Summary Report

Benzocaine

Prepared for:

Food and Drug Administration
Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
Grant number: 2U01FD005946

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February 2020

This report was supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award (U01FD005946) totaling $2,342,364, with 100 percent funded by the FDA/HHS. The contents are those of the authors and do not necessarily represent the official views of, nor an endorsement by, the FDA/HHS or the U.S. Government.

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REVIEW OF NOMINATIONS

Benzocaine (UNII codes: U3RSY48JW5 and 41KZS5432U) was nominated for inclusion on the 503B Bulks List by Sincerus Florida, LLC, David Smith, AnazaoHealth Corporation, the Outsourcing Facilities Association (OFA), Triangle Compounding Pharmacy, the Specialty Sterile Pharmaceutical Society (SSPS), and Pine Pharmaceuticals.

Benzocaine was nominated for various indications:

While the exact medical condition for which the compounded product is being requested is generally unknown, benzocaine is generally used as a local anesthetic. Benzocaine will be compounded as various topical dosage forms and strengths based on the prescriber's request; the therapeutic dose is 20%. Benzocaine will also be compounded as a topical oral gel in concentrations ranging from 5-20% for use as a numbing agent for local pain relief. Additionally, benzocaine will be compounded as a 20% topical cream for use as a topical anesthetic prior to painful skin procedures. Benzocaine will also be compounded in various dosage forms for topical, vaginal, rectal, oral, and otic use in concentrations ranging from 0.47%-30% to reduce pain caused by minor skin irritations, sore throat, sunburn, teething pain, vaginal or rectal irritation, ingrown toenails, hemorrhoids, ear pain, and other sources of minor pain on a surface of the body. Lastly, benzocaine will be compounded as a topical 20% solution for use as a local anesthetic.

Benzocaine was recommended for combination use with lidocaine, prilocaine, and tetracaine, refer to Table 7 for the nominated combination formulations.

Reasons provided for nomination to the 503B Bulks List include:

- Commercially available medications may contain excipients such as fillers and preservatives that patients may not be able to tolerate due to allergies or sensitivities. Compounding from bulk allows using only the necessary ingredients to achieve the desired clinical outcome ensuring that no irritating, hazardous, or allergenic ingredients are included.
- The dosage form, strength, or flavor of commercially available products may be inappropriate for the patient.
- Compounded products are requested by prescribers to treat the individual needs of the prescriber's patients. As a result, these may be the only formulations to effectively treat the intended indication.
- Commercially available finished products have an inherent variance in potency creating an uncertain final concentration for the new product.
- There are no FDA-approved drug products containing benzocaine.
- There are no commercially available products that combine benzocaine with lidocaine and tetracaine.
- There are no commercially available products that combine benzocaine with prilocaine, and lidocaine into a topical oral gel.
- Prescriber and hospital preferences for varying concentrations, dosage forms, volumes, or final product containers.
- It is relatively unsafe to expose the direct compounding area to hundreds of vials or ampules and hundreds of aseptic manipulations during the compounding of a typical batch size for an outsourcing facility; compounding from bulk is safer and more efficient and reduces sterility risk.
- Use of state-of-the-art equipment, like the SKAN isolator technology, requires the use of bulk starting materials.
- Benzocaine is shorter acting than other topical anesthetics.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of benzocaine products in the United States (US) and around the world. The World Health Organization, the European Medicines Agency (EMA), and globalEDGE were used to identify regulatory agencies in non-US countries. The medicine registers of non-US regulatory agencies were selected for inclusion if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information (product trade name, active ingredient, strength, form, route of administration (ROA), and approval status) provided in a useable format. Based on these criteria, the medicine registers of 13 countries/regions were searched: US, Canada, European Union (EU), United Kingdom (UK), Ireland, Belgium, Latvia, Australia, New Zealand, Saudi Arabia, Abu Dhabi, Hong Kong, and Namibia. Both the EMA and the national registers of select EU countries (Ireland, UK, Belgium, and Latvia) were searched because some medicines were authorized for use in the EU and not available in a member country and vice versa.

Each medicine register was searched for benzocaine; name variations of benzocaine were entered if the initial search retrieved no results. The following information from the search results of each register was recorded in a spreadsheet: product trade name; active ingredient(s); strength; form; ROA; status and/or schedule; approval date. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations.

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.4) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing benzocaine. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

Search strategy

Two databases (PubMed and Embase) were searched including any date through December 20, 2018. The search included a combination of (benzocaine[TIAB] OR "ethyl 4-aminobenzoate"[TIAB] OR "ethyl p-aminobenzoate"[TIAB] OR "4-aminobenzoic acid ethyl ester"[TIAB]) AND (clinical[TIAB] OR treatment[TIAB] OR therapy[TIAB] OR therapeutic*[TIAB] OR anesthe*[TIAB] OR topical*[TIAB] OR local*[TIAB] OR numb*[TIAB] OR analges*[TIAB] OR pain*[TIAB]) AND humans[MeSH Terms] AND English [lang] NOT autism. Peer-reviewed articles as well as grey literature were included in the search. Search results from each database were exported to Covidence®, merged, and sorted for removal of duplicate citations.

Study selection

Articles were not excluded on the basis of study design. Articles were considered relevant based on the identification of a clinical use of benzocaine or the implementation of benzocaine in clinical practice. Articles were excluded if not in English, a clinical use was not identified, incorrect salt form, or if the study was not conducted in humans. Screening of all titles, abstracts, and full-text were conducted independently by two reviewers. All screening disagreements were reconciled by a third reviewer.

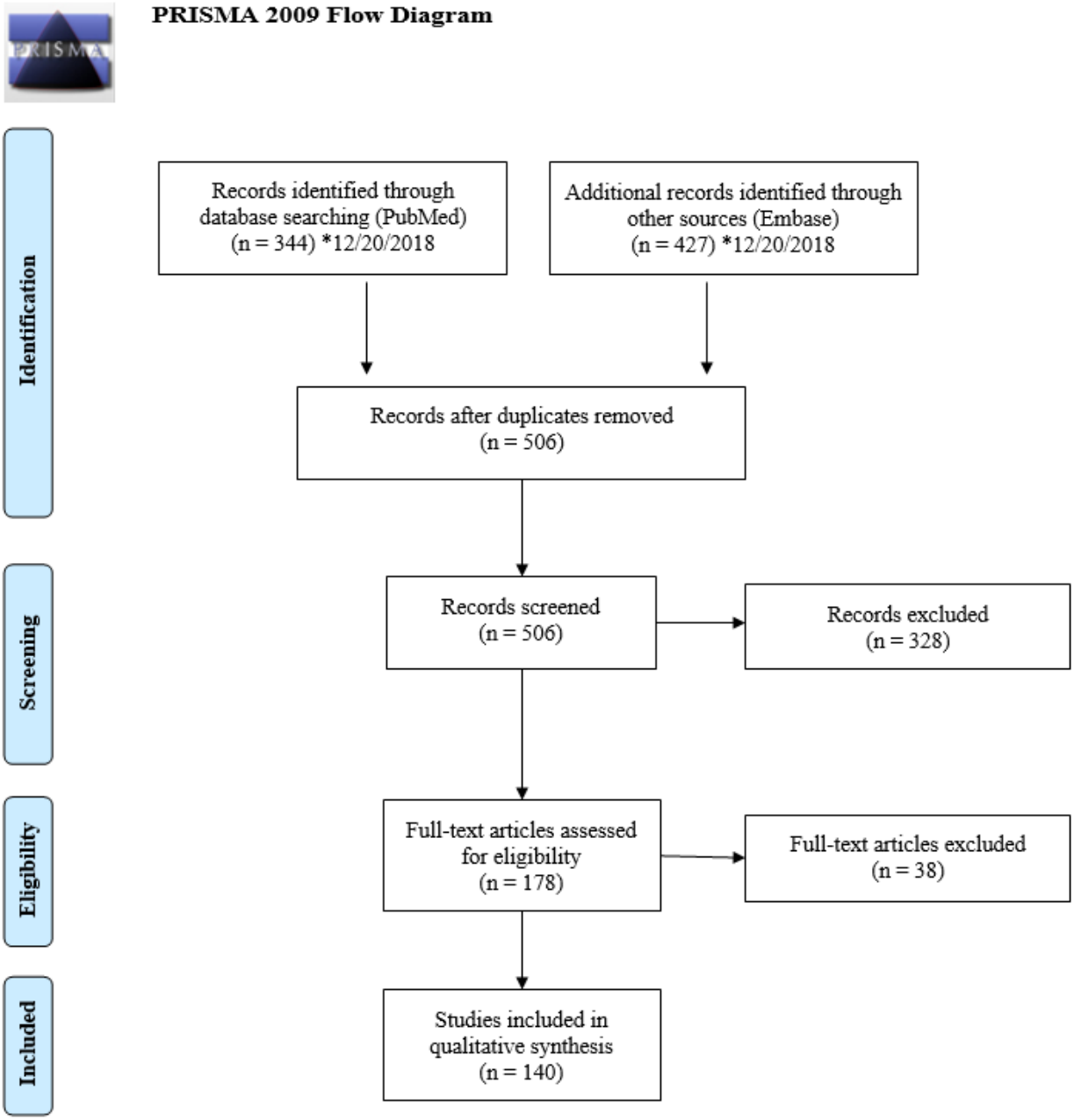
Data extraction

A standard data extraction form was used to collect study authors; article title; year published; journal title; country; indication for benzocaine use; dose; strength; dosage form; ROA; frequency and duration of therapy; any combination therapy utilized; if applicable, formulation of compounded products; study design; and any discussion surrounding the use of benzocaine compared to alternative therapies.

Results

Please refer to Figure 1.

Figure 1. Summary of literature screening and selection (PRISMA 2009 Flow Diagram)



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Outreach to medical specialists and specialty organizations

Using the indications from the nominations and the results of the literature review, eight (8) medical specialties that would potentially use benzocaine were identified: anesthesiology, dermatology, endocrinology, otolaryngology, pain management, primary care, surgery, and wound care. Semi-structured interviews were conducted with subject matter experts within these specialties. Interviews lasted from 30-75 minutes and were conducted either via telephone or in-person. Criteria for selecting subject matter experts included recommendations provided by specialty professional associations, convenient geographic location, authorship within the specialty, or referral by an interviewee. Up to nine (9) interviews were conducted per substance. To determine if a formal interview was warranted, one (1) medical expert in pain management was provided the list of substances pertinent to their specialty via email. The expert replied that they do not utilize any of the substances listed. Four (4) experts were contacted for interviews, of which four (4) accepted and zero (0) declined interviews. Two (2) experts were interviewed at the same time. Two (2) interviews were recorded and transcribed via ©Rev.com, while one (1) interview was not recorded due to equipment failure. QSR International's NVivo 12 software was utilized for qualitative data analysis. The University of Maryland, Baltimore IRB and the Food & Drug Administration RIHSC reviewed the study and found it to be exempt. Subject matter experts provided their oral informed consent to participate in interviews.

Survey

Utilizing the specialties identified from the nominations, literature review, and interviews, the relevant professional associations were identified to facilitate distribution of an online survey. A Google™ search was conducted to identify relevant professional associations within each specialty. Associations were included if their members are predominantly practitioners, national associations, and organizations focused on practice within the US. Organizations without practicing physicians and state or regional organizations were excluded. The association's website was searched in order to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used.

An online survey was created using Qualtrics® software (Provo, UT). The survey link was distributed to 16 associations. If an association had more than one (1) substance with indications relevant to that specialty, substances were combined into one (1) survey with no more than 14 substances per survey. Table 1 highlights the associations that agreed to distribute the survey link and Table 2 includes the associations that declined to participate. Additionally, single substance surveys were created and posted on the project website which was shared with survey participants.

Participation was anonymous and voluntary. The estimated time for completion was 30 minutes with a target of 50 responses per survey. The Office of Management and Budget (OMB) approved this project.

Table 1. Participating associations

Specialty	Association
Dermatology	American Academy of Dermatology (AAD)
	American Society for Dermatologic Surgery (ASDS)
Pain Medicine	American Academy of Pain Medicine (AAPM)
Primary Care	American Academy of Environmental Medicine (AAEM)

Table 2. Associations that declined participation

Specialty	Association	Reasons for Declining
Anesthesiology	American Society of Anesthesiologists (ASA)	Declined, requires a PI who is an ASA member
Endocrinology	American Association of Clinical Endocrinologists (AACE)	Declined, "endocrinologists are not generally in the compounding space."
Medicine	American Medical Association (AMA)	Failed to respond
	American Osteopathic Association (AOA)	Failed to respond
Otolaryngology	American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS)	Failed to respond
	American Academy of Otolaryngic Allergy (AAOA)	Declined, stated they did not think otolaryngologists were the target market for the survey
	American Rhinologic Society (ARS)	Declined, stated they do not send out surveys unless they are requested by a member; unable to identify a member to request survey distribution
Primary Care	American Academy of Family Physicians (AAFP)	Failed to respond
	American College of Physicians (ACP)	Failed to respond
Surgery	American College of Surgeons (ACS)	Failed to respond
Wound Care	American Professional Wound Care Association (APWCA)	Failed to respond
	Wound Healing Society (WHS)	Failed to respond

CURRENT AND HISTORIC USE

Summary of background information

- Benzocaine is not available as an FDA-approved product.
- Benzocaine is available in various topical, dental, buccal, and oral dosage forms as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for benzocaine.
- Benzocaine is available in Australia, Belgium, Hong Kong, Namibia, New Zealand, Saudi Arabia, and UK.

Table 3. Currently approved products – US

No approved products in the US

Table 4. Currently approved products–select non-US countries and regions[a]

Active Ingredient	Concentration	Dosage Form	ROA	Approved For Use		
				Country	Status	Approval Date[b]
Benzocaine	10%, 20%	Gel	Dental, mucosal	Australia	Prescription	10/08.1991
				Saudi Arabia	Prescription	–
				UK	Pharmacy[c]	09/21/2000
			–	Hong Kong	Pharmacy[c]	04/11/2001
				Namibia	–	08/18/2004
Benzocaine	10mg	Lozenge	Buccal	Australia	Pharmacy[c]	04/27/1992
			–	Hong Kong	Pharmacy[c]	02/28/1983
Benzocaine	200 mg/g	Gel, solution, spray	Gingival	Belgium	Prescription	10/26/1989
Benzocaine, tetracaine	18%, 2%	Gel	Oral, topical	New Zealand	Prescription	10/21/2010

Abbreviations: "–", not mentioned; ROA, route of administration.

[a]Medicine registers of national regulatory agencies were searched if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information (product trade name, active ingredient, strength, form, ROA, and approval status) provided in a useable format. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations. See Methodology for full explanation.

[b]If multiple approval dates and/or multiple strengths, then earliest date provided.

[c]Pharmacy-only medications may only be sold in a pharmacy, and a pharmacist must make or supervise the sale.

Summary of literature review

- Total number of studies included: 140 studies (13 descriptive, 125 experimental, and 2 observational).
- Most of the studies were from the US (79).
- There were five (5) studies identified with the nominated combinations.
- The most common indications for the use of benzocaine in both the US and non-US studies were anesthesia and analgesia.
- Compounded products were identified from both the US (20% ointment and 20% gel) and non-US (5% gel, 8 mg lozenges, and pastilles) studies.

Table 5. Types of studies

Types of Studies	Number of Studies
Descriptive[1-13]	13
Experimental[14-138]	125
Observational[139,140]	2

Table 6. Number of studies by country

Country	Number of Studies
Australia[130]	1
Brazil[23,45,57-60,103,109]	8
Canada[117,139]	2
Egypt[14]	1
Germany[4,26,27,33,39,99]	6
Haiti[9]	1
India[8,18,37,46,78,92,96,106,121,137]	10
Iran[52-54,63,74,91]	6
Israel[6,98,116,118]	4
Italy[3]	1
Japan[61,76,126]	3
Kuwait[15,20,21]	3

Poland[86]	1
Saudi Arabia[22]	1
South Africa[120]	1
Spain[34,87]	2
Switzerland[55]	1
Syria[43]	1
Thailand[102,112]	2
Turkey[128]	1
UK[10,47,75,89]	4
US[1,2,5,7,11-13,16,17,19,24,25,28-32,35,36,38,40-42,44,48-51,56,62,64-73,77,79-85,88,90,93-95,97,100,101,104,105,107,108,110,111,113-115,119,122-125,127,129,131,132,134-136,138,140]	79
	Total US: 79 Total Non-US Countries: 60

Table 7. Number of studies by combinations

	Combination Formula	Number of Studies
Nominated	Benzocaine 5-20% / Lidocaine / Prilocaine	0
	Benzocaine 20% / Lidocaine 6-10% / Tetracaine 4-10%[28,30,81,111,129]	5
Others found in literature	Benzocaine 15% / Amehtocaine 1.7%[130]	1
	Benzocaine / Antipyrine – otic drops[88,135]	2
	Benzocaine 10 mg / Cetyl-pyridinium 1.54 mg (Merocaine) – lozenge[75]	1
	Benzocaine 1 mg / Lebline sulfate 0.5 mg (SmoKurb) – gum[125]	1
	Benzocaine / Lidocaine 1% – gel[126]	1
	Benzocaine 20% / Lidocaine 2% – oral spray[94]	1
	Benzocaine 20% / Lidocaine 4% – gel[100,101]	2
	Benzocaine / Tetracaine (Endospray) – spray[139]	1
	Benzocaine 18% / Tetracaine 2% (Onetouch) – gel[102]	1
	Benzocaine 3.5 mg / Tyrothricin 2 mg – lozenge[116]	1
	Benzocaine 5 mg / Tyrothricin 1 mg (Tyrozets) – lozenge[75]	1
	Benzocaine / Antipyrine / Oxyquinolone sulfate (Auralgan) – otic solution[71]	1
	Benzocaine 1.5 mg / Benzalkonium chloride 1 mg / Tyrothricin 0.5 mg – lozenge[99]	1
	Benzocaine 14%, / Butamben 2% / Tetracaine 2% (Cetacaine)[16,119]	2
	Benzocaine / Gramicidin / Neomycin sulfate – troche[56]	1

	Benzocaine 20% / Potassium nitrate 35% / Tetracaine 10% – gel [72]	1
	Benzocaine 10% / Amethocaine 1.4% / Butacaine 0.7% / Butyl aminobenzoate 4% (Topicaina spray)[34]	1
	Benzocaine / Bacitracin / Hydrocortisone / Neomycin undecylenate (Bacimycin) – otic drops[51]	1
	Benzocaine 20% / Diphenhydramine / Lidocaine 6% / Tetracaine 4% – cream[133]	1
	Benzocaine / Benzyl alcohol 10% / Boric acid / Hydroxypropyl cellulose base / Salicylic acid (Zilactin B) – gel[11]	1
	Benzocaine 4.5% /Benzethonium chloride 0.1% / 8-hydroxyquinolone benzoate 1.2% / Menthol 0.5% / Methylbarabene 2% Dermoplast) – spray[90]	1

Table 8. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Anesthesia[5,11-13,16,17,19,24,25,28-30,32,35,36,38,40-42,44,48,50,62,65,66,72,73,79-83,85,90,93-95,97,104,105,107,108,110,111,113-115,119,122-125,127,129,131,132,134-136,138]	–	20%	–	Oral	Once
	1-12mg/day	1mg	Gum		–
	–	–	Solution	Otic	–
	–	20%	-	Topical	Once
		20%	Cream		Once
		6-20%	Gel		Once
		10-14%	Liquid		Once
		20%	Paste		–
		0.5-20%	Ointment		Once
		4.5-20%	Spray		Once

		0.5-20%	Solution		–
		4%	Wipes		–
Analgesia[1,31,67-70,77,84,88,100,101,140]	–	–	–	Otic	–
	–	–	–	Topical	–
	–	10-20%	Gel		Once
	–	20%	Liquid		Once
	12mg/day	12mg	Patch		Once
	–	20%	Spray		–
	–	20%	Wax		1 day
	–	–	Suppository	Vaginal	–
Pruritus[1,2,49]	–	6%	Cream	Topical	Once
Pharygnitis[1,56]	–	0.3-5%	–	–	–
	–	–	Troche	Oral	2.5 days
Obesity[7,64]	96mg/day	6-12 mg	Gum	Oral	8-12 weeks
Edema[31]	–	20%	Spray	Topical	–
Otitis externa[51]	6-8 drops/day	–	Solution	Otic	7-10 days
Otitis media[71]	5 drops/day	–	Solution	Otic	Once
Vaginitis[1]	–	–	–	Topical	–

Abbreviations: "–", not mentioned; ROA, route of administration.

Table 9. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Anesthesia[3,4,6,8-10,15,18,20-23,34,37,43,45,46,52,55,57-61,63,74,76,78,86,87,89,91,92,96,103,106,109,112,116,117,120,121,126,128,130,133,137,139]	–	2-22%	Gel, liquid, spray	–	Once
	–	0.75%	–	Intraduodenal	–
	3-3.5mg/day	3.5mg	Lozenge	Oral	3 days
	–	–	Solution		–
	–	5%	Cream	Topical	Once
		10-20%	Gel		
		20%	Jelly		
		10%	Spray		
		20%	Paste		
		20%	Patch		
	–	2%	Solution	Subcutaneous	–
Analgesia[6,26,47,53,54,98,102,118]	–	5-20%	Gel	Topical	Once-1 month
		10%	Ointment		Once
		20%	Solution		
	60mg/day	10mg	Lozenge	Oral	2 days
	–	2%	Solution	Subcutaneous	–
Pharyngitis[33,39,75,99]	3-80mg/day	1.5-10mg	Lozenge	Oral	2-3 days

Pruritis[6,26]	–	10%	Ointment	Topical	Once
		2%	Solution	Subcutaneous	–
Esophagitis[27]	150mg/day	0.75%	Solution	Oral	1-6 days
Oral Mucositis[14]	7.5%	7.5%	Gel	Topical	At most 10 days

Abbreviations: "–", not mentioned; ROA, route of administration.

Table 10. Compounded products – US

Indication	Publication Year	Compounding Method	Dosage Form	Final Strength
Anesthesia[28,30,72,81]	2003-2017	• Compounded benzocaine 20%, lidocaine 6%, and tetracaine 4%[28]	Ointment	20%
		• Benzocaine, Lidocaine, Tetracaine compounded mixture of powdered forms of abrasive particles that are mixed together in an oil base[30]	–	–
		• KNO_3 35%, Benzocaine 20%, Tetracaine 10% added to an aqueous hydroxyethyl cellulose gel[72]	Gel	20%
		• Benzocaine 20%, lidocaine 6%, and tetracaine 4% in proprietary vehicle consisting of dimethyl sulfoxide and pluronic lecithin organogel[81]		

Abbreviation: "–", not mentioned; KNO_3, potassium nitrate.

Table 11. Compounded products – non-US countries

Indication	Compounding Method	Dosage Form	Final Strength
Analgesia[53,54]	• Gel maker material of 934P (carbomer 934P)(50 g) as the gelling agent, methylparaben 5 g and propyleparabone 1 g as the preservatives, glycerin as a humectant (400 ml), sodium hydroxide as the pH adjusting agent (pH=6), benzocaine 200 g, and enough ethanol as the co-solvent and distilled water to reach desired concentration[54]	Gel	5%
	• Gel maker material of 934P (carbomer 934P)(50 g), Preservative agents of methyl parabone (5 g), Propyleparabone (1 g), Glycerin as a humectant (400 ml), pH regulator (soda), Benzocaine powder (200 g)[53]		
Pharygnitis[33]	• Benzocaine with isomalt, lemon and peppermint oil, tartaric acid and colorants	Lozenges	8 mg
	• Benzocaine with maltitol syrup, gelatine, medium chain triglycerides, sodium chloride, saccharine sodium, peppermint and anise oil, liquid paraffin oil, bleached wax and colorants	Pastilles	

Summary of focus groups/interviews of medical experts and specialty organizations

Three (3) interviews were conducted. One (1) interview was conducted with two (2) interviewees; this interview was not recorded. A medical expert in pain management was provided the list of substances, including benzocaine, pertinent to their specialty via email. Per the pain management expert, they do not use benzocaine.

Table 12. Overview of interviewees

Interviewee	Level of Training	Specialty	Current Practice Setting	Experience with Benzocaine	Interview Summary Response
ANE_01	MD	Anesthesiology	Trauma center	Not specified	• Interested in having access to compounded "caine" products
ANE_02	NP	None	Trauma center	Not specified	• Interested in having access to compounded "caine" products
DER_05	MD	Dermatology/ Immunology	Independent consultant	No	• There are significant safety concerns, especially with use in young children. • There are better alternatives with less risk
END_02	MD	Endocrinology, Diabetes and Metabolism	Academic medical institution	No	• Does not use this substance

Abbreviations: MD, Doctor of Medicine; NP, Nurse Practitioner.

Experience with benzocaine

- One (1) interviewee stated they have not previously used benzocaine and preferred to not use topical caines if possible.
- Two (2) interviewees did not go into detail about benzocaine use but expressed interest in having access to compounded "caine" products as a class.

Need for office stock

- One (1) interviewee expressed that for procedures, physicians will typically use a topical cocktail where they mix together a short-acting and longer-acting caine. However, the interviewee stated that benzocaine is not usually the anesthetic utilized.
- Safety issues
    - There was a recent FDA announcement where new warnings of methemoglobinemia were added to benzocaine products marketed to pediatric patients younger than two years old. Methemoglobinemia does not occur very often but is "a very severe potential catastrophic event."
        - People with genetic dermatology diseases where the skin barrier is lacking (a classic example is salicylism in kids with Netherton syndrome or dystrophic epidermolysis bullosa) are at increased risk for methemoglobinemia.
    - The interviewee questioned if providers who dispense benzocaine to patients will include all of the necessary warning labels.
        - One interviewee commented that benzocaine was the most frequent of the topical anesthetics that scored positive in the patch test for contact allergies in a study completed by the North American Contact Dermatitis Group (NACDG). The interviewee was not a fan of topical caine anesthetics in OTC products because of the increased risk contact allergy development, especially if the patient has open abraded skin (for example, sunburn). They were "worried about whether everyone who is a prescriber and potential user is sensitive to this new issue."
- Overall, the interviewee felt that there are better alternatives that have less risk.

Summary of survey results

Table 13. Characteristics of survey respondents [10 people responded to survey.[a]]

Board Certification	MD	PhD	No Response
Anesthesiology	1	0	0
Dermatology	1	0	0
Neurology	1	0	0
Pain Medicine	3	0	0
No Board Certification	0	1	1
No Response	0	0	4

Abbreviations: MD, Doctor of Medicine; PhD, Doctor of Philosophy.
[a]Some respondents reported more than one terminal clinical degree or board certification.

Table 14. Types of products used, prescribed, or recommended

No survey respondents provided this information

Table 15. Compounded use of benzocaine in practice

No survey respondents provided this information

Table 16. Indications for which benzocaine is considered a standard therapy

No survey respondents provided this information

Table 17. Reasons for using a compounded product instead of any FDA-approved product

No survey respondents provided this information

Table 18. Change in frequency of compounded benzocaine usage over the past 5 years

No survey respondents provided this information

Table 19. Do you stock non-patient specific compounded benzocaine in your practice?

No survey respondents provided this information

Table 20. Questions related to stocking non-patient specific compounded benzocaine

No survey respondents provided this information

CONCLUSION

Benzocaine (UNII code: U3RSY48JW5) was nominated for inclusion on the 503B Bulks List for various indications via various topical, oral, otic, and rectal formulations. Benzocaine is available in various topical, dental, buccal, and oral dosage forms as an OTC product in the US and has a current USP monograph. Benzocaine is also available in Australia, Belgium, Hong Kong, Namibia, New Zealand, Saudi Arabia, and UK.

From the literature review, the most common indications in both the US and non-US studies were anesthesia and analgesia. Compounded products were identified from both the US (20% ointment and 20% gel) and non-US (5% gel, 8 mg lozenges, and pastilles) studies. There were five (5) studies identified with the nominated combinations.

From the interviews, two (2) interviewees were interested in having access to compounded "caine" products. One (1) interviewee does not use benzocaine. Another interviewee had safety concerns about benzocaine, especially with its use in young children. This interviewee stated that there are less risky alternatives.

From the survey responses, none of the 10 survey respondents used benzocaine.

APPENDICES

Appendix 1. References

1. Adriani J., Taylor M.K. Benzocaine's properties and uses as a topical anesthetic: Part I. Physicochemical and pharmacological description. *Anesthesiol Rev*. 1990;17(1):27-33.
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Appendix 2. Survey instrument

Start of Block: Welcome Page

The University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), in collaboration with the Food and Drug Administration (FDA), is conducting research regarding the use of certain bulk drug substances nominated for use in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act. In particular, we are interested in the current and historic use of these substances in clinical practice. This survey is for **benzocaine**. As a medical expert, we appreciate your input regarding the use of this substance in your clinical practice. This information will assist FDA in its development of a list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Act. All responses are anonymous.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

The time required to complete this information collection is estimated to average 30 minutes, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number. If you have additional questions or concerns about this research study, please email: compounding@rx.umaryland.edu. If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

End of Block: Welcome Page

Start of Block: Benzocaine

Q1. What type(s) of product(s) do you use, prescribe, or recommend for **benzocaine**? Please check all that apply.

- ☐ Compounded drug product
- ☐ FDA-approved drug product
- ☐ Over the counter drug product
- ☐ Dietary supplement (e.g. vitamin or herbal supplement products sold in retail setting)
- ☐ Unsure

Skip To: Q13 If What type(s) of product(s) do you use, prescribe, or recommend for benzocaine? Please check all th... != Compounded drug product

Skip To: Q2 If What type(s) of product(s) do you use, prescribe, or recommend for benzocaine? Please check all th... = Compounded drug product

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Display This Question:

If What type(s) of product(s) do you use, prescribe, or recommend for benzocaine? Please check all th... = Compounded drug product

Q2. Please list any conditions or diseases for which you use compounded **benzocaine** in your practice. Please include the strength(s), dosing frequency(ies), dosage form(s), route(s) of administration, duration of therapy, and patient population (ex. age, gender, comorbidities, allergies, etc).

	Strength(s) (please include units)	Dosing frequency(ies)	Dosage form(s)	Route(s) of administration	Duration of therapy	Patient population
Condition 1 (please describe)						
Condition 2 (please describe)						
Condition 3 (please describe)						
Condition 4 (please describe)						
Condition 5 (please describe)						

Q3. Do you use compounded **benzocaine** as a single agent active ingredient, or as one active ingredient in a combination product? Please check all that apply.

- ☐ Single
- ☐ Combination

Skip To: Q5 If Do you use compounded benzocaine as a single agent active ingredient, or as one active ingredient... != Combination

Display This Question:

If Loop current: Do you use compounded benzocaine as a single agent active ingredient, or as one active ingredient... = Combination

Q4. In which combination(s) do you use compounded **benzocaine**? Please check all that apply.

- ☐ Benzocaine 5-20% / Lidocaine / Prilocaine
- ☐ Benzocaine 505 / Lidocaine 8-10% / Tetracaine 4-10%
- ☐ Other (please describe) _____

Q5. For which, if any, diseases or conditions do you consider compounded **benzocaine** standard therapy?

_____

Q6. Does your specialty describe the use of compounded **benzocaine** in medical practice guidelines or other resources?

_____

Q7. Over the past 5 years, has the frequency in which you have used compounded **benzocaine** changed?

- ○ Yes - I use it **MORE** often now (briefly describe why) _____
- ○ Yes - I use it **LESS** often now (briefly describe why) _____
- ○ No - use has remained consistent

Q8. Why do you use compounded **benzocaine** instead of any FDA-approved drug product?

_____

Q9. Do you stock non-patient-specific compounded **benzocaine** in your practice location?

- o Yes
- o No

Skip To: End of Block If Do you stock non-patient-specific compounded benzocaine in your practice location? = No

Display This Question:

If Do you stock non-patient-specific compounded benzocaine in your practice location? = Yes

Q10. In what practice location(s) do you stock non-patient-specific compounded **benzocaine**? Please check all that apply.

- ☐ Physician office
- ☐ Outpatient clinic
- ☐ Emergency room
- ☐ Operating room
- ☐ Inpatient ward
- ☐ Other (please describe) _____

Q11. How do you obtain your stock of non-patient-specific compounded **benzocaine**? Please check all that apply.

- ☐ Purchase from a compounding pharmacy
- ☐ Purchase from an outsourcing facility
- ☐ Compound the product yourself
- ☐ Other (please describe) _____

Q12. Why do you keep a stock of non-patient-specific compounded **benzocaine**? Please check all that apply.

- ☐ Convenience
- ☐ Emergencies
- ☐ Other (please describe) _____

Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded benzocaine? Please check all that apply. = Convenience

Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded benzocaine? Please check all that apply. = Emergencies

Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded benzocaine? Please check all that apply. = Other (please describe)

Q13. For which, if any, diseases or conditions do you consider **benzocaine** standard therapy?

_____

Q14. Does your specialty describe the use of **benzocaine** in medical practice guidelines or other resources?

_____

End of Block: Benzocaine

Start of Block: Background Information

Q15. What is your terminal clinical degree? Please check all that apply.

- ☐ Doctor of Medicine (MD)
- ☐ Doctor of Osteopathic Medicine (DO)
- ☐ Doctor of Medicine in Dentistry (DMD/DDS)
- ☐ Naturopathic Doctor (ND)
- ☐ Nurse Practitioner (NP)
- ☐ Physician Assistant (PA)
- ☐ Other (please describe) _____

Q16. Which of the following Board certification(s) do you hold? Please check all that apply.

- ☐ No Board certification
- ☐ Allergy and Immunology
- ☐ Anesthesiology
- ☐ Cardiovascular Disease
- ☐ Critical Care Medicine
- ☐ Dermatology
- ☐ Emergency Medicine
- ☐ Endocrinology, Diabetes and Metabolism
- ☐ Family Medicine
- ☐ Gastroenterology
- ☐ Hematology
- ☐ Infectious Disease
- ☐ Internal Medicine
- ☐ Medical Toxicology
- ☐ Naturopathic Doctor
- ☐ Naturopathic Physician
- ☐ Nephrology
- ☐ Neurology
- ☐ Obstetrics and Gynecology
- ☐ Oncology
- ☐ Ophthalmology
- ☐ Otolaryngology
- ☐ Pain Medicine
- ☐ Pediatrics
- ☐ Psychiatry
- ☐ Rheumatology
- ☐ Sleep Medicine
- ☐ Surgery (please describe) _____
- ☐ Urology
- ☐ Other (please describe) _____

End of Block: Background Information