

1987-2002



EPO Saga to Augur Regulatory Change?

by Gordon Kelley

Turning points in pharmaceutical regulation have often hinged on tragedy. The Pure Food and Drugs Act of 1906 resulted from publication of Upton Sinclair's *The Jungle*, an exposé of Chicago meatpacking plants. The 1938 Food, Drug, and Cosmetic Act has been attributed to the sulfanilamide tragedy of 1937, in which "Dr. Massengill's Elixir Sulfanilamid," an anti-infective, caused more than 100 deaths and prompted public outcry. Our industry may look back in a few years on the widely reported news that recombinant erythropoietin (EPO) has been linked to pure red cell aplasia (PRCA) as a similar defining moment for biopharmaceuticals.

Johnson & Johnson's (J&J) EPO Epnex is the best-selling genetically engineered drug ever, with \$3.4 billion in sales last year. Over the past 12 years, Epnex and other EPOs have been given to more than three million kidney disease patients worldwide.

Early in 1999, the first few reports linking EPO and aplasia began trickling in to J&J and Roche from doctors and hospitals. By November 2001, J&J sent a notice to healthcare providers that 40 cases of confirmed or suspected PRCA had been reported in patients treated with Epnex. *The Wall Street Journal* ran a short article on Epnex in December 2001 that treated the issue as a minor setback. But in February 2002, French scientist Nicole Casadevall published an article in *The New England Journal of Medicine* entitled "Pure Red-Cell Aplasia and Antierythropoietin Antibodies in Patients Treated With Recombinant Erythropoietin." Shortly after, FDA released a tally of EPO-related PRCA cases in response to Casadevall's report and newspapers around the globe began to pick up on the story. By July, there was a flurry of articles in most major media on both the aplasia cases and J&J's plummeting stock prices. The number of suspected PRCA cases hit 160 by September. That's when J&J published an extensive report on their ongoing investigation into the problems with Epnex.

A definitive cause of the PRCA cases has yet to be determined. One factor may be a change in how EPO is administered: The rise in PRCA cases is coincident with a shift from intravenous to subcutaneous administration. It is also coincident with J&J's reformulation of Epnex: Albumin, a serum derived from human blood, was replaced with a chemical stabilizer following European authorities' concerns about the risks from the human form of "mad cow" disease. Although other companies manufacture EPOs, most EPO-related PRCA cases have been linked to Epnex. Amgen and Roche, J&J's main EPO competitors, say the problems are with

Epnex and not with EPO drugs in general. J&J disagrees. "We believe there is evidence of a class phenomenon," their report says. It outlines steps they believe EPO manufacturers should take, including retrospective searches for all PRCA cases and open public reporting of all suspected cases.

Amgen and Roche clearly want to distance themselves from Epnex. *The Los Angeles Times* reported that at a recent meeting of the American Society of Nephrologists, Amgen accused J&J of stacking a panel discussion on PRCA. J&J sponsored the session, and three of the five panelists were J&J specialists. During the session, J&J drug safety director John Knight was asked which drug he personally would use of the three EPOs on the market. Knight's answer, which drew murmurs from the audience, was that he would leave the decision up to his physician. J&J scientist Linda Joliff presented data showing that mice developed antibodies when given a drug similar to Amgen's EPO Aranesp. Amgen's product development vice president Tony Gringeri called that experiment "bad science" and questioned why J&J didn't test Aranesp itself.

Biopharmaceutical companies need to be aware not only that EPOs are on the public's radar, but that regulatory change affecting all biopharmaceuticals may be afoot. In July, Europe's Committee for Proprietary Medicinal Products (CPMP) published a "Note for Guidance on Comparability of Medicinal Products Containing Biotechnology-derived Proteins as Drug Substances." The CPMP is particularly concerned with predicting immunogenicity and may require periodic postmarketing monitoring of antibodies for at least a year. Although the document does not mention EPOs, the timing of the CPMP's interest in comparability and immunogenicity issues regarding biopharmaceuticals is unlikely to be entirely coincidental. The guidance specifically addresses changes in manufacturing processes and products claimed to be similar to others already marketed.

Gail Sofer, director of regulatory services for BioReliance, a contract service organization that tests, develops, and manufactures biologics, feels that the EPO problems may delay introduction of generic biologics, particularly for diseases that require chronic administration of biotech drugs. What seems likely in the short term is increased emphasis on the approval process, including clinical trial design.

But long term, regulatory change is likely to come in two waves. The first wave of documents is currently under development and consists of general immunogenicity guidance for biopharmaceuticals. However, because drugs can affect people differently, the second wave will be tailored to address specific classes of drugs in specific patient sectors.

The EPO tragedies — and their media coverage — have intensified the already growing concern about immunogenicity and comparability in biotech drugs. Biopharmaceutical manufacturers would be wise to show their commitment to the public's health by addressing those concerns in their development processes before they are required to do so. **BPI**



Gordon Kelley is
BioPharm International's
assistant editor,
541.984.5243,
fax 541.984.5250.
gkelley@advanstar.com.