

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**Food and Drug Administration**

[Docket No. 1999D-1651] (formerly Docket No. 99D-1651)

**Guidance for Industry: Chemistry, Manufacturing, and Control Changes to an Approved New Animal Drug Application or Abbreviated New Animal Drug Application**

**AGENCY:** Food and Drug Administration.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is announcing the availability of a guidance for industry (#83) entitled "Chemistry, Manufacturing, and Control Changes to an Approved NADA or ANADA." This guidance is intended to provide recommendations to holders of new animal drug applications (NADAs) and abbreviated new animal drug applications (ANADAs) on how they should report certain changes to such applications, in accordance with the final regulation, 21 CFR 514.8, which was issued in the **Federal Register** of December 13, 2006 (71 FR 74766).

**DATES:** Comments on agency guidances are welcome at any time.

**ADDRESSES:** Submit written requests for single copies of the guidance document to the Communications Staff (HFV-12), Center for Veterinary Medicine, Food and Drug Administration, 7519 Standish Pl., Rockville, MD 20855. Send one self-addressed adhesive label to assist that office in processing your request. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the guidance document. Submit written comments on the guidance document 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>.

**FOR FURTHER INFORMATION CONTACT:** Dennis Bensley, Jr., Center for Veterinary Medicine (HFV-140), Food and Drug Administration, 7519 Standish Pl., Rockville, MD 20855, 301-827-6956, e-mail: [dennis.bensley@fda.hhs.gov](mailto:dennis.bensley@fda.hhs.gov).

**SUPPLEMENTARY INFORMATION:**
**I. Background**

In the **Federal Register** of October 1, 1999 (64 FR 53281), FDA published a proposed rule to implement section 506A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356a) for NADAs and ANDAs. In that same issue of the **Federal Register** (64 FR 53393),

FDA published a notice announcing the availability of a draft guidance for industry entitled "Chemistry, Manufacturing, and Control Changes to an Approved NADA or ANADA," giving interested persons until December 15, 1999, to submit comments. FDA considered all comments received and, where appropriate, incorporated them into the guidance.

This guidance covers recommended reporting categories for various postapproval manufacturing changes and provides recommendations to holders of NADAs and ANADAs on how they should report such changes in accordance with the final regulation, 21 CFR 514.8, issued in the **Federal Register** of December 13, 2006 (71 FR 74766). Recommendations are provided for postapproval changes in: (1) Components and composition, (2) manufacturing sites, (3) manufacturing process, (4) specifications, (5) container closure system, as well as (6) miscellaneous changes and (7) multiple related changes. This guidance does not provide recommendations on the specific information that should be developed by an applicant to assess the effect of the change on the identity, strength (e.g., assay, content uniformity), quality (e.g., physical, chemical, and biological properties), purity (e.g., impurities and degradation products), or potency (e.g., biological activity, bioavailability, bioequivalence) of a drug as these factors may relate to the safety or effectiveness of the drug. An applicant should consider all relevant FDA guidance documents for recommendations on the information that should be submitted to support a given change.

**II. Significance of Guidance**

This level 1 guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). This guidance represents the agency's current thinking on the topic. 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 method may be used as long as it satisfies the requirements of applicable statutes and regulations.

**III. Paperwork Reduction Act of 1995**

This guidance refers to previously approved collections of information found in FDA regulations. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collections of information in sections II through XI of the guidance

have been approved under OMB Control No. 0910-0600.

**IV. Comments**

As with all of FDA's guidance, the public is encouraged to submit written or electronic comments with new data or other new information pertinent to this guidance. FDA periodically will review the comments in the docket and, where appropriate, will amend the guidance. The agency will notify the public of any such amendments through a notice in the **Federal Register**.

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this 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 should be identified with the full title of the guidance document and the docket number found in brackets in the heading of this document. A copy of the document and received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

**V. Electronic Access**

Persons with access to the Internet may obtain a copy of the guidance document entitled "Chemistry, Manufacturing and Control Changes to an Approved NADA or ANADA" from the CVM home page at <http://www.fda.gov/cvm>.

Dated: May 22, 2007.

**Jeffrey Shuren,**

*Assistant Commissioner for Policy.*

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**BILLING CODE 4160-01-S**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**Food and Drug Administration**

[Docket No. 2007D-0168]

**Draft Guidances for Industry Describing Product-Specific Bioequivalence Recommendations; Availability**

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

**ACTION:** Notice.

**SUMMARY:** This notice announces the availability of draft guidances for industry that describe recommendations on how to design bioequivalence (BE) studies for 200 specific drug products to support abbreviated new drug applications (ANDAs). These draft guidances are being made available

concurrently with the publication of a draft guidance for industry entitled "Draft Guidance for Industry—Bioequivalence Recommendations for Specific Products" (product specific BE recommendations). This draft guidance describes the new process for making available guidance on product-specific BE studies. Under the process described in the draft guidance, draft and final product-specific BE study guidance will be made available on the FDA Web site. FDA believes that making this information available on the Internet will streamline the guidance process and provide a meaningful opportunity for the public to consider and comment on product-specific BE study recommendations. Elsewhere in this issue of the **Federal Register**, FDA is announcing the availability of a related guidance document entitled "Draft Guidance for Industry—Bioequivalence Recommendations for Specific Products."

**DATES:** Submit written or electronic comments on the draft guidances by September 28, 2007. General comments on agency guidance documents are welcome at any time.

**ADDRESSES:** Submit written requests for single copies of draft product-specific BE study guidances 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:** Doan T. Nguyen, Center for Drug Evaluation and Research (HFD-600), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-827-0495.

#### **SUPPLEMENTARY INFORMATION:**

##### **I. Background**

To receive approval for an ANDA, an applicant generally must demonstrate, among other things, that its product has the same active ingredient, dosage form, strength, route of administration and conditions of use as the listed drug, and that the proposed drug product is bioequivalent to the reference listed drug (21 U.S.C. 355(j)(2)(A); 21 CFR 314.94(a)). Bioequivalent drug products

show no significant difference in the rate and extent of absorption of the therapeutic ingredient (21 U.S.C. 355(j)(8); 21 CFR 320.1(e)). BE studies are undertaken in support of ANDA submissions with the goal of demonstrating BE between a proposed generic drug product and its reference listed drug. The regulations governing BE are provided at 21 CFR in part 320.

The draft guidance entitled "Bioequivalence Recommendations for Specific Products" describes the following process for making available draft and final product-specific BE recommendations:

- FDA will develop product-specific BE recommendations and post them on the Center for Drug Evaluation and Research (CDER) guidance page (<http://www.fda.gov/cder/index.html>) in draft to facilitate public consideration and comment. The recommendations can be viewed by clicking on the URL associated with the "Bioequivalence Recommendations for Specific Products" guidance on the CDER guidance page or on the Office of Generic Drugs Page (see [www.fda.gov/cder/ogd/index.htm](http://www.fda.gov/cder/ogd/index.htm)). Users can also search for a specific product BE recommendation using the search tool on the CDER guidance page.

- Newly posted draft and final BE recommendations will be announced in the "Newly Added Guidance Documents" list, which is posted monthly on the CDER guidance page.

- The agency will issue a notice in the **Federal Register** announcing the availability on the FDA web site of new product-specific draft and final BE recommendations. The notice will identify a comment period for the recommendations.

- Comments on product-specific BE recommendations will be considered in developing final BE recommendations.

- The BE recommendations will be revised as appropriate to ensure that the most up-to-date BE information is available to the public.

FDA is making the first group of draft product-specific BE recommendations available concurrently with the issuance of the draft guidance document describing the process.

##### **II. Drug Products for Which Draft Product-Specific BE Recommendations Are Available**

The FDA is making available draft recommendations for drug products containing the following active ingredients:

**A**  
Abacavir Sulfate  
Abacavir Sulfate; Lamivudine; Zidovudine  
Acamprosate Calcium

Acitretin  
Acyclovir  
Almotriptan Malate  
Alosetron HCl  
Alprazolam  
Amlodipine Besylate  
Amlodipine Besylate; Benazepril HCl  
Amoxicillin; Clavulanate Potassium  
Anagrelide HCl  
Anastrozole  
Aprepitant  
Atazanavir Sulfate  
Atomoxetine HCl  
Atorvastatin Calcium

**B**  
Benzonatate  
Benzphetamine HCl  
Bicalutamide  
Bisoprolol Fumarate  
Bisoprolol Fumarate; Hydrochlorothiazide

**C**  
Candesartan Cilexetil  
Candesartan Cilexetil; Hydrochlorothiazide  
Carbamazepine  
Carbidopa; Entacapone; Levodopa  
Carvedilol  
Cefditoren Pivoxil  
Celecoxib  
Cetirizine HCl  
Cevimeline HCl  
Cilostazol  
Cinacalcet HCl  
Clarithromycin  
Clonidine HCl  
Clopidogrel

**D**  
Danazol  
Dantrolene Sodium  
Darifenacin HBr  
Deferasirox  
Desloratadine  
Dextromethorphan Polistirex  
Diclofenac Sodium; Misoprostol  
Dicloxacillin Sodium  
Didanosine (multiple dosage forms)  
Digoxin  
Dipyridamole  
Divalproex Sodium  
Dofetilide  
Donepezil HCl  
Doxazosin Mesylate  
Drospirenone; Estradiol  
Duloxetine HCl (multiple dosage forms)  
Dutasteride

**E**  
Efavirenz (multiple dosage forms)  
Emtricitabine  
Entacapone  
Entecavir  
Eplerenone  
Erlotinib HCl  
Escitalopram Oxalate  
Esomeprazole Magnesium  
Etidronate Disodium  
Exemestane

**F**  
Famotidine (multiple dosage forms)  
Felbamate (multiple dosage forms)  
Fenofibrate  
Fexofenadine HCl (multiple dosage forms)  
Flavoxate HCl  
Fluconazole  
Fluoxetine HCl; Olanzapine

Fosamprenavir Calcium  
Fosinopril Sodium; Hydrochlorothiazide

**G**

Gabapentin (multiple dosage forms)  
Galantamine HBr  
Ganciclovir  
Gemifloxacin Mesylate  
Glimepiride  
Glipizide; Metformin HCl  
Glyburide; Metformin HCl  
Granisetron HCl

**H**

Hydrochlorothiazide  
Hydrochlorothiazide; Lisinopril  
Hydrochlorothiazide; Losartan Potassium  
Hydrochlorothiazide; Moexipril HCl  
Hydrochlorothiazide; Olmesartan Medoxomil  
Hydrochlorothiazide; Valsartan

**I**

Ibandronate Sodium  
Ibuprofen; Pseudoephedrine HCl  
Indinavir Sulfate  
Irbesartan  
Isosorbide Mononitrate  
Isradipine (multiple dosage forms)  
Itraconazole

**L**

Lamivudine  
Lamivudine; Zidovudine  
Lamotrigine (multiple dosage forms)  
Leflunomide  
Liothyronine Sodium  
Losartan Potassium

**M**

Mefloquine HCl  
Meloxicam (multiple dosage forms)  
Mercaptopurine  
Mesalamine  
Metaxalone  
Metformin HCl  
Metformin HCl; Pioglitazone HCl  
Miglustat  
Mirtazapine  
Modafinil  
Moexipril HCl  
Montelukast Sodium  
Morphine Sulfate  
Mycophenolate Mofetil  
Mycophenolate Mofetil HCl

**N**

Nabumetone  
Nateglinide  
Nelfinavir Mesylate  
Nevirapine

**O**

Olanzapine  
Olmesartan Medoxomil  
Olsalazine Sodium  
Omeprazole (multiple dosage forms)  
Omeprazole Magnesium  
Ondansetron (multiple dosage forms)  
Oxcarbazepine (multiple dosage forms)

**P**

Pantoprazole Sodium  
Perindopril Erbumine  
Pilocarpine HCl  
Pravastatin Sodium

**Q**

Quetiapine Fumarate

Quinapril HCl

**R**

Raloxifene HCl  
Ramipril  
Ribavirin (multiple dosage forms)  
Rifampin  
Riluzole  
Risedronate Sodium; Calcium Chloride  
Risedronate Sodium  
Risperidone  
Ritonavir  
Rizatriptan Benzoate  
Rosiglitazone Maleate  
Rosuvastatin Calcium

**S**

Sertraline HCl  
Sibutramine HCl  
Sildenafil Citrate  
Simvastatin  
Sirolimus  
Stavudine  
Sulfamethoxazole; Trimethoprim  
Sumatriptan Succinate

**T**

Tacrolimus  
Tadalafil  
Tamsulosin HCl  
Telithromycin  
Telmisartan  
Terbinafine HCl  
Testosterone  
Ticlopidine HCl  
Tizanidine HCl  
Tolterodine Tartrate  
Topiramate (multiple dosage forms)  
Torsemide  
Tramadol HCl  
Tramadol HCl; Acetaminophen  
Trandolapril  
Triamterene

**V**

Valacyclovir HCl  
Valsartan  
Vardenafil HCl  
Venlafaxine HCl  
Verapamil HCl (multiple dosage forms)  
Voriconazole

**Z**

Zaleplon  
Zidovudine (multiple dosage forms)  
Ziprasidone HCl  
Zolpidem Tartrate

These draft guidances are available on the CDER guidance page and may be viewed by clicking on the URL associated with the draft "Bioequivalence Recommendations for Specific Products" guidance on the CDER guidance page or on the Office of Generic Drugs Page (see [www.fda.gov/cder/ogd/index.htm](http://www.fda.gov/cder/ogd/index.htm)). Users can also search for a specific product BE recommendation using the search tool on the CDER guidance page.

These draft guidances are being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidances represent the agency's current thinking on the design of product-specific

bioequivalence studies to support ANDAs. Guidance 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.

**III. Comments**

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments on the draft guidance. Two copies of mailed 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 document. The draft guidance and received comments are available for public examination in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

**IV. Electronic Access**

Persons with access to the Internet may obtain the draft product-specific BE recommendations at either <http://www.fda.gov/cder/guidance/index.htm> or <http://www.fda.gov/ohrms/dockets/default.htm>.

Dated: May 22, 2007.

**Jeffrey Shuren,**

*Assistant Commissioner for Policy.*

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES****Food and Drug Administration**

[Docket No. 2007D-0169]

**Draft Guidance for Industry on Bioequivalence Recommendations for Specific Products**

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

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is announcing the availability of a draft guidance for industry entitled "Bioequivalence Recommendations for Specific Products" that describes a new process for making available recommendations on how to design product-specific bioequivalence (BE) studies to support abbreviated new drug applications (ANDAs). Under this process, applicants planning to carry out such studies in support of their ANDAs will be able to access BE study guidance on the FDA Web site. FDA believes that making this information available on the Internet