DRUG INTERACTIONS OF CYTOKINES AND ANTICYTOKINE THERAPEUTIC PROTEINS

J. GREG SLATTER, LARRY C. WIENKERS, and LESLIE J. DICKMANN

If it were not for the great variability among individuals, medicine might as well be a science and not an art.

Sir William Osler, 1892[1]

13.1 INTRODUCTION

The suppression of drug metabolism by proinflammatory cytokines and the relief of suppression by disease treatment are a current issue in the development of drug interaction labels for new biologic products. This topic has been the subject of a number of recent reviews that capture the history of related work as well as current regulatory and pharmaceutical industry thinking.[1–12] This chapter provides an overview of some recent data developed in industrially relevant preclinical models and outlines the pros and cons of these models with respect to the generation of actionable data–that is data that are robust enough to preclude the need for a clinical drug–disease interaction study, and/or a class label for a new cytokine or anticytokine therapeutic agent.

Because small molecule clearance mechanisms are suppressed by inflammation, proinflammatory cytokine treatment and/or active inflammatory disease may afford patient populations with impaired drug clearance.[6] As such, the effective treatment of inflammatory disease would be expected to normalize or "desuppress" drug clearance. When clearance is mediated by cytochromes P450 (CYP), suppression works in the same direction as CYP inhibition, leading to increased systemic exposure. In contrast, CYP desuppression increases CYP activity (similar to CYP induction), leading to lower drug concentrations. The caveat with desuppression is that the upper limit of the effect is the clearance

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