Edetate Disodium and Edetate Disodium Calcium: Summary Report

Summary Report

Edetate Disodium and Edetate Disodium Calcium

Prepared for:

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

Prepared by:

University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI)
University of Maryland School of Pharmacy

February 2020

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

Table of Contents

REVIEW OF NOMINATIONS 4
METHODOLOGY 4
Background information 4
Systematic literature review 5
Outreach to medical specialists and specialty organizations 7
Survey 7
CURRENT AND HISTORIC USE 9
Summary of background information 9
Summary of literature review 10
Summary of focus groups/interviews of medical experts and specialty organizations 15
Summary of survey results 20
CONCLUSION 24
APPENDICES 25
Appendix 1. References 25
Appendix 2. Survey instrument 29

Table of Tables

Table 1. Participating associations 8
Table 2. Associations that declined participation 8
Table 3. Currently approved products – US[a] 9
Table 4. Currently approved products – select non-US countries and regions 9
Table 5. Types of studies 10
Table 6. Number of studies by country 11
Table 7. Number of studies by combinations 12
Table 8. Dosage by indication – US 12
Table 9. Dosage by indication – non-US countries 13
Table 10. Compounded products – US 14
Table 11. Compounded products – non-US countries 14
Table 12. Overview of interviewees 15
Table 13. Characteristics of survey respondents 20
Table 14. Types of products used, prescribed, or recommended 21
Table 15. Compounded use of disodium EDTA in practice 21
Table 16. Indications for which disodium EDTA is considered standard therapy 22
Table 17. Reasons for using a compounded product instead of any FDA-approved product 22
Table 18. Change in frequency of compounded disodium EDTA usage over the past 5 years 22
Table 19. Do you stock non-patient specific compounded disodium EDTA in your practice? 23
Table 20. Questions related to stocking non-patient specific compounded disodium EDTA 23

REVIEW OF NOMINATIONS

Edetate disodium (disodium EDTA; UNII code: 7FLD91C86K) and edetate disodium calcium (calcium disodium EDTA; UNII code: 25IH6R4SGF) were nominated for inclusion on the 503B Bulks List.

Disodium EDTA was nominated by Fagron, the American Association of Naturopathic Physicians (AANP), the American College for Advancement in Medicine (ACAM), and the Integrative Medicine Consortium (ICM) for use as a 0.4-1% ophthalmic drop for calcific band keratopathy and as a 150mg/mL intravenous infusion for treatment and prevention of atherosclerotic cardiovascular disease, heavy metals detoxification, diabetic neuropathy, and other unspecified conditions.

Calcium disodium EDTA was nominated by the Alliance for Natural Health USA (ANH-USA) and McGuff Compounding Pharmacy Services, Inc. for use as a 200mg/mL intravenous injection in: chelation therapy to reduce blood levels and depot stores of lead in lead poisoning (acute and chronic); chelation therapy for other toxic metals (mercury, arsenic, uranium, cesium, etc); cardiovascular disease; diabetes; hypercholesterolemia; arthritis; cancer; chronic renal failure; and high blood pressure.

The reasons provided for nomination to the 503B Bulks List include:

- There are no FDA-approved products for calcific band keratopathy.
- There are no FDA-approved products that contain solely EDTA.
- Compounded disodium EDTA is an aqueous injection that can be administered intravenously for a more rapid onset of action, especially in critical emergency cases
- Manufacturer backorder.
- British anti-lewisite (BAL), dimercaprol, and Chemet theoretically address the same medical conditions, but they appear unacceptable from a safety and efficacy standpoint to many alternative physicians.
    - Dimercaprol has too many side effects and as an oily injection cannot be given intravenously.
    - Dimercaptosuccinic acid (DMSA) is only available orally and does not have the available clinical scientific data that would justify it as a substitute.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of disodium EDTA and calcium disodium EDTA 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 disodium EDTA and calcium disodium EDTA; name variations of disodium EDTA and calcium disodium EDTA 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 5.1.4) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing disodium EDTA and calcium disodium EDTA. 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 September 7, 2018. The search included a combination of (EDTA[TIAB] OR "edetic acid"[TIAB] OR edetate[TIAB] OR "disodium salt"[TIAB]) AND (atherosclerosis[TIAB] OR chelation[TIAB] OR neuropathy[TIAB] OR detoxification[TIAB] OR treatment[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.

Calcium disodium EDTA is a component of an FDA approved product and the nominated compounded product does not differ from the commercially available product. Therefore, calcium disodium EDTA was not included in the search strategy.

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 disodium EDTA or the implementation of disodium EDTA 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.

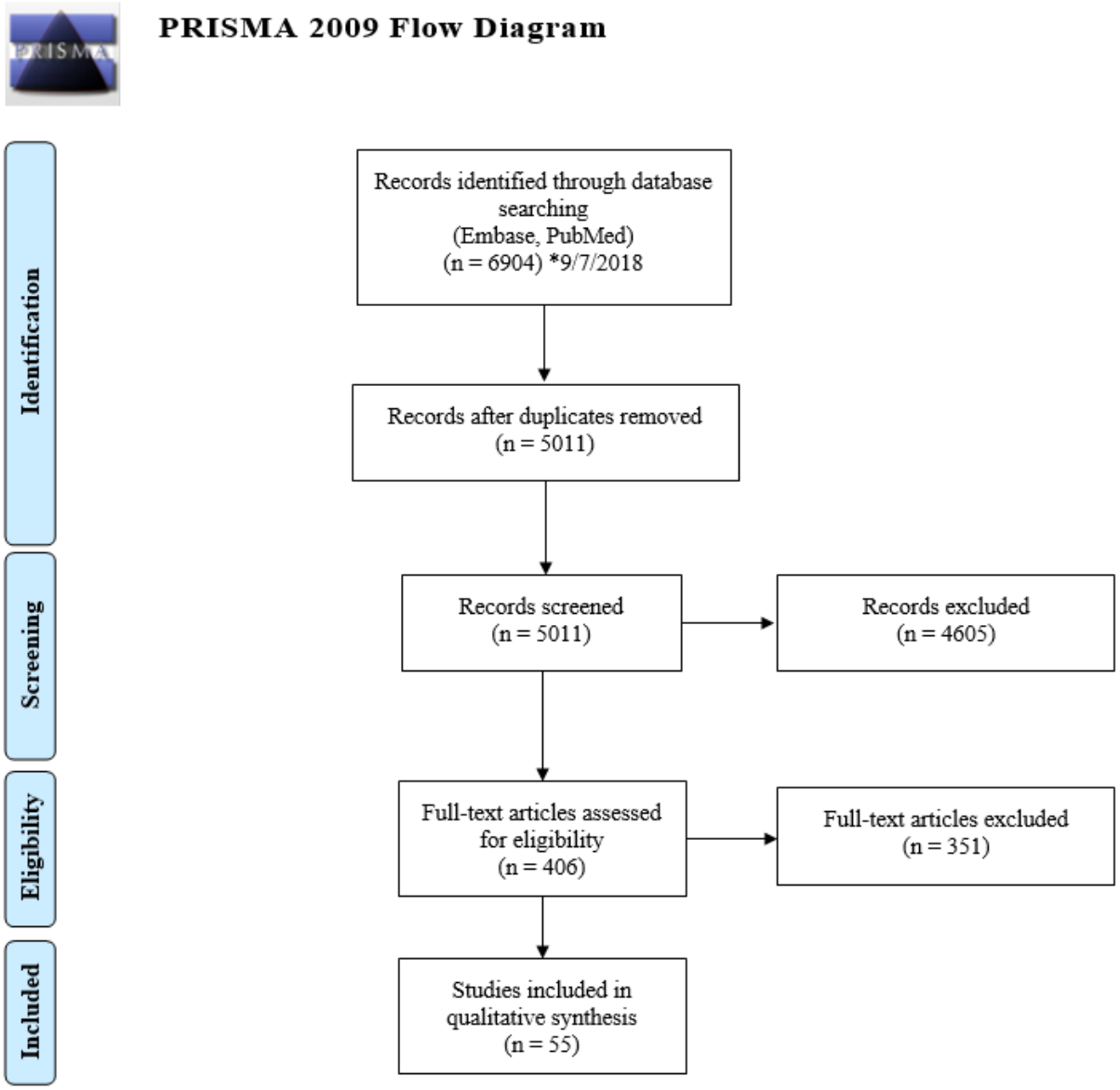
Data extraction

A standard data extraction form was used to collect study authors; article title; year published; journal title; country; indication for disodium EDTA use; dose; strength; dosage form; route of administration; frequency and duration of therapy; any combination therapy utilized; if applicable, formulation of compounded products; study design; and any discussion surrounding the use of disodium EDTA 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). *Preferred Reporting Items for Systematic Reviews and Meta-Analyses:* The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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

Outreach to medical specialists and specialty organizations

Using the indications from the nominations and the results of the literature review, seven (7) medical specialties that would potentially use disodium EDTA were identified: dermatology, naturopathy, neurology, ophthalmology, primary care, rheumatology, and toxicology. All of these medical specialties were also considered relevant for the use of calcium disodium EDTA, except for ophthalmology. Semi-structured interviews were conducted with subject matter experts within these specialties. Interviews lasted from 30-75 minutes and were conducted either via telephone or in-person. Criteria for selecting subject matter experts included recommendations provided by specialty professional associations, convenient geographic location, authorship within the specialty, or referral by an interviewee. Twelve (12) experts were contacted for interviews, of which eleven (11) accepted, zero (0) declined, and one (1) expert specializing in neurology failed to respond to the interview request. Interviews were recorded and transcribed via ©Rev.com. QSR International's NVivo 12 software was utilized for qualitative data analysis. The University of Maryland, Baltimore IRB and the Food & Drug Administration RIHSC reviewed the study and found it to be exempt. Subject matter experts provided their oral informed consent to participate in interviews.

Survey

General professional medical associations and specialty associations for dermatology, naturopathy, neurology, ophthalmology, primary care, rheumatology, and toxicology, identified from the nominations, literature review, and interviews, 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, 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 twelve (12) 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 that was shared with survey participants. Only disodium EDTA was included on the survey.

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

Table 1. Participating associations

Specialty	Association
Dermatology	American Academy of Dermatology (AAD)
	American Society for Dermatologic Surgery (ASDS)
Naturopathy	American Association of Naturopathic Physicians (AANP)
Ophthalmology	American Academy of Ophthalmology (AAO)
	American Society of Cataract and Refractive Surgery (ASCRS)
	American Society of Retina Specialist (ASRS)
Primary Care	American Academy of Environmental Medicine (AAEM)
Rheumatology	American College of Rheumatology (ACR)
Toxicology	American College of Medical Toxicology (ACMT)

Table 2. Associations that declined participation

Specialty	Association	Reasons for Declining
Medicine	American Medical Association (AMA)	Failed to respond
	American Osteopathic Association (AOA)	Failed to respond
Neurology	American Academy of Neurology (AAN)	Failed to respond

CURRENT AND HISTORIC USE

Summary of background information

- Calcium disodium EDTA is available as an FDA-approved product in the US. Disodium EDTA is not available as an FDA-approved product nor an OTC product in the US.
    - Disodium EDTA, marketed under the trade name Endrate, was initially approved by the FDA in 1959 for use in hypercalcemia and for the control of ventricular arrhythmias associated with digitalis toxicity. However, in 2007 the FDA issued a letter regarding the reevaluation of the safety and efficacy of Endrate based on reports of fatal medication errors with edetate calcium disodium and reports of serious adverse reactions. In 2008, all three manufacturers of disodium EDTA were notified of the withdrawal of the approval and disodium EDTA was removed from the market.[1]
- There is a current United States Pharmacopeia (USP) monograph for disodium EDTA and calcium disodium EDTA.
- Disodium EDTA is available in Australia and New Zealand and calcium disodium EDTA is available in Abu Dhabi.

Table 3. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	ROA	Status	Approval Date
Edetate calcium disodium	200mg/mL	Injection	Injection	Prescription	7/16/1953

Abbreviations: ROA, route of administration.
[a]Source: US FDA *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).

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

Active Ingredient	Concentration	Dosage Form	ROA	Approved For Use		
				Country	Status	Approval Date
Disodium edetate	3g	Powder	Intravenous	Australia	Prescription	10/08/1991
	30-60mg/mL	Solution				
	150mg/mL		Injection	New Zealand	Prescription	4/18/1984
Edetate calcium disodium	50mg/mL	–	Injection	Abu Dhabi	Active	5/3/2012
	200mg/mL					4/26/2011

Abbreviations: "– ", not mentioned; ROA, route of administration.
[a]Medicine registers of national regulatory agencies were searched if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information (product trade name, active ingredient, strength, form, route of administration and approval status) provided in a useable format. Information was recorded only for products with strengths, forms and/or routes of administration similar to those requested in the nominations. See Methodology for full explanation.

Summary of literature review

- A total of 55 studies were included (22 descriptive, 24 experimental, and 9 observational).
- Most of the studies were from the US (23).
- The most common indication for the use of disodium EDTA in both the US and non-US studies was cardiovascular disease.
- Five (5) US studies utilized disodium EDTA as a compounded product, with four (4) using an injection and one (1) a suppository.

Table 5. Types of studies

Types of Studies	Number of Studies
Descriptive[2–23]	22
Experimental[24–47]	24
Observational[48–56]	9

Table 6. Number of studies by country

Country	Number of Studies
Australia[27,42]	2
Canada[23,25,32]	3
Denmark[28–30,38]	4
Germany[20]	1
India[2,3,14,44,45,49,51,55,56]	9
Israel[26]	1
Italy[16,43]	2
Japan[11,52]	2
Lebanon[22]	1
New Zealand[40]	1
Norway[5]	1
Sweden[37]	1
The Netherlands[34]	1
UK[21,48]	2
US[4,6–10,12,13,15,17–19,24,31,33,35,36,39,41,46,50,53,54]	23
Multiple Countries • US and Canada[47]	1
	Total US: 24[a] Total non-US countries: 32[a]

[a]Study 46 counted in both US and non-US total.

Table 7. Number of studies by combinations

No combination products were nominated

Table 8. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Cardiovascular disease[6–9,18,31,33,36,46,50,53]	1.5-5g/infusion	0.54%-1.07%	Solution	Intravenous	15-40 infusions
	1.5g/day	1.5g	Suppository	Rectal	4 months
Scleroderma[10,12,17,41,54]	2.5-3g/infusion 50mg/kg/day	0.25%-0.6%	Solution	Intravenous	1-50 infusions
	1-1.5g/day	–	–	Oral	–
Band keratopathy[13,19]	–	0.01-0.05M	Solution	Ophthalmic irrigation	–
Calcium/mineral metabolism[24,35]	3g	0.3%	Solution	Intravenous	30 infusions
	–	–	–	Continuous intravenous infusion	–
Cardiac arrhythmias[39]	0.5g-4g	10%	Solution	Intravenous	Once
Calcinosis universalis[15]	50mg/kg/day	–	Solution	Intravenous	15 infusions
Wegener's granulomatosis[4]	2g/day	0.2%	Solution	Intravenous	–
	–	–	–	Oral	–

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

Table 9. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Cardiovascular disease[25,27–30,32,37,38,40,47]	1.5-3g/infusion	0.3%-0.6%	Solution	Intravenous	20-40 infusions
Infection[3,14,42,44,45,49,51,55,56]	74mg/day 60-150mg/kg/day	–	Solution	Intravenous	3-14 days
	100mM/day	–	Solution	Nebulizer	3 months
Band keratopathy[2,5,20,26,48,52]	–	0.37%-4% 0.01mol/L	Solution	Ophthalmic irrigation	Once
	–	1.87%	Solution	Ophthalmic	–
Hypercalcemia[23,34]	10mg/kg/day	–	Solution	Intravenous	Once
	150mg/kg/day				7 days
Calcific tendonitis[43]	1mL/week	–	Solution	Mesotherapy	3 weeks
	–	15%	Gel	Ultrasound	3 weeks
Calcinosis circumscripta[21]	70mg/kg	–	Solution	Intravenous	Once
	4g/month				1 year
Mercury poisoning[16]	2g/infusion	0.4%	Solution	Intravenous	–
Renal calculus dissolution[11]	–	5%-100%	Solution	Renal irrigation	–
Scleroderma[22]	–	–	–	–	–

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

Table 10. Compounded products – US

Indication	Publication Year	Compounding Method	Dosage Form	Final Strength
Cardiovascular disease[6,7,33,50]	1992, 1999, 2013	• Disodium EDTA 1.5-3g[6,7,33,50] • Magnesium chloride 800-2g[6,7,33,50] • Vitamin C 0.5-15g[6,7,33,50] • Procaine 40-100mg[6,7,33,50] • Heparin 1000-2500 units[6,7,33] • Vitamin B6 100mg[6,33,50] • Pantothenic acid 250mg[33,50] • Sodium bicarbonate 840mg[33,50] • Potassium complex 2mEq[33,50] • B-complex[50] • Thiamine 100mg[33] • Sterile water to total volume of 280mL-500mL[6,7,33,50]	Solution	0.54%-1.1%
Cardiovascular disease[53]	2004	• Disodium EDTA 1.5g • Rectal suppository base	Suppository	1.5g

Table 11. Compounded products – non-US countries

No compounded products from reported studies

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

Eleven (11) interviews were conducted. Two (2) interviewees were interviewed at the same time; one (1) interview was cut short and a follow-up interview was need to continue the discussion. One (1) medical expert specializing in neurology was contacted for an interview, however the interviewee failed to respond to the interview request.

Table 12. Overview of interviewees

Interviewee	Level of Training	Specialty	Current Practice Setting	Experience with Disodium EDTA	Interview Summary Response
TOX_04	MD	Medical Toxicology Addiction Medicine Emergency Medicine	Tertiary referral center	No	• Calcium disodium ETA is the only form that should ever be used to treat metal toxicity. • Would never stock disodium EDTA due to the potential for a medication error and the adverse effects.
TOX_05	MD	Medical Toxicology	Tertiary referral center	No	• Should be a preference for calcium disodium EDTA for all indications. • Concerns with severe hypocalcemia from use of disodium EDTA. • Deaths have occurred from office-based practice of using disodium EDTA, which the interviewee considers as inappropriate. • Disodium EDTA is a potential fourth-line agent for symptomatic hypercalcemia or cardiac dysrhythmias but multiple agents would be used first.
TOX_06	MD	Medical Toxicology Occupational Medicine Internal Medicine	Independent Consultant Faculty at a School of Medicine	No	• Disodium EDTA should never be used for heavy metal poisoning.
NAT_03	MD	Internal Medicine	Private Practice	Yes	• Has used EDTA for over 20 years in cardiovascular disease and patients who wanted it for health or preventative reasons.

NAT_04	ND	Family Practice	Private, multi-physician clinic	Yes	• Uses disodium EDTA for pathological calcification cases.
NAT_05	ND	Environmental Medicine	Private Practice	Yes	• Uses for cardiac reasons. • Anecdotal evidence supports use of disodium EDTA over calcium disodium EDTA.
CAR_01	MD	Cardiology	Community-based Hospital	Yes	• Conducts clinical trials regarding use of disodium EDTA for cardiovascular disease. Most promising results were in diabetic patients.
NAT_01	ND	None	Private Practice	Yes	• Uses for high blood pressure and cardiovascular issues. • Predominately uses an IV formulation.
END_03	MD	Endocrinology	Academic medical Institution	No	• Does not use.
INF_01	MD	Internal Medicine Infectious Disease	Academic Medical Institution	No	• Has not heard of use. • Would want to see more safety studies.
OPH_04	MD	Ophthalmology	Academic Medical Institution	Yes	• Has not used since residency, primarily used by cornea specialists and general ophthalmologists for band keratopathy.

Conditions or diseases in which EDTA is used

- NAT_05 stated that historically it was used in Germany and Russia, then the US saw benefit. Interviewee stated it was put into the water in Europe to remove lead. This is when it was determined that if too much disodium EDTA was given too fast the result was hypocalcemia.
- CAR_01 stated that disodium EDTA was removed from the market due to patients receiving IV push disodium EDTA instead of calcium disodium EDTA leading to patient deaths.
- Three (3) interviewees stated that only calcium disodium EDTA should be used for heavy metal poisoning.
    - TOX_04 and TOX_05 stated there has always been, and should always be, a preference for calcium disodium EDTA for all indications, except for rare endocrine-related hypercalcemia issues, due to the severe hypocalcemia that can result from disodium EDTA.
    - TOX_05 stated that disodium EDTA should never be used in an outpatient setting stating that deaths have occurred from the inappropriate use of disodium EDTA in an office setting.
    - TOX_06 stated that disodium EDTA should never be used for heavy metal poisoning.
    - TOX_05 stated that use of disodium EDTA predating the 1960s might have been due to the consideration for digitalis or related glycoside toxicity because of its chelating effect on calcium. However, once digitalis became available in the 1970s this may have eliminated the need of disodium EDTA for this indication.
- Two (2) interviewees stated use in cardiovascular disease is another "world-view philosophy" that "actually makes no sense the way the body actually works."
    - TOX_05 stated that once calcium becomes part of plaque, removing micromolar amounts with a chelator does not make any difference to the outcome. The interviewee continued that "any alteration you'd want to do would be way back of the point of where the endophilin is being altered and the macrophages are invading, which has nothing to do with calcium."
    - TOX_04 stated that there is a lack of convincing evidence for use in coronary artery disease and that disodium EDTA is being used even though the preponderance of evidence states that it probably should not be used.
- Five (5) interviewees discussed the use in cardiovascular disease.
    - NAT_03 stated has used EDTA for over 20 years in cardiovascular disease and for overall health and preventative reasons. The interviewee continued that EDTA binds lead and cadmium as well as it may increase nitric oxide. The TACT [Trial to Assist Chelation Therapy] trial used disodium EDTA in addition to the five standard post-MI medications, which is what the interviewee does as well. The interviewee stated that either the sodium or calcium salt form could be used because the goal is to remove lead and cadmium.
        - The interviewee stated that the vascular protocol from the TACT trial is 40 treatments, administered once a week for 20 weeks then every other week. Treatment then is as needed approximately once a month to once every two months for maintenance.
    - NAT_05 stated use for cardiac reasons. The interviewee continued that it is administered as an IV infusion based on the patient's weight and height, with a maximum dose of 3g, administered over 3 hours. Administers with magnesium, potassium B vitamins,

pyridoxine, dexpanthenol, B complex, hydroxocobalamin in a 500mL normal saline or half normal saline bag. Administration is in conjunction with other cardiac medications.
        - The interviewee cites anecdotal evidence that supports use of disodium over calcium for cardiac issues.
    - NAT_04 uses for pathological calcification cases or for patients that test above the CDC NHANES level for lead or another appropriate metal. The interviewee stated that both calcium and disodium EDTA are used, with disodium EDTA accounting for approximately 20-25% of cases.
        - The interviewee stated that generally, patients receive calcium EDTA unless a patient has pathologic calcification or a history of a safety index with disodium EDTA.
    - NAT_01 uses disodium EDTA for high blood pressure, cardiovascular issues. The interviewee continued discussing use as an eye drop to decrease inflammation and as a suppository for heavy metal detoxification.
        - The interviewee mostly uses as an IV formulation dosed based on weight.
        - The interviewee reports use of calcium disodium EDTA for lead and heavy metal binding.
    - CAR_01 has done clinical trials using disodium EDTA for reduction of cardiovascular events with positive results.
        - Conducting additional trials with diabetic patients due to the beneficial effects seen.
        - Is administered in conjunction with other cardiac medications.
        - The interviewee is unsure of the mechanism, but the hypothesis is due to binding of metals.
        - The interviewee stated that chelation has moved from a class 3 agent to a class 2B in the American Heart Association and American College of Cardiology for the treatment of stable ischemic heart disease.
- OPH_01 discussed the use in band keratopathy; no other medications are currently available.

Administration of EDTA

- NAT_03 uses the ACAM protocol, which has a maximum dose of 3g; adjusted by a formula that utilizes the age, weight, and serum creatinine of a patient. Patients receive between one and three grams of EDTA per dose administered intravenously with vitamin C, three B vitamins, magnesium, and a few other things. It is infused over 2.5-3 hour periods, not to exceed a rate that causes renal interstitial disease.
- NAT_04 administers EDTA intravenously with doses adjusted up to a maximum of 50mg/kg or 3g, whichever is lower, over 3-4 hours. The interviewee continued that it is administered with B-complex and amino acids.
    - Since EDTA also binds other minerals, after every 1-3 administrations the next IV is a re-mineralization IV with calcium, zinc, copper, and B vitamins.
- CAR_01 states that the dose of disodium EDTA is adjusted based on renal function. The formulation contains additional vitamins and minerals administered in a 500mL bag over 3 hours for 40 infusions, 2 infusions a week for the first 20 infusions.
- OPH_01 states that a flap is made, then the epithelium is peel off, and the disodium EDTA is rubbed on the eye to bind the calcium; depending on how dense the deposit is the time varies.
    - The concentration is 2.6%.

Stocking of EDTA

- NAT_03 reported obtaining from a 503B facility, continuing that requiring a patient-specific prescription would reduce efficiency.
- NAT_04 stocks in-office but it is patient specific obtained from a 503A pharmacy. The interviewee continued that having available from a 503B would be beneficial due to cost savings and reduced waste.
- NAT_05 previously stocked in-office, but now obtains from a compounding pharmacy; has not seen a negative impact on practice.
- CAR_01 obtains disodium EDTA from a compounding pharmacy under an IND.
- NAT_01 states obtaining from a compounding pharmacy, but would stock in the office so the lab can administer when the patient comes in.
- OPH_01 stated that patients pick up a prescription for EDTA and bring to their appointment. The interviewee stated that there are concerns regarding what happens to the drug between the time the patient picks it up and the actual procedure, but that this is not a common procedure.

Summary of survey results

Table 13. Characteristics of survey respondents [121 people responded to the survey[a]]

Board Certification	DO	MD	ND	NP	PharmD	PhD	No Response
Addiction Medicine	0	3	0	0	0	0	0
Cardiovascular Disease	0	0	0	1	0	0	0
Clinical Pharmacology	0	1	0	0	0	0	0
Emergency Medicine	5	25	0	0	0	0	0
Dermatology	0	1	0	0	0	0	0
Family Medicine	0	2	0	0	0	0	0
Integrative Medicine	0	1	0	0	0	0	0
Internal Medicine	0	6	0	0	0	0	0
Medical Toxicology	3	31	0	0	1	1	0
Naturopathic Doctor	0	0	3	0	0	0	0
Naturopathic Physician	0	0	3	0	0	0	0
Nephrology	0	1	0	0	0	0	0
NRCC	0	0	0	0	0	1	0
Occupational Medicine	0	2	0	0	0	1	0
Ophthalmology	0	29	0	0	0	0	0
Pediatrics	0	2	0	0	0	0	0
Preventative Medicine	0	1	0	0	0	0	0
Rheumatology	1	0	0	0	0	0	0
No Response	0	0	0	0	0	0	45

Abbreviations: DO, Doctor of Osteopathic Medicine; MD, Doctor of Medicine; ND, Naturopathic Doctor; NP, Nurse Practitioner; PharmD, Doctor of Pharmacy; PhD, Doctor of Philosophy; NRCC, National Registry of Certified Chemists.

[a]Multiple respondents reported more than one (1) terminal clinical degree or board certification.

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

Types of Products	Respondents, n (N=75[a,b])
Compounded	24[c]
FDA-approved	26
Over-the-counter	0
Dietary	0
Unsure	5
No Response	22

[a]Out of 121 respondents, 75 reported using, prescribing, or recommending disodium EDTA products.
[b]Two (2) respondents reported use of multiple types of products.
[c]One (1) respondent reported use in combination with antioxidants and mineral supplements and one (1) respondent reported use in combination with colloidal silver.

Table 15. Compounded use of disodium EDTA in practice

Indication	Strength	Dosing Frequency	Dosage Form	ROA	Duration of Treatment	Patient Population
Band keratopathy	0.12 molar	Once (during procedure)	Solution	Topical	During procedure	Any
	0.37-3%					
CIRS with MARCoNS colonization	0.5%	TID	Nasal spray	Nasal spray	2-3 months	Any
Hematological cancers	0.5-1g	Daily	Solution	IV	Duration of induction	Clinical trials
Metal poisonings	1g	Daily	Solution	IV	1-2 weeks	Adults

Abbreviations: CIRS, chronic inflammatory response syndrome; MARCoNS, multiple antibiotic resistant coagulase negative Staph; TID, three times daily; IV, intravenous; ROA, route of administration.

Table 16. Indications for which disodium EDTA is considered standard therapy

Indication	Standard Therapy			
	Compounded, n (N=24)	Non-compounded, n (N=26)	Unsure, n (N=5)	No Response, n (N=22)
Band keratopathy	18	3	1	0
Lead poisoning	1[a]	17[b]	1[c]	0
MARCoNS	1	0	0	0
Metal poisoning	1	1	1	0
No response	3	5	2	22

Abbreviation: MARCoNS, multiple antibiotic resistant coagulase negative Staph.
[a]Respondent reported that only calcium disodium EDTA is accepted for lead poisoning, not disodium EDTA.
[b]Five (5) respondents reported that only calcium disodium EDTA should be used for lead poisoning, not disodium EDTA, due to the risk of life threatening hypocalcemia.
[c]Respondent reported that only calcium disodium EDTA is used for lead poisoning, not disodium EDTA.

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

Theme	Reasons
Availability	• No FDA approved alternative for band keratopathy

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

	Respondents, n (N=24)
No–use has remained consistent	15
Yes–I use it LESS often now • Inability to obtain • Patients receive PO chelation or if IV is needed the commercially available product is used	3
Yes–I use it MORE often now • More patients referred for this condition • Other nasal sprays do not work as well	4
No Response	2

Abbreviations: PO, oral; IV, intravenous.

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

	Respondents, n (N=24)
No	20
Yes	2
No Response	2

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

	Respondents, n (N=2[a])
In what practice location(s) do you stock non-patient-specific compounded disodium EDTA?	
Physician office	1
Outpatient clinic	2
Emergency room	0
Operating room	0
Inpatient ward	0
How do you obtain your stock of non-patient-specific compounded disodium EDTA?	
Purchase from a compounding pharmacy	0
Purchase from an outsourcing facility	1
Compound the product yourself	0
Have the product compounded by an in-house pharmacy	1
Why do you keep a stock of non-patient-specific compounded disodium EDTA?	
Convenience	2
Emergencies	1

[a]Respondents reported multiple methods of obtaining non-patient specific stock and reasons for stocking.

CONCLUSION

Disodium EDTA was nominated for inclusion on the 503B Bulks List for use as a 0.4-1% ophthalmic drop for calcific band keratopathy and as a 150mg/mL intravenous infusion for treatment and prevention of atherosclerotic cardiovascular disease, heavy metals detoxification, diabetic neuropathy, and other unspecified conditions. Calcium disodium EDTA was nominated for use as a 200mg/mL intravenous injection in: chelation therapy to reduce blood levels and depot stores of lead in lead poisoning (acute and chronic); chelation therapy for other toxic metals (mercury, arsenic, uranium, cesium, etc); cardiovascular disease; diabetes; hypercholesterolemia; arthritis; cancer; chronic renal failure; and high blood pressure.

Disodium EDTA is not available as an FDA-approved product or an OTC product in the US. Disodium EDTA, marketed under the trade name Endrate, was initially approved by the FDA in 1959 for use in hypercalcemia and for the control of ventricular arrhythmias associated with digitalis toxicity. However, in 2007 the FDA issued a letter regarding the reevaluation of the safety and efficacy of Endrate based on reports of fatal medication errors with edetate calcium disodium and reports of serious adverse reactions. In 2008, all three manufacturers of disodium EDTA were notified of the withdrawal of the approval and disodium EDTA was removed from the market. Calcium disodium EDTA is available as an FDA-approved product in the US. There is a current USP monograph for disodium EDTA and calcium disodium EDTA. Disodium EDTA is available in Australia and New Zealand and calcium disodium EDTA is available in Abu Dhabi.

From the literature review, 55 studies were included of which 23 were from the US. The most common indication for use in both the US and non-US studies was cardiovascular disease. Five (5) US studies utilized disodium EDTA as a compounded product, with four (4) using an injection and one (1) a suppository. Calcium disodium EDTA is a component of an FDA-approved product and therefore was not included in the search strategy.

From the interviews, three (3) interviewees stated that calcium disodium EDTA is the only formulation that should be used for lead poisoning stated that disodium EDTA should never be used for this indication. Five (5) interviewees use EDTA for cardiovascular disease in combination with routine cardiac medications. The Trial to Assess Chelation Therapy (TACT) is the first randomized controlled trial to assess the use of disodium EDTA to treat cardiovascular disease, and several interviewees cited this study as a reference for their use.[33] One (1) interviewee reported use of disodium EDTA for band keratopathy.

From the surveys, 24 respondents reported use of compounded disodium EDTA. Respondents reported that disodium EDTA is considered standard therapy for treatment of band keratopathy, lead poisoning, and metal poisoning; however, multiple respondents stated that only calcium disodium EDTA should be used for lead poisoning due to risks of hypocalcemia with disodium EDTA. Respondents reported the reasoning for use of compounded disodium EDTA is the lack of availability of an FDA-approved product for band keratopathy. Two (2) respondents reported stocking non-patient specific compounded disodium EDTA obtained from an outsourcing facility or compounded by an in-house pharmacy in a physician office and an outpatient clinic for convenience and emergency reasons.

APPENDICES

Appendix 1. References

1. Food and Drug Administration. *Hospira, Inc., et Al.; Withdrawal of Approval of One New Drug Application and Two Abbreviated New Drug Applications.*; 2008.
2. Arora R, Shroff D, Kapoor S, et al. Familial calcific band-shaped keratopathy: Report of two new cases with early recurrence. *Indian J Ophthalmol*. 2007;55(1):55-57.
3. Bery A, Sodhi C, Bhanot R. Successful management of urosepsis with ceftriaxone+sulbactam+EDTA: A case report of penem sparing approach. *J Clin Diagnostic Res*. 2017;11(9):18-19. doi:10.7860/JCDR/2017/29146.10661
4. Hansotia P, Peters H, Bennett M, Brown R. Chelation therapy in Wegener's granulomatosis treatment with EDTA. *Ann Otol Rhinol Laryngol*. 1969;78(2):388-402.
5. Høisen H, Kopstad G, Elsås T, Ringvold A, Tvedt KE, Ødegaard A. Idiopathic haemochromatosis and eye symptoms: A case report. *Acta Ophthalmol*. 1985;63(2):192-198. doi:10.1111/j.1755-3768.1985.tb01533.x
6. Jackson JA, Riordan HD, Schultz M, Lewis R. Intravenous EDTA chelation treatment of a patient with atherosclerosis. *J Orthomol Med*. 1999;14(2):91-92.
7. Jackson JA, Riordan HD. Improvement of essential hypertension after EDTA intravenous infusion treatment. *J Orthomol Med*. 1992;7(1):16.
8. Kidd PM. Integrative cardiac revitalization : Bypass cardiac revitalization. *Altern Med Rev*. 1998;3(1):4-17.
9. Lamar CP. Chelation therapy of occlusive arteriosclerosis in diabetic p. *Angiology*. 1964;15(9):379-395.
10. Mongan ES. The treatment of progressive systemic sclerosis with disodium edetate. *Arthritis Rheum*. 1965;8(6):1145-1151. doi:10.1111/j.1600-0447.1976.tb02354.x
11. Nakatsuka S, Kinoshita H, Ueda H, Araki T, Tanaka H. Combined treatment of medullary sponge kidney by EDTA potassium citrate and extracorporeal shock wave lithotripsy. *Eur Urol*. 1988;14(4):339-342.
12. Rukavina JG, Mendelson C, Price JM, Brown RR, Johnson SAM. Scleroderma (Acrosclerosis): Treatment of three cases of the non-calcific variety by chelation (EDTA). *J Invest Dermatol*. 1957;29(4):273-288. doi:10.1038/jid.1957.101
13. Youssef PN, Herlihy E, Shen TT. Management of calcium band keratopathy using EDTA chelation and LASEK instruments. *Tech Ophthalmol*. 2006;4(3):108-111. doi:10.1097/01.ito.0000242546.94614.65
14. Bhambri V. Significance of CSE-1034 (Elores™) in treatment of urinary tract infections due to multi-drug resistant extended spectrum beta-lactamases positive Escherichia Coli. *Asian J Pharm Clin Res*. 2016;9(6):12-13. doi:10.22159/ajpcr.2016.v9i6.14409
15. Herd JK, Vaughan JH. Calcinosis universalis complicating dermatomyositis - Its treatment with Na2EDTA: Report of two cases in children. *Arthritis Rheum*. 1964;7(3):259-271.
16. Corsello S, Fulgenzi A, Vietti D, Ferrero ME. The usefulness of chelation therapy for the remission of symptoms caused by previous treatment with mercury-containing pharmaceuticals: A case report. *Cases J*. 2009;2(11):199. doi:10.1186/1757-1626-2-199
17. Birk RE, Rupe CE. Systemic sclerosis: Fourteen cases treated with chelation (disodium EDTA)

and/or pyridoxine, with comments on the possible role of altered tryptophan metabolism in pathogenesis. *Henry Ford Hosp Med Bull*. 1962;10:523-553.

18. Clarke NES. Atherosclerosis, occlusive vascular disease and EDTA. *Am J Cardiol*. 1960;6:233-236.

19. Closson RG, Skolnickk EB. Edetate calcium disodium is not the edetate disodium indicated for chelation therapy of corneal calcifications in band keratopathy or lime injury. *Hosp Pharm*. 1995;30(11):971-976.

20. de Ortueta D, Schreyger F, Baatz H. Band keratopathy: A modified treatment. *Eur J Ophthalmol*. 2006;16(4):618-620.

21. Dent CE, Stamp TCB. Treatment of calcinosis circumscripta with probenecid. *Br Med J*. 1972;1(5794):216-218. doi:10.1136/bmj.1.5794.216

22. Fuleihan FJD, Kurban AK, Abboud RT, Beidas-Jubran N, Farah FS. An objective evaluation of the treatment of systemic scleroderma with disodium EDTA, pyridoxine and reserpine. *Br J Dermatol*. 1968;80(3):184-189.

23. Gault MH, Kinsella TD. Carcinoma of lung with adrenal hyperfunction and hypercalcemia treated by parathyroidectomy. *Can Med Assoc J*. 1965;92:317-324.

24. Abraham E, Papadakos PJ, Tharratt RS, Hall JB, Williams GJ. Effects of propofol containing EDTA on mineral metabolism in medical ICU patients with pulmonary dysfunction. *Intensive Care Med*. 2000;26(Suppl 4):S422-432. doi:10.1007/PL00003786

25. Anderson TJ, Hubacek J, George Wyse D, Knudtson ML. Effect of chelation therapy on endothelial function in patients with coronary artery disease: PATCH substudy. *J Am Coll Cardiol*. 2003;41(3):420-425. doi:10.1016/S0735-1097(02)02770-5

26. Golan A, Savir H, Bar-Meir S, Oliver I, De Vries A. Band keratopathy due to hyperparathyroidism. *Ophthalmologica*. 1975;171(2):119-122. doi:10.1159/000307477

27. Green DJ, O'Driscoll JG, Maiorana A, Scrimgeour NB, Weerasooriya R, Taylor RR. Effects of chelation with EDTA and vitamin B therapy on nitric oxide- related endothelial vasodilator function. *Clin Exp Pharmacol Physiol*. 1999;26(11):853-856. doi:10.1046/j.1440-1681.1999.03156.x

28. Guldager B, Brixen KT, Jorgensen SJ, Nielsen HK, Mosekilde L, Jelnes R. Effects of intravenous EDTA treatment on serum parathyroid hormone (1-84) and biochemical markers of bone turnover. *Dan Med Bull*. 1993;40(5):627-630.

29. Guldager B, Jelnes R, Jorgensen SJ, et al. EDTA treatment of intermittent claudication: A double-blind, placebo-controlled study..pdf. *J Intern Med*. 1992;231(3):261-267.

30. Guldager B, Jørgensen PJ, Grandjean P. Metal excretion and magnesium retention in patients with intermittent claudication treated with intravenous disodium EDTA. *Clin Chem*. 1996;42(12):1938-1942.

31. Kitchell JR, Palmon FJ, Aytan N, Meltzer LE. The treatment of coronary artery disease with disodium EDTA: A reappraisal. *Am J Cardiol*. 1963;11(4):501-506.

32. Knudtson ML, Wyse DG, Galbraith PD, et al. Chelation therapy for ischemic heart disease: A randomized controlled trial. *J Am Med Assoc*. 2002;287(4):481-486.

33. Lamas GA, Goertz C, Boineau R, et al. Effect of disodium EDTA chelation regimen on cardiovascular events in patients with previous myocardial infarction: The TACT randomized trial. *J Am Med Assoc*. 2013;309(12):1241-1250. doi:10.1001/jama.2013.2107

34. Landman JO, Schweitzer DH, Frolich M, Hamdy NAT, Papapoulos SE. Recovery of serum calcium concentrations following actue hypocalcemia in patients with osteoporosis on long-term oral therapy with bisphosphonate pamidronate. *J Clin Endocrinol Metab*. 1995;80(2):524-528.

35. McDonagh EW, Rudolph CJ, Cheraskin E. The effect of intravenous disodium EDTA plus supportive multivitamin/trace mineral supplementation upon fastin serum calcium. *Med Hypotheses*. 1983;11(4):431-438.

36. Arenas I, Navas-Acien A, Lamas G. Enhanced vasculotoxic metal excretion in post-myocardial infarction patients receiving edetate disodium-based infusion. *J Am Coll Cardiol*. 2016;67(13):2125. doi:10.1016/S0735-1097(16)32126-X

37. Öckerman PA. Improvement of arterial stiffness by EDTA-chelation in combination with vitamin, mineral, trace element and antioxidant supplements. *J Orthomol Med*. 2011;26(2):93-97.

38. Sloth-Nielsen J, Guldager B, Mouritzen C, et al. Arteriographic findings in EDTA chelation therapy on peripheral arteriosclerosis. *Am J Surg*. 1991;162(2):122-125.

39. Surawicz B, MacDonald MG, Kaljot V, Bettinger JC. Treatment of cardiac arrhythmias with salts of ethylenediamine tetraacetic acid (EDTA). *Am Heart J*. 1959;58(4):493-503.

40. van Rij AM, Solomon C, Packer SGK, Hopkins WG. Chelation therapy for intermittent claudication: A double-blind, randomized, controlled trial. *Circulation*. 1994;90:1194-1199.

41. Birk RE, Rupe CE. The treatment of systemic sclerosis with disodium EDTA, pyridoxine, and reserpine. *Henry Ford Hosp Med Bull*. 1966;14(2):109-118.

42. Brown J, Mellis CM, Wood RE. Edetate sodium aerosol in Pseudomonas lung infection in cystic fibrosis. *Am J Dis Child*. 1985;139(8):836-839. doi:10.1001/archpedi.1985.02140100098043

43. Cacchio A, De Blasis E, Desiati P, Spacca G, Santilli V, De Paulis F. Effectiveness of treatment of calcific tendinitis of the shoulder by disodium EDTA. *Arthritis Care Res*. 2009;61(1):84-91. doi:10.1002/art.24370

44. Chaudhary M, Mir MA, Ayub SG. Safety and efficacy of a novel drug elores (ceftriaxone+sulbactam+disodium edetate) in the management of multi-drug resistant bacterial infections in tertiary care centers: A post-marketing surveillance study. *Brazilian J Infect Dis*. 2017;21(4):408-417. doi:10.1016/j.bjid.2017.02.007

45. Chaudhary M, Payasi A. Clinical, microbial efficacy and tolerability of Elores, a novel antibiotic adjuvant entity in ESBL producing pathogens: Prospective randomized controlled clinical trial. *JOPR J Pharm Res*. 2013;7(4):275-280. doi:10.1016/j.jopr.2013.04.017

46. Clarke NES, Clarke NEJ, Mosher RE. Treatment of occlusive vascular disease with disodium ethylene diamine tetraacetic acid (EDTA). *Am J Med Sci*. 1960;239:732-744.

47. Escolar E, Lamas GA, Mark DB, et al. The effect of an EDTA-based chelation regimen on patients with diabetes mellitus and prior myocardial infarction in the Trial to Assess Chelation Therapy (TACT). *Circ Cardiovasc Qual Outcomes*. 2014;7(1):15-24. doi:10.1161/CIRCOUTCOMES.113.000663

48. Al-Hity A, Ramaesh K, Lockington D. EDTA chelation for symptomatic band keratopathy: Results and recurrence. *Eye*. 2018;32(1):26-31. doi:10.1038/eye.2017.264

49. Aziz I, Mir MA. Clinical and economic impact of appropriate empirical antibiotic therapy in complicated intra-abdominal infections: A retrospective study. *Curr Med Res Pract*. 2015;5(6):262-269. doi:10.1016/j.cmrp.2015.11.003

50. Born T, Kontoghiorghe CN, Spyrou A, Kolnagou A, Kontoghiorghes GJ. EDTA chelation

reappraisal following new clinical trials and regular use in millions of patients: Review of preliminary findings and risk/benefit assessment. *Toxicol Mech Methods*. 2013;23(1):11-17. doi:10.3109/15376516.2012.730562

51. Chakravorty S, Arun P. Antibiotic/adjuvant combinations (ceftriaxone+sulbactam+adjuvant disodium edetate) as an alternative empiric therapy for the treatment of nosocomial infections: Results of a retrospective study. *Indian J Cancer*. 2018;55(1):685-690.

52. Kobayashi W, Yokokura S, Hariya T, Nakazawa T. Two percent ethylenediaminetetraacetic acid chelation treatment for band-shaped keratopathy, without blunt scratching after removal of the corneal epithelium. *Clin Ophthalmol*. 2015;9:217-223. doi:10.2147/OPTH.S75938

53. Maniscalco BS, Taylor KA. Calcification in coronary artery disease can be reversed by EDTA-tetracycline long-term chemotherapy. *Pathophysiology*. 2004;11(2):95-101. doi:10.1016/j.pathophys.2004.06.001

54. Neldner KH, Winkelmann RK, Perry HO. Scleroderma: An evaluation of treatment with disodium edetate. *Arch Dermatol*. 1962;86:305-309.

55. Patil UN, Jambulingappa KL. A combination strategy of ceftriaxone, sulbactam and disodium edetate for the treatment of multi-drug resistant (MDR) septicaemia: A retrospective, observational study in Indian tertiary care hospital. *J Clin Diagnostic Res*. 2015;9(11):29-32. doi:10.7860/JCDR/2015/14129.6840

56. Sathe P, Maddani S, Kulkarni S, Munshi N. Management of ventilator associated pneumonia with a new antibiotic adjuvant entity (ceftriaxone+sulbactam+disodium edetate) - A novel approach to spare carbapenems. *J Crit Care*. 2017;41:145-149. doi:10.1016/j.jcrc.2017.04.002

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 **disodium EDTA**. 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: Disodium EDTA

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

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

Display This Question:

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

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

Display This Question:

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

Q4. Please list all combination products in which you use compounded **disodium EDTA**.

_____

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

_____

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

_____

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

_____

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

- Yes
- No

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

Display This Question:

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

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

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

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

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

_____

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

_____

End of Block: Disodium EDTA

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