DRUG INTERACTIONS FOR THERAPEUTIC PROTEINS: A JOURNEY JUST BEGINNING

HONGHUI ZHOU and BERND MEIBOHM

1.1 INTRODUCTION

Over the last three decades, therapeutic proteins, in particular, antibody-based biotherapeutics, have played an increasingly important role in pharmacotherapy, and in some therapeutic areas, such as immune-mediated inflammatory diseases (IMIDs) and oncology, therapeutic proteins have fundamentally changed the therapeutic paradigm. Therapeutic proteins have also presented enormous commercial potential. For example, the top 10 antibody-based biotherapeutics accounted for around $50 billion of worldwide sales in 2011.[1] The majority of these are either in IMID (adalimumab, etanercept, infliximab, rituximab, natalizumab, omalizumab) or in oncology (rituximab, bevacizumab, trastuzumab, cetuximab) therapeutic areas. Hundreds of investigational antibody-based and other protein therapeutics are currently under development at different stages, spanning discovery to phase III clinical investigations.

Owing to an expected increase in the coadministration of biotherapeutic agents with established pharmacotherapy regimens, there is an increasing likelihood for the occurrence of clinically relevant drug interactions. Therapeutic proteins, however, have long been perceived to have a very low propensity for drug–drug interactions because they are eliminated via catabolic routes, either nonspecific pathways or target-mediated pathways, that are independent from the elimination pathways of small molecules, which are usually eliminated by noncatabolic pathways such as hepatic metabolism via cytochrome P450 (CYP), renal excretion, and biliary excretion. Though it has been known for decades that some cytokines such as interferons, tumor necrosis factor α (TNF-α), and

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