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BIOTECH FINANCE REPORT

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New attention has been drawn to companies in the biotech sector as a result of the joint announcement by the Human Genome Project and Celera Genomics, Inc. that they have completed a preliminary map of the human genome. This major scientific breakthrough will lead to more gene-based medicines and disease treatment.

In spite of the significant scientific progress, the financing of emerging or development-stage biotech companies continues to be difficult. This has historically been caused by a number of factors: (1) it takes expensive clinical trials over many years to develop a new pharmaceutical product; (2) less than 10% of the drugs which enter Phase I clinical trials ever complete the clinical trials and become an approved drug; (3) some emerging biotech companies lack skilled management, financial and/or marketing expertise; (4) many development-stage biotech companies have high "burn rates" and, as a result, have a continual need for additional capital and uncertainties as to whether the capital markets will be receptive when they need it; (5) an exit strategy in the form of an IPO or acquisition by another company is problematic; (6) other pharmaceutical companies may develop superior pharmaceutical products or have greater financial strength or much stronger marketing capabilities; (7) patent infringement suits can seriously damage the prospects of an emerging biotech company and (8) venture capitalists and other sophisticated investors have often found more attractive opportunities in other types of technology investments, including internet-related investments.

In 1999, \$41.5 billion in venture capital investments were made but only about \$1.4 billion (or about 3.4%) was invested in biotech companies, according to Venture Economics Information Services. While there are some venture capital firms that focus on or invest in biotech firms, the more limited number of capital-raising choices hinders access to capital.

This report discusses five sources of funding: (1) SBIR and other government grants; (2) collaborations coupled with equity investments; (3) collaborations coupled with milestone payments; (4) equity investments from institutional investors and (5) angel investors.

SBIR and other Government Grants

One opportunity for early-stage biotech companies to access capital is the Small Business Innovation Research (SBIR) Program administered by the National Institutes of Health. The NIH accepts grant applications from small businesses in various areas of biomedical

research, such as tumor biology, cancer genetics, cancer immunology, cancer diagnosis, and biochemistry and pharmacology. The SBIR program supports innovative research that has the potential for commercialization. Support under the program is normally provided for six months/\$100,000 for Phase I and two years/\$750,000 for Phase II. Approximately 59% of the Phase I awards result in Phase II awards.

The NIH has made SBIR grants in greater amounts than \$750,000 under certain circumstances. For example, NOVIRIO Pharmaceuticals, Inc. received this year a fast-track award of up to \$1.1 million for the development of a novel class of Hepatitis B compounds. Ligocyte Pharmaceuticals, Inc., in collaboration with the University of Michigan School of Medicine, received a \$2.8 million Phase II SBIR grant this year for the formulation and synthesis of therapeutics based on polyvalent liposome nanoparticles.

In fiscal year 1999 (October 1, 1998 – September 30, 1999), the NIH made SBIR grants and contract awards totaling \$307 million. Approximately, 830 grants were approved out of almost 3,000 applicants. In 1999, less than 2% of all SBIR grant applications were awarded through the fast-track program.

The advantage of receiving an SBIR grant is twofold: (1) it is a grant and not a loan or equity investment and (2) it provides some independent validation of the scientific or technical merit of the biotech company's drug development platform and (3) the SBIR grant may help to attract additional funding. A disadvantage of the program is that even if SBIR funding is obtained, the funding usually does not go far enough. For more information on SBIR grants, see <http://grants.nih.gov/grants/funding/sbir.htm>.

The National Institute of Health also makes grants under the Small Business Technology Transfer (STTR) program. This smaller grant program is designed to support innovative research that has the potential for commercialization and is conducted cooperatively by a small business concern and a research institution. In fiscal year 1999, the NIH made STTR grant awards totaling \$19.7 million. As an example, AVI BioPharma received an STTR grant and a SBIR grant totalling in excess of \$850,000 to study applications of the company's antisense drug program. The Phase II award under the STTR program is to be performed in conjunction with the University of Nebraska Medical Center.

Many state development agencies also have grant, loan, equity investment and technical assistance programs which might be used in tandem with or in addition to NIH grants.

Collaborations Coupled with Equity Investments

Another significant source of equity funding is through collaboration with major pharmaceutical companies or other biotech companies which have stronger financial resources or a reason to collaborate. A few examples of these collaborations show their value to an emerging company.

In June, Millennium Pharmaceuticals, Inc. and Aventis S.A. announced that they had formed an alliance covering the joint development and commercialization of drugs for the treatment of

inflammatory diseases, joint development of new drug discovery technologies, transfer of key elements of Millennium's technology platform to Aventis and purchase of an equity investment in Millennium by Aventis. Under the technology transfer agreement, Millennium will provide Aventis with rights to its drug discovery technologies in exchange for payments of up to \$200 million over a five-year period. A \$150 million stock purchase will be made at closing and two \$50 million stock purchases will be made in 2001. Observers have described this significant agreement as evidencing the growing power of biotech companies to negotiate more attractive terms in collaborations.

Also, in June, Atrix Laboratories, Inc. and Elan Corporation, plc agreed to form a research joint venture to commercialize oncology and pain management products. Elan will provide funding to develop these compounds. Atrix will initially be the majority owner of the joint venture. Elan made an equity investment of \$5 million in Atrix at a premium over the then current market price of Atrix.

In January, Isis Pharmaceuticals, Inc. entered into an agreement with Elan Corporation, plc to form a new subsidiary of Isis, OraSense (TM) Ltd., to develop an antisense drug for the hepatitis c virus. As part of the transaction, Elan purchased in April \$7.5 million of Isis common stock and is obligated to purchase an additional \$7.5 million of common stock upon completion of a mutually agreed milestone. The initial \$7.5 million purchase was at a premium to Isis' market price and, if the second purchase is triggered, it would also be at a premium to the market. Elan will also purchase Isis Series B Preferred Stock which will be convertible in the future into either Isis stock or stock in the subsidiary. In addition, Elan will make available to Isis a \$12 million line of credit for Isis' funding commitment to the subsidiary.

Another example of a collaboration in which an equity investment is made is the April agreement between SuperGen Inc. and AVI BioPharma, Inc. in which SuperGen acquired exclusive U.S. sales and marketing rights to Avicine (TM), a therapeutic cancer vaccine. Under the terms of the agreement SuperGen will be responsible for U.S. sales and marketing of Avicine and AVI will be responsible for product manufacturing. SuperGen will receive the right of first discussion with respect to all of AVI's oncology compounds. Both companies share clinical development and regulatory costs for the FDA approval process, and profits will be split equally.

SuperGen will make an up-front equity investment of \$20 million in AVI BioPharma in the form of cash and SuperGen common stock. The use of SuperGen's stock preserves its cash, but such shares could be sold by AVI BioPharma to raise cash. Additional equity investments and cash milestone payments are contemplated based upon the commercial success of Avicine. SuperGen will receive an option to purchase an additional 10% of AVI's common stock at a price of \$35.625 per share, which was three times the closing price of AVI stock at the time the transaction was entered into.

As the above examples illustrate, collaboration agreements are a significant way for an emerging biotech company to obtain funding for development costs and an equity investment. The participation of a well-known collaboration partner also adds considerable credibility and scientific validation of the drug development platform. The existence of collaboration arrangements are very helpful in attracting other sources of equity capital.

Collaborations coupled With Milestone Payments

Biotech companies also may obtain funding from larger pharmaceutical companies in which an up-front licensing fee, milestone payments and royalties are paid to the biotech company but no equity investment is made by the larger company.

One example of a large collaboration of this type is the May agreement between Vertex Pharmaceuticals Incorporated and Novartis Pharma AG to form an alliance to discover and commercialize small molecule drugs in the kinase protein family. Under the terms of the agreement, Novartis will provide Vertex with an initial payment of \$15 million and further research funding of \$200 million over six years. Novartis will have exclusive worldwide development, manufacturing and marketing rights to eight drug candidates. License fees, milestone payments and reimbursements of \$600 million or more are possible for Vertex.

As another example, Celgene Corporation in April granted an exclusive worldwide license (excluding Canada) to Novartis Pharma AG, for the development and marketing of its chirally pure version of Ritalin (R). Celgene will receive substantial up front fees, milestone payments and royalties on all formulations of the enhanced Ritalin family of drugs.

As another example, Alkermes, Inc. entered into an agreement with Glaxo Wellcome in June relating to Alkermes' pulmonary drug delivery technology. Glaxo Wellcome obtained a license to the Alkermes technology, in exchange for development funding, payments based on the achievement of certain milestones and royalties based on the sale of such products. Alkermes and Glaxo Wellcome each have manufacturing rights and obligations and Glaxo Wellcome has responsibility for conducting clinical trials, securing regulatory approvals and marketing any products on a worldwide basis.

The difficulty with collaboration agreements is well recognized in the industry. On the one hand, they provide a source of funding for research and development. When structured with license fees, milestone payments, and royalties, they do not involve giving up equity in the biotech company, but the larger pharmaceutical partners may have a big share of the profits and potential from the development and marketing of the product. The recent Vertex transaction, however, is an example of a biotech company obtaining good financial terms in a collaboration.

Equity Investments from Institutional Investors

If a biotech company has a drug development platform with scientific promise, has successfully completed some clinical trials or has well-known collaboration partners, it becomes much more feasible to attract equity capital from institutional investors even if the public securities markets may be inhospitable. For example, institutional investors made an equity investment of \$100 million in Transkaryotic Therapies, Inc., which is enmeshed in a major patent infringement lawsuit with Amgen. Under the agreement, investment funds affiliated with E.M. Warburg, Pincus & Co., LLC purchased a newly-issued preferred stock convertible into approximately 3,570,000 shares of Transkaryotic common stock at a conversion price of \$28 per share. The preferred stock conversion price was close to the trading price of the common stock at the time the agreement was entered into.

The terms of the preferred stock give the holders greater downside protection than the purchase of common stock.

Another example of an equity investment is the April private placement by Endorex Corporation of common stock and warrants with institutional investors, raising a total of \$8.6 million in new capital. The private placement consisted of 1.81 million newly issued common shares priced at \$4.725 per share plus warrants to purchase approximately 455,000 shares of common stock. The warrants are exercisable at \$5.91 per common share and expire in April, 2005.

The use of warrants in biotech equity investments is not unusual, particularly with companies that have gone public, such as Endorex, or are expected to go public within a reasonable period. From the standpoint of the company, the exercise of the warrants by the holders would provide additional equity capital. From the standpoint of the investor, the warrants provide an additional equity kicker if the company does well and provides the investor more appreciation potential for the risks that the investor is taking.

In some cases, institutional investors have provided equity lines of credit to a biotech company. Such an arrangement, if feasible, provides the biotech company with flexibility as to the amount and timing of equity infusions. This also may be beneficial to provide a backstop to other potential sources of funding.

For example, in June, Acqua Wellington North American Equities Fund, Ltd. entered into an agreement to provide an equity financing facility covering the sale of up to \$75 million of the common stock of ARIAD Pharmaceuticals, Inc. over an eighteen month period. These shares may be sold to the investor, at ARIAD's discretion, at a small discount to market at the time of sale. ARIAD controls the amount and financing of stock sold with the total amount of investment dependent on ARIAD's stock price. In addition, ARIAD sold the institutional investor 680,851 shares of its registered common stock in a direct equity placement at \$11.75 per share.

In July, a similar \$29 million equity financing facility was provided by the same institutional investor to Genelabs Technologies, Inc. An initial investment of \$4 million was made to purchase 1,000,000 shares of Genelab stock at \$4 per share. Additional shares may be sold to the investor over the next 18 months, at Genelabs' discretion, at prices determined pursuant to the agreement.

Angel Investors

In addition to equity capital provided by institutional investors, equity capital may be provided by sophisticated individuals or angel investors, as they are sometimes known. With the aid of the internet, more and varied sources of angel investors are beginning to emerge. At an early stage of development of a company, angel investors may be one of the best possibilities.

Angel investors vary in their degree of sophistication. Compliance with the securities laws is critically important in such financing since SEC Regulation D imposes various requirements for investors to qualify as accredited investors. A disadvantage of angel investors is that it may be more complicated to deal with them if there are a sizable number of them or they invest at different times.

Different series of preferred stock make the corporate structure more complex. On the other hand, if venture capital firms rather than individual angel investors are involved early, greater management assistance and support may be provided. This is generally very useful to an early stage company.

Conclusion

The Human Genome Project and other scientific breakthroughs in drug discovery offer great promise to the biotech industry. These developments present the promise of speedier and more certain development of promising drugs. They offer the prospect that drug development will become less risky and, thus, favorably alter the risk-reward ratio from an investor perspective.

These developments, however, will not alter the fundamental dilemmas which many emerging biotechs face. What drug prospects should be targeted for development? Should one or more collaborators be sought, when and at what terms? Better terms can generally be achieved at later stages of development. Will venture capitalists or angel investors find the biotech's story compelling? Will an IPO be in the future? When will the company be profitable? Considering all these dilemmas and problems that the industry has already made great progress in solving, one has good reason to be hopeful for the future financing of emerging biotech companies.

ABOUT SIDLEY & AUSTIN

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Chicago, our largest office, was opened in 1866. Approximately 425 lawyers work in our Chicago office where we represent clients in a broad range of transactional, litigation and regulatory matters. Lawyers in our Chicago, Dallas, Los Angeles, New York and Washington, D.C. offices have been in the forefront of advising clients engaged in the biotechnology and pharmaceutical industry as well as health care providers and professional organizations. For example, we provide general representation to Baxter International and have advised Bristol-Myers Squibb, The Samuel Roberts Noble Foundation, Baylor Medical Research Foundation, Oklahoma Medical Research Foundation, Cytoclonal Pharmaceuticals and Fountain Pharmaceuticals in licensing, patent and other intellectual property areas.

Sidley & Austin has represented investors interested in technology companies and has conducted analysis of the technology and patents owned by target companies. In addition, our firm has conducted analysis of licenses and ownership rights by assignment of the technology and provided counseling on whether licenses from others may be necessary in order for the prospective business plan to be carried out without infringing the patent rights of others.

Our Biotechnology Pharmaceutical & Biochemical Patent Prosecution Group is headed by Eugenia S. Hansen, a partner in our Dallas office who specializes in patent litigation and prosecution of biochemical, chemical and microbiological patents. Scott Bass, a partner in our Washington, D.C. office, is recognized as a leading authority on FDA enforcement practices, pharmaceutical advertising and drug promotion.

Pharmacia Corporation has retained Sidley & Austin to defend the company and two other named defendants --- Monsanto Company and G.D. Searle Co. – in a significant patent infringement case brought by the University of Rochester involving the blockbuster arthritis drug Celebrix.® Sidley & Austin has been retained to represent an online healthcare information and commercial exchange to be launched by Johnson & Johnson, GE Medical Systems, Baxter International, Inc., Abbott Laboratories and Medtronic Inc. Oncology.com, a leading healthcare Website, has retained Sidley & Austin to provide advice on mergers and acquisitions, finance and general corporate matters, trademark litigation and registration, employment matters, commercial litigation and health regulatory issues. Cordis Corporation, a subsidiary of Johnson & Johnson, retained Sidley & Austin in a patent infringement suit filed by a competing manufacturer of coronary stents.

For additional information about our health care practice, see www.sidley.com.

ABOUT RICHARD G. CLEMENS

Richard G. Clemens is a partner in the Chicago office of Sidley & Austin. He joined the firm in 1965 and became a partner in 1973. His principal areas of practice include public and private securities offerings, venture capital financing, initial public offerings, mergers, acquisitions, sales of businesses, joint ventures, corporate structuring and a broad range of counseling in corporate and securities law matters.

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