



4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2015-N-2008]

Unapproved and Misbranded Otic Prescription Drug Products; 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 unapproved and misbranded otic drug products labeled for prescription use and containing benzocaine; benzocaine and antipyrine; benzocaine, antipyrine, and zinc acetate; benzocaine, chloroxylenol, and hydrocortisone; chloroxylenol and pramoxine; or chloroxylenol, pramoxine, and hydrocortisone; and against persons who manufacture or cause the manufacture or distribution of such products in interstate commerce. These unapproved and misbranded prescription drug products are marketed without evidence of safety and effectiveness; may present safety concerns; and pose a direct challenge to the new drug approval system and, in some cases, the over-the-counter (OTC) drug monograph system.

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

ADDRESSES: For all communications in response to this notice, identify with Docket No. FDA-2015-N-2008 and direct to the appropriate office listed in this ADDRESSES section as follows:

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 drug products with analgesic and anti-inflammatory indications), or Division of Anti-Infective Drug Products (for drug products with anti-infective 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, 10903 New Hampshire Ave., Bldg. 75, Silver Spring, MD 20993-0002.

All other communications about this action should be directed to: Kathleen Joyce, Division of Prescription Drugs, Office of Unapproved Drugs and Labeling Compliance, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 5236, Silver Spring, MD 20993-0002; 301-796-3329 or email: Kathleen.Joyce@fda.hhs.gov.

FOR FURTHER INFORMATION CONTACT: Kathleen Joyce, Division of Prescription Drugs, Office of Unapproved Drugs and Labeling Compliance, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 5236, Silver Spring, MD 20993-0002; 301-796-3329 or email: Kathleen.Joyce@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing its intention to take enforcement action against certain unapproved and misbranded otic drug products labeled for prescription use. These marketed unapproved and misbranded otic drug products are labeled for, among other things, the temporary relief of pain associated with ear infections or inflammation, including acute otitis media (middle ear infection), otitis media with effusion (fluid in the ear, but without infection), and acute otitis externa (infection in the outer ear or “swimmer’s ear”). Other indications for these unapproved drug products include anti-infective and anti-inflammatory claims, as well as claims for the removal of cerumen (earwax).

This notice covers the following marketed unapproved prescription otic drug products: (1) Single-ingredient otic drug products containing benzocaine; (2) fixed-dose combination otic drug products containing benzocaine and antipyrine; (3) fixed-dose combination otic drug products containing benzocaine, antipyrine, and zinc acetate; (4) fixed-dose combination otic drug products containing benzocaine, chloroxylenol, and hydrocortisone; (5) fixed-dose combination otic drug products containing chloroxylenol and pramoxine; and (6) fixed-dose combination otic drug products containing chloroxylenol, pramoxine, and hydrocortisone. These drug products are marketed without evidence of safety and effectiveness, present safety concerns, and pose a direct challenge to the new drug approval system and, in some cases, the OTC drug monograph system.

For example, FDA is aware of many unapproved and misbranded prescription fixed-dose combination drug products containing benzocaine and antipyrine that are labeled for use for the prompt relief of pain and reduction of inflammation in the congestive and serous stages of acute otitis media and for adjuvant therapy during systemic antibiotic administration for resolution of acute otitis media. These products have also been labeled to facilitate the removal of excessive

or impacted cerumen. FDA has received at least five adverse event reports of allergic reactions to these drug products, including angioedema of the ear, eye, face, neck, and/or mouth. We are also aware of at least one case of methemoglobinemia associated with the administration of an otic product containing benzocaine in an infant, which resulted in death (Ref. 1).

Methemoglobinemia is a serious blood disorder in which an abnormal amount of methemoglobin (a form of hemoglobin) is produced (Ref. 2). Other less serious adverse reactions associated with these products include contact hypersensitivity, pruritus, stinging, burning, and irritation.

FDA is also aware of at least one unapproved and misbranded prescription single-ingredient otic drug product containing benzocaine that is labeled for use as a topical anesthetic in the external auditory canal to relieve ear pain, and for the treatment of acute otitis media, acute swimmer's ear, and other forms of otitis externa. Potential adverse reactions include methemoglobinemia, local burning, stinging, tenderness or edema, and hypersensitivity reactions.

FDA is aware of an unapproved and misbranded prescription fixed-dose combination drug product containing benzocaine, antipyrine, and zinc acetate that is labeled with an indication to relieve pain, congestion, and swelling caused by middle ear inflammation (acute otitis media), and to help remove earwax. Potential adverse reactions include methemoglobinemia and contact hypersensitivity, pruritus, stinging, burning, and irritation.

FDA is also aware of an unapproved and misbranded prescription fixed-dose combination drug product containing benzocaine, chloroxylenol, and hydrocortisone that is labeled for the treatment of superficial infections of the external auditory canal complicated by inflammation caused by organisms susceptible to the action of the antimicrobial, and to control itching in the auditory canal. Unapproved and misbranded prescription fixed-dose combination

products containing chloroxylenol and pramoxine are also on the market and labeled for treating superficial external ear infections and the associated itching. Potential adverse reactions for these fixed-dose combination products include contact hypersensitivity, pruritus, stinging, burning, and irritation.

In addition, FDA is aware of various unapproved and misbranded prescription fixed-dose combination drug products containing chloroxylenol, pramoxine, and hydrocortisone that are labeled with analgesic, anti-inflammatory and anti-infective indications. The chloroxylenol, pramoxine, and hydrocortisone drug products are labeled for the treatment of superficial infections of the outer ear, inflammation, and itching. Potential adverse reactions include pruritus, stinging, burning, and irritation.

In addition to the safety concerns listed previously, these drugs present direct challenges to the FDA drug approval system and, in some cases, the OTC monograph system. These drugs directly challenge the new drug approval system by competing with approved otic drug products appropriately labeled for anti-inflammatory uses and the treatment of otitis externa. The unapproved and misbranded drug products covered by this notice also pose a direct challenge to the OTC drug monograph system because they compete with legally marketed OTC products labeled for cerumen removal and ear drying aid indications under an OTC drug monograph (part 344 (21 CFR part 344)).

For the reasons described in sections II and III, among others, FDA's drug approval process is critical to protecting the public health. Drugs are evaluated by FDA before being marketed to ensure that they are safe and effective for their intended uses and are only approved

for marketing after a careful risk-benefit analysis. The drug approval process is designed to avoid the risks associated with potentially unsafe, ineffective, and fraudulent drugs.¹

II. Safety and Effectiveness Concerns With Unapproved New Drugs

The new drug approval process affords FDA the opportunity to review and evaluate a drug before it is marketed to ensure safety, efficacy, and quality. This includes reviewing the processes used to manufacture the active pharmaceutical ingredient(s) and the finished drug product, and the labeling of the drug product. Because marketed unapproved new drug products have not undergone FDA's rigorous premarket review and approval process, they may present safety risks. This is particularly true because FDA has not reviewed and approved the label for unapproved new drugs, so some unapproved drug labeling omits or modifies safety warnings or other information that is important to ensure safe use, such as drug interactions or potential adverse experiences.

With respect to the otic drug products subject to this notice, FDA is particularly concerned about pediatric labeling because these drug products are often prescribed for young children, a population most susceptible to ear infections (Ref 3). FDA has not assessed the scientific support, if any, for the use of these drug products in pediatric populations. In other words, none of these products have been shown to be safe for use in any population, including children or infants. In fact, as described in section I, FDA has received at least five adverse events reports associated with unapproved prescription otic products. There is also the potential for rare, but serious adverse events to occur, including methemoglobinemia, a dangerous blood disorder. Not all of these adverse events are included in the labeling for these unapproved drug products.

¹ See "Marketed Unapproved Drugs --Compliance Policy Guide" (Marketed Unapproved Drugs CPG) at 5, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070290.pdf>.

FDA also has concerns regarding the manufacturing processes for unapproved new drugs. When new drugs are marketed without FDA approval, FDA does not have an opportunity, prior to product marketing, to determine whether the manufacturing processes for the drugs are adequate to ensure that they are of suitable quality.

For example, the Agency scrutinizes the chemistry, manufacturing, and controls involved in producing the active pharmaceutical ingredient (API or drug substance) and finished dosage form or drug product.² With respect to the drug substance, FDA's examination includes the following: (1) Physical and chemical characteristics and stability of the drug substance; (2) the process controls used in manufacturing and packaging; and (3) specifications necessary to ensure the identity, strength, quality, and purity of the drug substance. For the drug product, FDA's review includes the following: (1) The specifications for the components used in the manufacture of the drug product; (2) manufacturing and packaging procedures and process controls; and (3) the specifications necessary to ensure the identity, strength, quality, and purity of the drug product. Unapproved drug products do not undergo this review process, and therefore the quality of the finished drug product is uncertain.

Because unapproved new drugs have not been subject to FDA's premarket review and approval process, FDA cannot be sure that unapproved drugs are effective. Section 505(d) of the FD&C Act requires "substantial evidence" of safety and effectiveness. "Substantial evidence" is evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be

² See, generally, § 314.50(d) (21 CFR 314.50(d)). See also section 505(d)(3) of the FD&C Act requiring FDA to determine whether the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such a drug are adequate to preserve its identity, strength, quality, and purity.

concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof (section 505(d)(7) of the FD&C Act).

Among other characteristics, an adequate and well-controlled study must use a design that permits a valid comparison with a control to provide a quantitative assessment of the pertinent drug effects (§ 314.126(b)(2)) (21 CFR 314.126(b)(2)). The method of selection of subjects must assure that those subjects have the disease or condition being studied (§ 314.126(b)(3)) .

A review of the current literature suggests that the efficacy of unapproved prescription otic drugs in managing pain associated with ear infections is uncertain (Ref. 4). Use of unapproved products of uncertain efficacy may delay treatment with products that have been proven to be effective, leading to undue prolonged pain and discomfort.

In conclusion, these drug products are marketed without evidence of safety and effectiveness; present actual and potential safety concerns; and pose a direct challenge to the new drug approval system. In some cases, they may directly challenge the OTC drug monograph system.

III. Legal Status of Products Identified in This Notice

FDA has reviewed the publicly available scientific literature for the following unapproved prescription drug products: (1) Single-ingredient otic drug products containing benzocaine; (2) fixed-dose combination otic drug products containing benzocaine and antipyrine; (3) fixed-dose combination otic drug products containing benzocaine, antipyrine, and zinc acetate; (4) fixed-dose combination otic drug products containing benzocaine, chloroxylenol, and hydrocortisone; (5) fixed-dose combination otic drug products containing chloroxylenol and

pramoxine; and (6) fixed-dose combination otic drug products containing chloroxylonol, pramoxine, and hydrocortisone. 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 new drug applications (NDAs) or abbreviated new drug applications (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. If an unapproved drug product covered by this notice 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. A 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 FDA-approved labeling (21 CFR 201.100(c)(2) and 201.115). Because the 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 are misbranded under section 502(f)(1) of the FD&C Act.

If a drug covered by this notice 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).

The final OTC drug monograph in part 344, “Topical Otic Drug Products for Over-the-Counter Human Use” (Topical Otic Drug monograph), permits the use of carbamide peroxide 6.5 percent formulated in an anhydrous glycerin vehicle as an active ingredient for earwax removal, in the amounts and under the conditions specified in the final Topical Otic Drug monograph (see § 344.10). The final OTC drug monograph also permits the use of isopropyl alcohol 95 percent in an anhydrous glycerin 5 percent base as an ear drying aid in the amounts and under the conditions specified in the final Topical Otic Drug monograph (see § 344.12).

The final Topical Otic Drug monograph is the only monograph that specifies the requirements for marketing an OTC drug for cerumen removal. Unless a product included in this notice was reformulated and labeled to meet all the requirements of the final Topical Otic Drug monograph, the product would require an approved NDA or ANDA to be legally marketed.³

IV. Notice of Intent to Take Enforcement Action

Although not required to do so by the Administrative Procedure Act, by the FD&C Act (or any rules issued under its authority), or for any other legal reason, FDA is providing this notice to persons⁴ who are marketing the following unapproved and misbranded drugs labeled for prescription use: (1) Single-ingredient otic drug products containing benzocaine; (2) fixed-dose combination otic drug products containing benzocaine and antipyrine; (3) fixed-dose combination otic drug products containing benzocaine, antipyrine, and zinc acetate; (4) fixed-dose combination otic drug products containing benzocaine, chloroxylenol, and hydrocortisone; (5) fixed-dose combination otic drug products containing chloroxylenol and pramoxine; and (6) fixed-dose combination otic drug products containing chloroxylenol, pramoxine, and

³ In addition to any other applicable requirements, firms that manufacture OTC drugs must comply with the labeling requirements in 21 CFR 201.66.

⁴ The term “person” includes individuals, partnerships, corporations, and associations (21 U.S.C. 321(e)).

hydrocortisone. 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.⁵ Consistent with policies described in the Agency's Marketed Unapproved Drugs CPG (available at <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 (see Marketed Unapproved Drugs CPG at 5).

As described in the Marketed Unapproved Drugs CPG, the Agency may, at its discretion, identify a period of time (i.e., a grace period) during which the Agency does not intend to initiate an enforcement action against a currently marketed unapproved drug solely on the grounds that the drug lacks an approved application under section 505 of the FD&C Act. In deciding whether to allow such a grace period, the Agency considers several factors, which are described in the Marketed Unapproved Drugs CPG. With respect to drug products covered by this notice, the Agency intends to exercise its enforcement discretion for only a limited period of

⁵ In fact, U.S. Marshals seized \$16.5 million of Auralgan Otic Solution (which contains antipyrine and benzocaine) after Deston continued to market the unapproved new drug following an FDA warning letter. See <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm243638.htm>.

time, because there are readily available legally marketed alternatives. Therefore, the Agency intends to implement this notice as follows.

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 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 1, 2015, and is manufactured, shipped, or otherwise introduced or delivered for introduction into interstate commerce by any person on or after July 1, 2015. 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 sold⁶ in the United States before July 1, 2015, 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 notice 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 July 1, 2015 (“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

⁶ For the purpose 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.

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]. Furthermore, 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 ensure a smooth transition for consumers. 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 either of the following applies: (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 drug 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.⁷

Nothing in this notice, 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

⁷ If FDA decides to take enforcement action against a product covered by this notice, the Agency may simultaneously take action relating to defendant's other violations of the FD&C Act. 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").

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 a National Drug Code (NDC) number listed with the Agency in full compliance with section 510 of the FD&C Act before July 1, 2015. 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 discontinuing the listing as required under section 510(j) of the FD&C Act. Other firms may discontinue manufacturing or distributing listed products in response to this notice. All 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 notice (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) have been discontinued.

The letter should be sent electronically to Kathleen Joyce (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 considering enforcement action.

VI. Reformulated Products

FDA cautions firms against reformulating their products into unapproved new drugs without benzocaine; benzocaine and antipyrine; benzocaine, antipyrine, and zinc acetate; benzocaine, chloroxylenol, and hydrocortisone; chloroxylenol and pramoxine; or chloroxylenol, pramoxine, and hydrocortisone 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 but have not been brought into compliance with the law. 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.

VIII. References

The following references have been placed on display in the Division of Dockets Management (see ADDRESSES) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday, and are available electronically at <http://www.regulations.gov>.

1. Logan, B. K. and A.M. Gordon, "Case Report: Death of an Infant Involving Benzocaine," Journal of Forensic Sciences, vol. 50, pp. 1486-1488, 2005.

2. Cortazzo, J. A. and A. D. Lichtman, "Methemoglobinemia: A Review and Recommendations for Management." Journal of Cardiothoracic and Vascular Anesthesia, vol. 28(4), pp. 1055-1059. 2014.

3. Lieberthal, A. S., A. E. Carroll, T. Chonmaitree, et al., "The Diagnosis and Management of Acute Otitis Media," Pediatrics, vol. 131, pp. e964-e999, 2013.

4. Wood, D. N., N. Naas, and C. W. Gregory, "Clinical Trials Assessing Otological Agents in the Treatment of Pain Associated with Acute Otitis Media in Children," International Journal of Otorhinolaryngology, vol. 76, pp. 1229-1335, 2012.

Dated: June 26, 2015.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2015-16360 Filed: 7/1/2015 08:45 am; Publication Date: 7/2/2015]