Summary Report

Squaric Acid Dibutyl Ester

Prepared for:

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

Prepared by:

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REVIEW OF NOMINATION

Squaric acid dibutyl ester (SADBE; UNII code: 4RTO57VG65) was nominated for inclusion on the 503B Bulks List by the American Society of Health-System Pharmacists (ASHP) for the treatment of extensive alopecia areata and warts. The nominated administration methods include a topical solution at various strengths; initial treatment starts at 2% followed by and ranges from 0.0001-0.001% for maintenance dosing.

The reason provided for nomination to the 503B Bulks List is that currently there is no available topical sensitizer to treat alopecia areata.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of SADBE 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 SADBE; name variations of SADBE 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(s); strength; form; ROA; status and/or schedule; approval date. Information was recorded only for products with strengths, forms and/or ROAs 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 SADBE. 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 November 30, 2018. The search included a combination of (SADBE[TIAB] OR "squaric acid dibutyl ester"[TIAB] OR "dibutyl squarate"[TIAB]) AND (alopecia[TIAB] OR wart*[TIAB] OR topical[TIAB] OR derm*[TIAB] OR skin[TIAB] OR clinical[TIAB] OR therapy[TIAB] OR therapeutic*[TIAB] OR treatment[TIAB]) AND (humans[MeSH Terms] AND English[lang]) NOT "autistic disorder"[MeSH Terms]. 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 SADBE or the implementation of SADBE 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.

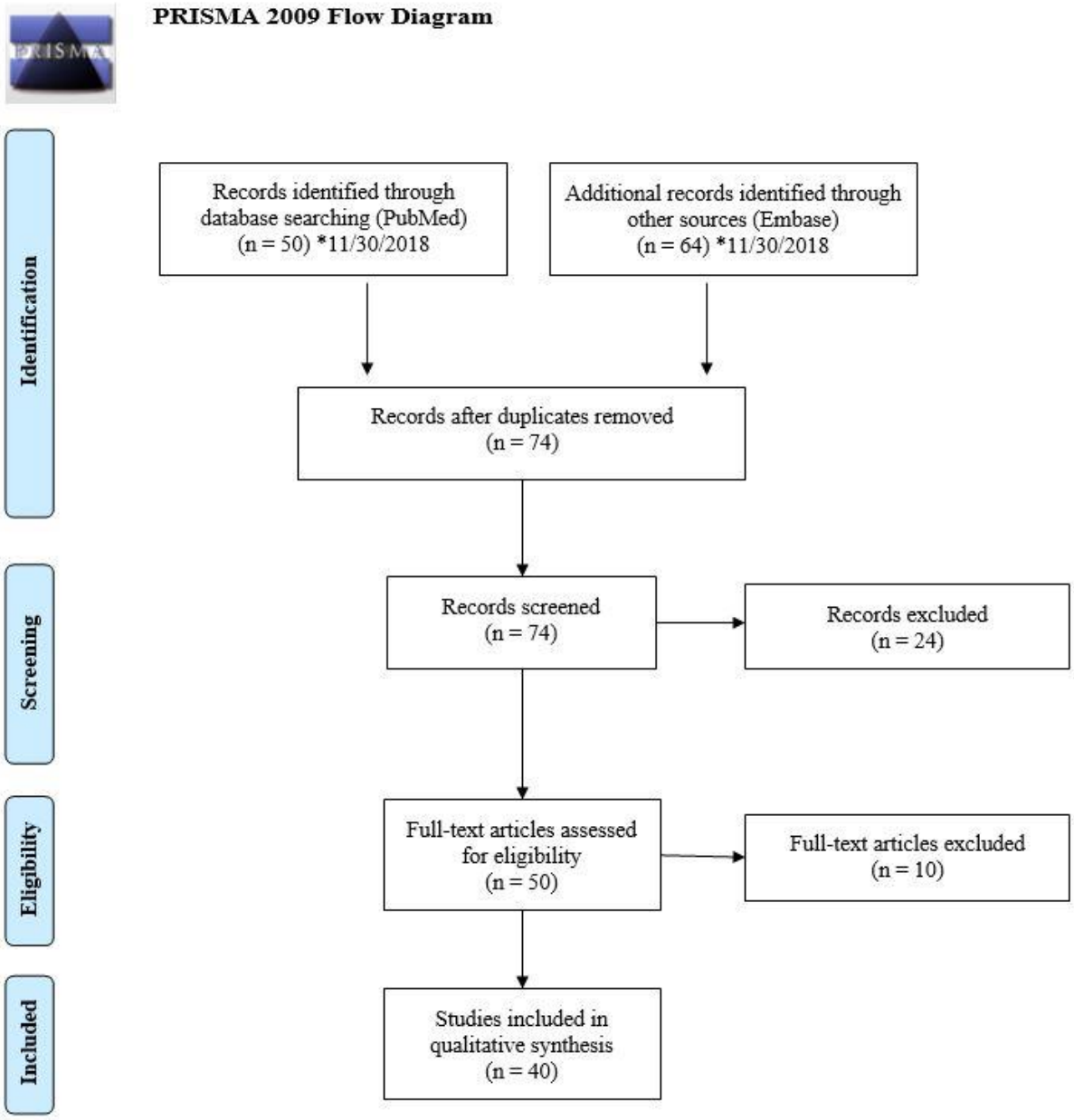
Data extraction

A standard data extraction form was used to collect study authors; article title; year published; journal title; country; indication for SADBE 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 SADBE 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 nomination and the results of the literature review, one (1) medical specialty that would potentially use SADBE was identified: dermatology. Semi-structured interviews were conducted with subject matter experts within this specialty. 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. Two (2) experts were contacted for an interview, of which two (2) 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 dermatology, 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 four (4) 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)

Table 2. Associations that declined participation

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

CURRENT AND HISTORIC USE

Summary of background information

- SADBE is not available as an FDA-approved product.
- SADBE is not available as an OTC product in the US.
- There is no current USP monograph for SADBE.
- SADBE 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 select non-US countries and regions

Summary of literature review

- Total number of studies included: 40 studies (11 descriptive, 20 experimental, and 9 observational).
- Most of the studies were from Italy (12) and the US (12).
- The most prevalent indication for SADBE was alopecia areata followed by warts.
- Application of SADBE ranged from once per month to daily application.
- Compounded SADBE products were identified from US and non-US studies that reflected the nominated indications and dosage form.

Table 5. Types of studies

Types of Studies	Number of Studies
Descriptive[1-11]	11
Experimental[12-31]	20
Observational[32-40]	9

Table 6. Number of studies by country

Country	Number of Studies
Finland[23]	1
Germany[21]	1
India[12]	1
Italy[2,16-18,20,25-29,32,40]	12
Japan[8,9,11,22,31]	5
Korea[7]	1
Poland[10]	1
Singapore[15,35,36]	3
The Netherlands[37]	1
UK[1,13]	2
US[3-6,14,19,24,30,33,34,38,39]	12
	Total US: 12 Total non-US Countries: 28

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
Alopecia areata[3-5,14,19,38,39], totalis[14], and universalis[19]	Apply once every 2 months – daily	0.0001-5%	Solution	Topical	2-24 months
Warts[5,24,30,33,34]	Apply once every month – daily	0.2-5%	Solution	Topical	1-12 months
Epidermodysplasia verruciformis[6]	–	0.2, 2%	Solution	Topical	48 hours

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

Table 9. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Alopecia areata[1,2,7-13,15,18,20,21,23,25,27-29,32,35-37,40], totalis[15,18,20,28,29], and universalis[18,20,28,29]	Apply once-twice weekly	0.00000001-3%	Solution	Topical	2 weeks-10 years
Warts[1,16,17,22,26,32]	Apply once every 2 weeks – twice weekly	0.0003-3%	Solution	Topical	2-18 months
Vitiligo vulgaris[31]	–	0.001-1%	–	Topical	–

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

Table 10. Compounded products – US

Indication	Publication Year	Compounding Method	Dosage Form	Final Strength
Alopecia areata[19], alopecia universalis[19]	1982	• SADBE dissolved in acetone	–	0.0001-2%

Abbreviations: "–", not mentioned.

Table 11. Compounded products – non-US countries

Indication	Compounding Method	Dosage Form	Final Strength
Alopecia areata[12,13,18,21,32]	• SADBE diluted/dissolved in acetone	Solution	0.000001-3%
Warts[17,32]	• SADBE diluted in acetone	Solution	0.01-3%

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

Two (2) interviews were conducted.

Table 12. Overview of interviewees

Interviewee	Level of Training	Specialty	Current Practice Setting	Experience with SADBE	Interview Summary Response
DER_01	MD	Dermatology	Academic medical institution Faculty at a School of Medicine	Not specified	• Thinks of all topical irritants (DPCP, DNCP, SADBE) in the same category when used for alopecia areata
DER_04	MD	Dermatology Dermatology/Immunology	Independent consultant	Yes	• Not preferred choice • Better options exist; topical irritants typically last resort

Abbreviation: MD, Doctor of Medicine.

SADBE in alopecia areata

- One (1) interviewee considered SADBE the "last resort" treatment; the interviewee stated that there are other treatments that have more data to support efficacy over topical irritants like SADBE.

SADBE compared to other topical irritants

- One (1) interviewee stated they think of the topical irritants (DPCP, DNCP, and SADBE) in the same category, and while they are not molecularly related, they would be comparable regarding indications, ROA, and frequency of use. Said that prescribers can pick one, and if it does not work, then try a different one.
- One (1) interviewee stated that "The problem is you can't compare across studies. It's a concentration of what somebody used, the scenario under which somebody was sensitized, and then how they were then being challenged in order to try to look for outcomes, and all of these are going to be such small studies, they're not powered for statistical significance so I don't know that you could even try to say, 'Oh, well this one's better,' or, 'This one's stronger'. If you lined them all up, I could pick apart every one of those studies and tell you what the major flaws were, because the patient populations are also gonna be different and that's really important."
    - The interviewee reported if they were taking care of a patient and patient did not respond to one topical irritant, they would likely move to a different therapeutic class.
        - Did not think the difference between the sensitizing compounds was likely to be clinically meaningful.

Need for "office stock"

- One (1) interviewee confirmed that this is a product that would be administered in an office setting; while it is something that could have an individual patient-specific prescription for instead of being compounded in bulk, it would depend on how many patients are being seen.

Summary of survey results

Table 13. Characteristics of survey respondents [5 people responded to the survey.]

Board Certification	MD	No Response
Dermatology	2	0
No Response	0	3

Abbreviation: MD, Doctor of Medicine.

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

Types of Products	Respondents, n (N=4[a])
Compounded	2
FDA-approved	0
Over-the-counter	0
Dietary	0
Unsure	0
No response	2

[a]Out of five (5) respondents, four (4) reported using, prescribing, or recommending SADBE products.

Table 15. Compounded use of SADBE in practice[a]

Indication	Strength	Dosing frequency	Dosage Form	ROA	Duration of Treatment	Patient Population
Alopecia areata	2%, 0.0001%	Weekly	Acetone-based solution	Topical	Regrowth of hair As long as beneficial	All Adult male and female
	1%	Daily	Solution			
Verruca plana Verruca vulgaris	2%, 0.2%	3x/week	Acetone-based solution	Topical	Clearance	All

Abbreviation: ROA, route of administration.
[a]Two (2) respondents.

Table 16. Indications for which SADBE is considered a standard therapy

Indication	Standard Therapy		
	Compounded, n (N=2)	Non-compounded, n (N=0)	No Response, n (N=2)
Alopecia areata	2	0	0
No response	0	0	2

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

Reasons
"Only available compounded"
"No approve FDA product available"

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

	Respondents, n (N=2)
No–use has remained consistent	1
Yes–I use it LESS often now	0
Yes–I use it MORE often now[a]	1

[a]One (1) respondent wrote "lack of other effective treatment."

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

	Respondents, n (N=2)
No	2
Yes	0

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

No survey respondents provided this information

CONCLUSION

SADBE (UNII code: 4RTO57VG65) was nominated for inclusion on the 503B Bulks list for the treatment of extensive alopecia areata and warts. The nominated administration methods include a topical solution at various strengths; initial treatment starts at 2% followed by and ranges from 0.0001-0.001% for maintenance dosing. SADBE is not available in any of the national medical registries reviewed and there is no USP monograph for this substance.

From the literature review conducted, the most prevalent indication in US and non-US studies was alopecia areata, followed by warts. Compounded SADBE products were identified from both the US and non-US studies that reflected the nominated indications (alopecia areata and warts) and dosage forms (topical solutions).

One (1) interviewee felt that topical irritants are "last resort" treatments for alopecia areata, and there are more options that have better data to support efficacy. Another interviewee stated that they consider all of the topical irritants in the same category as topical sensitizers for alopecia areata, and that they consider them to be comparable as far as indications, ROA, and frequency of use are concerned.

From the survey responses, four (4) out of five (5) respondents used SADBE. The most common indication respondents used compounded SADBE for was alopecia areata with one (1) respondent also using SADBE for verruca plana and verruca vulgaris. Lack of availability of SADBE as an FDA-approved product was the reason cited for using the compounded product. One (1) respondent reports using SADBE more often over the past five years due to "lack of other effective treatment."

APPENDICES

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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 **squaric acid dibutyl ester (SADBE)**. 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: Squaric acid dibutyl ester (SADBE)

Q1. What type(s) of product(s) do you use, prescribe, or recommend for **squaric acid dibutyl ester (SADBE)**? 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 squaric acid dibutyl ester (SADBE)?... != Compounded drug product Is Not Selected

Skip To: Q2. If What type(s) of product(s) do you use, prescribe, or recommend for squaric acid dibutyl ester (SADBE)?... = Compounded drug product Is Selected

Display This Question:

If What type(s) of product(s) do you use, prescribe, or recommend for squaric acid dibutyl ester (SADBE)?... = Compounded drug product

Q2. Please list any conditions or diseases for which you use compounded **squaric acid dibutyl ester (SADBE)** 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 **squaric acid dibutyl ester (SADBE)** 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 squaric acid dibutyl ester (SADBE) as a single agent active ingredient, or as on... != Combination Is Not Selected

Display This Question:

If Loop current: Do you use compounded squaric acid dibutyl ester (SADBE) as a single agent active ingredient, or as on... = Combination Is Selected

Q4. Please list all combination products in which you use compounded **squaric acid dibutyl ester (SADBE)**.

_____

Q5. For which, if any, diseases or conditions do you consider compounded **squaric acid dibutyl ester (SADBE)** standard therapy?

_____

Q6. Does your specialty describe the use of compounded **squaric acid dibutyl ester (SADBE)** in medical practice guidelines or other resources?

_____

Q7. Over the past 5 years, has the frequency in which you have used compounded **squaric acid dibutyl ester (SADBE)** 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 **squaric acid dibutyl ester (SADBE)** instead of any FDA-approved drug product?

_____

Q9. Do you stock non-patient-specific compounded **squaric acid dibutyl ester (SADBE)** in your practice location?

- Yes
- No

Skip To: End of Block If Do you stock non-patient-specific compounded squaric acid dibutyl ester (SADBE) in your practice locat... = No

Display This Question:

If Do you stock non-patient-specific compounded squaric acid dibutyl ester (SADBE) in your practice locat... = Yes

Q10. In what practice location(s) do you stock non-patient-specific compounded **squaric acid dibutyl ester (SADBE)**? 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 **squaric acid dibutyl ester (SADBE)**? 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 **squaric acid dibutyl ester (SADBE)**? 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 squaric acid dibutyl ester (SADBE)? Please... = Convenience

Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded squaric acid dibutyl ester (SADBE)? Please... = Emergencies

Skip To: End of Block If Why do you keep a stock of non-patient-specific compounded squaric acid dibutyl ester (SADBE)? Please... = Other (please describe)

Q13. For which, if any, diseases or conditions do you consider **squaric acid dibutyl ester (SADBE)** standard therapy?

_____

Q14. Does your specialty describe the use of **squaric acid dibutyl ester (SADBE)** in medical practice guidelines or other resources?

_____

End of Block: Squaric acid dibutyl ester (SADBE)

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