Summary Report

Calcium gluconate

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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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Frequently Used Abbreviations

API	Active Pharmaceutical Ingredient
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
IRB	Institutional Review Board
OTC	Over-the-counter
ROA	Route of administration
SME	Subject matter expert
TPN	Total parenteral nutrition
UK	United Kingdom
US	United States

INTRODUCTION

This report was created to assist the Food and Drug Administration (FDA) in their evaluation of the use of calcium gluconate (UNII code: SQE6VB453K), which was nominated for use as a bulk drug substance in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act.

The aim of this report was to describe how calcium gluconate is used in clinical research and practice to diagnose, prevent, or treat disease. Due to the broad, exploratory nature of this aim, scoping review methodology was used. Following the scoping review framework, a systematic literature review was conducted and healthcare practitioners were consulted to identify how calcium gluconate has been used historically and currently.[1-3] Assessment of study quality and risk of bias were not performed because the aim of this report was not to make specific recommendations on the use of this substance in clinical practice.[1,4,5] Rather, the aim was to summarize the available evidence on the use of calcium gluconate and thereby assist the FDA to determine whether there is a need for the inclusion of this substance on the 503B Bulks List.

REVIEW OF NOMINATIONS

Calcium gluconate was nominated for inclusion on the 503B Bulks List by David Smith, Pine Pharmaceuticals, the Specialty Sterile Pharmaceutical Society (SSPS), and US Compounding Pharmacy. Calcium gluconate was nominated for use in combination with additional Active Pharmaceutical Ingredients (API) (refer to Table 8).

Calcium gluconate was nominated for vitamin deficiency via an intramuscular injection in combination with vitamin B complex, vitamin C (sodium ascorbate), and magnesium chloride.

Calcium gluconate was also nominated for treating allergic disorders, electrolyte disturbances (hypocalcemia, hyperkalemia, hypermagnesemia, hyperphosphatemia), nutritional supplementation, verapamil or calcium agonist toxicity, beta-blocker overdose, exudative dermatitis, diagnosis of gastrinoma or insulinoma, non-thrombocytopenic purpura, and hydrofluoric acid burns via:

- 2.5-5% inhalation solution
- 1% irrigation solution
- 2-32.5% topical gel
- 16.7% oral suspension
- 5-23% injection solution
- 0.1% preservative free intravenous solution
- 1-10% ophthalmic drops

Nominators provided references from published peer-reviewed literature to describe the pharmacology, and support the clinical use, of calcium gluconate.[6-20]

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

- There is no FDA-approved product that contains calcium gluconate in combination with vitamin B complex, vitamin C (sodium ascorbate), and magnesium chloride in an injection.
- Patient sensitivities to fillers, preservatives, or other excipients in commercially available medications.
- Prescriber or hospital preference for various strengths, combinations with other drugs, volumes and/or final product containers for administration.

- Unsafe to expose the direct compounding area to hundreds of vials or ampoules and hundreds of aseptic manipulations during the compounding of a typical size batch for outsourcing facilities; a single vessel compounded from bulk API is safer and more efficient than unmanageable amounts of small vials.
- As required by Current Good Manufacturing Practices, bulk API powders can be formulated to 100 percent potency, but finished products cannot; commercially available finished products have an inherent variance in potency, creating an uncertain final concentration for the new product.
- According to SPSS, in order to utilize the most advanced technology available to provide the greatest level of sterility assurance and quality, bulk starting material is required; it is not feasible financially, nor from a processing standpoint, to use finished pharmaceutical dosage forms with advanced isolated robotic equipment or other advanced aseptic processing equipment.
- Different concentrations may be needed in elderly or young populations and those with sensitivities to inactive ingredients.
- FDA-approved versions of calcium gluconate are only available as a solution for intravenous injection which is commonly mixed with a diluent of 5% dextrose in water or normal saline; this may make it unsuitable to be used in the eye due to pH and tonicity requirements, justifying the need for ophthalmic irrigation solution.
- FDA-approved strengths of calcium gluconate are not the same as those needed for topical application or irrigation solution, both of which are used in practice; using the FDA-approved concentrations to reach the desired concentration needed for other dosage forms would add unnecessary complexity to the compounding procedure and increase risk.
- Calcium gluconate is only obtainable from FDA-approved sources as a 10% vial of 10 mL calcium gluconate, which has been on the drug shortage list for many years; even if 503B facilities were able to get a hold of the product, the package size would add unnecessary complexity and manipulations to the compounding process and increase risk of contamination.
- Manufacturer backorder.
- When a different strength or dosage form is ordered by the practitioner or when ready-to-use packaging is required by the facility.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of calcium gluconate 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: 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 calcium gluconate; name variations of calcium gluconate 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; 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 5.1.5) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing calcium gluconate. 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

A medical librarian constructed comprehensive search strategies for Ovid MEDLINE and Embase. The search strategies used a combination of controlled vocabulary terms and keywords to describe two concepts: burns, injury or poisoning, and hydrofluoric acid (refer to Appendix 1 for full search strategies). Controlled vocabulary terms and keywords for calcium gluconate and the nominated ROA were not included in these search strategies to ensure that any study that discussed hydrofluoric acid injury was retrieved. Intravenous administration for the other nominated indications were not considered for the literature review due to the availability of FDA-approved injectable calcium gluconate products. Results were limited to human studies in English language. Searches were conducted on April 7, 2020. The reference lists of relevant systematic reviews and meta-analyses were reviewed to identify additional studies. In addition, the ECRI Guidelines Trust® repository was searched on April 7, 2020 for clinical practice guidelines on hydrofluoric acid injury, or that recommended the use of calcium gluconate and provided sufficient information on dosing and administration.

Results were exported to EndNote for Windows version X9.2 (Clarivate Analytics), and duplicates were removed. The de-duplicated results were uploaded to Covidence (Veritas Health Innovation) for screening.

Study selection

Studies in which calcium gluconate was used in the nominated dosage form, ROA, and/or combination product to diagnose, prevent or treat the nominated disease or condition, or other conditions not specified in the nomination, were included. Studies were excluded if they were: written in a language other than English; reviews or meta-analyses; surveys or questionnaires (cross-sectional design); designed to evaluate cost-effectiveness, mechanism of action, pre-clinical use, safety, or toxicity; or any study design other than a randomized controlled trial conducted in a non-US country. Studies were also excluded if calcium gluconate was used as: a brand or proprietary product; an FDA-approved product in the nominated dosage form, ROA, or combination; or a dosage form, ROA, or combination that was not nominated. Studies in which calcium gluconate was used to diagnose, prevent, or treat autism were excluded due to a separate project examining the use of compounded substances in individuals with autism. Studies that did not meet the inclusion criteria but provided valuable information about the pharmacological or current or historical use of the substance were noted and put in a separate group in the EndNote library. Two reviewers independently screened titles and abstracts and reviewed full-text articles. A third reviewer reconciled all disagreements.

Data extraction

The following information was recorded in a standard data extraction form: author names; article title; journal; year of publication; country; study type; historical use of calcium gluconate; setting; total number of patients; number of patients who received calcium gluconate; patient population; indication for use of calcium gluconate; dosage form and strength; dose; ROA; frequency and duration of therapy; use of calcium gluconate in a combination product; use and formulation of calcium gluconate in a compounded product; use of calcium gluconate compared to FDA-approved drugs or other treatments; outcome measures; authors' conclusions. One reviewer extracted data from the included studies; a second reviewer checked the data extraction.

Interviews

Semi-structured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances calcium gluconate was used in a clinical setting. The systematic literature review and indications from the nominations were reviewed to identify the following medical specialties that would potentially use calcium gluconate: critical care, naturopathy, nutrition, pediatrics, primary care and internal medicine, and surgery. Potential SMEs within the relevant medical specialties were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. In addition, the American Society of Health-System Pharmacists (ASHP) and select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided oral informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were entered into NVivo 12 (QSR International) for qualitative data analysis. Several members of the research team independently coded the transcriptions of two representative interviews for themes. The team members discussed the codes that emerged from their independent analysis, as well as those codes that were determined a priori. The code book was developed out of the integration of these coding schemes.

Survey

A survey was distributed to the members of professional medical associations to determine the use of calcium gluconate in clinical practice. The online survey was created using Qualtrics® software (refer to Appendix 2 for complete survey). A Google™ search was conducted to identify the professional associations in the US for the relevant medical specialties. An association's website was searched 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 email describing the project and requesting distribution of the survey to the association's members was sent to the identified person(s). Associations that declined, did not respond, or did not provide significant data in project Year 1 were not contacted to distribute the project Year 2 surveys.

The survey was posted on the project website and the survey link was distributed to the associations that agreed to participate (refer to Appendix 3 for associations that participated and those that did not).

Participation was anonymous and voluntary. The estimated time for completion was 15 minutes with a target of 50 responses per survey.

The University of Maryland, Baltimore Institutional Review Board (IRB) and the FDA IRB reviewed the interview and survey methods and found both to be exempt. The Office of Management and Budget approved this project.

CURRENT AND HISTORIC USE

Results of background information

- Calcium gluconate is available as an FDA-approved intravenous product. Calcium gluconate is not available as an FDA-approved product in the other nominated dosage forms and ROA.
- Calcium gluconate is available as an OTC topical gel in the US.
- There is a current United States Pharmacopeia (USP) monograph for calcium gluconate.
- Calcium gluconate is available in the nominated dosage form and ROA in Canada, Hong Kong, Saudi Arabia, and the UK.

Table 1. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Status	Approval Date[b]
Calcium gluconate	20-100 mg/mL	Solution	Intravenous	Prescription	06/15/2017

[a]Source: US FDA *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).
[b]If multiple approval dates and/or multiple strengths, then earliest date provided.

Table 2. Currently approved products – select non-US countries and regions[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date[b]
Calcium gluconate	1-10%	Solution, sterile injection	Infusion, injection, intravenous	Canada	Ethical	07/19/1984
				Hong Kong	Prescription only	08/01/1994
				Saudi Arabia	Prescription	–
				UK	Prescription-only medication	12/08/1983

Abbreviations: "– ", not mentioned.

[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.

Results of literature review

Study selection

Database searches yielded 668 references; 0 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 425 titles and abstracts were screened. After screening, the full text of 268 articles was reviewed. Finally, 26 studies were included. Two hundred forty-two studies were excluded for the following reasons: wrong study design (193 studies); wrong dosage form or ROA (13); wrong substance (12); calcium gluconate not used clinically (10); FDA-approved dosage form or ROA (6); language other than English (3); duplicate study (2); unable to obtain full text (2); calcium gluconate only mentioned briefly (1).

Refer to Figure 1 for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Characteristics of included studies

The 26 included studies were published between 1963 and 2018. There were 0 experimental studies, 0 observational studies, 26 descriptive studies, and 0 clinical practice guidelines. The 26 studies were conducted in the following countries: Brazil and the US.

A total of 355 patients participated in the 26 included studies. The number of patients in each study ranged from 1 to 237.

Outcome measures differed among the included studies and included: arterial blood gas; morbidity; pulmonary function and respiratory symptoms; resolution of eye irritation and pain; serum electrolyte levels (calcium, magnesium, potassium).

Refer to Table 5 for a summary of study country, design, patient population, intervention and comparator, and outcome measures.

Use of calcium gluconate

One hundred seventy-four patients received calcium gluconate as a treatment for hydrofluoric acid burns, administered via intraarterial, intravenous, nasal, ophthalmic, subcutaneous, and topical routes. Duration of treatment ranged from once to 11 days. Fifteen patients received calcium gluconate as a treatment for hydrofluoric acid inhalation, administered via inhalation, ophthalmic, and topical routes. Duration of treatment ranged from 12 hours to 48 hours. One patient received calcium gluconate as a treatment for trifluoroacetic acid burns, administered topically through a calcium gluconate-soaked gauze.

Refer to Tables 6 and 7 for a summary of the dosage by indication.

Calcium gluconate was used as a compounded product but not as a combination product (refer to Tables 8 and 9).

In 19 studies, the authors' concluding statement recommended the use of calcium gluconate for the treatment of hydrofluoric acid burns and hydrofluoric acid inhalation.[11,21-38] In 1 study, the authors concluded that the use of calcium gluconate was not recommended for the treatment of trifluoroacetic acid burns.[39] In 1 study, the authors concluded that further studies were necessary for the nebulized use of calcium gluconate for hydrofluoric acid inhalation.[40] In 5 studies, the authors' concluding statement did not address the use of calcium gluconate.[41-45] Refer to Table 5 for a summary of authors' conclusions.

Pharmacology and historical use

In addition to the 26 included studies, 2 studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of calcium gluconate.

According to Micromedex®, intravenous calcium gluconate has been used to treat a variety of conditions related to calcium deficiencies such as hypocalcemic tetany, hypocalcemia related to hypoparathyroidism, and hypocalcemia related to rapid growth or pregnancy.[46] Additionally, it is used for muscle cramping due to black widow spider bites and as an adjunct for the treatment of rickets, osteomalacia, lead colic, and magnesium sulfate overdose.[46] Further indications for intravenous calcium gluconate include allergic conditions (by decreasing the capillary permeability), nonthrombocytopenic purpura, and exudative dermatoses.[46] The calcium gluconate injection is also used for primary medical treatment of large burns resulting from hydrofluoric acid exposure if pain is not significantly relieved after other treatments or if treatment has been delayed.[46] Calcium citrate and calcium carbonate are the preferred forms for oral supplementation compared to the less concentrated calcium gluconate.[46] Finally, according to Micromedex®, calcium gluconate in gel or slurry form may be administered topically for burns, and solutions may be administered for burns to the eyes.[46]

Hydrofluoric acid is one of the "most common and most deadly industrial chemicals in the world."[43] Despite being commonly used, hydrofluoric acid exposure is fairly rare, though actual incidence rates are not known.[47] Exposure to hydrofluoric acid can cause injury to the patient via two mechanisms: the initial corrosive burn due to free hydrogen ions, and a chemical burn that occurs as free fluoride ions penetrate the soft tissues and can persist for days if not sufficiently treated.[26,32] The free fluoride ions are capable of binding with calcium and magnesium, resulting in electrolyte abnormalities (hypocalcemia and hypomagnesemia) which can result in fatal cardiac arrhythmias.[26,48] Inhalation injury is rare; when it occurs, it is associated with rapid hemorrhagic pulmonary edema, atelectasis, frank tracheobronchial hemorrhage, and death.[42] With hydrofluoric acid, there is a large focus on preventing exposure and quick and immediate decontamination of the burn before transportation to a medical facility.[48] In addition, according to guidelines put out by the Agency for Toxic Substances and Disease Registry, the pain resulting from the burn should not be curbed through administration of local anesthetics, since pain resolution is used as an indication of treatment effectiveness.[48]

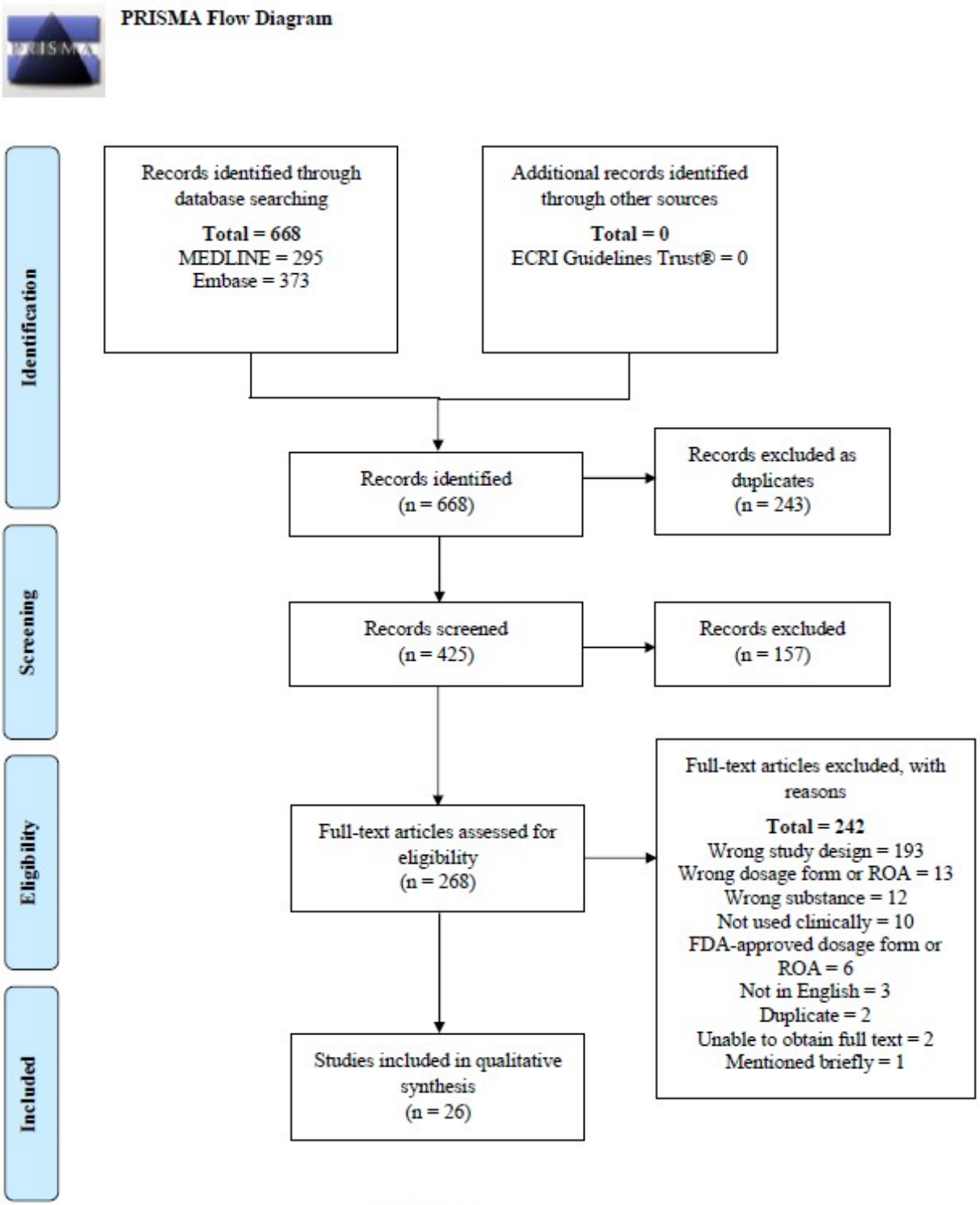
One study noted 3 treatment options for hydrofluoric acid burns: iced benzalkonium chloride (Zephiran®) soaks, calcium gluconate gel, and calcium gluconate injections.[43] In this 1994 study, the author noted that calcium gluconate gel was not commercially manufactured at the time, and therefore the pharmacist or nurse must mix 2.5 g calcium gluconate with 100 mL of a water-soluble gel, with frequent and copious applications until pain is relieved and does not recur.[43] The author also described using 5% or 10% calcium gluconate via intradermal and subcutaneous routes in and around the burns and stated that "calcium chloride should never be used because it stimulates sensory fibers, further exacerbating pain."[43] The author also stated that regardless of the presentation of symptoms and the concentration of hydrofluoric acid solution, any and all exposure is a life-threatening situation.[43]

In a 2018 document produced by Honeywell Industrial Products, the authors described their recommended medical treatments for hydrofluoric acid exposure. In this document, options for treating hydrofluoric acid burns included a 0.13% benzalkonium chloride solution that is cooled with ice cubes, 2.5-5% calcium gluconate injections, and 2.5% calcium gluconate gel.[49] They also stated that a nebulized solution of 2.5% calcium gluconate may be administered with 100% oxygen in the

scenario a patient inhales hydrofluoric acid.[49] It should be noted that calcium gluconate is available as a 10% solution, and therefore must be diluted with normal saline to make 2.5% or 5% solutions.[49]

Alternative treatments options for hydrofluoric acid burns include benzethonium chloride (Hyamine®), magnesium oxide paste, and Hexafluorine®, a hypertonic washing solution with chelating properties formulated for emergency decontamination following hydrofluoric acid exposure.[24,45] Honeywell Industrial Products stated in their recommendations that looking at the Hexafluorine® product in animal studies, they felt that there was not sufficient evidence for them to recommend its use, "Given the equivocal results and the cost of the product (versus decontamination with water)."[49]

Figure 1. PRISMA flow diagram showing literature screening and selection.



Adapted from:
Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006-1012. Available from: http://www.prisma-statement.org/.

Table 3. Types of studies

Types of Studies	**Number of Studies**
Descriptive[11,21-45]	26
Observational	0
Experimental	0

Table 4. Number of studies by country

Country	**Number of Studies**
US[11,21-44]	25
Multiple Countries • Brazil and US[45]	1
	Total US[a]: 26 Total Non-US Countries[a]: 1

[a]Study 45 counted in both US and non-US total.

Table 5. Summary of included studies

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 1: Hydrofluoric acid burns					
Alper *et al.*, 2014, US[21]	Case report	1 In-patient with hydrofluoric acid burns to both hands (100%, 45 y)	• Debridement and treatment with calcium gluconate (1)	Healing of burns	After extensive debridement and treatment, the wounds showed excellent recovery
Anderson and Anderson, 1988, US[22]	Case series	14 In-patients with hydrofluoric acid burns to hands (64%, range 24-51 y)	• Calcium gluconate gel, then calcium gluconate solution and palmar fasciotomy in pain persisted; placement of wound dressings with calcium gluconate gel (14)	Wound healing, range of motion, grip and pinch strength, need for job modification	Calcium gluconate gel and (when necessary) calcium gluconate injection, is effective in slowing development of severe burns if exposed to hydrofluoric acid solutions less than 51%
Blodgett *et al.*, 2001, US[41]	Case reports	9 In-patients as fatality reports from OSHA, containing an entry for hydrofluoric acid (100%, mean 45 y)	• Calcium gluconate (5)	Hydrofluoric acid-related work injuries and deaths	–
Carpenter *et al.*, 1999, US[23]	Case reports	2 In-patients with hydrofluoric acid burns (100%, range 29-36 y)	• Subcutaneous and topical calcium gluconate (2)	Resolution of pain, wound healing	If appropriate and early treatment is provided, it is very effective to decrease morbidity and mortality associated with hydrofluoric acid burns
Chan *et al.*, 1987, US[24]	Case reports	2 In-patients with hydrofluoric acid burns (100%, range 50-60 y)	• Calcium gluconate irrigation of eyes plus subcutaneous and IV injection (1)	–	The authors emphasized the importance of prevention and getting proper treatment quickly

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Conway and Sockolow, 1991, US[42]	Case report	1 In-patient with hydrofluoric acid burns to arms, thighs, face, and eye (100%, 8 y)	• Irrigation of eyes with normal saline; burns were cleaned with normal saline, then calcium gluconate gel was applied (1)	Resolution of burning, irritation	The usual signs of tetany are absent with these burns, therefore frequent determinations of serum calcium concentrations and electrocardiographic monitoring should be instituted
El Saadi *et al.*, 1989, US[25]	Case series	237 Patients with dermal exposure to dilute (6-11%) hydrofluoric acid in rust remover (gender and age not specified)	• Topical calcium gluconate gel (116) • Subcutaneous calcium gluconate injection (1) • Topical magnesium oxide paste (1)	Time to initial application of gel, time to noted clinical improvement	Quick application of topical calcium gluconate gel may be enough for burns due to dilute hydrofluoric acid; therefore, more invasive forms of therapy may not be routinely required; "The ready availability of an appropriate gel preparation would be desirable"
Foster *et al.*, 2003, US[26]	Case report	1 Out-patient with hydrofluoric acid burn to both hands (0%, 30 y)	• Calcium gluconate gel, observed for several hours; wounds were then dressed with silver sulfadiazine (1)	Pain relief, wound healing	Patients burned from the combustion of compressed air dusters should be considered to have chemical burns in addition to thermal burns; treatment may include irrigation, cardiac monitoring, and topical or systemic calcium
Greco *et al.*, 1988, US[27]	Case reports	3 In-patients with hydrofluoric acid burns (100%, range 38-62 y)	• Subcutaneous and IV calcium (1) • Topical, subcutaneous, and intravenous calcium gluconate (1)	Pain relief, serum calcium, mortality (1 patient died)	Hydrofluoric acid exposure may cause lethal hypocalcemia; death can be prevented by replenishing calcium in a timely manner
Madsen and Curtis, 2010, US[28]	Case report	1 In-patient with hydrofluoric acid burn to hand (100%, 23 y)	• Calcium gluconate gel, intra-arterial calcium gluconate (1)	Pain relief	The pros and cons of intra-arterial therapy for hydrofluoric acid exposure should be considered before administering via this route

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Mayer and Gueliich, 1963, US[29]	Case reports	10 In-patients and out-patients with hydrofluoric acid burns (100%, age not specified)	• Subcutaneous calcium gluconate (2) • Topical calcium gluconate (2) • Hydrofluoric acid neutralizing ointment composed of magnesium sulfate, magnesium oxide, and procaine (4)	Pain relief, wound healing	The utilization of calcium gluconate will save the patient many hours or days of suffering
Nguyen *et al.*, 2004, US[30]	Case report	1 In-patient with hydrofluoric acid burn to face and ear (100%, 37 y)	• Benzalkonium chloride (Zephiran®) applied within 5 minutes of injury, subcutaneous, intra-arterial, and topical calcium gluconate (1)	Pain relief, wound healing	Continual administration of calcium gluconate infusion eventually provided symptomatic relief and may have prevented systemic hypocalcemia
O'Neil, 1994, US[43]	Case report	1 In-patient with hydrofluoric acid burns to forehead, chest, and arms (100%, 37 y)	• Calcium gluconate gel (1)	–	It is important for the emergency department to prepare properly for hazardous material victims
Roberts and Merigian, 1989, US[38]	Case report	2 Out-patients with hydrofluoric acid burns (100%, range 22-26 y)	• Calcium gluconate paste, digital nerve block (1) • Soaking in magnesium sulfate solution, cold water, and 1% calcium chloride solution; digital nerve block; calcium gluconate paste (1)	Pain relief	The authors did not notice any efficacy with topical therapy in reducing acute pain; intra-arterial calcium gluconate infusion is good for serious injuries where the patient has received industrial-strength hydrofluoric acid burns, but is generally too aggressive for most fingertip injuries due to hydrofluoric acid concentrations less than 10%
Rubinfeld *et al.*, 1992, US[31]	Case reports	2 In-patients and out-patients with hydrofluoric acid injury to face and eyes (100%, range 25-30 y)	• Ophthalmic prednisolone, gentamicin, scopolamine; topical and intradermal calcium gluconate; topical magnesium sulfate (1) • Ophthalmic erythromycin, sulfacetamide, prednisolone, scopolamine (1)	Pain relief, damage to eye, visual acuity	If an ophthalmologist treats a patient with chemical exposure, they should learn the history of hydrofluoric acid exposure and consult with the burn team quickly to avoid potentially fatal complications

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Sadove *et al.*, 1990, US[32]	Case report	1 In-patient due to accidental immersion in tank of hydrofluoric acid (100%, 51 y)	• Irrigation of eyes and nose with calcium gluconate in saline; topical calcium gluconate; IV calcium and magnesium (1)	Pain relief, damage to eye, visual acuity	A multidisciplinary approach to hydrofluoric acid burns is important to recovery
Schmidt and Bryant, 2007, US[33]	Case report	1 Out-patient with hydrofluoric acid burn to penis (100%, 50 y)	• Calcium gluconate gel (1)	Pain relief	Treatment of hydrofluoric acid burns typically involves cardiac monitoring, correction of electrolyte abnormalities (calcium, magnesium, potassium), and treatment with calcium gluconate
Sheridan *et al.*, 1995, US[34]	Case reports	3 In-patients with hydrofluoric acid burns (100%, range 23-49 y)	• Subcutaneous calcium gluconate (1) • IV calcium chloride (1) • Topical calcium gluconate (1)	Pain relief, mortality	Minor hydrofluoric acid exposures can be managed with irrigation and calcium gluconate gel; major hydrofluoric acid burns should be managed with irrigation and immediate subeschar injection of calcium gluconate 10% and supplementation of serum calcium, followed by excision of resulting wounds
Strausberg *et al.*, 2012, US[44]	Case report	1 In-patient with hydrofluoric acid burns to fingers (100%, 49 y)	• Calcium gluconate gel, prednisone, pain medication (1)	Pain relief, wound healing	Dermatologists should be aware of clinical findings and complications of hydrofluoric acid exposure, and be aware that the presentation may belie the true nature of the injury

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Stuke *et al.*, 2008, US[35]	Case series	35 In-patients with hydrofluoric acid burns (100%, mean 36.2 y ± 10)	• Topical calcium gluconate gel (not specified) • Intra-arterial infusion calcium (12)	Pain relief, wound healing, long-term functional disability or surgical reconstruction	Recommend use of irrigation and calcium gel as the primary treatment on small hydrofluoric acid burns; routine monitoring of electrolytes and admission to intensive care should not be part of the management of small burns; use of intra-arterial calcium infusion is not mandated unless required for unrelenting pain
Vance *et al.*, 1986, US[36]	Case series	10 In-patients with hydrofluoric acid burns of the fingers (40%, range 21-48 y)	• Intraarterial calcium gluconate (7) • Intraarterial calcium chloride (3)	Pain relief	Intra-arterial calcium infusion is highly effective for digital hydrofluoric acid burns; the disadvantages of this treatment seem to be outweighed by excellent clinical results and relatively little morbidity
Yoshimura *et al.*, 2011, Brazil and US[45]	Case report	1 In-patient with hydrofluoric acid burn (100%, 38y)	• Hexafluorine (Laboratoire Prevor, active decontamination solution for hydrofluoric acid burns); IV, intradermal, and topical calcium gluconate (1)	Pain relief	Hexafluorine should be considered for use in cases where the patient has had concentrated hydrofluoric acid skin exposure
Indication 2: Hydrofluoric acid inhalation					
Chapa *et al.*, 2009, US[37]	Case report	1 In-patient with exposure to hydrofluoric acid vapor cloud (100%, 39 y)	• Calcium gluconate solution, gel, and nebulization (1)	Resolution of pain, eye irritation, and dyspnea	Prompt decontamination through workplace application of eye irrigation and dermal gel were instrumental in limiting systemic absorption and toxicity

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Lee *et al.*, 1993, US[11]	Case reports	13 In-patient and out-patient workers exposed to hydrofluoric acid mist (gender and age not specified)	• Nebulized calcium gluconate (13)	Respiratory symptoms, occurrence of pulmonary edema	Due to risk of life-threatening injuries from the exposure of hydrofluoric acid (such as airway obstruction and pulmonary edema), the authors recommend nebulized calcium gluconate
Tosnis *et al.*, 2008, US[40]	Case report	1 In-patient with inhalation injury from hydrofluoric acid (100%, 40 y)	• Nebulized calcium gluconate (1)	Respiratory symptoms, arterial blood gas, serum calcium, pulmonary function	While the use of calcium gluconate in cutaneous exposure to hydrofluoric acid has been studied, experimental research for the use of nebulized calcium gluconate in treating inhalation of hydrofluoric acid is lacking
Indication 3: Trifluoroacetic acid burns					
Sun and Corbett, 2018, US[39]	Case report	1 In-patient with dermal exposure to trifluoroacetic acid (100%, 27 y)	• Calcium gluconate-soaked wound dressings, IV analgesics (1)	Pain relief, and serum calcium, magnesium, and potassium	Trifluoroacetic acid does not have systemic effects similar to hydrofluoric acid, despite structural similarities

Abbreviations: "–", not mentioned; IV, intravenous.
[a]As defined by authors.

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Hydrofluoric acid burns[21-36,38,41-45]	10 mL/hour	–	Solution	Intraarterial	36 hours
	10 mL	10%			Once or twice, as needed for pain
	–	10-25%	Solution	Intradermal	At least once or twice
	Every 2-6 hours	1%	Irrigation solution	Ophthalmic, nasal	Once – 2 days
	17-60 mL	10%	Solution	Subcutaneous	Once or twice
	55.8 mEq	–	Solution	Subeschar	Twice
	Every 2-3 hours	–	–	Topical	–
	–	–	Ointment		–
	Apply twice	–	Paste		24 hours
	Apply 1-3 times per day	2.5-10%	Gel		At least once or twice – 11 days
	Every 15 minutes – 4 hours				Until symptomatic relief
Hydrofluoric acid inhalation[11,37,40]	4 mL	2.5%	Nebulization solution	Inhalation	Once
	Every 4 hours				12 – 48 hours
	–	–	Irrigation solution	Ophthalmic	Once
	–	–	Gel	Topical	Once
Trifluoroacetic acid burns[39]	–	–	–	Topical	–

Abbreviation: "–", not mentioned.

Table 7. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Hydrofluoric acid burns[45]	–	10%	Solution	Intradermal	–
	–	2.5%	–	Topical	–

Abbreviation: "–", not mentioned.

Table 8. Number of studies by combination

	Combination Formula	Number of Studies
Nominated	Calcium gluconate / Magnesium chloride / Sodium ascorbate / Vitamin B complex – intramuscular injection	0

Table 9. Compounded products – US

Indication	Publication Year	Compounding Method	Dosage Form	Final Strength
Hydrofluoric acid burns[22,25,38]	1988	• Calcium gluconate 3.5 g mixed with 5 ounces of water-soluble lubricant	Gel	2.5%
	1989	• "Extemporaneous preparation of topical calcium gluconate gel"	Gel	–
	1989	• Calcium gluconate tablets were crushed and mixed with sterile lubricant	Paste	–

Table 10. Compounded products – non-US countries

No compounded products from reported studies

Results of interviews

Two hundred eighty-five SMEs were contacted for interviews; 96 agreed to be interviewed, and 189 declined or failed to respond to the interview request. Twenty-four SMEs discussed calcium gluconate. Amongst these 24 SMEs, there were 4 medical doctors, 18 pharmacists, and 2 naturopathic doctors. The SMEs specialized and/or were board-certified in critical care, naturopathy, neonatal/perinatal medicine, nutrition, pediatrics, pharmacotherapy, primary care and family practice, and sterile compounding, working in academia, academic medical center, consulting, hospital/health system, pharmacy/pharma company, and private practice/clinic. The SMEs had been in practice for 6 to 44 years.

Intravenous calcium is used to either balance other minerals (such as magnesium or potassium) in general intravenous nutrient formulations or to treat patients with hypocalcemia. One SME said they also use it in infants who are not receiving food yet to prevent low calcium levels. When compounding total parenteral nutrition (TPN) and parenteral nutrition (PN) admixtures, most SMEs said that they only use calcium gluconate. Calcium gluconate is stable in sterile parenteral solution, is compatible with most water-soluble agents, and is used almost universally for nutrient therapy. The calculations for calcium solubility are based upon the gluconate salt form, not the chloride; as a result, using the chloride salt form could result in adding too much phosphate and causing dangerous precipitation of the TPN solution. This occurs because the organic salt makes calcium gluconate more stable; there is less free calcium available to interact with lipids and other components when compared to calcium chloride. It was also emphasized that calcium gluconate needs to be available for neonates; the calcium requirements of neonates are unattainable with the chloride form "and the babies tend to be very acidotic. They like acetate salts. Hydrochloride is already a big contributor, so another chloride source would not be wise." Some facilities have made the decision to stop using calcium chloride completely in order to prevent practitioners from ordering it.

Calcium chloride also has three times the elemental calcium as calcium gluconate. Several SMEs said that calcium chloride is preferred in an emergent code-type situation, such as severe hyperkalemia causing heart rhythm changes on electrocardiogram (EKG), or overdose of calcium channel blockers or beta blockers. Unlike with TPN, the data and equations for these indications are for the chloride salt form. Calcium gluconate can also be used in those situations, but they would have to use more of it to get the same effect.

Multiple SMEs said that they would not consider injectable calcium to treat deficiency because "calcium is so easy to deliver orally." In addition, they noted that intravenous calcium should be monitored very closely, since levels changing too quickly can cause metabolic and cardiac complications. The SMEs also said that they would not add calcium to other vitamins and minerals either, instead preferring to only replete the necessary vitamin deficiency without other active ingredients. They would want to be able to tailor the dose of individual components to the patient, something not possible with a compounded combination product. However, one SME used injectable calcium as part of a "modified Myers' Cocktail," composed of calcium, magnesium, trace minerals, and vitamins B and C. The SME prescribed this combination for acute infection, or those recovering from an infection. They also prescribed the modified Myers' Cocktail for chronic fatigue and chronic hepatitis C; the latter was before hepatitis C had an effective treatment.

Most of the SMEs have had issues with intravenous calcium gluconate shortages, both currently and in the past, and said that "having the ability to quickly ramp up and have a 503B make some if there happened to be a big shortage is important." One SME said that their facility addressed the shortage by reserving calcium gluconate for their TPN solutions, since those were compounded in-house, and then used alternative salt forms (such as calcium chloride) for supplementation outside of the TPN. For some

patients, they would evaluate their absorptive capacity to see if they could take something orally under close observation or restrict use, but they hope shortages do not reach that point. One SME said that most people who do intravenous nutrient therapies switch between gluconate and chloride, depending on which one is readily available.

503A and 503B compounding facilities typically produce a 5% calcium gluconate solution, which is less prone to precipitation compared to the commercially available 10% stock manufactured product. However, one SME said that they would be concerned with using compounded products, especially calcium gluconate, due to the possibility of dissociation and precipitating with phosphate, and that they would be more comfortable with a commercially available product. Several SMEs commented that they would be worried about batches reacting differently than expected, and that they would want to question the compounding facility about changes in the formulation that might affect the stability or compatibility and if they were following USP. Container design is also a concern; calcium gluconate is more prone to leaching aluminum when stored in glass vials, which can be especially problematic with the FDA mandate of no more than 5 mcg/kg/day of aluminum. In the US, the containers used for PN compounds are glass, but there is a movement to switch to plastic, which is how it is done in Europe. However, changing containers requires the full FDA review process. They also said that since traditional industry does not make prefilled syringes, 503B facilities would be useful for facilities wanting prefilled calcium gluconate syringes for their code carts.

Calcium gluconate is also used topically for hydrofluoric acid burns. Multiple SMEs said that they do not treat hydrofluoric acid burns in their practice. One SME said that their facility did not have a burn unit, so they do not stock it, but added that "even if you were a burn unit, I imagine you probably have a very small bit on hand and it probably ends up just expiring."

Results of survey

Zero people responded to the survey distributed via professional medical associations and available on the project website.

A separate survey was distributed by the Ambulatory Surgery Center Association (ASCA); 230 people responded to this survey (refer to Appendix 2.2 for survey instrument).

Amongst respondents to the ASCA survey, 97 (42% of 230 total respondents) were very familiar with the term '503B outsourcing facility,' 86 (37%) were somewhat familiar with this term, and 47 (20%) were not familiar with this term (refer to Table 15).

One hundred ten survey respondents (54% of 203 people who responded to this question) utilized a 503B outsourcing facility to acquire compounded drugs; 93 survey respondents (46%) did not utilize a 503B outsourcing facility. Two respondents (0.69% of 290 responses, where respondents were allowed to select multiple drug products) obtained calcium gluconate from a 503B outsourcing facility (refer to Table 16).

The most common types of procedures performed at the facilities where the ASCA survey respondents worked were: ophthalmology (115, 17% of responses, where respondents were allowed to select multiple procedure types); orthopedics (89, 13%); pain (80, 12%); podiatry (74, 11%); and plastics (72, 10%) (refer to Table 17).

Table 11. Characteristics of survey respondents

No respondents to survey distributed via professional medical associations

Table 12. Conditions for which calcium gluconate prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded calcium gluconate

No respondents to survey distributed via professional medical associations

Table 14. Use of non-patient-specific compounded calcium gluconate

No respondents to survey distributed via professional medical associations

Table 15. Ambulatory Surgery Center Association respondents' familiarity with compounding terms

Compounded drugs (medications prepared to meet a patient-specific need)	**Responses, n (N=230)**
Very familiar	153
Somewhat familiar	70
Not familiar	7
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed to meet a patient-specific need)	**Responses, n (N=230)**
Very familiar	118
Somewhat familiar	91
Not familiar	21
503B Outsourcing facility (a facility that compounds larger quantities without a patient-specific prescription)	**Responses, n (N=230)**
Very familiar	97
Somewhat familiar	86
Not familiar	47

Table 16. Products obtained from a 503B outsourcing facility

Product	Responses, n (N=290)[a]
Amitriptyline / Ketoprofen / Oxymetazoline	1
Budesonide	2
Calcium gluconate	2
Droperidol	2
Epinephrine	11
Epinephrine for ophthalmic administration	16
Epinephrine / Lidocaine for ophthalmic administration	31
Epinephrine / Bupivacaine / Fentanyl	3
Fentanyl	10
Flurbiprofen	3
Flurbiprofen for ophthalmic administration	6
Hydromorphone	5
Ipamorelin	1
Ketoprofen / Nifedipine	3
Lidocaine / Epinephrine / Tetracaine	13
Meperidine	3
Morphine	5
Naloxone	5
Neomycin	5
Phentolamine	1
Promethazine	5
Remifentanil	4
Sufentanil	2
Tramadol	2
None of the above	75

Do not obtain any compounded drugs from 503B outsourcing facility	74

[a]Survey respondents allowed to select multiple products.

Table 17. Type of specialty procedures performed at ambulatory surgery facility

Procedure Type	**Responses, n (N=686)[a]**
Dental	23
Dermatology	9
Endoscopy	65
Neurosurgery	22
Obstetrics/gynecology	39
Ophthalmology	115
Otolaryngology	58
Orthopedics	89
Pain	80
Plastics	72
Podiatry	74
Other[b]	40

[a]Survey respondents were allowed to select multiple procedure types.
[b]No respondents provided description for 'Other' procedure type.

CONCLUSION

Calcium gluconate was nominated for inclusion on the 503B Bulks List as solutions for administration via inhalation, irrigation, injection, and intravenous ROA, a topical gel, and ophthalmic drops for electrolyte disturbances, allergic disorders, hydrofluoric acid chemical burns, exudative dermatitis, and non-thrombocytopenic purpura. Calcium gluconate is available in the nominated dosage form and ROA in Canada, Hong Kong, Saudi Arabia, the UK, and the US.

From the literature review and interviews, calcium gluconate is a commercially available injectable solution that is used to treat electrolyte disturbances. Most of the SMEs reported that the gluconate salt form is preferred for TPN solutions due to greater stability and data compared to calcium chloride, which contains more elemental calcium and is preferred for emergent code-type situations. While calcium gluconate is commercially available as an FDA-approved injection, practitioners reported issues with obtaining calcium gluconate due to shortages, both in the past and currently ongoing; this is especially important considering that using calcium chloride is not a simple and easy alternative. The SMEs said that they would be concerned with phosphate precipitation with using calcium chloride as well as other interactions. They also said that calcium gluconate is very important in treating neonates, who tend to be acidotic and therefore adding another chloride source would be unwise. Some facilities have stopped using calcium chloride completely in order to prevent practitioners from ordering it. Calcium gluconate is also used to treat hydrofluoric acid burns via multiple ROA including intraarterial, intravenous, nasal, ophthalmic, subcutaneous, and topical. It is also used topically to treat trifluoroacetic acid burns. None of the SMEs had direct experience in treating chemical burns but speculated that a hospital burn unit would probably only keep a small amount of calcium gluconate on hand which would probably end up expiring before being used.

Zero people responded to the survey distributed via professional medical associations and available on the project website. From the responses to the ASCA survey, 2 respondents (0.69% of 290 responses, where respondents were allowed to select multiple drug products) obtained calcium gluconate from a 503B outsourcing facility.

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APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process and other non-indexed citations and daily 1946 to April 6, 2020
- Date last searched: April 7, 2020
- Limits: Humans (search hedge); English language
- Number of results: 295
- Notes: Tested with two concepts: calcium and hydrofluoric acid. This search did not retrieve all potentially relevant studies because calcium was often used in treatment, but not mentioned in title, abstract, keywords or indexing. Tested keyword 'hydrogen fluoride', additional results not relevant.

1	exp burns/	57213
2	in.fs.	237513
3	po.fs.	65560
4	to.fs.	420278
5	burn?.tw.	58780
6	injur$.tw.	782358
7	poisoning?.tw.	66587
8	intoxic$.tw.	45979
9	fluorosis.tw.	3166
10	fluoridosis.tw.	0
11	or/1-10	1481162
12	hydrofluoric acid/	1398
13	hydrofluoric acid$.tw.	2049
14	hydrofluoride.tw.	25
15	fluo?hydric acid$.tw.	10
16	fluorane.tw.	7
17	fluoric acid$.tw.	23
18	fluorin$ monohydride.tw.	1

19	or/12-18	2762
20	and/11,19	453
21	exp animals/ not humans/	4686330
22	20 not 21	378
23	limit 22 to english language	295

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: April 7, 2020
- Limits: Humans (search hedge); English language
- Number of results: 373

1	burn'/exp	78286
2	chemical injury'/exp	8526
3	intoxication'/de	207740
4	fluorosis'/de	3312
5	toxic inhalation'/de	585
6	burn$':ti,ab	81097
7	injur*':ti,ab	1058857
8	poisoning$':ti,ab	90593
9	intoxic*':ti,ab	69756
10	fluorosis':ti,ab	4379
11	fluoridosis':ti,ab	1
12	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	1424535
13	hydrofluoric acid'/mj	1129
14	hydrofluoric acid*':ti,ab	2057
15	hydrofluoride':ti,ab	32
16	fluo$hydric acid*':ti,ab	18
17	fluorane':ti,ab	10
18	fluoric acid*':ti,ab	24
19	fluorin* monohydride':ti,ab	0
20	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	2715
21	#12 AND #20	602
22	[animals]/lim NOT [humans]/lim	6013584

23	#21 NOT #22	513
24	#21 NOT #22 AND [english]/lim	373

Appendix 2.1. Survey instrument for professional medical associations

Welcome. We want to understand your clinical use of compounded calcium gluconate. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

If you have additional questions or concerns about this 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.

Thank you,

Dr. Ashlee Mattingly
Principal Investigator
The University of Maryland School of Pharmacy

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.

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

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	o	o	o
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	o	o	o
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	o	o	o

2. Do you prescribe or administer calcium gluconate to your patients?

   - o Yes
   - o No

3. Do you prescribe or administer calcium gluconate by any of the following dosage forms and/or routes of administration? (check all that apply)

   - o Intramuscular injection
   - o Topical gel
   - o Irrigation solution
   - o Inhalation solution
   - o None of the above

4. I prescribe or administer calcium gluconate for the following conditions or diseases: (check all that apply)

   - o Vitamin deficiency
   - o Cardiac arrhythmias
   - o Hydrofluoric acid burns
   - o Electrolyte abnormalities (please explain) _____
   - o Other (please explain) _____

5. I use compounded calcium gluconate because: (check all that apply)

    - o Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
    - o Patient allergies prevent me from using commercially available products. (please explain) _____
    - o Patient conditions prevent me from using commercially available products. (please explain) _____
    - o There are no commercially available products containing calcium gluconate.
    - o Other (please explain) _____

6. Do you stock non-patient-specific compounded calcium gluconate at your practice?

    - o Yes
    - o No
    - o I'm not sure

7. I obtain compounded calcium gluconate from the following: (check all that apply)

    - o Compound myself at my practice
    - o Have the product compounded by an in-house pharmacy
    - o Purchase, or have a patient purchase, from a compounding pharmacy
    - o Purchase, or have a patient purchase, from an outsourcing facility
    - o Other (please explain) _____

8. What is your practice setting? (check all that apply)

    - o Physician office/private practice
    - o Outpatient clinic
    - o Hospital/health system
    - o Academic medical center
    - o Emergency room
    - o Operating room
    - o Other (please describe) _____

9. What degree do you hold? (check all that apply)

    - o Doctor of Medicine (MD)
    - o Doctor of Osteopathic Medicine (DO)
    - o Doctor of Medicine in Dentistry (DMD/DDS)
    - o Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
    - o Naturopathic Doctor (ND)
    - o Nurse Practitioner (NP)
    - o Physician Assistant (PA)
    - o Other (please describe) _____

Appendix 2.2. Survey instrument for Ambulatory Surgery Center Association

Welcome. We want to understand your clinical use of compounded drugs. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in bulk compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

If you have additional questions or concerns about this 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.

Thank you,

Dr. Ashlee Mattingly
Principal Investigator
The University of Maryland School of Pharmacy

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.

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

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	o	o	o
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	o	o	o
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	o	o	o

2. Do you utilize a 503B outsourcing facility to acquire compounded drugs?

   - o Yes. If yes, why? _____
   - o No. If no, why not? _____

3. Do you obtain any of the following products from a 503B outsourcing facility? (check all that apply)

   - o I do not obtain any compounded drugs from 503B outsourcing facilities
   - o Amitriptyline / Ketoprofen / Oxymetazoline
   - o Budesonide
   - o Calcium gluconate
   - o Droperidol
   - o Epinephrine
   - o Epinephrine for ophthalmic administration
   - o Epinephrine / Lidocaine for ophthalmic administration
   - o Epinephrine / Bupivacaine / Fentanyl
   - o Fentanyl
   - o Flurbiprofen
   - o Flurbiprofen for ophthalmic administration
   - o Hydromorphone
   - o Ipamorelin
   - o Ketoprofen / Nifedipine
   - o Lidocaine / Epinephrine / Tetracaine HCl
   - o Meperidine
   - o Morphine
   - o Naloxone
   - o Neomycin
   - o Phentolamine
   - o Promethazine

- Remifentanil
- Sufentanil
- Tramadol
- None of the above

4. What type of specialty procedures are performed in your facility? (check all that apply)

    - Dental
    - Dermatology
    - Endoscopy
    - Neurosurgery
    - Obstetrics/gynecology
    - Ophthalmology
    - Otolaryngology
    - Orthopedics
    - Pain
    - Plastics
    - Podiatry
    - Other (please describe) _____

Appendix 3. Survey distribution to professional associations

Specialty	Association[a]	Agreed/Declined, Reason for Declining
Allergy/Immunology	American Academy of Allergy, Asthma, and Immunology (AAAI)	Declined – survey not approved
Anesthesia	American Society of Regional Anesthesia and Pain Medicine (ASRA)	Declined – failed to respond
	Society for Ambulatory Anesthesia (SAMBA)	Declined – failed to respond
	Society for Neuroscience in Anesthesiology and Critical Care	Declined – failed to respond
Critical Care	Critical Care Societies Collaborative	Declined – failed to respond
Dentistry & Oral Medicine	Academy of General Dentistry (AGD)	Declined – provided interview referrals
	American Dental Association (ADA)	Declined – failed to respond
Dermatology	American Academy of Dermatology (AAD)	Agreed
	American Osteopathic College of Dermatology (AOCD)	Declined – not interested
Endocrinology	The Endocrine Society (ENDO)	Agreed
	Pediatric Endocrine Society	Agreed
Gastroenterology	American Gastroenterological Association (AGA)	Declined – failed to respond
	Obesity Medicine Association (OMA)	Declined – did not have anyone to contribute to research
Hematology	American Society of Hematology (ASH)	Declined – does not distribute surveys
Infectious Disease	American Academy of HIV Medicine (AAHIVM)	Declined – failed to respond
Medicine	American Medical Association (AMA)	Declined – failed to respond

Naturopathy	American Association of Naturopathic Physicians (AANP)	Agreed
	The Oncology Association of Naturopathic Physicians (OncANP)	Agreed
Nephrology	American College of Clinical Pharmacists: Nephrology Practice Network	Agreed
	American Society of Nephrology	Declined – provided interview referrals
Nutrition	American Society for Parenteral and Enteral Nutrition (ASPEN)	Declined – provided interview referrals
Obstetrics and Gynecology	American Gynecological and Obstetrical Society (AGOS)	Declined – failed to respond
	Nurse Practitioners in Women's Health	Agreed
Ophthalmology	American Academy of Ophthalmology (AAO)	Agreed
Otolaryngology	American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS)	Declined – survey not approved
Pain Management	American Academy of Pain Medicine (AAPM)	Declined – survey not approved
	American Academy of Physical Medicine and Rehabilitation	Declined – failed to respond
Pediatrics and Neonatology	American Academy of Pediatrics (AAP)	Agreed
Primary Care	American College of Physicians (ACP)	Declined – failed to respond
Psychiatry	American Academy of Clinical Psychiatrists	Declined – failed to respond
	American Association for Geriatric Psychiatry	Declined – failed to respond
Rheumatology	American College of Rheumatology (ACR)	Agreed

Surgery	Ambulatory Surgery Center Association (ASCA)	Agreed
	American Academy of Orthopaedic Surgeons (AAOS)	Declined – no interest in participation from members
	American Association of Hip and Knee Surgeons (AAHKS)	Declined – only send surveys from members
	American College of Surgeons (ACS)	Agreed
	American Society for Metabolic and Bariatric Surgery (AMBS)	Declined – only send surveys from members
	The Association of Bone and Joint Surgeons	Declined – failed to respond
	Physician Assistants in Orthopaedic Surgery	Declined – failed to respond
	Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)	Declined – failed to respond
	Society of Gynecologic Surgeons (SGS)	Declined – policy limits number of surveys per year and do not have a method to identify if any of the SGS members are using ipamorelin
Toxicology	American Academy of Environmental Medicine (AAEM)	Declined – failed to respond
Urology	Sexual Medicine Society of North America (SMSNA)	Agreed

[a]Associations that declined in Year 1 were not contacted in Year 2.