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July 28, 2014

Margaret A. Hamburg, M.D.
Commissioner
Food and Drug Administration
Department of Health and Human Services
WO 2200
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Dear Commissioner Hamburg:

Public Citizen, a consumer advocacy organization with more than 300,000 members and supporters nationwide, hereby petitions the Food and Drug Administration (FDA), pursuant to the Federal Food, Drug, and Cosmetic Act 21 U.S.C. § 352 and 21 C.F.R. §§ 10.30 and 330.10(a)(7)(v), to immediately take the following actions with respect to over-the-counter (OTC) benzocaine products.

I. Actions Requested

We request that the FDA 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.

Specifically, we ask that the FDA eliminate the following subsection from the proposed regulation for OTC oral health care drug products:¹

§ 356.52(b)(6): For products containing benzocaine identified in § 356.12(a) or phenol identified in § 356.12(g) when used as anesthetic/analgesics for teething

¹ Our recommended change would also include removing the teething indication for phenol. To the best of our knowledge, phenol is not used in infant teething products except in combination with benzocaine.

pain. “For the temporary relief of sore gums due to teething in infants and children 4 months of age and older.”

For consistency, 21 C.F.R. §§ 356.52(c)(5) and 356.52 (d)(iii) should also be eliminated, as both discuss additional labeling requirements for products intended to be used as teething preparations.

In addition, we ask that the FDA amend 21 C.F.R. §§ 356.52(c) 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.

- (3) Require a warning label for all remaining OTC benzocaine products covered by the monograph. This required warning should state:

METHEMOGLOBINEMIA WARNING (these two words in bold print and capital letters as the first statement under the heading “WARNINGS”): Use of this product may cause methemoglobinemia, a rare but serious condition that must be treated promptly because it reduces the amount of oxygen carried in blood. **Methemoglobinemia can occur in individuals who have used the product before and who follow the directions for use.** 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.

Our proposed warning is modeled on the current voluntary warning already authorized by the FDA but includes additional language in bold to emphasize the unpredictable nature of the risk.

II. Statement of Grounds

A. Background on Benzocaine and Methemoglobinemia

Benzocaine is an active ingredient commonly found in many OTC medications. It is used as a topical anesthetic (a substance that induces insensitivity to pain) and analgesic for both non-oral uses (skin burns, poison ivy, and ear infections) and oral use. Benzocaine-containing gels such as Baby Orajel and Anbesol Baby are used to relieve irritation and pain associated with infant teething. Benzocaine is also found in spray products such as HurriCaine and Cetacaine, which are commonly used by health care providers to anesthetize (numb) the oropharynx (throat) of

patients undergoing various medical procedures such as endoscopies and endotracheal intubations.² Benzocaine works by binding to sodium channels in neurons (nerve cells) and decreasing the permeability of sodium ions across the neuronal membrane. As a result, depolarization of the membrane is inhibited, and conduction of nerve impulses that allow the body to detect pain is blocked.³

Methemoglobinemia is a blood disorder characterized by the decreased ability of red blood cells to carry oxygen due to increasing levels of methemoglobin. Under normal physiological conditions, 99% of red blood cells have hemoglobin, which contains four iron atoms that are in a ferrous state (Fe^{2+}). This state allows hemoglobin to bind oxygen easily when red blood cells pass through the lungs and transport it to various tissues in the body. However, iron in hemoglobin may oxidize into a ferric state (Fe^{3+}). Hemoglobin with iron in its ferric state, known as methemoglobin, can no longer bind oxygen. In addition, methemoglobin impedes the ability of other functioning hemoglobin molecules to release oxygen to various tissues in the body.⁴

Under normal conditions, low levels of methemoglobin in the blood are maintained by the enzyme NADH cytochrome-b5-reductase. This enzyme reduces iron in hemoglobin from a ferric to a ferrous state, thereby converting methemoglobin to functional oxygen-carrying hemoglobin.⁵

Methemoglobinemia is a disorder that can be either congenital (inherited) or acquired. Congenital forms are rare, and most cases of methemoglobinemia are acquired, with the most frequent cause being an acute drug reaction.^{6,7} Benzocaine is one drug known to induce methemoglobinemia.^{8,9,10,11,12}

² Institute for Safe Medication Practices. Benzocaine-containing topical sprays and methemoglobinemia. October 3, 2002. <https://www.ismp.org/newsletters/acutecare/articles/20021003.asp>. Accessed July 16, 2014.

³ National Center for Biotechnology Information. PubChem Compound: Benzocaine.

<http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=2337#x94>. Accessed July 16, 2014.

⁴ Abu-Laban RB, Zed PJ, Pursell RA, Evans KG. Severe methemoglobinemia from topical anesthetic spray: case report, discussion, and qualitative systematic review. *CJEM*. 2001;3(1):51-56.

⁵ Mansouri A, Lurie AA. Methemoglobinemia. *Am J Hematol*. 1993;42(1):7-12.

⁶ Ashurst J, Wasson M. Methemoglobinemia: a systematic review of the pathophysiology, detection, and treatment. *Del Med J*. 2011;83(7):203-208.

⁷ Wright RO, Lewander WJ, Woolf AD. Methemoglobinemia: etiology, pharmacology, and clinical management. *Ann Emerg Med*. 1999;34(5):646-656.

⁸ Ashurst J, Wasson M. Methemoglobinemia: a systematic review of the pathophysiology, detection, and treatment. *Del Med J*. 2011;83(7):203-208.

⁹ Abu-Laban RB, Zed PJ, Pursell RA, Evans KG. Severe methemoglobinemia from topical anesthetic spray: case report, discussion, and qualitative systematic review. *CJEM*. 2001;3(1):51-56.

¹⁰ Dashan A, Donovan KG. Severe methemoglobinemia complicating topical benzocaine use during endoscopy in a toddler: a case report and review of the literature. *Pediatrics*. 2006;117(4):e806-e809.

¹¹ Moore TJ, Walsh CS, Cohen MR. Reported adverse event cases of methemoglobinemia associated with benzocaine products. *Arch Intern Med*. 14 June 2004;164:1192-1196.

¹² Bong CL, Hilliard J, Seefelder C. Severe methemoglobinemia from topical benzocaine 7.5% (Baby Orajel) use for teething pain in a toddler. *Clin Pediatr*. 2009; 48(2):209-211.

Although the mechanism by which benzocaine causes methemoglobinemia is not well understood,¹³ it has been hypothesized that benzocaine may be metabolized to aniline, which can be transformed to phenylhydroxylamine and nitrosobenzene, both known to be methemoglobin-forming compounds.¹⁴

Signs and symptoms of benzocaine-induced methemoglobinemia can occur minutes¹⁵ to days¹⁶ after benzocaine exposure. Symptoms of benzocaine-induced methemoglobinemia include headache, fatigue, dizziness, difficulty breathing, weakness, and altered mental status.^{17,18} Signs and laboratory abnormalities of this disorder include tachycardia (an abnormally rapid heart rate), cyanosis (blue or purple coloration of the skin), chocolate-brown arterial blood, elevated methemoglobin concentration, and an oxygen saturation gap (the difference between oxygen saturation determined from a blood gas machine using an arterial blood sample and that from a pulse oximeter measurement) greater than 5%.¹⁹ With severe methemoglobinemia, patients may develop seizures, coma, dysrhythmias (abnormal heart rhythms), and metabolic acidosis and may die.^{20,21}

It is critical that drug-induced methemoglobinemia be recognized and treated promptly to avoid a fatal outcome. The most important initial intervention is to immediately discontinue use of the offending drug. Subsequently, the treatment of choice is intravenous administration of methylene blue.²² Indications for treatment with methylene blue include a methemoglobinemia level 20% or lower in a symptomatic patient and greater than 30% in an asymptomatic patient.²³

B. Regulatory Background and History for Benzocaine

Benzocaine is one of the many OTC products that are currently regulated by the FDA under a “tentative final monograph,” meaning that the drug has not been approved by the FDA under a new drug application and that no final regulation (i.e., a final monograph) has been published

¹³ Lehr J, Masters A, Pollack B. Benzocaine-induced methemoglobinemia in the pediatric population. *J Pediatr Nurs.* 2012;27:583-588.

¹⁴ Liebelt EL, Shannon MW. Small doses, big problems: a selected review of highly toxic common medications. *Pediatr Emerg Care.* 1993;9(5):292-297.

¹⁵ Bong CL, Hilliard J, Seefelder C. Severe methemoglobinemia from topical benzocaine 7.5% (Baby Orajel) use for teething pain in a toddler. *Clin Pediatr.* 2009; 48(2):209-211.

¹⁶ Food and Drug Administration. FDA drug safety communication: FDA continues to receive reports of a rare, but serious and potentially fatal adverse effect with the use of benzocaine sprays for medical procedures. April 7, 2011. <http://www.fda.gov/Drugs/DrugSafety/ucm250040.htm>. Accessed July 16, 2014.

¹⁷ Ashurst J, Wasson M. Methemoglobinemia: a systematic review of the pathophysiology, detection, and treatment. *Del Med J.* 2011;83(7):203-208.

¹⁸ So T, Farrington E. Topical benzocaine-induced methemoglobinemia in the pediatric population. *J Pediatr Health Care.* 2008;22(6):335-339.

¹⁹ *Ibid.*

²⁰ Curtis LA, Dolan TS, Seibert EH. Are one or two dangerous? Lidocaine and topical anesthetic exposures in children. *J Emerg Med.* 2009;37(1):32-39.

²¹ Liebelt EL, Shannon MW. Small doses, big problems: a selected review of highly toxic common medications. *Pediatr Emerg Care.* 1993;9(5):292-297.

²² So T, Farrington E. Topical benzocaine-induced methemoglobinemia in the pediatric population. *J Pediatr Health Care.* 2008;22(6):335-339.

²³ *Ibid.*

recognizing the conditions under which the product may be legally introduced into interstate commerce.²⁴

Under the FDA's current system for regulating OTC medications, an OTC drug may be legally marketed if it is either (a) approved through a new drug application for premarket approval, or (b) meets the conditions set forth in a final published regulation identifying the drug as "generally recognized as safe and effective (GRASE)" under specific conditions.²⁵ Such regulations are referred to as "final monographs."²⁶

Creation of a drug monograph requires several rulemaking steps, including publication in the Federal Register of a tentative final monograph, which precedes publication of the final monograph.²⁷ While the system for creating OTC drug monographs has been in place for over 40 years, there remain at least 25 tentative monographs for which the FDA has not yet completed the rulemaking process.²⁸ Drugs covered by such monographs exist in a state of regulatory limbo: By law, these drugs are considered unapproved "new drugs" that may not be legally introduced into interstate commerce.²⁹ Nevertheless, the FDA has generally exercised its enforcement discretion to allow the products to be marketed, provided they meet the conditions set forth in the tentative final monograph.³⁰

Oral use of benzocaine is covered under a tentative final monograph that merged two different rulemaking proceedings. Documents from these proceedings relevant to benzocaine include:

- A report on OTC drug products for the relief of oral discomfort from the Advisory Review Panel on OTC Dentifrice and Dental Drug Care Products ("the Advisory Review Panel" or "the Panel"), received by the FDA on July 13, 1978.³¹
- An advance notice of proposed rulemaking to establish a monograph for OTC oral health care drug products, published on May 25, 1982 (47 Fed. Reg. 22760).³²
- An advance notice of proposed rulemaking to establish a monograph for OTC relief of oral discomfort drug products, published on May 25, 1982 (47 Fed. Reg. 22712).³³

²⁴ Food and Drug Administration. Rulemaking history for OTC oral healthcare drug products. Pending final monograph (21 CFR part 356).

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Over-the-CounterOTCDrugs/StatusofOTCRulemakings/ucm072609.htm>. Accessed July 16, 2014.

²⁵ 21 C.F.R. § 330.1.

²⁶ 21 C.F.R. § 330.10.

²⁷ 21 C.F.R. § 330.10.

²⁸ Food and Drug Administration. Over-the-counter drug monograph system past, present, and future: Public hearing transcript. March 25, 2014. <http://www.fda.gov/downloads/drugs/newsevents/ucm395178.pdf>. Accessed July 16, 2014.

²⁹ 21 U.S.C. § 321(p)(1).

³⁰ See, e.g., Food and Drug Administration. Warning letter to Quadex Pharmaceuticals, LLC. May 7, 2012.

<http://www.fda.gov/iceci/enforcementactions/warningletters/2012/ucm304010.htm>. Accessed July 16, 2014. The FDA also exercises enforcement discretion regarding products that "were otherwise marketed prior to the inception of the FDA's OTC Drug Review." *Ibid.*

³¹ 47 Fed. Reg. 22712-01 (May 25, 1982).

³² 56 Fed. Reg. at 48302.

³³ 56 Fed. Reg. at 48302.

- A tentative final monograph for OTC oral health care covering anesthetic, analgesic, astringent, debriding agent/oral wound cleanser, and demulcent drug products (“the tentative final monograph”), published on January 27, 1988 (53 Fed. Reg. 2436).³⁴
- An amended tentative final monograph for OTC oral health care covering anesthetic, analgesic, astringent, debriding agent/oral wound cleanser, and demulcent drug products (“the amended tentative final monograph”), published on September 24, 1991.³⁵

Use of benzocaine for pain relief during infant teething was first addressed by the 1978 report of the Advisory Review Panel, which recommended that benzocaine and phenol be considered GRASE when indicated, among other things, “[f]or the temporary relief of sore gums due to teething in infants and children 4 months of age and older.”³⁶

In making its GRASE determination, the Panel recognized that benzocaine is widely used as a topical anesthetic but did not discuss any studies of benzocaine efficacy specifically for use in teething.³⁷ Regarding safety, the Panel was aware of several cases of methemoglobinemia related to use of benzocaine “in high doses” in infants and children ages 12 days to 6 years.^{38,39,40} Notably, none of these cases were related to teething medication, but instead involved the use of benzocaine as a suppository^{41,42,43} or widely applied over an infant’s skin.⁴⁴ The Panel recognized that “[i]nfants may be more susceptible [to developing methemoglobinemia] due to a deficiency of DPNH (diphosphopyridine nucleotide)-dependent methemoglobin reductase which protects against methemoglobin-inducing foreign compounds,” and therefore recommended against benzocaine for OTC use in infants under 4 months of age “except under the advice and supervision of a dentist or physician.”⁴⁵ However, the Panel did not recommend a warning label concerning methemoglobinemia.⁴⁶

The FDA subsequently incorporated the Panel’s recommendations into the amended tentative final monograph, which would permit products containing benzocaine or phenol to be labeled “[f]or the temporary relief of sore gums due to teething in infants and children 4 months of age and older.”⁴⁷

Use of benzocaine-containing sprays for medical or surgical procedures such as endoscopies and transesophageal echocardiography was not covered as an indication under the amended tentative

³⁴ 56 Fed. Reg. at 48302.

³⁵ 56 Fed. Reg. at 48302-01 (September 24, 1991).

³⁶ 47 Fed. Reg. at 22740.

³⁷ 47 Fed. Reg. at 22718.

³⁸ 47 Fed. Reg. at 22724.

³⁹ Wolfe JA. Clinical conference: methemoglobinemia due to benzocaine. *Pediatrics*. 1957;20(5):915-916.

⁴⁰ Bloch A. More on infantile methemoglobinemia due to benzocaine suppository. *J Pediatrics*. 1965;67(3):509-510.

⁴¹ Hughes JR. Infantile methemoglobinemia due to benzocaine suppository. *J Pediatrics*. 1965;66:797-799.

⁴² Peterson HC. Acquired methemoglobinemia in an infant due to benzocaine suppository,” *N Engl J Med*. 1960; 263(9):454.

⁴³ Bloch A. More on infantile methemoglobinemia due to benzocaine suppository. *J Pediatrics*. 1965;67:509-510.

⁴⁴ Wolfe JA. Clinical conference: methemoglobinemia due to benzocaine. *Pediatrics*. 1957;20(5):915-16.

⁴⁵ 47 Fed. Reg. at 22724.

⁴⁶ 47 Fed. Reg. at 22724.

⁴⁷ 56 Fed. Reg. at 48343.

final monograph. This means that marketing the product for this use remains “off-label” and could potentially expose a manufacturer to risk of FDA enforcement action.⁴⁸

On October 4, 2007, Beutlich LP Pharmaceuticals, the manufacturer of HurriCaine anesthetic spray, petitioned the FDA to expand the tentative final monograph for OTC products containing benzocaine to cover control of the involuntary “gag” reflex and numbing of the mouth and throat for minor medical and surgical procedures or for insertion of a tube into the stomach or airway.⁴⁹ The FDA denied this petition on February 14, 2012, citing concern over risk of methemoglobinemia and lack of data supporting the effectiveness of benzocaine for the proposed expanded indications.⁵⁰

Between 2003 and 2014, the FDA issued several safety announcements related to the risk of methemoglobinemia with benzocaine OTC products. Three of these announcements focused on benzocaine sprays for use in surgical procedures.^{51,52,53} Three other announcements, issued on April 7, 2011, May 31, 2012, and June 26, 2014, addressed benzocaine OTC oral products for relief of teething pain in infants.^{54,55,56} In the May 2012 announcement, the FDA noted that gel and liquid products containing benzocaine, which are used for pain relief of mouth and gum irritation as well as for teething in infants, had been associated with 29 cases of methemoglobinemia. Nineteen of those cases involved children, 15 of whom were under the age of 2.⁵⁷

Finally, on May 12, 2014, in response to a request from the Consumer Healthcare Products Association, the FDA advised manufacturers of OTC benzocaine-containing oral health drug products that the agency would “not object” if the labeling for such products were to include a

⁴⁸ 56 Fed. Reg. at 48342-3.

⁴⁹ Food and Drug Administration. Letter to Beutlich LP Pharmaceuticals. February 14, 2012. <http://www.regulations.gov/#!documentDetail;D=FDA-1981-N-0013-0029>. Accessed July 16, 2014.

⁵⁰ *Ibid.*

⁵¹ Food and Drug Administration. Anesthetic sprays and methemoglobinemia. January 2003. <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/transcript.cfm?show=11#6>. Accessed July 16, 2014.

⁵² Food and Drug Administration. Benzocaine sprays. February 10, 2006. <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm150501.htm>. Accessed July 16, 2014.

⁵³ Food and Drug Administration. FDA drug safety communication: FDA continues to receive reports of a rare, but serious and potentially fatal adverse effect with the use of benzocaine sprays for medical procedures. April 7, 2011. <http://www.fda.gov/Drugs/DrugSafety/ucm250040.htm>. Accessed July 16, 2014.

⁵⁴ Food and Drug Administration. Reports of a rare, but serious and potentially fatal adverse effect with the use of over-the-counter (OTC) benzocaine gels and liquids applied to the gums or mouth. April 7, 2011. <http://www.fda.gov/Drugs/DrugSafety/ucm250024.htm>. Accessed July 16, 2014.

⁵⁵ Food and Drug Administration. Benzocaine and babies: not a good mix. May 31, 2012. <http://www.fda.gov/forconsumers/consumerupdates/ucm306062.htm>. Accessed July 16, 2014.

⁵⁶ Food and Drug Administration. Do teething babies need medicine on their gums? No. June 26, 2014. <http://www.fda.gov/forconsumers/consumerupdates/ucm385817.htm>. Accessed July 16, 2014.

⁵⁷ Food and Drug Administration. Benzocaine and babies: not a good mix. May 31, 2012. <http://www.fda.gov/forconsumers/consumerupdates/ucm306062.htm>. Accessed July 16, 2014.

warning label regarding the risk of methemoglobinemia.⁵⁸ The warning permitted by the FDA included the following language:

METHEMOGLOBINEMIA WARNING (these two words in bold print and capital letters as the first statement under the heading “WARNINGS”): Use of this product may cause methemoglobinemia, a rare but serious condition that must be treated promptly because it reduces the amount of oxygen carried in blood. 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

The FDA explained that while the warning “is outside the current label specifications of the tentative final monograph,” it would be permitted (but not required) based on agency discretion.

C. Legal Standard to Demonstrate Good Cause for the FDA to Reopen the Administrative Record for the Tentative Final Monograph for OTC Oral Health Care Drug Products and for GRASE Determinations

Under § 330.10(a)(7)(v), new data and information submitted more than 12 months after the publication of a tentative final monograph may be considered by the FDA prior to publication of a final monograph if the FDA “finds that good cause has been shown that warrants earlier consideration.”

To determine whether an OTC product is GRASE under the conditions of use proposed in the monograph, the FDA must apply the following standards:⁵⁹

(i) Safety means a low incidence of adverse reactions or significant side effects under adequate directions for use and warnings against unsafe use as well as low potential for harm which may result from abuse under conditions of widespread availability. Proof of safety shall consist of adequate tests by methods reasonably applicable to show the drug is safe under the prescribed, recommended, or suggested conditions of use. This proof shall include results of significant human experience during marketing. General recognition of safety shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data.

(ii) Effectiveness means a reasonable expectation that, in a significant proportion of the target population, the pharmacological effect of the drug, when used under adequate directions for use and warnings against unsafe use, will provide clinically significant

⁵⁸ Food and Drug Administration. FDA permits manufacturers of oral health care benzocaine products to include a methemoglobinemia warning. May 12, 2014. <http://www.fda.gov/Drugs/DrugSafety/ucm396985.htm>. Accessed July 16, 2014.

⁵⁹ 21 CFR 330.10(a)(4).

relief of the type claimed. Proof of effectiveness shall consist of controlled clinical investigations ... unless this requirement is waived on the basis of a showing that it is not reasonably applicable to the drug or essential to the validity of the investigation and that an alternative method of investigation is adequate to substantiate effectiveness. Investigations may be corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered. General recognition of effectiveness shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data.

(iii) The benefit-to-risk ratio of a drug shall be considered in determining safety and effectiveness.

D. Good Cause to Open the Administrative Record

Good cause has been shown to support reopening the administrative record under 21 C.F.R. § 330.10(a)(7)(v). Over two decades have passed since the FDA published the amended tentative final monograph for OTC oral health care drug products on September 24, 1991. As discussed below, new data are now available on the risk of methemoglobinemia, including case reports of the condition associated with use of benzocaine as a teething gel, which were not available in 1991. We therefore ask that the FDA reopen the administrative record and consider this new evidence prior to establishing a final monograph.

We are aware that the FDA recently held a public hearing to consider comments to revise the current OTC monograph system.⁶⁰ Even as the FDA considers reforms to the overall OTC monograph system, we urge the agency not to delay in reconsidering and finalizing the tentative final monograph for OTC oral health care drug products, as urgent regulation of these products is needed to protect consumers from the rare but serious risks described below.

E. Justification for Removal of the Teething Indication

The FDA should revise the amended tentative final monograph to exclude infant teething pain as an indication for benzocaine. Case reports demonstrate that methemoglobinemia, a life-threatening condition, can occur with benzocaine treatment even when the product is used in accordance with its labeling. Further cases may have gone unreported, possibly including lethal cases misdiagnosed as suffocation, airway obstruction, or sudden infant death syndrome (SIDS). Moreover, any potential benefits of the product are not sufficient to outweigh this life-threatening risk: Benzocaine teething products have never demonstrated effectiveness in relieving teething pain in clinical trials, and safer nondrug alternatives are available to address teething pain in infants. Indeed, on June 26, 2014, the FDA itself advised consumers and health care providers not to use topical pain medicines for teething pain, noting the following:⁶¹

⁶⁰ Food and Drug Administration. Over-the-counter drug monograph system past, present and future: Public hearing transcript. March 25, 2014. <http://www.fda.gov/downloads/drugs/newsevents/ucm395178.pdf>. Accessed July 16, 2014.

⁶¹ Food and Drug Administration. Lidocaine viscous: drug safety communication – boxed warning required – should not be used to treat teething pain. June 26, 2014.

Topical pain relievers and medications that are rubbed on the gums are not necessary or even useful because they wash out of the baby's mouth within minutes. ...

RECOMMENDATION: Health care professionals should not prescribe or recommend this product for teething pain. Parents and caregivers should follow the American Academy of Pediatrics' recommendations for treating teething pain.

- Use a teething ring chilled in the refrigerator (not frozen).
- Gently rub or massage the child's gums with your finger to relieve the symptoms.

FDA is also encouraging parents and caregivers not to use topical medications for teething pain that are available over the counter (OTC) because some of them can be harmful. FDA recommends following the American Academy of Pediatrics' recommendations to help lessen teething pain.

Given benzocaine's benefit-to-risk ratio, discussed in greater detail below, the FDA should prohibit manufacturers from marketing teething products containing benzocaine because it does not meet the GRASE regulatory standard.

Teething in infants begins around 6 months and ends near 3 years of age.⁶² During this time, infants develop swollen gums that may cause pain and irritation. As a result, they may become fussy and have trouble sleeping.⁶³ Some parents use OTC products that contain benzocaine in order to alleviate their infant's teething discomfort. Baby Orajel and Anbesol Baby are two examples of OTC benzocaine-containing gels currently marketed for this purpose.

The amended tentative final monograph covering benzocaine-containing OTC oral health drug products includes teething as an indication for benzocaine-containing OTC products:

21 C.F.R. § 356.52(b)(6): For products containing benzocaine identified in § 356.12(a) ... 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."

It also includes the following dosing instructions:

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

http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm402790.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery. Accessed July 16, 2014.

⁶² Henningfeld DA. Teething. *Salem Press Encyclopedia of Science* [serial online]. Ipswich, MA:Research Starters; September 2013. Accessed July 16, 2014.

⁶³ Lehr J, Masters A, Pollack B. Benzocaine-induced methemoglobinemia in the pediatric population. *J Pediatr Nurs*. 2012;27:583-588.

recommended dosage or treatment except under the advice and supervision of a dentist or doctor.⁶⁴

Infants may be particularly susceptible to developing methemoglobinemia for three reasons. First, fetal hemoglobin is more susceptible to oxidation than adult hemoglobin.⁶⁵ Second, infants' cytochrome b5 reductase levels, the enzyme responsible for converting methemoglobin back to functional hemoglobin, are only 50% of those seen in adults.⁶⁶ Third, although adult levels of the enzyme are reached by 6 months of age,⁶⁷ infants over the age of 6 months still have high body surface area to body mass ratios. Because infants have a higher body surface area to body weight ratio compared to adults, they will absorb a higher proportion of the drug per kilogram body weight than adults, which can put them at higher risk of developing methemoglobinemia following exposure to benzocaine.⁶⁸ As discussed above, the Advisory Review Panel that recommended the teething indication was aware of the increased risks for very young children but discussed only cases of methemoglobinemia following exposure to benzocaine suppositories or ointments for eczema treatment, failing to consider cases caused by benzocaine preparations intended for teething treatment. However, since the Panel issued its report, a large number of new reports involving methemoglobinemia in infants due to benzocaine teething preparations have become available.

On April 7, 2011, the FDA issued a safety communication analyzing 21 methemoglobinemia cases involving the use of benzocaine gel or liquid OTC products, representing all cases reported to the agency through March 16, 2011.⁶⁹ The cases were reported to the agency through its Adverse Event Reporting System (AERS) database. The agency summarized the data as follows:

Of the 21 cases, ten cases were categorized as life-threatening, defined as those patients with a reported methemoglobin level greater than 55%. Six cases were categorized as serious, defined as those patients with a reported methemoglobin level of 30% to 55% or who were administered methylene blue regardless of the level of methemoglobin.

Most of these cases (n=15) involved children, and of these, most involved children age 2 years or younger who were administered benzocaine gel for teething pain (n = 11). The other six cases occurred in adults who used the product to relieve toothache (an "off-label" indication not authorized under the current amended tentative final monograph⁷⁰).

⁶⁴ Food and Drug Administration. *Oral Health Care Drug Products for Over-the-Counter Human Use; Amendment to Tentative Final Monograph to Include OTC Relief of Oral Discomfort Drug Products*. Rockville, MD: Food and Drug Administration;1991. Publication 53 FR 48344.

⁶⁵ Venkateswari R, Ganesh R, Deenadayalan M, et al. Transient methemoglobinemia in an infant. *Indian J Pediatr*. 2007;74(11):1037-1038.

⁶⁶ *Ibid.*

⁶⁷ Zenk KE. Use of methylene blue to treat methemoglobinemia in infancy. *Neonatal Network*. 2001;20(5):62-68.

⁶⁸ Lehr J, Masters A, Pollack B. Benzocaine-Induced methemoglobinemia in the pediatric population. *J Pediatr Nurs*. 2012;27:583-588.

⁶⁹ Food and Drug Administration. FDA drug safety communication: reports of a rare, but serious and potentially fatal adverse effect with the use of over-the-counter (OTC) benzocaine gels and liquids applied to the gums or mouth. April 7, 2011. <http://www.fda.gov/Drugs/DrugSafety/ucm250024.htm>. Accessed July 16, 2014.

⁷⁰ 56 Fed. Reg. at 48306-48307.

Methemoglobinemia occurred even in several cases where the product was administered in accordance with the product label: Of the 14 cases that provided information on dosage, there were five cases suggesting that the product was administered in accordance with the labeling, and nine cases in which the product was used inappropriately or excessively.⁷¹

These reports also indicate that methemoglobinemia can occur when the gel is used appropriately in otherwise healthy infants with no particular risk factors. As the agency summarized:⁷²

Among the five cases of methemoglobinemia reported following the labeled use of the product, two cases (one life-threatening case in an adult and one serious case in a pediatric patient) occurred following a single administration of benzocaine gel to the oral mucosa. In the pediatric case that occurred following a single exposure to the product, the reporting physician noted that the one-year-old patient was found to have “normal methemoglobin reducing capacity.” Three cases described application frequencies that did not exceed the recommendations in the label (i.e., up to four times daily).

Existing labeling is also not sufficient to prevent methemoglobinemia resulting from cases of unsupervised or excessive use. As the agency stated:⁷³

Among the nine cases in which the product was used inappropriately or excessively, six cases described unsupervised self-administration or accidental ingestion of the gel by a child and three cases suggested overuse of the product (n=3) where excessive quantities or applications of the products were administered.

The agency noted that symptoms occurred with both the first and subsequent applications of the gel, meaning that even infants who had previously been treated with benzocaine teething gel without experiencing adverse effects may remain at risk upon subsequent exposure.

The FDA analysis noted that only one death associated with use of benzocaine to relieve teething pain had been reported to the agency.⁷⁴ As the FDA later disclosed in a second publication discussing the AERS data, that death occurred in 2008 in an infant whose mother applied three consecutive doses of benzocaine gel to the infant’s gum.⁷⁵ Twenty minutes later, the infant turned blue and died. However, the FDA did not conclusively link this death to methemoglobinemia, because the autopsy report listed the cause of death as “airway obstruction.”

The FDA updated its analysis in a safety alert to consumers on May 31, 2012. In that announcement, entitled “Benzocaine and Babies: Not a Good Mix,” the agency noted that since

⁷¹ Food and Drug Administration. FDA drug safety communication: reports of a rare, but serious and potentially fatal adverse effect with the use of over-the-counter (OTC) benzocaine gels and liquids applied to the gums or mouth. April 7, 2011. <http://www.fda.gov/Drugs/DrugSafety/ucm250024.htm>. Accessed July 16, 2014.

⁷² *Ibid.*

⁷³ *Ibid.*

⁷⁴ *Ibid.*

⁷⁵ Food and Drug Administration. Letter to Beutlich LP Pharmaceuticals. February 14, 2012. <http://www.regulations.gov/#!documentDetail;D=FDA-1981-N-0013-0029>. Accessed July 16, 2014.

2006, it had received 29 reports of benzocaine-gel-related cases of methemoglobinemia.⁷⁶ According to the agency, 19 of those cases occurred in children, and 15 of the 19 occurred in children under 2 years of age.

In addition to the FDA’s AERS case reports, other reports of methemoglobinemia associated with benzocaine teething gels have appeared in the literature. The infants involved in these cases ranged from 6 months to 15 months of age and were administered anywhere from a “pea-sized amount” to excessive amounts of the teething preparation.

These cases from the literature, summarized in the table below, provide additional evidence that benzocaine teething gels lead to life-threatening episodes of methemoglobinemia, even when used according to labeling directions. In one case reported by Bong et al. in 2009,⁷⁷ a 15-month old female infant was given a pea-sized amount of Baby Orajel (7.5% benzocaine) by her mother for teething pain while the child was hospitalized in an intensive care unit following a medical procedure. Shortly after administration of the benzocaine product, the patient experienced a drop in her blood oxygen saturation level, which the medical staff attributed to a partial lung collapse. The infant’s condition improved after several hours with oxygen supplementation. The patient’s mother subsequently administered another dose of Baby Orajel to the infant’s gums the following day after the patient had been transferred out of the intensive care unit, and the infant immediately became cyanotic and tachycardic. Methemoglobinemia was diagnosed with a level of 42.5%. Methylene blue treatment ultimately resolved the condition. The Baby Orajel was discontinued, and the patient had no further cyanotic episodes during her hospital stay.

Case Report Author, Year	Age	Product Used	Dose Administered	Methemoglobin Level	Treatment/ Patient Outcome
Bong et al., 2009	15 months	Baby Orajel (7.5% benzocaine)	Pea-sized amount	42.5%	1 mg/kg methylene blue, condition improved within minutes
Gentile, 1987 ⁷⁸	13 months	Ora-Jel Maximum Strength (20% benzocaine)	10-15x in a 24 hour period, “large amounts”	57%	1mg/kg methylene blue followed by a second 1.5 mg/kg dose, condition resolved
McGuigan, 1981 ⁷⁹	6 months	Baby Orajel (7.5% benzocaine)	Unmeasured amount	40.5%	Supplemental oxygen, condition resolved

⁷⁶ Food and Drug Administration. Benzocaine and babies: not a good mix. May 31, 2012.

<http://www.fda.gov/forconsumers/consumerupdates/ucm306062.htm>. Accessed July 16, 2014.

⁷⁷ Bong CL, Hilliard J, Seefelder C. Severe methemoglobinemia from topical benzocaine 7.5% (Baby Orajel) use for teething pain in a toddler. *Clin Pediatr*. 2009;48(2):209-211.

⁷⁸ Gentile DA. Severe methemoglobinemia induced by a topical teething preparation. *Pediatr Emerg Care*. 1987;3:176-178.

⁷⁹ McGuigan MA. Benzocaine-induced methemoglobinemia. *Can Med Assoc J*. October 15, 1981;125:816.

Townes et al., 1977 ⁸⁰	14 months	Baby Orajel (7.5% benzocaine)	Unmeasured amount	33%	Ascorbic acid, condition resolved
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Additional cases of methemoglobinemia have likely gone unreported. The symptoms of methemoglobinemia (including blue coloration of the skin, weakness, difficulty breathing, seizures, and coma) could be incorrectly attributed to airway obstruction, suffocation, or SIDS. The reaction can also occur hours or even days after administration of the product, where directions for use were followed correctly, and in infants who previously had been exposed to the product without experiencing adverse effects.

Most parents and even many health care providers may be unlikely to attribute such a life-threatening condition to an OTC product marketed for infants, particularly if used as directed. For example, in the case reported by Bong et al. in 2009,⁸¹ trained pediatric specialists failed to recognize an infant's symptoms as being due to benzocaine-induced methemoglobinemia, even after a link was suggested by the infant's mother.

The mother (a biochemist) noticed the temporal association of the episodes with the application of Baby Orajel, but she was reassured by the medical staff [in the intensive care unit] that this was an unlikely cause for the patient's acute desaturation because it was within the recommended dose.

It was only after re-application of the product, and a subsequent attack of methemoglobinemia, that the treating physicians recognized benzocaine as the cause of the infant's symptoms. Fortunately, this child was being treated in a hospital setting where methylene blue was readily available. If her condition had been left untreated, the results could have been fatal.

While the risk of methemoglobinemia is very low, the serious nature of this condition means that a high potential for harm can result from misuse — or even appropriate use — of benzocaine products under conditions of widespread availability. Even a product effective at relieving gum pain during teething would not provide sufficient benefit to outweigh this serious risk. However, there is little evidence that benzocaine products are actually effective for teething. The Advisory Review Panel recommended benzocaine as effective as a topical anesthetic.⁸² However, the panel apparently did not consider any clinical studies specifically designed to assess benzocaine's effectiveness in relieving gum pain due to teething. Benzocaine has a short onset of effectiveness of 30 seconds and a single administration of the medication lasts only about 10-15 minutes.⁸³ Because of this short duration of action, benzocaine is unlikely to be effective at

⁸⁰ Townes PL, Geertsma MA, White MR. Benzocaine-induced methemoglobinemia. *Am J Dis Child.* 1977;131(6):697-698.

⁸¹ Bong CL, Hilliard J, Seefelder C. Severe methemoglobinemia from topical benzocaine 7.5% (Baby Orajel) use for teething pain in a toddler. *Clin Pediatr.* 2009;48(2):209-211.

⁸² 47 Fed. Reg. at 22737.

⁸³ VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel and the National Center for Patient Safety. A guidance on the use of topical anesthetics for naso/oropharyngeal and laryngotracheal procedures. <http://www.pbm.va.gov/PBM/clinicalguidance/criteriaforuse/benzocaine.pdf>. Accessed July 16, 2014.

providing clinically significant relief from teething pain. Moreover, well-meaning parents intent on relieving their child's pain may be inclined to administer the medication in amounts or at frequencies that exceed the recommended dose, thereby increasing the infant's risk of developing methemoglobinemia.

As previously noted, the FDA itself stated on June 26, 2014, that “[t]opical pain relievers and medications that are rubbed on the gums are not necessary or even useful because they wash out of the baby’s mouth within minutes.”⁸⁴ There is also the possibility that the topical anesthetic may not penetrate deeply enough to assist in relieving pain. Evidence of benzocaine’s general efficacy as a short-term topical anesthetic is therefore not sufficient to establish that the product is effective in relieving gum pain due to teething.

Moreover, benzocaine is not needed for gum pain relief because safer remedies for teething are readily available. The American Academy of Pediatrics reports that the safest remedies for teething include the use of cold items such as refrigerated teething rings, wet washcloths, and bananas.⁸⁵ Gently massaging the infant’s gums with one’s finger is also recommended.⁸⁶

A warning label alone would not be sufficient to protect infants from this potentially fatal adverse reaction. Not only is the product typically used at home, where medical care is not readily available, but parents may not be present to monitor for symptoms that occur hours after use, potentially at night when the family is sleeping. In fact, some products are marketed specifically for “nighttime” use, making it even more likely that they will be used at night. For example, Orajel Medicated Teething Nighttime Gel is advertised for children who “have trouble falling, or staying asleep, because of mouth pain and sore gums.”⁸⁷ (The only apparent difference between the Orajel “nighttime” product and its standard benzocaine product is a higher concentration of benzocaine (10% versus 7.5%). We know of no evidence that this higher concentration helps infants sleep better or relieves pain for longer than the lower dosage.) Were an infant to develop methemoglobinemia at night, parents would likely not recognize that the infant was in distress until the following morning, at which point it may be too late to seek medical treatment. Fatal cases of this nature may already have occurred, been misattributed to suffocation or SIDS, and therefore not reported to the FDA or identified through the medical literature as a fatal drug reaction.

It would also not be sufficient to amend the labeling to limit use of benzocaine in children under age 2. In its April 2011 and May 2012 safety announcements on OTC benzocaine gels and liquids, the FDA has stressed that these products should not be used on children under the age of

⁸⁴ Food and Drug Administration. Lidocaine viscous: drug safety communication – boxed warning required – should not be used to treat teething pain. June 26, 2014.

http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm402790.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery. Accessed July 16, 2014.

⁸⁵ American Academy of Pediatrics. Teething care & anticipatory guidance.

http://www2.aap.org/oralhealth/pact/ch2_sect5.cfm. Accessed July 16, 2014.

⁸⁶ American Academy of Pediatrics. Teething: 4 to 7 months. <http://www.healthychildren.org/English/ages-stages/baby/teething-tooth-care/pages/Teething-4-to-7-Months.aspx>. Accessed July 16, 2014.

⁸⁷ Church & Dwight Inc. Orajel medicated teething nighttime gel. <http://www.orajel.com/en/Products/child-oral-care/Orajel-Nighttime-Teething-Formula>. Accessed July 16, 2014.

2 except under the advice and supervision of a health care professional.^{88,89} Some manufacturers have already revised their labels in accordance with this recommendation, though such a change is not required by regulation. For example, the product label for Orajel Medicated Teething Gel (benzocaine 7.5%) states that the product should be used “[f]or the temporary relief of sore gums due to teething in children 2 years of age and older. For use in children under the age of 2, consult a physician or healthcare provider.”⁹⁰

Such labeling changes are more likely to trigger confusion among consumers than prevent further life-threatening adverse events. More importantly, teething in infants generally begins around 6 months of age, and very few children cut their first tooth after age 2. Marketing the product over the counter for use in teething while advising against use in children under 2 creates a confusing trap for unsuspecting parents, who will assume the product may be used in infants at the time teething typically begins. Few parents will infer from the recommendation to “consult a physician” that this apparently benign OTC product, marketed for a condition that only affects babies, harbors fatal risks for their infant child.

In addition to removing the teething indication for benzocaine products, we ask the FDA to amend the monograph for OTC oral health care drug products to require that the labels for all benzocaine products available in liquid or gel dosage forms include the following warning:

Do not use to treat sore gums due to infant teething. Cases of methemoglobinemia have developed among teething infants exposed to benzocaine.

A specific contraindication against using benzocaine products to treat teething is needed because parents are likely to use adult OTC benzocaine products in infant teething. We are aware of at least one case in the medical literature involving an infant diagnosed with methemoglobinemia after administration of an adult product not specifically marketed for infant teething.⁹¹ Moreover, we note that the FDA recently added a boxed warning to lidocaine prescription drug products cautioning against their use in teething, after the FDA received 22 reports of teething babies suffering serious adverse reactions following administration of viscous lidocaine, a gel-like anesthetic syrup.⁹² While viscous lidocaine is prescribed to treat pain due to conditions such as mouth or throat ulcers, parents nevertheless have been known to use this product off-label to relieve teething pain by placing it on their child’s gums, putting it into infant formula, or soaking

⁸⁸ Food and Drug Administration. Reports of a rare, but serious and potentially fatal adverse effect with the use of over-the-counter (OTC) benzocaine gels and liquids applied to the gums or mouth. April 7, 2011.

<http://www.fda.gov/Drugs/DrugSafety/ucm250024.htm>. Accessed July 16, 2014.

⁸⁹ Food and Drug Administration. Benzocaine and babies: not a good mix. May 31, 2012.

<http://www.fda.gov/forconsumers/consumerupdates/ucm306062.htm>. Accessed June 30, 2014.

⁹⁰ Orajel Medicated Teething Gel. Drug Facts. <http://www.orajel.com/en/Products/child-oral-care/Orajel-Teething-Instant-Relief-Gel>. Accessed June 30, 2014.

⁹¹ Gentile DA. Severe methemoglobinemia induced by a topical teething preparation. *Pediatr Emerg Care*. 1987;3:176-178.

⁹² Food and Drug Administration. FDA drug safety communication: FDA recommends not using lidocaine to treat teething pain and requires new Boxed Warning. June 26, 2014.

<http://www.fda.gov/Drugs/DrugSafety/ucm402240.htm>. Accessed July 13, 2014.

a pacifier or cloth which is then placed in the infant's mouth.⁹³ A contraindication is necessary to prevent similar off-label use with OTC benzocaine liquid and gel products.

The FDA's most recent consumer safety announcement addressing benzocaine in infant teething was entitled "Do Teething Babies Need Medicine on Their Gums? No."⁹⁴ In it, the agency reiterated the risk of methemoglobinemia with benzocaine, as well as additional safety risks with lidocaine products. The FDA cautioned consumers against using either product to treat teething:

One thing doctors and other health care professionals agree on is that teething is a normal part of childhood that can be treated without prescription or over-the-counter (OTC) medications.

Too often well-meaning parents, grandparents and caregivers want to soothe a teething baby by rubbing numbing medications on the tot's gums, using potentially harmful drugs instead of safer, non-toxic alternatives.⁹⁵

We agree with the FDA that babies do not need potentially harmful drugs on their gums to treat a mild condition that is a normal part of child development, particularly when safer alternatives are readily available. In the case of benzocaine, the indication for teething does not meet the GRASE standard because the threat of a rare but life-threatening side effect, methemoglobinemia, more than outweighs any as-yet-unproven potential benefits in terms of teething pain relief. We therefore urge the FDA to revise the amended tentative final monograph to exclude infant teething pain as an indication for benzocaine, and add a contraindication warning parents against this dangerous and ineffective use.

F. Justification for Requiring a Warning Label for All Remaining OTC Benzocaine Products Covered by the Monograph

In addition to benzocaine teething preparations, other OTC benzocaine products have also been associated with methemoglobinemia. These include sprays used off-label for minor medical and surgical procedures, gels used for fever blisters and canker sores, and liquids used for sore throat relief. The FDA currently does not require manufacturers to incorporate a warning label on OTC benzocaine oral products regarding the risk of methemoglobinemia and the signs and symptoms that accompany it.⁹⁶ However, as noted above, the FDA recently issued a statement advising manufacturers that the agency would allow, but not require, companies to place a methemoglobinemia warning on benzocaine products on a voluntary basis.⁹⁷ Given the number of reports of benzocaine-induced methemoglobinemia associated with non-teething products, some of which have resulted in fatalities, a mandatory warning label is necessary so that

⁹³ Food and Drug Administration. Do teething babies need medicine on their gums? No. June 26, 2014. <http://www.fda.gov/forconsumers/consumerupdates/ucm385817.htm>. Accessed July 13, 2014.

⁹⁴ *Ibid.*

⁹⁵ *Ibid.*

⁹⁶ Food and Drug Administration. FDA continues to receive reports of a rare, but serious and potentially adverse effect with the use of benzocaine sprays for medical procedures. April 7, 2011. <http://www.fda.gov/Drugs/DrugSafety/ucm250040.htm>. Accessed July 13, 2014.

⁹⁷ Food and Drug Administration. FDA permits manufacturers of oral health care benzocaine products to include a methemoglobinemia warning. May 12, 2014. <http://www.fda.gov/Drugs/DrugSafety/ucm396985.htm>. Accessed July 13, 2014.

consumers and health care professionals are made aware of the signs and symptoms of this condition and seek and initiate prompt evaluation and treatment, if needed, when they occur.

As noted in the preceding section, the FDA has already published two analyses of methemoglobinemia associated with gel and liquid products. Of the 29 case reports received by the FDA and discussed in its May 31, 2012, consumer health article titled “Benzocaine and Babies: Not a Good Mix,”⁹⁸ 19 occurred in children, and it is likely that a substantial portion of these were related to teething use.⁹⁸ Nevertheless, we note that at least 10 cases occurred in adults for whom the product was certainly not used for teething purposes.

Most reports of methemoglobinemia associated with benzocaine-containing products have occurred not with liquid or gel products, but with benzocaine-containing sprays. In 2011, the FDA published an analysis of 319 reports of methemoglobinemia associated with use of benzocaine sprays, reported up through 2011. Of these, seven led to fatalities, and 32 were identified as life-threatening.⁹⁹ The appendix discusses other cases of methemoglobinemia as a result of using benzocaine OTC oral products. The true number of cases is probably much higher, as many cases likely go unreported to the FDA and are not published in the medical literature.

While adults using benzocaine-containing products may be at lower risk compared with infants, a warning label is necessary to advise adults to avoid excessive application of the product, to identify the symptoms of methemoglobinemia, and to seek urgent medical attention if such symptoms develop.

In addition, we strongly urge the FDA to strengthen the existing voluntary warning with wording emphasizing the unpredictable nature of the risks. This additional warning would state, “Methemoglobinemia can occur in individuals who have used the product before and who follow the directions for use.” This warning is necessary because cases of methemoglobinemia have occurred despite individuals following the directions on the product label. Not only has a single administration of a benzocaine OTC product lead to methemoglobinemia,^{100,101,102} but individuals have developed the adverse reaction using benzocaine products despite having not manifested this complication following prior exposures to benzocaine.^{103,104,105} Nevertheless,

⁹⁸ Food and Drug Administration. Benzocaine and babies: not a good mix. May 31, 2012.

<http://www.fda.gov/forconsumers/consumerupdates/ucm306062.htm>. Accessed July 13, 2014.

⁹⁹ Food and Drug Administration. FDA drug safety communication: FDA continues to receive reports of a rare, but serious and potentially adverse effect with the use of benzocaine sprays for medical procedures. April 7, 2011.

<http://www.fda.gov/Drugs/DrugSafety/ucm250040.htm>. Accessed July 13, 2014.

¹⁰⁰ Dashan A, Donovan KG. Severe methemoglobinemia complicating topical benzocaine use during endoscopy in a toddler: a case report and review of the literature. *Pediatrics*. 2006;117(4):e806-e809.

¹⁰¹ El-Husseini A, Azarov N. Is the threshold for treatment of methemoglobinemia the same for all? A case report and literature review. *Am J Emerg Med*. 2010;28:748e5-748e10.

¹⁰² So T, Farrington E. Topical benzocaine-induced methemoglobinemia in the pediatric population. *J Pediatr Health Care*. 2008;22(6):335-339.

¹⁰³ Young B. Intraoperative detection of methemoglobinemia in a patient given benzocaine spray to relieve discomfort from nasogastric tube: a case report. *AANA J*. 2008;76(2):99-102.

¹⁰⁴ Udeh C, Bittikofer J, Sum-Ping J. Severe methemoglobinemia on reexposure to benzocaine. *J Clin Anesthesia*. 2001;13:128-130.

consumers and health care professionals may mistakenly believe that side effects are not possible with correct use or in patients who have used the product in the past without difficulty, making them less likely to attribute symptoms to drug-induced methemoglobinemia and seek or administer appropriate treatment.

A mandatory warning on all OTC benzocaine products is therefore necessary to satisfy the GRASE standard and prevent unsafe use of benzocaine products by appropriately informing consumers and physicians about the risk of methemoglobinemia. Such a warning will deter excessive use and facilitate prompt identification and treatment of this life-threatening condition when it occurs.

G. Conclusions

The available evidence strongly supports removal of the teething indication from the tentative monograph for OTC oral health care drug products and the addition of a teething contraindication to all OTC benzocaine oral product labels.

With respect to the teething indication, not only is there a lack of evidence demonstrating the effectiveness of benzocaine for teething pain relief, but there is overwhelming evidence from FDA's review of AERS reports and from the medical literature that the drug causes methemoglobinemia, a life-threatening reaction, in infants. This reaction is difficult to detect and fatal if left untreated, meaning it may have led to an unknown number of deaths wrongly attributed to other causes of infant mortality. The addition of a contraindication against use for treating teething to the labeling of all benzocaine OTC products is also necessary to prevent parents or caretakers of young children from using such products on infants who have a much higher risk of developing methemoglobinemia. Because, as the FDA itself has concluded, there are plenty of nondrug remedies available for teething pain relief, there is no reasonable justification for allowing the OTC marketing of benzocaine as a teething treatment.

With the increasing number of reported benzocaine-induced methemoglobinemia cases, a mandatory warning label on all benzocaine-OTC oral products also is vital so that both health care professionals and consumers can identify the condition promptly. Furthermore, because of benzocaine's unpredictable nature, all users must be aware that this medication can cause methemoglobinemia even when the recommended dose is administered and even if the product has been used previously without complication. A warning label also can help curtail inappropriate or excessive use of the product, which could put individuals at higher risk of developing this life-threatening adverse reaction.

Unless the FDA removes the teething indication from the current tentative monograph and mandates a warning about methemoglobinemia on the labeling of all OTC benzocaine oral products, both infants and adults will develop this preventable adverse reaction. Since the reaction can occur a significant amount of time after administering the medication, infants may not be monitored when symptoms arise and lifesaving medical intervention may be significantly delayed. Delayed treatment of methemoglobinemia can be fatal in infants and adults, and the

¹⁰⁵ Gunaratnam NT, Vazquez-Sequeiros E, Gostout CJ, Alexander GL. Methemoglobinemia related to topical benzocaine use: is it time to reconsider the empiric use of topical anesthesia before sedated EGD? *Gastrointestinal Endoscopy*. 2000;52(5):692-693.

risks that come with infants using benzocaine as a teething preparation for outweigh its unproven minimal, short-acting benefits. With a warning label on all OTC benzocaine oral products, consumers who use these products will be able to identify symptoms of methemoglobinemia and seek medical attention promptly. In addition, health care professionals will become aware of the unpredictable nature of benzocaine and the signs and symptoms of methemoglobinemia and will be able to promptly treat this potentially fatal condition.

III. Summary of Requested Actions

For the reasons stated above, pursuant to the Federal Food, Drug, and Cosmetic Act 21 U.S.C. § 352 and 21 C.F.R. §§ 10.30 and 330.10(a)(7)(v), we hereby petition the FDA to immediately take the following actions with respect to OTC benzocaine oral products.

- (1) Reopen the administrative record for the monograph for OTC oral health care drug products.
- (2) Revise the proposed required labeling for benzocaine OTC oral health products to remove the infant teething indication and include a contraindication advising against using gel and liquid benzocaine products for teething pain.
- (3) Require a warning label for all remaining OTC benzocaine products covered by the monograph concerning the risk of methemoglobinemia and the signs and symptoms of this life-threatening disorder.

IV. Environmental Impact Statement

We claim categorical exclusion under 21 C.F.R. § 25.31(a) from the environmental assessment requirement. An assessment is not required because the requested action involves an OTC monograph and would not increase the use of the active moiety.

V. Certification

We certify that, to the best of our knowledge and belief, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Sincerely,

Roma Rajput
Researcher
Public Citizen's Health Research Group

Sarah Sorscher, J.D., M.P.H.
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Appendix: Additional Cases of Methemoglobinemia from Use of Oral Benzocaine Products

Case Report Author(s), Year	Age (Yrs)	Product	Indication	Dose Administered	Methemoglobin Level	Treatment/ Patient Outcome
Afzal et al., 2014 ¹⁰⁶	56	Benzocaine	Intubation	Not reported	45%	Methylene blue; condition resolved within 2.5 hours after administration; however, patient died 7 days later due to complications related to surgery
Husseini & Azarov, 2010 ¹⁰⁷	78	20% benzocaine spray	Transesophageal echocardiography	1 spray, 1 second	Not reported	Methylene blue; condition improved within 10 minutes of administration
Chung et al., 2010 ¹⁰⁸	6	Baby Orajel (7.5% benzocaine)	Toothache	One application to teeth, amount not reported	69.9%	1 mg/kg methylene blue; condition improved within 10 minutes after administration and resolved within 1 day
So & Farrington, 2008 ¹⁰⁹	17	20% benzocaine	Bronchoscopy	1 spray	Greater than 20%	2 mg/kg methylene blue; condition improved within 20 minutes of administration
Young, 2008 ¹¹⁰	27	HurriCaine spray (20% benzocaine) and Cepacol lozenges (7.5% benzocaine)	Nasogastric tube	1-2 sprays every 4-6 hours and lozenges as needed	30.1%	65 mg of methylene blue; condition improved within 30 minutes of administration

¹⁰⁶ Afzal A, Collazo R, Fenves AZ, Schwartz J. Methemoglobinemia precipitated by benzocaine used during intubation. *Proc Bayl Univ Med Cent.* 2014;27(2):133-135.

¹⁰⁷ El-Husseini A, Azarov N. Is the threshold for treatment of methemoglobinemia the same for all? A case report and literature review. *Am J Emerg Med.* 2010;28:748e5-748e10.

¹⁰⁸ Chung NM, Batra R, Itzkevitch M, et al. Severe methemoglobinemia linked to gel-type topical benzocaine use: a case report. *J Emerg Med.* 2010;38(5):601-606.

¹⁰⁹ So T, Farrington E. Topical benzocaine-induced methemoglobinemia in the pediatric population. *J Pediatr Health Care.* 2008;22(6):335-339.

¹¹⁰ Young B. Intraoperative detection of methemoglobinemia in a patient given benzocaine spray to relieve discomfort from nasogastric tube: a case report. *AANA J.* 2008;76(2):99-102.

Dashan & Donovan, 2006 ¹¹¹	3	HurriCaine spray (20% benzocaine)	Endoscopy	1 spray	39%	1 mg/kg methylene blue; condition improved promptly
Abu-Laban et al., 2001 ¹¹²	56	HurriCaine spray (20% benzocaine)	Endoscopy	1 spray	51%	2 mg/kg methylene blue; condition improved within 10 minutes of administration
Udeh et al., 2001 ¹¹³	65	HurriCaine (20% benzocaine)	Fiberoptic intubation	Not reported	55%	100 mg of methylene blue initial dose, followed by 50 mg dose; condition rapidly improved after first dose, resolved after second
Wurderman et al., 2000 ¹¹⁴	69	HurriCaine liquid (20% benzocaine)	Transesophageal echocardiography	15 mL swish and swallow	67.8%	3 doses of 1 mg/kg methylene blue; condition improved immediately after administration and resolved within 7 hours
Gunaratnam et al., 2000 ¹¹⁵	72	HurriCaine spray (20% benzocaine)	Extended upper endoscopy	2 sprays	33%	180 mg of methylene blue; condition improved within 6 hours after administration
Gupta et al., 2000 ¹¹⁶	71	20% Benzocaine spray	Transesophageal echocardiography	Not reported	47.7%	80 mg of methylene blue; condition improved within 2 hours of administration

¹¹¹ Dashan A, Donovan KG. Severe methemoglobinemia complicating topical benzocaine use during endoscopy in a toddler: a case report and review of the literature. *Pediatrics*. 2006;117(4):e806-e809.

¹¹² Abu-Laban RB, Zed PJ, Pursell RA, Evans KG. Severe methemoglobinemia from topical anesthetic spray: case report, discussion, and qualitative systematic review. *CJEM*. 2001;3(1):51-56.

¹¹³ Udeh C, Bittikofer J, Sum-Ping J. Severe methemoglobinemia on reexposure to benzocaine. *J Clin Anesthesia*. 2001;13:128-130.

¹¹⁴ Wurderman RL, Mohiuddin SM, Holmberg MJ, Shalaby A. Benzocaine-induced methemoglobinemia during an outpatient procedure. *Pharmacotherapy*. 2000;20(6):735-738.

¹¹⁵ Gunaratnam NT, Vazquez-Sequeiros E, Gostout CJ, Alexander GL. Methemoglobinemia related to topical benzocaine use: is it time to reconsider the empiric use of topical anesthesia before sedated EGD? *Gastrointestinal Endoscopy*. 2000;52(5):692-693.

¹¹⁶ Gupta PM, Lala DS, Asura EL. Benzocaine-induced methemoglobinemia. *Southern Med J*. 2000;93(1): 83-86.

Gupta et al., 2000 ¹¹⁷	65	20% Benzocaine spray	Transesophageal echocardiography	Not reported	43.7%	80 mg of methylene blue; condition improved within 2 hours of administration
Gupta et al., 2000 ¹¹⁸	50	20% Benzocaine spray	Endotracheal intubation	Not reported	32%	Methylene blue, condition improved (timeframe not reported)
Gupta et al., 2000 ¹¹⁹	51	20% Benzocaine spray	Endoscopic retrograde cholangio-pancreatography	Not reported	Not reported	200 mg of methylene blue, condition resolved (timeframe not reported)
Ellis et al., 1995 ¹²⁰	76	HurriCaine spray (20% benzocaine)	Fiberoptic intubation	4 sprays, 1-2 seconds each during procedure	24%	1.3 mg/kg methylene blue, condition improved within 4 hours of administration and resolved within 1 day
Grum & Rice, 1990 ¹²¹	59	20% benzocaine	Gastroduodenoscopy	2 30 ml rinse-and-gargle doses with swallowing of an unknown amount	67%	120 mg of methylene blue and 500 mg of ascorbic acid with a second 120 mg dose of methylene blue, condition improved within 2 hours of administration of first dose and resolved within one day
Anderson et al., 1988 ¹²²	52	Cetacaine (14% benzocaine)	Laryngoscopy and intubation	2 1-second sprays	26%	1.5 mg/kg methylene blue, condition improved within 30 minutes of administration and almost completely resolved within 1 hour

¹¹⁷ *Ibid.*

¹¹⁸ *Ibid.*

¹¹⁹ *Ibid.*

¹²⁰ Ellis FD, Seiler JG, Palmore MM Methemoglobinemia: a complication after fiberoptic orotracheal intubation with benzocaine spray. *J Bone Joint Surg.* 1995;77-A(6):937-939.

¹²¹ Grum DF, Rice TW. Methemoglobinemia from topical benzocaine. *Clev Clin J Med.* 1990;57(6):357-359.

¹²² Anderson ST, Hajduczek J, Barker SJ. Benzocaine-induced methemoglobinemia in an adult: accuracy of pulse oximetry with methemoglobinemia. *Anesth Analg.* 1988;67:1099-1101.

O'Donohue et al., 1980 ¹²³	28	Cetacaine spray (14% benzocaine)	Nasotracheal tube insertion	1 spray, 3-5 seconds	29%	80 mg of methylene blue, condition improved within a few minutes of administration and resolved within 7 hours
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¹²³ O'Donohue WJ, Moss LM, Angelillo V. Acute methemoglobinemia induced by topical benzocaine and lidocaine. *JAMA Arch Int Med.* 1980 (November);140:1508-1509.