

CHAPTER 1

DRUG INTERACTIONS FOR THERAPEUTIC PROTEINS: A JOURNEY JUST BEGINNING

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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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interleukin 6 (IL-6) can down-regulate CYPs,² very few drug–drug interactions had been reported for biotherapeutics until 2007, when two review articles containing examples of drug interactions involving therapeutic proteins were published.^{3,4} The majority of reported drug interactions associated with therapeutic proteins seem to be indirect; however, a mechanistic understanding for many of the observed interactions is still lacking.^{5–7}

1.2 SCIENTIFIC/REGULATORY LANDSCAPE OF THERAPEUTIC PROTEIN–DRUG INTERACTIONS

To help assess the common practice of evaluating therapeutic protein–drug interactions across the biotech/pharma industry and to shed some light on how and when a sensible therapeutic protein–drug interaction assessment strategy should be incorporated into therapeutic protein drug development, a survey was conducted within the Biotechnology Industry Organization (BIO) member companies in 2010. It is not surprising that a majority of the responder companies did not have internal strategies for evaluating therapeutic protein–drug interactions at the time of the survey. Nevertheless, the most favored approach employed to address potential drug–drug interactions of therapeutic proteins at that time was a tailored and integrated (i.e., case-by-case) strategy that addressed the possibility of the therapeutic protein acting as either an initiator (perpetrator) or target (victim) of the interaction. Despite the fact that many of the companies responding to the survey reported drug–drug interactions involving therapeutic proteins, the majority of the clinical therapeutic protein–drug interactions studied did not warrant dose adjustment. In other words, most of the observed clinical therapeutic protein–drug interactions did not reach a clinically significant level. Routine *in vitro* screening and preclinical drug–drug interaction studies were not widely used for the evaluation of therapeutic proteins. For clinical development, dedicated clinical pharmacology drug–drug interaction studies were the most frequently used methodology, followed by population pharmacokinetics-based and clinical cocktail approaches.⁸

The BIO survey results indicated that there was a pressing need to have a science-driven and risk-based assessment strategy for therapeutic protein–drug interactions (TP-DIs). A closer collaboration among scientists from the biotech/pharma industry, regulatory agencies, and academia appeared to be essential in reaching that goal. As a result, a TP-DI steering committee from industry, the FDA, and academia was founded in 2009 to address this challenge. The initial scope of this committee was focused only on pharmacokinetics (PK) and metabolism-based drug–drug interactions for the major classes of therapeutic proteins, including monoclonal antibodies, fusion proteins, cytokines (excluding antibody–drug conjugates). The committee intended to investigate the potential for therapeutic proteins to interact, either as initiators or targets, with drugs that are metabolized via CYP enzyme pathways. Two major focus areas the committee concentrated on were (1) to critically assess standard *in vitro* screening techniques and methodologies

(e.g., for cytokine-related drug–drug and drug–disease interactions) and (2) to provide guidance for study designs with consideration of specific disease area (e.g., oncology) issues and timings.

Several scientific knowledge gaps were identified from a 2010 American Association of Pharmaceutical Scientists (AAPS) workshop on Strategies to Address Therapeutic Protein–Drug Interactions during Clinical Development.⁹ One gap was associated with the relevance of *in vitro* systems to assess potential therapeutic protein–drug interactions, and another gap was a lack of best practices for using population PK-based approaches to assess potential therapeutic protein–drug interactions. The steering committee also identified similar gaps and consequently formed two working groups to specifically tackle them.

During the same time period, scientists from the FDA published two important review articles on TP-DI, but these were mostly from a regulatory perspective.^{10,11} In 2012, a draft of a new drug–drug interaction guidance document was made available by the FDA for public comments.¹² That draft included a dedicated section on therapeutic protein–drug interaction to address specifically the newly emerging area of drug–drug interactions with therapeutic proteins.

The Workshop on Recent Advances in the Investigation of Therapeutic Protein Drug–Drug Interactions: Preclinical and Clinical Approaches was held on June 4–5, 2012. The workshop, co-sponsored by the FDA Office of Clinical Pharmacology and the Drug Metabolism and Clinical Pharmacology Leadership Group of the IQ Consortium, was intended to facilitate a better understanding of the current science, investigative approaches, knowledge gaps, and regulatory requirements related to the evaluation of therapeutic protein–drug interactions. The workshop also provided an opportunity to discuss the current views from the two (*in vitro* and population PK approaches) therapeutic protein–drug interaction working groups. The proceedings from this workshop are being compiled with the intent of issuing white papers in these subject areas. It is anticipated that the recommendations from both white papers will soon provide pharmaceutical scientists with sensible and scientifically sound best practices and an assessment framework for using *in vitro* and population PK-based approaches for evaluating therapeutic protein–drug interactions.

Our current understanding of the mechanisms of many therapeutic protein–drug interactions is still in its infancy. Much basic research needs to be conducted to verify several existing hypotheses related to therapeutic protein–drug interactions. Continued close collaborations among fellow scientists in industry, academia, and regulatory agencies will be vital to generate more plausible mechanistic hypotheses and collectively address the many challenges in this area. Through these collaborative efforts, the knowledgebase on therapeutic protein–drug interactions will likely be largely expanded in the near future, and it is hoped and anticipated that over the next decade a similar level of mechanistic understanding and systemic assessment methodology will be achieved and developed for drug interactions with protein therapeutics as it has been established in the last two decades for small molecule drugs. The journey toward that goal has just begun.

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