The extensive clinical use of therapeutic proteins (TPs) in various inflammatory diseases has drawn increased attention to assessing the potential risk of therapeutic protein drug-drug interactions (TP-DDI). Disease-drug interactions have been found under some inflammatory situations where significantly elevated proinflammatory cytokines down-regulate the expression and activity of specific drug-metabolizing cytochrome P450 (CYP) enzymes, leading to the decreased clearance of co-administered small molecule drugs that are substrates of the affected CYP enzymes. Treatment with TPs that modulate proinflammatory cytokines may thus result in a “normalization” of CYP activities and a subsequent increase in the clearance of concomitant small molecule drugs. This phenomenon is referred to as disease related TP-DDI. At present, in vitro and preclinical systems have shown limited value in predicting a clinically relevant effect of cytokine-mediated TP-DDI, and clinical evidence is preferred to inform the potential risk for a TP-DDI. A recent IQ Consortium/ FDA TP-DDI workshop (San Diego, 2012) recommended a four-step risk assessment approach including: 1) the disease effect on cytokine levels and CYP expression; 2) TP mechanism of action and its potential impact on cytokine-mediated DDI; 3) DDI liability of the small molecule concurrent medications; and 4) the in vivo clinical studies in assessing TP-DDI risk for cytokines or cytokine modulators on CYP enzymes. This presentation will discuss the recent evolving thinking on the strategy of TP-DDI assessment and review case studies to provide examples of clinical TP-DDI evaluations and the impact of these clinical TP-DDI study outcomes on the product label.