Guidance for Industry

Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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Guidance for Industry[1]

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I. INTRODUCTION

This guidance provides recommendations for sponsors of new drug applications (NDAs) and biologics license applications (BLAs) for therapeutic biologics[2] who are performing in vitro and in vivo drug metabolism, drug transport, and drug-drug interaction studies. The guidance reflects the Agency's current view that the metabolism of an investigational new drug should be defined during drug development and that its interactions with other drugs should be explored as part of an adequate assessment of its safety and effectiveness. For drug-drug interactions, the approaches considered in the guidance are offered with the understanding that the relevance of a particular study depends on the characteristics and proposed indication of the drug under development. Furthermore, not every drug-drug interaction is metabolism-based, but may arise from changes in pharmacokinetics caused by absorption, distribution, and excretion interactions. Drug-drug interactions related to transporters are being documented with increasing frequency and are important to consider in drug development. Although less well studied, drug-drug interactions may alter pharmacokinetic/pharmacodynamic (PK/PD) relationships. These important areas are not considered in detail in this guidance.

Discussion of metabolic and other types of drug-drug interactions is also provided in other guidances, including the International Conference on Harmonization (ICH) *E7 Studies in Support of Special Populations: Geriatrics,* and *E3 Structure and Content of Clinical Study Reports,* and FDA guidances for industry on *Studying Drugs Likely to be Used in the Elderly* and *Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs*.

[1] This guidance has been prepared by the Drug-Drug Interaction Working Group in the Clinical Pharmacology Section of the Medical Policy Coordinating Committee in the Center for Drug Evaluation and Research, with input from the Center for Biologics Evaluation and Research, at the Food and Drug Administration.

[2] For more information on what constitutes a therapeutic biologic product, please see Internet site http://www.fda.gov/cder/biologics/qa.htm.

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II. BACKGROUND

A. Metabolism

The desirable and undesirable effects of a drug arising from its concentrations at the sites of action are usually related either to the amount administered (dose) or to the resulting blood concentrations, which are affected by its absorption, distribution, metabolism, and/or excretion. Elimination of a drug or its metabolites occurs either by metabolism, usually by the liver or gut mucosa, or by excretion, usually by the kidneys and liver. In addition, protein therapeutics may be eliminated through a specific interaction with cell surface receptors, followed by internalization and lysosomal degradation within the target cell. Hepatic elimination occurs primarily by the cytochrome P450 family (CYP) of enzymes located in the hepatic endoplasmic reticulum, but may also occur by non-P450 enzyme systems, such as N-acetyl and glucuronosyl transferases. Many factors can alter hepatic and intestinal drug metabolism, including the presence or absence of disease and/or concomitant medications, or even some foods, such as grapefruit juice. While most of these factors are usually relatively stable over time, concomitant medications can alter metabolism abruptly and are of particular concern. The influence of concomitant medications on hepatic and intestinal metabolism becomes more complicated when a drug, including a prodrug, is metabolized to one or more active metabolites. In this case, the safety and efficacy of the drug/prodrug are determined not only by exposure to the parent drug but by exposure to the active metabolites, which in turn is related to their formation, distribution, and elimination. Therefore, adequate assessment of the safety and effectiveness of a drug includes a description of its metabolism and the contribution of metabolism to overall elimination. For this reason, the development of sensitive and specific assays for a drug and its important metabolites is critical to the study of metabolism and drug-drug interactions.

B. Drug-Drug Interactions

1. Metabolism-Based Drug-Drug Interactions

Many metabolic routes of elimination, including most of those occurring through the P450 family of enzymes, can be inhibited or induced by concomitant drug treatment. Observed changes arising from metabolic drug-drug interactions can be substantial — an order of magnitude or more decrease or increase in the blood and tissue concentrations of a drug or metabolite — and can include formation of toxic and/or

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