



Michael A. Carome, M.D.
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Roma Rajput
Public Citizen
1600 20th Street, NW
Washington, DC 20009

Re: Docket No. FDA-2014-P-1256

MAY 24 2018

Dear Dr. Carome, Ms. Sorscher, and Ms. Rajput:

This letter responds to Public Citizen's citizen petition dated July 28, 2014 (Petition). In the Petition, you request that the Food and Drug Administration (FDA or Agency) take the following actions:

- (1) "Reopen the administrative record for the monograph for OTC oral health care drug products.";
- (2) "Revise the proposed required labeling for OTC benzocaine oral health care drug products to remove the infant teething indication and include a contraindication advising against using gel and liquid benzocaine products for teething pain."; and
- (3) "Require a warning label for all remaining OTC benzocaine products covered by the monograph."

(Petition at 1, 3).

We have carefully considered your requests and share your concerns regarding the risk to public health posed by over-the-counter (OTC) oral health care drug products containing benzocaine. In particular, we agree that any potential benefits of using OTC oral health care drug products containing benzocaine to treat sore gums in infants and children due to teething do not outweigh the risks of methemoglobinemia associated with these products. We also agree that there are methemoglobinemia risks for adults and children 2 years and older when using OTC oral health care drug products containing benzocaine.

In light of the serious and potentially fatal risk of methemoglobinemia that OTC oral health care drug products containing benzocaine pose to the public, we believe that the most appropriate immediate steps are: (1) to seek swift action from industry to relabel or discontinue the distribution and sale of such products as described further below, and (2) to communicate with patients and health care providers to alert them of the serious health risks associated with these products.

Accordingly, FDA recently wrote to each registered manufacturer, repackager, relabeler, and distributor of OTC oral health care drug products containing benzocaine requesting that they promptly take the following steps:

1. Address the risk 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; and
 - b. Revising the Drug Facts Label (DFL) 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 to add contraindications and other statements warning against use of the product in infants and children under 2 years of age.
2. Address the risk to adults and children 2 years and older by adding a methemoglobinemia warning to the DFL of products intended for this age group.

At the same time, FDA has issued extensive public communications to alert patients and health care providers of the serious health risks associated with OTC oral health care benzocaine products. FDA's recent outreach efforts include a Drug Safety Communication and several materials directed to consumers and the general public.¹ In these communications, FDA has made it clear that "[i]f companies do not comply, the FDA will initiate a regulatory action to remove these products from the market."²

We believe these initial measures are appropriate to address the risk of methemoglobinemia associated with OTC oral health care benzocaine products, given the evolving legislative landscape for reforming FDA's system of regulating OTC drugs.³

¹ FDA, Safety Information on Benzocaine-Containing Products webpage, available at, <https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm273111.htm> (updated May 23, 2018, accessed on May 23, 2018).

² See FDA News Release, "FDA takes action against the use of OTC benzocaine teething products due to serious safety risk, lack of benefit", May 23, 2018, available at <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm608325.htm>.

³ 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.

Thus, to the extent your Petition requests that the Agency issue a new proposed rule in the first instance to address this risk, the Petition is denied. Nonetheless, FDA continues to actively review safety and effectiveness data, including information regarding the risks of methemoglobinemia, for OTC oral health care drug products containing benzocaine and intends to take administrative action in the near future with respect to these products, either by rulemaking or by the process that would be established under OTC monograph reform legislation.

This response discusses the Agency's current approach for addressing the risk of methemoglobinemia posed by OTC oral health care drug products containing benzocaine.

I. BACKGROUND

A. Regulatory Framework

1. The OTC Drug Review

The OTC Drug Review is FDA's process for establishing conditions under which OTC drugs are generally recognized as safe and effective (GRASE) and not misbranded.⁴ FDA does not require a drug that meets each of the conditions in 21 CFR part 330 and an applicable OTC drug final monograph to have an approved new drug application (NDA) under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) prior to marketing.

The notice and comment rulemaking procedures for evaluating therapeutic categories of drugs and establishing OTC drug monographs for each category are set forth in § 330.10. This regulation describes a multi-step rulemaking process to establish an OTC monograph for a therapeutic category of drugs. These steps include publication of a (1) Proposed Monograph or Advance Notice of Proposed Rulemaking (ANPR), (2) Tentative Final Monograph (TFM) or Proposed Rule, and (3) Final Monograph or Final Rule.

Prior to the publication of a Final Monograph, drugs that are the subject of an ongoing monograph rulemaking proceeding are not GRASE and therefore are "new drugs" under section 201(p) of the FD&C Act (21 U.S.C. 321(p)).⁵ Such products lacking approved NDAs are unapproved new drugs under section 505 of the FD&C Act. Generally, FDA's regulatory approach to unapproved new OTC drugs has been to exercise enforcement discretion with respect to the marketing of products that are in conformance with the conditions proposed in a TFM or have the same or similar formulation and labeling as a product marketed at the inception of the OTC Drug Review.⁶

⁴ 21 CFR 330.1.

⁵ 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." 21 C.F.R. 330.10(a)(7) (emphasis added).

⁶ See 79 FR 10168 at 10169 (Feb. 24, 2014); 68 FR 75585 at 75590 (Dec. 31, 2003).

2. *Benzocaine Under the Oral Health Care Drug Products Tentative Final Monograph*

On September 24, 1991, FDA published the amended TFM for OTC oral health care drug products (hereinafter OHDP TFM) based on the recommendations of the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products (Dental Panel) and the Advisory Review Panel on OTC Oral Cavity Drug Products (Oral Cavity Panel).⁷ As amended, the OHDP TFM proposed that anesthetic/analgesic oral health care drug products containing benzocaine as an active ingredient would be GRASE under certain conditions of use.

The OHDP 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 GRASE under certain conditions of use. Therefore, prior to the publication of a Final Monograph for OTC oral health care drug products containing benzocaine, such products lacking approved NDAs are unapproved new drugs, including those that are marketed in conformance with the proposed conditions in the OHDP TFM.⁸ Consistent with the Agency's regulatory approach to unapproved new OTC drugs, FDA generally has exercised enforcement discretion with respect to the marketing of OTC oral health care drug products containing benzocaine that meet the conditions proposed in the OHDP TFM or have the same or similar formulation and labeling as products marketed at the inception of the OTC Drug Review.

a. Proposed indications

One indication proposed by the OHDP TFM for OTC oral health care drug products containing benzocaine is the temporary relief of minor painful conditions of the mouth such as canker sores, minor dental procedures, sore throat, irritation or injury of the mouth and gums, and irritation caused by dentures or orthodontic appliances in adults and children 2 years of age and older.⁹ Another proposed indication for such products is the temporary relief of sore gums due to teething in infants and children 4 months of age and older.¹⁰

b. Proposed warnings

The OHDP TFM proposed the following warning for OTC oral health care drug products containing benzocaine indicated for the temporary relief of occasional minor irritation, pain, sore mouth, and sore throat:

If sore throat is severe, persists for more than 2 days, is accompanied or followed by fever, headache, rash, swelling, nausea, or vomiting, consult a doctor

⁷ 56 FR 48302 (Sept. 24, 1991).

⁸ See *supra* note 5.

⁹ 56 FR 48302 at 48343 (Sept. 24, 1991).

¹⁰ *Id.*

promptly. If sore mouth symptoms do not improve in 7 days, or if irritation, pain, or redness persist or worsens, see your dentist or doctor promptly.¹¹

The OHDP TFM proposed the following warning for OTC oral health care drug products containing benzocaine labeled with any other anesthetic/analgesic indication:

Do not use this product for more than 7 days unless directed by a dentist or doctor. If sore mouth symptoms do not improve in 7 days; if irritation, pain, or redness persists or worsens; or if swelling, rash or fever develops, see your dentist or doctor promptly.¹²

The OHDP TFM proposed the following warning for OTC oral health care drug products containing benzocaine in denture adhesive products: "See your dentist as soon as possible."¹³

The OHDP TFM proposed the following warnings for all OTC oral health care drug products containing benzocaine: "Do not exceed recommended dosage. . . . Do not use this product if you have a history of allergy to local anesthetics such as procaine, butacaine, benzocaine, or other 'caine' anesthetics."¹⁴

c. Proposed dosage forms and directions for use

The OHDP TFM proposed the following dosage forms and directions for use for OTC oral health care drug products containing benzocaine:

(i) *For dosage forms other than solid, the product is a 5- to 20-percent solution or suspension.* Adults and children 2 years of age and older: Apply to the affected area. Gargle, swish around in the mouth, or allow to remain in place at least 1 minute and then spit out. Use up to 4 times daily or as directed by a dentist or doctor. Children under 12 years of age should be supervised in the use of the product. Children under 2 years of age: Consult a dentist or doctor.

(ii) *For solid dosage forms, the product contains 2 to 15 milligrams benzocaine.* Adults and children 2 years of age and older: Allow product to dissolve slowly in the mouth. May be repeated every 2 hours as needed or as directed by a dentist or doctor. Children under 2 years of age: Consult a dentist or doctor.

(iii) *For products intended to be used as teething preparations, the product is a 5- to 20-percent solution or suspension.* Apply to the affected area not more than four times daily or as directed by a dentist or doctor. For infants under 4 months of age there is no recommended dosage or treatment except under the advice and supervision of a dentist or doctor.¹⁵

¹¹ Id.

¹² Id.

¹³ Id.

¹⁴ Id.

¹⁵ Id. at 48343-48444.

(iv) *For denture adhesive products the product contains 5 to 20 percent benzocaine. Apply on area of denture that comes in contact with sore gums.*

d. Proposed professional labeling

The OHDP TFM also proposed professional labeling for benzocaine for the temporary relief of pain associated with tonsillitis, pharyngitis, throat infections, Vincent's infection (periodontal disease), or stomatitis (inflammation of the mucous lining of the mouth).¹⁶

3. *Content and Format of Warnings in Labeling for OTC Drugs*

Nonprescription drugs, including those marketed in conformance with the conditions proposed in a TFM, are subject to the labeling requirements in 21 CFR 201.66.¹⁷ This regulation establishes standardized content and format requirements for OTC drug product labeling (Drug Facts labeling). The requirements for the content of warnings in OTC DFLs are described in § 201.66(c)(5). The "Warnings" section contains information that is relevant to both the product selection decision and to proper use by the consumer.¹⁸ This section contains information regarding when the product should absolutely not be used, drug-drug and drug-food interactions, when to consult a doctor or pharmacist before taking the product, possible side effects, and when to stop use and contact a doctor after taking the product.¹⁹

Requirements for contraindications on OTC DFLs are specified at § 201.66(c)(5)(iii). Contraindications are absolute and are intended for situations in which consumers should not use the product unless a prior diagnosis has been established by a doctor or for situations in which certain consumers should not use the product under any circumstances regardless of whether a doctor or health professional is consulted.²⁰

B. Association Between Use of OTC Oral Health Care Drug Products Containing Benzocaine and Methemoglobinemia

1. *Marketed OTC Oral Health Care Drug Products Containing Benzocaine*

Benzocaine is an ester-type local anesthetic and 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

¹⁶ Id. at 48,347.

¹⁷ 21 CFR 201.66(a); see also FDA's guidance for industry *Labeling OTC Human Drug Products – Questions and Answers*. We update guidances periodically. For the most recent version of a guidance, check the FDA Drugs guidance web page at

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

¹⁸ See 64 FR 13254 at 13258 (Mar. 17, 1999).

¹⁹ Id. at 13258-13259.

²⁰ 21 CFR 201.66(c)(5)(iii).

injury of the mouth and throat.²¹ OTC oral health care drug products containing benzocaine are marketed in a variety of dosage forms, including gels, liquids, sprays, ointments, solutions, and lozenges.

Benzocaine products are used in both the inpatient and outpatient settings. Some of these products are accompanied by professional labeling that describes uses such as minor dental procedures,²² whereas others are only labeled with nonprescription uses such as the anesthetic/analgesic indications proposed by the OHDP TFM.

2. *Risk of Methemoglobinemia*

Following the topical application of benzocaine to mucous membranes in the oropharyngeal cavity, it undergoes rapid absorption. Patients exposed to topical benzocaine products have developed methemoglobinemia, a potentially life-threatening blood disorder where too much of the hemoglobin in red blood cells becomes unable to bind and carry oxygen effectively.²³ Methemoglobinemia can be hereditary or acquired. Benzocaine may cause acquired methemoglobinemia by interfering with the reconversion of methemoglobin to hemoglobin. Methemoglobin develops when the iron moiety within hemoglobin is oxidized to the ferric state (Fe^{3+}). Methemoglobin cannot bind oxygen, and the state of methemoglobinemia impairs oxygen offloading into tissues by the remaining circulating hemoglobin. The normal concentration of methemoglobin in the blood is typically less than 1 percent, but concentrations above these levels occur when the production of methemoglobin overwhelms the body's capacity for methemoglobin reduction via enzymatic processes.²⁴ Excessive replacement of hemoglobin with methemoglobin leads to functional anemia and tissue hypoxia.²⁵ In other words, the amount of oxygen carried in blood is reduced.

²¹ Benzocaine is also an active ingredient in several marketed unapproved prescription drug products, including anesthetic and analgesics drug products labeled for topical use on oral mucosa. When we refer to "benzocaine products" in this document, however, we are referring to OTC oral health care benzocaine products.

²² See, e.g., 56 FR 48302 at 48347 (Sept. 24, 1991) (OHDP TFM proposed professional labeling for benzocaine "[f]or the temporary relief of discomfort in patients with an excessive gag reflex when having impressions of the teeth made or during intraoral radiography" and "[f]or use as a preinjection topical anesthetic on oral mucosa").

²³ Coleman, MD and Coleman, NA, 1996. Drug-induced methemoglobinemia: treatment issues. *Drug Saf.* 14, 394–405; Mansouri, A., 1985. Review: methemoglobinemia. *Am. J. Med. Sci.* 289, 200–209; Skold, A., et al., 2011. Methemoglobinemia: pathogenesis, diagnosis, and management. *South. Med. J.* 104, 757–761; Umbreit, J., 2007. Methemoglobin-it's not just blue: a concise review. *Am. J. Hematol.* 82, 134–144.

²⁴ Hartman N.R., et al., *More Methemoglobin Is Produced by Benzocaine Treatment than Lidocaine Treatment in Human In Vitro Studies*, 70 REGULATORY TOXICOLOGY & PHARMACOLOGY 182-188 (2014); Guay J. Methemoglobinemia related to local anesthetics: a summary of 242 episodes. *Anesth. Analg.* 2009 Mar;108(3):837-45. doi: 10.1213/ane.0b013e318187c4b1.

²⁵ Kane, GC, Hoehn, SM, Behrenbeck, TR, Mulvagh, SL, 2007, Benzocaine-Induced Methemoglobinemia Based on the Mayo Clinic Experience From 28 478 Transesophageal Echocardiograms: Incidence, Outcomes, and Predisposing Factors, *Arch Intern Med*;167(18):1977-1982.

Signs and symptoms of acquired methemoglobinemia include pale, gray, or blue colored skin (cyanosis), headache, rapid heart rate, shortness of breath, dizziness or lightheadedness, and fatigue or lack of energy.²⁶ These signs and symptoms may appear within minutes to one or two hours after using benzocaine.²⁷ Benzocaine-induced methemoglobinemia can be fatal, particularly when it is not identified and treated promptly.²⁸ Furthermore, benzocaine-induced methemoglobinemia can occur after a single exposure and in persons who have previously been exposed to benzocaine without incident.²⁹

3. *FDA Reviews of Benzocaine-Associated 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.³⁰ FDA has conducted multiple reviews of the FDA Adverse Event Reporting System (FAERS)³¹ and published literature to identify and evaluate cases of

²⁶ Kaufman, MR, Aouad, RK, 2017, Benzocaine-Induced Methemoglobinemia, *J Emerg Med*, Dec;53(6):912-913. doi: 10.1016/j.jemermed.2017.09.004. Epub 2017, Nov 6.

²⁷ Guay, J, 2009, Methemoglobinemia related to local anesthetics: a summary of 242 episodes, *Anesth Analg*, Mar;108(3):837-45. doi: 10.1213/ane.0b013e318187c4b1.

²⁸ Aryal, MR, Gupta, S, Giri, S, Diaz Fraga, J, 2013, Benzocaine-induced methaemoglobinaemia: a life-threatening complication after a transoesophageal echocardiogram (TEE), *BMJ Case Reports*; 2013:bcr2013009398. doi:10.1136/bcr-2013-009398.

²⁹ RCM# 2017-2053 (Nov. 22, 2017); Guay, J, 2009, Methemoglobinemia related to local anesthetics: a summary of 242 episodes, *Anesth. Analg*, Mar;108(3):837-45. doi: 10.1213/ane.0b013e318187c4b1.

³⁰ In addition to the reviews described in this section, 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* 182-188, 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 Prods. Ass'n (CHPA) (May 12, 2014), available at <https://wayback.archive-it.org/7993/20170113092434/http://www.fda.gov/downloads/Drugs/DrugSafety/UCM396988.pdf> (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).

³¹ U.S. Food and Drug Administration, Questions and Answers on FDA's Adverse Event Reporting System (FAERS), available at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/> (updated March 20, 2018, accessed on March 22, 2018).

benzocaine-associated methemoglobinemia.³² Based on these reviews, FDA estimates that more than 400 cases of benzocaine-associated methemoglobinemia occurring in the United States have been reported to FAERS or published in the medical literature since 1971.³³ The results of FDA's most recent reviews, which were finalized on November 22, 2017, and February 5, 2018 (hereinafter FDA's 2017 Reviews) (Records Case Management (RCM) # 2017-2053 and RCM# 2017-2053-1), covering the time period from February 26, 2009 to October 6, 2017, are summarized below.

FDA's 2017 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, 4 resulted in death, including the death of one 4-month old infant who was administered a topical OTC oral health care drug product containing benzocaine to treat sore gums due to teething. The vast majority of the reported outcomes in these cases were serious (97.5 percent, 116/119).³⁴ Eight pediatric cases involved the use of benzocaine products to treat teething pain.

FDA continues to receive reports of benzocaine-associated methemoglobinemia in adult and pediatric patients. At least 35 cases have been reported to FAERS or 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.³⁵ The cases occurring after this date include two deaths, one of which was the 4-month old infant who was administered an OTC oral health care drug product containing benzocaine to treat sore gums due to teething.

II. DISCUSSION

In the Petition, you request that FDA: (1) "Reopen the administrative record for the monograph for OTC oral health care drug products"; (2) "Revise the proposed required labeling for OTC benzocaine oral health care drug products to remove the infant teething indication and include a contraindication advising against using gel and liquid benzocaine products for teething pain"; and (3) "Require a warning label for all remaining OTC benzocaine products covered by the monograph" concerning methemoglobinemia (Petition at 1, 2). We construe your Petition to request that FDA submit for publication

³² RCM# 2017-2053-1 (Feb. 5, 2018); RCM# 2017-2053 (Nov. 22, 2017); RCM# 2014-820 (Apr. 28, 2014); RCM# 2009-164 (June 17, 2009); RCM# 2002-87 (Feb. 9, 2006).

³³ 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 percent involved life-threatening or serious outcomes, and 7 resulted in death.

³⁴ Under 21 CFR 314.80, an adverse drug experience is serious if it 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.

³⁵ See Letter from FDA to CHPA, *supra* note 30.

in the *Federal Register* a notice of proposed rulemaking amending the OHDP TFM by revising the proposed conditions under which OTC oral health care drug products containing benzocaine would be GRASE and not misbranded. We discuss your request for FDA to publish a new proposed rule and the contents of your requested revisions to the labeling conditions in the OHDP TFM below.

A. Request to Publish a New Proposed Rule Amending the OHDP TFM

At the present time, the Agency declines to reopen the administrative record and amend the OHDP TFM. We share your concerns regarding the serious risk of methemoglobinemia associated with OTC oral health care drug products containing benzocaine. However, at this time, we believe that the initial steps we have recently taken – directly requesting prompt action from each manufacturer, repackager, relabeler, and distributor of OTC oral health care drug products containing benzocaine and alerting the public to the risks associated with such products – constitute a more expeditious approach to address this public health concern than publishing a revised tentative determination in the *Federal Register* regarding the GRASE status of these products. As we have previously expressed, the lengthy notice and comment rulemaking procedures for establishing an OTC drug monograph are generally not well-suited to either addressing safety concerns that arise before a monograph is finalized or keeping pace with evolving science.³⁶ FDA expects that responsible members of industry will adopt the measures that FDA has requested, especially since we have taken the extraordinary step of individually and directly communicating our serious concerns to each registered firm that markets these products, and have widely disseminated these concerns to the general public to alert them to the risks of these products.³⁷

This initial measure, which is consistent with the findings described in section I.B and requests set forth in your Petition, is one that FDA intends to follow up with administrative action. We note that the Agency's administrative processes for regulating OTC monograph drugs are currently the subject of an evolving legislative landscape. Recently, there has been significant movement in Congress toward advancing proposals that would fundamentally transform these administrative processes and grant FDA new tools to more expeditiously address safety concerns for OTC monograph drugs.³⁸ In light of the significant possibility that this transformative shift in our authorities will occur in the near future, and with the expectation that our initial steps will significantly mitigate the current risk posed by OTC oral health care benzocaine products, FDA believes that

³⁶ See generally 79 FR 10168 (Feb. 24, 2014).

³⁷ This expectation is supported by our experience. In the past, industry has taken prompt, voluntary action to relabel or discontinue the distribution of a class of OTC drugs for which the Agency has voiced serious safety concerns. Two months after FDA announced an upcoming meeting of the Pediatric Advisory Committee and Non-Prescription Drugs Advisory Committee to consider the safety of OTC cough and cold syrups for children, CHPA announced – before the meeting was even held – that its members would voluntarily withdraw products intended for infants from the market. Shortly after FDA held the meeting and published a safety communication, CHPA announced that its members would also voluntarily revise the labeling of these products to address additional safety concerns.

³⁸ See *supra* note 3. These legislative proposals are intended to address challenges to regulating OTC drugs under the current rulemaking paradigm.

initiating notice and comment rulemaking is not the appropriate course of action at this time. Nonetheless, FDA will continue to actively monitor the effects of our recent measures on mitigating the risk of methemoglobinemia (including by monitoring FAERS and the medical literature) and the course of legislative reforms, and we will take rulemaking action if it proves necessary.

Accordingly, our recent letter to each registered manufacturer, repackager, relabeler, or distributor of OTC oral health care drug products containing benzocaine urged firms to promptly take the following actions:

- (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 old; and
 - b. Revising the DFL of OTC oral health care drug products containing benzocaine intended for individuals 2 years and older to:
 - 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.”³⁹
- (2) Address the risks to adults and children by revising the DFL of OTC oral health care drug products containing benzocaine intended for adults and children 2 years of age and older by adding a warning that is the first statement under the heading “Warnings” as follows:

³⁹ This statement should replace any directions that are currently in the DFL directing caregivers to consult a health care provider before using the product to treat children under 2 years of age.

“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”.

B. Requested Labeling Revisions for OTC Oral Health Care Drug Products Containing Benzocaine

You request that FDA revise the OHDP TFM by (1) removing the proposed conditions under which such products would be GRASE and not misbranded for use to treat sore gums due to teething; and (2) revising the proposed labeling conditions under which OTC oral health care drug products containing benzocaine would be GRASE and not misbranded for all other proposed anesthetic/analgesic indications by including (a) a contraindication against use for teething, and (b) a methemoglobinemia warning (Petition at 2). As described in section II.A, FDA has sent a letter to industry seeking prompt action to relabel or discontinue the distribution and sale of OTC oral health care drug products containing benzocaine. Further, the Agency intends to take administrative action concerning these products in the near future. In this section, we explain the labeling revisions outlined in our recent letter to industry, which are responsive to the concerns you have raised in your Petition.

1. Teething Indication

You request that FDA remove the following proposed indication from the OHDP TFM (Petition at 2):

(6) For products containing benzocaine identified in § 356.12(a) or phenol identified in § 356.12(g) when used as anesthetic/analgesics for teething pain. “For the temporary relief of sore gums due to teething in infants and children 4 months of age and older.”

For consistency, you also request that FDA remove the following proposed conditions for teething preparations containing benzocaine (Petition at 2):

(5) For all products labeled with the indication identified in § 356.52(b)(6). “Fever and nasal congestion are not symptoms of teething and may indicate the presence of infection. If these symptoms persist, consult your doctor.” . . .

(iii) *For products intended to be used as teething preparations, the product is a 5- to 20-percent solution or suspension. Apply to the affected area not more than four times daily or as directed by a dentist or doctor. For infants under 4 months of age there is no recommended dosage or treatment except under the advice and supervision of a dentist or doctor.*

You state that any potential benefits of OTC oral health care drug products containing benzocaine intended to treat sore gums due to teething are not sufficient to outweigh the risk of methemoglobinemia associated with these products (Petition at 9). You further assert that, given the benefit-to-risk ratio of such products, they do not meet the GRASE regulatory standard (Petition at 10). You also note that a warning label alone would not be sufficient to protect infants from methemoglobinemia, and that it would also not be sufficient to amend the labeling to limit use of benzocaine in children under age 2 (Petition at 15). Further, you assert that cases of benzocaine-associated methemoglobinemia may have gone unreported because of cases misdiagnosed as suffocation, airway obstruction, or sudden infant death syndrome (SIDS) (Petition at 9). Additionally, you state that benzocaine teething products have never demonstrated effectiveness in relieving teething pain in clinical trials, and safer non-drug alternatives are available for teething pain (Petition at 9).

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. As noted in section I.B.3, our recent review found 119 unique cases of benzocaine-associated methemoglobinemia that were reported to FDA or in the published literature between February 26, 2009 and October 6, 2017. Of the 119 cases, 11 involved a patient less than 2 years of age. Eight of the 119 cases involved the use of a benzocaine product to treat teething pain. One case reported the death of a 4-month old patient due to benzocaine-associated methemoglobinemia after use of a benzocaine product for teething pain.

We agree that warnings would provide insufficient protection to infants against the risk of benzocaine-associated methemoglobinemia. Caregivers may not recognize that an infant is experiencing methemoglobinemia 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 with methemoglobinemia symptoms is unlikely to be useful to include in the labeling of OTC oral health care drug products containing benzocaine intended for use in infants.

Additionally, infants are at increased risk for benzocaine-induced methemoglobinemia.⁴⁰ 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.⁴¹

⁴⁰ Lehr, J, Masters, A, Pollack, B, 2012, Benzocaine-Induced Methemoglobinemia in the Pediatric Population, *Journal of Pediatric Nursing*/27:583–588.

⁴¹ Id. citing Yaffe, SJ and Aranda, JV, (2011), *Neonatal and pediatric pharmacology: Therapeutic principles in practice* (4th ed.), Philadelphia, PA: Wolters Kluwer; see also, May 25, 1982, Advance Notice of

Being less than 6 months old is also a predisposing risk factor for methemoglobinemia.⁴² 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.^{43,44} Thus, younger infants may be sensitive to even low methemoglobin levels.⁴⁵

We also agree that 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. We also agree that safer non-drug alternatives are available for teething pain. The American Academy of Pediatrics (AAP) recommends against the use of any prescription or OTC pain relievers or medications that contain benzocaine on infants' gums because they wash out of an infant's mouth within minutes of application and thus are not useful to relieve teething pain.⁴⁶ Instead, the AAP recommends caregivers give babies a teething ring to dull pain.⁴⁷ 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.⁴⁸

With regard to your assertion that cases of benzocaine-associated methemoglobinemia may have gone unreported because of cases misdiagnosed as suffocation, airway obstruction, or SIDS, we acknowledge the possibility of such misdiagnoses. However, we are unaware of any data supporting this assertion.

For the reasons outlined in this section and the previous section, the Agency has determined that OTC products containing benzocaine intended to treat sore gums due to

Proposed Rulemaking (ANPR, 47 FR 22712 at 22738), noting that infants are more susceptible to methemoglobinemia due to a deficiency of DPNH (diphosphopyridine nucleotide) - dependent methemoglobin reductase (DPNH is now referred to a nicotinamide adenine dinucleotide (NADH)).

⁴² 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>.

⁴³ Lehr, J, et al., citing Hanukoglu, A, and Danon, P, (1996), Endogenous methemoglobinemia associated with diarrheal disease in infancy, *Journal of Pediatric Gastroenterology and Nutrition*, 23, 1-7.

⁴⁴ See also ODHP Monograph Advance Notice of Proposed Rulemaking, 47 FR 22712 at 22738 (May 25, 1982), explaining that infants under 4 months may be more susceptible than older infants, children, or adults because of their relative deficiency of DPNH-dependent methemoglobin reductase (now referred to as nicotinamide adenine dinucleotide), an enzyme with protects against methemoglobin-inducing foreign compounds, citing Wolff, JA, *Methemoglobin Due to Benzocaine*, *Pediatrics*, 20:915-916, 1957.

⁴⁵ See also 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>.

⁴⁶ American Academy of Pediatrics, Teething Pain webpage, available at <https://www.healthychildren.org/English/ages-stages/baby/teething-tooth-care/Pages/Teething-Pain.aspx> (updated Nov. 28, 2015, accessed on May 17, 2018).

⁴⁷ Id.

⁴⁸ American Dental Association, Teething, <https://www.mouthhealthy.org/en/az-topics/t/teething>, accessed April 4, 2018.

teething or infants and children under 2 years of age pose the serious risk of methemoglobinemia to infants and has requested industry discontinue the distribution and sale of OTC products containing benzocaine intended for infants and children under 2 years of age, including such products intended for the temporary relief of sore gums due to teething. We believe the Agency's actions will significantly mitigate this risk, and we intend to take administrative action regarding OTC oral health care drug products containing benzocaine in the near future.⁴⁹

2. Contraindication Against Use For Teething

In conjunction with your request to remove the teething indication for OTC oral health care drug products containing benzocaine from the OHDP TFM, you request that FDA amend proposed 21 CFR 356.52(c)(5) by adding the following subsection:

For products containing benzocaine identified in §§ 356.12(a) that are available in liquid or gel dosage forms: Do not use to treat sore gums due to infant teething. Cases of methemoglobinemia have developed among teething infants exposed to benzocaine.

(Petition at 2).

You argue that a specific contraindication against using OTC benzocaine products to treat sore gums due to teething is needed because parents are likely to use adult OTC benzocaine products in infants to treat sore gums due to teething (Petition at 16). You point to lidocaine as an example of a product that is not marketed for teething but has been used off-label to relieve teething pain to support your request (Petition at 16).

Based in part on recent adverse event information in FDA's 2017 Reviews, we agree that OTC oral health care benzocaine products should not be used to treat teething pain, even under the advice and supervision of a health care provider. As discussed in section II.B.1, infants are at increased risk for a serious methemoglobinemia adverse event when using benzocaine teething preparations, and FDA is not aware of any data demonstrating any benefit from benzocaine products for teething. Because OTC oral health care benzocaine products have been indicated and used for the temporary relief of sore gums due to teething for many years, we concur that 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 of age, even when they are not labeled for these uses, especially once products intended for teething become unavailable. Therefore, we agree that it would be appropriate for all OTC oral health care drug products containing benzocaine that remain on the market to bear labeling that includes a contraindication against use to treat teething pain. We believe OTC oral health care drug

⁴⁹ You also request that the proposed teething indication for OTC phenol products be removed from the OHDP TFM (Petition at 1, 2). To our knowledge, there are no marketed OTC products containing phenol (either as the sole active ingredient or in combination with other active ingredients) that are intended for the treatment of sore gums due to teething. Thus, we find your request to lack a basis for action at this time. However, FDA will continue to monitor for adverse events involving OTC oral health care drug products containing phenol and may consider regulatory action in the future if there is a justifiable basis to do so.

products containing benzocaine should not be used in infants under any circumstances, regardless of whether a health care professional is consulted.⁵⁰

However, we do not agree that the specific language proposed in your Petition for the contraindication -- “[d]o not use to treat sore gums due to infant teething. Cases of methemoglobinemia have developed among teething infants exposed to benzocaine” -- would be appropriate to include in the labeling of OTC oral health care drug products containing benzocaine. The Drug Facts labeling regulation at § 201.66 sets forth a standardized labeling format that is meant to be concise and easy to read.⁵¹ To be consistent with these objectives, FDA has requested that industry add the following contraindication on the DFL of OTC oral health care drug products containing benzocaine:

[Do not use] • for teething.

We note that the OHDP TFM’s proposed directions for OTC oral health care drug products containing benzocaine intended for adults and children 2 years of age and older state as follows: “Children under 2 years of age: Consult a dentist or doctor.” To be consistent with the contraindication described above, the Agency has also requested firms add the following contraindication to labeling:

[Do not use] • in children under 2 years of age.

In sum, we believe that OTC oral health care drug products containing benzocaine pose a serious risk of methemoglobinemia to infants. Thus, our recent letter urged industry to promptly discontinue the distribution of OTC oral health care drug products intended for treating teething pain or for infants and children under 2 years old, and to relabel products intended for adults and children 2 years and older with contraindications and statements warning against the use of these products in infants. FDA believes that this approach is an appropriate initial measure and intends to follow up with administrative action in the near future.

3. *Methemoglobinemia Warning*

Lastly, you request that FDA require a warning for all remaining OTC benzocaine products covered by the OHDP TFM concerning the risk of methemoglobinemia and the signs and symptoms of this disorder (Petition at 2, 20). You argue that a warning is necessary because of the number of benzocaine-induced methemoglobinemia reports associated with non-teething products so that consumers and health care professionals are made aware of the signs and symptoms of methemoglobinemia and seek and initiate prompt evaluation and treatment, if needed, when they occur (Petition at 17). You note that cases of methemoglobinemia have occurred in adults, with benzocaine products in

⁵⁰ See 21 CFR 201.66(c)(5)(iii).

⁵¹ See generally FDA’s guidance for industry *Labeling OTC Human Drug Products—Questions and Answers*, available on the FDA Drugs guidance web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

dosage forms other than liquid or gel (e.g., sprays), and for uses other than to treat teething pain (Petition at 17). Your requested warning would largely track the language in FDA's May 2014 letter to CHPA,⁵² with this addition: "Methemoglobinemia can occur in individuals who have used the product before and who follow the directions for use" (Petition at 2). You argue that this language is necessary because of the unpredictable nature of methemoglobinemia and because cases of methemoglobinemia have occurred despite individuals following the directions on the product label (Petition at 18).

We agree that there are methemoglobinemia risks for adults and children older than 2 years when using OTC oral health care drug products containing benzocaine for anesthetic/analgesic uses other than to treat teething pain. FDA's reviews identified cases of benzocaine-associated methemoglobinemia involving patients of all ages. FDA's 2017 Reviews, which evaluated cases of benzocaine-associated methemoglobinemia from FAERS and published literature from February 26, 2009 to October 6, 2017, found 119 cases of benzocaine-associated methemoglobinemia.⁵³ The patient ages ranged from 1-day-old to 85 years, with a mean age of 47.2 years and a median age of 53 years. Of the 116 cases that included information on age, 11 involved children under 2 years, 11 involved children 2 to 18 years, 58 involved adults 18 years to 65 years, and 36 involved adults 65 years or older. Of the 119 cases, the formulation type for benzocaine product involved varied dosage forms (gel – 20, liquid – 2, lollipop with gel – 1, spray – 73, spray and lozenge – 2, not reported – 21). The reported reason for using the benzocaine product also varied (bronchoscopy – 3, endoscopy – 7, esophageal stent – 1, intubation – 6, NG-tube pain/G-tube exchange⁵⁴ – 10, oral pain [e.g., toothache or dental pain, teething, throat pain, etc.] – 30, "post-franulectomy" – 1,⁵⁵ post-partum pain – 1, suicide – 1, transesophageal echocardiogram – 53, unintentional exposure – 2, vulvar carcinoma – 1, not reported – 3).

Deaths and other adverse events due to benzocaine-associated methemoglobinemia have continued despite the Agency's previous safety actions (see section I.B.3). This includes FDA's 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' DFLs.⁵⁶ 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 May 2014, FDA is aware of at least 35 cases of benzocaine-associated methemoglobinemia that have been reported to FAERS or in the medical literature, including the death of an infant. Reporting adverse events to FAERS is voluntary for consumers and healthcare professionals, so there are likely additional

⁵² Letter from FDA to CHPA, *supra* note 30. Some OTC oral health care drug products containing benzocaine marketed today are labeled with this warning whereas others are not.

⁵³ See *supra* section I.B.3.

⁵⁴ NG-tube refers to a nasogastric intubation tube, and G-tube refers to a gastrostomy tube.

⁵⁵ We have included the term "*post-franulectomy*" verbatim from this FAERS report. The correct spelling for this procedure is "*frenulectomy*," not "*franulectomy*."

⁵⁶ Letter from FDA to CHPA, *supra* note 30.

cases about which we are unaware.⁵⁷ Although manufacturers are required to submit adverse event reports to FDA, this requirement did not go into effect until 2007 for OTC monograph drugs.⁵⁸ In addition, underreporting of adverse events is a recognized limitation of spontaneous reporting systems such as the FAERS database, and has been described in detail elsewhere.⁵⁹ For these reasons, the Agency has chosen to take the actions outlined in this response and the letter to industry.

One of those actions was to urge 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 the following warning on the DFL:

“Methemoglobinemia warning [these two words in bold print as the first statement under the heading “Warnings”]: 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.”⁶⁰

FDA agrees with including a sentence discussing how methemoglobinemia can occur in individuals who have previously used benzocaine products without incident. Various related circumstances (e.g., amount of drug used, inflammation at the application site, age, concomitant medications, etc.) may combine to produce the reaction. Therefore, we agree that this is a helpful piece of information that should be included in the methemoglobinemia warning. We have chosen, however, to include more succinct

⁵⁷ FDA, Questions and Answers on FDA’s Adverse Event Reporting System (FAERS), available at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/> (updated March 20, 2018, accessed on March 22, 2018).

⁵⁸ The Dietary Supplement and Nonprescription Drug Consumer Protection Act (Public Law 109-462, 120 Stat. 3469), which created section 502(x) of the FD&C Act (21 U.S.C. 352(x)).

⁵⁹ Hazell, L, and Shakir, SA, 2006, Under-reporting of adverse drug reactions: a systematic review, *Drug Saf*; 29: 385-96; Alatawi, YM, and Hansen, RA, 2017, Empirical estimation of under-reporting in the US Food and Drug Administration Adverse Event Reporting System (FAERS), *Expert Opinion on Drug Safety*; 16: 761-7.)

⁶⁰ See also the sample letter to industry and the “Sample Drug Facts Label” available on our website, Safety Information on Benzocaine-Containing Products webpage, <https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm273111.htm> (updated May 23, 2018, accessed on May 23, 2018). The latter document 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 the letter to industry and in this response are made.

wording ("This can occur even if you have used the product before") instead of the language you have requested on this issue ("Methemoglobinemia can occur in individuals who have used the product before").

We disagree with including the phrase "who follow the directions for use" because all drugs carry a certain amount of risk every time they are used, even when individuals follow the directions on product labeling. The proposed language reiterates that methemoglobinemia can occur if one uses the product as directed. This language is uninformative and would result in a less succinct Warnings statement, contrary to OTC drug product labeling objectives to provide consumers labeling that is concise and easy to read.⁶¹

III. CONCLUSION

For the reasons described above, FDA is addressing the serious risk posed by OTC oral health care drug products containing benzocaine by urging industry to take swift action to remove certain OTC oral health care drug products containing benzocaine from the market and to relabel certain others, and by issuing extensive communications to alert the public of the risks associated with these products. In accordance with this approach, FDA wrote to each registered manufacturer, repackager, relabeler, and distributor of OTC oral health care drug products containing benzocaine that the Agency expects firms to promptly (1) address the risk of methemoglobinemia to infants by (a) discontinuing the distribution and sale of such products intended for the temporary relief of sore gums due to teething or for use in infants and children under 2 years of age, and (b) revising the DFL of products intended for adults and children 2 years and older by including contraindications and statements warning against use for teething and in infants; and (2) address the risk of methemoglobinemia to adults and children by revising the DFL of products intended for adults and children 2 years and older to include a methemoglobinemia warning.

FDA continues to review information regarding the risks of methemoglobinemia posed by OTC oral health care drug products containing benzocaine and intends to take additional administrative action in the near future.

Sincerely,



Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

⁶¹ 21 CFR 201.66.