A "VALUABLE CATEGORY"

IMMUNOCONJUGATE LOGJAM ENDS

NEW YORK—The gridlocked approval process for monoclonal-antibody immunoconjugates is finally showing signs of movement. Last November, the U.S. Food and Drug Administration's (FDA, Bethesda, MD) Biological Response Modifiers Advisory Committee made public its view of acceptable clinical endpoints for monoclonal diagnostic imaging agents. At the same meeting, the panel also made its first recommendation for approval of a diagnostic immunoconjugate, Centocor's (Malvern, PA) Myoscint product for detecting myocardial necrosis. Centocor had submitted its product licensing application (PLA) in March of 1988.

Then in January the same FDA panel unanimously recommended approval for Cytogen's (Princeton, NJ) OncoScint diagnostic imaging agents for subgroups of patients with colorectal and ovarian cancer. Those recommendations follow the panel's earlier recommendation that FDA approve Xoma's (Berkeley, CA) Orthozyme-CD5+ therapeutic immunoconjugate for treatment of graft-versus-host disease. For immunoconjugates, "it's the end of a long logjam at FDA," says Jonathan Frank, a securities analyst with Swiss Bank (New York).

With positive recommendations in both areas, diagnostic and therapeutic, the committee has "sent a big signal to the industry that immunoconjugates are a valuable category," says James Taylor, vice president and chief regulatory officer of ImmunoGen (Cambridge, MA), a company that is developing therapeutic immunoconjugates.

Murine monoclonal okayed

In recommending OncoScint approval, Taylor notes, the FDA panel has made the leap of okaying a murine monoclonal in the diagnostic area. Centocor's Myoscint, for its part, is based on an antibody fragment. Taken together, he says, the various recommendations address another concern: Do immunoconjugates work before falling apart? "That's been put to rest," Taylor says.

But human anti-mouse antibody (HAMA) reactions do remain a serious concern with Cytogen's product. The FDA advisory committee noted HAMA reactions in 40 percent of the patients in the company's clinical trials. In recommending OncoScint, the FDA panel noted that multiple use of murine monoclonals in patients who test positive for HAMA is probably limited.

OncoScint CR103, Cytogen's colorectal imaging agent, and OncoScint OV 103, its ovarian cancer diagnostic agent, are both indium-labeled immunoconjugate products in a product line that includes other cancer imaging and therapy products carrying either indium, technetium, or yttrium. The company has also developed a technetium imaging agent for deep vein thrombosis.

Development of most of these products will continue at Cytogen. To develop immunoconjugates for imaging and treatment of prostate and bladder cancer, however, Cytogen is spinning off a new unit, CytoRad. Because of the CytoRad offering, Cytogen executives were unable to comment on the advisory committee's recommendations.

Both Cytogen and Centocor have signed marketing deals for the products recommended by the FDA panel, all three of which have already been approved for sale in some European countries. In Europe, Cytogen will sell through EuroCetus, while BASF's Knoll (Ludwigshafen, Germany) will handle the U.S. market for Cytogen. For its part, Centocor is selling directly in Europe but will sell through Johnson & Johnson's McNeil Pharmaceutical (Ft. Washington, PA) in the U.S.

Immunomedics and NeoRx

At least two other companies with diagnostic immunoconjugates are also waiting to hear from FDA. Immunomedics (Warren, NJ) filed a PLA in April for its colorectal cancer imaging agent, a technetium-labeled antibody-fragment product. "Using the fragment, we don't have the HAMA problem," a spokesman says. Although the company says it has no clear indication of when the agency might review the product, "we use for planning two years from the filing date," says the spokesman. Immunomedics has five imaging products in clinical trials as well as two therapeutic immunoconjugates.

NeoRx (Seattle, WA) has had the longest wait at FDA. The company submitted a PLA at the end of 1987 for a technetium-labeled murine monoclonal for melanoma imaging that has yet to be approved. "That was the first time FDA had dealt with a diagnostic imaging product," says Paul Abrams, NeoRx's president and chief executive officer. At the time, he says, there was "a great deal of uncertainty as to what would be required to get an agent like this approved," and the agency "went through it piece by piece."

In the meantime, NeoRx filed a PLA in December 1989 for OncoTrac, a murine monoclonal for imaging of small cell lung cancer. FDA has completed its review of clinical data for that product. "It seems to have passed clinical muster, but we don't have that in writing," Abrams says, adding, "We've been pleased with the progress at FDA on this product." FDA, however, has requested a new trial with a "very, very small number of patients," Abrams says, because NeoRx is working with a new manufacturer for its monoclonal. Although NeoRx won't have to file a new PLA, its new manufacturer will have to file one, as well as an establishment licensing application. NeoRx's former manufacturer, Invitron, was purchased by Centocor last year.

Immunoconjugate development isn't confined to the U.S. In Canada, Biomira (Edmonton, Alta) has developed a line of four different technetium-labeled murine monoclonals intended for cancer imaging. Phase I and II trials of the products are underway in Europe, with trials slated to begin in Canada as well. Biomira has also developed chimeric antibodies, which it will test following trials of its murine products, and it plans to follow up with a therapeutic line of yttrium-labeled immunoconjugates.

A $700-million market

Immunoconjugate products are intended to confirm and further the diagnosis of cancer and are not intended for primary diagnosis. As a followup diagnostic tool, they will have to compete against "anybody who images cancer," says Michael Martorelli, a securities analyst with Janney, Montgomery Scott (Philadelphia, PA). "It's not like erythropoietin, where there's no other therapy." Cancer imaging is currently a $700-million market in the U.S.

Martorelli calls Cytogen's sales projection of $150-180 million within four years of introduction "reasonable."

At Alex Brown & Sons (New York), analyst Neal Bradsher estimates that the market for radiolabeled monoclonals could reach $300-400 million worldwide by the end of the decade.

But some analysts are less impressed with the market potential for immunoconjugate diagnostics. "Looking at that field, I always thought it was a big bust," says Joseph Edelman of Prudential Bache (New York). "It's going to be smaller than people think."

—**Mimi Bluestone**