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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2005D-0203]

6-3-05  
6-6-05  
J. Cooke

**Draft Guidance for Industry on Safety Testing of Drug Metabolites;  
Availability**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

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**SUMMARY:** The Food and Drug Administration (FDA) is announcing the availability of a draft guidance for industry entitled "Safety Testing of Drug Metabolites." This draft guidance provides recommendations on the safety assessment of unique or major human metabolites of small molecule (nonbiologic) therapeutic products under development. This draft guidance is intended to serve as a resource for general testing considerations as well as provide recommendations on the timing of these studies in relation to the clinical development.

**DATES:** Submit written or electronic comments on the draft guidance by [*insert date 60 days after date of publication in the Federal Register*]. General comments on agency guidance documents are welcome at any time.

**ADDRESSES:** Submit written requests for single copies of the draft guidance to the Division of Drug Information (HFD-240), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Send one self-addressed adhesive label to assist that office in processing your requests. Submit written comments on the draft guidance to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630

Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the draft guidance document.

**FOR FURTHER INFORMATION CONTACT:** Aisar Atrakchi, Center for Drug Evaluation and Research (HFD-120), Food and Drug Administration, 1451 Rockville Pike, Rockville, MD 20852, 301-594-2850.

**SUPPLEMENTARY INFORMATION:**

**I. Background**

FDA is announcing the availability of a draft guidance for industry entitled “Safety Testing of Drug Metabolites.” There are quantitative and qualitative differences in metabolic profiles across species. These differences become important when exposure parameters of a drug in a nonclinical species are used to assess safety in humans during risk assessment. In the past, contribution of metabolites to the overall toxicological potential of the parent drug was generally unknown or not considered; analytical technologies to identify and measure metabolites have only become available over the past decade.

Although in general there is adequate correlation in metabolic profiles between humans and those obtained in standard nonclinical safety studies, there are, however, cases when these studies do not adequately evaluate clinically relevant and/or biologically active metabolites. This may be due to such metabolites being unique to humans or present at very low levels in the animal species used in the standard toxicity studies. As a result, FDA has developed a draft guidance to provide recommendations on the safety assessment of unique or major human metabolites of small molecule

(nonbiologic) therapeutic products. These recommendations should help applicants conduct adequate safety assessments of metabolites.

This draft guidance provides general testing considerations for unique or major drug metabolites including study design, identification of metabolites, structure activity relationship, and types of nonclinical studies needed to assess metabolite toxicity. It also addresses the timing of these studies in relation to the clinical development.

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the agency's current thinking on safety testing of drug metabolites. 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 and regulations.

## **II. Comments**

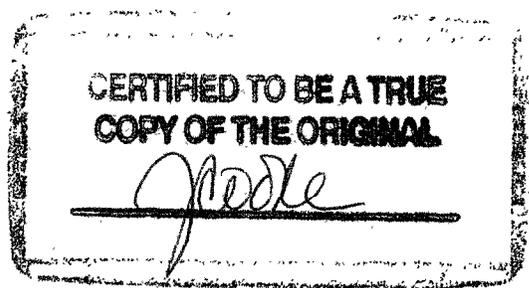
Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding the document. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

**III. Electronic Access**

Persons with access to the Internet may obtain the document at either <http://www.fda.gov/cder/guidance/index.htm> or <http://www.fda.gov/ohrms/dockets/default.htm>.

Dated: 5/27/05  
May 27, 2005.

  
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Jeffrey Shuren,  
Assistant Commissioner for Policy.



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