Summary Report

Iodoform

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Food and Drug Administration
Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
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REVIEW OF NOMINATION

Iodoform (UNII code: KXI2J76489) was nominated for inclusion on the 503B Bulks List by the Specialty Sterile Pharmaceutical Society as a topical solution in combination with bismuth nitrate oxide for use as an antiseptic agent.

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

- Prescribers' preference to varying concentration, volumes, or final product container for administration.
- It is relatively unsafe to expose the direct compounding area to hundreds of vials or ampoules 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.
- Commercially available finished products have an inherent variance in potency creating an uncertain final concentration for the new product.
- Use of state-of-the-art equipment, like the SKAN isolator technology, requires the use of bulk starting materials.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of iodoform 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, specifically, 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: United States, 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, United Kingdom, 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 iodoform; name variations of iodoform 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 iodoform. 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 24, 2018. The search included a combination of (iodoform[TIAB] OR triiodomethane[TIAB] OR "75-47-8"[TIAB] OR jodoform[TIAB] AND (therapy[TIAB] OR treatment[TIAB] OR clinical[TIAB] OR disinfect*[TIAB] OR wound[TIAB] OR antiseptic[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 iodoform or the implementation of iodoform 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.

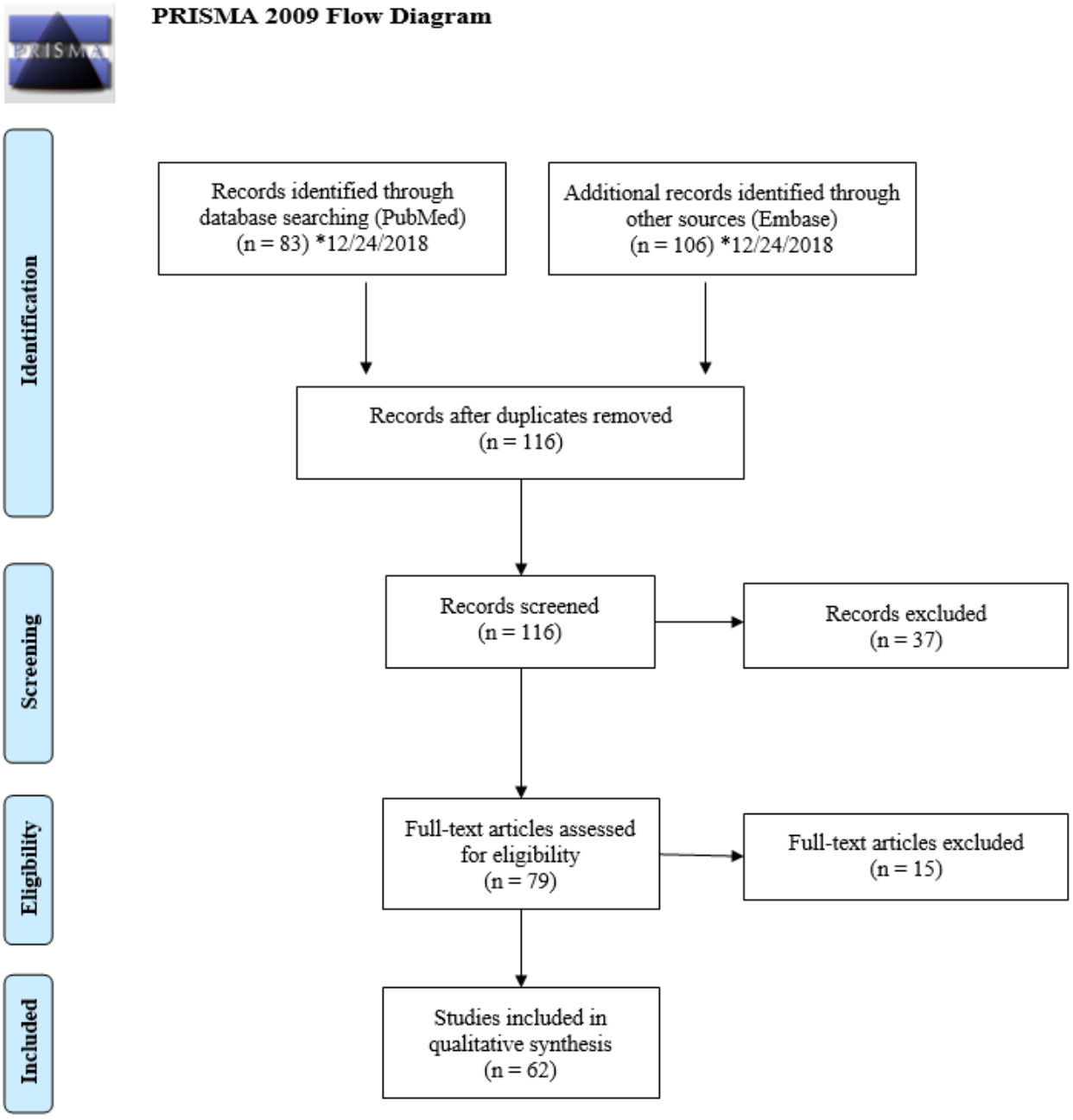
Data extraction

A standard data extraction form was used to collect study authors; article title; year published; journal title; country; indication for iodoform 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 iodoform 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 indication from the nomination and the results of the literature review, five (5) medical specialties that would potentially use iodoform were identified: dentistry, oral medicine, otolaryngology, surgery, and wound care. Criteria for selecting subject matter experts included recommendations provided by specialty professional associations or regulatory organizations, convenient geographic location, authorship within the specialty, or referral by an interviewee. Up to nine (9) interviews were conducted per substance. Two (2) medical experts were contacted for an interview, neither of which responded to the interview request. No interviews were conducted.

Survey

General professional medical associations and specialty associations for dentistry, oral medicine, otolaryngology, surgery, and wound care, identified from the nominations and literature review, were contacted 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, leading professional organizations within that specialty, 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 ten (10) 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
Oral Medicine	American Academy of Oral Medicine (AAOM)

Table 2. Associations that declined participation

Specialty	Association	Reasons for Declining
Dentistry	American Dental Association (ADA)	Declined, ADA concluded that this issue does not affect enough dentists to warrant a significant investment of time"
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, stating that they did not think otolaryngologists are the target market for the survey
	American Rhinologic Society (ARS)	Declined, stating they do not send out surveys unless they are requested by a member, unable to identify a member to request survey distribution
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

- Iodoform is not available as an FDA-approved product.
- Iodoform is available as an OTC product in the US.
- There is a current USP monograph for iodoform.
- Iodoform is available in UK, only as a general sale list medication.

Table 3. Currently approved products – US

No approved products in the US

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

No approved products in the selected non-US countries and regions

Summary of literature review

- Total number of studies included: 62 studies (27 descriptive, 32 experimental, and 3 observational).
- Most of the studies were from the US (16 studies).
- The most common indication in the US was wound packing. The most common indications from the non-US studies were root canal filling, wound healing, and pulpectomy.
- Compounded products were identified from both US and non-US studies, but no studies utilized iodoform in the products that were identified in the nomination.

Table 5. Types of studies

Types of Studies	Number of Studies
Descriptive[1-27]	27
Experimental[28-59]	32
Observational[60-62]	3

Table 6. Number of studies by country

Country	Number of Studies
Brazil[32,35,41,43,49]	5
China[3,23,33,40,55,58,59,61]	8
India[2,12,21,24,38,50-52,54,56]	10
Iran[45]	1
Israel[7,46]	2
Japan[18,44]	2
Jordan[29]	1
Kenya[4]	1
Mexico[26]	1
Poland[11]	1
Russia[18]	1
Switzerland[1]	1
Thailand[57]	1

Turkey[30,48]	2
UK[6,15,34,42,53,62]	6
US[5,8-10,13,14,16,20,22,27,28,31,36,37,47,60]	16
Multiple Countries • France, UK[19]	1
	Total US: 16 Total Non-US Countries: 48

Studies 25 and 39 did not mention country.

Table 7. Number of studies by combinations

	Combination Formula	Number of Studies
Nominated	Iodoform 500mg/g / Bismuth nitrate 250mg/g	0
Others found in literature	Iodoform / Barium sulfate / Calcium hydroxide[24]	1
	Iodoform 40.6% / Barium sulphate 1.63% / Calcium hydroxide 1.07% / Eugenol / Zinc oxide 56.5% - Paste[19,46,52,54]	4
	Iodoform / Bismuth paraffin paste[2,6,9,12,15,25,34,39,42,62]	10
	Iodoform 15.8g / Butamben 25.7g / Eugenol 13.7g[6]	1
	Iodoform / Calcium hydroxide (VITAPEX, Metapex)[10,16,18,19,26,32,45,50,51,54,57]	11
	Iodoform 40.4% / Calcium hydroxide 30.3%[14,21,29,30,47,48]	6
	Iodoform 38.3% / Calcium hydroxide 2.1% / Eugenol 14.9% / Zinc oxide 44.7%[33]	1
	Iodoform 15.5% / Calendula oil 5% - Topical pomade[35]	1
	Iodoform / Camphor / Menthol / Parachlorophenol (Walkhoff)[10,32]	2
	Iodoform 80.8% / Camphor 4.86% / Menthol 1.215% / Parachlorophenol 2.025% (KRI 1)[7,8,32,36]	4
	Iodoform / Camphor / Menthol / Lanolin / Parachlorophenol / Thymol / Zinc oxide (Maisto's paste)[1,7,10,32]	4
	Iodoform 80.8% / Camphor 4.9% / Parachlorophenol 2% (KRI)[10]	1
	Iodoform / Camphor / Parachlorophenol / Prednisolone acetate / Rifamycin sodium salt / Propylene glycol[49]	1
	Iodoform / Eugenol / Zinc oxide[1,50,51]	3
	Iodoform / Zinc oxide[38,56]	2

Table 8. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Wound packing[13,20,22,27,28,31,60]	–	–	Gauze	Topical	11 days-6 weeks
Root canal filling[10,14,16,47]	–	40.4-50%	Paste	Dental	Once-12 weeks
Root canal therapy[36]	–	80.8%	Paste	Dental	–
Pulpectomy[5,8]	–	80.8%	Paste	Dental	–
Alveolar osteitis[37]	–	–	Gauze	Dental	–
Epistaxis[9]	–	–	Gauze	Nasal	–

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

Table 9. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Wound healing[2-4,17,24,25,29,42,58,61,63]	–	–	Paste	Dental/Topical	Once-2 weeks
	–	–	Ointment	Topical	4 days
	–	–	Wick	Dental	–
	–	–	Gauze	Topical	Once-4 weeks
Wound packing[23,39,55,59]	–	–	Gauze	Topical	7-15 months
Wound debridement[44]	–	–	Gauze	Topical	–
Root canal filling/obturation[1,7,11,21,32,45,46,48,50-52,54,57]	–	30 - 40.6%	Paste	Dental	Once-1 month
	–	–	Powder		Once

Pulpectomy/pulpotomy/apexification[18,19,21,30,33,38,41,43]	–	38.3-40.4%	Paste	Dental	Once-3 minutes
Odontogenic cyst[12,40]	–	–	Gauze	Dental	6 months
	–	50%	Paste		2 months
Pulp capping[26]	–	–	Paste	Dental	Once
Alveolar osteitis[6]	–	–	–	–	–
Bacterial prophylaxis/antiseptic[6,35,49,56]	–	50%	Paste	Dental/Topical	Once-30 minutes
	–	15.5%	Pomade	Topical	Once
	–	–	Gauze		–
	–	10g/100ml	Varnish	–	–
Epistaxis[15,34,62]	–	–	Paste/Gauze	Nasal	–
Pain control[53]	–	10g/100ml	Varnish	Topical	Once

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

Table 10. Compounded products – US

Indication	Published year	Compounding Method	Dosage Form	Final Strength
Root canal filling[16]	1986	• Calcium hydroxide and iodoform powder (Endoflas) in equal proportions mixed with glycerin to a thick paste • Equal parts of iodoform crystal and calcium hydroxide mixed with glycerin to a paste	Paste	–

Abbreviation: "–", not mentioned.

Table 11. Compounded products – non-US countries

Indication	Compounding Method	Dosage Form	Final Strength
Root canal filling[32]	• K-Dent, mixed with Rifocort and camphorate parachlorophenol sterilized on a glass plate	Paste	–
Pulpectomy/pulpotomy[33]	• 0.21g zinc oxide, 0.07g eugenol, 0.18g iodoform, and 0.01g calcium hydroxide combined in sequence to medium consistency	Paste	38.3%
Bacterial prophylaxis/ antiseptic[49,56]	• 1 part iodoform, 1 drop camphorated parachlorophenol (3 parts of parachlorophenol and 7 parts of camphor), 1 part Rifocort (topical medication containing 5mg prednisolone acetate, 1.5mg rifamycin sodium salt, and 0.25mg of propylene glycol) made as a paste • A homogenous mix of iodoform and zinc oxide mixed with distilled water	Paste	–
Pain control[53]	• 10g iodoform, 10g benzoin, 7.5g starch, 5g natural balsams, and solvent ether to 100ml	Varnish	–
Wound healing[25]	• Ointment consisting of bismuth subnitrate, iodoform powder, and white petrolatum	Ointment	–

Abbreviation: "–", not mentioned.

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

No interviews were conducted. Two (2) medical experts, one (1) in denistry and one (1) in otolaryngology were contacted however both failed to respond to the interview request.

Table 12. Overview of interviewee

No interviews were conducted

Summary of survey results

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

Board Certification	DMD/DDS	PhD	No Response
Oral medicine	2	0	0
Pain medicine	1	0	0
Sleep medicine	1	0	0
No Board certification	0	1	0
No Response	0	0	7

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

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

Types of Products	Respondents, n (N=4[a])
Compounded	0
FDA-approved	1
Over-the-counter	1
Dietary	0
Unsure	0
No Response	2

[a]Out of 10 respondents, 4 reported using, prescribing, or recommending multiple types of iodoform product.

Table 15. Compounded use of iodoform in practice

No survey respondents provided this information

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

Indication	Standard therapy		
	Compounded, n (N=0)	**Non-compounded, n (N=2)**	**No response, n (N=2)**
Post biopsy	0	1	0
No response	0	1	2

Table 17. Reasons for using compounded product instead of the FDA-approved products

No survey respondents provided this information

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

No survey respondents provided this information

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

No survey respondents provided this information

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

No survey respondents provided this information

CONCLUSION

Iodoform (UNII code: KXI2J76489) was nominated for inclusion on the 503B Bulks List by the Specialty Sterile Pharmaceutical Society as a topical solution in combination with bismuth nitrate oxide for use as an antiseptic agent. Iodoform is available in UK as a general sale list medication.

From the literature review conducted, the most common indication in the US was wound packing. The most common indication in the non-US studies were root canal filling, wound healing, and pulpectomy. Use of iodoform as a compounded product was identified from one (1) of the US studies but it was not the product identified in the nomination.

No interviews were conducted. Two (2) medical experts, one (1) in denistry and one (1) in otolaryngology were contacted however both failed to respond to the interview request. From the survey responses, four (4) out of ten (10) respondents used iodoform. Out of four (4), zero (0) respondents used compounded iodoform.

APPENDICES

Appendix 1. References

1. Castagnola L, Wirz J. The use of iodoform paste (Walkhoff method) in modern endodontic therapy. *Quintessence international, dental digest.* 1976;7(4):19-23.
2. Charlu AP, Kumar S, Chacko R. Qualitative evaluation of 'BIPP dressing' for intraoral mucosal defect. *Journal of Clinical and Diagnostic Research.* 2018;12(4):ZC11-ZC14.
3. Chen HM, Cai ZG, Zhao FY, Wu J, Jiang RP. Reconstruction of a huge oral maxillofacial defect caused by necrotic fasciitis secondary to leukaemia. *Journal of plastic, reconstructive & aesthetic surgery : JPRAS.* 2008;61(12):e1-5.
4. Chindia ML. A conservative management of an extensive odontogenic residual cyst: a case report. *East Afr Med J.* 1991;68(2):143-148.
5. Dunston B, Coll JA. A survey of primary tooth pulp therapy as taught in US dental schools and practiced by diplomates of the American Board Of Pediatric Dentistry. *Pediatr Dent.*30(1):42-48.
6. Freedman M, Stassen LF. Commonly used topical oral wound dressing materials in dental and surgical practice--a literature review. *J Ir Dent Assoc.*59(4):190-195.
7. Fuks AB, Eidelman E. Pulp therapy in the primary dentition. *Curr Opin Dent.* 1991;1(5):556-563.
8. Holan G, Fuks AB. A comparison of pulpectomies using ZOE and KRI paste in primary molars: a retrospective study. *Pediatr Dent.*15(6):403-407.
9. Iqbal IZ, Jones GH, Dawe N, et al. Intranasal packs and haemostatic agents for the management of adult epistaxis: systematic review. *The Journal of laryngology and otology.* 2017;131(12):1065-1092.
10. Kubota K, Golden BE, Penugonda B. Root canal filling materials for primary teeth: a review of the literature. *ASDC J Dent Child.*59(3):225-227.
11. Małyszko M, Pawińska M. Endodontic treatment of complicated traumatic deciduous teeth damage--a case report. *Ann Acad Med Stetin.* 2008;54(3):81-88.
12. Morawala A, Shirol D, Chunawala Y, Kanchan N, Kale M. Bismuth subnitrate iodoform parafin paste used in the management of inflammatory follicular cyst - Report of two cases. *J Indian Soc Pedod Prev Dent.*35(3):269-274.
13. Nallegowda M, Ayyoub Z, Brandstater M, et al. Recurrent esophagocutaneous fistula in a SCI patient: A case report. *PM and R.* 2010;2(9):S183.
14. Nurko C, Ranly DM, García-Godoy F, Lakshmyya KN. Resorption of a calcium hydroxide/iodoform paste (Vitapex) in root canal therapy for primary teeth: a case report. *Pediatr Dent.*22(6):517-520.
15. Sadri M, Midwinter K, Ahmed A, Parker A. Assessment of safety and efficacy of arterial embolisation in the management of intractable epistaxis. *European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery.* 2006;263(6):560-566.

16. Salamat K, Rezai RF. Nonsurgical treatment of extraoral lesions caused by necrotic nonvital tooth. *Oral surgery, oral medicine, and oral pathology.* 1986;61(6):618-623.

17. Shinkevich D, Afanasiev V, Zorenko V, Chenchikov M. The silicone membranes use for alveolus bleeding prevention after teeth extraction in the patients with haemophilia. *Haemophilia.* 2013;19((Zorenko V.) Department of Hemophilia, National Center of Hematology, Moscow, Russian Federation):58.

18. Shintani S, Tsuji M, Toyosawa S, Ooshima T. Intentional replantation of an immature permanent lower incisor because of a refractory peri-apical lesion: case report and 5-year follow-up. *Int J Paediatr Dent.* 2004;14(3):218-222.

19. Smaïl-Faugeron V, Glenny AM, Courson F, Durieux P, Muller-Bolla M, Fron Chabouis H. Pulp treatment for extensive decay in primary teeth. *Cochrane Database Syst Rev.* 2018;2018(5).

20. Som ML, Garlock JH. New approach to the treatment of esophageal varices. *JAMA (Chicago, Ill).* 1947;135(10):628-629.

21. Sridhar N, Tandon S. Continued root-end growth and apexification using a calcium hydroxide and iodoform paste (Metapex®): three case reports. *The journal of contemporary dental practice.* 2010;11(5):063-070.

22. Statham MM, Vohra A, Mehta DK, Baker T, Sarlay R, Rutter MJ. Serratia marcescens causing cervical necrotizing oropharyngitis. *Int J Pediatr Otorhinolaryngol.* 2009;73(3):467-473.

23. Su L, Wang D, Han Y, Wang Z, Fan X. Salvage treatment of hemorrhagic arteriovenous malformations in jaws. *Journal of cranio-maxillo-facial surgery : official publication of the European Association for Cranio-Maxillo-Facial Surgery.* 2015;43(7):1082-1087.

24. Thomas K, T PD, Simon EP. Management of large periapical cystic lesion by aspiration and nonsurgical endodontic therapy using calcium hydroxide paste. *The journal of contemporary dental practice.* 2012;13(6):897-901.

25. Tuig AV, Chen B, Higgins S, Chin T, Gallego D, Gibran N. Iatrogenic bismuth-associated encephalopathy treated with dimercaptosuccinic acid. *Clin Toxicol.* 2017;55(7):754-755.

26. Weisleder R, Benitez CR. Maturogenesis: is it a new concept? *J Endod.* 2003;29(11):776-778.

27. Work WP. Newer concepts of first branchial cleft defects. *Laryngoscope.* 2015;125(3):520-532.

28. Agrawal T, Fuentes Rojas S, Adigun R, Badam M. A Rare Catch in a Nonhealing Wound. *Wounds : a compendium of clinical research and practice.* 2018;30(9):E87-E88.

29. Al Khasawnah Q, Hassan F, Malhan D, et al. Nonsurgical Clinical Management of Periapical Lesions Using Calcium Hydroxide-Iodoform-Silicon-Oil Paste. *BioMed research international.* 2018;2018:8198795.

30. Alaçam A, Odabaş ME, Tüzüner T, Sillelioğlu H, Baygin O. Clinical and radiographic outcomes of calcium hydroxide and formocresol pulpotomies performed by dental students. *Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics.* 2009;108(5):e127-133.

31. Alimov V, Lovecchio F, Sinha M, Foster KN, Drachman D. Use of a silver-containing hydrofiber dressing for filling abscess cavity following incision and drainage in the emergency department: a randomized controlled trial. *Adv Skin Wound Care.* 2013;26(1):20-25.

32. Cerqueira DF, Mello-Moura ACV, Santos EM, Guedes-Pinto AC. Cytotoxicity, histopathological, microbiological and clinical aspects of an endodontic iodoform-based paste used in pediatric dentistry: A review. *J Clin Pediatr Dent.* 2007;32(2):105-110.

33. Chen X, Liu X, Zhong J. Clinical and radiographic evaluation of pulpectomy in primary teeth: a 18-months clinical randomized controlled trial. *Head Face Med.* 2017;13(1):12.

34. Corbridge RJ, Djazaeri B, Hellier WP, Hadley J. A prospective randomized controlled trial comparing the use of merocel nasal tampons and BIPP in the control of acute epistaxis. *Clin Otolaryngol Allied Sci.* 1995;20(4):305-307.

35. Cruz F, Leite F, Cruz G, et al. Sutures coated with antiseptic pomade to prevent bacterial colonization: a randomized clinical trial. *Oral surgery, oral medicine, oral pathology and oral radiology.* 2013;116(2):e103-109.

36. Garcia-Godoy F. Evaluation of an iodoform paste in root canal therapy for infected primary teeth. *ASDC J Dent Child.*54(1):30-34.

37. Garibaldi JA, Greenlaw J, Choi J, Fotovatjah M. Treatment of post-operative pain. *Journal of the California Dental Association.* 1995;23(4):71-72, 74.

38. Grover R, Mehra M, Pandit IK, Srivastava N, Gugnani N, Gupta M. Clinical efficacy of various root canal obturating methods in primary teeth: a comparative study. *European journal of paediatric dentistry : official journal of European Academy of Paediatric Dentistry.* 2013;14(2):104-108.

39. Javed F, Whitwell R, Macleod I, et al. Pack or no pack after ear surgery: A randomized controlled trial. *Otolaryngology - Head and Neck Surgery (United States).* 2012;147((Javed F.; Whitwell R.; Macleod I.; Hajioff D.; Robinson P.; Rea D.; Nunez D.)):P91.

40. Li M, Zhang X, Li Z, An J, Qian M. Clinical research of jaw marsupialization by applying obturator made by hot pressure casting technique. *Int J Clin Exp Med.* 2016;9(2):1850-1856.

41. Lourenço Neto N, Marques NC, Fernandes AP, et al. Clinical and radiographic evaluation of Portland cement added to radiopacifying agents in primary molar pulpotomies. *European archives of paediatric dentistry : official journal of the European Academy of Paediatric Dentistry.* 2015;16(5):377-382.

42. Lyall JB. Third molar surgery: the effect of primary closure, wound dressing and metronidazole on postoperative recovery. *J R Army Med Corps.* 1991;137(2):100-103.

43. Marques N, Lourenço Neto N, Fernandes AP, et al. Pulp tissue response to Portland cement associated with different radio pacifying agents on pulpotomy of human primary molars. *J Microsc.* 2015;260(3):281-286.

44. Mizokami F, Murasawa Y, Furuta K, Isogai Z. Iodoform gauze removes necrotic tissue from pressure ulcer wounds by fibrinolytic activity. *Biol Pharm Bull.* 2012;35(7):1048-1053.

45. Mortazavi M, Mesbahi M. Comparison of zinc oxide and eugenol, and Vitapex for root canal treatment of necrotic primary teeth. *Int J Paediatr Dent.* 2004;14(6):417-424.

46. Moskovitz M, Tickotsky N, Ashkar H, Holan G. Degree of root resorption after root canal treatment with iodoform-containing filling material in primary molars. *Quintessence international (Berlin, Germany : 1985).* 2012;43(5):361-368.

47. Nurko C, Garcia-Godoy F. Evaluation of a calcium hydroxide/iodoform paste (Vitapex) in root canal therapy for primary teeth. *The Journal of clinical pediatric dentistry.* 1999;23(4):289-294.

48. Olmez A, Tuna D, Ozdoğan YT, Ulker AE. The effectiveness of different thickness of mineral trioxide aggregate on coronal leakage in endodontically treated deciduous teeth. *Journal of dentistry for children (Chicago, Ill).*75(3):260-263.

49. Ortega KL, Rezende NP, Araújo NS, Magalhães MH. Effect of a topical antimicrobial paste on healing after extraction of molars in HIV positive patients: randomised controlled clinical trial. *The British journal of oral & maxillofacial surgery.* 2007;45(1):27-29.

50. Pramila R, Muthu MS, Deepa G, Farzan JM, Rodrigues SJ. Pulpectomies in primary mandibular molars: a comparison of outcomes using three root filling materials. *Int Endod J.* 2016;49(5):413-421.

51. Ramar K, Mungara J. Clinical and radiographic evaluation of pulpectomies using three root canal filling materials: an in-vivo study. *J Indian Soc Pedod Prev Dent.*28(1):25-29.

52. Rewal N, Thakur AS, Sachdev V, Mahajan N. Comparison of endoflas and zinc oxide eugenol as root canal filling materials in primary dentition. *J Indian Soc Pedod Prev Dent.*32(4):317-321.

53. Stanley D, Emerson DJ, Daley JC. Whitehead's varnish and Jelonet--a better dressing for skin graft donor sites than Jelonet alone. *Ann R Coll Surg Engl.* 1988;70(6):369-371.

54. Subramaniam P, Gilhotra K. Endoflas, zinc oxide eugenol and metapex as root canal filling materials in primary molars--a comparative clinical study. *The Journal of clinical pediatric dentistry.* 2011;35(4):365-369.

55. Tan XJ, Wu M, Lang JH. Feasibility and clinical value of modified electrosurgical knife conization. *Int J Gynecol Cancer.* 2012;22((Tan X.J.; Wu M.; Lang J.H.) Obstetrics and Gynecology, Peking Union Medical College Hospital, Chinese Academy of Medical Science, Beijing, China):E1057.

56. Thomas AM, Chandra S, Chandra S, Pandey RK. Elimination of infection in pulpectomized deciduous teeth: a short-term study using iodoform paste. *J Endod.* 1994;20(5):233-235.

57. Trairatvorakul C, Chunlasikaiwan S. Success of pulpectomy with zinc oxide-eugenol vs calcium hydroxide/iodoform paste in primary molars: a clinical study. *Pediatr Dent.*30(4):303-308.

58. Zhang M, Zhang X, Zheng C. Application of buccal fat pads in pack palate relaxing incisions on maxillary growth: A clinical study. *Int J Clin Exp Med.* 2015;8(2):2689-2692.

59. Zhou H, Hou R, Ma Q, et al. Secondary healing after removal of large keratocystic odontogenic tumor in the mandible: enucleation followed by open packing of iodoform gauze. *Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons.* 2012;70(7):1523-1530.

60. Giles WC, Iverson KC, King JD, Hill FC, Woody EA, Bouknight AL. Incision and drainage followed by mattress suture repair of auricular hematoma. *The Laryngoscope.* 2007;117(12):2097-2099.

61. Liu G, Liu Y, Yang Y, Wang W, Cheng X. Conservative treatment of large mandibular radiolucent benign lesions: A preliminary report of enucleation and curettage with radiofrequency ablation. *Int J Oral Maxillofac Surg.* 2013;42(10):1173.

62. Upile T, Jerjes W, Sipaul F, et al. The role of surgical audit in improving patient management; nasal haemorrhage: an audit study. *BMC Surg.* 2007;7:19.

63. Lagarce L, Tessier B, Harry P, et al. The dangers of iodoform gauze: A retrospective study. *Fundam Clin Pharmacol.* 2013;27((Lelievre B.) Laboratoire de Pharmacologie-Toxicologie, Département des Agents Infectieux, CHU Angers, Angers, France):93.

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 **iodoform**. 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: Iodoform

Q1. What type(s) of product(s) do you use, prescribe, or recommend for **iodoform**? 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 iodoform? Please check all th... != Compounded drug product

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

Q2. Please list any conditions or diseases for which you use compounded **iodoform** 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 **iodoform** 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 iodoform as a single agent active ingredient, or as one active ingredient... != Combination

Display This Question:

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

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

- ☐ Iodoform 500mg/g / Bismuth nitrate 250mg/g
- ☐ Other (please describe) _____

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

_____

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

_____

Q7. Over the past 5 years, has the frequency in which you have used compounded **iodoform** 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 **iodoform** instead of any FDA-approved drug product?

_____

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

- Yes
- No

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

Display This Question:

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

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

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

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

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

_____

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

_____

End of Block: Iodoform

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