Summary Report

Metronidazole

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Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
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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
USP	United States Pharmacopeia

INTRODUCTION

This report was created to assist the Food and Drug Administration (FDA) in its evaluation of the use of metronidazole (UNII code: 140QMO216E), 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 metronidazole 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 metronidazole has been used historically and currently.[1-3] Assessments 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 metronidazole 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 NOMINATIONS

Metronidazole was nominated for inclusion on the 503B Bulks List by the Outsourcing Facilities Association (OFA) and Sincerus Florida, LLC. Metronidazole was nominated for use in combination with additional Active Pharmaceutical Ingredients (API) (refer to Table 8).

Metronidazole was nominated to treat unspecified medical conditions; however, metronidazole is generally used to treat rosacea and fungating wounds, via various topical dosage forms at strengths based on the prescriber's request; therapeutic doses range from 1% to 2%.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of metronidazole.[6-15]

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

- Individual finished products have considerable variance in the actual API, and the use of finished product has the potential to introduce unacceptable inaccuracies into the compounded medication.
- Patient sensitivities to dyes, fillers, preservatives, or other excipients in manufactured products.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of metronidazole 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 the 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 metronidazole; name variations of metronidazole 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 metronidazole. 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 3 concepts: metronidazole, topical administration or form, and substances nominated for use in combination with metronidazole (refer to Appendix 1 for full search strategies). A literature review was not conducted for topical single-ingredient metronidazole products due to the availability of FDA-approved single-ingredient metronidazole products for this ROA. Results were limited to human studies in the English language. Searches were conducted on February 10, 2021. In addition, the ECRI Guidelines Trust® repository was searched on February 10, 2021, for clinical practice guidelines that recommended the use of metronidazole and provided sufficient information on dosing and administration.

Results were exported to EndNote for Windows version X9.3.3 (Clarivate Analytics), and duplicates were removed. The de-duplicated results were uploaded to Covidence (Veritas Health Innovation) for screening.

Study selection

Studies in which metronidazole 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); designed to evaluate cost-effectiveness, mechanism of action, preclinical use, safety, or toxicity; or any study design other than a randomized controlled trial conducted in a non-US country. Studies were also excluded if metronidazole was used as an FDA-approved product in the nominated dosage form, ROA, or combination; a dosage form, ROA, or combination that was not nominated; or an unspecified dosage form or ROA. Studies in which metronidazole 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 metronidazole; setting; total number of patients; number of patients who received metronidazole; patient population; indication for

use of metronidazole; dosage form and strength; dose; ROA; frequency and duration of therapy; use of metronidazole in a combination product; use and formulation of metronidazole in a compounded product; use of metronidazole 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

Semistructured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances metronidazole was used in a clinical setting. The systematic literature review and indications from the nominations were reviewed to identify medical specialties that would potentially use metronidazole. Potential SMEs were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. Select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided verbal 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 synthesized for qualitative data analysis.

In addition to interviews with individual SMEs, a roundtable discussion with pharmacists was held. Participants were identified through outreach to professional associations that would potentially purchase compounded products from outsourcing facilities. A prequestionnaire was distributed to those who agreed to participate to collect information about the types of facilities at which participants worked and the products they purchased from outsourcing facilities (refer to Appendix 2 for complete survey and *Results of survey* section for results of prequestionnaire). The roundtable lasted 60 minutes and was conducted via Zoom, audio recorded, and professionally transcribed. The transcriptions and notes were synthesized for qualitative data analysis.

Survey

A survey was distributed to the members of professional medical associations to determine the use of metronidazole 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 Years 1 and 2 were not contacted to distribute the project Year 3 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

- Metronidazole is available as an FDA-approved product in the nominated dosage form and ROA. Metronidazole is also available as an FDA-approved oral tablet, oral capsule, and injection.
- Metronidazole is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for metronidazole.
- Metronidazole is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, Latvia, Namibia, New Zealand, Saudi Arabia, and the UK.

Table 1. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Status	Approval Date[b]
Metronidazole	0.75-1.00%	Cream, gel, lotion	Topical	RX	11/22/1988

Abbreviation: RX, prescription.
[a]Source: US FDA Orange Book: *Approved Drug Products with Therapeutic Equivalence Evaluations.*
[b]If multiple approval dates and/or multiple strengths, then earliest date provided.

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

Active Ingredient	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date[b]
Metronidazole	0.5-1.0%	Cream, gel	Cutaneous, topical	Abu Dhabi	Active	–
				Australia	S4 – Prescription only medicine	07/07/1991
				Belgium	Medical prescription	10/12/1997
				Canada	Prescription	12/31/1994
				Hong Kong	Prescription only medicine	11/20/1990
				Ireland	Prescription-only, non-renewable	06/26/1991
				Latvia	RX	07/05/2006
				Namibia	–	12/28/2003
				New Zealand	Prescription	07/25/1991
				Saudi Arabia	Prescription	–
				UK	Prescription-only medication	06/18/1997

Abbreviations: –, not provided; RX, prescription.

[a]Medicine registers of national regulatory agencies were searched if they met the following criteria: freely accessible; able to search and retrieve results in the 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.

Results of literature review

Study selection

Database searches yielded 760 references; 3 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 640 titles and abstracts were screened. After screening, the full text of 121 articles was reviewed. Finally, 3 studies were included. One hundred eighteen studies were excluded for the following reasons: wrong study design (84 studies); used in an FDA-approved ROA or dosage form (15); used in a non-nominated ROA or dosage form (11); unable to obtain full text (6); metronidazole not used clinically (1); 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 3 included studies were published between 2005 and 2020. There were 2 experimental studies, 0 observational studies, 1 descriptive study, and 0 clinical practice guidelines. The 3 studies were conducted in the following countries: Colombia and the US.

A total of 86 patients participated in the 3 included studies. The number of patients in each study ranged from 1 to 60.

Outcome measures differed among the included studies and included the following: number of *Demodex* mites in the eyelashes, resolution of ulcer, clinical improvement of signs, adverse events, skin barrier condition, rosacea severity, erythema, desquamation, irritation, patient's perceptions of stinging/burning, roughness, and redness.

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

Use of metronidazole

Thirty patients received metronidazole as an experimental treatment at a concentration of 1% for blepharitis caused by *Demodex* infestation, administered topically every 15 days for 3 applications. Twenty-five patients received metronidazole as an experimental treatment for rosacea at a concentration of 1%, administered topically twice a day for 2 weeks. One patient received metronidazole as an experimental treatment for an ulcerated lower-lip hemangioma, administered topically.

Refer to Tables 6 and 7 for summaries of dosage by indication.

Metronidazole was used as a compounded product and as a combination product (refer to Tables 8-10).

In 1 study, the authors concluded that further studies were necessary for the treatment of *Demodex* blepharitis. In 2 studies, the authors' conclusions did not address the use of metronidazole. Refer to Table 5 for the summary of authors' conclusions.

Pharmacology and historical use

Additional studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of metronidazole.

Metronidazole is a nitroimidazole antibiotic first discovered in the late 1950s when researchers were attempting to create a compound with activity against *Trichomonas vaginalis*.[16] Since its discovery, metronidazole has been found to have antimicrobial activity against protozoa, such as *Trichomonas vaginalis*, *Entamoeba histolytica*, and *Giardia lamblia*; gram-negative anerobic bacteria belonging to *Bacteroides* and *Fusobacterium* species; and gram-positive anerobic bacteria, including *Peptococcus niger* and *Peptostreptococcus*, *Eubacterium*, and *Clostridium* species.[16-20] Metronidazole exerts its antibacterial effects by entering the organism via passive diffusion where intracellular electron transport proteins transfer an electron to the nitro group of metronidazole, forming a nitroso free radical. This alternation leads to the creation of a concentration gradient that allows for the intracellular transport of metronidazole.[17-20] The reduced form of metronidazole and the nitroso free radicals interact with the intracellular DNA of the bacteria, which leads to inhibition of DNA synthesis and DNA degradation, resulting in death of the bacteria.[17-20] Metronidazole is commercially available as an oral tablet and capsule, a solution for intravenous injection, and a vaginal gel, and is effective for the treatment of susceptible infections.[17-20]

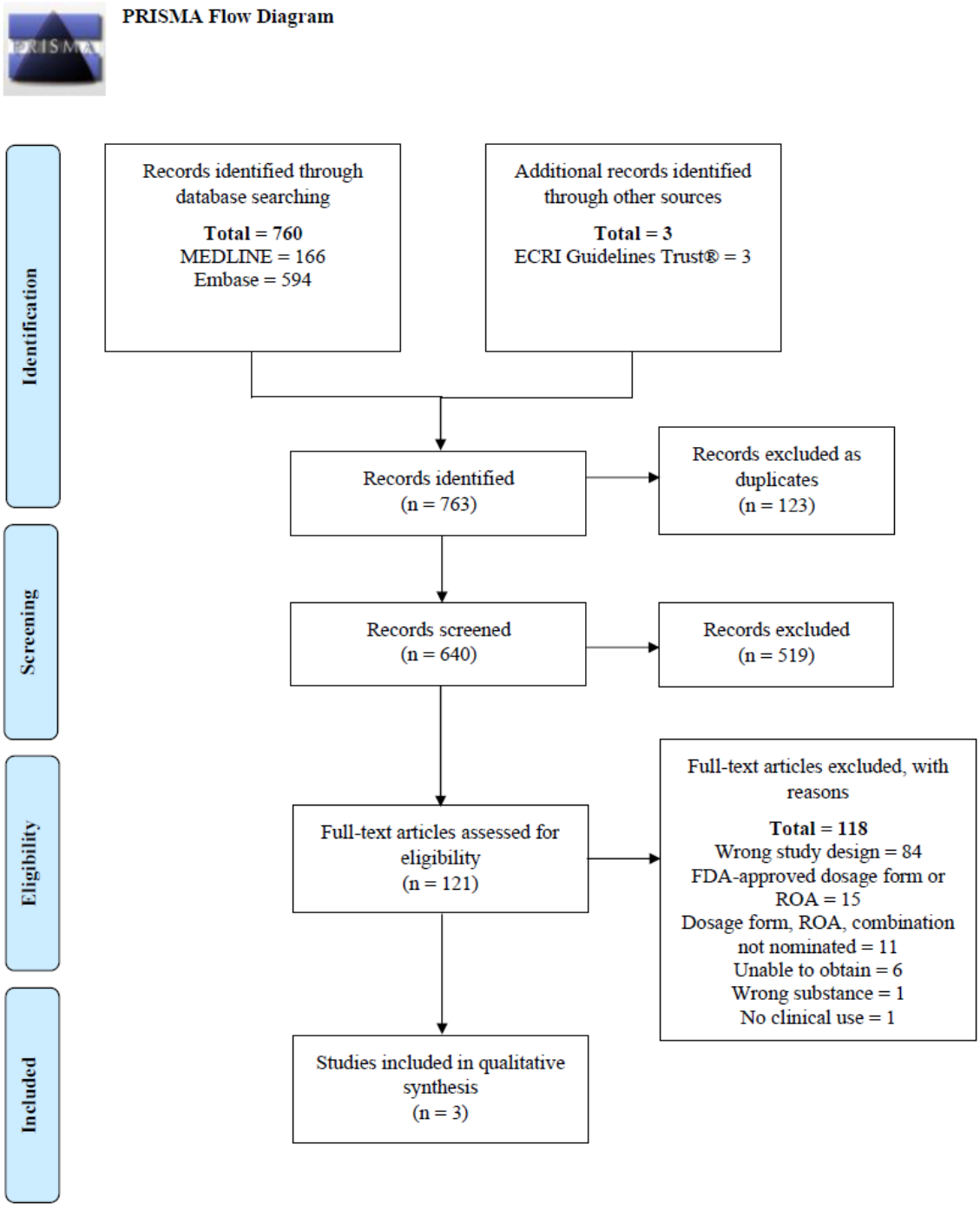
Metronidazole is also available as a topical cream, gel, and lotion approved for treatment of acne rosacea.[17-20] Metronidazole reduces the inflammatory component of rosacea, and while this mechanism is unknown, it may be due to its "ability to decrease the reactive oxygen species generation and inactive existing reactive oxygen species production," unrelated to the suppression of skin bacteria.[21,22] Metronidazole, as a 10% ointment, has an orphan drug designation for the topical treatment of active perianal Crohn's disease.[23] Topical metronidazole also had an orphan drug designation for treatment of grade III and IV, anaerobically infected decubitus ulcers; however, this designation has been withdrawn.[23] Studies have also been conducted evaluating the use of topical metronidazole for the treatment of other dermatologic conditions, including perioral dermatitis, cheilitis granulomatoses, and lichen planus, as well as various dental conditions, such as dry socket and chronic periodontitis.[16,22]

Several studies were identified in which metronidazole was used to treat odor related to fungating wounds. A fungating wound is a "malignant lesion that infiltrates the skin and its supporting blood and lymph vessels."[24] These wounds occur in approximately 0.6-9.0% of cancer, with breast cancer having the highest incidence at 62% followed by head and neck cancer at 24%.[25,26] Fungating wounds initially present as "multiple nontender nodules that are skin-toned, pink, violet-blue, or black-brown in color" and typically expand quickly into papillary lesions that can become locally invasive forming shallow craters.[24] As they grow, they "disrupt the local blood supply, resulting in necrosis of the malignant tumor and underlying tissue," which leads to the growth of anerobic organisms.[24] With the growth of anerobic organisms there is the development of an exudate and the characteristic malodor that is often described as "intolerable and nauseating," resulting in a negative impact on a patient's quality of life.[24-26] Treatment is focused on managing the symptoms, including pain, cutaneous irritation, exudate, bleeding, odor, and offering psychosocial support.[24]

Because of its antimicrobial activity against protozoa and anerobic bacteria, metronidazole has been studied for use as a topical agent to reduce wound odor.[24] A systematic review conducted in 2010 evaluated topical treatments for managing odor, and while there were few high-quality studies identified, the authors concluded that metronidazole had grade B evidence.[27] Two additional systematic reviews also concluded that, while the studies identified did support the use of metronidazole in controlling wound odor, with one review recommending its use, the evidence supporting its use was not strong.[25,26] A 2014 systematic review evaluating topical agents and dressings for fungating wounds concluded that there is insufficient evidence available to provide a practice recommendation.[28]

However, the World Health Organization (WHO) recommended the use of topical metronidazole for treatment of malodorous tumors in their 1998 publication *Symptom Relief in Terminal Illness*, and the American Society of Clinical Oncology recommended its use in their 2001 curriculum *Optimizing Cancer Care: The Importance of Symptom Management*.[29,30] According to a 2015 review by Samala and Davis, metronidazole is "the most widely used topical antibacterial for malodor management"; however, it can take up to 2-3 days before the odor is reduced.[24,31,32] Typically, metronidazole is applied once or twice daily topically and then covered with a "nonadherent primary dressing followed by an absorbent secondary dressing."[31,32] However, metronidazole may be ineffective if the wound is wet due to the exudate washing the gel off, inhibiting the gel from working as well as if the wound is extremely dry, as the gel is not able to penetrate the necrotic tissue.[31] An alternative approach to treatment in wounds with a heavy exudate is to crush and sprinkle metronidazole tablets over the wound surface.[24,32,33] In 2020, Hu et al reported the successful reduction in odor of 2 patients with fungating tumors in which a 500 mg metronidazole tablet was crushed and sprinkled over the tumor twice daily.[34] While this approach may reduce cost, additional studies are needed.[33]

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[35]	1
Observational	0
Experimental[36,37]	2
Clinical practice guideline	0

Table 4. Number of studies by country

Country	**Number of Studies**
Colombia[37]	1
United States (US)[35,36]	2
	Total US: 2 Total Non-US Countries: 1

Table 5. Summary of included studies

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 1: Blepharitis caused by *Demodex* infestation					
Avila et al, 2020, Colombia[37]	Randomized clinical trial	60 Patients with symptomatic *Demodex* blepharitis • Ivermectin-metronidazole (sex not provided, range 21-85 y) • Placebo (sex not provided, range 24-85 y)	• Ivermectin-metronidazole (30) • Placebo (30)	Number of *Demodex* mites in the eyelashes, clinical improvement of signs, adverse events	"*Demodex* infection was controlled satisfactorily with the ivermectin (0.1%)-metronidazole (1%) gel, and no adverse effects were observed. Application of this gel for the treatment of different parasitic infections of the eyelids could be feasible, and this requires further exploration."
Indication 2: Rosacea					
Draelos et al, 2005, US[36]	Not defined	25 Patients with rosacea (0%, range 20-75 y)	• Metronidazole formulated with a gel vehicle containing niacinamide, beta cyclodextrin, and propylene glycol (25)	Adverse events, skin barrier condition, rosacea severity, erythema, desquamation, irritation, patient's perceptions of stinging/burning, roughness, and redness	"This study demonstrated that the novel metronidazole vehicle did not damage the skin barrier as evidenced by no increase in TEWL [transepidermal water loss] and no decrease in corneometry."
Indication 3: Ulcerated lower-lip hemangioma					
Strand et al, 2012, US[35]	Case presentation	1 Patient with an ulcerated lip hemangioma (0%, 3 months)	• Orabase®, prednisolone, metronidazole, mupirocin, acetaminophen with codeine (1)	Resolution of ulcer	"We propose the use of Orabase paste as a useful adjunct treatment option for local pain management for ulcerated hemangiomas, especially in anatomically difficult-to-treat areas such as the lip."

Abbreviations: TEWL, transepidermal water loss; US, United States.
[a]As defined by authors.

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Rosacea[36]	Applied twice daily	1%	Gel	Topical	2 weeks
Ulcerated lower-lip hemangioma[35]	–	–	–	Topical	–

Abbreviations: –, not provided.

Table 7. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Blepharitis caused by *Demodex* infestation[37]	Applied every 15 days	1%	Gel	Topical	3 applications

Table 8. Number of studies by combination

	Combination Formula	Number of Studies
Nominated	Metronidazole 1% / Niacinamide 4% – topical cream, gel[36]	1[a]
	Metronidazole 1% / Ivermectin 1% / Potassium azeloyl diglycinate 8% – topical gel	0
	Metronidazole 1% / Mupirocin 2% / Tranilast 1% – topical ointment	0
	Metronidazole 1% / Aloe vera 0.2% / Mupirocin 2% / Tranilast 1% – topical ointment	0
	Metronidazole 1% / Ivermectin 1% / Niacinamide 4% / Potassium azeloyl diglycinate 5% – topical gel	0
	Metronidazole 1% / Brimonidine tartrate 0.25% / Ivermectin 1% / Niacinamide 4% / Potassium azeloyl diglycinate 5% – topical gel	0
	Metronidazole 2% / Clioquinol 1% / Coal tar solution 2% / Hydrocortisone 1% / Salicylic acid 2% – topical cream	0
Others found in literature	Metronidazole 1% / Ivermectin 0.1% – topical gel[37]	1

[a]Niacinamide concentration not provided.

Table 9. Compounded products – US

No compounded products from included studies

Table 10. Compounded products – non-US countries

Indication	Compounding Method	Dosage Form	Final Strength
Blepharitis caused by *Demodex* infestation[37]	100 mL of water, USP is stabilized at 7.2 pH with triethanolamine, then 0.4 g of carbomer 940, USP was added and mixed obtaining a gel base, them metronidazole, USP at 1.0%, and ivermectin, USP at 0.1%, were prepared in this gel base	Gel	1%-0.1%

Abbreviations: USP, United States Pharmacopeia.

Results of interviews

One hundred ninety-nine SMEs were contacted for interviews; 63 agreed to be interviewed, and 136 declined or failed to respond to the interview request. Five SMEs discussed metronidazole. Amongst these 5 SMEs, there were 2 medical doctors and 2 doctors of podiatric medicine. The SMEs specialized and/or were board-certified in dermatology and infectious disease, working in academic medical institutions, private practice, and inpatient practice. The SMEs had been in practice for 1 to 56 years. Additional information was collected as a part of the Expanded Information Initiative referred to as Phase 3, in which outreach was conducted to the nominators of the bulk drug substances to remedy information gaps in the initial nomination.

Several SMES stated that metronidazole is commonly used to treat rosacea and is commercially available as both a cream and gel with one SME stating, "I think there really isn't a need to have compounded formulation of that for rosacea because it exists commercially." However, metronidazole has also shown benefit in patients with fungating wounds. As one SME commented, "Chronic ulcers or chronic wounds, fungating tumors, they develop not quite super infection, but colonization with gram-negative organisms, and that makes them very stinky." The SME continued that "the preferable thing would be to cut them out and treat them and have them gone, but for some people that's not an option." Anerobic bacteria tend to be the organisms that cause the foul odor, and since metronidazole has activity against anaerobes, for these patients, the use of a topical formulation of metronidazole can help to decrease the odor by reducing the bacterial colonization. The SME has used metronidazole for this a few times stating that "sometimes we tell people to just get metronidazole and crush it up and put it on the wound." The powder can be beneficial in these situations because these wounds tend to have a lot of discharge and the powder helps to dry this up. While there are commercially available formulations of topical metronidazole, the SME stated that these would not be ideal. The gel formulation "would sting quite a bit because it has the alcohol component. It would be drying but it would just hurt to put on," and about the cream "maybe you'd be okay, but that's not going to be very drying, it's going to be kind of slidy on there." There would be a benefit in having a compounding pharmacy "formulate it however is needed." There also could be a need for prescribers to have a stock in their office if "you were doing Unna boots." Occasionally for patients with chronic leg ulcers, a pressure wrap, or Unna boot, is used. This is changed once or twice a week and when a patient comes to have it changed, stated the SME, "you might want the metronidazole available to include in the wrap." The SME was not familiar with the need for any of the combination products but stated that the tranilast "sort of makes sense if it's helping to reduce, or if theoretically, it's helping to reduce scarring you could see it in wound management potentially" but continued that they have never seen it used.

Three SMEs stated that they had never used metronidazole but 1 did reference research done many years ago on metronidazole's ability to reduce odor related to diabetic foot wounds, mentioning that "at least there's some evidence behind it."

One SME commented on the use of metronidazole for the treatment of bacterial vaginosis stating that oral metronidazole is "limited by side effects," continuing that "it's a poorly tolerated drug." As a result, "you are limited for how long you can give it." Additionally, high-dose oral regimens can affect white cell counts, cause bone marrow suppression, and "a variety of other adverse, serious potential toxicities" leading to dose limitations. Vaginal preparations are not associated with the same adverse effects, but, as other SMEs had stated, there is a metronidazole gel that is currently available.

Three SMEs expressed concerns about the lack of evidence for the efficacy of compounded combination products. An SME who specializes in podiatry commented on the use of compounded combination products, saying, "A lot of doctors do use them. But I do not." This SME had concerns about the

miscibility of the compounds in these products and overall stability of the products once packaged. If necessary, this SME had patients apply multiple topical products "separately at different times of the day." The SME who specialized in wound care said, "We don't send anything to a compounding pharmacy or really have any special concoctions made," and continued by saying, "We don't do a lot of our own compounding because we feel like there's not a lot of evidence for some of the combinations that we see others using or have reported when we see patients that are managed in other clinics because we weren't real comfortable with combining things that don't have at least a little science behind [them]—this doesn't inactivate that and these two can play together and not cause a really bad reaction of some sort."

Two SMEs observed that, when multiple topical products are required to treat a patient, healthcare practitioners had different strategies for the application. One SME noted that some dermatologists recommend mixing multiple products together prior to application, while others recommend applying the products in a layered manner, one after the other. The SME was of the opinion that the former method, mixing prior to application, was often easier for patients, stating, "I would say probably it doesn't matter because, I mean, for the most part, I suppose it's possible that something matters, but yeah, a lot of times, if it's intended to be applied at the same time and the excipients are consistent, then I'll say mix the two and put them on. Because that's usually easier for people to remember to do."

Regarding the use of compounded products in their respective specialties, 1 SME who specializes in podiatry remarked, "Once upon a time compounding was what you did in dermatology and medicine, because things weren't available. Then I think people again, did some really shady things and bad things. I've seen bad things over the years. So, I only use those compounding agencies when absolutely necessary. So, I end up prescribing a lot of things or some of the things that are already available over the counter."

Another SME who specialized in podiatry thought that the use of compounded products within the specialty varied amongst practitioners. This SME observed, "I think there are podiatrists who are strictly doing traditional medications for the overall indications for which they've been approved. There are certainly people who are using compounded products. I have been to a number of lectures and meetings. They tend to be not true continuing education meetings, but rather lunch and learn meetings, promotional meetings, where compounding pharmacies have spoken to podiatrists. And in some of them, the podiatrist is actually speaking to other podiatrists, and they have all their preprinted prescription forms off with this pain treatment and this antifungal treatment and this antibiotic treatment."

Regarding the need for products to be compounded without certain excipients, 1 SME stated that they have not encountered challenges with excipients contained in commercially available products, but continued that, "I don't have a specialty contact dermatitis clinic . . . and yes, for them, it is really important to be able to have the flexibility because they do find real allergic reactions that they need to exclude certain ingredients from and so compounding can be really useful there."

As part of Phase 3, 1 nominator provided additional information regarding the multi-ingredient products contained within the metronidazole nomination.

Metronidazole 1% / ivermectin 1% will be compounded as a topical gel to treat rosacea, applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: oleyl alcohol, methylparaben, mineral oil, and polyethylene glycol, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants, with concerns including the following: classified as expected

to be toxic or harmful, found to cause seizures and severe neurological symptoms, possible human carcinogen, violation of industry recommendations—restricted in cosmetics, use, concentration, or manufacturing restrictions—not safe for use on injured or damaged skin, human immune and respiratory toxicant or allergen, human endocrine disruptor, and classified as a skin irritant. Metronidazole is added for its antibacterial properties and ivermectin for its anti-inflammatory properties. This product is needed because it will result in a clinical difference to patients, as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Metronidazole 1% / niacinamide 4% will be compounded as a topical cream and gel to treat rosacea applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: oleyl alcohol, methylparaben, mineral oil, and polyethylene glycol, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants with concerns including the following: classified as expected to be toxic or harmful, found to cause seizures and severe neurological symptoms, possible human carcinogen, violation of industry recommendation—restricted in cosmetics, use, concentration, or manufacturing restrictions—not safe for use on injured or damaged skin, human immune and respiratory toxicant or allergen, human endocrine disruptor, and classified as a skin irritant. Metronidazole is added for its antibacterial properties and niacinamide for its skin-conditioning benefits. This product is needed because it will result in a clinical difference to patients, as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Metronidazole 1% / ivermectin 1% / niacinamide 4% will be compounded as a topical gel to treat rosacea, applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: oleyl alcohol, methylparaben, mineral oil, and polyethylene glycol, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants with concerns including the following: classified as expected to be toxic or harmful, found to cause seizures and severe neurological symptoms, possible human carcinogen, violation of industry recommendations—restricted in cosmetics, use, concentration, or manufacturing restrictions—not safe for use on injured or damaged skin, human immune and respiratory toxicant or allergen, human endocrine disruptor, and classified as a skin irritant. Metronidazole is added for its antibacterial properties, ivermectin for its anti-inflammatory properties, and niacinamide for its skin conditioning benefits. This product is needed because it will result in a clinical difference to patients, as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Metronidazole 1% / mupirocin 2% / tranilast 1% will be compounded as a topical ointment to treat fungating wounds, applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: oleyl alcohol, methylparaben, mineral oil, polyethylene glycol, and sodium hydroxide, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants with concerns including the following: classified as expected to be toxic or harmful, found to cause seizures and severe neurological symptoms, possible human carcinogen, violation of industry recommendations—restricted in cosmetics, use, concentration, or manufacturing restrictions—not safe for

use on injured or damaged skin, human immune and respiratory toxicant or allergen, human endocrine disruptor, and classified as a skin irritant. Metronidazole is added for its antibacterial properties, mupirocin for its antibacterial properties, and tranilast for its anti-inflammatory properties. This product is needed because it will result in a clinical difference to patients, as it does not include harmful excipients found in FDA-approved drug products, and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Metronidazole 1% / brimonidine tartrate 0.25% / ivermectin 1% / niacinamide 4% will be compounded as a topical gel to treat rosacea, applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: oleyl alcohol, methylparaben, mineral oil, and polyethylene glycol, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants with concerns including the following: classified as expected to be toxic or harmful, found to cause seizures and severe neurological symptoms, possible human carcinogen, violation of industry recommendations—restricted in cosmetics, use, concentration, or manufacturing restrictions—not safe for use on injured or damaged skin, human immune and respiratory toxicant or allergen, human endocrine disruptor, and classified as a skin irritant. Metronidazole is added for its antibacterial properties, brimonidine tartrate for its anti-inflammatory properties, ivermectin for its anti-inflammatory properties, and niacinamide for its skin conditioning benefits. This product is needed because it will result in a clinical difference to patients, as it does not include harmful excipients found in FDA-approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Metronidazole 2% / clioquinol 1% / coal tar solution 2% / hydrocortisone 1% / salicylic acid 2% will be compounded as a topical cream to treat rosacea, applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylated hydroxytoluene, butylparaben, ethanol, silicon dioxide, benzalkonium chloride, butylene glycol, chlorocresol, hexylene glycol, methylparaben, oleyl alcohol, polyethylene glycol, potassium hydroxide, propylene glycol, sodium hydroxide, titanium dioxide, trolamine, and white petrolatum, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants with concerns including the following: allergen, classified as expected to be toxic or harmful, classified as irritant, classified as skin irritant, determined safe for use in cosmetics, subject to concentration or use limitations—safe for use in cosmetics with some qualifications, human endocrine disruptor, human immune and respiratory toxicant or allergen, human irritant, human respiratory irritant, human skin toxicant or allergen, human toxicant or allergen, persistent or bioaccumulative, possible human carcinogen, restricted in cosmetics (recommendations or requirements)—use, concentration, or manufacturing restrictions, violation of industry recommendations, restricted in cosmetics, and use, concentration, or manufacturing restrictions—not safe for use on injured or damaged skin (only for products for use on damaged skin). Metronidazole is added for its antibacterial properties, clioquinol is added for its anti-infective properties, hydrocortisone for its anti-inflammatory properties, and salicylic acid for its keratolytic properties. This product is needed because it will result in a clinical difference to patients, as it does not include harmful excipients found in FDA-approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

A roundtable discussion with representatives from a variety of practice settings was held to discuss the use of outsourcing facilities to obtain compounded products. Forty-three participants attended the event;

refer to Table 16 for characteristics of the facilities that the participants represented. A prequestionnaire was also distributed to participants; refer to Tables 16-19 for results of the prequestionnaire.

While a majority of the participants purchased some compounded products from an outsourcing facility, the percentage of products obtained varied from less than 1% to the majority of compounded products used at one participant's facility. A participant stated, "We have this method that we use where if we can buy it commercially ready to administer, we do that. If we can't buy it in that format, then we buy it in a vial, for example, that can be snapped into a Mini-Bag Plus because we're a Baxter house, as a second preference. If we can't buy it in either of those two formats and we can get it from a 503B, then we do that. And our last resort is compounding internally." Two participants commented that they will not outsource a product unless 2 outsourcing facilities that they contract with are able to compound the product. This redundancy will allow for a quick flip to the other outsourcing facility if there is an issue with a product compounded from 1 outsourcing facility, minimizing the impact to the participant's facility.

Participants were asked to discuss the decision-making process used at their facility to determine what products to obtain from an outsourcing facility. One major theme that emerged from this discussion was that many of the products purchased from outsourcing facilities are used in critical care areas, like emergency departments and operating rooms. Participants commented that outsourcing facilities are able to provide ready-to-use products that have longer beyond-use dates compared to products compounded in-house, allowing these products to be stocked in automated dispensing cabinets in these units. One participant commented that "we're always going to outsource a PCA [patient-controlled analgesia] syringe because we can store it in a Pyxis machine versus us making it and storing it in a fridge." Another participant commented on the benefits of storing medications in an automated dispensing cabinet, stating that "operationally, if you have a stat medication or something that needs to be delivered within 10 to 15 minutes, if you're looking at us doing it, you're looking at a 5-minute gown and glove. If we don't have somebody in the IV [intravenous] room, if you're doing 797 right, it's 5 minutes. It's 4 minutes to tube it. It's 3 minutes to make it, and then you have a dosage system or a camera system, a few minutes more. We are not able to meet that need or they're just contaminating the IV room if they are trying to do it."

Having ready-to-use products available also minimizes the need for compounding and product manipulations to occur on the floor. This can be especially beneficial in children's hospitals as they face a unique need in that they are already having to perform a lot of manipulations to products due to a lack of concentrations or sizes available. One participant commented that "at baseline, already, we manipulate about 80% of what we dispense to patients" and another stated that "there's a number of drugs that require additional manipulation, to get them to a concentration that's appropriate for kids." One participant stated that "we're trying to minimize compounding, expedite actual therapies to patients in that setting [operating room], minimize manipulations as much as possible." Similarly in the emergency department, one participant stated they prefer ready-to-use products for some floor-stock items, like vasopressor infusions, to prevent compounding from occurring on the floor, and another commented that "we absolutely buy as many pressor drips as we can." One participant remarked that they have received requests from anesthesiologists for products that are commercially available in vials that require manipulation prior to administration to be purchased as syringes from outsourcing facilities stating that "they would prefer to have a syringe form."

Another theme regarding deciding what products to purchase from an outsourcing facility was focused on the utilization and volume of a product that is needed and the overall impact this would have on the pharmacy workload. Critical care areas, like the emergency department and operating room, typically have a high product utilization and overall turnover, leading to several participants obtaining products

intended for use in these areas from outsourcing facilities. Participants stated that they evaluate the volume of product needed and the frequency in which that volume is needed compared to the time it would take pharmacy staff to prepare this volume. One participant commented that "we look at the impact that it'll have on staff. If our staff are needing to batch, or if we need to mass produce these in particular to meet the patient demand, then those are the items that we're going to look to potentially move out." Another participant stated that, while they do not obtain a lot of products from outsourcing facilities, "when we do purchase from 503Bs, typically it would be if we just don't have the capacity to keep up with what the demand is." One participant also commented that they will obtain labor-intensive and more complicated products, like epidurals and cardioplegia solutions, from outsourcing facilities to reduce the workload on pharmacy staff. The coronavirus disease 2019 (COVID-19) pandemic has also impacted the operations of hospitals, as noted by 1 participant who stated that "it's just really high volume, and the bigger the hospital, the higher the volume, especially when you have one disease state in half of your hospital" and another who expressed that "without 503B, we would've been in significant trouble." One participant commented that "even though the number might be small [percent of products obtained from outsourcing facilities], some of the reasoning is quite critical, and the amount of time that it saves is very significant for beyond what we're able to do and when." Additionally, challenges with recruiting and retaining pharmacy technicians impact decision-making, with 1 participant stating, "It is not feasible for us to meet the high volume for some common medications to repackage or compound from commercial presentations to a convenient, ready-to-use dosage form or package. The outsourcing facilities thus become a force multiplier, if you will, to offset some of the shortages in staffing."

In addition to the evaluation of the workload on pharmacy staff, the type and capabilities of the facility also impacted the decision-making process. One participant commented that they do not have an established cleanroom and therefore perform sterile compounding in a segregated compounding area. United States Pharmacopeia (USP) <797> standards limit the beyond-use date that can be assigned to these products and, as the participant stated, "We obviously need to provide product with much extensive beyond use dating than we can provide." Several participants also commented that they do not perform high-risk compounding in-house, and therefore, all of these products are outsourced. There are challenges with midsize hospitals being able "to operationalize testing compounds we make for extended stability." One participant stated, "We might make our own syringes if we could get extended dating, but I believe my operations' colleagues don't always know how to do this and adhere to the letter of the law."

One participant also commented on the impact that The Joint Commission has had on pushing pharmacies to obtain products from outsourcing facilities. The 2018 medication management standard MM.05.01.07 was intended to move IV admixture preparation out of the nursing unit. This forced pharmacies to consider strategies to make IV admixtures available for use on the floor. Additionally, NPSG.03.04.01 states that all medications and solutions should be adequately labeled, including in the operating room and other settings in which procedures are performed. USP <795> and <797> are applicable in operating room settings, stating that products should be labeled and used within 1 hour, which may be problematic if syringes are drawn up at the beginning of the day and cases are canceled or delayed. The participant also commented on the cost related to purchasing premade products from manufacturers, stating that "predatory pricing on premixes is present in the market."

Standardization of products, including concentration, volume, and labeling, was also a driver for obtaining products from an outsourcing facility. However, such standardization may not always be possible. One participant stated that when evaluating similar facilities, you would expect them to have similar needs regarding the concentrations and volumes of products utilized. However, the products utilized in a facility are often developed in-house over decades based on physician and nurse requests, and, more recently, appropriateness for an automated dispensing cabinet. As a result, one participant

observed, “These practices had evolved somewhat disparately; even if we had clinical practice guidelines, nobody was putting concentrations into those guidelines and volumes into those guidelines.” This has led to challenges with obtaining certain products from outsourcing facilities. As another participant said, “I think we made 9 different epidural concentrations, all driven by anesthesia, and they want what they want and 503Bs may not offer that. No one else in the country is buying that same concentration; a 503B isn’t going to go through the expense of adding that to their product list.” The participant continued that “similar with the ADCs [automated dispensing cabinets], we’ve run into situations where dextrose 50% goes on shortage and the 503Bs would be selling it in a syringe. For safety reasons and for crash cart reasons, without having to retrain thousands of nurses of where things are placed, they said, ‘No, we can’t have it, and that’s too big it won’t fit,’ we want it in this format—and then we’re stuck again because there’s no 503B offering a format during that shortage that fits where it needs to go. Then we’re stuck in sourcing.” Additionally, while a commercially available product may be available, the volume may not be appropriate. One participant stated that “3% saline for instance, is sold in a 500 mL bag, but the clinical guideline is a 150 mL bolus. We’re either going to draw that out or we’re sending it to the ER with stickers all over it saying only give 150 [mL].” The participant continued that “it would be great if the FDA could look at the size of the container that they’re approving and whether that’s a realistic dose; is it a unit dose or isn’t it?”

Participants had differing opinions on the use of outsourcing facilities to obtain drugs during a shortage. Several participants stated that they will typically first restrict use of a drug on shortage, in order to conserve supply, before turning to an outsourcing facility. One participant commented that “most of the time, I will probably pursue restricting, conserving, and looking at all available options prior to going to an outsourcer on my end,” and another stated, “I can only think of one time in recent history where we went to an outsourcer.” One participant commented that “503Bs can’t accept the additional volume if it’s a true shortage. If you’re not with them preshortage, you’re not going to get products when you need it during the shortage,” continuing that “typically in a shortage, you learn to live without them. You have to.” Additionally, in the event of the shortage being the result of lack of an API, outsourcing facilities are likely to be equally affected and unable to provide assistance. However, one participant stated that they first began working with outsourcing facilities because of shortages. This participant commented that “what the 503Bs are starting to do, some of the large ones, is that they are also conducting validation studies on API. If sterile becomes short, they quickly switch to producing through API, which ASHP [American Society of Health-System Pharmacists] and the FDA allows.” This “adds a lot of flexibility so they can bounce back and forth and really try to insulate us from shortages.”

A few participants commented on the use of API by outsourcing facilities. One commented that as long as they are conducting end-product sterility and stability testing and the product meets quality standards, they are not concerned with the starting ingredients. As long as buyers are familiar with regulations and know what to look for, another participant commented, there should not be any issues with purchasing products compounded starting from API. Another participant stated that as more outsourcing facilities began using API, they became more comfortable with them doing so. However, one participant observed that most outsourcing facilities are switching to sterile-to-sterile and only using API if there is a shortage, stating, “I think the FDA has really looked closely at API, and they’re slowly pushing the 503B outsourcers to a sterile-to-sterile.” Only 1 participant commented that they prefer sterile-to-sterile. Another participant stated that the companies they use are all sterile-to-sterile.

A few participants commented on the need for preservative-free products, particularly in pediatric patients. The example of methadone was provided as it is used for patients with neonatal abstinence syndrome but is only available as a preservative-containing product. So, there is a need for this product to be compounded from API as a preservative-free product. One participant stated that “if there’s not a

preservative-free containing option, it really should be something that should be able to be compounded from bulk ... especially for the pediatric patient population." However, another participant from a children's hospital stated that the need for a preservative-free option has never been a reason why they have obtained a product from an outsourcing facility. Preservative-free is also an issue for ophthalmic products; however, 1 participant observed this is more on the 503A side. One participant stated that obtaining ophthalmic products from outsourcing facilities has been a challenge and that there are products they would like to obtain from outsourcing facilities but are not able to, forcing them to compound them in-house. This participant also commented that there are 2 outsourcing facilities that compound ophthalmic products, but when they reviewed the facilities, they did not pass their internal quality standards; 1 facility had been banned from distributing products in California by the Board of Pharmacy. There is an additional challenge with obtaining cephalosporins and beta-lactams due to the potential cross-reactivity in patients with allergies. One participant stated that there are some cephalosporins they would like to obtain from an outsourcing facility but cannot because "they would have to build a separate cleanroom with a dedicated HVAC [heating, ventilation, and air conditioning], so you're talking millions of dollars in investment for actually very low volume. Right now, the ROI [return on investment] isn't there." Another participant stated that the concentrations required for ophthalmic antibiotics are not available, but the labor and risk of compounding these products in-house is not worth it.

A few participants commented on purchasing nonsterile products from outsourcing facilities. LET (lidocaine-epinephrine-tetracaine) gel, for use as a topical anesthetic, was the most commonly obtained product along with buffered lidocaine to put in J-Tips. Another participant stated that they obtain diclofenac suppositories from an outsourcing facility due to the high cost of indomethacin suppositories. One participant commented that most of the products they outsource are nonsterile products, generally for oral or topical administration due to a lack of commercially available products being available. The participant stated that they purchase low-dose naltrexone for oral use in patients with refractory fibromyalgia and ketamine troches for patients with chronic pain. The participant continued that, while the evidence does not support many of the ingredients used in topical pain products, "However, there are select patients. It's very rare that taking that cream away from them actually causes more harm than good." A few participants commented that there is a gap in the market for nonsterile products with 1 stating, "I think that there is a large opportunity for more nonsterile products to be produced by 503Bs." Another stated that as their facility grows and acquires more outpatient clinics, they receive a lot of questions regarding obtaining products for office use. The participant noted that they often have to refer these clinics to outsourcing facilities but stated "There's not many 503Bs [that] are doing the nonsterile for clinic use." As a result, the inpatient pharmacy is often asked to take on this role but "you don't have the space or the staff to do that."

Based on the responses to the prequestionnaire (refer to *Results of survey*), participants were asked questions regarding specific products obtained from outsourcing facilities. Several participants reported using alum (aluminum potassium) as a bladder irrigation for hemorrhagic cystitis refractory to other treatment options. Participants commented that this is high-risk compounding; they purchase alum from an outsourcing facility because they do not perform high-risk compounding in their facility. One participant commented that their policy states that high-risk compounding is not allowed except for alum. This participant wanted to move away from compounding alum in-house and stated that the addition of aluminum potassium to the bulks list might allow this to happen. Another participant had compounded alum in-house from nonsterile ingredients; however, there had been challenges with crystallization after storage. A few participants commented that there is a sterile alum powder available, which they purchase to compound in-house. One participant had concerns regarding this powder, stating that "I've talked to that company, but I've had some concerns for them because they don't sell it as a drug. The owner was

selling you a chemical; we're selling you a bulk API. It's just sterile. They were fuzzy and I never followed up, but when I asked about their process for verifying the sterility, as you would with a sterile product—we do USP <71> Sterility Testing—they couldn't really give me an answer. They just say they tested for sterility." The participants commented that alum is only needed a few times a year. However, as one participant observed, "When you need it, it's an emergency," and another noted that it "is a challenge for anybody who has the cyclophosphamide-induced hemorrhagic cystitis." As a result, one participant maintains a small inventory of alum product that is purchased from an outsourcing facility, but "more times than not, they go unused and expire." Another stated that they do not keep it in stock because there is a minimum purchase and there are only a few cases a year for whom they need to use alum. The participant had it stat shipped when needed. Another participant stated that "we had a meeting with the head of urology who was baffled why they're even ordering it. He was like, 'This is an old, really old. I don't even know why we're using it' and basically approved for us to not even make it anymore for now."

Two participants commented on the use of glycerin at their facility. One stated that they purchase it from a 503A because they were not able to find an outsourcing facility that provides this product. The participant commented that glycerin is used in 3 different concentrations at their facility, 1 for ophthalmic use, 1 for neurologic use in trigeminal neuralgia, and 1 for instilling into "a very specific kind of pump that's used to deliver a very specific kind of chemotherapy." When there are breaks in the chemotherapy regimen, the pump has to be filled with something, and by using glycerin "it can go 3 months or something like that, so it's a huge patient satisfier to have that concentration available." The participant also commented that since they have been unable to find an outsourcing facility that compounds the concentration needed for trigeminal neuralgia, they have patients who have been waiting years for treatment. The other participant stated that they compound it in-house but said that it is not done very frequently. The participant commented that it is very difficult to sterilize due to the thickness of the product.

Four participants stated that they obtain sodium citrate as ready-to-use syringes for use as a locking solution in patients undergoing dialysis, with 1 commenting that "our nephrologists, like it in place of heparin for some patients to keep the ports patent or so they don't have to go to alteplase or some of the other drugs." There is a commercially available product; however, it is only available as a 500-mL bag and the dose needed is typically less than 30 mL. If the syringes are prepared in-house, then the beyond-use date is limited to 12 to 24 hours depending on storage, which results in waste.

One participant stated that they obtain papaverine from outsourcing facilities for use in urology as Bimix (papaverine/phentolamine) and Trimix (papaverine/phentolamine/alprostadil).

While none of the participants obtained sodium phosphate or aspartic acid from outsourcing facilities for use in cardioplegic solutions, a few commented that they do obtain cardioplegic solutions from outsourcing facilities. The del Nido formulation was the product most commonly obtained. One participant commented that they compound this formulation in-house because the outsourcing facilities did not offer the volume needed at their institution. Another participant commented that while they do obtain the del Nido formulation from an outsourcing facility, they also compound a proprietary formulation in-house. This participant observed that "it is complicated to do in-house. We do it on a Baxa 1200 or 2400, either one, compounder. Then we send it up [sic] for pH and potassium testing. Obviously, then we're confined to 797 beyond-use dates versus longer beyond-use dates that we get from the 503B." Another participant commented that cardioplegic solutions are managed by the perfusion department, not pharmacy, and they use del Nido solution as well as 3 other formulations.

The participants also discussed challenges with utilizing outsourcing facilities. One participant stated that their facility does not use outsourcing facilities because "it just hasn't been financially, not just the money

worth it, but just the lead time for how much time you have to give them and how much you have to ... It just isn't worth the dating that they gave us or can give us." Another commented that they obtain very little product from outsourcing facilities due to "the amount of work for vetting and continually validating quality of these 503B outsourcing facilities." The participant stated that they have a robust validation process that takes several months and includes a site visit prior to purchasing from an outsourcing facility, followed by continuous reviewing of quality reports and warning letters. Another challenge has been the reliability of the outsourcing facility. One participant commented that "traditionally, we've found 503Bs to be fairly unreliable, when we have partnered with certain ones, to be able to keep up with the volume. Everybody knows PharMEDium just closed, but we've had some other smaller 503Bs where we've had agreements for certain products to take it off our plate, and then low and behold they're shut down, or closed, or whatever it may be." Minimum purchase amounts were also reported as a concern, with one participant stating that "what we see consistently is the 503Bs, they want us to commit to giving them a certain volume, but then will not give us a reciprocal commitment or at least will not fulfill that reciprocal commitment. That's a huge problem for us making that type of commitment, when we do ultimately have to split our volume in order to make sure that we consistently are able to take care of our patients." Another challenge was related to outsourcing facilities utilizing API to compound narcotics. One participant commented that this often worsens drug shortages due to the quotas that the Drug Enforcement Administration (DEA) places on the quantity that can be produced. The participant stated that "they [outsourcing facilities] want to buy the product that we're trying to buy to take care of our patients today, to sell us tomorrow. We really need the FDA to say that, especially for controlled substances, that 503Bs can consistently prepare those products so that we don't end up with a shortage year after year, after year and then chasing our tail. Also, we may actually want to tell 503Bs, they can't buy those products or that they're limited in the amount of their ability to buy those products to make what are essentially copies of commercially available products, because it actually induces the shortage in many ways."

Results of survey

Thirty-three people responded to the survey distributed via professional medical associations and available on the project website; refer to Table 11 for respondent characteristics.

Among respondents, 4 (6% of 64 responses, where respondents were allowed to select multiple products) used metronidazole as a compounded topical product (refer to Table 12). Fourteen (100% of 14 responses) respondents reported utilizing compounded topical products in combination with other active pharmaceutical ingredients as a multi-ingredient product.

Ten respondents (50% of 20 responses, where respondents were allowed to select multiple reasons) reported using compounded topical products due to lack of commercial products in an appropriate dosage form, strength or combination, patient allergies preventing use of commercially available products (1, 5%), other patient conditions preventing use of commercial products (3, 15%), or no commercially available products (3, 15%). Three respondents (15%) used compounded topical products because "oral medications are contraindicated due to comorbidities," because they are "very good for medication use, patient compliance is improved with need to apply medication," and because they "decreased systemic effects and higher concentrations at specific areas of need." Refer to Table 13 for reasons for using compounded topical products.

The majority of respondents (11 of 13 responses, 85%) did not stock non-patient-specific compounded products at their practice. Respondents reported obtaining compounded topical products by purchasing, or having the patient purchase, the product from a compounding pharmacy (12 of 14 responses, where

respondents were allowed to select multiple avenues, 86%) or outsourcing facility (2, 14%). Refer to Table 15 for how respondents obtained compounded products.

A prequestionnaire was distributed to participants of the roundtable discussion (refer to Appendix 2.3 for survey instrument).

Forty-three people responded to the prequestionnaire; refer to Table 16 for respondent characteristics. Amongst respondents, 35 (81% of 43 total respondents) utilized outsourcing facilities to obtain drug products, 4 (9%) did not utilize outsourcing facilities, and 4 (9%) did not respond to this question.

Twenty-seven respondents (19% of 143 responses, where respondents were allowed to select multiple reasons) obtained drug products from outsourcing facilities due to a need for ready-to-use products, and 20 respondents (14%) obtained drug products from outsourcing facilities due to backorders (refer to Table 17).

Fourteen respondents (31% of 45 total responses, where respondents were allowed to select multiple types) obtained nonsterile products from outsourcing facilities, and 31 (69%) obtained sterile products from outsourcing facilities. Refer to Table 18 for the categories of products obtained from outsourcing facilities.

Metronidazole was not included on the prequestionnaire (refer to Table 19).

Table 11. Characteristics of survey respondents

Terminal Clinical Degree	**Responses, n (N = 29)**
Doctor of Medicine (MD)	0
Doctor of Osteopathic Medicine (DO)	0
Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)	2
Physician Assistant (PA)	0
Doctor of Podiatric Medicine (DPM)	27
No response	6
Practice Setting	**Responses, n (N = 35)[a]**
Physician office or private practice	23
Outpatient clinic	6
Hospital or health system	3
Academic medical center	1
Emergency room	0
Operating room	2

No response	6

[a]Some respondents reported more than one practice setting.

Table 12. Compounded topical products prescribed or administered

Condition	Responses, n (N = 64)[a]
Clotrimazole	15
Fluconazole	6
Itraconazole	9
Ketoconazole	11
Metronidazole	4
Mupirocin	9
Zinc oxide	3
None of the above	15
No response	4

[a]Survey respondents were allowed to select multiple products.

Table 13. Reasons for using compounded topical products

Reason	Responses, n (N = 20)[a,b]
Commercial product not available in desired dosage form, strength, or combination	10
Patient allergies prevent use of commercial products	1
Patient conditions prevent use of commercial products	3
No commercial products	3
Other[b]	3

[a]Survey respondents were allowed to select multiple reasons.
[b]Respondents stated, “Oral medications are contraindicated due to comorbidities”; “very good for medication use, patient compliance is improved with need to apply medication”; and “decreased systemic effects and higher concentrations at specific areas of need.”

Table 14. Stock of non-patient-specific compounded topical products

Do you stock non-patient-specific compounded topical products at your practice?	**Responses, n (N = 13)**
Yes	2
No	11
Not sure	0
No response	20

Table 15. Obtainment of compounded topical products

How do you obtain compounded topical products?	**Responses, n (N = 14)[a]**
Compound yourself at practice	0
Product compounded by in-house pharmacy	0
Purchase from compounding pharmacy	12
Purchase from outsourcing facility	2
No response	21

[a]Survey respondents were allowed to select methods.

Table 16. Demographics of prequestionnaire respondents' facilities

Type of Facility	**Responses, n (N = 102)[a]**
Academic medical center	15
Acute care hospital	16
Children's hospital	8
Community hospital	11
Critical access hospital	2
Dialysis center	2
Federal government hospital	4
Health system	15
Inpatient rehabilitation center	4

Long-term acute care hospital	3
Outpatient surgery center	6
Rural hospital	2
Skilled nursing facility	0
Specialty hospital[b]	4
Trauma center	5
Urban hospital	5
Number of Beds	**Responses, n (N = 39)**
< 50	4
50-99	3
100-199	1
200-299	4
300-399	5
400-599	3
> 600	19

[a]Respondents were allowed to select more than one type of facility.
[b]Specialties provided include cardiology, pulmonary, vascular, home infusion, neurology, psychiatry, and oncology.

Table 17. Reasons for obtaining products from outsourcing facilities

Categories	Responses, n (N = 143)[a]
Backorders	20
Convenience	19
Cost	10
Need for concentrations not commercially available	19
Need for multi-ingredient products not commercially available	10
Need for preservative-free products	3
Need for ready-to-use products	27

No FDA-approved product available	7
No onsite compounding facility	1
Onsite compounding facility not equipped to compound all necessary products	19
Other[b]	8

Abbreviation: FDA, US Food and Drug Administration.
[a]Respondents were allowed to select multiple categories.
[b]Respondents reported staffing shortages, need for extended dating, volume of product used, and standardization projects as additional reasons for utilizing outsourcing facilities.

Table 18. Categories of products obtained from outsourcing facilities

Categories	**Responses, n (N = 142)[a]**
Cardioplegic solutions	14
Dermatologic preparations	6
Dialysate solutions	0
Fluids	8
Ophthalmic preparations	10
Patient-controlled analgesia	20
Ready-to-use anesthesia syringes	25
Ready-to-use antibiotic syringes and/or bags	14
Ready-to-use electrolyte solutions	5
Ready-to-use vasopressor solutions	18
Total parenteral nutrition solutions	16
Other[b]	6

[a]Respondents were allowed to select multiple categories.
[b]Respondents reported obtaining alum for bladder irrigation, oxytocin, anticoagulant sodium citrate solution, narcotic drips, high-cost antiseizure medications, antiviral medications, topical pain, and oral tablets/capsules.

Table 19. Products obtained from an outsourcing facility

Product	Responses, n (N=108)[a]
Acetylcysteine	1
Adenosine	2
Aluminum potassium sulfate	2
Aspartic acid	0
Atenolol	0
Atropine	9
Baclofen	4
Betamethasone	0
Biotin	0
Bupivacaine	8
Calcium chloride	1
Caffeine sodium benzoate	0
Cholecalciferol	1
Chromium chloride	0
Clonidine	0
Dexamethasone sodium phosphate	0
Diclofenac	0
Gentamicin	0
Glycerin	1
Hydroxyzine	0
Ketamine	14
Levocarnitine	0
Lidocaine	8
Lorazepam	2
Magnesium sulfate	4

Manganese chloride	0
Methylprednisolone	0
Midazolam	15
Mupirocin	1
Norepinephrine	15
Ondansetron	0
Phytonadione	0
Potassium chloride	0
Potassium phosphate	0
Prilocaine	0
Proline	0
Propranolol	1
Ropivacaine	6
Sodium chloride	0
Sodium citrate	3
Sodium phosphate	0
Tetracaine	2
Triamcinolone acetonide	0
Tropicamide	0
None of the above	8

[a]Respondents were allowed to select multiple products.

CONCLUSION

Metronidazole was nominated for inclusion on the 503B Bulks List as various topical dosage forms in strengths based on the prescriber's request to treat unspecified medical conditions. Metronidazole is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, Latvia, Namibia, New Zealand, Saudi Arabia, the UK, and the US.

From the literature review, 3 studies were included in which metronidazole was used topically to treat blepharitis, rosacea, and ulcerated lip hemangiomas. Metronidazole was used as a compounded product in combination with ivermectin to treat blepharitis and with niacinamide to treat rosacea.

As part of Phase 3, 1 nominator provided additional information regarding the multi-ingredient products contained within the metronidazole nomination. Metronidazole will be compounded in combination with additional APIs as several multi-ingredient topical products to treat rosacea and fungating wounds. Metronidazole is added to each formulation for its antibacterial properties. The authors' conclusions either did not provide a recommendation regarding the use of metronidazole or stated that additional studies were needed.

From the interviews, metronidazole is commonly used topically to treat rosacea, but there are products that are commercially available. Metronidazole is also used orally to treat bacterial vaginosis but is associated with adverse effects and poor tolerance. However, there is a commercially available gel formulation that can be used vaginally to treat bacterial vaginosis. Metronidazole can also be used topically to alleviate the odor associated with chronic wounds and fungating tumors. Anerobic bacteria are typically the cause of these odors and metronidazole can reduce bacterial colonization, reducing the odor. One SME did see a use for compounded formulations for these patients, as the commercially available formulations are not ideal. Additionally, there is a potential need for these products to be stocked in-office to facilitate dressing changes for patients with these wounds or tumors.

From the survey responses, 4 out of 33 respondents used compounded topical metronidazole. Metronidazole was not included on the prequestionnaire.

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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 February 9, 2021
- Date last searched: February 10, 2021
- Limits: Humans (search hedge); English language
- Number of results: 166

1	metronidazole/	12,905
2	metr#nida$.tw.	16,373
3	or/1-2	20,498
4	administration, topical/	38,880
5	administration, cutaneous/	22,485
6	skin absorption/	11,854
7	topical$.tw.	108,790
8	transcutaneous$.tw.	14,874
9	epicutaneous$.tw.	2046
10	transdermal$.tw.	15,024
11	((cutanous$ or dermal$ or skin) adj3 (absorb$ or absorpt$ or appl$)).tw.	11,624
12	exp gels/	53,656
13	emulsions/	18,512
14	suspensions/	7853
15	liniments/	124
16	ointments/	12,865
17	skin cream/	1105
18	pharmaceutical solutions/	3316
19	gel?.tw.	312,628
20	emulsion?.tw.	34,428

21	suspension?.tw.	111,582
22	liniment?.tw.	148
23	ointment?.tw.	12,167
24	salve?.tw.	345
25	paste?.tw.	12,942
26	unguent$.tw.	114
27	lotion?.tw.	2385
28	cream?.tw.	19,546
29	shampoo?.tw.	1451
30	solution?.tw.	723,580
31	or/4-30	1,348,139
32	drug combinations/	74245
33	aloe/	1401
34	aloe.tw.	2839
35	azeloglycin$.tw.	1
36	azeloyl.tw.	8
37	brimonidine tartrate/	1489
38	br#monidin$.tw.	1023
39	br#moratio$.tw.	0
40	br#mostad.tw.	0
41	br#mot$.tw.	1311
42	br#mozept.tw.	0
43	br#moxidin$.tw.	34
44	brymont.tw.	0
45	clioquinol/	981
46	chlor?iodoquin$.tw.	5

47	cli?quinol$.tw.	603
48	iodoch?or? hydroxycholin$.tw.	0
49	iodoch?or?hydroxycholin$.tw.	0
50	iodoch?or? hydroxyquin$.tw.	2
51	iodoch?or?hydroxyquin$.tw.	96
52	iodoch?or?xyquin$.tw.	22
53	iodohydroxych?or?quin$.tw.	1
54	isoch?or?xychinolin$.tw.	0
55	quiniodochlor$.tw.	2
56	coal tar/	2334
57	((coal or doak) adj tar).tw.	1319
58	hydrocortisone/	72,676
59	17 hydroxycorticosterone.tw.	78
60	compound f.tw.	173
61	h#dro#ortis$.tw.	16,609
62	ivermectin/	6522
63	ivermect$.tw.	6199
64	mupirocin/	1253
65	mupirocin$.tw.	1872
66	pseudomonic acid$.tw.	89
67	niacinamide/	12,603
68	amid$ pp.tw.	4
69	nicotinamid$.tw.	21,909
70	niacetamid$.tw.	0
71	niacinamid$.tw.	520
72	niacin amid$.tw.	3

73	nicamid$.tw.	0
74	nicosedin$.tw.	0
75	nicotamid$.tw.	14
76	(nicotinic adj2 amid$).tw.	115
77	nicotinoylamid$.tw.	1
78	ni#otinsaureamid$.tw.	0
79	nikotamin$.tw.	0
80	vitamin$ b3.tw.	446
81	vitamin$ b 3.tw.	54
82	vitamin$ pp.tw.	164
83	salicylic acid/	6717
84	((hydroxybenzoic or salicylic) adj2 acid$).tw.	15,821
85	anthranilic acid$.tw.	1391
86	tranilast$.tw.	628
87	or/32-86	221,880
88	and/3,31,87	196
89	exp animals/ not humans/	4,786,326
90	88 not 89	183
91	limit 90 to english language	166

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: February 10, 2021
- Limits: Humans (search hedge); English language
- Number of results: 594

1	‘metronidazole’/de	70,819
2	‘metranida*’:ti,ab,tn	64
3	‘metronida*’:ti,ab,tn	23,979
4	#1 OR #2 OR #3	73,137
5	‘topical drug administration’/de	84,198
6	‘cutaneous drug administration’/de	749
7	‘transdermal drug administration’/de	9283
8	‘skin absorption’/de	8169
9	‘topical treatment’/de	13,793
10	‘topical*’:ti,ab	153,930
11	‘epicutaneous*’:ti,ab	3475
12	‘transdermal*’:ti,ab	22,013
13	((cutaneous* OR dermal* OR skin) NEAR/3 (absorb* OR absorp* OR appl*)):ti,ab	18,377
14	‘cream’/de	9810
15	‘gel’/exp	81,063
16	‘liniment’/de	257
17	‘lotion’/de	2964
18	‘ointment’/de	18,258
19	‘paste’/de	2550
20	‘salve’/de	170
21	‘suspension’/de	28,563
22	‘emulsion’/exp	47,835

23	‘shampoo’/de	2340
24	‘cream$’:ti,ab	30,545
25	‘emulsion$’:ti,ab	46,560
26	‘liniment$’:ti,ab	242
27	‘lotion$’:ti,ab	4114
28	‘ointment$’:ti,ab	21,988
29	‘paste$’:ti,ab	15,469
30	‘salve$’:ti,ab	486
31	‘unguent*’:ti,ab	242
32	‘gel$’:ti,ab	368,162
33	‘suspension$’:ti,ab	148,336
34	‘shampoo$’:ti,ab	2271
35	‘solution$’:ti,ab	895,285
36	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #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	1,717,718
37	‘drug combination’/de	170,854
38	‘aloe’/exp	3862
39	‘aloe’:ti,ab,tn	4420
40	‘azeloglycin*’:ti,ab,tn	2
41	‘azeloyl’:ti,ab,tn	9
42	‘brimonidine’/de	4899
43	‘brimonidin*’:ti,ab,tn OR ‘bromonidin*’:ti,ab,tn	1290
44	‘brimoratio*’:ti,ab,tn OR ‘bromoratio*’:ti,ab,tn	0
45	‘brimostad’:ti,ab,tn OR ‘bromostad’:ti,ab,tn	0
46	‘brimot*’:ti,ab,tn OR ‘bromot*’:ti,ab,tn	1818
47	‘brimozept’:ti,ab,tn OR ‘bromozept’:ti,ab,tn	0
48	‘brimoxidin*’:ti,ab,tn OR ‘bromoxidin*’:ti,ab,tn	35

49	‘brymont’:ti,ab,tn	0
50	‘clinimicin*’:ti,ab,tn	0
51	‘clinimycin*’:ti,ab,tn	10
52	‘clioquinol’/de	3136
53	‘chlor$iodoquin*’:ti,ab,tn	8
54	‘cli$quinol*’:ti,ab,tn	823
55	‘iodochor hydroxycholin*’:ti,ab,tn	0
56	‘iodochorhydroxycholin*’:ti,ab,tn	0
57	‘iodochor hydroxyquin*’:ti,ab,tn	3
58	‘iodochorhydroxyquin*’:ti,ab,tn	180
59	‘iodochorxyquin*’:ti,ab,tn	43
60	‘iodohydroxychorquin*’:ti,ab,tn	1
61	‘isochorxychinolin*’:ti,ab,tn	0
62	‘quiniodochlor*’:ti,ab,tn	4
63	‘coal tar’/de	2959
64	((coal OR doak) NEAR/1 tar):ti,ab,tn	1929
65	‘hydrocortisone’/de	144,823
66	‘17 hydroxycorticosterone’:ti,ab,tn	180
67	‘compound f’:ti,ab,tn	346
68	‘hidrocortis*’:ti,ab,tn	24
69	‘hidrokortis*’:ti,ab,tn	0
70	‘hydrocortis*’:ti,ab,tn	27,977
71	‘hydrokortis*’:ti,ab,tn	7
72	‘ivermectin’/de	12,822
73	‘ivermect*’:ti,ab,tn	7633
74	‘pseudomonic acid’/de	7170

75	‘mupirocin*’:ti,ab,tn	2662
76	‘pseudomonic acid*’:ti,ab,tn	128
77	‘nicotinamide’/exp	16,732
78	‘amid* pp’:ti,ab,tn	7
79	‘nicotinamid*’:ti,ab,tn	26,503
80	‘niacetamid*’:ti,ab,tn	0
81	‘niacinamid*’:ti,ab,tn	819
82	‘nicamid*’:ti,ab,tn	1
83	‘nicosedin*’:ti,ab,tn	0
84	‘nicotamid*’:ti,ab,tn	26
85	(nicotinic NEAR/2 acid*):ti,ab,tn	9650
86	‘nicotinoylamid*’:ti,ab,tn	2
87	‘nicotinsaureamid*’:ti,ab,tn	6
88	‘nikotinsaureamid*’:ti,ab,tn	2
89	‘nikotamin*’:ti,ab,tn	0
90	‘vitamin* b3’:ti,ab,tn	525
91	‘vitamin* b 3’:ti,ab,tn	20
92	‘vitamin* pp’:ti,ab,tn	297
93	‘salicylic acid’/de	26,899
94	‘salicylic acid*’:ti,ab,tn	15,641
95	‘carboxyphenol’:ti,ab,tn	9
96	‘hydroxybenzoic acid*’:ti,ab,tn	3402
97	‘tranilast’/de	1569
98	‘anthranilic acid*’:ti,ab,tn	2026
99	‘tranilast*’:ti,ab,tn	844
100	#37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68	438,239

	OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99	
101	#4 AND #36 AND #100	678
102	[animals]/lim NOT [humans]/lim	6,167,026
103	#101 NOT #102	643
104	#101 NOT #102 AND [english]/lim	594

Appendix 2.1 Survey instrument for professional medical associations

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)	○	○	○
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	○	○	○
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	○	○	○

2. Do you prescribe or administer any of the following as a compounded topical product? (please check all that apply)
    - Clotrimazole
    - Fluconazole
    - Itraconazole
    - Ketoconazole
    - Metronidazole
    - Mupirocin
    - Zinc oxide
    - None of the above
3. Do you prescribe the compounded topical products that you selected in combination with other active pharmaceutical ingredients as a multi-ingredient product?
    - Yes
    - No
    - I'm not sure
4. Why do you use the compounded topical products that you selected? (please check all that apply)
    - Commercial products are not available in the dosage form, strength, or combination I need (please explain) _____
    - Patient allergies prevent me from using commercially available products (please explain) _____
    - Patient conditions prevent me from using commercially available products (please explain) _____
    - I am not aware of any commercially available products containing these products
    - Other (please explain) _____
5. Do you stock non-patient-specific compounded products at your practice?
    - Yes
    - No
    - I'm not sure
6. I obtain compounded products from the following: (please check all that apply)
    - Compound myself at my practice
    - Have the product compounded by an in-house pharmacy

- Purchase, or have a patient purchase, from a compounding pharmacy
- Purchase, or have a patient purchase, from an outsourcing facility
- Other (please explain) _____

7. What is your practice setting? (please check all that apply)
   - Physician office/private practice
   - Outpatient clinic
   - Hospital/health system
   - Academic medical center
   - Emergency room
   - Operating room
   - Other (please describe) _____
8. What degree do you hold? (please check all that apply)
   - Doctor of Medicine (MD)
   - Doctor of Osteopathic Medicine (DO)
   - Doctor of Medicine in Dentistry (DMD/DDS)
   - Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
   - Naturopathic Doctor (ND)
   - Nurse Practitioner (NP)
   - Physician Assistant (PA)
   - Other (please describe) _____

Appendix 2.2. Survey instrument for professional medical associations

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)	○	○	○
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	○	○	○
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	○	○	○

2. Do you prescribe or administer any of the following as a compounded topical product? (please check all that apply)
    - ○ Betamethasone acetate
    - ○ Betamethasone dipropionate
    - ○ Betamethasone sodium phosphate
    - ○ Cholestyramine resin
    - ○ Cimetidine
    - ○ Clobetasol propionate
    - ○ Clotrimazole
    - ○ Cromolyn sodium
    - ○ Dexamethasone sodium phosphate
    - ○ Diclofenac sodium
    - ○ Finasteride
    - ○ Fluconazole
    - ○ Fluticasone propionate
    - ○ Hydrocortisone
    - ○ Itraconazole
    - ○ Ketoconazole
    - ○ Lidocaine hydrochloride
    - ○ Methylprednisolone acetate
    - ○ Metronidazole
    - ○ Mupirocin
    - ○ Niacinamide
    - ○ Phytonadione (vitamin K1)
    - ○ Prilocaine
    - ○ Spironolactone
    - ○ Sulfacetamide sodium monohydrate
    - ○ Terbinafine hydrochloride
    - ○ Tetracaine hydrochloride
    - ○ Triamcinolone acetonide
    - ○ Zinc oxide

- None of the above

3. Do you prescribe the compounded topical products that you selected in in combination with other active pharmaceutical ingredients as a multi-ingredient product?
    - Yes
    - No
    - I'm not sure
4. Why do you use the compounded topical products that you selected? (please check all that apply)
    - Commercial products are not available in the dosage form, strength, or combination I need (please explain) _____
    - Patient allergies prevent me from using commercially available products (please explain) _____
    - Patient conditions prevent me from using commercially available products (please explain) _____
    - I am not aware of any commercially available products containing these products
    - Other (please explain) _____
5. Do you stock non-patient-specific compounded products at your practice?
    - Yes
    - No
    - I'm not sure
6. I obtain compounded products from the following: (please check all that apply)
    - Compound myself at my practice
    - Have the product compounded by an in-house pharmacy
    - Purchase, or have a patient purchase, from a compounding pharmacy
    - Purchase, or have a patient purchase, from an outsourcing facility
    - Other (please explain) _____
7. What is your practice setting? (please check all that apply)
    - Physician office/private practice
    - Outpatient clinic
    - Hospital/health system
    - Academic medical center
    - Emergency room
    - Operating room
    - Other (please describe) _____
8. What degree do you hold? (please check all that apply)
    - Doctor of Medicine (MD)
    - Doctor of Osteopathic Medicine (DO)
    - Doctor of Medicine in Dentistry (DMD/DDS)
    - Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
    - Naturopathic Doctor (ND)
    - Nurse Practitioner (NP)
    - Physician Assistant (PA)
    - Other (please describe) _____

Appendix 2.3. Survey instrument for pharmacy roundtable prequestionnaire

1. Please select all that apply regarding the facility with which you are affiliated.
    - Academic medical center
    - Acute care hospital
    - Children's hospital
    - Community hospital
    - Critical access hospital
    - Dialysis center
    - Federal government hospital
    - Health system
    - Inpatient rehabilitation center
    - Long-term acute care hospital
    - Outpatient surgery center
    - Rural hospital
    - Skilled nursing facility
    - Specialty hospital, please identify specialty(ies)
    - Trauma center
    - Urban hospital
2. Please select the number of beds in the facility with which you are affiliated.
    - < 50
    - 50-99
    - 100-199
    - 200-299
    - 300-399
    - 400-599
    - > 600
3. Do you use an outsourcing facility (503B facility) to obtain any products used in your facility? A list of FDA registered outsourcing facilities can be found at https://www.fda.gov/drugs/human-drug-compounding/registered-outsourcing-facilities.
    - Yes
    - No
4. Why do you use an outsourcing facility to obtain product(s)? Please select all that apply
    - Backorders
    - Convenience
    - Cost
    - Need for concentrations not commercially available
    - Need for preservative-free products
    - Need for ready-to-use products
    - No FDA-approved products available
    - No onsite compounding facility
    - Onsite compounding facility not equipped to compound all necessary products
    - Other, please explain _____
5. Please select the type(s) of products obtained from an outsourcing facility.
    - Nonsterile products
    - Sterile products
6. Please select the category(ies) of products obtained from an outsourcing facility.
    - Cardioplegic solutions
    - Dermatologic preparations
    - Dialysate solutions

- Fluids
- Ophthalmic preparations
- Patient-controlled analgesia
- Ready-to-use anesthesia syringes
- Ready-to-use antibiotic syringes and/or bags
- Ready-to-use electrolyte solutions
- Ready-to-use vasopressor solutions
- Total parenteral nutrition solutions
- Other, please identify _____

7. From the list below, please select the drug(s) that you obtain as either a single ingredient or multi-ingredient product from an outsourcing facility.
    - Acetylcysteine
    - Adenosine
    - Aluminum potassium sulfate
    - Aspartic acid
    - Atenolol
    - Atropine
    - Baclofen
    - Betamethasone
    - Biotin
    - Bupivacaine
    - Calcium chloride
    - Caffeine sodium benzoate
    - Cholecalciferol
    - Chromium chloride
    - Clonidine
    - Dexamethasone sodium phosphate
    - Diclofenac
    - Gentamicin
    - Glycerin
    - Hydroxyzine
    - Ketamine
    - Levocarnitine
    - Lidocaine
    - Lorazepam
    - Magnesium sulfate
    - Manganese chloride
    - Methylprednisolone
    - Midazolam
    - Mupirocin
    - Norepinephrine
    - Ondansetron
    - Phytonadione
    - Potassium chloride
    - Potassium phosphate
    - Prilocaine
    - Proline
    - Propranolol
    - Ropivacaine
    - Sodium chloride
    - Sodium citrate

- Sodium phosphate
- Tetracaine
- Triamcinolone acetonide
- Tropicamide
- None of the above

Appendix 3. Survey distribution to professional associations

Specialty	Association[a]	Agreed/Declined, Reason for Declining
Anesthesiology	Society of Cardiovascular Anesthesiologists	Declined – failed to respond
Cardiology	American Academy of Cardiovascular Perfusion	Declined
	American Board of Cardiovascular Perfusion	Declined – failed to respond
	American Society of Extracorporeal Technology	Declined – failed to respond
Dermatology	American Academy of Dermatology	Declined – failed to respond
Naturopathy	American Association of Naturopathic Physicians	Agreed
Nephrology	American Society of Diagnostic and Interventional Nephrology	Declined
Ophthalmology	American Academy of Ophthalmology	Declined – failed to respond
	American Society of Cataract and Refractive Surgery	Agreed
	American Society of Retina Specialists	Declined
Podiatry	American Podiatric Medical Association	Agreed
Psychiatry	The International Society for Electroconvulsive Therapy and Neurostimulation	Agreed
Rheumatology	American College of Rheumatology	Agreed
Surgery	American Association of Neurological Surgeons	Declined – failed to respond
	American Association for Thoracic Surgery	Declined – failed to respond
	American College of Surgeons	Declined – failed to respond
	American Society for Reconstructive Microsurgery	Declined – failed to respond
Urology	Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction	Declined
Wound Care	Association for the Advancement of Wound Care	Declined – failed to respond

[a]Associations that declined in Year 1 and/or Year 2 were not contacted in Year 3.