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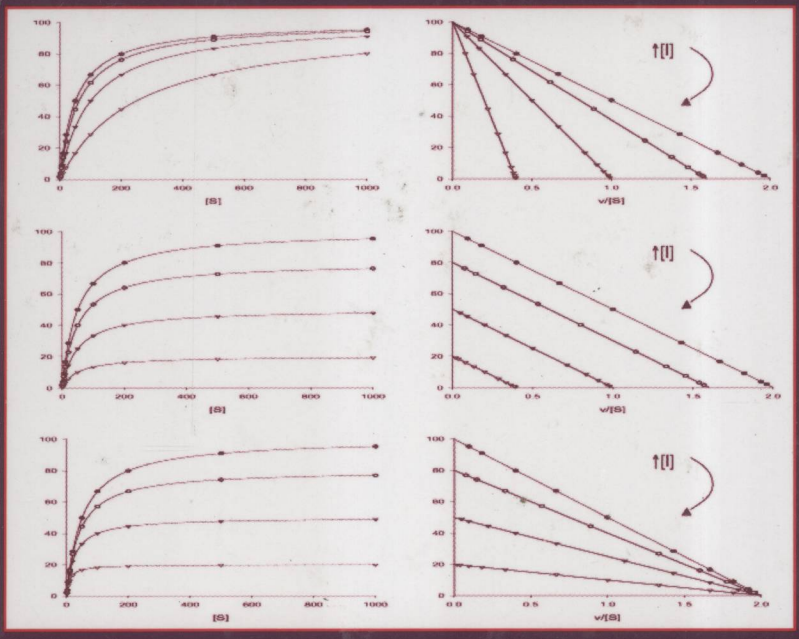

Edited by

Albert P. Li

DRUG–DRUG INTERACTIONS IN PHARMACEUTICAL DEVELOPMENT

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DRUG–DRUG INTERACTIONS IN PHARMACEUTICAL DEVELOPMENT

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PREFACE

Exposure of a patient simultaneously to multiple pharmaceuticals is a highly probable and nearly unavoidable phenomenon due the use of multiple drugs to treat a certain disease (e.g., cancer, HIV infection), or the treatment of multiple diseases in a single patient. Adverse interactions among coadministered drugs have led to fatalities and subsequent withdrawal of marketed drugs. Mechanistic understanding of the drug–drug interaction (DDI) potential is an active area of scientific research. Evaluation of the DDI potential of drug candidates represents an important and necessary activity in drug development.

In decades past, significant progress has been made in the scientific understanding of adverse drug–drug interactions. It is generally agreed that DDI potential is best evaluated via a mechanistic approach, by defining the interaction of the drugs in question with the biochemical pathways that are responsible for drug absorption, distribution, metabolism, and elimination. An especially important advancement is the application of human-based *in vitro* experimental systems for the preclinical evaluation of DDI potential. This approach has received overall scientific consensus and is generally accepted by international regulatory agencies, including the U.S. Food and Drug Administration.

In this book, the major scientific concepts and preclinical experimental approaches for the evaluation of DDI are reviewed by a distinguished international panel of experts. This book should be of interest to all those involved in the field of drug–drug interactions, including industrial scientists and regulatory specialists in drug development as well as academic researchers and students in the fields of pharmacology, drug metabolism, and toxicology.

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CONTENTS

1

IN VITRO EVALUATION OF METABOLIC DRUG–DRUG INTERACTIONS: CONCEPTS AND PRACTICE

ALBERT P. LI

CONTENTS

Drug–Drug Interactions in Pharmaceutical Development, Edited by Albert P. Li

1.1 INTRODUCTION

Simultaneous coadministration of multiple drugs to a patient is highly probable. A patient may be coadministered multiple drugs to allow effective treatment of a disease (e.g., cancer, HIV infection) or for the treatment of multiple disease or disease symptoms. It is now known that drug–drug interactions may have serious, sometimes fatal, consequences. Serious drug–drug interactions have led to the necessity of a drug manufacturer to withdraw or limit the use of marketed drugs. Examples of fatal drug–drug interactions are shown in Table 1.1. As illustrated by the examples in Table 1.1, a major mechanism of adverse drug–drug interactions is the inhibition of the metabolism of a drug by a coadministered drug, thereby elevating the systemic burden of the affected drug to a toxic level.

Besides toxicity, loss of efficacy can also result from drug–drug interactions. In this case, the metabolic clearance of a drug is accelerated due to the inducing effects of a coadministered drug on drug metabolism. A well-known example is the occurrence of breakthrough bleeding and contraceptive failures of women taking oral contraceptives but were coadministered with the enzyme inducer rifampin (Zhang et al., 2007). Examples of drug–drug interactions leading to the loss of efficacy are shown in Table 1.2.

Estimation of drug–drug interaction potential is therefore an essential element of drug development. Screening for drug–drug interaction in early phases of drug development allows the avoidance of the development of drug candidates with high potential for adverse drug interactions. Estimation of drug–drug interaction potential is a regulatory requirement—it is required for new drug applications (NDA) to U.S. FDA (Huang et al., 1999). In this chapter, the scientific principles, technologies, and experimental approaches for the preclinical evaluation of drug–drug interactions are reviewed.

TABLE 1.1 Drugs Withdrawn from Market due to Fatal Interactions with Coadministered Drugs

Drug–drug interaction	Mechanism of interactions	References
Terfenadine/ketoconazole interaction, leading to fatal arrhythmia (torsade de pointes). Terfenadine has been withdrawn from the market in January 1997 and replaced by a safer alternative drug (fexofenadine) that is the active metabolite of terfenadine	Terfenadine is metabolized mainly by CYP3A4 and has been found to interact with CYP3A4 inhibitors (e.g., ketoconazole) leading to the elevation of plasma terfenadine level to cardiotoxic levels	Vazquez and Whitfield (1997); Carlson and Morris (1996); Von Moltke et al. (1996); www.fda.gov/bbs/topics/answers/ans00853.html
Mibefradil interaction with multiple drugs, leading to serious adverse effects. Mibefradil interactions with statins has led to rhabdomyolysis. Mibefradil was withdrawn from the market in June 1998, less than a year after it was introduced to the market in August 1997	Mibefradil is a potent CYP3A4 inhibitor known to elevate the plasma levels of over 25 coadministered drugs to toxic levels. Statins, especially simvastatin and cerivastatin, are known to cause rhabdomyolysis	Omar and Wilson (2002); www.fda.gov/bbs/topics/answers/ans00876.html
Sorivudine/5-fluorouracil (5-FU) interaction, leading to severe or fatal gastrointestinal and bone marrow toxicities. Soruvidine was withdrawn from the market in 1993	Sorivudine inhibits dihydropyrimidine dehydrogenase, an enzyme pathway responsible for fluoropyrimidine metabolism	Diasio (1998)
Gemfibrozil–cerivastatin interaction, leading to rhabdimyolysis. Cerivastatin was withdrawn from the market in August, 2001	Inhibition of cerivastatin metabolism by gemfibrozil, apparently due to CYP2C8 inhibitory effects of gemfibrozil	Ozdemir et al. (2000); www.fda.gov/medwatch/safety/2001/Baycol2.html