

Summary Report

Malic Acid

Prepared for:

Food and Drug Administration

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

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REVIEW OF NOMINATION

Malic acid (UNII code: 817L1N4CKP) was nominated for inclusion on the 503B Bulks List by Specialty Sterile Pharmaceutical Society for prevention of reperfusion injury via a 27g irrigation solution.

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

- Prescribers and hospital formularies have different preferences or requirements for concentrations, volumes, or final product containers for administration.
- It is relatively unsafe to expose the direct compounding area to hundreds of vials or ampules and hundreds of aseptic manipulations during the compounding of a typical batch size for an outsourcing facility; compounding from bulk is more safe and efficient.
- Commercially available finished products have an inherent variance in potency creating an uncertain final concentration for the new product.
- Use of state-of-the-art equipment, like the SKAN isolator technology, requires the use of bulk starting materials.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of malic acid 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 malic acid; name variations of malic acid 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 malic acid. 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 March 30, 2019. The search included a combination of ("malic acid"[TIAB] OR malate[TIAB]) AND (clinical[TIAB] OR treat*[TIAB] OR therapeutic*[TIAB] OR therapy[TIAB] OR reperfusion[TIAB] OR

heart[TIAB] OR cardi*[TIAB] OR ischemi*[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 malic acid or the implementation of malic acid 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.

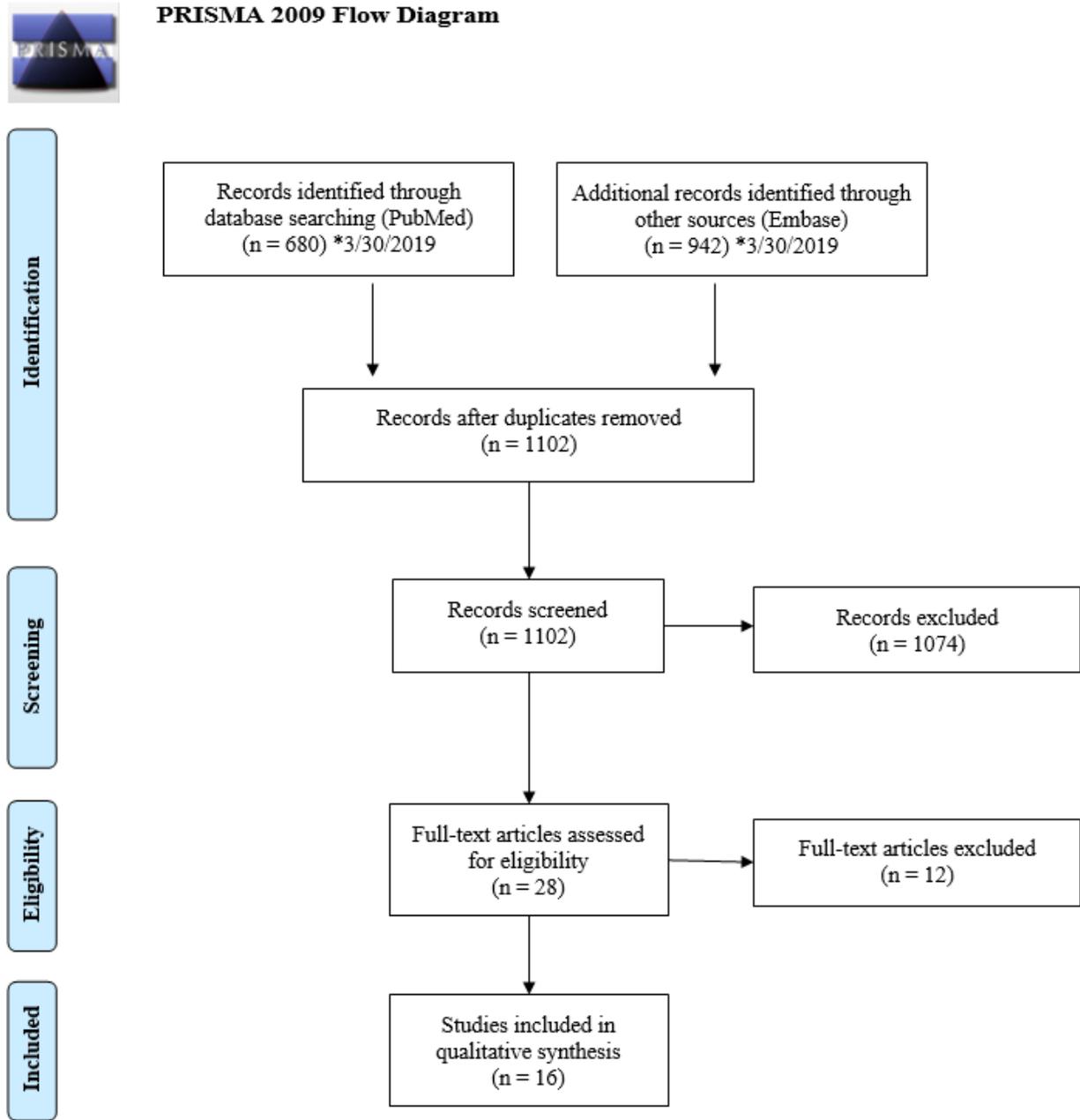
Data extraction

A standard data extraction form was used to collect study authors; article title; year published; journal title; country; indication for malic acid 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 malic acid 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 nomination and the results of the literature review, six (6) medical specialties that would potentially use malic acid were identified: cardiology, dentistry, dermatology, neurology, oral medicine, and rheumatology. 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. One (1) expert was contacted for interviews, of which one (1) accepted and zero (0) declined interviews. The interview was 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 cardiology, dentistry, dermatology, naturopathy, neurology, oral medicine, and rheumatology, identified from the nomination, literature review, and interview, 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 eight (8) 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
Dermatology	American Academy of Dermatology (AAD)
	American Society for Dermatologic Surgery (ASDS)
Oral Medicine	American Academy of Oral Medicine (AAOM)
Rheumatology	American College of Rheumatology (ACR)

Table 2. Associations that declined participation

Specialty	Association	Reasons for Declining
Dentistry	American Dental Association (ADA)	Declined - ADA concluded that “this issue does not affect enough dentists to warrant a significant investment of time”
Medicine	American Medical Association (AMA)	Failed to respond
	American Osteopathic Association (AOA)	Failed to respond
Neurology	American Academy of Neurology (AAN)	Failed to respond

CURRENT AND HISTORIC USE

Summary of background information

- Malic acid is not available as an FDA-approved product.
- Malic acid is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for malic acid.
- Malic acid is not available in any of the foreign medicine 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: 16 studies (2 descriptive and 14 experimental).
- Most of the studies were from the US (6).
- There was not a most common indication for the use of malic acid in the US. Indications for use in the US studies included: Alzheimer’s disease, fibromyalgia, melasma, prevention of rhinovirus infection, propionic academia, and rheumatoid arthritis. The most common indication from the non-US studies was xerostomia.
- No compounded products were identified from any studies.

Table 5. Types of studies

Types of Studies	Number of Studies
Descriptive ^{1,2}	2
Experimental ³⁻¹⁶	14
Observational	0

Table 6. Number of studies by country

Country	Number of Studies
Chile ⁹	1
Germany ⁸	1
India ^{2,11}	2
Italy ^{3,4}	2
Romania ¹	1
Spain ⁵⁻⁷	3
US ^{10,12-16}	6
Total US: 6 Total non-US Countries: 10	

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
Alzheimer's disease ¹⁶	10g/day	5g	Liquid	Oral	1 year
Fibromyalgia ¹²	1.2-2.4g/day	0.2g	Tablet	Oral	4 weeks-6 months
Melasma ¹⁴	–	6-10%	–	Topical	1-2 months
Prevention of rhinovirus infection ¹⁵	–	2%	Lotion	Topical	9 weeks
Propionic academia ¹⁰	–	–	–	Oral	–
Rheumatoid arthritis ¹³	0.3-0.4mL/day	8mg/mL	Injection, solution	–	30-40 days

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

Table 9. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Xerostomia ^{2-7,9}	–	1%	Spray, solution	Oral, topical	2 days-6 months
Calculus deposits on teeth ¹¹	–	5%	Solution	Oral	15 days
DL-2HGA metabolic disorder ⁸	–	–	–	–	–
Recalcitrant warts ¹	–	10g/10mL	–	Topical	10 days

Abbreviations: “–”, not mentioned; ROA, route of administration; DL-2HGA, D, L-2-hydroxyglutaric aciduria.

Table 10. Compounded products – US

No compounded products from reported studies

Table 11. Compounded products – non-US countries

No compounded products from reported studies

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

One (1) interview was conducted.

Table 12. Overview of interviewee

Interviewee	Level of Training	Specialty	Current Practice Setting	Experience with Malic acid	Interview Summary Response
DER_06	MD	Dermatology Dermatology/Immunology	Independent Consultant	No	<ul style="list-style-type: none"> Does not use this substance

Abbreviation: MD, Doctor of Medicine.

Summary of survey results

Table 13. Characteristics of survey respondents [11 people responded to survey^a]

Board Certification	DMD/DDS	DO	No Response
Oral Medicine	2	0	0
Pain Medicine	1	0	0
Rheumatology	0	1	0
Sleep Medicine	1	0	0
No Board Certification	0	0	0
No Response	0	0	8

Abbreviations: DMD/DDS, Doctor of Medicine in Dentistry; DO, Doctor of Osteopathic Medicine.

^aSome 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=2^a)
Compounded	0
FDA-approved	0
Over-the-counter	0
Dietary	0
Unsure	0
No Response	2

^aOut of 11 respondents, two (2) reported using, prescribing, or recommending malic acid products.

Table 15. Compounded use of malic acid in practice

No survey respondents provided this information

Table 16. Indications for which malic acid is considered a standard therapy

No survey respondents provided this information

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

No survey respondents provided this information

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

No survey respondents provided this information

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

No survey respondents provided this information

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

No survey respondents provided this information

CONCLUSION

Malic acid (UNII code: 817L1N4CKP) was nominated for inclusion on the 503B Bulks List for prevention of reperfusion injury via a 27g irrigation solution. Malic acid is not available as an FDA-approved product, nor is it available in any of the national medicine registries searched.

From the literature review, there was not a most common indication for the use of malic acid in the US. Indications for use in the US studies included: Alzheimer's disease, fibromyalgia, melasma, prevention of rhinovirus infection, propionic academia, and rheumatoid arthritis. The most common indication from the non-US studies was xerostomia. No compounded products were identified from any studies.

The interviewee did not use malic acid.

From the survey responses, two (2) out of 11 respondents used malic acid. The two (2) respondents did not provide further information.

APPENDICES

Appendix 1. References

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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 **malic acid**. 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: Malicacid

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

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

Display This Question:

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

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

Display This Question:

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

Q4. Please list all combination products in which you use compounded **malic acid**.

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

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

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

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

- Yes
- No

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

Display This Question:

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

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

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

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

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

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

End of Block: Malic acid

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