STATISTICAL CONSIDERATIONS IN ASSESSING DRUG–DRUG INTERACTIONS FOR THERAPEUTIC BIOLOGICS

CHUANPU HU and HONGHUI ZHOU

9.1 INTRODUCTION

Therapeutic biologics have different mechanisms of action from small molecules, usually making drug–drug interactions (DDIs) less likely, although this may depend on the specific circumstances. That is, the *a priori* expectation of specific DDIs is different with therapeutic biologics. In addition, therapeutic biologics usually have long half-lives, preventing the effective use of the usual crossover trials to assess drug–drug interactions. These issues influence the design and analysis of DDI assessments. Furthermore, population pharmacokinetics modeling has been used increasingly in drug development and has promising potential in DDI assessment. This chapter discusses the associated statistical issues, particularly to ensure appropriate power and type I error.

DDIs can adversely affect the safety or efficacy of a treatment. Therefore a new drug's DDI potential needs to be fully assessed. Namely, the objective is to obtain estimates of AUC and $C_{\max}$ ratios of interest and their corresponding 90% confidence intervals (CIs). The 90% CIs falling within a predetermined interval–for example, (0.80, 1.25)–indicates the absence of a pharmacokinetic DDI. Dedicated DDI study designs may be the conventional 2×2 crossover, single sequence crossover, or parallel designs. A specifically selected sequence of *in vitro* and *in vivo* studies can generally define a new experimental drug's clinically relevant DDI potential. The FDA has published a draft guidance on the design and analysis of DDI studies.[1] While AUC assessments are the mainstay of DDI studies, $C_{\max}$ is not assessed in all situations.

Pharmaceutical Sciences Encyclopedia: Drug Discovery, Development, and Manufacturing,
Edited by Shayne C. Gad