Guidance for Industry

In Vivo Drug Metabolism/Drug Interaction Studies — Study Design, Data Analysis, and Recommendations for Dosing and Labeling

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)
November 1999
Clin/Pharm

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I. INTRODUCTION

This guidance provides recommendations to sponsors of new drug applications (NDAs) and biologics license applications (BLAs) for therapeutic biologics (hereafter drugs) who intend to perform in vivo drug metabolism and metabolic 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 metabolic drug-drug interactions, the approaches considered in the guidance are offered with the understanding that whether a particular study should be performed will vary, depending on the drug in development and its intended clinical use. Furthermore, not every drug-drug interaction is metabolism-based, but may arise from changes in pharmacokinetics caused by absorption, tissue and/or plasma binding, distribution, and excretion interactions. Drug interactions related to transporters are being documented with increasing frequency and may be addressed more fully in future guidances. 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.

Previous guidance from FDA on the use of in vitro approaches to study drug metabolism and metabolic drug-drug interactions is available in a guidance document entitled *Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro* (April 1997). The present guidance should be viewed as a companion to this earlier guidance. Discussion of metabolic and other types of drug-drug interactions is also provided in other guidances, including the International Conference on Harmonisation (ICH) *E8 General Considerations for Clinical Trials* (December 1997), *E7 Studies in Support of Special Populations: Geriatrics* (August 1994), and *E3 Structure and Content of Clinical Study Reports* (July 1996), and the Agency guidances *Studying Drugs Likely to be Used in the Elderly* (November 1989) and *Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs* (July 1993).

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[1] This guidance has been prepared by the In Vivo Metabolic 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. This guidance document represents the Agency's current thinking on the subject of in vivo drug metabolism and metabolic drug-drug interactions. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

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 by excretion, usually by the kidneys and liver. In addition, protein therapeutics may be eliminated via 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 of enzymes located in the hepatic endoplasmic reticulum but may also occur by non-P450 enzyme systems, such as N-acetyl and glucuronosyl transferases. P450 enzyme systems located in gut mucosa can also significantly affect the amount of drug absorbed into the systemic circulation.[2] Many factors can alter hepatic and intestinal drug metabolism, including the presence or absence of disease and/or concomitant medications. While most of these factors are usually relatively stable over time, concomitant medications can alter metabolic routes of absorption and elimination 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.

B. Metabolic Drug-Drug Interactions

Many metabolic routes of elimination, including most of those occurring via the P450 family of enzymes, can be inhibited, activated, 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 metabolites or increased exposure to a toxic parent compound. Examples of substantially changed exposure associated with administration of another drug include (1) increased levels of terfenadine, cisapride, or astemizole with ketoconazole or erythromycin (inhibition of CYP3A4); (2) increased levels of simvastatin and its acid metabolite with mibefradil or itraconazole (inhibition of CYP3A4); (3) increased levels

[2] No distinction is made in this document between the effects of concomitant drugs and/or alterations in metabolism on gastrointestinal absorption and hepatic elimination, although the pharmacokinetic effects of the two may be different.

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