

Summary Report

Sodium molybdate

Prepared for:

Food and Drug Administration

Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List

Grant number: 5U01FD005946

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December 2020

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

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Frequently Used Abbreviations

API	Active Pharmaceutical Ingredient
AuSPEN	Australasian Society for Parenteral and Enteral Nutrition
EMA	European Medicines Agency
CSPEN	Chinese Society for Parenteral and Enteral Nutrition
ESPGHAN	European Society for Pediatric Gastroenterology, Hepatology and Nutrition
ESPR	European Society of Pediatric Radiology
ESPEN	European Society for Parenteral and Enteral Nutrition
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 parental 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 sodium molybdate (UNII code: 948QAQ08I1), 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 sodium molybdate 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 sodium molybdate 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 sodium molybdate 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 NOMINATION

Sodium molybdate was nominated for inclusion on the 503B Bulks List by the Outsourcing Facilities Association (OFA) for nutritional supplementation and molybdenum deficiency via a 25 mcg/mg intravenous injection.

The nominator provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of sodium molybdate.^{6,7}

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

- Compounded product may be the only product to effectively treat the indication for which it is intended.
- Patient need for dosage form or strength that is not available commercially.
- Patient sensitivities to dyes, fillers, preservatives, or other excipients in manufactured products.
- Manufacturer backorder.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of sodium molybdate 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 sodium molybdate; name variations of sodium molybdate 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 sodium molybdate. 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 two separate search strategies for both Ovid MEDLINE and Embase. The first search strategy used a combination of controlled vocabulary terms and keywords to describe two concepts: sodium molybdate, and injectable administration or therapeutic use. The decision was made to expand the initial search from ‘sodium molybdate’ to ‘molybdate’; therefore, the second search strategy used a combination of controlled vocabulary terms and keywords to describe three concepts: molybdenum, injectable administration and therapeutic use (see Appendix 1 for full search strategies). Results were limited to original human studies in English language. The first search strategies were conducted on December 22 and 23, 2019. The second search strategies were conducted on January 22, 2020. The reference lists of relevant systematic reviews and meta-analyses, retrieved in a separate search of Ovid MEDLINE on November 8, 2019, were reviewed to identify additional studies. In addition, the ECRI Guidelines TrustTM repository was searched on November 8, 2019 for clinical practice guidelines that recommended the use of sodium molybdate 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 for screening.

Study selection

Studies in which sodium molybdate 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 sodium molybdate 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 sodium molybdate 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 sodium molybdate; setting; total number of patients; number of patients who received sodium molybdate; patient population; indication for use of sodium molybdate; dosage form and strength; dose; ROA; frequency and duration of therapy; use of sodium molybdate in a combination product; use and formulation of sodium molybdate in a compounded product; use of sodium molybdate 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 sodium molybdate was used in a clinical setting. The systematic literature review and indications from the nomination were reviewed to identify the following medical specialties that would potentially use sodium molybdate: gastroenterology, 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 sodium molybdate 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

- Sodium molybdate is not available as an FDA-approved product in the nominated dosage form and ROA.
- Sodium molybdate is not available as an OTC product in the US.
- There is no current United States Pharmacopeia (USP) monograph for sodium molybdate.
- Sodium molybdate is not available in any of the national medical registries searched. It is available as part of a multiple API solution for infusion in Abu Dhabi, Australia, Belgium, Hong Kong, Ireland, and New Zealand.

Table 1. Currently approved products – US

No approved products in the US

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

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

Results of literature review

Study selection

Database searches yielded 427 references. After duplicates were removed, 365 titles and abstracts were screened. After screening, the full text of 54 articles was reviewed. Finally, 1 study was included. Fifty-three studies were excluded for the following reasons: wrong study design (24); sodium molybdate not used clinically (15); wrong dosage form or ROA (10); sodium molybdate only mentioned briefly (3); wrong substance (1).

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

Characteristics of included studies

The included descriptive study was published in 1981 and conducted in the US.

One patient was described in the included study.

The outcome measure was improvement in the clinical symptoms (tachycardia, tachypnea, severe headache, night blindness, nausea, vomiting, central scotomas, generalized edema, lethargy, disorientation, coma) and correction of the biochemical abnormalities.

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

Use of sodium molybdate

There was 1 case report of a 24-year-old Caucasian man with Crohn's disease who had diet-induced molybdenum deficiency due to a combined effect of high sulfur amino acid load and low molybdenum intake.⁶ Ammonium molybdate 300 mcg/day was administered. There were no studies found that mentioned using sodium molybdate specifically.

Refer to Table 6 for a summary of dosage by indication.

Sodium molybdate was not used as a compounded product.

In the included study, the author concluded that this patient's condition was total parental nutrition (TPN) induced by the combined effect of high sulfur amino acid load and very low molybdenum intake. This represents the first case report of a diet-induced molybdenum deficiency in humans.

Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

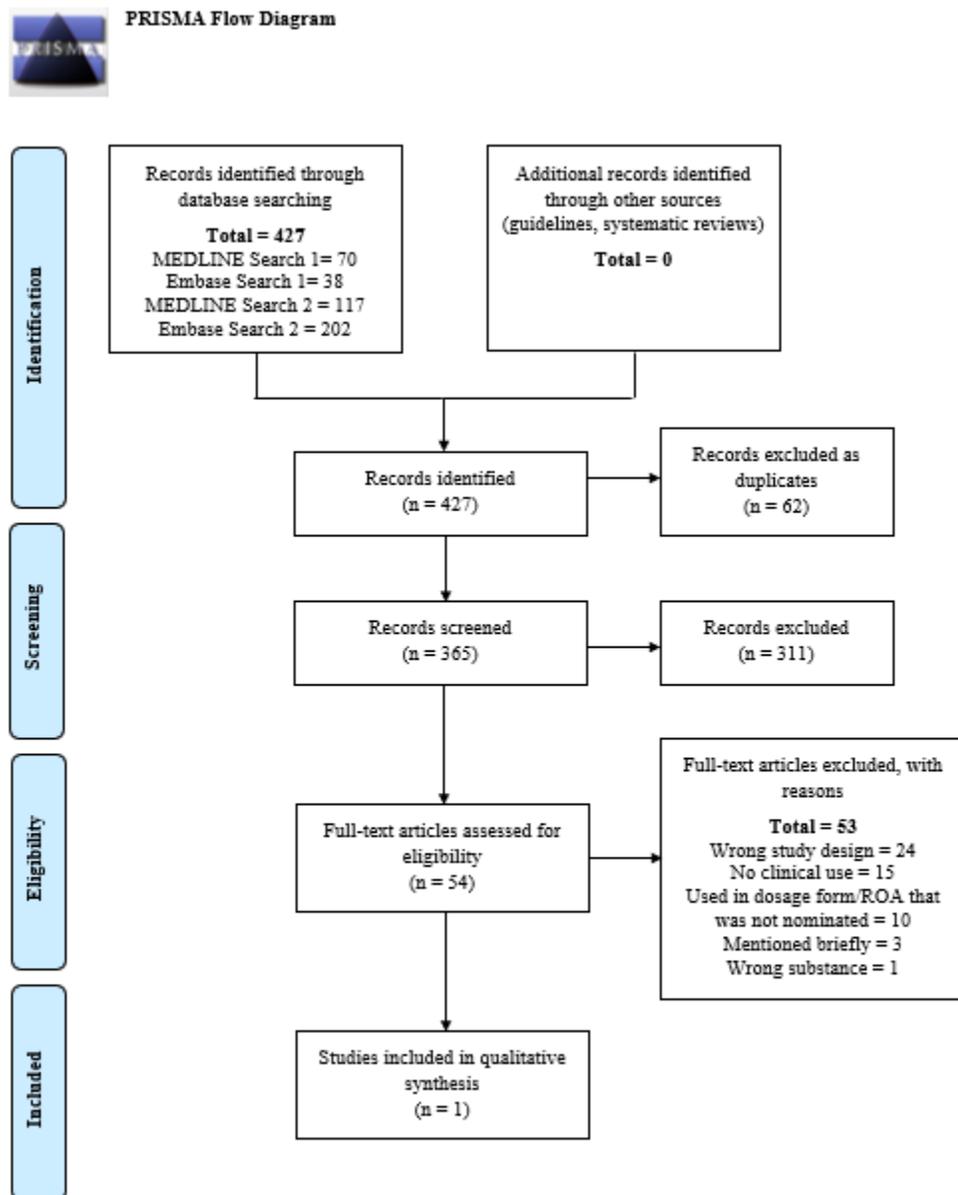
In addition to the included study, 5 studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of sodium molybdate.

Molybdenum is an essential trace element (atomic number 42) and there are several molybdenum-containing enzymes in the body, including xanthine oxidase/dehydrogenase, aldehyde oxidase, and sulfite oxidase.⁸ Molybdenum deficiency is rare and there has only been one known case of molybdenum deficiency in the literature.⁶

Several guidelines have mentioned molybdenum supplementation. The European Society for Parenteral and Enteral Nutrition (ESPEN) 2009 guidelines recommended molybdenum 20 mcg as a daily requirement in adult "patients after surgery who are unable to be fed via the enteral route, and in whom total or near total parenteral nutrition is required, a full range of vitamins and trace elements should be supplemented on a daily basis (Grade C recommendation)."⁹ The European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) / ESPEN/European Society of Pediatric Radiology (ESPR) / Chinese Society for Parenteral and Enteral Nutrition (CSPEN) 2018 guidelines on pediatric parenteral nutrition for iron and trace minerals reported that there are no cases of molybdenum deficiency in infants, however low birth weight infants might be at risk.¹⁰ They conditionally recommended that molybdenum should be provided in long-term parenteral nutrition at a dose of 1 mcg/kg/day in low birth weight infants and 0.25 mcg/kg/day (max 5 mcg/day) in infants and children.¹⁰ The Australasian Society for Parenteral and Enteral Nutrition (AuSPEN) 2014 guidelines for supplementation of trace elements during parenteral nutrition stated that patients on short term parenteral nutrition probably do not need daily molybdenum supplementation.¹¹ For stable patients on longer term parenteral nutrition, a safe daily and adequate supplementation of molybdenum is 19 mcg.¹¹

Several studies reported that ammonium molybdate tetrahydrate is available in North America as a concentration of 25 mcg/mL in 10 mL vials.^{12,13} On the American Society of Hospital Pharmacist's (ASHP) drug shortage website, ammonium molybdate injection is not available because American Regent, who was the sole supplier of the ammonium molybdate injection, is not marketing this product anymore.¹⁴

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 ⁶	1
Experimental	0
Observational	0

Table 4. Number of studies by country

Country	Number of Studies
US ⁶	
Total US: 1 Total Non-US Countries: 0	

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
Abumrad <i>et al.</i> , 1981, US ⁶	Case report	1 Patient (100%, 24 y)	<ul style="list-style-type: none"> Ammonium molybdate (1) 	Improvement in the clinical symptoms (tachycardia, tachypnea, severe headache, night blindness, nausea, vomiting, central scotomas, generalized edema, lethargy, disorientation, coma) and correction of the biochemical abnormalities (mild hypermethioninemia, hypouricemia, hypouricosuria, low excretion of inorganic sulfate in the urine).	This patient's condition was total parental nutrition (TPN) induced by the combined effect of high sulfur amino acid loading and very low molybdenum intake. This represents the first case of a diet-induced molybdenum deficiency in humans.

^aAs defined by authors.

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of administration	Duration of Treatment
Diet-induced molybdate deficiency ⁶	300 mcg/day	–	–	Intravenous	–

Abbreviation: “–”, not mentioned.

Table 7. Dosage by indication – non-US countries

No non-US studies included

Table 8. Number of studies by combinations

No combination products were nominated

Table 9. Compounded products – US

No compounded products from reported studies

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. Sixteen SMEs discussed sodium molybdate. Amongst these 16 SMEs, there were 2 medical doctors, 13 pharmacists, and 1 physician assistant. The SMEs specialized and/or were board-certified in critical care, gastroenterology, hepatology, occupational medicine, pediatrics, primary care/family practice, nutrition, and sterile compounding, working in academia, academic medical centers, consulting, hospital/health systems, pharmacy/pharma companies, and private practice/clinics. The SMEs had been in practice for 7 to 50 years.

None of the SMEs had experience with molybdenum deficiency. Except for one case reported in the literature, there is no clear characterization of the risk factors and symptoms that may lead to molybdenum deficiency. One SME stated that in the 1970s, serum levels for molybdenum started to be measured and this was what drove the availability of the product in Europe. Most SMEs commented that molybdenum levels are not routinely monitored with one SME who added that a sophisticated lab is probably needed to measure levels. A couple of SMEs commented that there are no recommended dietary allowance requirements for molybdenum so practitioners would not even know if it is a problem. One SME stated that “The true incidence of molybdenum deficiency is probably less than 0.1%.” A SME also added that “some people associate molybdenum deficiency as a risk factor for liver injury, but we never bought into that.” One SME voiced that “if you [do not] know what to do, [do not] do anything [as] acts of omission are always better than acts of commission. To [them], giving molybdenum as a supplement is an act of commission. A few SMEs also stated that molybdenum is similar to manganese because it contaminates many products. One SME added that toxicity would be more of a concern than deficiency.

While most of the SMEs had no experience using molybdenum, there were a few SMEs who had used molybdenum. A SME shared they have never needed to correct molybdenum deficiency in their practice but have supplemented molybdenum in a few instances. Another SME added they had a colleague who provided molybdenum supplementation in their parenteral nutrition formulations, but this is not standard practice. Several SMEs commented that there used to be a commercially available multiple trace element product with molybdenum and there are still some European products available with molybdenum. When there was a shortage of trace elements in the US, Addamel®, which has molybdenum in it, could be imported from Europe. One SME commented that it would be nice to have a trace element formulation with molybdenum available in the US for babies.

Results of survey

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

Table 11. Characteristics of survey respondents

No respondents to survey distributed via professional medical associations

Table 12. Conditions for which sodium molybdate prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded sodium molybdate

No respondents to survey distributed via professional medical associations

Table 14. Use of non-patient-specific compounded sodium molybdate

No respondents to survey distributed via professional medical associations

CONCLUSION

Sodium molybdate was nominated for inclusion on the 503B Bulks List for nutritional supplementation and molybdenum deficiency via a 25 mcg/mg intravenous injection. Sodium molybdate is not available in the nominated dosage form and ROA in any of the national medical registries searched. However, it is available as part of a multiple API solution for infusion in Abu Dhabi, Australia, Belgium, Hong Kong, Ireland, and New Zealand.

From the literature review and interviews conducted, molybdenum deficiency is rare and there has only been 1 case report of a patient with diet-induced molybdenum deficiency. There is also no clear characterization of the risk factors and symptoms that may lead to molybdenum deficiency. Several guidelines mentioned molybdenum supplementation. The ESPEN 2009 guidelines recommended molybdenum 20 mcg as a daily requirement in adult “patients after surgery who are unable to be fed via the enteral route, and in whom total or near total parenteral nutrition is required, a full range of vitamins and trace elements should be supplemented on a daily basis (Grade C recommendation).”⁹ The 2018 ESPGHAN / ESPEN / ESPR / CSPEN guidelines on pediatric parenteral nutrition for iron and trace minerals conditionally recommended that molybdenum should be provided in long-term parenteral nutrition at a dose of 1 mcg/kg/day in low birth weight infants and 0.25 mcg/kg/day (max 5 mcg/day) in infants and children.¹⁰ The 2014 AuSPEN guidelines for supplementation of trace elements during parenteral nutrition stated that for stable patients on longer term parenteral nutrition, a safe daily and adequate supplementation molybdenum amount is 19 mcg.¹¹

Most of the SMEs had no experience using molybdenum. One SME stated they have never needed to correct molybdenum deficiency in their practice but have supplemented molybdenum in a few instances. Another had a colleague who provided molybdenum supplementation in their parenteral nutrition formulations, but this is not standard practice. Several SMEs commented that there used to be a commercially available multiple trace element product with molybdenum and there are still some European products such as Addamel® available with molybdenum. One SME commented that it would be nice to have a trace element formulation with molybdenum available in the US for babies.

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

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APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy 1

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process and other non-indexed citations and daily 1946 to December 20, 2019
- Date last searched: December 22, 2019
- Limits: Humans (search hedge); English language
- Number of results: 70

1	((sodium or monosodium or disodium) adj2 (molybd\$ or dimolybd\$)).tw.	567
2	drug administration routes/	5605
3	exp administration, intravenous/	141354
4	infusions, parenteral/	26202
5	inject\$.tw.	722118
6	infusion\$.tw.	240755
7	perfusion.tw.	156056
8	(parenteral\$ adj2 (administ\$ or therap\$ or treat\$ or deliver\$)).tw.	11926
9	intravenous\$.tw.	332752
10	intra venous\$.tw.	564
11	intravascular\$.tw.	46560
12	intra vascular\$.tw.	296
13	drug therapy/	30272
14	nutrition therapy/	2211
15	nutritional support/	6076
16	exp parenteral nutrition/	23685
17	drug effects.fs.	2931056
18	drug therapy.fs.	2165840
19	administration & dosage.fs.	1383167
20	tu.fs.	2177114

21	(nutrition\$ adj2 (parenteral\$ or supplement\$ or support\$)).tw.	36608
22	therap\$.tw.	2664073
23	(molybd\$ adj3 deficien\$).tw.	301
24	or/2-23	7698711
25	and/1,24	210
26	exp animals/ not humans/	4654789
27	25 not 26	76
28	limit 27 to english language	70

MEDLINE search strategy 2

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process and other non-indexed citations and daily 1946 to January 20, 2019
- Date last searched: January 22, 2019
- Limits: Humans (search hedge); English language
- Number of results: 117
- Notes: Decision was made to expand initial search from 'sodium molybdate' to 'molybdate'

1	molybdenum/	7769
2	(dimolybd\$ or molybd\$).tw.	14824
3	or/1-2	18026
4	drug administration routes/	5617
5	exp administration, intravenous/	141670
6	infusions, parenteral/	26212
7	exp parenteral nutrition/	23711
8	inject\$.tw.	724845
9	infusion\$.tw.	241338
10	perfusion.tw.	156593
11	(parenteral\$ adj2 (administ\$ or deliver\$ or nutrition\$ or therap\$ or treat\$ or supplement\$)).tw.	31124
12	administration & dosage.fs.	1388307

13	intravenous\$.tw.	333811
14	intra venous\$.tw.	566
15	intravascular\$.tw.	46720
16	intra vascular\$.tw.	298
17	or/4-16	2445277
18	drug therapy/	30315
19	nutrition therapy/	2240
20	nutritional support/	6110
21	malnutrition/	13050
22	drug effects.fs.	2940756
23	drug therapy.fs.	2174862
24	tu.fs.	2184579
25	((mineral? or trace element? or ultratrace or ultra trace) adj3 supplement\$.tw.	3172
26	(molybd\$ adj3 deficien\$.tw.	302
27	therap\$.tw.	2680677
28	treat*.tw.	5313190
29	or/18-28	9240880
30	and/3,17,29	333
31	exp animals/ not humans/	4666012
32	30 not 31	128
33	limit 32 to english language	117

Embase search strategy 1

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: December 23, 2019
- Limits: Humans (search hedge); English language
- Number of results: 38

1	molybdate sodium'/de	387
2	((sodium OR monosodium OR disodium) NEAR/2 (molybd* OR dimolybd*)):ti,ab,tn	599
3	#1 OR #2	757
4	drug administration route'/de	7723
5	parenteral drug administration'/de	2058
6	intravascular drug administration'/de	306
7	intravenous drug administration'/de	391097
8	drug administration':lnk	1702061
9	inject*':ti,ab	1071786
10	infusion*':ti,ab	349141
11	(parenteral* NEAR/2 (administ* OR deliver*)):ti,ab	11185
12	intravenous*':ti,ab	476886
13	intra venous*':ti,ab	1420
14	intravascular*':ti,ab	66317
15	intra vascular*':ti,ab	668
16	drug therapy'/de	693324
17	drug therapy':lnk	3806966
18	nutrition supplement'/exp	17309
19	parenteral nutrition'/exp	49464
20	mineral supplementation'/de	1582
21	nutritional support'/de	18496
22	(nutrition* NEAR/2 (parenteral* OR supplement* OR support*)):ti,ab	52226

23	therap*':ti,ab	4013225
24	drug dose':lnk	620195
25	(molybd* NEAR/3 deficien*):ti,ab	377
26	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25	8746082
27	#3 AND #26	83
28	[animals]/lim NOT [humans]/lim	5966287
29	#27 NOT #28	43
30	#27 NOT #28 AND [english]/lim	38

Embase search strategy 2

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: January 22, 2019
- Limits: Humans (search hedge); English language
- Number of results: 202
- Notes: Decision was made to expand initial search from 'sodium molybdate' to 'molybdate'

1	molybdenum'/de	15436
2	molybdate sodium'/de	391
3	molybd*':ti,ab,tn	14751
4	dimolybd*':ti,ab,tn	134
5	#1 OR #2 OR #3 OR #4	23109
6	drug administration route'/de	7746
7	parenteral drug administration'/de	2084
8	intravascular drug administration'/de	310
9	intravenous drug administration'/de	391481
10	parenteral nutrition'/exp	49617
11	drug administration':lnk	1708199
12	inject*':ti,ab	1076218

13	infusion*':ti,ab	350621
14	(parenteral* NEAR/2 (administ* OR deliver* OR nutrition* OR therap* OR treat* OR supplement*)):ti,ab	45807
15	intravenous*':ti,ab	478913
16	intra venous*':ti,ab	1428
17	intravascular*':ti,ab	66570
18	intra vascular*':ti,ab	671
19	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	3334153
20	drug therapy'/de	702755
21	drug therapy':lnk	3820591
22	nutrition supplement'/exp	17481
23	mineral supplementation'/de	1619
24	nutritional support'/de	18578
25	molybdenum deficiency'/de	10
26	((mineral\$ OR 'trace element\$' OR ultratrace OR 'ultra trace') NEAR/3 supplement*):ti,ab	4113
27	(molybd* NEAR/3 deficien*):ti,ab	379
28	therap*':ti,ab	4038293
29	treat*':ti,ab	7705692
30	#20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29	11301155
31	#5 AND #19 AND #30	410
32	[animals]/lim NOT [humans]/lim	5983555
33	#31 NOT #32	224
34	#31 NOT #32 AND [english]/lim	202

Appendix 2. Survey instrument for professional medical associations

Welcome. We want to understand your clinical use of compounded sodium molybdate. 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)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

2. Do you prescribe or administer sodium molybdate to your patients?

- Yes
- No

3. I prescribe or administer sodium molybdate for the following conditions or diseases: (check all that apply)

- Molybdenum deficiency
- Nutritional supplementation
- Other (please explain) _____

4. I use sodium molybdate with my patients as the following: (check all that apply)

- FDA-approved drug product
- Compounded drug product
- Over-the-counter drug product
- Dietary supplement (e.g. vitamin or herbal supplement sold in retail)
- Other (please describe) _____

5. I use compounded sodium molybdate because: (check all that apply)
- Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
 - Patient allergies prevent me from using commercially available products. (please explain) _____
 - Patient conditions prevent me from using commercially available products. (please explain) _____
 - There are no commercially available products containing sodium molybdate.
 - Other (please explain) _____
6. Do you stock non-patient-specific compounded sodium molybdate at your practice?
- Yes
 - No
 - I'm not sure
7. I obtain compounded sodium molybdate from the following: (check all that apply)
- Compound myself at my practice
 - Have the product compounded by an in-house pharmacy
 - Purchase, or have a patient purchase, from a compounding pharmacy
 - Purchase, or have a patient purchase, from an outsourcing facility
 - Other (please explain) _____
8. What is your practice setting? (check all that apply)
- Physician office/private practice
 - Outpatient clinic
 - Hospital/health system
 - Academic medical center
 - Emergency room
 - Operating room
 - Other (please describe) _____
9. What degree do you hold? (check all that apply)
- Doctor of Medicine (MD)
 - Doctor of Osteopathic Medicine (DO)
 - Doctor of Medicine in Dentistry (DMD/DDS)
 - Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
 - Naturopathic Doctor (ND)
 - Nurse Practitioner (NP)
 - Physician Assistant (PA)
 - 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 (AAAAI)	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

^aAssociations that declined in Year 1 were not contacted in Year 2.