Methylsulfonylmethane: Summary Report

Summary Report

Methylsulfonylmethane

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

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

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REVIEW OF NOMINATIONS

Methylsulfonylmethane (MSM; UNII code: 9H4PO4Z4FT) was nominated for inclusion on the 503B Bulks List by McGuff Compounding Pharmacy Services, Inc. (McGuff CPS), the American Association of Naturopathic Physicians (AANP), the Alliance for Natural Health USA (ANH-USA), and the Integrative Medicine Consortium (IMC). MSM was nominated for use in osteoarthritis and there may be a benefit in alleviating GI upset, musculoskeletal pain, allergies, boosting the immune system, and fighting antimicrobial infection. MSM will be compounded as a 150mg/mL preservative-free intravenous injection.

Reasons provided for nomination to the 503B Bulks List include that there are no FDA-approved injectable products containing MSM as a single active pharmaceutical ingredient (API) or in a combination, in the concentration prescribed. Additionally, the FDA-approved drugs available are more potent chemicals with more severe side effects.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of MSM 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 MSM; name variations of MSM 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 MSM. 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 August 27, 2018. The search included a combination of (methylsulfonylmethane[TIAB] OR “dimethyl sulfone”[TIAB] OR “methyl sulfone”[TIAB] OR DMSO2[TIAB]) AND (therapy[TIAB] OR therapeutic[TIAB] OR treatment[TIAB] OR clinical[TIAB] OR osteoarthritis[TIAB] OR collagen[TIAB] OR

inflammation[TIAB] OR muscle[TIAB] OR pain[TIAB] OR gastro*[TIAB] OR allerg*[TIAB] OR immun*[TIAB]) AND (humans[MeSH Terms] AND English[lang]) NOT autism. Peer-reviewed articles as well as grey literature were included in the search. Search results from each database were exported to Covidence®, merged, and sorted for removal of duplicate citations.

Study selection

Articles were not excluded on the basis of study design. Articles were considered relevant based on the identification of a clinical use of MSM or the implementation of MSM 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.

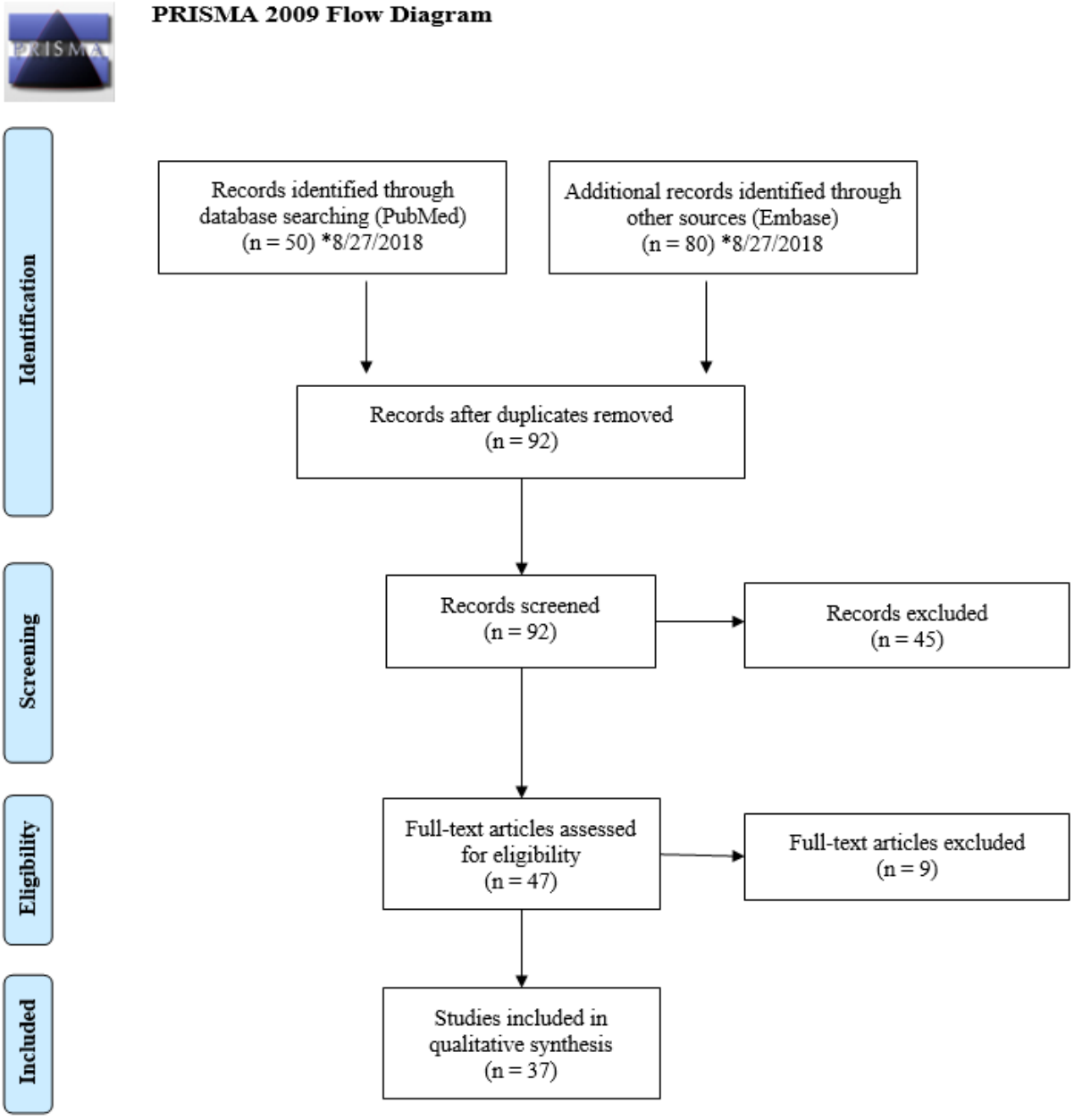
Data extraction

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

Results

Please refer to Figure 1.

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



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

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

Outreach to medical specialists and specialty organizations

Using the indications from the nominations and the results of the literature review, nine (9) medical specialties that would potentially use MSM were identified: allergy and immunology, infectious disease, naturopathy, otolaryngology, pain medicine, pain management, primary care, rheumatology, and urology. Semi-structured interviews were conducted with subject matter experts within these specialties. Interviews lasted from 30-75 minutes and were conducted either via telephone or in-person. Criteria for selecting subject matter experts included recommendations provided by specialty professional associations, convenient geographic location, authorship within the specialty, or referral by an interviewee. Up to nine (9) interviews were conducted per substance. Five (5) people were contacted for interviews, of which two (2) accepted. Two (2) otolaryngologists were contacted for interviews. One (1) otolaryngologist referred us to a colleague. The referred otolaryngologist indicated interest but did not respond to the interview request. A national organization specializing in rheumatology was contacted for assistance in identifying a specialist; they replied with a statement that even though MSM is indicated for rheumatology, the clinical use is not very prevalent, and they were unable to identify an expert to provide more information about utilization. The 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 allergy and immunology, infectious disease, naturopathy, otolaryngology, pain medicine, pain management, primary care, rheumatology, and urology, 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 14 associations. If an association had more than one (1) substance with indications relevant to that specialty, substances were combined into one (1) survey with no more than 14 substances per survey. Table 1 highlights the associations that agreed to distribute the survey link and Table 2 includes the associations that declined to participate. Additionally, single substance surveys were created and posted on the project website which was shared with survey participants.

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

Table 1. Participating associations

Specialty	Association
Allergy/Immunology	American Academy of Allergy, Asthma and Immunology (AAAI)
Naturopathy	American Association of Naturopathic Physicians (AANP)
Pain Medicine	American Academy of Pain Medicine (AAPM)
Primary Care	American Academy of Environmental Medicine (AAEM)
Rheumatology	American College of Rheumatology (ACR)

Table 2. Associations that declined participation

Specialty	Association	Reasons for Declining
Allergy/Immunology	American College of Allergy, Asthma & Immunology (ACAAI)	Declined, "unaware of any bulk drug substances used by allergies in their practices"
Medicine	American Medical Association (AMA)	Failed to respond
	American Osteopathic Association (AOA)	Failed to respond
Otolaryngology	American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS)	Failed to respond
	American Academy of Otolaryngic Allergy (AAOA)	Declined stating that they did not think otolaryngologists were the target market for the survey
	American Rhinologic Society (ARS)	Declined stating they do not send out surveys unless they are requested by a member; unable to identify a member to request survey distribution
Primary Care	American Academy of Family Physicians (AAFP)	Failed to respond
	American College of Physicians (ACP)	Failed to respond
Urology	American Urology Association (AUA)	Declined, "our physicians are inundated with surveys and I'm afraid you won't be able to get the information you need"

CURRENT AND HISTORIC USE

Summary of background information

- MSM is not available as an FDA-approved product.
- MSM is available as an oral OTC supplement in the US in combination with other substances.
- There is a current United States Pharmacopeia (USP) dietary monograph for MSM.
- MSM is not available in any of the national medical registries searched.

Table 3. Currently approved products – US

No approved products in the US

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

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

Summary of literature review

- Total number of studies included: 37 (9 descriptive, 23 experimental, 5 observational).
- Most of the studies were from the US (14).
- The most common indication for use of MSM in the US was exercise-induced muscle damage, followed by osteoarthritis. The most common indication from the non-US studies was osteoarthritis.
- Compounded products were identified from both the US and non-US studies; however, only one (1) study used MSM for osteoarthritis but a topical formulation was used.

Table 5. Types of studies

Types of Studies	Number of Studies
Descriptive[1-9]	9
Experimental[10-32]	23
Observational[33-37]	5

Table 6. Number of studies by country

Country	Number of Studies
Australia[7]	1
Canada[36]	1
China[32]	1
India[19,29,30]	3

Indonesia[23]	1
Iran[10]	1
Israel[17]	1
Italy[12-16,18,20,26,27]	9
Japan[25]	1
Switzerland[1]	1
UK[2,3,6]	3
US[4,5,8,9,11,21,22,24,28,31,33-35,37]	14
	Total US: 14 Total non-US Countries: 23

Table 7. Number of studies by combinations

No combination products were nominated

Table 8. Dosage by indication – US[a]

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Exercise-induced muscle damage[4,9,21,24,31]	3g/day	–	Capsule	Oral	23-28 days
	2-4g/day	–	–	–	14 days
Osteoarthritis[4,8,9,22]	2-6g/day	–	Capsule	Oral	12 weeks
	2-3g/day	–	–	–	At least 6 weeks
Interstitial cystitis[5,9]	30-50cc	–	–	Intravesical	Once-6 months
Oxidative stress[4,35]	3g/day	–	–	–	28 days
Seasonal allergic rhinitis[4,11]	2.6-5.2g/day	–	Capsule	Oral	30-44 days
Fibromyalgia[37]	–	–	–	–	–
Inflammation[34]	–	–	–	–	–
Photodamage, superficial scarring, melasma[4]	–	–	–	–	–
Prevent knee pain[28]	3g/day	–	Tablet	Oral	At least 8 weeks
Rotator cuff tear repair[4]	–	–	–	–	–
Scar, burn[33]	–	5%	Gel	Topical	–
Severe X-linked type ichthyosis[4]	–	–	Moisturizer	Topical	4 weeks

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

Table 9. Dosage by indication – non-US countries[a]

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Osteoarthritis[1-3,6,7,17,19,23,25-27,30,32,36]	500mg-6g/day	–	Capsule, Tablet, Sachet	Oral	12 weeks-3 months
	Apply 4.5g/day	5%	Gel	Topical	12 weeks
Allergies[6]	–	–	–	–	–
Chemotherapy-induced peripheral neuropathy (CIPN)[18]	200mg/day	–	Capsule	Oral	12 weeks
Chronic bacterial prostatitis[15]	900mg/day	–	Sachet	Oral	14 days
Constipation[6]	–	–	–	–	–
Dyspareunia in fibromyalgia[14]	Place 3x/day	–	–	Sublingual	2 months
Exercise-induced muscle damage[10]	50mg/kg/day	–	–	Oral	10 days
Hyperacidity[6]	–	–	–	–	–
Immunomodulation[6]	–	–	–	–	–
Nail psoriasis[16]	Apply 1x/day	–	Nail lacquer	Topical	24 weeks
Parasites[6]	–	–	–	–	–
Photodamage, superficial scarring, melasma[13]	1 session/2 weeks	–	Peel	Topical	4 peeling sessions
Pitting edema[29]	Apply 2x/day	5.4%	Lotion	Topical	1-2 weeks
Rosacea[12]	Apply 2x/day	–	Cream	Topical	1 month
Rotator cuff repair[20]	2 sachets/day	–	Sachet	Oral	3 months

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

Table 10. Compounded products – US

Indication	Publication Year	Compounding Method	Dosage Form	Final Strength
Scars, burns[33]	2018	• MSM with naltrexone and caffeine in anhydrous silicone base with carapa guaianensis plant seed oil	Gel	5%

Table 11. Compounded products – non-US countries

Indication	Compounding Method	Dosage Form	Final Strength
Exercise-induced muscle damage[10]	• MSM in water	Solution	–
Osteoarthritis[19]	• MSM with Carbopol 940, propylene glycol, ethanol, triethanolamine, methylparaben, and either Aloe Vera gel or sesame oil	Gel	5%
	• MSM with sodium carboxymethylcellulose, propylene glycol, methylparaben, and either Aloe Vera gel or sesame oil	Gel	5%

Abbreviation: "–", not mentioned.

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

Three (3) interviews were conducted. One (1) interview was cut short and a follow-up interview was needed to continue the discussion.

Table 12. Overview of interviewees

Interviewee	Level of Training	Specialty	Current Practice Setting	Experience with MSM	Interview Summary Response
NAT_01, NAT_02	ND	No Board Specialty	Private Practice	Yes	• Uses oral and topical products. • Does not stock in office. • Uses as an injection if necessary.
PED_01	MD	Internal Medicine Pediatrics HIV Medicine	Academic medical institution	No	• Has seen other people use it; "I don't know if it was positive reinforcement or if it was actually the supplementation."

Abbreviations: MD, Doctor of Medicine; ND, Naturopathic Doctor.

MSM indications, dosage forms, and doses

- The interviewee stated that they typically use MSM orally but uses a transdermal cream as well.
    - Doses 1000mg three times per day, usually for joint pain and "for finding of mercury to excrete it from the body."
    - MSM is used for "Anybody with metal fillings in their mouth, mercury amalgams, anybody with joint pain. Not anybody with joint pain, but some patients with joint pain, and then people who have found to have mercury toxicity."
    - They reported obtaining oral MSM through supplement companies, and transdermal cream through a compounding pharmacy.
- The interviewee stated that they usually use MSM for joint pain, to increase glutathione (if unable to tolerate oral glutathione), to find mercury, and as an antioxidant. The interviewee considers MSM to be first line therapy for autism, mercury fillings, and joint pain.
    - The interviewee usually gives it orally; intravenous routes are only used if patient cannot tolerate oral dosing, especially since the interviewee is not allowed to inject medications.
    - Reasons the interviewee might obtain compounded MSM would be for a cream for a child with autism or if the patient had an allergy/sensitivity.

MSM as office stock

- The interviewee stated that they typically write a patient-specific prescription for MSM.
    - They typically prescribe it five or six times per year, but that their office uses a lot of it. The interviewee felt that the body does a good job with getting rid of things on its own but will try MSM if necessary.

Why MSM over other FDA-approved products

- The interviewee stated they do not know many FDA products approved for mercury toxicity, therefore it is their first line for that.

Summary of survey results

Table 13. Characteristics of survey respondents [25 people responded to the survey[a]]

Board Certification	DO	MD	ND	No Response
Allergy and Immunology	0	1	0	0
Anesthesiology	0	1	0	0
Cardiovascular Disease	0	0	0	1
Fellow of the American Board of Naturopathic Oncology	0	0	1	0
Naturopathic Doctor	0	0	6	0
Naturopathic Physician	0	0	5	0
Neurology	0	1	0	0
Pain Medicine	0	3	0	0
Rheumatology	1	0	0	0
No Board Certification	0	1	2	0
No Response	0	0	0	10

Abbreviations: DO, Doctor of Osteopathic Medicine; MD, Doctor of Medicine; ND, Naturopathic Doctor.
[a]Some 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=7[a])
Compounded	1
FDA-approved	0
Over-the-counter	2
Dietary	5
No Response	1

[a]Out of 25 respondents, seven (7) reported using, prescribing, or recommending multiple types of MSM product.

Table 15. Compounded use of MSM in practice

No survey respondents provided this information

Table 16. Indications for which MSM is considered a standard therapy[a]

Indication	Standard Therapy		
	Compounded, n (N=1)	Non-compounded, n (N=5)	No Response, n (N=1)
Arthritis	0	1	0
Joint pain	0	3	0
Other[b]	0	1	0
Skin integrity	0	1	0
No Response	1	0	1

[a]Some respondents reported multiple indications.
[b]"Varies depending on individual patient circumstances."

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

Reasons
"Inflam [*sic*]"

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

	Respondents, n (N=1)
No–use has remained consistent	0
Yes–I use it LESS often now	1
Yes–I use it MORE often now	0

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

	Respondents, n (N=1)
No	1
Yes	0

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

No survey respondents provided this information

CONCLUSION

MSM (UNII code: 9H4PO4Z4FT) was nominated for inclusion on the 503B Bulks List for use in osteoarthritis and there may be a benefit in alleviating GI upset, musculoskeletal pain, allergies, boosting the immune system, and fighting antimicrobial infection as an intravenous injection. MSM is not approved in any of the national medical registries searched.

From the literature review conducted, the most common indications were exercise-induced muscle damage and osteoarthritis. Compounded products were identified from both the US and non-US studies; however, only one (1) study reported using MSM for osteoarthritis. In addition, this study used topical MSM, rather than the nominated intravenous ROA.

One (1) interviewee stated that they typically use MSM orally or topically but does use it as an injection if necessary. The injections are used infrequently, especially since the interviewee is not allowed to inject medications. They use it for joint pain, for mercury toxicity, to increase glutathione, and as an antioxidant. The interviewee typically writes a patient-specific prescription for MSM and prescribes it about five or six times per year, but said the interviewee stated that others in the office use it frequently. The other interviewee stated that they have seen MSM used, but has never used it themselves, and does not know if benefits from use are related to positive reinforcement or the supplement itself.

From the survey responses, seven (7) out of 25 respondents reported using, prescribing, or recommending multiple types of MSM product, one (1) of which reported using compounded products. However, no information was provided regarding indications for compounded MSM, and the respondent stated that over the past 5 years, their use of MSM has decreased. The respondent does not stock non-patient-specific compounded MSM in their practice. The most common indication respondents reported using non-compounded MSM for was joint pain.

APPENDICES

Appendix 1. References

1. Ameye LG, Chee WSS. Osteoarthritis and nutrition. From nutraceuticals to functional foods: a systematic review of the scientific evidence. *Arthritis Research & Therapy.* 2006;8(4):R127-R127.
2. Brien S, Prescott P, Bashir N, Lewith H, Lewith G. Systematic review of the nutritional supplements dimethyl sulfoxide (DMSO) and methylsulfonylmethane (MSM) in the treatment of osteoarthritis. *Osteoarthritis and Cartilage.* 2008;16(11):1277-1288.
3. Brien S, Prescott P, Lewith G. Meta-Analysis of the Related Nutritional Supplements Dimethyl Sulfoxide and Methylsulfonylmethane in the Treatment of Osteoarthritis of the Knee. *Evidence-based Complementary & Alternative Medicine (eCAM).* 2011;8(1):1-12.
4. Butawan M, Benjamin RL, Bloomer RJ. Methylsulfonylmethane: Applications and Safety of a Novel Dietary Supplement. *Nutrients.* 2017;9(3).
5. Childs SJ. Dimethyl sulfone (DMSO2) in the treatment of interstitial cystitis. *The Urologic Clinics Of North America.* 1994;21(1):85-88.
6. Ely A, Lockwood B. What is the evidence for the safety and efficacy of dimethyl sulfoxide and methylsulfonylmethane in pain relief? *Pharmaceutical Journal.* 2002;269:685-687.
7. Liu X, Machado G, Eyles J, Ravi V, Hunter D. Dietary supplements for treating osteoarthritis: A systematic review and meta-analysis. *Osteoarthritis and Cartilage.* 2017;25:S292-S293.
8. Nahin RL, Boineau R, Khalsa PS, Stussman BJ, Weber WJ. Evidence-Based Evaluation of Complementary Health Approaches for Pain Management in the United States. *Mayo Clinic Proceedings.* 2016;91(9):1292-1306.
9. Parcell S. Sulfur in human nutrition and applications in medicine. *Alternative Medicine Review: A Journal Of Clinical Therapeutic.* 2002;7(1):22-44.
10. Barmaki S, Bohlooli S, Khoshkhahesh F, Nakhostin-Roohi B. Effect of methylsulfonylmethane supplementation on exercise - Induced muscle damage and total antioxidant capacity. *Journal of Sports Medicine & Physical Fitness.* 2012;52(2):170-174.
11. Barrager E, Veltmann JR, Jr., Schauss AG, Schiller RN. A multicentered, open-label trial on the safety and efficacy of methylsulfonylmethane in the treatment of seasonal allergic rhinitis. *Journal of Alternative & Complementary Medicine.* 2002;8(2):167-173.
12. Berardesca E, Cameli N, Cavallotti C, Levy JL, Piérard GE, de Paoli Ambrosi G. Combined effects of silymarin and methylsulfonylmethane in the management of rosacea: clinical and instrumental evaluation. *Journal of Cosmetic Dermatology.* 2008;7(1):8-14.
13. Berardesca E, Cameli N, Primavera G, Carrera M. Clinical and instrumental evaluation of skin improvement after treatment with a new 50% pyruvic acid peel. *Dermatologic Surgery: Official Publication For American Society For Dermatologic Surgery [Et Al].* 2006;32(4):526-531.
14. Bettoni L, Facchetti S, Bani L, Manisco L. Dyspareunia in fibromyalgic women: Is there a role for antioxidant agents? *Sexologies.* 2010;19:S69.
15. Cai T, Tiscione D, Gallelli L, et al. Serenoa repens associated with selenium and lycopene extract and bromelain and methylsulfonylmethane extract are able to improve the efficacy of levofloxacin in chronic bacterial prostatitis patients. *Archivio Italiano di Urologia, Andrologia: Organo Ufficiale di Societí.* 2016;88(3):177.

16. Cantoresi F, Caserini M, Bidoli A, et al. Randomized controlled trial of a water-soluble nail lacquer based on hydroxypropyl-chitosan (HPCH), in the management of nail psoriasis. *Clinical, Cosmetic and Investigational Dermatology.* 2014(default):185.

17. Debbi EM, Agar G, Fichman G, et al. Efficacy of methylsulfonylmethane supplementation on osteoarthritis of the knee: a randomized controlled study. *BMC Complementary And Alternative Medicine.* 2011;11:50-50.

18. Desideri I, Francolini G, Becherini C, et al. Use of an alpha lipoic, methylsulfonylmethane and bromelain dietary supplement (Opera®) for chemotherapy-induced peripheral neuropathy management, a prospective study. *Medical Oncology.* 2017;34(3).

19. Ghorpade V, Mali K, Dias R, Karande P. Carbopol and sodium carboxymethylcellulose based methylsulfonylmethane gels for treatment of osteoarthritis: In-vitro and In-vivo evaluation. *Indian Journal of Pharmaceutical Education and Research.* 2012;46(3):235-242.

20. Gumina S, Passaretti D, Gurzì MD, Candela V. Arginine L-alpha-ketoglutarate, methylsulfonylmethane, hydrolyzed type i collagen and bromelain in rotator cuff tear repair: A prospective randomized study. *Current Medical Research and Opinion.* 2012;28(11):1767-1774.

21. Kalman D, Feldman S, Samson A, Krieger D. A randomized double blind placebo controlled evaluation of MSM for exercise induced discomfort/pain. *FASEB Journal.* 2013;27.

22. Kim LS, Axelrod LJ, Howard P, Buratovich N, Waters RF. Efficacy of methylsulfonylmethane (MSM) in osteoarthritis pain of the knee: A pilot clinical trial. *Osteoarthritis and Cartilage.* 2006;14(3):286-294.

23. Lubis AMT, Siagian C, Wonggokusuma E, Marsetyo AF, Setyohadi B. Comparison of Glucosamine-Chondroitin Sulfate with and without Methylsulfonylmethane in Grade I-II Knee Osteoarthritis: A Double Blind Randomized Controlled Trial. *Acta medica Indonesiana.* 2017;49(2):105-111.

24. Melcher DA, Lee SR, Peel SA, Papaquette MR, Bloomer RJ. Effects of methylsulfonylmethane supplementation on oxidative stress, muscle soreness, and performance variables following eccentric exercise. *Gazzetta Medica Italiana Archivio per le Scienze Mediche.* 2017;176(5):271-283.

25. Nakasone Y, Watabe K, Watanabe K, et al. Effect of a glucosamine-based combination supplement containing chondroitin sulfate and antioxidant micronutrients in subjects with symptomatic knee osteoarthritis: A pilot study. *Experimental and Therapeutic Medicine.* 2011;2(5):893-899.

26. Notarnicola A, Maccagnano G, Moretti L, et al. Methylsulfonylmethane and boswellic acids versus glucosamine sulfate in the treatment of knee arthritis: Randomized trial. *International Journal of Immunopathology and Pharmacology.* 2016;29(1):140-146.

27. Notarnicola A, Tafuri S, Fusaro L, Moretti L, Pesce V, Moretti B. The "mESACA" study: Methylsulfonylmethane and boswellic acids in the treatment of gonarthrosis. *Advances in Therapy.* 2011;28(10):894-906.

28. Tennent DJ, Hylden CM, Kocher BK, Aden JK, Johnson AE. A Randomized Controlled Trial Evaluating Methylsulfonylmethane Versus Placebo to Prevent Knee Pain in Military Initial Entry Trainees. *US Army Medical Department Journal.* 2017:21-25.

29. Tripathi R, Gupta S, Rai S, Mittal PC. Effect of topical application of methylsulfonylmethane (MSM), EDTA on pitting edema and oxidative stress in a double blind, placebo-controlled study. *Cellular And Molecular Biology (Noisy-Le-Grand, France).* 2011;57(1):62-69.

30. Usha PR, Naidu MUR. Randomised, Double-Blind, Parallel, Placebo-Controlled Study of Oral Glucosamine, Methylsulfonylmethane and their Combination in Osteoarthritis. *Clinical Drug Investigation.* 2004;24(6):353-363.

31. Withee ED, Tippens KM, Dehen R, Tibbitts D, Hanes D, Zwickey H. Effects of Methylsulfonylmethane (MSM) on exercise-induced oxidative stress, muscle damage, and pain following a half-marathon: a double-blind, randomized, placebo-controlled trial. *Journal Of The International Society Of Sports Nutrition.* 2017;14:24-24.

32. Xie Q, Shi R, Xu G, Cheng L, Shao L, Rao J. Effects of AR7 Joint Complex on arthralgia for patients with osteoarthritis: results of a three-month study in Shanghai, China. *Nutrition Journal.* 2008;7:31-31.

33. Harris D, Visser J, Hurwitz P, Dietze D. Physician- and patient-reported outcomes following use of a compounded scar/burn gel: Results from a prospective observational survey study. *Journal of Burn Care and Research.* 2018;39:S94.

34. Kantor ED, Lampe JW, Vaughan TL, Peters U, Rehm CD, White E. Association between use of specialty dietary supplements and c-reactive protein concentrations. *American Journal of Epidemiology.* 2012;176(11):1002-1013.

35. Kantor ED, Ulrich CM, Owen RW, et al. Specialty supplement use and biologic measures of oxidative stress and DNA damage. *Cancer Epidemiology Biomarkers and Prevention.* 2013;22(12):2312-2322.

36. Tsui T, Boon H, Boecker A, Kachan N, Krahn M. Understanding the role of scientific evidence in consumer evaluation of natural health products for osteoarthritis an application of the means end chain approach. *BMC Complementary and Alternative Medicine.* 2012(1):198.

37. Wall GC, Krypel LL, Miller MJ, Rees DM. A pilot study of complementary and alternative medicine use in patients with fibromyalgia syndrome. *Pharmacy Practice.* 2007(4):185.

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 **methylsulfonylmethane (MSM)**. 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: Methylsulfonylmethane (MSM)

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

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

Display This Question:

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

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

Display This Question:

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

Q4. Please list all combination products in which you use compounded **methylsulfonylmethane (MSM)**.

_____

Q5. For which, if any, diseases or conditions do you consider compounded **methylsulfonylmethane (MSM)** standard therapy?

_____

Q6. Does your specialty describe the use of compounded **methylsulfonylmethane (MSM)** in medical practice guidelines or other resources?

_____

Q7. Over the past 5 years, has the frequency in which you have used compounded **methylsulfonylmethane (MSM)** changed?

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

Q8. Why do you use compounded **methylsulfonylmethane (MSM)** instead of any FDA-approved drug product? _____

Q9. Do you stock non-patient-specific compounded **methylsulfonylmethane (MSM)** in your practice location?

- Yes
- No

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

Display This Question:

If Do you stock non-patient-specific compounded methylsulfonylmethane (MSM) in your practice location? = Yes

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

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

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

Q13. For which, if any, diseases or conditions do you consider **methylsulfonylmethane (MSM)** standard therapy? _____

Q14. Does your specialty describe the use of **methylsulfonylmethane (MSM)** in medical practice guidelines or other resources?

_____

End of Block: Methylsulfonylmethane (MSM)

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