Denise Myshko

New Course for BIOTHERAPEUTICS

Companies developing biotherapeutics are beginning to study indications beyond cancer and autoimmune and infectious diseases and are researching how antibodies and proteins can be used to treat other conditions, such as pain and cardiovascular conditions, that have traditionally been treated with small molecules.

The demand for biologics continues to increase. In fact, the market for biologics is expected to exceed $100 billion in 2015, according to a report by Freedonia. Continued growth will be impacted by dramatic shifts in production technology and expansion of targeted diseases, as well as by the introduction of biosimilar products.

During the past five years, U.S. companies have dramatically increased their biologics development, with almost 6,000 clinical trials involving a biological intervention being reported since 2005, according to a report last year by Thomson Reuters.

A majority of the biologics currently in the development pipelines of the companies studied by Kalorama Information are aimed at the treatment of cancers. The next largest group of biologics address cardiovascular diseases and autoimmune and hormone disorders. Monoclonal antibodies account for the largest share of the innovation with almost 30 new antibody compounds in development.

Experts say biotechnology companies are beginning to see success with biotherapeutics beyond cancer in the areas of inflammation and cardiovascular, as well as other therapeutic areas where biologics have not been traditionally developed.

Randall Schatzman, Ph.D., president and CEO of Alder Biopharmaceuticals, agrees that biotech companies are pushing therapeutic boundaries in the biologics space.

"We are working to extend into other spaces where biologics, and in particular monoclonal antibodies, have not played a role in the past," he says. "Migraine and pain is an open space to play with these molecules. We are also looking at the cardiovascular space, which has been the traditional home of small molecules. We think an antibody actually is an outstanding candidate to treat some of these diseases, but with the drug being administered infrequently. Instead of taking a lipid-lowering agent every morning, one might take a biotherapeutic quarterly because of the long half-life that antibodies have."

FAST FACT

ALMOST 6,000 CLINICAL TRIALS WITH A BIOLOGICAL INTERVENTION HAVE BEEN REPORTED SINCE 2005.

Source: Thomson Reuters

Dr. Schatzman points out that because compliance with daily therapies is often an issue for patients, an antibody therapy could provide an advantage.

"Patients have to be motivated to take their medications every day and do so consistently," he says. "The KOLs who we have interacted with suggest that one way to deal with noncompliance is to have therapies that are administered less frequently."

Another advantage of biologics is the plethora of technologies that can potentially improve safety.

"Because biologics can be designed to modulate the specific targets, the off-target effect is less likely with biologics than it is with small molecules, therefore presenting a better safety profile," says Bahija Jallal, Ph.D., executive VP, R&D, at MedImmune.

In addition, biotech companies are working to develop alternative manufacturing methods that will allow for larger-scale production of large molecules, which could help lower pricing on traditionally more expensive biologics.

Mark Litton, Ph.D., chief business officer of Alder Biopharmaceuticals, explains that the company's proprietary manufacturing process allows it to compete on a pricing level with small molecules.

"We're able to make a lot of product to address some of the very large chronic disease indications," he says.

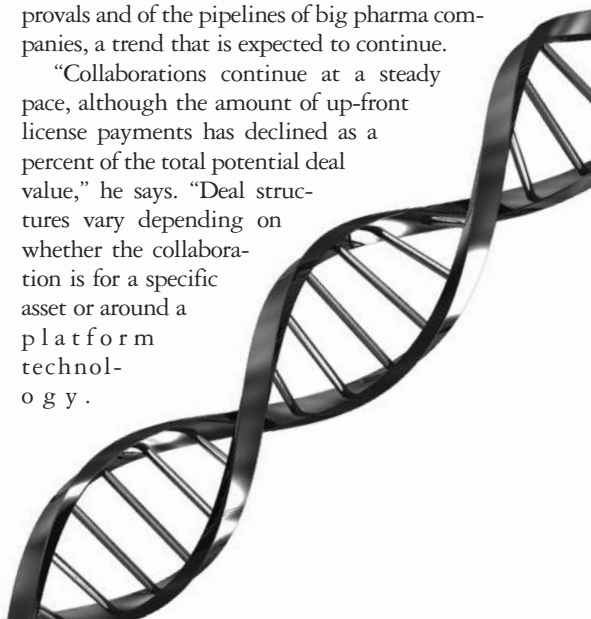
Collaborations for Biotherapeutics

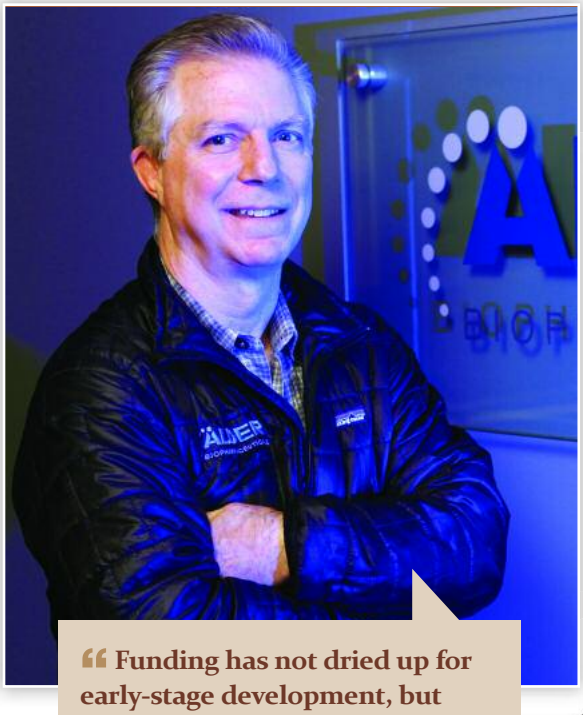
The current biopharmaceutical market (excluding vaccines) is valued at $105.5 billion, accounting for almost 20% of the total human medicines market for 2010, according to Kalorama Information. With compound growth expected at 7.1%, the market is anticipated to be $148.6 billion by 2015. New developments, including both new compounds and indication/formulation improvements, will contribute more than $20 billion to the market over the forecast period.

The biologics market is still dominated by the top five pharmaceutical companies — Amgen, GlaxoSmithKline, Novartis, Pfizer, and Roche — which combined hold more than a quarter of the late-stage biologic products, according to Kalorama.

Glen Giovannetti, global life-sciences sector leader at Ernst & Young, says biologics now comprise a significant portion of recent approvals and of the pipelines of big pharma companies, a trend that is expected to continue.

"Collaborations continue at a steady pace, although the amount of up-front license payments has declined as a percent of the total potential deal value," he says. "Deal structures vary depending on whether the collaboration is for a specific asset or around a platform technology.





> "Funding has not dried up for early-stage development, but investors have gotten smarter about what programs they want to invest in and which ones are more likely to succeed."
>
> **DR. RANDALL SCHATZMAN**
> Alder Biopharmaceuticals

> "We have seen a rebound in the aggregate funding totals for biotech companies. But these numbers only tell part of the story, as about 80% of capital is going to only 20% of companies."
>
> **GLEN GIOVANNETTI** / Ernst & Young

> "We will see more peer-to-peer research collaborations between pharma and biotech that bring more value to research and development."
>
> **DR. BAHIJA JALLAL** / MedImmune

Platform technology deals generally include some option that allows the pharma company the opportunity to select and/or substitute product candidates covered by the license."

Biologics that are specific and have targeted intervention capabilities have sparked the interest of pharma companies, says William Newell, CEO of Sutro Biopharma.

"Larger biopharmaceutical companies understand the potential of the large molecule market and know that to continue to be successful, they need to be much more committed to this marketplace than they were 10 or 15 years ago," he says.

Growth in the biologic markets is being driven by the fact that many proteins are very specific for targets.

"If chosen wisely, biologics have the potential to limit off-target effects that are often the downfall of a small molecule," Mr. Newell says. "Additionally, with biologics, there is the potential for very specific, very targeted therapies that can be modulated to take into account the evolving understanding of pathways and intervention points much more readily than with a small molecule."

Experts say there is a trend toward more peer-to-peer collaborations between pharmaceutical and biotechnology companies.

Dr. Schatzman says Alder's relationship with Bristol-Myers Squibb is unusual in that BMS was willing to contemplate a novel structure wherein both companies are able to access signficant value from a single agent by each taking separate development paths. In this collaboration, BMS was granted the rights to develop ALD518 for all indications except cancer. Alder continues to hold the rights to develop the product for cancer.

ALD518 is a monoclonal antibody in Phase IIb trials. The product is designed to block interleukin-6 (IL-6), which plays a key role in the inflammatory cascade leading to the inflammation, swelling, pain, and destruction of large and small joints associated with rheumatoid arthritis.

"There will be ongoing collaborations as companies combine the innovative technologies needed to design and manufacture biologic therapeutics," Dr. Schatzman says.

In the future, Dr. Litton says there will be more product relationships and collaborations.

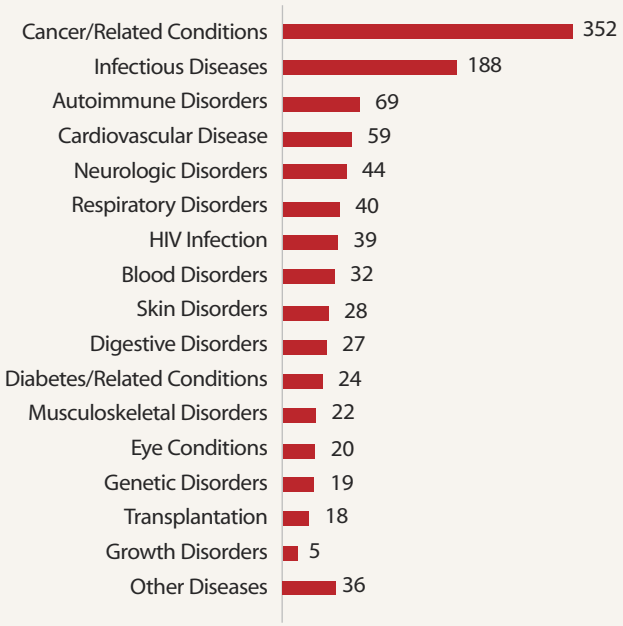
"There will be creative structures so that biotech companies can retain more of the value of their products and technologies," he says.

The Funding Environment

Mr. Giovannetti says there has been a rebound in the aggregate funding totals for biotech companies immediately following the 2008 financial crisis.

"These numbers only tell part of the story; about 80% of the capital is only going to 20% of the companies, which are typically more mature, commercial-stage entities," he says. "The majority of precommercial stage biotech companies continue to face a challenging funding environment in which investors are setting a high bar on the types of companies they will support. In addition to the scientific risks of a particular product candidate, investors are also evaluating the regulatory risks associated with the clinical development plan and commercial risks associated with securing adequate reimbursement upon approval. As a result, companies will need to continue to seek ways to be capital efficient and to demonstrate

Biotechnology Medicines in Development
By therapeutic category



Source: Pharmaceutical Research and Manufacturers of America.
For more information, visit phrma.org.

that their product candidates are truly differentiated."

U.S. venture capital funding for the life-sciences sector, which includes biotechnology and medical devices, increased 21% during 2011, according to the February 2012 MoneyTree Report from PwC and the National Venture Capital Association. Venture capitalists invested $7.5 billion in 785 life-sciences deals during the year.

Biotechnology companies received $4.7 billion in funding for 446 deals in 2011, second only to software companies. Compared with 2010, biotech funding increased 22% in dollars and 9% in deal volume.

Dr. Schatzman says companies that can show good data about their products and the way they are addressing unmet needs can attract funding.

"There is a lot of cash sitting on the sidelines," he says. "Investors' interest in products where there is a higher likelihood of value creation and liquidity has increased."

Mr. Giovannetti says IPOs remain an option for a select number of companies in the life sciences, typically those that have drugs in late-stage trials or companies that already are generating revenue, but cash remains tight.

"Even for those companies able to enter the public markets, we are seeing most offerings failing to price within their desired price ranges as IPO investors have become increasingly sophisticated in evaluating development and commercialization risk," he says. "As a result, the vast majority of biotech companies will continue to aggressively seek alternative sources of funding to sustain innovation. Furthermore, while the recently passed JOBS bill in the United States will lower the cost and complexity of becoming a public company, it will not impact the underlying business proposition or investor sentiment."

In March, both the Senate and the House voted to approve the JOBS Act, which is intended to ease access to capital. The JOBS Act, which President Obama is expected to sign, would designate a new category of "emerging growth" companies that could conduct initial public offerings of stock while being exempt from certain financial disclosure and governance requirements for up to five years. It would also provide a new form of financing to small companies. Through crowd-funding, or the sale of small amounts of stock to many individuals, companies could solicit equity investments through the Internet or elsewhere, raising up to $1 million annually without being required to register the shares for public trading with the SEC.

Mr. Giovannetti says from the pharma perspective, there has been a sizeable increase in activity by the VC sector, either through direct investments in companies or through investments made in venture capital firms.

> **"Going forward partnerships will be less focused on technologies and more focused on products with more creative structures so that biotech firms can retain more of the value of those products."**
>
> **DR. MARK LITTON** / Alder Biopharmaceuticals

"In addition to achieving a return on investment, many pharma companies see these arrangements as providing early visibility into new technologies and as filling an important gap that has been created by the decline in traditional venture investing," he says. "These structures also provide opportunities for creative collaborations, such as the recent funding of Warp Drive Bio. This funding included a sizeable investment by Sanofi, which also received an option to acquire the remainder of the company's shares from the venture investors." PV

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