LSLR ISSN 1935-7257