BUSINESS AND REGULATORY NEWS

rFactor VIII deficit questioned

There is a serious worldwide shortage of recombinant factor VIII, a critical blood-clotting protein that hemophilic patients use to prevent and control their bleeds, according to the National Hemophilia Foundation (NHF; New York); although recombinant factor VIII has been on the market since 1993, manufacturing capacity is falling short of demand. At the same time, leaders of the hemophilia community charge Bayer AG (Leverkusen, Germany) of using the shortage to drive fearful patients into its new, controversial direct purchase program.

About 35,000 people in North America and Europe have hemophilia A, an X-chromosome-linked bleeding disorder caused by a defective factor VIII gene. Beginning in the 1960s, factor VIII concentrate, which is prepared from multiple plasma donations, was used to stop bleeds. However, during the 1970s and '80s, more than 40% of hemophilia patients contracted HIV from concentrate and cryoprecipitate, and the majority of adults that injected concentrate now harbor hepatitis C. Since its introduction, recombinant factor VIII, which is produced in fermentation tanks from hamster ovary or kidney cells, has become the treatment of choice because the chance of viral contamination is virtually nonexistent. "Eighty percent of the US has transitioned [from concentrate] to recombinant product," says NHF president-elect Mark Skinner.

Although recombinant factor VIII periodically is in short supply, the current shortage is especially severe. According to an August NHF survey of hemophilia treatment centers, half were having difficulty obtaining the drug and the NHF expects the situation to worsen. "Many companies have cut back on orders and have stopped accepting new customers," reads a recent NHF medical advisory. "At the present rate, the companies stated they could not keep up with existing demand much longer."

One factor is the rapid adoption of recombinant factor VIII by the hemophilia population, many of whom are starting to take factor VIII prophylactically to prevent bleeds. "Worldwide demand is growing tremendously….Production has just not kept pace," says Skinner.

In addition, only three companies account for all recombinant factor VIII made in the US, and there have been delays in the construction and approval of new production facilities. Baxter (Deerfield, IL), which owns over half the market share, recently doubled the capacity of its Thousand Oaks, CA manufacturing facility, and is awaiting FDA clearance to ship product. It is also constructing a third production site. Genetics Institute (Cambidge, MA), which received US marketing approval for its recombinant factor VIII product, Refacto, in March, has postponed product launch until 2001 due to production problems and high demand in Europe. It is building a production plant in St. Louis, MO. Meanwhile, Bayer is awaiting FDA approval for a new, 200-liter fermenter (to replace one half the size) in its Berkeley, CA facility. "We've moved forward as quickly as science would allow, and keeping safety and efficacy in mind," says Doug Bell, Bayer's director of global public policy and communications

Recombinant proteins were expected to be a virtually unlimited source of blood products and a permanent solution to chronic shortages. Although the fast growth in demand appears to have caught all the companies by surprise, they admit no responsibility for the shortfall. "I don't think it's a failure of strategic planning, I think it's a matter of timing," says Margaret Shubny, director of corporate communications for Baxter. "If the planets had been aligned a little bit differently, I think we might not find ourselves in the same situation."

Moreover, Bayer claims recombinant factor VIII, an enormous, 265 kDa protein, is exceptionally hard to make compared to other recombinant proteins. "The folding, the processing, and the glycosylation—there are 26 separate glycosylation steps—all are challenging," says Mike Kamarck, senior vice president of operations for Bayer's biological products unit. He says Bayer is only able to recover 1/1000th the level of the typical antibody or cytokine expressed in mammalian cells because the size of factor VIII makes it exquisitely sensitive to denaturing by proteases from ruptured cells. As a result, Bayer continually removes protein and adds new medium to the fermenter to avoid denaturing—an expensive and inefficient process prone to glitches.

However, some in the hemophilia community suspect other factors are at work besides technical problems and lack of foresight. Specifically, they wonder about price manipulation, especially as treatment with recombinant factor VIII can cost well over $100,000 a year per patient. Some suspect stockpiling by manufacturers or distributors to keep prices high—something the companies strongly deny. "I would not want to directly make that allegation," says Skinner. "I would say there's a lot of information that we don't have…There are some who believe that there are supplies of product that aren't being released to the market. If that were the case, it would be tragic."

In addition, Bayer is under fire from the NHF for plans to sell its "next-generation" recombinant factor VIII product, Kogenate FS, directly to consumers who sign up to its Bayer Direct program, bypassing normal distribution channels. Kogenate FS, unlike Kogenate (the previous version), does not use human albumin to stabilize the protein during purification or formulation, thus further reducing the theoretical risk of viral contamination.

While Bayer says it wants to ensure the drug gets into the hands of patients and doesn't sit in a distribution chain, the hemophilia community is angry that the limited supply of Kogenate FS will only be available to enrollees of Bayer Direct, and that patients could be "cherry-picked" based on the reimbursement generosity of their insurance plans (something Bayer denies). "There's a concern that Bayer will be using the [current factor VIII] shortage as a way of getting people to sign up for the program. Coercion is the word," says Skinner. "Forced into a sole vendor at a higher price, just to get the next generation product." The NHF finds Bayer Direct so objectionable that it no longer accepts donations from Bayer. (In 1999 Bayer gave $185,000 to the Foundation.) Although Bayer points out that Kogenate FS will also be available through Aventis Behring (King of Prussia, PA) as Helixate, NHF believes supplies will be very limited. Lou Aledort, a prominent hemophilia clinical investigator at Mt. Sinai Medical Center in New York, says Bayer Direct "is a ploy to directly sell and make more money," adding, "What they're doing is probably legal, but totally immoral and unethical."

These accusations coincide with US state and federal investigations of more than 20 drug makers for drug-pricing schemes. Prosecutors reportedly obtained Bayer AG (Germany) documents outlining the need to quote higher average wholesale prices to doctors and providers as a way to get them to choose Bayer products over those of competitors. (The higher the price, the higher the reimbursement to the provider). Kogenate was one of the drugs cited. Bayer settled with the government at the end of September for $14 million, without admitting wrong doing.

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