

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 98D-0994]

DMB

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Certifier	<i>[Signature]</i>

**Guidance for Industry on BACPAC I: Intermediates in Drug Substance Synthesis;  
Bulk Actives Postapproval Changes: Chemistry, Manufacturing, and Controls  
Documentation; 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 guidance for industry entitled “BACPAC I: Intermediates in Drug Substance Synthesis; Bulk Actives Postapproval Changes: Chemistry, Manufacturing, and Controls Documentation.” This guidance provides recommendations to holders of new drug applications, abbreviated new drug applications, new animal drug applications, abbreviated new animal drug applications, and drug master files or veterinary master files who intend, during the postapproval period, to change the site of manufacture, the scale of manufacture, the equipment, the specification(s), and/or the manufacturing process of intermediates in the synthetic pathway leading to the drug substance.

**DATES:** Submit written comments on agency guidances at any time.

**ADDRESSES:** Submit written requests for single copies of this guidance to the Drug Information Branch (HFD-210), 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 guidance to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the guidance document.

**FOR FURTHER INFORMATION CONTACT:** Kasturi Srinivasachar, Center for Drug Evaluation and Research (HFD-1 10), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-5376; or Dennis M. Bensley, Center for Veterinary Medicine (HFV-143), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-827-6956.

**SUPPLEMENTARY INFORMATION:**

**I. Background**

FDA is announcing the availability of a guidance for industry entitled “BACPAC I: Intermediates in Drug Substance Synthesis; Bulk Actives Postapproval Changes: Chemistry, Manufacturing, and Controls Documentation.” This guidance describes chemistry, manufacturing, and controls information and documentation in support of each change and provides recommendations on reporting categories. The guidance applies to synthetic drug substances and the synthetic steps involved in the preparation of semisynthetic drug substances. It is limited to structurally well-characterized drug substances where impurities can be monitored at the levels recommended. The guidance covers changes as follows: (1) Site, scale, and equipment changes involving the synthetic steps up to, and including, the step that produces the final intermediate; (2) specification changes for raw materials, starting materials, and intermediates, excluding the final intermediate; and (3) manufacturing process changes involving the synthetic steps up to and including the final intermediate. The guidance does not cover postapproval changes affecting: (1) Synthetic peptides, (2) oligonucleotides, (3) radiopharmaceuticals, (4) drug substances derived exclusively by isolation from natural sources or produced by procedures involving biotechnology, or (5) nonsynthetic steps for semisynthetic drug substances. Also excluded from this guidance are certain changes in specification and process associated with the use of raw materials or starting materials derived from natural sources or biotechnology.

In the **Federal Register** of November 30, 1998 (63 FR 65793), FDA announced the availability of a draft version of this guidance. The November 1998 guidance gave interested persons an opportunity to submit comments through March 31, 1999. All comments received during

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the comment period have been carefully reviewed and incorporated in this revised guidance where appropriate. As a result of the public comment, the guidance is clearer and more concise than the draft version.

This Level 1 guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115; 65 FR 56468, September 19, 2000). The guidance represents the agency's current thinking on intermediates in drug substance synthesis, bulk actives postapproval changes, chemistry, manufacturing, and controls documentation. 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**

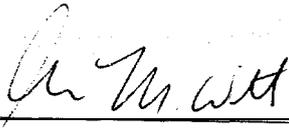
Interested persons may, at any time, submit written comments on the guidance to the Dockets Management Branch (address above). Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this guidance. The guidance and received comments are available for public examination in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

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**III. Electronic Access**

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

Dated: February 8, 2001  
February 8, 2001



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Ann M. Witt,  
Acting Associate Commissioner for Policy.

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