Summary Report

Neomycin sulfate

Prepared for:

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

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Frequently Used Abbreviations

API	Active Pharmaceutical Ingredient
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
IRB	Institutional Review Board
OTC	Over-the-counter
ROA	Route of administration
SME	Subject matter expert
UK	United Kingdom
US	United States

INTRODUCTION

This report was created to assist the Food and Drug Administration (FDA) in their evaluation of the use of neomycin sulfate (UNII code: 057Y626693), which was nominated for use as a bulk drug substance in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act.

The aim of this report was to describe how neomycin sulfate is used in clinical research and practice to diagnose, prevent, or treat disease. Due to the broad, exploratory nature of this aim, scoping review methodology was used. Following the scoping review framework, a systematic literature review was conducted and healthcare practitioners were consulted to identify how neomycin sulfate has been used historically and currently.[1-3] Assessment of study quality and risk of bias were not performed because the aim of this report was not to make specific recommendations on the use of this substance in clinical practice.[1,4,5] Rather, the aim was to summarize the available evidence on the use of neomycin sulfate and thereby assist the FDA to determine whether there is a need for the inclusion of this substance on the 503B Bulks List.

REVIEW OF NOMINATION

Neomycin sulfate was nominated for inclusion on the 503B Bulks List by the Specialty Sterile Pharmaceutical Society (SSPS).

Neomycin sulfate was nominated for perioperative infection prophylaxis in gastrointestinal surgery via a 40 mg/mL irrigation solution.

The nominators provided a reference from published peer-reviewed literature to describe the pharmacology and support the clinical use of neomycin sulfate.[6]

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

- Prescriber or hospital preference for various strengths, combinations with other drugs, volumes and/or final product containers for administration.
- Unsafe to expose the direct compounding area to hundreds of vials or ampoules and hundreds of aseptic manipulations during the compounding of a typical size batch for outsourcing facilities; a single vessel compounded from bulk API is safer and more efficient than unmanageable amounts of small vials.
- As required by Current Good Manufacturing Practices, bulk API powders can be formulated to 100 percent potency, but finished products cannot; commercially available finished products have an inherent variance in potency, creating an uncertain final concentration for the new product.
- In order to utilize the most advanced technology available to provide the greatest level of sterility assurance and quality, bulk starting material is required; it is not feasible financially, nor from a processing standpoint, to use finished pharmaceutical dosage forms with advanced isolated robotic equipment or other advanced aseptic processing equipment.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of neomycin sulfate 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 neomycin sulfate; name variations of neomycin sulfate were entered if the initial search retrieved no results. The following information from the search results of each register was recorded in a spreadsheet: product trade name; active ingredient; strength; form; ROA; status and/or schedule; approval date. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations.

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.5) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing neomycin sulfate. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

Search strategy

A medical librarian constructed comprehensive search strategies for Ovid MEDLINE and Embase. The search strategies used a combination of controlled vocabulary terms and keywords to describe three concepts: neomycin sulfate, ROA, and therapeutic use to prevent perioperative infection (refer to Appendix 1 for full search strategies). Keywords for brand or proprietary products were not included in the search strategy because studies that utilized such products were excluded. Results were limited to human studies in English language. Searches were conducted on March 6, 2020. The reference lists of relevant systematic reviews and meta-analyses were reviewed to identify additional studies. In addition, the ECRI Guidelines Trust® repository was searched on March 6, 2020 for clinical practice guidelines that recommended the use of neomycin sulfate and provided sufficient dosing and administration instructions.

Results were exported to EndNote for Windows version X9.2 (Clarivate Analytics), and duplicates were removed. The de-duplicated results were uploaded to Covidence (Veritas Health Innovation) for screening.

Study selection

Studies in which neomycin sulfate was used in the nominated dosage form, ROA, and/or combination product to diagnose, prevent or treat the nominated disease or condition, or other conditions not specified in the nomination, were included. Studies were excluded if they were: written in a language other than English; reviews or meta-analyses; surveys or questionnaires (cross-sectional design); or designed to evaluate cost-effectiveness, mechanism of action, pre-clinical use, safety, or toxicity. Studies were also excluded if neomycin sulfate was used as: a brand or proprietary product; an FDA-approved product in the nominated dosage form, ROA, or combination; or a dosage form, ROA, or combination that was not nominated. Studies in which neomycin sulfate was used to diagnose, prevent, or treat autism were excluded due to a separate project examining the use of compounded substances in individuals with autism. Studies that did not meet the inclusion criteria but provided valuable information about the pharmacological or current or historical use of the substance were

noted and put in a separate group in the EndNote library. Two reviewers independently screened titles and abstracts and reviewed full-text articles. A third reviewer reconciled all disagreements.

Data extraction

The following information was recorded in a standard data extraction form: author names; article title; journal; year of publication; country; study type; historical use of neomycin sulfate; setting; total number of patients; number of patients who received neomycin sulfate; patient population; indication for use of neomycin sulfate; dosage form and strength; dose; ROA; frequency and duration of therapy; use of neomycin sulfate in a combination product; use and formulation of neomycin sulfate in a compounded product; use of neomycin sulfate compared to FDA-approved drugs or other treatments; outcome measures; authors' conclusions. One reviewer extracted data from the included studies; a second reviewer checked the data extraction.

Interviews

Semi-structured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances neomycin sulfate was used in a clinical setting. The systematic literature review and indication from the nomination were reviewed to identify the following medical specialties that would potentially use neomycin sulfate: surgery. Potential SMEs within the relevant medical specialties were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. In addition, the American Society of Health-System Pharmacists (ASHP) and select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided oral informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were entered into NVivo 12 (QSR International) for qualitative data analysis. Several members of the research team independently coded the transcriptions of two representative interviews for themes. The team members discussed the codes that emerged from their independent analysis, as well as those codes that were determined a priori. The code book was developed out of the integration of these coding schemes.

Survey

A survey was distributed to the members of professional medical associations to determine the use of neomycin sulfate in clinical practice. The online survey was created using Qualtrics® software (refer to Appendix 2 for complete survey). A Google™ search was conducted to identify the professional associations in the US for the relevant medical specialties. An association's website was searched to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used. An email describing the project and requesting distribution of the survey to the association's members was sent to the identified person(s). Associations that declined, did not respond, or did not provide significant data in project Year 1 were not contacted to distribute the project Year 2 surveys.

The survey was posted on the project website and the survey link was distributed to the associations that agreed to participate (refer to Appendix 3 for associations that participated and those that did not).

Participation was anonymous and voluntary. The estimated time for completion was 15 minutes with a target of 50 responses per survey.

The University of Maryland, Baltimore Institutional Review Board (IRB) and the FDA IRB reviewed the interview and survey methods and found both to be exempt. The Office of Management and Budget approved this project.

CURRENT AND HISTORIC USE

Results of background information

- Neomycin sulfate is not available as an FDA-approved product in the nominated dosage form and ROA. However, it is available as an irrigation solution in combination with polymyxin B sulfate and as an oral product.
- Neomycin sulfate is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for neomycin sulfate.
- Neomycin sulfate is not available in the nominated dosage form and ROA in any of the national medical registries searched.

Table 1. Currently approved products – US

No approved products in the US

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

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

Results of literature review

Study selection

Database searches yielded 531 references; 0 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 405 titles and abstracts were screened. After screening, the full text of 58 articles was reviewed. Finally, 4 studies were included. Fifty-four (54) studies were excluded for the following reasons: wrong study design (41 studies); language other than English (4); unable to obtain full text (4); wrong dosage form or ROA (2); wrong indication (2); wrong substance (1).

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

Characteristics of included studies

The 4 included studies were published between 1956 and 1968. There were 0 experimental studies, 0 observational studies, 4 descriptive studies, and 0 clinical practice guidelines. The 4 studies were conducted in the US.

A total of 42 patients participated in the 4 included studies. The number of patients in each study ranged from 1 to 38.

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

Use of neomycin sulfate

Twenty-two (22) patients received neomycin sulfate for infection prophylaxis, administered as an intraperitoneal or irrigation solution.

Refer to Table 6 for summaries of dosage by indication.

Neomycin sulfate was not used as a compounded product, nor was it used in a combination product.

In 4 studies, the authors' conclusion did not address the use of neomycin sulfate.[7-10]

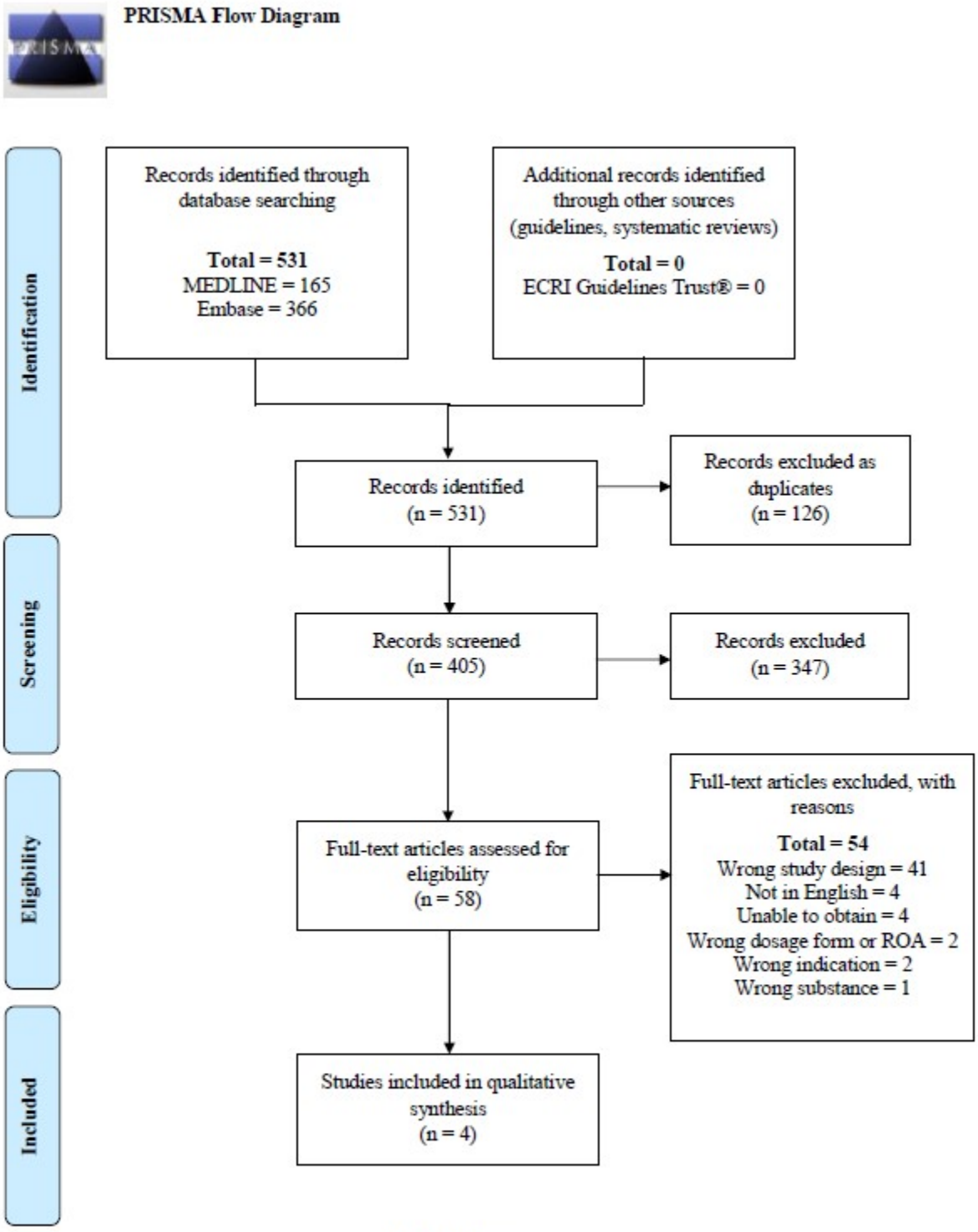
Pharmacology and historical use

In addition to the 4 included studies, 2 studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of neomycin sulfate.

According to a 2010 review, surgical site infections and anastomotic leakage "occur in as many as 30% of colon resections," resulting in increases in cost, mortality, and morbidity.[11] Another major complication, anastomotic dehiscence, "occurs in 3%-6% of colonic anastomosis," and is associated with the same increases.[11] As a result, the author describes a 3-tier regimen to decrease the risk through lowering intestinal bacteria content through: mechanical bowel preparation, preoperative non-absorbed oral antibiotics (neomycin in combination with either erythromycin base or metronidazole), and perioperative parenteral antibiotics.[11] However, the author concludes that despite a majority of surgeons following this practice in the US, there is no statistically significant evidence supporting the use of this method.[11]

In a 2014 review, the author discusses antibiotics used in irrigation fluids, stating that they are the most commonly used additives, "despite a shortage of evidence supporting their usage and a growing body of evidence suggesting their usage can have deleterious consequences."[12] Specifically, neomycin has been connected to "systemic absorption and toxicity."[12] The author also mentioned that some surgeons will mix their own irrigation solutions in the operating room for decreased cost but increased variability in concentration, while others will have them compounded by the hospital pharmacy for increased cost and decreased variability.[12]

Figure 1. PRISMA flow diagram showing literature screening and selection.



Adapted from:
Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006-1012. Available from: http://www.prisma-statement.org/.

Table 3. Types of studies

Types of Studies	**Number of Studies**
Descriptive[7-10]	4
Observational	0
Experimental	0

Table 4. Number of studies by country

Country	**Number of Studies**
US[7-10]	4
	Total US: 4 Total Non-US Countries: 0

Table 5. Summary of included studies

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication: Infection prophylaxis					
Allen, 1968, US[7]	Cases	2 In-patients with rectal injury (100%, range 54-80 y)	• Neomycin sulfate (2)	–	Inadvertent rectal injury during surgical procedure was managed successfully with primary closure and supplemented with rectal tube decompression and irrigation with neomycin of the lower bowel.
Poth *et al.*, 1961, US[8]	Case report	1 Patient receiving prophylaxis for contaminated deep wounds (0%, 51 y)	• Neomycin sulfate (1)	–	"The patient was convalescing smoothly, her temperature was normal, and the electrolyte pattern was completely normal when, suddenly, she died. At autopsy the peritonitis had completely subsided except for serum around barium collections."
Schatten, 1956, US[9]	Cases	38 In-patients with acute diffuse peritonitis (not specified, range 16-67 y)	• Neomycin sulfate (18) • Oxytetracycline (20)	–	When administered via the intraperitoneal route, neomycin caused less discomfort than oxytetracycline.
Shumacker and Mandelbaum, 1963, US[10]	Cases	1 In-patient presenting with reopening of wound (100%, 36 y)	• Neomycin sulfate (1)	–	"The patient recovered uneventfully. The mediastinal tube was removed on the 17th day, and the patient was discharged 3 days later. He has remained well and free of infection."

Abbreviations: "–", not mentioned.
[a]As defined by authors.

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Infection prophylaxis[7-10]	Loading 0.5-12.5 g 2 g/day	0.2-0.5%	Solution	Intraperitoneal	Once, followed by 8-12 doses
	10 g/day	0.5-1%	–	Irrigation	3 days
			Solution		

Abbreviations: "–", not mentioned.

Table 7. Dosage by indication – non-US countries

No studies included

Table 8. Number of studies by combination

No combination products were nominated

Table 9. Compounded products – US

No compounded products from reported studies

Table 10. Compounded products – non-US countries

No studies included

Results of interviews

Two hundred eighty-five SMEs were contacted for interviews; 96 agreed to be interviewed, and 189 declined or failed to respond to the interview request. One SME discussed neomycin sulfate. This one SME was a pharmacist who specialized and/or was board-certified in infectious diseases, working in an academic medical center. The SME had been in practice for 11 years.

Neomycin is frequently used for gastrointestinal decolonization prior to colorectal procedures but is administered as a tablet dispensed alongside metronidazole. Patients take it on the day leading up to surgery.

Results of survey

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

A separate survey was distributed by the Ambulatory Surgery Center Association (ASCA); 230 people responded to this survey (refer to Appendix 2.2 for survey instrument).

One hundred ten survey respondents (54% of 203 people who responded to this question) utilized a 503B outsourcing facility to acquire compounded drugs; 93 survey respondents (46%) did not utilize a 503B outsourcing facility. Five respondents (1.72% of 290 responses, where respondents were allowed to select multiple drug products) obtained neomycin sulfate from a 503B outsourcing facility (refer to Table 15).

The most common types of procedures performed at the facilities where the ASCA survey respondents worked were: ophthalmology (115, 17% of responses, where respondents were allowed to select multiple procedure types); orthopedics (89, 13%); pain (80, 12%); podiatry (74, 11%); and plastics (72, 10%) (refer to Table 16).

Table 11. Characteristics of survey respondents

No respondents to survey distributed via professional medical associations

Table 12. Conditions for which neomycin sulfate prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded neomycin sulfate

No respondents to survey distributed via professional medical associations

Table 14. Use of non-patient-specific compounded neomycin sulfate

No respondents to survey distributed via professional medical associations

Table 15. Ambulatory Surgery Center Association respondents' familiarity with compounding terms

Compounded drugs (medications prepared to meet a patient-specific need)	**Responses, n (N=230)**
Very familiar	153
Somewhat familiar	70
Not familiar	7
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed to meet a patient-specific need)	**Responses, n (N=230)**
Very familiar	118
Somewhat familiar	91
Not familiar	21
503B Outsourcing facility (a facility that compounds larger quantities without a patient-specific prescription)	**Responses, n (N=230)**
Very familiar	97
Somewhat familiar	86
Not familiar	47

Table 16. Products obtained from a 503B outsourcing facility

Product	**Responses, n (N=290)[a]**
Amitriptyline / Ketoprofen / Oxymetazoline	1
Budesonide	2
Calcium gluconate	2
Droperidol	2
Epinephrine	11
Epinephrine for ophthalmic administration	16
Epinephrine / Lidocaine for ophthalmic administration	31
Epinephrine / Bupivacaine / Fentanyl	3

Fentanyl	10
Flurbiprofen	3
Flurbiprofen for ophthalmic administration	6
Hydromorphone	5
Ipamorelin	1
Ketoprofen / Nifedipine	3
Lidocaine / Epinephrine / Tetracaine	13
Meperidine	3
Morphine	5
Naloxone	5
Neomycin	5
Phentolamine	1
Promethazine	5
Remifentanil	4
Sufentanil	2
Tramadol	2
None of the above	75
Do not obtain any compounded drugs from 503B outsourcing facility	74

[a]Survey respondents allowed to select multiple products.

Table 17. Type of specialty procedures performed at ambulatory surgery facility

Procedure Type	Responses, n (N=686)[a]
Dental	23
Dermatology	9
Endoscopy	65
Neurosurgery	22
Obstetrics/gynecology	39
Ophthalmology	115
Otolaryngology	58
Orthopedics	89
Pain	80
Plastics	72
Podiatry	74
Other[b]	40

[a]Survey respondents were allowed to select multiple procedure types.
[b]No respondents provided description for 'Other' procedure type.

CONCLUSION

Neomycin sulfate was nominated for inclusion on the 503B Bulks List as an irrigation solution for perioperative infection prophylaxis in gastrointestinal surgery. Neomycin sulfate is not available in the nominated dosage form and ROA in any of the national medical registries searched. However, it is available as an FDA-approved irrigation solution in combination with polymyxin B sulfate.

From the literature review and interview, increases in cost, mortality, and morbidity are associated with the occurrence of surgical site infections and anastomotic leakage (30% of colon resections) and anastomotic dehiscence (3-6% of colonic anastomosis). There is a 3-tier regimen to decrease the risk of these occurrences by lowering intestinal bacteria content through mechanical bowel preparation, preoperative non-absorbed oral antibiotics, and perioperative parenteral antibiotics. One SME said that oral neomycin is frequently used with metronidazole for gastrointestinal decolonization prior to colorectal procedures. However, there is no statistically significant evidence supporting use of these methods, and there is some evidence that antibiotics used in irrigation fluids can have poor consequences linked to systemic absorption and toxicity.

Zero people responded to the survey distributed via professional medical associations and available on the project website. Two hundred thirty people responded to the survey distributed via the ASCA. Five respondents reported obtaining neomycin sulfate from a 503B outsourcing facility.

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APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process and other non-indexed citations and daily 1946 to March 5, 2020
- Date last searched: March 6, 2020
- Limits: Humans (search hedge); English language
- Number of results: 165

1	neomycin/	7569
2	neom#cin$.tw.	9513
3	or/1-2	13358
4	administration, topical/	38043
5	administration, intravesical/	3927
6	instillation, drug/	1439
7	therapeutic irrigation/	17366
8	lavage$.tw.	49358
9	instill$.tw.	27092
10	irrigat$.tw.	32463
11	intraperitoneal$.tw.	110428
12	intra peritoneal$.tw.	2206
13	intravesical$.tw.	9544
14	intra vesical$.tw.	120
15	or/6-14	227223
16	exp surgical procedures, operative/	3095265
17	exp infections/	2558249
18	antibiotic prophylaxis/	13646
19	dt.fs.	2184421
20	ad.fs.	1393565

21	tu.fs.	2191416
22	pc.fs.	1264278
23	su.fs.	1959136
24	surg$.tw.	1866025
25	perioperat$.tw.	92684
26	peri operat$.tw.	6899
27	intraoperat$.tw.	130937
28	intra operat$.tw.	14714
29	postoperat$.tw.	520094
30	post operat$.tw.	70453
31	preoperat$.tw.	283444
32	pre operat$.tw.	32148
33	infect$.tw.	1689031
34	prevent$.tw.	1377442
35	prophyla$.tw.	160996
36	or/16-35	10656862
37	and/3,15,36	262
38	exp animals/ not humans/	4675291
39	37 not 38	198
40	limit 39 to english language	165

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: March 5, 2020
- Limits: Humans (search hedge); English language
- Number of results: 366
- Notes: Tested Emtree term ‘drug administration, topical’; did not include because results related to skin or eye.

1	neomycin'/de	25146
2	neomicin':ti,ab,tn	12
3	neomycin':ti,ab,tn	12108
4	#1 OR #2 OR #3	28648
5	intraperitoneal drug administration'/de	124188
6	intravesical drug administration'/de	2638
7	lavage'/exp	86119
8	drug instillation'/de	1782
9	lavage*':ti,ab	71545
10	instill*':ti,ab	40130
11	irrigat*':ti,ab	44108
12	intraperitoneal*':ti,ab	158707
13	intra peritoneal*':ti,ab	4564
14	intravesical*':ti,ab	14411
15	intra vesical*':ti,ab	278
16	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	424738
17	surgery'/exp	5209141
18	infection'/exp	3806950
19	antibiotic prophylaxis'/de	30956
20	infection prevention'/de	59415
21	drug administration':lnk	1718339

22	drug therapy':lnk	3843164
23	prevention':lnk	1159690
24	surgery':lnk	2140168
25	surg*':ti,ab	2709477
26	perioperat*':ti,ab	147004
27	peri operat*':ti,ab	14984
28	intraoperat*':ti,ab	206903
29	intra operat*':ti,ab	28169
30	postoperat*':ti,ab	830025
31	post operat*':ti,ab	147039
32	preoperat*':ti,ab	453009
33	pre operat*':ti,ab	65649
34	infect*':ti,ab	2274904
35	prevent*':ti,ab	1877243
36	prophyl*':ti,ab	257638
37	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36	13732945
38	#4 AND #16 AND #37	571
39	[animals]/lim NOT [humans]/lim	6001155
40	#38 NOT #39	463
41	#38 NOT #39 AND [english]/lim	366

Appendix 2.1 Survey instrument for professional medical associations

Welcome. We want to understand your clinical use of compounded neomycin sulfate. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

If you have additional questions or concerns about this study, please email: compounding@rx.umaryland.edu.

If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Thank you,

Dr. Ashlee Mattingly
Principal Investigator
The University of Maryland School of Pharmacy

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	o	o	o
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	o	o	o
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	o	o	o

2. Do you prescribe or administer neomycin sulfate to your patients?

   - o Yes
   - o No

3. Do you prescribe or administer neomycin sulfate by any of the following dosage forms and/or routes of administration? (check all that apply)

   - o Irrigation solution
   - o None of the above

4. I prescribe or administer neomycin sulfate for the following conditions or diseases: (check all that apply)

   - o Perioperative infection prophylaxis in gastrointestinal surgery
   - o Other (please explain) _____

5. I use compounded neomycin sulfate because: (check all that apply)

   - o Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
   - o Patient allergies prevent me from using commercially available products. (please explain) _____
   - o Patient conditions prevent me from using commercially available products. (please explain) _____
   - o There are no commercially available products containing neomycin sulfate.
   - o Other (please explain) _____

6. Do you stock non-patient-specific compounded neomycin sulfate at your practice?

    - o Yes
    - o No
    - o I'm not sure

7. I obtain compounded neomycin sulfate from the following: (check all that apply)

    - o Compound myself at my practice
    - o Have the product compounded by an in-house pharmacy
    - o Purchase, or have a patient purchase, from a compounding pharmacy
    - o Purchase, or have a patient purchase, from an outsourcing facility
    - o Other (please explain) _____

8. What is your practice setting? (check all that apply)

    - o Physician office/private practice
    - o Outpatient clinic
    - o Hospital/health system
    - o Academic medical center
    - o Emergency room
    - o Operating room
    - o Other (please describe) _____

9. What degree do you hold? (check all that apply)

    - o Doctor of Medicine (MD)
    - o Doctor of Osteopathic Medicine (DO)
    - o Doctor of Medicine in Dentistry (DMD/DDS)
    - o Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
    - o Naturopathic Doctor (ND)
    - o Nurse Practitioner (NP)
    - o Physician Assistant (PA)
    - o Other (please describe) _____

Appendix 2.2 Survey instrument for Ambulatory Surgery Center Association

Welcome. We want to understand your clinical use of compounded drugs. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in bulk compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

If you have additional questions or concerns about this study, please email: compounding@rx.umaryland.edu.

If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Thank you,

Dr. Ashlee Mattingly
Principal Investigator
The University of Maryland School of Pharmacy

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	o	o	o
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	o	o	o
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	o	o	o

2. Do you utilize a 503B outsourcing facility to acquire compounded drugs?

   - o Yes. If yes, why? _____
   - o No. If no, why not? _____

3. Do you obtain any of the following products from a 503B outsourcing facility? (check all that apply)

   - o I do not obtain any compounded drugs from 503B outsourcing facilities
   - o Amitriptyline / Ketoprofen / Oxymetazoline
   - o Budesonide
   - o Calcium gluconate
   - o Droperidol
   - o Epinephrine
   - o Epinephrine for ophthalmic administration
   - o Epinephrine / Lidocaine for ophthalmic administration
   - o Epinephrine / Bupivacaine / Fentanyl
   - o Fentanyl
   - o Flurbiprofen
   - o Flurbiprofen for ophthalmic administration
   - o Hydromorphone
   - o Ipamorelin
   - o Ketoprofen / Nifedipine
   - o Lidocaine / Epinephrine / Tetracaine HCl
   - o Meperidine
   - o Morphine
   - o Naloxone
   - o Neomycin
   - o Phentolamine

- o Promethazine
- o Remifentanil
- o Sufentanil
- o Tramadol
- o None of the above

4. What type of specialty procedures are performed in your facility? (check all that apply)

    - o Dental
    - o Dermatology
    - o Endoscopy
    - o Neurosurgery
    - o Obstetrics/gynecology
    - o Ophthalmology
    - o Otolaryngology
    - o Orthopedics
    - o Pain
    - o Plastics
    - o Podiatry
    - o Other (please describe) _____

Appendix 3. Survey distribution to professional associations

Specialty	Association[a]	Agreed/Declined, Reason for Declining
Allergy/Immunology	American Academy of Allergy, Asthma, and Immunology (AAAI)	Declined – survey not approved
Anesthesia	American Society of Regional Anesthesia and Pain Medicine (ASRA)	Declined – failed to respond
	Society for Ambulatory Anesthesia (SAMBA)	Declined – failed to respond
	Society for Neuroscience in Anesthesiology and Critical Care	Declined – failed to respond
Critical Care	Critical Care Societies Collaborative	Declined – failed to respond
Dentistry & Oral Medicine	Academy of General Dentistry (AGD)	Declined – provided interview referrals
	American Dental Association (ADA)	Declined – failed to respond
Dermatology	American Academy of Dermatology (AAD)	Agreed
	American Osteopathic College of Dermatology (AOCD)	Declined – not interested
Endocrinology	The Endocrine Society (ENDO)	Agreed
	Pediatric Endocrine Society	Agreed
Gastroenterology	American Gastroenterological Association (AGA)	Declined – failed to respond
	Obesity Medicine Association (OMA)	Declined – did not have anyone to contribute to research
Hematology	American Society of Hematology (ASH)	Declined – does not distribute surveys
Infectious Disease	American Academy of HIV Medicine (AAHIVM)	Declined – failed to respond
Medicine	American Medical Association (AMA)	Declined – failed to respond

Naturopathy	American Association of Naturopathic Physicians (AANP)	Agreed
	The Oncology Association of Naturopathic Physicians (OncANP)	Agreed
Nephrology	American College of Clinical Pharmacists: Nephrology Practice Network	Agreed
	American Society of Nephrology	Declined – provided interview referrals
Nutrition	American Society for Parenteral and Enteral Nutrition (ASPEN)	Declined – provided interview referrals
Obstetrics and Gynecology	American Gynecological and Obstetrical Society (AGOS)	Declined – failed to respond
	Nurse Practitioners in Women's Health	Agreed
Ophthalmology	American Academy of Ophthalmology (AAO)	Agreed
Otolaryngology	American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS)	Declined – survey not approved
Pain Management	American Academy of Pain Medicine (AAPM)	Declined – survey not approved
	American Academy of Physical Medicine and Rehabilitation	Declined – failed to respond
Pediatrics and Neonatology	American Academy of Pediatrics (AAP)	Agreed
Primary Care	American College of Physicians (ACP)	Declined – failed to respond
Psychiatry	American Academy of Clinical Psychiatrists	Declined – failed to respond
	American Association for Geriatric Psychiatry	Declined – failed to respond
Rheumatology	American College of Rheumatology (ACR)	Agreed

Surgery	Ambulatory Surgery Center Association (ASCA)	Agreed
	American Academy of Orthopaedic Surgeons (AAOS)	Declined – no interest in participation from members
	American Association of Hip and Knee Surgeons (AAHKS)	Declined – only send surveys from members
	American College of Surgeons (ACS)	Agreed
	American Society for Metabolic and Bariatric Surgery (AMBS)	Declined – only send surveys from members
	The Association of Bone and Joint Surgeons	Declined – failed to respond
	Physician Assistants in Orthopaedic Surgery	Declined – failed to respond
	Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)	Declined – failed to respond
	Society of Gynecologic Surgeons (SGS)	Declined – policy limits number of surveys per year and do not have a method to identify if any of the SGS members are using ipamorelin
Toxicology	American Academy of Environmental Medicine (AAEM)	Declined – failed to respond
Urology	Sexual Medicine Society of North America (SMSNA)	Agreed

[a]Associations that declined in Year 1 were not contacted in Year 2.