Summary Report

Sulfan Blue

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

Sulfan blue (UNII code: FH1929ICIT) was nominated for inclusion on the 503B Bulks List by Cantrell Drug Company. Sulfan blue was nominated for use as a dye to reveal edema of total or partial lymphatic origin. The desired compounded product is a 10mg/mL (1%) subcutaneous injection.

The reason provided for nomination to the 503B Bulks List is that there is no FDA-approved product of this isomer available and allergenicity to the commercially available isosulphan blue 1% has been reported.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of sulfan blue 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 (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 sulfan blue; name variations of sulfan blue 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 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 sulfan blue. 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 December 20, 2018. The search included a combination of ("sulfan blue"[TIAB] OR "acid blue 1"[TIAB] OR "alphazurine 2G"[TIAB] OR "blue patent violet"[TIAB] OR "blue vrs"[TIAB] OR "disulfine blue"[TIAB] OR "disulphine blue"[TIAB] OR "patent blue v"[TIAB] OR "patent blue violet"[TIAB] OR "sulphan blue"[TIAB]) AND (therapy[TIAB] OR therapeutic[TIAB] OR clinical[TIAB] OR edema[TIAB] OR swell[TIAB] OR lymph*[TIAB] OR chyl*[TIAB]) AND humans [MeSH Terms] AND English[lang]. 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. Microsoft Excel® was used for screening purposes.

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 sulfan blue or the implementation of sulfan blue in clinical practice. Screening of all titles, abstracts, and full-text were conducted independently by two reviewers. All screening disagreements were reconciled by a third reviewer.

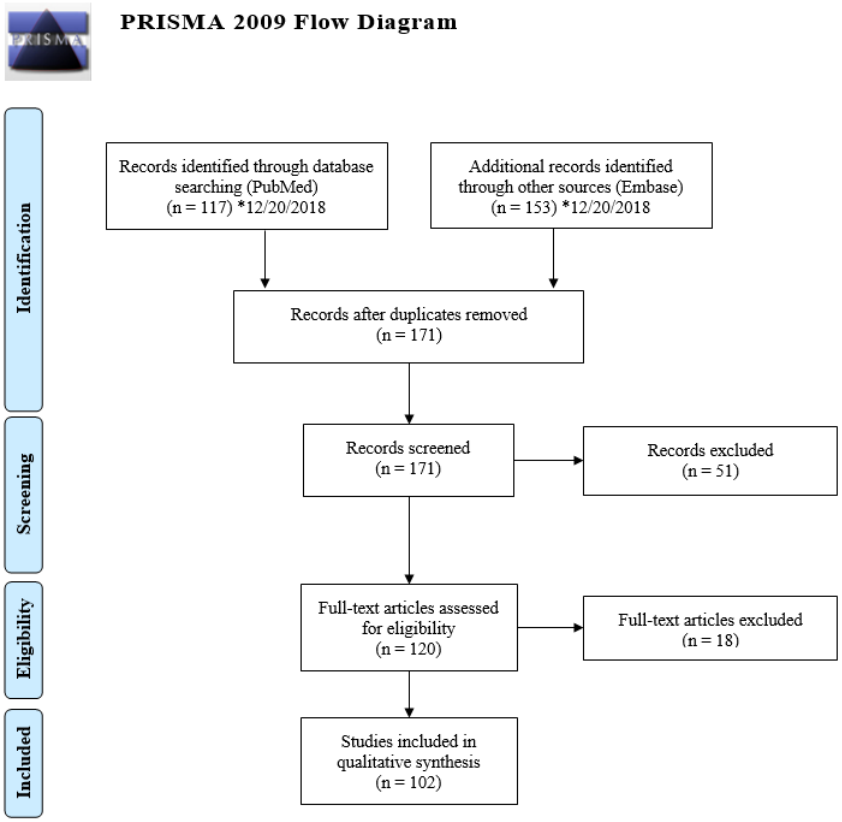
Data extraction

A standard data extraction form was used to collect study authors; article title; year published; journal title; country; indication for sulfan blue 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 sulfan blue 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 indication from the nomination and the results of the literature review, two (2) medical specialties that would potentially use sulfan blue were identified: oncology and radiology. 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 an interview, of which zero (0) accepted and zero (0) declined interview; the medical expert failed to respond to interview requests.

Survey

General professional medical associations and specialty associations for oncology and radiology, identified from the nomination, 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
Radiology	American College of Radiology (ACR)

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
Oncology	American Society for Clinical Oncology (ASCO)	Declined

CURRENT AND HISTORIC USE

Summary of background information

Sulfan blue is not available as an FDA-approved product, an OTC product in the US, nor does it have an United States Pharmacopeia (USP) monograph. The isomer of sulfan blue, isosulfan blue, however is an FDA-approved product commercially available as a 1% injection in the US. Sulfan blue is available under the name Patent Blue V manufactured by Guerbet in Australia, Belgium, Canada, and Hong Kong as a 2.5% solution for subcutaneous injection.

Table 3. Currently approved products – US

No approved products in the US

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

Product	Active Ingredient	Concentration	Dosage Form	ROA	Approved For Use		
					Country	Status	Approval Date[b]
Patent blue V	Patent blue V	2.5%	Solution	Subcutaneous Intravascular	Australia	Active	10/21/1991
					Belgium	Commercialized	12/28/1971
					Canada	Marketed	12/31/1979
					Hong Kong	Prescription only	4/7/1998

Abbreviation: ROA, route of administration.
[a]Medicine registers of national regulatory agencies were searched if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information (product trade name, active ingredient, strength, form, ROA and approval status) provided in a useable format. Information was recorded only for products with strengths, forms and/or ROA similar to those requested in the nominations. See Methodology for full explanation.
[b]If multiple approval dates and/or multiple strengths, then earliest date provided.

Summary of literature review

Of the studies identified, most were published in Italy (23) followed by the UK (20). Only three (3) studies were identified from the US. The most frequent indication in the US was as a visual aid in lymphography and visualization of boundaries of skin destruction due to burns. All of the US studies were published prior to 1980 and two (2) discussed the use as a compounded product. Of the non-US studies, the most common indication was in sentinel lymph node identification in various types of cancer followed by visualization of the lymphatic system.

The nomination identified the need for compounded sulfan blue due to the allergenicity of isosulfan blue. Hypersensitivity reactions to isosulfan blue have a 2% incidence.[1]

Table 5. Types of studies

Types of Studies	Number of Studies
Descriptive[2–12]	11
Experimental[13–94]	82
Observational[95–103]	9

Table 6. Number of studies by country

Country	Number of Studies
Australia[20,90,92]	3
Austria[61]	1
Brazil[19,93,95]	3
Bulgaria[35,37,69]	3
China[39,98,99]	3
Czech Republic[33,34]	2
Denmark[3,41,42]	3
France[8,76]	2
Germany[30,31,48,64,102]	5
India[66,88,89]	3
Iran[14,38,54,58,70–72,103]	8
Italy[7,11,17,18,22–24,49,50,52,53,57,62,63,74,78,79,86,87,91,94,96,100]	23

Japan[4,9,75,81,82,101]	6
Poland[26,55,65]	3
Portugal[47]	1
Singapore[2]	1
The Netherlands[10,15,16,32,83,84]	6
Turkey[5]	1
UK[6,12,13,21,27–29,40,44–46,51,59,60,67,68,73,80,85,97]	20
US[43,56,77]	3
Multi-country • UK and The Netherlands[25,36]	2
	Total US: 3 Total non-US Countries: 99

Table 7. Number of studies by combination

No combination products were nominated

Table 8. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Visualization of boundaries of skin destruction due to burns[43,56]	10mg/kg	10%	Solution	Intravenous injection	Once
	20mg/kg	11%			
Visual aid in lymphography[56,77]	0.5mL	–	Solution	Subcutaneous injection	Once
	0.1mL	11%		Intradermal injection	

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

Table 9. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	ROA	Duration of Treatment
Sentinel lymph node identification in breast cancer[12–14,17,18,20,22,27–29,32,38,39,41,42,47,51,52,59–61,67,69,70,72,76,83,87–89,92,93,97–99,101,102]	0.25-4mL	0.6%-15% 0.018mmol/L	Solution	Intradermal, subcutaneous, peritumoral, subareolar injection	Once
Sentinel lymph node identification in skin cancer[2,9,11,23–25,45,46,48,50,53,54,68,79,81,82,84,86,100,103]	0.1-2mL	1%-2.5%	Solution	Intradermal, peritumoral, subcutaneous injection	Once
Sentinel lymph node identification in colorectal cancer[7,10,15,16,19,21,35,37,55,74,85,90,91,94]	0.25-4mL	2.5%	Solution	Subserosal, peritumoral injection	Once
Visualization of lymphatic system[3,4,6,26,40,44,57,78,80,96]	0.05-3mL	0.1%-11%	Solution	Subcutaneous, intradermal, intramuscular, foot lymphatic injection	Once
Sentinel lymph node identification in endometrial cancer[33,34,49,63]	2-4mL	2.5%	Solution	Subserosal, pericervical injection	Once
Sentinel lymph node identification in gastric cancer[5,30,31,75]	0.1-1.2mL	2%	Solution	Submucosal, subserosal injection	Once

Sentinel lymph node identification in thyroid cancer[58,62,71]	0.25mL/cm	0.5%	Solution	Intratumoral injection	Once
	0.5-1mL	–			
Sentinel lymph node identification in cervical cancer[8,66]	1-4mL	2.5%	Solution	Peritumoral injection	Once
Sentinel lymph node identification in vulvar carcinoma[36,65]	1-2mL	2.5%	Solution	Intradermal injection	Once
Sentinel lymph node identification in head and neck cancer[73]	0.5-1mL	–	Solution	Peritumoral injection	Once
Sentinel lymph node identification in non-small cell lung cancer[95]	2mL	–	Solution	Peritumoral injection	Once
Sentinel lymph node identification in testicular cancer[64]	44mg	0.18%	Liposome	Foot lymphatic injection	Once

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

Table 10. Compounded products – US

Indication	Compounding Method	Dosage Form	Final Strength
Visualization of boundaries of skin destruction due to burns[43]	• Powder diluted and autoclaved	Solution	10%
Visual aid in lymphography	• Alpha azurine 2G 5% • Lidocaine HCl injection, 1%, a sufficient quantity	Solution	5%

Abbreviation: HCl, hydrochloride.

Table 11. Compounded products – non-US countries

No compounded products from reported studies

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

No interviews were conducted. Outreach to a Doctor of Medicine (MD) specializing in oncology was contacted, however the interviewee did not respond to the interview request.

Table 12. Overview of interviewees

No interviews were conducted

Table 13. Characteristics of survey respondents (1 person responded to the survey)

Board Certification	MD
Nuclear medicine	1

Abbreviation: MD, Doctor of Medicine.

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

No respondents reported using sulfan blue

Table 15. Compounded use of sulfan blue in practice

No respondents reported using sulfan blue

Table 16. Indications for which sulfan blue is considered standard therapy

No respondents reported using sulfan blue

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

No respondents reported using sulfan blue

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

No respondents reported using sulfan blue

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

No respondents reported using sulfan blue

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

No respondents reported using sulfan blue

CONCLUSION

Sulfan blue was nominated for inclusion on the 503B Bulks List by Cantrell Drug Company. Sulfan blue was nominated for use as a dye to reveal edema of total or partial lymphatic origin as a 10mg/mL (1%) subcutaneous injection.

The reason provided for nomination to the 503B Bulks List is that there is no FDA-approved product of this isomer available. While there is no FDA-approved product currently available, the isomer of sulfan blue, isosulfan blue, is an FDA-approved product commercially available as a 1% injection in the US. Additionally, the nomination stated the need for compounded sulfan blue due to the allergenicity of isosulfan blue; there is a 2% incidence of hypersensitivity reactions reported to isosulfan blue.

Sulfan blue is available under the name Patent Blue V manufactured by Guerbet in Australia, Belgium, Canada, and Hong Kong as a 2.5% solution for subcutaneous injection.

Of the studies identified, most were published in Italy (23) followed by the UK (20); only three (3) studies were identified from the US. The most frequent indication in the US was as a visual aid in lymphography and visualization of boundaries of skin destruction due to burns. All of the US studies were published prior to 1980 and two (2) discussed the use as a compounded product. Of the non-US studies, the most common indication was in sentinel lymph node identification in various types of cancer followed by visualization of the lymphatic system.

No interviews were conducted. No survey respondents reported using sulfan blue.

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 **sulfan blue**. 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: Sulfan blue

Q1. Which of the following substances do you use in your practice? Please check all that apply.

- ☐ Sulfan blue
- ☐ None of the above

End of Block: List of substances

Start of Block: Sulfan blue

Q2. What type(s) of product(s) do you use, prescribe, or recommend for **sulfan blue**? 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: Q14 If What type(s) of product(s) do you use, prescribe, or recommend for sulfan blue? Please check all... != Compounded drug product

Skip To: Q3 If What type(s) of product(s) do you use, prescribe, or recommend for sulfan blue? Please check all... = Compounded drug product

Display This Question:

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

Q3. Please list any conditions or diseases for which you use compounded sulfan blue 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)						

Q4. Do you use compounded sulfan blue 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 sulfan blue as a single agent active ingredient, or as one active ingredien... != Combination

Display This Question:

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

Q5. Please list all combination products in which you use compounded **sulfan blue**.

_____

Page Break

Q6. For which, if any, diseases or conditions do you consider compounded sulfan blue standard therapy?

_____

Q7. Does your specialty describe the use of compounded sulfan blue in medical practice guidelines or other resources?

_____

Q8. Over the past 5 years, has the frequency in which you have used compounded sulfan blue 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

Q9. Why do you use compounded sulfan blue instead of any FDA-approved drug product?

_____

Q10. Do you stock non-patient-specific compounded sulfan blue in your practice location?

- ○ Yes (1)
- ○ No (2)

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

Page Break

Display This Question:

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

Q11. In what practice location(s) do you stock non-patient-specific compounded sulfan blue? Please check all that apply.

- ☐ Physician office
- ☐ Outpatient clinic
- ☐ Emergency room
- ☐ Operating room
- ☐ Inpatient ward
- ☐ Other (please describe)_____

Q12. How do you obtain your stock of non-patient-specific compounded sulfan blue? Please check all that apply.

- ☐ Purchase from a compounding pharmacy
- ☐ Purchase from an outsourcing facility
- ☐ Compound the product yourself
- ☐ Other (please describe)_____

Q13. Why do you keep a stock of non-patient-specific compounded sulfan blue? 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 sulfan blue? Please check all that app... = Convenience

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

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

Page Break

Q14. For which, if any, diseases or conditions do you consider sulfan blue standard therapy?

_____

Q15. Does your specialty describe the use of sulfan blue in medical practice guidelines or other resources?

_____

End of Block: Sulfan blue

Start of Block: Background Information

Q16. 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) _____

Q17. 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