CHAPTER 52 – UNAPPROVED NEW DRUGS

SUBJECT: Unapproved New Drugs (Marketed, Human, Prescription Drugs only)	IMPLEMENTATION DATE: 10/19/2009
REVISION: 1	COMPLETION DATE: Continuing

DATA REPORTING	
PRODUCT CODES	PROGRAM ASSIGNMENT CODES
60-66	63002

FIELD REPORTING REQUIREMENTS:

A. For inspection classified as Official Action Indicated (OAI) due to noncompliance with an effective Federal Register Notice (FRN) with manufacturing or distribution cessation dates[1] or previous Advisory, Administrative, or Judicial Action (Action)[2]. (See Part V for the recommended action to submit in CMS):

1. Forward a copy of each Establishment Inspection Report (EIR) as part of any regulatory action recommendation to CDER/Office of Compliance via CMS; and

2. In the Endorsement of the EIR, state that a review of a potential unapproved Rx drug(s) is needed and whether the OAI recommendation is based upon non-compliance with a FRN or another Action.

B. For the inspection classified as OAI due to the Current Good Manufacturing Practices (cGMP) deficiencies or Post Marketing Adverse Drug Experience (ADE) reporting deficiencies, follow the Field Reporting Requirements procedures for the respective Compliance Program (CP) and add in the Endorsement of the EIR that a review of a potential unapproved prescription (Rx) drug(s) is needed and whether the OAI recommendation is based upon non-compliance with cGMP or ADE deficiencies.

[1] One way the agency notifies manufacturers and marketers of its intent to no longer exercise enforcement discretion for certain Unapproved New Drugs is through the issuance of a Federal Register Notice (FRN). Often the FRNs include manufacturing and marketing cessation dates.
[2] The Regulatory Procedures Manual (RPM) Chapters 4, 5, and 6 explain that an Advisory Action is a Warning or Untitled Letter, an Administrative Action is a Citation, and a Judicial Action is a Seizure or Injunction, respectively.

C. For OAI cases, upload into CMS an electronic copy of each firm's response to any Form FDA-483 or Action submitted under this program to CDER/Office of Compliance. For other firm correspondence related to this program, forward to CDER's Office of Compliance at unapproveddrugs@fda.hhs.gov.

PART I - BACKGROUND

This CP acts, in part, as an adjunct to CPs 7353.001 *Enforcement of the Postmarketing Adverse Drug Experience Reporting Regulations*, 7356.002 *Drug Manufacturing Inspections*, and 7356.002B *Drug Repackagers and Relabelers* by directing the field's activity when the inspected firm is a manufacturer, repacker, relabeler, or own label distributor of an unapproved Rx drug(s).[3]

The Federal Food, Drug, and Cosmetic Act (the Act) generally requires that drugs marketed in the United States (U.S.) be shown to be both safe and effective prior to marketing and widespread use in the general population. Drugs that are marketed without required FDA approval may not meet FDA standards for safety, effectiveness, quality, and labeling. Some drugs (mostly older products) continue to be marketed illegally in the United States without required FDA approval. [4]

In June 2006, the agency issued a revised Compliance Policy Guide (CPG) Section 440.100 entitled *Marketed New Drugs Without Approved NDAs or ANDAs*. This revised CPG articulates the agency's risk based enforcement approach with respect to marketed unapproved drugs. This approach is intended to protect the public health without imposing undue burdens on consumers or unnecessarily disrupting the market. (See the CPG for more information on the agency's approach to prioritizing enforcement actions with regard to the universe of unapproved, illegally marketed drug products.) The goals of the CPG are to: (1) clarify for FDA personnel and the regulated industry how we intend to exercise our enforcement discretion regarding unapproved drugs and (2) emphasize that illegally marketed drugs must obtain FDA approval.

This compliance program does not include coverage of violations to approved drug applications (ANDAs and NDAs). Refer to CP 7346.843 *Post-Approval Audit Inspections* for those violations. [**Note**: This CP is for marketed unapproved drugs. For ADE and Postmarketing Inspections, refer to ADE and Postmarketing CPGM:

ADE link:

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/ucm129115.htm.

Postmarketing link:

http://www.fda.gov/downloads/ICECI/ComplianceManuals/CompliancePrograMManual/ucm125398.pdf

[3] Compliance of over the counter (OTC) drugs with OTC monographs is discussed separately in the Compliance Program Guidance Manual 7361.003 OTC Monograph Implementation, Chapter 61 – OTC Drug Evaluation.
[4] A brief summary of the various categories of marketed unapproved drugs and their regulatory status is provided in the Appendix of the CPG: http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074382.htm

PART II - IMPLEMENTATION

A. OBJECTIVES

To provide direction and guidance to field personnel for implementation of the CPG and to make the most efficient use of agency resources:

1. When it has been determined that a firm has not complied with a FRN such as manufacturing and/or distribution cessation dates or other Action pertaining to an unapproved Rx drug;

2. When a cGMP or ADE inspection of an unapproved Rx drug establishment is likely to result in an OAI recommendation;[5]

3. When there is a Center-Directed inspection assignment.

B. PROGRAM MANAGEMENT INSTRUCTIONS

1. When it has been determined that a firm has not complied with a FRN manufacturing and/or distribution cessation date(s) or with another Action, the District should contact the Center and collect the necessary evidence for follow-up Action.

2. When the cGMP or ADE inspection is likely to result in an OAI recommendation, collect information on manufactured and marketed unapproved Rx drugs in addition to the cGMP or ADE inspectional requirement. [**Note**: CDER decides whether to include new drug charges after it has examined the other observations and considered whether they are violations of the Act that can support an Action. These cGMPs or ADE observations do not need to be related to the unapproved Rx drug(s).]

3. When a CDER-directed inspection assignment is issued to cover specific unapproved Rx drug(s), collect the necessary evidence for follow-up Action.

CDER's Office of Compliance, ORA's Office of Enforcement (OE), and the Districts should routinely communicate when cGMP or ADE inspections may result in an OAI recommendation and the firm markets or manufactures unapproved Rx drugs. Additionally, CDER is available to work with the field to review the firm's unapproved Rx drugs.

PRODUCTS COVERED UNDER THIS COMPLIANCE PROGRAM

Marketed unapproved Rx drugs. [**Note**: For compliance purposes, any other products such as dietary supplements, OTC drugs, and health fraud drugs are being or will be addressed in separate CPs as appropriate.]

[5] See CPG 440.100 which describes the circumstances under which the agency will pursue unapproved drug charges. See also Part V – Regulatory/Administrative Strategy.

Current changes *{ED: Retain "current changes" only in sections where changes made}*

FIRMS COVERED UNDER THIS COMPLIANCE PROGRAM

Manufacturers, repackagers, relabelers, and own-label distributors of unapproved Rx drugs.

PART III - INSPECTIONAL

A. GENERAL

1. Inspectional Planning

When planning for a routine cGMP and ADE surveillance inspection of an Rx drug establishment, cover the following:

a. Determine whether the firm is subject to a previous FRN or Action by reviewing CDER's Intranet website at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA for the most up-to-date information regarding the unapproved new drugs program as follows:

i. FRNs;
ii. Actions;
iii. Drug Study Bulletins (DSBs); and
iv. Other helpful information.

b. Review the firm's establishment factory jacket for any Action, inspection, or correspondence that addresses:

i. Regulatory status of unapproved Rx drug(s);[6] or
ii. Registration and Listing.

2. Inspectional Coverage

For firms that are subject to a FRN or Action pertaining to an unapproved Rx drug, cover the following:

a. At the initiation of the inspection, please determine if the firm is in violation of the applicable cessation dates in a FRN or Action. If a firm is in violation, please request and verify the following information:

i. Request a list of Rx drugs (include active pharmaceutical ingredients) manufactured and/or distributed for the commercial market at the site under inspection including drugs manufactured for own label distributors and request the application number (A/NDA number) for each drug.

ii. For those drugs that lack an A/NDA number, request the most recent date of manufacturing and distribution. [**Note**: If the firm is unwilling to provide a complete

[6] In some instances, firms have expressed their opinions to the District regarding their unapproved drugs as being "grandfathered," subject to a Drug Efficacy Study Implementation (DESI), or Generally Recognized as Safe or Effective (GRAS/E).

Current changes *{ED: Retain "current changes" only in sections where changes made}*

list, consider this a refusal of requested information as per IOM Chapter 5, the Act, and contact CDER (see PART VI - PROGRAM CONTACTS) to discuss the refusal.]

iii. If the firm is violating a manufacturing cessation date, additional documentation, such as batch records showing date of manufacturing, will be necessary. [**Note**: Some unapproved Rx drugs subject to a FRN or Action have approved versions (i.e., hydrocodone), and some may have the same active ingredients as the drug subject to a FRN or Action (i.e., guaifenesin) but actually meet the conditions of an OTC monograph.]

iv. If the inspection identifies a violation of a cessation date, please contact CDER and DFI (see PART VI - PROGRAM CONTACTS). CDER will help identify drug products that may be subject to an enforcement action, do not have an approved A/NDA, and/or do not meet the conditions of an OTC monograph.

3. Documentary Sample

If the firm is violating any of the applicable cessation date(s), collect a Documentary Sample (DOC sample) (as per IOM Chapter 4) on all of the firm's marketed unapproved Rx drugs identified by CDER.

a. For each DOC sample please ensure that the following information is included in an affidavit and/or collection report:

i. National Drug Code (NDC) number; and

ii. The firm's role in the manufacturing or distribution of the unapproved Rx drug(s) and the names and addresses of every manufacturer, repackager, relabeler, or other firm involved in the manufacturing, marketing or distribution of the unapproved Rx drug.

b. It is necessary to document the firm's manufacturing and distribution of marketed, unapproved Rx drugs and to obtain "301(k)-type" documentation (refer to IOM Chapter 4) showing that one or more components (usually the active ingredients) in each product have been received in interstate commerce.

c. If the firm is violating a distribution cessation date, in support of 301(d), the DOC sample must include documentation of interstate distribution of the marketed unapproved Rx drug products in finished dosage forms after the cessation date.

d. If the firm is violating a manufacturing cessation date, other documentation (batch records showing date of manufacture) will be necessary.

e. The DOC sample should consist of the drugs' labeling (including immediate container label, package label, package insert, promotional material, any other labeling) and documentation of interstate movement (freight bills, bills of lading, affidavits, etc.) (refer to IOM Chapter 4) for the marketed unapproved Rx drugs for an inspection likely to result in an Action.

4. Reporting Requirements

   In the EIR, explain in what way the firm is out of compliance with the FRN or Action, note any communications that occurred between the firm and the District or the firm and CDER, and describe the DOC sample if possible.

   a. For firms that have cGMP or ADE observations that are likely to support an OAI recommendation, cover the following:

      i. Registration and Listing. [**Note**: Do not cite an observation on the Form FDA-483 (refer to IOM Chapter 5, Item 6).]

      ii. Request a list of all Rx drugs (include active pharmaceutical ingredients) manufactured and/or distributed for the commercial market at the site under inspection including drugs manufactured for own label distributors and request the A/NDA number for each drug.

For those drugs that lack approval, request the most recent date of manufacturing and distribution. [**Note**: If the firm is unwilling to provide a complete list, consider this a refusal of requested information as per IOM Chapter 5, the Act, and contact CDER. (See PART VI - PROGRAM CONTACTS) to discuss the refusal.]

For each own label distributor and for the manufacturer, select labels for three or more drug products that are manufactured at that site and that lack an A/NDA number. [**Note**: See Part III B(1) and (B)(2)Documentary Sample for instructions on when a DOC sample is required.]

When selecting these drugs and, when applicable, selecting products that were the subject of correspondence found in the establishment factory jacket or products that may pose a public health risk (i.e., drugs with labeling that omits significant warnings, drugs that are especially difficult to manufacture, or drugs that are labeled for use in children six years of age and under), Districts are encouraged to consult with CDER (see PART VI - PROGRAM CONTACTS) about which drugs to select. [**Note**: The products sampled do not need to be related to the cGMP or ADE observations that support the potential OAI recommendation.]

5. Documentary Sample - Unapproved Rx Drugs

   For inspections likely to result in an Action (i.e., seizure or injunction), collect a DOC sample (as per IOM Chapter 4) (i.e., at least three for each own label distributor and for the manufacturer's own products, if applicable) of marketed, unapproved Rx drugs. [**Note**: This CP does not supersede any requirement under any other CPs.]

   a. For each DOC sample, ensure that the following information is included in an affidavit and/or collection report:

      i. NDC number; and

ii. The firm's role in the manufacturing or distribution of the unapproved Rx drugs and the names and addresses of every manufacturer, repackager, relabeler, own label distributor, or other firm involved in the manufacturing, marketing or distribution of the unapproved Rx drug.

b. To support 301(d) violations for a Judicial Action such as Seizure at an interstate customer location, documenting the manufacturer's shipment of marketed, unapproved Rx drugs in interstate commerce will suffice. However, to support Seizure of unapproved Rx drugs at the manufacturer's location before they have been introduced into interstate commerce (Section 304 of the Act), it is necessary to obtain "301(k)-type" documentation (refer to IOM Chapter 4). This documentation shows that one or more ingredients or components (usually the active ingredients) of each product have been received in interstate commerce.

c. The DOC sample should consist of the drugs' labeling (including immediate container label, package label, package insert, promotional material, any other labeling), and documentation of interstate movement (freight bills, bills of lading, affidavits, etc.) (refer to IOM Chapter 4).

d. Do not advise the firm as to the regulatory status of the drug (i.e., "grandfathered," DESI, or GRAS/E). If the firm identifies a product as "grandfathered," DESI, GRAS/E or some other term that indicates approval is not required, the investigator should ask the firm management to explain its reasoning and provide documentation to the investigator that the firm believes supports this status. The information should be captured in the EIR but the investigator should not agree or disagree with the firm's conclusions. Mention a general concern that these products may be in violation of the Act and that a final determination will be made by CDER. [**Note**: Do not cite on a Form FDA-483 any apparent non-conformance with the drug approval requirement (refer to IOM Chapter 5, "Non-Reportable Observations") but capture the information in the EIR. [**Note**: There is an Attachment to this CP that summarizes the "grandfather," GRAS/E, and other pertinent standards and policies for your review (see also the Appendix in the CPG). If the firm requests additional information, you may provide the firm a copy of the Attachment that also provides a web link to the CPG.]

6. EIR Reporting Requirements

a. Note whether the factory jacket revealed any previous issues; the firm refused to provide a list and how this refusal was handled; any communications that occurred between the firm and the District or the firm and CDER; describe the Documentary Samples, if possible, and explain why the representative unapproved drugs were selected and whether they are involved with any of the GMP or ADE observations.

b. Note whether you verified and reminded the firm of its responsibility to register and list and whether the firm had failed to register its site and/or list any products.

c. Note whether the cGMP or ADE observations involve any of the selected drugs. [**Note**: Do not include in the EIR any conclusions of apparent new drug violations (as per IOM 5.10.4

Item 3). A determination of the regulatory status of a drug is a decision that will be made by CDER after considering all circumstances, facts, and evidence.]

7. For Center-Directed Inspections

   Cover Part III, Section A and B above, as appropriate, as well as any additional instructions provided in the assignment, as needed.

PART IV - ANALYTICAL

The collection of physical samples is not generally required under this CP; however, this CP does not supersede any collection of physical samples required under any other CP. Physical samples should be collected and analyzed under this CP only upon written assignment or oral direction from CDER, district management, or ORA's Division of Field Investigations.

PART V - REGULATORY/ADMINISTRATIVE STRATEGY

This CP is consistent with the policy expressed in the CPG concerning unapproved drugs that are marketed by a firm that is otherwise in violation of the law (i.e., cGMP or ADE violations). The Center and ORA should collaborate in order to prevent unnecessary utilization of resources by discussing potential cases during the inspection that could result in an OAI recommendation. The CPG describes the policy of the agency with respect to situations where there are unapproved drugs but not other violations.

The most frequent initial Action against a firm under this CP will primarily depend upon whether the firm violates FRN, cGMP or ADE requirements. For example, if a firm is in violation of a FRN, a Judicial Action will most likely result. For firms with cGMP or ADE violations, an Advisory Action that will usually be signed by ORA may result. However, depending on the agency's assessment of the risks and other factors, Administrative or Judicial Action may be considered in lieu of Advisory Action. Districts are encouraged to discuss their findings and considerations with CDER.

In most cases involving cGMP or ADE violations, CDER will decide whether to include new drug charges after it has determined that the other observations are violations of the Act that can support an Action. When CDER approves the inclusion of new drug charges in an Action, the Center intends to continue with such Action unless immediate, voluntary corrective action is taken to resolve the new drug matter, even if a firm corrects the underlying cGMP or ADE violations. CDER will consider the inclusion of new drug charges on a case-by-case basis. However, whether new drug charges are included will not affect the legal status of the drugs and will not relieve any individual or firm of their obligation to comply with the law.

CDER and/or the District will be responsible for forwarding to each other any response(s) to Actions received from firms with all appropriate attachments. CDER will be responsible for reviewing firms' responses to any new drug or misbranding violations and for preparing any follow-up correspondence with the firm for the appropriate signatory authority on these issues. CDER will notify the District via a directed inspection or other instructions if further Action is appropriate.

PART VI - REFERENCES, ATTACHMENTS, AND PROGRAM CONTACTS

A. REFERENCES

1. Federal Food, Drug, and Cosmetic Act as follows:

   a. Sections 301(d) and 505(a) [21 U.S.C. §§ 331(d) and 355(a)], for introduction or delivery for introduction into interstate commerce of a new drug without an approved new drug application.

   b. Section 301(k) [21 U.S.C. § 331(k)], the alteration, mutilation, destruction, obliteration, or removal of the whole or any part of the labeling of, or the doing of any other act with respect to, a food, drug, device, or cosmetic, if such act is done while such article is held for sale (whether or not the first sale) after shipment in interstate commerce and results in such article being adulterated or misbranded.

   c. Section 201(p) [21 U.S.C. § 321(p)], for definition of a new drug, which is any drug not generally recognized as safe and effective among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, for use under the conditions prescribed, recommended, or suggested in the labeling.

   d. Section 503(b)(1) [21 U.S.C. § 353(b)(1)], for definition of a prescription (Rx) drug, which is not safe for use except under the supervision of a practitioner licensed by law to administer such drug.

   e. Section 502(f)(1) [21 U.S.C. § 352(f)(1)], for failure of prescription drug labeling to reflect adequate directions for use to enable a layperson to safely use the drug for its intended use causing the drug to be misbranded and Section 301(a) [21 U.S.C. § 331(a)], which prohibits the introduction or delivery for introduction into interstate commerce of any misbranded drug.

2. Title 21 Code of Federal Regulations as follows:

   a. Section 201.5 defines adequate directions for use; however, by definition, a prescription drug's directions for use are not adequate to enable a layperson to safely use the drug for its intended use.

   b. Section 201.115 provides an exemption from the adequate directions for use labeling requirement; however, prescription drugs that lack an approved application are not exempt from this requirement.

   c. Section 310.502(a)(14) declares new drug status of timed release dosage forms and requires an approved application prior to marketing. [**Note**: FDA regards products with descriptions such as "sustained-release," "extended release," and "long acting" to be timed release dosage forms.]

d. Sections 310.6(b)(1) and (2) establish that drugs that are identical, related, or similar to drugs reviewed under a Drug Efficacy Study Implementation (DESI) proceeding are "new drugs."

3. IOM at http://www.fda.gov/ICECI/Inspections/IOM/default.htm.

4. RPM at http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/default.htm.

5. CDER's Internet website, Drugs Marketed in the United States That Do Not Have Required FDA Approval at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation.

6. Drug Study Bulletins at ORA OE website at http://inside.fda.gov:9003/ORA/OfficeofEnforcement/default.htm.

7. Compliance Program Guidance Manual as follows:

   - CP 7353.001 - Enforcement of the Postmarketing Adverse Drug Experience Reporting Regulations
   - CP 7356.002 - Drug Manufacturing Inspections (continuing)
   - CP 7356.002B - Drug Repackers and Relabelers
   - CP 7361.003 - OTC Drug Monograph Implementation
   - CP 7363.001 - Health Fraud Drugs

8. Compliance Policy Guide Section 440.100 entitled, Marketed New Drugs Without Approved NDAs or ANDAs at http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074382.htm.

B. CONTACTS

1. Send all inspectional correspondence not submitted in CMS to:

   Food and Drug Administration
   Center for Drug Evaluation and Research
   New Drugs and Labeling Team
   10903 New Hampshire Ave
   WO51-5203
   Silver Spring MD 20993-0002
   unapproveddrugs@fda.hhs.gov

2. New drug and labeling questions, or for assistance during inspections:

   Division of New Drugs and Labeling Compliance (HFD-310)
   New Drugs and Labeling Team
   Voice (301) 796-3110
   Fax (301) 872-8745

3. For assignment, inspectional or sampling guidance:

   Respective District Office or
   ORA/ORO/Division of Field Investigations (DFI) (HFC-130)
   Domestic Operations Branch
   Rm. 13-64, 5600 Fishers Lane
   Rockville, MD 20857
   Voice: (301) 827-5653

PART VII - CENTER RESPONSIBILITIES

1. Based on agency policy, maintains the unapproved drugs program by developing the basic strategy, directing inspections and/or follow up Actions and delegating authority (as appropriate);

2. Advises firms and the field regarding the current regulatory status of all marketed unapproved Rx drugs and provides the field with web links to FR notices and Actions against unapproved drugs;

3. Serves as a source of information for the districts regarding marketed unapproved Rx drugs;

4. Reviews all labeling and formulations of affected marketed unapproved drugs and determines their compliance status;

5. Determines the Action to be taken regarding unapproved Rx drugs. When appropriate, issues Advisory Actions to all violative firms with a copy to the appropriate district or concurs with district issuance of an Advisory Action;

6. Sends the district a copy of the firm's response to any FR notice or Action, if such notice or Action is CDER-initiated, and directs follow-up when indicated;

7. Monitors the effectiveness of this program;

8. Promptly advises districts of policy and/or significant status changes as they occur. CDER may use Drug Study Bulletins ("DSBs") for this purpose;

9. Resolves questions and makes final determinations concerning the applicability of this program to a product or situation.