blood components with recommendations for questioning and deferring donors of blood and blood components, and allowing their reentry, to reduce the risk of transfusion-transmitted malaria. This draft guidance document also provides recommendations for product management, including recommendations regarding product retrieval and quarantine, and notification of consignees of blood and blood components in the event that a blood establishment determines that blood or blood components have been collected from a donor who should have been deferred due to possible malaria risk. Finally, the draft guidance revises FDA's policy regarding donors who are residents of non-endemic countries and who have traveled to the Mexican states of Quintana Roo or Jalisco, and allows for donation without any deferral for malaria risk, provided the donor meets all other donor eligibility criteria.

The draft guidance replaces the draft guidance entitled ''Guidance for Industry: Recommendations for Donor Questioning Regarding Possible Exposure to Malaria'' dated June, 2000, and, when finalized, will supersede the FDA memorandum to all registered blood establishments entitled ''Recommendations for Deferral of Donors for Malaria Risk,'' dated July 26, 1994. Since publication of these documents, FDA convened a scientific workshop on ''Testing for Malarial Infections in Blood Donors'' in July 2006, and also discussed the issue of blood donor deferral for malaria risk with the FDA Blood Products Advisory Committee (BPAC) on several occasions. The recommendations contained in the draft guidance are based, in part, on recommendations from BPAC, the public comments received on the earlier documents, and the comments received during the scientific workshop. In addition, FDA is aware that dengue viruses are endemic in Quintana Roo and Jalisco. FDA is currently evaluating the risk of dengue virus infections in U.S. blood donors that are acquired either locally or elsewhere in the world, including in Mexico, and may address this issue in future guidance.

The draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent FDA's current thinking on this topic.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 approach may be used if such approach satisfies the requirement of the applicable statutes and regulations.

## II. Paperwork Reduction Act of 1995

This draft 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 21 CFR part 640 have been approved under OMB control number 0910–0116. The collections of information in 21 CFR 630.6 have been approved under OMB control number 0910–0116. The collections of information in 21 CFR 606.171 have been approved under OMB control number 0910–0458.

## III. Comments

The draft guidance is being distributed for comment purposes only and is not intended for implementation at this time. Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) either electronic or written comments regarding this document. It is only necessary to send one set of comments. Identify comments 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.

## IV. Electronic Access

Persons with access to the Internet may obtain the draft guidance at either *http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm* or *http://www.regulations.gov.*

Dated: June 26, 2012.

**Leslie Kux,**

*Assistant Commissioner for Policy.*

[FR Doc. 2012–16528 Filed 7–5–12; 8:45 am]

**BILLING CODE 4160–01–P**

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

**[Docket No. FDA–2012–N–0563]**

### Single-Ingredient, Immediate-Release Drug Products Containing Oxycodone for Oral Administration and Labeled for Human Use; Enforcement Action Dates

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

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA or Agency) is announcing its intention to take enforcement action against all unapproved single-ingredient, immediate-release drug products that contain oxycodone hydrochloride (hereinafter ''oxycodone'') for oral administration and are labeled for human use, and persons who manufacture or cause the manufacture or distribution of such products in interstate commerce. Unapproved oxycodone drug products have been implicated in reports of medication errors causing serious adverse events. In addition, some of these products omit important warning information in their labeling. Single-ingredient, immediate-release oxycodone drug products are new drugs that require approved new drug applications (NDAs) or abbreviated new drug applications (ANDAs) to be legally marketed.

**DATES:** This notice is effective July 6, 2012. For information about enforcement dates, see **SUPPLEMENTARY INFORMATION**, section IV.

**ADDRESSES:** All communications in response to this notice should be identified with Docket No. FDA–2012–N–0563 and directed to the appropriate office listed in this document.

*Applications under section 505(b) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355(b)):* Division of Anesthesia, Analgesia, and Addiction Products, Office of New Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Silver Spring, MD 20993–0002.

*Applications under section 505(j) of the FD&C Act:* Office of Generic Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, 7519 Standish Pl., Rockville, MD 20855.

*All other communications:* Astrid Lopez-Goldberg, Office of Unapproved Drugs and Labeling Compliance, Division of Prescription Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 5368, Silver Spring, MD 20993–0002.

**FOR FURTHER INFORMATION CONTACT:** Astrid Lopez-Goldberg, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 5368, Silver Spring, MD 20993–0002, 301–796–3485, *astrid.lopezgoldberg@fda.hhs.gov.*

**SUPPLEMENTARY INFORMATION:**

## I. Background

Oxycodone is an opioid drug that is primarily used as an analgesic to relieve

moderate to severe pain. Side effects are similar among all opioids and include light-headedness, dizziness, drowsiness, headache, fatigue, sedation, sweating, nausea, vomiting, constipation, itching, and skin reactions. Serious adverse effects include respiratory depression, decreased blood pressure, coma, respiratory arrest, and death.

This notice covers all unapproved single-ingredient, immediate-release drug products containing oxycodone for oral administration (including tablets, capsules, and oral solutions) that are labeled for human use. Oxycodone is a schedule II narcotic under the Controlled Substances Act (21 U.S.C. 801, *et seq.*) There are FDA-approved single-ingredient, immediate-release oxycodone tablets, capsules, and oral solutions. FDA has approved a number of immediate-release oxycodone tablets, ranging in strength from 5 milligrams (mg) to 30 mg. These products are indicated for the management of moderate to severe pain where the use of an opioid analgesic is appropriate.

In October 2010, FDA approved NDA 200534 for a single-ingredient oxycodone capsule, 5 mg, for the management of moderate to severe acute and chronic pain where the use of an opioid analgesic is appropriate, and NDA 200535, oxycodone oral solution, 100 mg/5 milliliters (mL), for the management of moderate to severe acute and chronic pain in opioid-tolerant patients. In January 2012, FDA approved NDA 201194, oxycodone oral solution, 5 mg/5mL, for the management of moderate to severe pain where the use of an opioid analgesic is appropriate.

FDA is aware of unapproved single-ingredient oxycodone 5 mg capsules and unapproved single-ingredient oxycodone oral solutions in 5 mg/5 mL and 20 mg/mL strengths that are currently being manufactured and distributed. In 2009, the Agency sent warning letters to companies manufacturing unapproved single-ingredient, immediate-release tablets containing oxycodone (available at *http://www.fda.gov/Drugs/GuidanceCompliance RegulatoryInformation/EnforcementActivitiesbyFDA/SelectedEnforcement ActionsonUnapprovedDrugs/ucm238675.htm).* This notice is issued under sections 502 and 505 of the FD&C Act and applies to any unapproved single-ingredient, immediate-release drug products containing oxycodone for oral administration and labeled for human use that are currently being manufactured or distributed, whether or not the drug products were the subject of a prior warning letter.

## II. Safety Concerns With Unapproved New Drugs

Although many of the types of adverse events associated with approved and unapproved products are similar, there are additional risks associated with unapproved products because the quality, safety, and efficacy of unapproved formulations have not been demonstrated to FDA. For example, the ingredients and bioavailability of unapproved products have not been submitted for FDA review, nor has the Agency had the opportunity to assess the adequacy of their chemistry, manufacturing, and controls specifications before marketing. Additionally, FDA does not have the opportunity to review any changes to the formulation of unapproved products prior to implementation, or to review product names, to avoid look-alike and sound-alike names that may lead to medication errors. Finally, with unapproved products FDA does not have the opportunity to review their labeling, e.g., warnings, potential adverse experiences, and drug interactions, before marketing to help ensure safe use.

Unapproved new drug products containing oxycodone pose particular safety concerns because of their potential for addiction. Oxycodone is a derivative of opium, and, like all opioid products, drugs that contain oxycodone can produce euphoria (a sense of well-being), have the potential to be highly addictive, and are extremely popular drugs of abuse. The particular risks associated with unapproved oxycodone-containing products are illustrated by an unapproved oxycodone 20 mg/mL oral solution. FDA found that the INDICATIONS AND USAGE section of the labeling of this unapproved product omits critical information, i.e., that the product is indicated for opioid-tolerant patients. Such an omission increases the chance that the product will be inappropriately prescribed for a patient who is not opioid-tolerant, with the potential for respiratory depression, respiratory arrest, and death. FDA also found that the DOSAGE AND ADMINISTRATION section of the labeling for this unapproved product lacks information about how to prevent dosing errors and that the WARNINGS AND PRECAUTIONS section does not include information regarding risks of medication errors. In addition, this product does not include a Medication Guide (see 21 CFR part 208), which is required to be issued with the approved oxycodone 20 mg/mL oral solution (see *www.fda.gov/Drugs/DrugSafety/ucm085729.htm*).

Another example of an unapproved product lacking appropriate labeling is a single-ingredient oxycodone 5-mg capsule. The DOSAGE AND ADMINISTRATION section of the labeling omits critical information regarding individualization of the dosing regimen, initiation of therapy in opioid-naive patients, conversion to oral oxycodone hydrochloride, maintenance therapy, and cessation of therapy. This unapproved capsule's WARNINGS AND PRECAUTIONS section also fails to mention precautions for patients taking CYP3A4 (cytochrome P450 3A4) inhibitors or inducers.

FDA has received reports of medication errors associated with unapproved oxycodone products and the strength of the active ingredient. Two reports were cases of the wrong dose of unapproved oxycodone oral solution being administered to the patient. A 21-month-old patient received a prescription for oxycodone at a strength of 1 mg/mL, but the product dispensed and administered to the patient was an oxycodone 20 mg/mL formulation, resulting in respiratory failure secondary to opioid overdose. The patient was admitted to the emergency room and successfully resuscitated. The second case was of an 18-year-old patient who was prescribed oxycodone solution with the direction to administer one teaspoonful (5 mg) every 4 hours. However, a 20 mg/mL oxycodone oral solution was dispensed, resulting in a 20-fold overdose (100 mg oxycodone). The patient went into a coma with organ failure, was put on a ventilator, and was admitted to the intensive care unit. At the time of the report, the patient was able to speak but only with a limited vocabulary. These medication errors may have been due to the visual similarity of the container labels and carton labeling of the two product strengths. Because unapproved products circumvent the FDA drug approval process, the Agency cannot take steps before marketing to help ensure that the labels and labeling of multiple strengths by the same manufacturer are sufficiently differentiated to prevent such medication errors.

## III. Legal Status of Products Identified in This Notice

FDA has reviewed the publicly available scientific literature for unapproved single-ingredient, immediate-release drug products containing oxycodone for oral administration and labeled for human use. In no case did FDA find literature

sufficient to support a determination that any of these products is generally recognized as safe and effective. Therefore, these products are ''new drugs'' within the meaning of section 201(p) of the FD&C Act (21 U.S.C. 321(p)), and they require approved NDAs or ANDAs to be legally marketed.

The unapproved drug products covered by this notice are labeled for prescription use. Prescription drugs are defined under section 503(b)(1)(A) of the FD&C Act (21 U.S.C. 353(b)(1)(A)) as drugs that, because of toxicity or other potentially harmful effect, are not safe to use except under the supervision of a practitioner licensed by law to administer such drugs. Because any drug product covered by this notice meets the definition of ''prescription drug'' in section 503(b)(1)(A), adequate directions cannot be written for it so that a layman can use the product safely for its intended uses (21 CFR 201.5). Consequently, it is misbranded under section 502(f)(1) of the FD&C Act (21 U.S.C. 352(f)(1)) in that it fails to bear adequate directions for use. An approved prescription drug is exempt from the requirement in section 502(f)(1) that it bear adequate directions for use if, among other things, it bears the NDA-approved labeling (21 CFR 201.100(c)(2) and 201.115). Because the unapproved prescription drug products subject to this notice do not have approved applications with approved labeling, they fail to qualify for the exemptions to the requirement that they bear ''adequate directions for use,'' and they are misbranded under section 502(f)(1).

## IV. Notice of Intent To Take Enforcement Action

Although not required to do so by the Administrative Procedure Act, the FD&C Act (or any rules issued under its authority), or for any other legal reason, FDA is providing this notice to persons [1] who are marketing unapproved and misbranded single-ingredient, immediate-release drug products containing oxycodone for oral administration and labeled for human use. The Agency intends to take enforcement action against such products and those who manufacture them or cause them to be manufactured or shipped in interstate commerce.

Manufacturing or shipping the drug products covered by this notice can result in enforcement action, including seizure, injunction, or other judicial or administrative proceeding. Consistent with policies described in the Agency's guidance entitled ''Marketed Unapproved Drugs—Compliance Policy Guide'' (Marketed Unapproved Drugs CPG) (*http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070290.pdf*), the Agency does not expect to issue a warning letter or any other further warning to firms marketing drug products covered by this notice before taking enforcement action. The Agency also reminds firms that, as stated in the Marketed Unapproved Drugs CPG, any unapproved drug marketed without a required approved application is subject to Agency enforcement action at any time. The issuance of this notice does not in any way obligate the Agency to issue similar notices (or any notice) in the future regarding marketed unapproved drugs. As described in the Marketed Unapproved Drugs CPG, the Agency may, at its discretion, identify a period of time during which the Agency does not intend to initiate an enforcement action against a currently marketed unapproved drug solely on the grounds that it lacks an approved application under section 505 of the FD&C Act. With respect to drug products covered by this notice, the Agency intends to exercise its enforcement discretion for only a limited period of time because there are safety issues with respect to the products covered by this notice and there are FDA-approved products to meet patient needs. Therefore, the Agency intends to implement this notice as explained in this document.

For the effective date of this notice, see the **DATES** section of this document. Any drug product covered by this notice that a company (including a manufacturer or distributor) began marketing after September 19, 2011, is subject to immediate enforcement action. For products covered by this notice that a company (including a manufacturer or distributor) began marketing in the United States on or before September 19, 2011, FDA intends to take enforcement action against any such product that is not listed with the Agency in full compliance with section 510 of the FD&C Act (21 U.S.C. 360) before July 5, 2012, and is manufactured, shipped, or otherwise introduced or delivered for introduction into interstate commerce by any person on or after July 5, 2012. FDA also intends to take enforcement action against any drug product covered by this notice that is listed with FDA in full compliance with section 510 of the FD&C Act but is not being commercially used or sold [2] in the United States before July 5, 2012, and that is manufactured, shipped, or otherwise introduced or delivered for introduction into interstate commerce by any person on or after July 6, 2012.

However, for drug products covered by this notice that a company (including a manufacturer or distributor) began marketing in the United States on or before September 19, 2011, are listed with FDA in full compliance with section 510 of the FD&C Act before July 5, 2012 (''currently marketed and listed''), and are manufactured, shipped, or otherwise introduced or delivered for introduction into interstate commerce by any person on or after July 6, 2012, the Agency intends to exercise its enforcement discretion as follows: FDA intends to initiate enforcement action regarding any such currently marketed and listed product that is manufactured on or after August 20, 2012, or that is shipped on or after October 4, 2012. Further, FDA intends to take enforcement action against any person who manufactures or ships such products after these dates. Any person who has submitted or submits an application for a drug product covered by this notice but has not received approval must comply with this notice.

The Agency, however, does not intend to exercise its enforcement discretion as outlined previously if (1) a manufacturer or distributor of drug products covered by this notice is violating other provisions of the FD&C Act, including, but not limited to, violations related to FDA's current good manufacturing practices, adverse event reporting, labeling, or misbranding requirements other than those identified in this notice, or (2) it appears that a firm, in response to this notice, increases its manufacture or interstate shipment of drug products covered by this notice above its usual volume during these periods.[3]

Nothing in this notice, including FDA's intent to exercise its enforcement

[1] The term ''person'' includes individuals, partnerships, corporations, and associations (21 U.S.C. 321(e)).

[2] For purposes of this notice, the phrase ''commercially used or sold'' means that the product has been used in a business or activity involving retail or wholesale marketing and/or sale.

[3] If FDA finds it necessary to take enforcement action against a product covered by this notice, the Agency may take action relating to all of the defendant's other violations of the FD&C Act at the same time. For example, if a firm continues to manufacture or market a product covered by this notice after the applicable enforcement date has passed, to preserve limited Agency resources, FDA may take enforcement action relating to all of the firm's unapproved drugs that require applications at the same time (see, e.g., *United States* v. *Sage Pharmaceuticals,* 210 F.3d 475, 479–480 (5th Cir. 2000) (permitting the Agency to combine all violations of the FD&C Act in one proceeding, rather than taking action against multiple violations of the FD&C Act in ''piecemeal fashion'')).

discretion, alters any person's liability or obligations in any other enforcement action, or precludes the Agency from initiating or proceeding with enforcement action in connection with any other alleged violation of the FD&C Act, whether or not related to a drug product covered by this notice. Similarly, a person who is or becomes enjoined from marketing unapproved or misbranded drugs may not resume marketing of such products based on FDA's exercise of enforcement discretion as described in this notice.

Drug manufacturers and distributors should be aware that the Agency is exercising its enforcement discretion as described previously only in regard to drug products covered by this notice that are marketed under an NDC number listed with the Agency in full compliance with section 510 of the FD&C Act before July 5, 2012. As previously stated, drug products covered by this notice that are currently marketed but not listed with the Agency on the date of this notice must, as of the effective date of this notice, have approved applications before their shipment in interstate commerce. Moreover, any person or firm that has submitted or submits an application but has yet to receive approval for such products is still responsible for full compliance with this notice.

### V. Discontinued Products

Some firms may have previously discontinued manufacturing or distributing products covered by this notice without removing them from the listing of their products under section 510(j) of the FD&C Act. Other firms may discontinue manufacturing or distributing listed products in response to this notice. Firms that wish to notify the Agency of product discontinuation should send a letter signed by the firm's chief executive officer and fully identifying the discontinued product(s), including the product NDC number(s), and stating that the manufacturing and/or distribution of the product(s) has (have) been discontinued. The letter should be sent electronically to Astrid Lopez-Goldberg (see **ADDRESSES**). Firms should also electronically update the listing of their products under section 510(j) of the FD&C Act to reflect discontinuation of unapproved products covered by this notice. FDA plans to rely on its existing records, including its drug listing records, the results of any subsequent inspections, or other available information when it targets violations for enforcement action.

### VI. Reformulated Products

In addition, FDA cautions firms against reformulating their products into unapproved new drugs without oxycodone and marketing them under the same name or substantially the same name (including a new name that contains the old name) in anticipation of an enforcement action based on this notice. As stated in the Marketed Unapproved Drugs CPG, FDA intends to give higher priority to enforcement actions involving unapproved drugs that are reformulated to evade an anticipated FDA enforcement action. In addition, reformulated products marketed under a name previously identified with a different active ingredient have the potential to confuse health care practitioners and harm patients.

Dated: June 21, 2012.

**Leslie Kux,**

*Assistant Commissioner for Policy.*

[FR Doc. 2012–16475 Filed 7–5–12; 8:45 am]

**BILLING CODE 4160–01–P**

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

**[Docket No. FDA–2012–N–0603]**

## Assessment of the Program for Enhanced Review Transparency and Communication for New Molecular Entity New Drug Applications and Original Biologics License Applications in Prescription Drug User Fee Act V; Request for Comments

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

**ACTION:** Notice; request for comments.

**SUMMARY:** The Food and Drug Administration (FDA) is announcing an opportunity for public comment on the statement of work for an assessment of the Program for Enhanced Review Transparency and Communication for New Molecular Entity (NME) New Drug Applications (NDAs) and Original Biologics License Applications (BLAs) (the Program). The Program is part of the FDA performance commitments under the proposed fifth authorization of the Prescription Drug User Fee Act (PDUFA), which, if enacted into law, will allow FDA to collect user fees for the review of human drug and biologics applications for fiscal years (FYs) 2013–2017. The Program is described in detail in section II.B of the document entitled ''PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017.'' [1] The Program will be evaluated by an independent contractor in an interim and final assessment. As part of the FDA performance commitment, FDA is providing a period of 30 days for public comment on the statement of work before letting the contract for the assessment.

**DATES:** Submit electronic or written comments by August 6, 2012.

**ADDRESSES:** Submit electronic comments to *http://www.regulations.gov.* Submit written comments to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number found in brackets in the heading of this document.

**FOR FURTHER INFORMATION CONTACT:** Andrea Tan, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 1173, Silver Spring, MD 20993–0002, 301–796–7641, *Andrea.Tan@fda.hhs.gov.*

**SUPPLEMENTARY INFORMATION:**

### I. Background

The timely review of the safety and effectiveness of new drugs and biologics is central to FDA's mission to protect and promote the public health. Before the enactment of PDUFA in 1992, FDA's drug review process was relatively slow and not very predictable compared to other countries. As a result of concerns expressed by industry, patients, and other stakeholders at the time, Congress enacted PDUFA, which provided the added funds through user fees that enabled FDA to hire additional reviewers and support staff and upgrade its information technology systems. In return for these additional resources, FDA agreed to certain review performance goals, such as completing reviews of NDAs and BLAs and taking regulatory actions on them in predictable timeframes. These changes revolutionized the drug approval process in the United States and enabled FDA to speed the application review process for new drugs and biologics without compromising the Agency's high standards for demonstration of safety, efficacy, and quality of new drugs and biologics prior to approval.

PDUFA provides FDA with a source of stable, consistent funding that has made possible our efforts to focus on

[1] The ''*PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017*'' is available on the Internet at *http://www.fda.gov/downloads/For Industry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf.*