during the year. Although we do not expect any firm legislative solutions, drug prices and drug-company margins will continue to be targeted. Those companies focusing on life-or-death indications, those focusing on markets for which there are no alternatives, those that make extra efforts to demonstrate that additional drug costs actually save far greater costs in terms of hospital stays or ancillary procedures, and those that use more efficient manufacturing processes to keep drug prices down will likely do well.

Recommendations

•Let the buyer beware. The euphoria of 1991 has generated many expectations for 1992. Yet, with such a large and diverse biotechnology group, sweeping generalizations can be dangerous. Not all products will work, not every product will capture 100 percent of the market, and not every company will survive. Even for those that will be ultimately successful there could be near-term disappointments.

•Own a diversified portfolio. One way to hedge the risks associated with biotechnology investing is to own a diversified portfolio of companies, including companies with different maturities, companies focusing on different markets, and companies developing different technologies. Smith Barney's method of stratifying the biotechnology sector into three tiers is well suited to this strategy because it separates the group by maturity and risk. First-tier companies are the most mature, least risky investments, with either a product on the market or one awaiting approval. Third-tier companies are on average one to two years away from beginning human clinical trials and, thus represent the highest-risk investments, yet they are also the ones with the highest upsides. With respect to diversifying according to target markets, one should focus on: markets that are large enough to afford competition; markets where the technology is leading to brand new therapeutic approaches to disease; and markets where we desperately need new therapies. This would include: cardiovascular diseases, infectious diseases, inflammatory diseases, and neurological disorders. ///

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VALUATION DROPS $550 MILLION

FDA PANEL NIXES ETHYOL

WASHINGTON, D.C.—Marketing approval of Ethyol, which U.S. Bioscience (W. Conshohocken, PA) is developing to protect patients against the toxic effects of cancer treatment, should be withheld pending additional clinical trials. So decided the Oncologic Drugs Advisory Committee of the U.S. Food and Drug Administration (FDA, Bethesda, MD) in late January. The share price of U.S. Bioscience took an immediate beating, dropping more than $12 to about $17 with over 5 million shares changing hands on the first day of trading after the FDA meeting. The plunge knocked $550 million off the company's valuation.

Just before the advisory meeting, Marion Merrell Dow (Kansas City, MO), a major shareholder of U.S. Bioscience, began selling its 17-percent stake in the company. U.S. Healthcare (Blue Bell, PA), which founded U.S. Bioscience, subsequently announced plans to distribute its 17-percent stake in the firm as a dividend to its stock holders. The move by Marion Merrell Dow, which it claimed was not tied to Ethyol's review at FDA, led to a suspension in trading of shares on the American Stock Exchange.

Company remains confident

Despite these gyrations, U.S. Bioscience officials remain confident in the company's future. "This product is one of ten, with four in Phase III trials," says Robert Kriebel, the firm's senior vice president for finance. "We'll make every effort to make sure Ethyol is approved promptly. The company will seek a prompt working session with FDA and will continue fully cooperating with the agency. There is optimism and excitement around the product from a medical perspective, but additional data are needed to establish safety and efficacy."

Ethyol has indeed raised high expectations for its use as an adjunct to chemotherapy and radiotherapy on cancer patients. Such treatments commonly cause a wide range of toxic side effects, including disruptions of bone-marrow functions, neurotoxicity, and kidney damage. In animal tests, Ethyol apparently protects against many of those side effects, even when widely used chemotherapeutic agents are administered at high doses.

Thus far, however, Ethyol clinical tests have not yielded such dramatic results. In light of several clinical trials, the company has revised its new drug application (NDA) for Ethyol several times since submitting it last September, gradually "downgrading" efficacy claims, according to FDA's Gerald Sokol. Thus, the company moved away from an initially broad designation, restricting Ethyol's NDA application for use with conventional doses of only two drugs, cisplatin and cyclophosphamide, and limiting its scope to only several of the originally claimed toxicities.

Working within that narrower framework, Sokol expressed strong doubts about the statistical significance of the clinical findings for purported protection against neurotoxicity, hearing loss, and decreases in normal blood cell levels (an indication of hematologic toxicity) during chemotherapy. Although the clinical studies are "supportive" of some of the claims, they are only "borderline adequate," he says.

Committee is more generous

Members of the advisory committee were more generous in their assessment of Ethyol's performance in clinical trials, but stopped short of saying it is ready for licensing. "It appears the product protects against neutropenia with standard doses of cisplatin," says committee member Waun Ki Hong of M.D. Anderson Cancer Center (Houston, TX). "I can't recommend it for high doses or for other toxicities; the data are less clear."

Daniel Ihde of the National Cancer Institute (Bethesda, MD), the other primary reviewer of the application, agreed with Hong. The preclinical data are "extremely promising," making the drug a potential "alternative to the colony stimulating factors for countering myelosuppression," Ihde says. However, he calls the clinical data "very preliminary, with the neurotoxicity data being very confusing." The committee also could not firmly conclude whether Ethyol had any effect protecting tumors against the antitumor drugs used in the clinical trials. Although such effects appear unlikely, they would be detrimental.

"The committee vote on hematologic toxicity in favor of Ethyol was a very positive statement," says U.S. Bioscience's Barbara Scheffler. "We are requesting a meeting with FDA within the next several weeks. If FDA feels that those data are strong, we'll work with them on that indication, and we will continue to accumulate data in other clinical studies." —**Jeffrey L. Fox**