4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2013-N-1485]

Unapproved and Misbranded Oral and Injectable Drugs Labeled for Prescription Use Containing Codeine Sulfate, Codeine Phosphate, or Dihydrocodeine Bitartrate; Enforcement Action Dates

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA or the Agency) is announcing its intention to take enforcement action against unapproved and misbranded oral and injectable drug products labeled for prescription use and containing codeine sulfate, codeine phosphate, or dihydrocodeine bitartrate, and against persons who manufacture or cause the manufacture or distribution of such products in interstate commerce. Prescription drug products containing these ingredients pose serious risks, including the risk of addiction, and some unapproved drug products may lack warnings or other information required in the labeling of approved drug products that is important for safe use. These unapproved drug products compete with approved drug products and thus pose a direct challenge to the drug approval system. This document covers the following unapproved drug products labeled for prescription use: single-ingredient codeine sulfate oral tablets and solutions, single-ingredient codeine phosphate injection products, fixed-dose combination products containing codeine phosphate, and fixed-dose combination products containing dihydrocodeine bitartrate. A new drug containing codeine sulfate, codeine phosphate, or dihydrocodeine bitartrate requires an approved new drug application (NDA) or abbreviated new drug application (ANDA) to be legally marketed.

DATES: This document is effective [INSERT DATE OF PUBLICATION IN THE FEDERAL REGISTER]. For information about enforcement dates, see the SUPPLEMENTARY INFORMATION, section IV.

ADDRESSES: All communications in response to this document should be identified with Docket No. FDA-2013-N-1485 and directed to the appropriate office listed in this ADDRESSES section:

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 (for products with analgesic indications) or Division of Pulmonary, Allergy, and Rheumatology Products (for products with antitussive indications), 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. 5185, 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. 5185, Silver Spring, MD 20993-0002, 301-796-3485, Astrid.LopezGoldberg@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

Codeine is an opioid used primarily as an analgesic to relieve pain or as an antitussive to treat coughs. Codeine sulfate and codeine phosphate are different salts of codeine, generally also for analgesic or antitussive use. Dihydrocodeine bitartrate is a chemical derivative of codeine and an opioid pain reliever that produces effects similar to those of codeine.

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 are respiratory depression, resulting in a slow breathing rate, and decreased blood pressure. Multiple active ingredients (including acetaminophen, aspirin, butalbital, caffeine, carisoprodol, promethazine, or phenylephrine) may be marketed in combination with codeine phosphate or dihydrocodeine bitartrate. Some of these fixed-dose combination products include more than one sedating component.

Single-ingredient products containing codeine, such as codeine sulfate oral tablets and solutions, and codeine phosphate injection products, are schedule II narcotics (§ 1308.12 (21 CFR 1308.12)) under the Controlled Substances Act (21 U.S.C. 801 et seq.). Single-ingredient prescription codeine sulfate oral tablets and a single-ingredient prescription codeine sulfate oral solution are approved for the relief of mild to moderately severe pain. On October 13, 2009, the Agency issued four warning letters to companies manufacturing and/or marketing unapproved prescription codeine sulfate oral tablets.[1] However, FDA is aware of at least one unapproved prescription codeine sulfate oral tablet that is still listed with FDA's Drug Registration and Listing System. Although FDA is unaware of any unapproved single-ingredient codeine

[1] Available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/SelectedEnforcementActionsonUnapprovedDrugs/ucm238675.htm#codeine_sulfate.

phosphate injection products on the market at this time, such products were on the market as recently as 2010.

Fixed dose combination products containing codeine phosphate are placed on different schedules under the Controlled Substances Act depending on their use:

● Fixed-dose combination products containing codeine, which are generally used as analgesics in pediatric and adult patients, are typically schedule III or schedule V drugs under the Controlled Substances Act depending on the amount of codeine contained in the drug (§§ 1308.13 and 1308.15 (21 CFR 1308.13 and 1308.15)).[2] FDA is aware of a safety concern with an unapproved fixed-dose combination product containing codeine phosphate and acetaminophen that is labeled for analgesic use. We note that this product does not have the Boxed Warning for liver toxicity that would be required if this were an approved product (76 FR 2691, January 14, 2011).

● Over-The Counter (OTC) Monograph compliant fixed-dose combination products containing codeine (21 CFR 341.14) for use as antitussives are schedule V drugs under the Controlled Substances Act (§1308.15). Also in schedule V are prescription fixed-dose combination drug products containing codeine phosphate that are approved to treat coughs in children 6 years old and older. FDA is aware of an unapproved prescription fixed dose combination product containing codeine phosphate that is labeled for antitussive use in children as young as 3 years old.

● Fixed dose combination products containing dihydrocodeine bitartrate are schedule III or schedule V drugs under the Controlled Substances Act, depending on the amount of

[2] We note that at dosages exceeding the maximum identified in § 1308.13 these fixed dose combination drug products would be Schedule II.

dihydrocodeine contained in the drug (§§ 1308.13 and 1308.15(c)(2)).[3] There are prescription dihydrocodeine fixed dose combination products that have approval for the relief of moderate to moderately severe pain. FDA is aware of unapproved prescription dihydrocodeine fixed-dose combination products that are labeled as antitussives.

II. Safety Concerns With Unapproved New Drugs

Because marketed unapproved new drug products have not been through FDA's approval process, there may be safety risks associated with them. Some unapproved drug product labeling omits or modifies safety warnings or other information that is important to ensure safe use, such as drug interactions or potential adverse experiences (e.g., the liver toxicity Boxed Warning discussed in section I of this document). Similarly, as noted in section I, FDA is aware of an unapproved prescription fixed-dose combination product that is inappropriately labeled for children as young as 3 years of age.

Furthermore, some of the products covered in this action include acetaminophen at doses higher than 325 milligrams (mg) in combination with codeine sulfate or dihydrocodeine bitartrate. FDA has taken steps to reduce the risk of acetaminophen-related severe liver injury by limiting the maximum amount of acetaminophen in approved oral prescription products to 325 mg per tablet, capsule, or other dosage unit and revising required warning information (76 FR 2691, January 14, 2011). Severe liver injury can lead to liver failure, liver transplant, and death. Limiting the amount of acetaminophen in oral prescription drug products increases the margin of safety for persons who mistakenly take too many doses or use more than one acetaminophen-containing product at the same time.[4]

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[3] We note that at dosages exceeding the maximum identified in § 1308.13 these fixed-dose combination drug products would be Schedule II.

[4] 76 FR 2691; for additional regulatory and safety information concerning acetaminophen, see http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm239871.htm.

Another concern with unapproved prescription fixed-dose combination products containing codeine sulfate or dihydrocodeine bitartrate is that they may include more than one sedating component, which may result in increased sedation or drowsiness. With an unapproved drug product, FDA does not have the opportunity to review the drug product before it is marketed to ensure the combination of ingredients is safe and that the labeling contains adequate dosing information and appropriate warnings and precautions.

Finally, even the expected risks associated with use of drug products containing codeine sulfate, codeine phosphate, or dihydrocodeine bitartrate are potentially greater for unapproved drug products because the quality, safety, and efficacy of unapproved formulations have not been demonstrated to FDA. For example, the ingredients and bioavailability of unapproved prescription drug products have not been submitted for FDA review, nor has FDA had the opportunity to assess the adequacy of their chemistry, manufacturing, and control specifications. Unapproved drug products have unapproved labeling that may not contain appropriate dosing and warning information.

III. Legal Status of Products Identified in This Document

FDA has reviewed the publicly available scientific literature for unapproved prescription single-ingredient codeine sulfate oral tablets, single-ingredient codeine sulfate oral solutions, single-ingredient codeine phosphate injection products, fixed-dose combination products containing codeine phosphate, and fixed-dose combination products containing dihydrocodeine bitartrate. In no case did FDA find literature sufficient to support a determination that any of these prescription products are generally recognized as safe and effective. Therefore, these prescription drug 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 document 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. If an unapproved drug product covered by this document meets the definition of "prescription drug" in section 503(b)(1)(A) of the FD&C Act, 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) of the FD&C Act 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 document 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 are misbranded under section 502(f)(1) of the FD&C Act.

If a drug covered by this document is labeled as a prescription drug but does not meet the definition of "prescription drug" under section 503(b)(1)(A) of the FD&C Act, the drug is misbranded under section 503(b)(4)(B). Additionally, the final OTC drug monograph at part 341 (21 CFR part 341), "Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Drug Products" (the final OTC Cold Cough monograph), permits the use of codeine, codeine sulfate, and codeine phosphate as active ingredients for antitussive use, in the amounts and under the conditions specified in the final OTC Cold Cough monograph (see § 341.14). The final OTC Cold Cough monograph is the only monograph that permits OTC use of the active ingredients covered by this

document. If a product covered by this document does not meet the definition of "prescription drug" under section 503(b)(1)(A) of the FD&C Act, in addition to being misbranded, unless the product was reformulated and labeled to meet all the requirements of the final OTC Cold Cough monograph, the product would still require an approved NDA or ANDA in order to be legally marketed.[5]

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[6] who are marketing the following unapproved and misbranded drugs labeled for prescription use: single-ingredient codeine sulfate oral tablets, single-ingredient codeine sulfate oral solutions, single-ingredient codeine phosphate injection products, fixed-dose combination products containing codeine phosphate, and fixed-dose combination products containing dihydrocodeine bitartrate. 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 document 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

[5] In addition to any other applicable requirements, firms that manufacture OTC drugs must comply with the labeling requirements at 21 CFR 201.66. Furthermore, States may have restrictions on the sale of OTC products that contain codeine.

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

warning to firms marketing drug products covered by this document 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 document does not in any way obligate the Agency to issue similar documents (or any document) in the future regarding marketed unapproved drugs (see Marketed Unapproved Drugs CPG, p. 5).

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 document, 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 document, and numerous marketed products that have approved applications or comply with an OTC drug final monograph are offered to treat the same or similar indications. Therefore, the Agency intends to implement this document as follows.

For the effective date of this document, see the DATES section of this document. Any drug product covered by this document 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 document that a company (including a manufacturer or distributor) began marketing 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 [INSERT DATE OF FILING AT THE OFFICE OF THE FEDERAL REGISTER], and is manufactured, shipped, or otherwise introduced or delivered for

introduction into interstate commerce by any person on or after [INSERT DATE OF FILING AT THE OFFICE OF THE FEDERAL REGISTER]. FDA also intends to take enforcement action against any drug product covered by this document that is listed with FDA in full compliance with section 510 of the FD&C Act but is not being commercially used or sold[7] in the United States before [INSERT DATE OF FILING AT THE OFFICE OF THE FEDERAL REGISTER], and that is manufactured, shipped, or otherwise introduced or delivered for introduction into interstate commerce by any person on or after [INSERT DATE OF PUBLICATION IN THE FEDERAL REGISTER].

However, for drug products covered by this document that a company (including a manufacturer or distributor) (1) began marketing in the United States on or before September 19, 2011, (2) are listed with FDA in full compliance with section 510 of the FD&C Act before [INSERT DATE OF FILING AT THE OFFICE OF THE FEDERAL REGISTER] ("currently marketed and listed"), and (3) are manufactured, shipped, or otherwise introduced or delivered for introduction into interstate commerce by any person on or after [INSERT DATE OF PUBLICATION IN THE FEDERAL REGISTER], 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 [INSERT DATE 45 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER], or that is shipped on or after [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]. Further, FDA intends to take enforcement action against any person who manufactures or ships such products after these dates. The purpose of these enforcement timeframes is to allow manufacturers and distributors to deplete their current inventory and

[7] For the purpose of this document, 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.

ensure a smooth transition for consumers. Any person who has submitted or submits an application for a drug product covered by this document, but has not received approval, must comply with this document.

The Agency, however, does not intend to exercise its enforcement discretion as outlined previously if the following apply: (1) A manufacturer or distributor of drug products covered by this document is violating other provisions of the FD&C Act, including, but not limited to, violations related to FDA's current good manufacturing practices, adverse drug event reporting, labeling, or misbranding requirements other than those identified in this document or (2) it appears that a firm, in response to this document, increases its manufacture or interstate shipment of drug products covered by this document above its usual volume during these periods.[8]

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

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 document that are marketed under a National Drug Code (NDC) number listed with the Agency

[8] If FDA finds it necessary to take enforcement action against a product covered by this document, 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 document after the applicable enforcement date, to preserve limited agency resources, FDA may at the same time take enforcement action relating to all of the firm's unapproved drugs that require applications (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")).

in full compliance with section 510 of the FD&C Act before [INSERT DATE OF FILING AT THE OFFICE OF THE FEDERAL REGISTER]. As previously stated, drug products covered by this document that are currently marketed but not listed with the Agency on the date of this document must, as of the effective date of this document, 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 document.

V. Discontinued Products

Some firms may have previously discontinued manufacturing or distributing products covered by this document 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 document. Firms are required to 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 document (21 CFR 207.21(b)). Questions on electronic drug listing updates should be sent to: eDRLS@fda.hhs.gov. In addition to the required update, firms can also notify the Agency of product discontinuation by sending 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). 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

FDA cautions firms against reformulating their products into unapproved new drugs without codeine sulfate, codeine phosphate, or dihydrocodeine bitartrate, 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 document. 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 healthcare practitioners and harm patients.

Dated: January 6, 2014.

Leslie Kux,

Assistant Commissioner for Policy.

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