European Union-mandated formulation change—intended to increase the safety of Johnson & Johnson’s Eprex (injected erythropoietin)—appears to have caused a 10- to 20-fold increase in the incidence of a rare but serious complication among recipients of the drug. Recent reports describe the origin of the adverse reactions and the detective work that found and fixed the source of the problem.

In 1998, the EU directed Johnson & Johnson (J&J, New Brunswick, NJ, www.jnj.com) to stop using human serum albumin (HSA) as a stabilizer in Eprex, the recombinant erythropoietin (EPO, a red blood cell growth factor) sold outside the United States. Polysorbate 80 replaced HSA in the formulation.

Over the next six years, dialysis centers, first in France and then world-wide, began to notice an increased rate of a serious anemia—pure red-cell aplasia (PRCA)—among patients receiving Eprex. The initial reports included 13 patients (11 receiving Eprex and two receiving NeoRecormon, an erythropoietin beta marketed by Roche). Further investigation—reported in the 30 September New England Journal of Medicine1 by a team of researchers from the Jesse Brown Veterans Affairs Medical Center (Chicago, IL), Northwestern University (Chicago, IL), Inserm (Paris), and several other institutions in the US and Western Europe—turned up 191 cases of PRCA with onset between January 1998 and April 2004: 175 associated with Eprex, 11 with NeoRecormon, and 5 with Epogen, the HSA-containing erythropoietin marketed by Amgen (Thousand Oaks, CA). Incidence of drug-associated PRCA was similar from region to region, so most of the cases appeared in the largest markets: France, Canada, the UK, and Spain. The researchers estimated exposure-adjusted incidence of PRCA per 100,000 patient years as follows: Eprex without HSA, 18; Eprex with HSA, 6; NeoRecormon, 1; Epogen, 0.2.

J&J initiated a 100-person crash program to locate and correct the cause of the problem. At October’s Biotech 2004 meeting in Philadelphia, Thomas S. Templeman, director of biotechnology development at J&J’s Global Biologics Supply Chain, LLC, reported the results of that effort. The polysorbate 80, added to replace the human serum albumin, interacted with the uncoated rubber stoppers long used in single-use Eprex syringes. The stoppers leached small amounts of plasticizers into the drug solution. These leachates acted as an adjuvant, stimulating a very small percentage of patients to mount a strong immunoglobulin G response to the recombinant human erythropoietin. These antibodies also attacked the body’s own erythropoietin, effectively halting almost all signals for the bone marrow to make red blood cells. The result was PRCA, a severe anemia requiring transfusions.

In 2002, J&J switched to PTFE-coated rubber stoppers, which have halted the leaching problem and greatly reduced immune response. The company now cites its experience as a strong argument for requiring new clinical trials whenever a new process begins to produce even tried-and-true biologicals—as would be the case with producers of follow-on biologicals.

–Douglas McCormick