IN brief

FDA balks at Myozyme scale-up

Myozyme raises awkward questions for would-be biogenerics manufacturers.

Genzyme ran into a snag in April when the US Food and Drug Administration (FDA) rejected its application to produce Myozyme (alglucosidase alfa, rhGAA) in its 2,000–liter-scale facility under the same approval authorization given for its 160-liter-scale plant. The FDA says the carbohydrate structure of the products manufactured at each scale differs and thus the 2,000-liter product requires a new biologic license application. Myozyme was approved in April 2006 for the treatment of Pompe disease, an autosomal recessive metabolic condition occurring in about one in 40,000 births. The condition, which arises from a mutation in the gene for α-glucosidase, leads to a buildup of glycogen in skeletal muscle, and its effects on heart, liver and the nervous tissue can be fatal. Genzyme, which has preferentially targeted child sufferers, is now maxed out on production, and to meet the growing demand from older patients, including those who would be finishing clinical trials, it has invested $53 million in facilities in Allston Landing, Massachusetts and Geel, Belgium. Although Genzyme still expects to receive approval of its 2,000-liter version of Myozyme by the end of this year and to begin commercial sales in the first quarter of 2009, the FDA's position has sent shudders through the generics industry. If the FDA is not satisfied that a brand-name company, with all its proprietary knowledge about biomanufacture, can replicate its own product, what chance do generics companies have of manufacturing biogenerics? The situation highlights "the difficulty a competitor would have coming into the market with a biosimilar," says senior biotech analyst Aaron Reames of Wachovia Capital Markets, in Charlotte, North Carolina. "It will be exploited by big brand-name pharmas and biopharmas," he adds. "They can change a molecule slightly, call it a new drug and evergreen the product with a new term of exclusivity." The FDA has said repeatedly that it does not have the authority to prescribe a definitive regulatory pathway for biogenerics, and big pharma has been happy to postpone the day when Congress would give FDA the framework and mandate. It would be ironic indeed if brand-name manufacturers find themselves unable to consistently get FDA's approval for scale-up projects.

—George Mack

Table 1 Selected HIV/AIDS vaccines in development

Producer	Product	Status	Vaccine
Aventis (Paris)/ Vaxgen (South San Francisco, California)	RV 144	Phase 3	Prime: canarypox viral vector with HIV *env* and *gag-pol* Boost: Env protein (gp120 subunits)
Vical (San Diego, California), GenVec (Gaithersburg, Maryland)	HVTN 204	Phase 2	Prime: DNA vaccine with *gag*, *pol*, *nef*, *env* Boost: Adenovirus vector with *gag*, *pol*, *env*
Aventis (Paris)	ANRS VAC 18	Phase 2	Five lipopeptides with CTL epitopes from *gag*, *nef*, *pol*
Vecura (Karolinska University Hospital, Sweden)	HIVIS 03	Phase 1/2	Prime: HIVIS DNA with *env*, *gag*, *rev*, RT Boost: MVA-CMDR with *env*, *gag*, *pol*
Pharmexa-Epimmune (San Diego, California)/Bavarian Nordic (Kvistgård, Denmark)	HVTN 067	Phase 1/2	DNA vaccine EP-1233 and recombinant MVA-HIV polytope vaccine MVA-mBN32, separately and in combined prime-boost regimen
Therion (Cambridge, Massachusetts)	IAVI D001	Phase 1	Modified vaccinia Ankara (MVA) viral vector with *env*, *gag*, *tat-rev*, *nef-RT*
Geovax (Atlanta, Georgia)	HVTN 065	Phase 1	Prime: DNA plasmid with *gag*, *pro*, *RT*, *env*, *tat*, *rev*, *vpu*, *env* Boost: MVA vector with *gag*, *pol*, *env*

very enthusiastically when they see a clear path toward getting a vaccine," he says.

NIAID's recent decision to shift the balance of funding back to discovery research is consistent with a growing trend in the field. Noncommercial funding for preclinical research on a preventative HIV vaccine grew 34% between 2005 and 2006, greatly outpacing the allocation of funds to clinical trials, which increased only 6% according to the HIV Vaccines and Microbicides Resource Tracking Working Group. IAVI, which originally dedicated nearly all funding to product development and clinical trials, has gradually shifted its portfolio toward a 50-50 split with discovery research over the past several years. "What became apparent really, really early on was that the first generation of candidate vaccine—right through to the Merck vaccine—was less than optimal," says Wayne Koff, IAVI's vice president for research and development.

Meanwhile, industry players stand behind their individual projects. Sanofi Pasteur, the vaccine arm of Paris-based Sanofi-Aventis, is awaiting the completion of a phase 3 trial of the RV 144 vaccine being carried out in Thailand. RV 144 combines two vaccines dispensed as a 'prime-boost' regime. The 'priming' vaccine is Aventis' vCP1521, ALVAC-HIV, a canarypox virus vector expressing the HIV *env*, *gag* and *pro* genes, and this is followed by a 'booster' vaccine—containing subunits of the HIV surface glycoprotein gp120—produced by VaxGen of South San Francisco, California. The trial passed an interim safety review last summer and should be completed by mid-2009. RV 144 rarely comes up in post-Merck discussions, however, because many in the community view it as a probable flop (*Science* **303**, 316, 2004). That pessimism is grounded in the knowledge that the two components of the vaccine failed when tested independently, but Sanofi Pasteur has extended its investment in HIV vaccine research and launched a project to develop vaccines that generate broadly neutralizing antibodies, and another project that targets T cells. "Vaccine development is an iterative process," says James Tartaglia, vice president of research and development, who doesn't think the Merck trial will discourage industry, though he admits that the past failures have made researchers more critical. "Certainly the way the field is now, people want to see more preclinical data and clinical proof of concept" before advancing a trial, he says. Fauci agrees: "We are going to look with a greater degree of scrutiny at the advancement of a trial from one stage to another." That could raise the bar for the small companies that populate the phase 1 trial list. Geovax, for example, is awaiting final approval to advance its product to phase 2.

For now, everyone is monitoring Merck, as it focuses much of its efforts on understanding what went wrong with its phase 2 trial. "We understand that a lot of people are looking at us and what we're going to do because they view our actions as a signal for the industry overall," says Feinberg.

That rings true. "If we have another trial like the Merck trial, then you can say goodbye to the HIV vaccine," says Rafick-Pierre Sékaly of the University of Montreal in Canada.

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