PRCA associated with SC administration of EPREX® in patients with CKD, beyond the very rare risk for all ESA's, escalating actions were taken to limit the use of SC EPREX®. This ultimately led to contraindication of the SC route of administration in the European Union (EU) and Switzerland in December of 2002.

Johnson & Johnson subsequently demonstrated through extensive clinical, non-clinical and technical investigations that the increased risk for PRCA was associated with one specific EPREX® presentation—prefilled syringes with uncoated rubber stoppers that contained the polysorbate 80 EPREX® formulation (Boven et al., 2005; Ryan et al., 2006). Further investigation showed that uncoated rubber stoppers, when exposed to polysorbate 80, released organic compounds (leachates) into the EPREX® formulation and that these leachates were the probable product-specific cause for the increase in EPO antibody-mediated PRCA (Sharma et al., 2004). The polysorbate 80 EPREX® formulation in prefilled syringes with uncoated stoppers was removed from the market. FluroTec®-coated stoppers are now used in all prefilled syringes containing the polysorbate 80 EPREX® formulation to prevent leachates from entering the formulation. Current data show that with the use of the FluroTec®-coated stopper product for SC administration in CKD the incidence rate of EPO antibody-mediated PRCA is similar to that for the HSA-containing EPREX® formulation, which has a long-standing and well-characterized safety profile.

The current cumulative reporting rate of EPO antibody-mediated PRCA, unadjusted for mixed exposure, for the polysorbate 80 EPREX® formulation in prefilled syringes with coated stoppers is almost 10-fold lower than the cumulative reporting rate of EPO antibody-mediated PRCA previously observed with the polysorbate 80 EPREX® formulation in prefilled syringes with uncoated stoppers. Moreover, the reporting rate of new cases with SC exposure to the EPREX® prefilled syringes with coated stopper continues to be very rare.

Based upon these data, SC administration of EPREX® use in patients with CKD for whom intravenous access is not readily available has recently been reapproved in major countries, including Australia, Canada, EU and Switzerland, and is reintroduced in major markets worldwide. As part of Johnson & Johnson's commitment to our patients ensuring the safety of our products, a risk management plan has been developed that includes proactive pharmacovigilance and awareness, and education of the medical community.

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Predictability of the preclinical development of CAMPATH-1H for man

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CAMPATH 1-H, now registered under the name Alemtuzumab, was the first humanised monoclonal antibody to be administered to man. This IgG1 antibody recognises CD52, an abundant glycolipid anchored protein, which is predominantly expressed on cells of the immune system in man. Because of the ability of this antibody to causes the prolonged depletion of peripheral blood lymphocytes, it has been licenced for the treatment of B cell lymphoma. In addition, because of its immunosuppressive properties CAMPATH 1-H has been used to prevent allograft rejection and the treatment of autoimmune diseases including multiple sclerosis and rheumatoid arthritis.

The development of this antibody, which commenced over 20 years ago, was challenging because of the absence of a good animal model to access drug safety. Although drug cross reactivity was observed in the cynomolgus monkey, toxicology studies in this species were complicated by the fact that antibody affinity of the antibody in this species was 16-fold less than that observed in man and the existence of a polymorphism causing receptor expression on the erythrocytes of some of the animals which was is not observed in man. Although lymphocyte depletion is observed in monkeys, especially at high doses, the extent of lymphocyte depletion and shallow recovery subsequently seen clinically was not predicted, due in all probability to the difference in antibody affinity between the species. Similarly the

rapid appearance of plasma cytokines shortly after the first dose in man was not observed in the monkeys, again presumably due to the difference in receptor affinity.

In a small clinical trial undertaken using a DDX, a significant number of multiple sclerosis patients who had been treated with CAMPTH 1-H on a named patient basis, developed the autoimmune Graves disease. Even though it might have been expected that such profound depletion of lymphocyte numbers might lead to perturbations in the balance of the immune system risking autoimmune disease, this could not have been predicted from preclinical studies due to the restricted species cross reactivity of the antibody, the absence of good primate models of autoimmune disease and the low incidence of Graves disease seen clinically.

With the increasing acceptance by the regulators of transgenic models and surrogate drugs as alternative approaches for the safety assessment of biopharmaceutical drugs, a different approach for the development of CAMPATH 1-H might have been taken today. However even with 20 years of hindsight it seems unlikely that any preclinical model would have revealed all the safety issues associated with this drug, which continues to show promise for the treatment of diseases such as multiple sclerosis.

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Herceptin and CD40L case examples

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A recent review of repeat dose, and particularly chronic toxicology studies in support of approved protein therapeutics revealed that in general, the toxicology studies predicted common clinical adverse effects (Clarke et al., submitted for publication). This was contingent on the studies using a relevant pharmacologically active species or an appropriate surrogate. The repeat dose toxicology studies were poorly predictive of low incidence clinical adverse effects as well as effects not assessed in traditional study designs such as infections (e.g. natalizumab and rituxan), psychological effects and drug–drug interactions among others. Both Herceptin and anti-CD40L are IgG1 monoclonal antibodies for which repeat dose toxicology studies were conducted and where those studies either predicted (anti-CD40L antibody) or did not predict (Herceptin) a clinical finding of significant concern.

Herceptin (trastuzumab) is a humanized monoclonal antibody against the HER2 protein that has substantially reduced the risk of recurrence and early death in women with HER2-positivebreast cancer. No toxicologically significant findings were noted in registration enabling studies that were conducted in cynomolgus monkeys for up to 6 months duration. However, beginning in late phase clinical trials, cardiotoxicity was noted in a percentage of treated patients. Congestive heart failure occurs in 1–4% of treated patients and 10% of patients have a decrease in cardiac function. The incidence of cardiotoxicity increases with exposure to anthracyclines. Mechanistic studies have suggested a “two hit” hypothesis involving loss of ErbB2 pathways and a role for ErbB2 in mycocyte survival and the impact of anthracyclines which may explain the increased incidence in combination with this agent (Chien, 2006). The lack of predicitivity of this finding with a non-human primate toxicology study is not surprising given the statistical power to detect a 4% event, and the absence of combination with an anthracycline. Specialized studies involving mutant erbB2 mice were used to elucidate this toxicity preclinically, after the clinical finding.

Anti-CD40L antibody is a humanized monoclonal antibody that inhibits the interaction of CD40 with its ligand, both are members of the TNF family. In a clinical trial with this antibody, thromboembolic events were noted in 8/100 patients and the trial was halted. Events occurred from 1 to 59 days after treatment. Toxicology studies in cynomolgus monkeys of up to 3 months did not identify any similar events. However, in a 6-month rhesus study pulmonary thrombosis and vasculopathic changes were noted in 14/24 animals at the highest dose. Subsequent studies clarified that this toxicity was evident only in rhesus, but not cynomolgus monkeys suggesting an exquisite species specificity. This example highlights that an apparent lack of predictivity of a toxicology study may be due to model selection and is a perennial challenge facing toxicologists working with biopharmaceuticals.

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