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. 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 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)). 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).

1 Available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/SelectedEnforcementActions/UndeclaredActiveDrugs/ucm238675.htm#codeine_sulfate.

2 We note that at dosages exceeding the maximum identified in § 1308.13 these fixed dose combination drug products would be Schedule II.
• 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 antitusive 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 dihydrocodeine contained in the drug (§§ 1308.13 and 1308.15(c)(2)). 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

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

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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 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
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 any other legal reason), FDA is providing this notice to persons 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/UCM702990.pdf), the Agency does not expect to issue a warning letter or any other further 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 oblige 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 January 9, 2014, and is manufactured, shipped, or otherwise introduced or delivered for introduction into interstate commerce by any person on or after January 9, 2014. 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 in the United States before January 9, 2014, and that is manufactured, shipped, or otherwise introduced or delivered for introduction into interstate commerce by any person on or after January 9, 2014.

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 January 9, 2014 ("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 January 10, 2014, the Agency intends to exercise its enforcement discretion against any such product covered by this document.

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.
Agency in full compliance with section 510 of the FD&C Act before January 9, 2014. 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 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.
[FR Doc. 2014–00257 Filed 1–9–14; 8:45 am]
BILLING CODE 4160–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Health Resources and Services Administration

Statement of Organization, Functions and Delegations of Authority

This notice amends Part R of the Statement of Organization, Functions and Delegations of Authority of the Department of Health and Human Services (HHS), Health Resources and Services Administration (HRSA) (60 FR 56605, as amended November 6, 1995; as last amended at 78 FR 42089–42090 dated July 15, 2013). This notice reflects organizational changes in the Health Resources and Services Administration. This notice corrects the administrative codes for the Bureau of Clinician Recruitment and Service (RU); the Division of Regional Operations (RU2) and the Office of Business Operations (RU3).

Chapter RU—Bureau of Clinician Recruitment and Service

Section RU–10, Organization

Delete and replace in its entirety. The Office of the Associate Administrator (RU) is headed by the Associate Administrator, Bureau of Clinician Recruitment and Service (BCRS), who reports directly to the Administrator, Health Resources and Services Administration. BCRS includes the following components:

(1) Office of the Associate Administrator (RU);
(2) Office of Legal and Compliance (RU1);
(3) Division of Regional Operations (RU2);
(4) Office of Business Operations (RU3);
(5) Division of National Health Service Corps (RU5);
(6) Division of Nursing and Public Health (RU6);
(7) Division of External Affairs (RU7);
(8) Division of Policy and Shortage Designation (RU8); and
(9) Division of Program Operations (RU9).

Section RU–30, Delegations of Authority

All delegations of authority and re-delegations of authority made to HRSA officials that were in effect immediately prior to this reorganization, and that are consistent with this reorganization, shall continue in effect pending further re-delegation.

This reorganization is effective upon date of signature.

Dated: December 26, 2013.

Mary K. Wakefield,
Administrator.
[FR Doc. 2014–00221 Filed 1–9–14; 8:45 am]
BILLING CODE 4165–15–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Indian Health Service

Organization, Function, and Delegations of Authority; Part G; Proposed Functional Statement

AGENCY: Indian Health Service, HHS.

ACTION: Notice of change in name of an organizational component.

SUMMARY: The Indian Health Service is announcing the name change of the Aberdeen Area Indian Health Service to the Great Plains Area Indian Health Service at the request of Tribes served by the Aberdeen Area Indian Health Service.

FOR FURTHER INFORMATION CONTACT: Ms. Mona Galpin, Office of Management Services, Management Policy and Internal Control Staff, 801 Thompson Avenue, TMP Suite 625A, Rockville, MD 20852, Telephone 301–443–2650.

Section GF–10, Indian Health Service Area Offices—Organization

An Area Office is a second echelon organization under the direction of an Area Director, who reports to the IHS Director.

Indian Health Service Area Offices of the Indian Health Service in alphabetical order:

- Alaska Area Office (GFB)
- Albuquerque Area Office (GFC)
- Bemidji Area Office (GFE)
- Billings Area Office (GFF)
- California Area Office (GFG)
- Great Plains Area Office (GFA)
- Nashville Area Office (GFH)
- Navajo Area Office (GFJ)
- Oklahoma Area Office (GFK)
- Phoenix Area Office (GFL)
- Portland Area Office (GFM)
- Tucson Area Office (GFN)