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FDA PANEL OKAYS TWO FACTOR VIIIs

WASHINGTON, D.C.—The Blood Products Advisory Committee (BPAC) recommended last month to the U.S. Food and Drug Administration (FDA, Bethesda, MD) that it approve two similar versions of recombinant Factor VIII (FVIII). However, because some hemophiliac patients developed an inhibitory antibody response to the blood-clotting glycoproteins during clinical trials, members of the committee hedged their endorsement of the two products, urging agency officials to mandate further clinical studies of this potentially detrimental immune response. Moreover, because of discrepancies in currently available clinical data, the committee's recommendations slightly favored one of the two company products.

The committee was asked to consider two nearly identical blood-clotting glycoproteins—one sponsored by Miles (Elkhart, IN) and initially developed by Genentech (So. San Francisco, CA) and the other sponsored by Baxter International (Deerfield, IL) and initially developed by the Genetics Institute (Cambridge, MA). The BPAC stance was clearer cut for the Miles product, which was recommended for use by all individuals with hemophilia A.

BPAC committee members did not give a full endorsement to the Baxter version of FVIII. Reservations about its use centered on a group of recipients known quaintly as PUPs—previously untreated patients, usually infants. In clinical trials for both versions of FVIII, some PUPs who were injected with the recombinant products developed an antibody response to them. The response apparently did not interfere with the ability of the products to stop bleeding episodes. However, special efforts were undertaken for several patients to reduce inhibitor levels, or, in rare instances, treatments were halted.

Ironically, because the Miles-sponsored clinical trials are further along, use of its product was associated with a greater number of cases where recipients developed measurable blood levels of inhibitors. With those results in mind, however, the committee concluded that clinical trials are still at too early a stage to judge whether the Baxter version of FVIII can be safely used on such patients. "This Baxter presentation has made us worry less because we have less information," says BPAC member Barbara Alving of the Walter Reed Army Institute of Research (Washington, DC). "We haven't seen anything that says it's dangerous, and we shouldn't hold it up. It isn't so simple."

After considerable debate, the committee chose not to recommend immediate licensure of the Baxter product for treating PUPs—advice that FDA officials say is useful but "not binding." The committee also recommended that clinical trials be continued on both the Baxter and Miles products, with attention to the development of inhibitor antibodies. FDA officials appeared to welcome this bit of advice. "To casually dismiss the inhibitors would be treating the problem superficially," says William Fricke, chief of FDA's Laboratory of Hemostasis and Thrombosis. "It's not a trivial problem, but we also don't want to overdramatize it."

The events leading to licensure for FVIII have enjoyed more than a few dramatic moments, some from technical developments and others because of courtroom or other commercial maneuverings. For instance, patent rights for FVIII have been tied up in a contentious lawsuit involving several parties besides those that came before FDA last month (*Bio/Technology* 9:327, April, '91). The issue of Orphan drug status also looms as an issue, although Miles, Baxter, and allied companies say they have agreed not to exclude one another from the U.S. market for the drug.

On the technical side, challenges have been formidable. The FVIII glycoprotein is gargantuan, containing more than 2,300 amino acids, almost two dozen cysteine residues, and 25 potential glycosylation sites. Efforts to bring it into clinical use represent a "pioneering project," says James Pennington, director of research at Miles. "This is the largest and most complex protein yet cloned for clinical use."

To achieve appropriate additions of sugars to the molecule, both sets of companies make the glycoprotein in mammalian cells—a practice that still leads to slight differences when the products are compared to FVIII purified from human plasma. Miles uses baby hamster kidney cells in continuous culture, whereas Baxter uses Chinese hamster ovary cells in a batch-refeed process. The Baxter production cells also contain the gene for the human von Willebrand protein, which forms a stabilizing complex with FVIII but then is removed during purification.

Currently licensed versions of FVIII are derived from human blood plasma. Contamination of the blood supply and fear of its consequences provided much of the impetus for developing a recombinant product. Hemophilia A, in which the factor is deficient or missing, is the most common inherited blood-clotting disorder. It is a sex-linked trait, affecting about one per 10,000 males. Although recent improvements in detection and purification techniques have helped clean up plasma-derived preparations of blood-clotting factors, more than 60 percent of individuals with hemophilia have been infected by blood-borne agents, including the hepatitis and HIV viruses, because of their reliance on such products.

Not surprisingly, the National Hemophilia Foundation (New York) recently issued a strong endorsement of recombinant FVIII. "Plasma will never be completely free of viruses," says Craig Kessler, associate director of the foundation, who repeated its recommendations to the FDA advisory committee. "We believe recombinat FVIII is the answer to viral contamination." David Goldman, a New Jersey lawyer and hemophiliac who is a member of the foundation, also urged the committee to recommend licensure of the recombinant products. "Hemophiliacs have been the canary in the mine shaft of our nation's blood supply," he says. "I want my physicians, my grandchildren, and me to be given access to all the options."

The advisory-committee meeting produced at least one other dramatic moment in recombinant FVIII's road to licensure. Citing potential conflict of interest, FDA officials required BPAC member Gilbert White II of the University of North Carolina School of Medicine (Chapel Hill) to withdraw from the deliberations over the two products. White, who participated in FVIII clinical trials, quietly fidgeted during the day-long deliberations before reading a protest statement at the close of the deliberations. "I protest my exclusion from these discussions. I have no conflict of interest," he says. "If I can't use my expertise, what good am I to the committee?" **—Jeffrey L. Fox**