IN brief

FDA crackdown on Genzyme

Genzyme's Allston Landing Facility in Massachusetts, one of the world's largest cell culture manufacturing plants, has become the focus of an enhanced enforcement action in what is perhaps a sign of an increasingly tough stance at the US Food and Drug Administration (FDA) on manufacturing standards. The action, announced in March, has led to a draft consent decree from FDA that requires Genzyme to pay a $175 million "up-front disgorgement of past profits," the company said. If the Allston plant continues to miss deadlines for domestic and exported products, the draft also calls for a 18.5% disgorgement of revenues from products produced and distributed from the plant, and it could include heavy fines ($15,000 per day per violation) if overall cGMP compliance is not met in coming years. The 185,000-square-foot Allston facility produces Genzyme's therapeutic enzymes for rare genetic diseases—products that bring in more than one-third of Genzyme's $4.5 billion in annual revenues. A February 2009 warning letter from the FDA and several '483 citations' (formal notices to a manufacturer of a violation) have documented problems at the plant that impact product quality and show a lack of written procedures, training, system maintenance and environmental testing. Genzyme, based in Cambridge, Massachusetts, has responded to the latest FDA action by bringing in The Quantic Group, a Livingston, New Jersey–based quality consulting firm, and moving its fill and finish operations to Hospira, a contract service company in Lake Forest, Illinois. In February, it also hired Scott Canute, formerly of Indianapolis, Indiana–based Eli Lilly, as president of global manufacturing and corporate operations. This followed the recruitment in January of Ron Branning—formerly with Gilead Sciences of Foster City, California—as senior vice president of global product quality. Until two years ago, FDA personnel had regularly inspected the Genzyme facility and had no complaints. It was only after a new inspector began to tour the facility that things changed. "It was like night and day," says a person familiar with the situation, who spoke to *Nature Biotechnology* on condition of anonymity. "Initially, the company didn't know what to think or how to respond." Genzyme's response took too long and fell short of the FDA's expectations. The FDA's move toward greater oversight and more stringent adherence to GMP is possibly the result of criticisms levied following the heparin contamination debacle (*Nat. Biotechnol.* **26**, 589, 2008) and other food and drug safety problems. In the 2010 budget, the agency received an increase of more than a half-billion dollars, up to $3.2 billion, with an emphasis on improving product safety. *Keith L Carson*

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Box 1 Weighing up the bids

Although Biogen Idec may technically be viewed as the underbidder on the Facet deal, the jury is out on whether its valuation of Facet's assets was more accurate than that of Abbott's. "Time will tell whether Biogen Idec was offering too little or too much at $17.50 [per share]," says Eric Schmidt, biotech analyst at Cowen and Company in New York. "Many of us are surprised that Abbott bid so much more than Biogen Idec because they [Biogen] have the inside track here," he says. "If I were an outside observer, I would certainly trust Biogen Idec's view of this asset because they know this drug better, and they know this market better." Schmidt dismisses any suggestions that Biogen management was discouraged from bidding any higher because of the attentions of investor Carl Icahn, who has, up until recently, been pushing for a sale of the Cambridge, Mass.–based company or its division into two separate firms, focused on neurology and oncology, respectively.

Instead, Schmidt interprets the Biogen's decision not to raise its bid beyond its final offer as simply an example of management maintaining its financial discipline. "I think it's kind of refreshing," he says. Conversely, Bret Holley, biotech analyst at Oppenheimer & Company in New York, believe Biogen might have been taking another approach—trying to pull off an acquisition at a heavily discounted price. "I think Biogen was trying to steal Facet on the cheap because of its cash position."

Schmidt is also unconcerned about the current safety problems besetting ocrelizumab, a next-generation successor to Rituxan (rituximab), which Biogen Idec is co-developing with Roche, of Basel, Switzerland. On March 8, the two firms announced a clinical hold on phase 3 trials of the anti-CD20 antibody in rheumatoid arthritis and lupus erythematosus, following the observation of serious and, in some cases, fatal infections in patients. A phase 2 trial in multiple sclerosis is ongoing, however. "No one cares about ocrelizumab," says Schmidt. Although the drug has the potential to extend or replace Biogen Idec's Rituxan franchise—which it also shares with Roche—its share of the profits would be lower. Termination of ocrelizumab's development is unlikely to have major negative consequences, therefore. "It could [even] be a positive," says Schmidt.

Biogen Idec's biggest issue lies elsewhere. "The principal concern and really the principal variable is Tysabri, and what they can do in the face of mounting PML [progressive multifocal leukoencephalopathy] cases," says Holley, adding that he is sceptical of the value of the viral assay that Biogen Idec and its partner Elan of Dublin, are promoting to reduce the risk of patients on Tysabri developing PML. *CS*

eye condition uveitis, T-cell leukemia, human T-cell lymphotropic virus (HTLV)-1 associated myelopathy/tropical spastic paraparesis, asthma and chronic immune thrombocytopenia. But its biggest commercial potential lies in MS, says Thomas Waldmann of the National Cancer Institute, in Bethesda, Maryland. Back in 1981, Waldman produced a murine predecessor to Zenapax, anti-Tac, and along with his National Institute of Health (NIH; Bethesda, Maryland) colleagues has built up a substantial body of clinical evidence on Zenapax in multiple indications (*J. Clin. Immunol.* **27**, 1–18, 2007).

In MS, the antibody was initially thought to selectively stop patients' activated T cells, as they express high levels of the CD25 receptor subunit. Resting T cells, in contrast, rarely express CD25. Antibody binding to CD25 prevents the subsequent recruitment of the beta (CD122) and gamma (CD132) subunits of IL-2R, which are necessary for IL-2–mediated signal transduction and further T-cell activation and proliferation. However, one important line of evidence, originally put forward by Waldmann's NIH colleague Bibiana Bielekova, suggests that the efficacy signals seen in MS patients treated with Zenapax are not due to the direct suppression of an abnormal T-cell response (which is generally considered to be the main pathological feature of the condition). Instead, administration of the antibody appears to result in an expansion of immunoregulatory $CD56^{bright}$ natural killer (NK) cells, which then suppress the activated T-cell population (*Proc. Natl. Acad. Sci. USA* **103**, 5941–5946, 2006). The precise details of how CD25 inhibition stimulates $CD56^{bright}$ NK cell growth, however, is not clear. "The issue of how daclizumab works is a continuing story," Waldmann says.

Market expectations surrounding the drug appear modest, notwithstanding recently reported efficacy data from a phase 2 trial in which the drug was administered in combination with interferon-beta (interferon-β; *Lancet Neurol.* **9**, 381–390, 2010). Patients given high-dose Zenapax plus interferon-β developed 72% fewer new lesions than those on interferon alone. "It's fairly easy to get good efficacy data in autoimmune disease," says Eric Schmidt, biotech analyst at Cowen and Company in New