Box 1 FDA setbacks

Emphasizing the ability of regulators to torpedo a company's best laid marketing plans, in May 2006 Dyax's DX-88 program was reassigned from the Center for Biologics Evaluation and Research division to the Center for Drug Evaluation and Research (CDER) as part of FDA's "Plan for Consolidation." The upshot of this change of oversight was that CDER asked Dyax for an extra small placebo-controlled trial to supplement data from Dyax's phase 3 trial (EDEMA3). And conducting the new trial, EDEMA4, took Dyax out of the pole position for US approval.

Jerini sits in that position now, though the FDA cancelled the Pulmonary-Allergy Drugs Advisory Committee panel meeting scheduled for February 20. Although some view the terminated meeting as the removal of one more obstacle to approval (it cheered investors at the time), others are whispering it means FDA has already decided to ask for more data. Jerini's filing contains a pooled analysis from two phase 3 trials, one of which missed a primary endpoint of median onset of symptom relief compared with tranexamic acid.

Most recently, in late January, Lev received a complete response letter from the FDA requesting additional information on chemistry, manufacturing and controls for Cinryze, its human C1 esterase inhibitor, as well as further analyses of existing trial data. Although it did not request any new trials, the response letter still delayed potential approval, prompting investors to trim 33% off the company's stock. The product is set to go before the FDA's Blood Products Advisory Committee on May 2.

a week, driving the cost per patient to $250,000 annually, so insurance carriers would probably begin pushing cheaper acute treatment as preferred.

Three of the five drugs vying for approval aim to address HAE by supplementing the individual's endogenous C1-INH with a functional version of the human protein (**Table 1**). Lev and CSL Behring are both developing a purified plasma protein version, whereas Pharming has developed a recombinant C1-INH produced in transgenic rabbits.

The other two companies—Dyax and Jerini—are developing proteins aimed at dampening the inflammatory cascade. Dyax's recombinant protein DX-88 (ecallantide) inhibits kallikrein, an enzyme that liberates bradykinin, which causes fluid to leak from blood vessels into the tissues. Jerini's Icatibant attacks one step further down the line; it's a competitive bradykinin B2 receptor antagonist. All five drugs are deemed comparably efficacious (though there have been no head-to-head clinical trials to help determine this), which means it's difficult to predict which product will have the competitive edge.

One differentiating factor is delivery. DX-88 is just 60 amino acids long and can be administered subcutaneously, as can Icatibant, but the C1-INH products must be given by intravenous (i.v.) infusion. Jerini CEO Jens Schneider-Mergener says that, based on feedback from physicians, his firm sees "a big advantage" in the subcutaneous route over the i.v. one. Bret Holley, analyst with New York-based Oppenheimer, which covers Lev but receives no compensation from the firm, tends to agree, venturing that i.v. infusion can be seen as a "killing handicap." But Holley also argues that attacks are foreseen by people with HAE, much like migraines, allowing them time to seek a physician for an infusion, and he points out that Dyax's DX-88 needs to be refrigerated anyway. So far, Jerini boasts the only subcutaneous administration that does not need to be refrigerated—the company has data showing sterility exceeding 18 months at room temperature. Dyax is working on a room-temperature formulation.

The final uncertainty is orphan drug status—all have it except CSL Behring. The FDA makes the final decision here, but it is assumed DX-88 and Icatibant will be viewed as independent molecules and thus each drug's orphan drug status will not block another from entering the market. Pharming's Samir says that his company's C1 inhibitor should stand alone, as it is a recombinant molecule. Whether the plasma-derived C1 inhibitors will be viewed as the same molecule isn't clear.

There is general consensus, however, on what's at risk: a $500 million-a-year market. The small patient population and unmet medical need means the community will tolerate a "Genzyme-like pricing," Holley says, referring to the empire Cambridge, Massachusetts-based Genzyme has built by developing niche products for rare diseases. The HAE market, Holley believes, will be shaped in much the same way as the one formed around Genzyme's products.

"Patients will be treated on a physician-by-physician basis," he says, so the first step is to "get a therapy out there." Only then, as patients choose the product that works best for them, physicians become comfortable and usage is bent to individual needs, will there be hints as to how these products will settle out.

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IN brief

Tear-free onions

Ever since the Flavr Savr debacle in which buyers roundly rejected a tomato modified to extend shelf-life, few have braved the consumer market. Perhaps the tearless onion developed by researchers in New Zealand will fare better. In collaboration with industrial partners House Foods Corporation, of Osaka, Japan, scientists at Crop & Food Research in Christchurch, New Zealand, have produced a tearless onion by silencing the gene that produces the lachrymatory factor synthase–the enzyme that makes people cry over the chopping board. The modified onions look and taste like the ordinary variety but, so far, have not induced a single case of tearing when crushed. Crop & Food Research is considering commercialization, though that is at least ten years away. "We have always thought that where there are clear benefits to the consumer, there will be better acceptance of this style of biotechnology,' says Crop and Food Research scientist Colin Eady. Public acceptance of genetically modified foods could also be boosted by using RNAi technology to eliminate food allergens. An allergy-free peanut variety has been developed by researchers at Alabama A & M University, who have used RNAi technology to lower the levels of a peanut allergen, Ara h2. "There is wide potential for this technology," says Eady, who predicts it will be applied to other crops in the future. *SA*

Thumbs up for Avastin

The US Food and Drug Administration (FDA) has cleared Genentech to use its top-selling drug, Avastin (bevacizumab), for breast cancer therapy. The decision is good news not only for the South San Francisco-based biotech, but also for the overall sector, as some observers believe it lowers the bar for cancer-drug approvals. The approval, made on February 22, was surprising since an FDA advisory committee had voted five-to-four against registration last December. At issue is how the agency judges the effectiveness of cancer treatments. Traditionally, FDA approved only cancer drugs that extended a patient's lifespan, but other measures of a drug's effectiveness have been offered by makers —one of the most controversial being progression-free survival (PFS). Genentech's studies showed that Avastin in chemotherapy halted tumor growth in breast cancer patients for twice as long as those who received chemotherapy only, though survival did not improve. The FDA gave Avastin accelerated approval, allowing the drug to reach the market but being subject to further study. The FDA's director of the division of oncologic drugs, Richard Pazdur, says that the agency sympathizes with the view that PFS "may be a direct clinical benefit," though he adds that the FDA still favors overall survival as an approval standard. FDA approval of Avastin is a big deal for Genentech. It should add hundreds of millions of dollars in annual sales to Avastin, which is already approved for colorectal cancer and lung cancer and racked up $2.3 billion last year. *BJS*