



May 21, 2018

Dear CEO or President:

This letter concerns over-the-counter (OTC) oral health care drug products containing benzocaine, which are now or have previously been manufactured, repackaged, relabeled, or distributed by your firm. Your firm is receiving this letter based on drug registration and listing information provided to the Food and Drug Administration (FDA or Agency). As described in further detail below, FDA requests that your firm take swift action to relabel or discontinue the distribution and sale of certain OTC oral health care drug products containing benzocaine, based on evidence that these products pose a serious and potentially fatal risk of methemoglobinemia to infants, children, and adults.

This letter is an initial FDA measure towards addressing the risk of methemoglobinemia associated with OTC oral health care drug products containing benzocaine. The Agency intends to take administrative action in the near future with respect to these products, either by rulemaking or by the processes established under OTC monograph reform legislation.¹

BACKGROUND

Benzocaine is an active ingredient in several types of OTC oral health care drug products, including oral anesthetic and analgesic drug products that are marketed for the temporary relief of pain due to minor irritation, soreness, or injury of the mouth and throat. OTC oral health care drug products containing benzocaine are marketed in a variety of dosage forms, including gels, sprays, ointments, solutions, and lozenges.

In 1991, the Agency amended the Oral Health Care Drug Products Tentative Final Monograph (TFM), proposing conditions under which OTC oral health care drug products containing benzocaine would be considered generally recognized as safe and effective (GRAS/E) and not misbranded.² FDA generally has exercised enforcement discretion to allow OTC oral health care

¹ Legislative reforms intended to modernize and support FDA's OTC drug monograph activities to better serve patients, consumers, and industry are under active consideration in Congress. *See generally* Over-the-Counter Drug Safety, Innovation, and Reform Act, S. 2315, 115th Cong. (2018); Over-the-Counter Monograph Safety, Innovation, and Reform Act, H.R. 5333, 115th Cong. (2018); *Executive Session: S. 2315 and Other Legislation: Hearing of the S. Comm. on Health, Education, Labor & Pensions*, 115th Cong. (2018); *Executive Session: H.R. 5333 and Other Legislation: Hearing of the H. Comm. on Energy & Commerce*, 115th Cong. (2018). Generally, a feature that is common to these proposed legislative reforms is that they would transform FDA's system of regulating OTC drugs from a rulemaking paradigm to an administrative order process.

² *See generally* 56 Fed. Reg. 48,302 (Sept. 24, 1991). The Oral Health Care Drug Products TFM is a proposed rule and thus does not represent a final determination by the Agency that OTC oral health care drug products containing benzocaine are GRAS/E under certain conditions of use. Therefore, prior to publication of a final OTC monograph for oral health care drug products containing benzocaine, such products lacking approved new drug applications are unapproved new drugs, including those that are marketed in accordance with the proposed conditions in the Oral

drug products containing benzocaine to be marketed, provided that they meet the conditions proposed in the TFM or have the same or similar formulation and labeling as products marketed at the inception of the OTC Drug Review.³

ASSOCIATION BETWEEN BENZOCAINE AND METHEMOGLOBINEMIA

In recent years, the association between the use of OTC oral health care drug products containing benzocaine and methemoglobinemia has become increasingly well-documented.⁴ Methemoglobinemia is a potentially serious condition where the amount of oxygen carried through the blood stream is greatly reduced. The symptoms of methemoglobinemia can include pale, gray, or blue colored skin, headache, light-headedness, shortness of breath, fatigue, and rapid heart rate.⁵ Benzocaine-induced methemoglobinemia can be fatal, particularly when it is not identified and treated promptly.⁶ Importantly, benzocaine-induced methemoglobinemia may occur after a single exposure and in persons who have previously been exposed to benzocaine without incident.⁷

Health Care Drug Products TFM. See 21 C.F.R. § 330.10(a)(7) (stating that a TFM is a “tentative order establishing conditions under which a category of OTC drugs or specific OTC drugs are generally recognized as safe and effective and not misbranded”) (emphasis added).

³ See 79 Fed. Reg. 10,168, 10,169 (Feb. 24, 2014); 68 Fed. Reg. 75,585, 75,590 (Dec. 31, 2003).

⁴ In addition to the reviews described in this letter, FDA has also investigated the association between methemoglobinemia and OTC oral health care drug products containing benzocaine by consulting the Drug Safety Oversight Board (DSB) and funding a published study. See Hartman N.R., et al., *More Methemoglobin Is Produced by Benzocaine Treatment than Lidocaine Treatment in Human In Vitro Studies*, 70 Regulatory Toxicology & Pharmacology 182 (2014) (investigating the relative ability of benzocaine and lidocaine to produce methemoglobin *in vitro*); FDA, Public Summary: DSB Meeting (Sept. 19, 2013), available at <https://wayback.archive-it.org/7993/20170406045837/https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm375153.htm>; FDA, Memorandum of Meeting Minutes (Benzocaine and Methemoglobinemia), DSB Meeting (Nov. 18, 2010).

FDA has issued several communications to consumers, health care providers, and manufacturers regarding the risks of methemoglobinemia associated with OTC oral health care benzocaine products as evidence of this association continued to mount. See, e.g., FDA, Consumer Update: Do Teething Babies Need Medicine on Their Gums? No (June 26, 2014), available at <https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm385817.htm> (communicating the risks of using local anesthetics such as viscous lidocaine- or benzocaine-containing products to treat teething pain and recommending the use of safer alternatives such as teething rings and washcloths instead); FDA, Letter to Consumer Healthcare Products Association (CHPA) (May 12, 2014) (stating that FDA did not intend to object if manufacturers of OTC oral health care benzocaine products labeled their products with the methemoglobinemia warning described in the letter).

⁵ Kaufman MR, Aouad RK. Benzocaine-induced methemoglobinemia. J Emerg Med. 2017 Dec;53(6):912-913.

⁶ Aryal MR, et al. Benzocaine-induced methaemoglobinaemia: a life-threatening complication after a transoesophageal echocardiogram (TEE). BMJ Case Reports. 2013.

⁷ Guay J. Methemoglobinemia related to local anesthetics: a summary of 242 episodes. Anesth Analg. 2009 Mar;108(3):837-45.

FDA has conducted multiple reviews of the FDA Adverse Event Reporting System (FAERS) and published literature to identify and evaluate cases of benzocaine-associated methemoglobinemia. Based on these reviews, FDA estimates that more than 400 cases of benzocaine-associated methemoglobinemia occurring in the U.S. have been reported to FAERS and published in the medical literature since 1971.⁸ FDA's most recent reviews found 111 FAERS cases involving methemoglobinemia associated with topical drug products containing benzocaine (including oral health care drug products), as well as 8 non-FAERS cases from the literature, for a total of 119 cases reported or published between February 26, 2009 and October 6, 2017.

Of the 119 cases, four resulted in death, including the death of a 4-month old infant who was administered a topical OTC oral health care product containing benzocaine to treat sore gums due to teething. The vast majority of the reported outcomes in these cases were serious (97.5%, 116/119).⁹ Eight pediatric cases involved the use of benzocaine products to treat teething pain. At least 35 cases have been reported to FAERS and in the medical literature since May 12, 2014, the date on which FDA stated that it did not intend to object if manufacturers of OTC oral health care drug products containing benzocaine labeled their products with a warning regarding methemoglobinemia.¹⁰ The cases occurring after this date include two deaths, one of which was the infant mentioned above.

REQUESTED ACTIONS

Based on the recent reviews of information described above demonstrating the well-documented association between OTC oral health care drug products containing benzocaine and methemoglobinemia, FDA believes it imperative for firms manufacturing and distributing these products to act expeditiously to mitigate the serious risks they pose to consumers and, therefore, requests that your firm take the following steps as soon as possible¹¹:

⁸ One of FDA's reviews summarized 322 cases of methemoglobinemia associated with benzocaine reported to FDA from 1971 to February 25, 2009. The review found that cases occurred across all age groups; more than 75% involved life-threatening or serious outcomes, and 7 resulted in death.

⁹ Under 21 CFR § 314.80, a serious adverse drug experience is one that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, congenital anomaly/birth defect, or other important medical events.

¹⁰ Letter from FDA to Consumer Healthcare Products Association (May 12, 2014), *available at* <https://wayback.archive-it.org/7993/20170113092434/http://www.fda.gov/downloads/Drugs/DrugSafety/UCM396988.pdf>.

¹¹ Please note that registrants of establishments that manufacture, repack, relabel, or salvage OTC drugs must review and update their drug listing information each June and December. 21 C.F.R. § 207.57(b). With respect to OTC benzocaine products indicated for the temporary relief of sore gums due to infant teething, registrants that discontinue the marketing of these products must submit a delisting for each product NDC. With respect to OTC oral health care benzocaine products intended for other uses, registrants must submit any material changes in the labeling of their products and any other information previously submitted pursuant to § 207.49 or other relevant sections of part 207. *Id.* Registrants are encouraged to update listing information at the time of any change affecting information previously submitted. § 207.57(c).

1. Address the risks to infants by:

- a. Discontinuing the distribution and sale of OTC oral health care drug products containing benzocaine whose labeling prescribes, recommends, or suggests that the product is intended for:***
 - i. the temporary relief of sore gums due to teething; or***
 - ii. use in infants or children under 2 years of age.***

Based on our reviews, we believe that OTC oral health care drug products containing benzocaine should not be used in infants (defined as one month to two years old) under any circumstances, including under the advice and supervision of a health care provider. Warnings directed to caregivers would provide insufficient protection to infants against the risk of benzocaine-induced methemoglobinemia, as infants are generally unable to communicate to caregivers that they are experiencing methemoglobinemia symptoms. As such, many caregivers may not recognize the infant's hypoxia and thus may not seek medical care in a timely fashion, leaving infants at increased risk for a serious adverse event. For these reasons, a warning for methemoglobinemia is unlikely to be useful to include in the labeling of anesthetic/analgesic products intended for use in infants.

Additionally, infants are at increased risk for benzocaine-induced methemoglobinemia, even when appropriate dosing guidelines are followed. The increased risk is due to a greater proportion of drug absorbed per kilogram of body weight due to their increased body-surface-area-to-body-mass ratio compared to adults.¹² Being less than 6 months old is also a predisposing risk factor for methemoglobinemia.¹³ Younger infants (especially those under 4 months of age) are at added risk for methemoglobinemia because they have a smaller supply of nicotinamide adenine dinucleotide (NADH)-dependent methemoglobin reductase, which supports methemoglobin homeostasis. Thus, younger infants may be sensitive to even low methemoglobin levels.

Moreover, any potential benefits of using OTC oral health care drug products containing benzocaine to treat sore gums due to teething do not outweigh the risks of methemoglobinemia associated with such products. In addition to the safety concerns discussed above, the Agency is unaware of any recent studies demonstrating the effectiveness of benzocaine for relieving teething pain. There are safer non-drug alternatives available for teething pain. The American Academy of Pediatrics (AAP) recommends against use of any prescription or OTC pain relievers or medications that contain benzocaine on infants' gums because they are not useful for the relief

¹² Lehr, J et al. Benzocaine-induced methemoglobinemia in the pediatric population. *J Pediatr Nurs* 2012;27:583-588.

¹³ See Institute for Safe Medication Practices (ISMP) Medication Safety Alert, Benzocaine-containing topical sprays and methemoglobinemia, October 3, 2002, available at <https://www.ismp.org/newsletters/acutecare/articles/20021003.asp>.

of teething pain due to the fact that they wash out of an infant's mouth within minutes of application. Instead, the AAP recommends that caregivers give infants a teething ring to dull pain. The American Dental Association recommends rubbing the child's gums or having the child chew on a clean teether to help with sore or tender gums.

b. Revising the Drug Facts Label of OTC oral health care drug products containing benzocaine with an intended use other than the temporary relief of sore gums due to teething or in infants and children under 2 years of age:

i. Add the following contraindications as the last two bullets in the contraindications section:

“[Do not use]

- [Any other contraindications described in the TFM or in the label of a product marketed at the inception of the OTC Drug Review]
- for teething
- in children under 2 years of age”; and

ii. Add a statement as the last statement under the heading “Directions” informing caregivers that the products should not be used to treat children under 2 years of age, e.g.:

“children under 2 years of age: do not use.”¹⁴

As noted above, OTC oral health care drug products containing benzocaine should not be used to treat teething pain or in infants and children under 2 years of age in any circumstances. Because OTC benzocaine products have been indicated and used for the temporary relief of sore gums due to teething for many years, there is reason to believe that consumers may use products labeled for use in adults and children 2 years and older to treat teething pain and sore gums in infants and children under 2 years, especially once teething products become unavailable. Therefore, we believe it would be appropriate for all OTC oral health care benzocaine anesthetic/analgesic products that remain on the market to bear labeling that includes a contraindication against use to treat teething pain. Additionally, given the Oral Health Care Drug Products TFM's proposed directions regarding consultation of a healthcare professional before use in children under 2 years of age, the Agency believes a contraindication against use in children under 2 years of age would be appropriate to ensure consistency with the contraindication against use for teething.

2. Address the risks to adults and children by revising the Drug Facts Label of OTC oral health care drug products containing benzocaine intended for adults and children 2

¹⁴ This statement should replace any directions that are currently in the Drug Facts Label directing caregivers to consult a health care provider before using the product to treat children under 2 years of age.

years of age and older by adding a warning that is the first statement under the heading “Warnings” providing as follows:

“Methemoglobinemia warning [these two words in bold print]: Use of this product may cause methemoglobinemia, a serious condition that must be treated promptly because it reduces the amount of oxygen carried in blood. This can occur even if you have used this product before. Stop use and seek immediate medical attention if you or a child in your care develops:

- pale, gray, or blue colored skin (cyanosis)
- headache
- rapid heart rate
- shortness of breath
- dizziness or lightheadedness
- fatigue or lack of energy”.

Deaths and other adverse events due to benzocaine-associated methemoglobinemia have continued despite the Agency’s previous safety actions, including its May 12, 2014 letter to CHPA in which the Agency stated that it did not intend to object if manufacturers added a methemoglobinemia warning to their products’ Drug Facts Labels (DFLs). To our knowledge, manufacturers of OTC oral health care drug products containing benzocaine did not widely adopt the methemoglobinemia warning on the DFL of their products. Additionally, since FDA’s decision not to object to the voluntary addition of a methemoglobinemia warning, FDA is aware of at least 35 cases of benzocaine-associated methemoglobinemia that have been reported to FAERS or in the medical literature after this date. For these reasons, the Agency now urges all manufacturers, repackagers, relabelers, and distributors of OTC oral health care drug products containing benzocaine intended for use in adults and children 2 years of age and older to take immediate steps to relabel their products with a warning on their DFL concerning the risk of methemoglobinemia and the signs and symptoms of this disorder.

Please see the enclosed “Sample Drug Facts Label,” which shows how the DFL of OTC oral health care drug products intended for adults and children 2 years and older should appear once the changes described above are made. Pending the outcome of forthcoming administrative action, FDA does not intend to object to the marketing of an OTC oral health care drug product intended for adults and children 2 years of age and older whose DFL is modified in response to the requested changes described above, so long as the product is otherwise in conformance with the conditions proposed in the Oral Health Care Drug Products TFM or otherwise has the same or similar labeling and formulation as products marketed at the inception of the OTC Drug Review.

FUTURE AGENCY ACTIONS

We expect that your firm will comply with our request to discontinue OTC oral health care drug products containing benzocaine intended for use to treat teething pain or in infants and children under 2 years of age, and to relabel other products to bear a warning regarding methemoglobinemia and a contraindication against use in infants as soon as possible.

In addition, please note that on Wednesday, May 23, 2018, FDA intends to issue public communications regarding this letter and to disseminate communications to consumers and health care providers to alert them of the serious health risks associated with these products.

Finally, we want to advise you that FDA continues to review information regarding the risks of methemoglobinemia posed by OTC oral health care drug products containing benzocaine and intends to monitor industry's response to this letter. This letter is an initial measure towards addressing this serious health risk, and the Agency intends to take administrative action in the near future with respect to these products, either by rulemaking or the processes established under OTC monograph reform legislation.

If you have any questions about the contents of this letter, please contact benzocaineinfo@fda.hhs.gov.

Sincerely,

A handwritten signature in black ink, appearing to read 'J. Woodcock', with a long horizontal flourish extending to the right.

Janet Woodcock, MD
Director, Center for Drug Evaluation and Research

Enclosure: Sample Drug Facts Label