# LOGISTIC CONSIDERATIONS IN STUDY DESIGN FOR BIOLOGIC DRUG–DRUG INTERACTION ASSESSMENTS

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## 8.1 INTRODUCTION

Evaluation of the drug interaction potential of biologics or therapeutic proteins (TPs) with other TPs or small molecule drugs is an area of emerging research. Different from the pharmacokinetics (PK) drug–drug interaction (DDI) among small molecule drugs in which there are clear mechanisms associated with metabolic pathways mediated by cytochrome P450 (CYP450) enzymes or transporters, there is limited understanding of the mechanistic basis for TP–drug interactions to date. Therefore the design of such interaction studies is challenging in many cases. As described in the literature,[1–3] the common TP elimination mechanisms may include filtration (e.g., into urine), secretion (e.g., into the bile), biotransformation (e.g., catabolism), and target-mediated disposition. Renal elimination, which is one of the primary pathways of small-molecule drugs, is relatively unimportant for large molecules, such as immunoglobin G (IgGs) with a molecular weight of $\sim$150 kDa that prevents efficient filtration through the glomerulus. Secretion into the bile is an important pathway of elimination of IgA antibodies, but this route is not a significant contributor to the elimination of IgG antibodies. The majority of IgG elimination occurs via intracellular catabolism, following fluid-phase or receptor-mediated endocytosis. TP elimination mechanisms distinguish themselves from the hepatic metabolism that is the dominant mechanism for small molecules. In addition, as TPs may be viewed as foreign substances by the body, immune responses that lead to the generation of endogenous antibodies against the TPs may be triggered, which can increase the clearance of TPs.

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