PHARMACOKINETIC AND PHARMACODYNAMIC-BASED DRUG INTERACTIONS FOR THERAPEUTIC PROTEINS

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2.1 INTRODUCTION

Therapeutic proteins (TPs) are protein products manufactured for pharmaceutical use. They include monoclonal antibodies (mAbs), antigen-binding fragments, antibody–drug conjugates (ADCs), cytokines, enzymes, growth factors, and miscellaneous proteins (e.g., fusion proteins and recombinant proteins). The development of therapeutic biologics, including TPs, is increasingly important in the pharmaceutical industry.[1] To achieve greater clinical benefits, TPs are often being combined with other TPs and small molecule drugs (SMDs). Whether drug interactions (DIs) in combination therapy result in an undesirable impact on efficacy and safety needs evaluation. To date, for the observed therapeutic protein–drug interactions (TP-DIs) that affect the exposure of TPs, only a modest change in exposure is observed and no impact on safety or efficacy has been documented, suggesting a limited clinical relevance.[2] This might be because most TPs have a relatively large therapeutic range compared to the majority of traditional SMDs. However, TP-DIs that affect the exposure of some drugs with a narrow therapeutic range (NTR), such as some SMDs and ADCs, may have an impact on efficacy and safety. The TP-DIs that result in enhanced toxicity due to undesirable pharmacodynamic (PD) interactions without a direct impact on exposures may also be clinically relevant. Thus the evaluation of TP-DIs is an important and evolving topic for the development of TPs in combination with other drugs.

This chapter reviews the major absorption, distribution, metabolism, and excretion (ADME) pathways of TPs, summarizes the potential mechanisms of

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