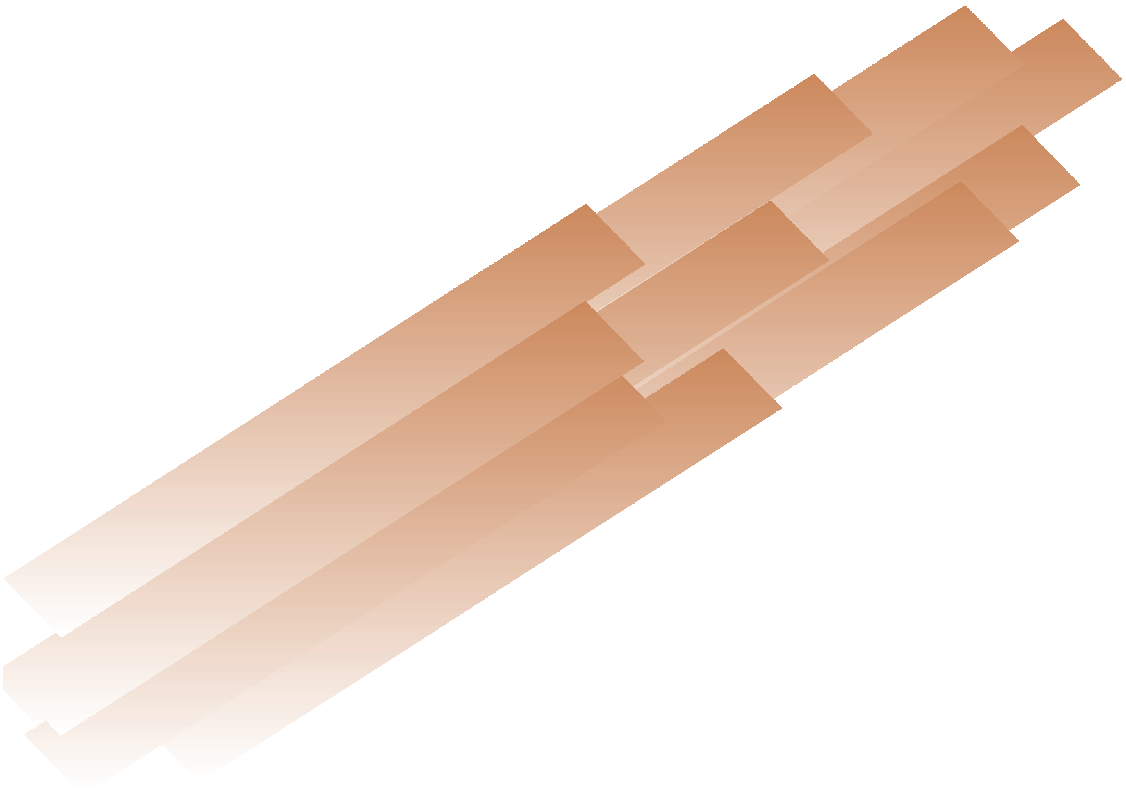
Guidance for Industry

Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro



Department of Health and Human Services
U.S. Food and Drug Administraion
Center for Drug Evaluation and Research
Center For Biologics Evaluation and Research
April 1997

CLIN 3

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Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro

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GUIDANCE FOR INDUSTRY[1]

DRUG METABOLISM/DRUG INTERACTION STUDIES IN THE DRUG DEVELOPMENT PROCESS: STUDIES IN VITRO

I. INTRODUCTION

After entering the body, a drug is eliminated either by excretion or by metabolism to one or more active or inactive metabolites. When elimination occurs primarily by metabolism, the routes of metabolism can significantly affect the drug's safety and efficacy and the directions for use. When elimination occurs via a single metabolic pathway, individual differences in metabolic rates can lead to large differences in drug and metabolite concentrations in the blood and tissue. In some instances, differences exhibit a bimodal distribution indicative of a genetic polymorphism (e.g., CYP450 2D6, CYP450 2C19, N-acetyl transferase). When a genetic polymorphism affects an important metabolic route of elimination, large dosing adjustments may be necessary to achieve the safe and effective use of the drug. Pharmacogenetics already has influenced therapeutics. For a drug that is primarily metabolized by CYP450 2D6, approximately 7 percent of Caucasians will not be able to metabolize the drug, but the percentage for other racial populations is generally far lower. Similar information is known for other pathways, prominently, CYP450 2C19 and N-acetyl-transferase. Equally important, if not more so, many enzymatic metabolic routes of elimination, including most of those occurring via the CYP450 enzymes, can be inhibited or induced by concomitant drug treatment. As a result, abrupt changes can occur with a co-administered agent in a single individual. Such interactions can lead to a substantial decrease or increase in the blood and tissue concentrations of a drug or metabolite or cause the accumulation of a toxic substance (e.g., certain antihistamine-antifungal interactions). These types of changes can alter a new drug's safety and efficacy profile in important ways, particularly a drug with a narrow therapeutic range.

An understanding of metabolic pathways and potential interactions sometimes allows the use of a drug that would produce an unacceptable level of toxicity if blood levels were not predictable. For these reasons, it is important to learn at an early stage of development whether a drug is eliminated primarily by excretion of unchanged drug or by one or more routes of metabolism. If elimination is primarily by metabolism, the principal metabolizing route(s) should be understood. This information will help identify the implications of

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[1]This guidance has been prepared by the Drug Metabolism/Drug Interactions--In Vitro Studies Working Group of the Clinical Pharmacology Section of the Medical Policy Coordinating Committee in the Center for Drug Evaluation and Research (CDER), with input from the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on drug metabolism and drug interaction studies in vitro. 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 requirement of the applicable statute, regulations, or both.

metabolic differences between and within individuals and the importance of certain drug-drug and other interactions. Having such information also will aid in determining whether the pharmacologic properties of certain metabolites should be explored further.

This FDA guidance to industry provides suggestions on current approaches to studies in vitro of drug metabolism and interactions. The guidance is intended to encourage routine, thorough evaluation of metabolism and interactions in vitro whenever feasible and appropriate. As is the case for all FDA guidance documents, suggestions are not requirements, but are offered for consideration by drug development scientists as a means to address potentially important safety concerns. FDA recognizes that the importance of any approach will vary depending on the drug in development and its intended clinical use. The FDA also recognizes that clinical observations can address some of the same issues identified in this document as being susceptible to in vitro study. The suggested approaches delineated in this document, however, are efficient and inexpensive considering the breadth of information they can provide, and often can reduce or eliminate the need for further clinical investigations. This particular guidance is directed toward a broad class of drugs: molecules with a molecular weight below 10 kiloDaltons.

Although the field of in vitro assessment of drug metabolism and drug interactions has progressed sufficiently to allow preparation of this guidance, additional work will be required to allow a comprehensive characterization of drug metabolism in vitro (including induction and inhibition) and its implications for subsequent clinical investigations and product labeling. Because the assessment of drug metabolism in vitro is a rapidly evolving area of drug development and regulation, this guidance may require frequent revision.

Review scientists at the FDA have long been interested in the impact of drug metabolism and drug-drug interactions on drug safety and efficacy. As a result, discussion of this topic also is contained in other FDA guidance documents, including *General Considerations for the Clinical Evaluation of Drugs* (FDA 77-3040), *Guideline for Studying Drugs Likely to be Used in the Elderly* (11/89), and *Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs* (58 FR 39406, July 22, 1993). To obtain these documents, contact the Drug Information Branch at the Center for Drug Evaluation and Research.

II. OBSERVATIONS AND CONCLUSIONS

The following general observations and conclusions underlie the suggestions found in this guidance:

- The concentrations of the parent drug and/or its active metabolite(s) circulating in the body are the effectors of desirable and/or adverse drug actions.

- A principal regulator of drug concentration in the body is clearance. Metabolism can be a major determinant of clearance.

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