Summary Report

Zinc oxide

Prepared for:

US Food and Drug Administration
Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
Grant number: 5U01FD005946-06

Prepared by:

University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI)
University of Maryland School of Pharmacy

November 2021

This report was supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award (U01FD005946) totaling $2,342,364, with 100 percent funded by the FDA/HHS. The contents are those of the authors and do not necessarily represent the official views of, nor an endorsement by, the FDA/HHS or the U.S. Government.

Table of Contents

INTRODUCTION 5
REVIEW OF NOMINATIONS 5
METHODOLOGY 5
Background information 5
Systematic literature review 6
Interviews 7
Survey 7
CURRENT AND HISTORIC USE 8
Results of background information 8
Results of literature review 9
Results of interviews 16
Results of survey 23
CONCLUSION 31
REFERENCES 32
APPENDICES 36
Appendix 1. Search strategies for bibliographic databases 36
Appendix 2. Summary of included studies 45
Appendix 3.1. Survey instrument for professional medical associations 64
Appendix 3.2. Survey instrument for professional medical associations 66
Appendix 3.3. Survey instrument for pharmacy roundtable prequestionnaire 68
Appendix 4. Survey distribution to professional associations 71

Table of Tables

Table 1. Currently approved products – US 8
Table 2. Currently approved products – select non-US countries and regions 8
Table 3. Types of studies 12
Table 4. Number of studies by country 12
Table 5. Summary of included studies 13
Table 6. Dosage by indication – US 13
Table 7. Dosage by indication – non-US countries 14
Table 8. Number of studies by combination 15
Table 9. Compounded products – US 15
Table 10. Compounded products – non-US countries 15
Table 11. Characteristics of survey respondents 24
Table 12. Compounded topical products prescribed or administered 25
Table 13. Reasons for using compounded topical products 25
Table 14. Stock of non-patient-specific compounded topical products 26
Table 15. Obtainment of compounded topical products 26
Table 16. Demographics of prequestionnaire respondents' facilities 26
Table 17. Reasons for obtaining products from outsourcing facilities 27
Table 18. Categories of products obtained from outsourcing facilities 28
Table 19. Products obtained from an outsourcing facility 29

Frequently Used Abbreviations

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

INTRODUCTION

This report was created to assist the Food and Drug Administration (FDA) in its evaluation of the use of zinc oxide (UNII code: SOI2LOH54Z), 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 zinc oxide 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 zinc oxide 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 zinc oxide 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

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

Zinc oxide was nominated to treat an unknown medical condition but is generally used as a mild astringent and topical protectant with some antiseptic action, in addition to being used in bandages, pastes, ointments, dental cements, and as a sunblock. It was nominated as a topical combination product (gel, cream, emulsion, ointment, solution, suspension, etc.), with a strength based on the prescriber's request (therapeutic dose ranges 5-10%).

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of zinc oxide.[6,7]

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

- Compounded product may be the only product to effectively treat the indication for which it is intended.
- Patient sensitivities to dyes, fillers, preservatives, or other excipients in manufactured products.
- Individual finished products have considerable variance in the final API; the use of finished product has the potential to introduce unacceptable inaccuracies into the compounded medication.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of zinc oxide 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 zinc oxide; name variations of zinc oxide 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 zinc oxide. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

Search strategy

A medical librarian constructed comprehensive search strategies for Ovid MEDLINE and Embase. The search strategies used a combination of controlled vocabulary terms and keywords to describe three concepts: zinc oxide; topical administration or form; and therapeutic use or substances nominated for use in combination with zinc oxide (refer to Appendix 1 for full search strategies). Results were limited to human studies in the English language. Searches were conducted on November 16, 2020. In addition, the ECRI Guidelines Trust® repository was searched on November 16, 2020 for clinical practice guidelines that recommended the use of zinc oxide 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 zinc oxide 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 zinc oxide 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 zinc oxide 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 zinc oxide; setting; total

number of patients; number of patients who received zinc oxide; patient population; indication for use of zinc oxide; dosage form and strength; dose; ROA; frequency and duration of therapy; use of zinc oxide in a combination product; use and formulation of zinc oxide in a compounded product; use of zinc oxide 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 zinc oxide 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 zinc oxide. 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 3 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 zinc oxide in clinical practice. The online survey was created using Qualtrics® software (refer to Appendix 3 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 4 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

- Zinc oxide is not available as an FDA-approved product in the nominated combination, form, and ROA. However, zinc oxide is available as a combination ointment including zinc oxide, miconazole nitrate, and white petrolatum.
- Zinc oxide is available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for zinc oxide.
- Zinc oxide is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Hong Kong, Ireland, Namibia, New Zealand, Saudi Arabia, and the UK.

Table 1. Currently approved products – US

No approved products in the US

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]
Zinc oxide	0.04-20% 75 mg/g	Cream Impregnated dressing Ointment	Cutaneous Topical	Abu Dhabi	Active	–
				Ireland	Pharmacy-only[c]	11/10/1994
				Saudi Arabia	Pharmacy	–

Abbreviation: –, not provided.

[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.

[c]Pharmacy-only medications may only be sold in a pharmacy, and a pharmacist must make or supervise the sale.

Results of literature review

Study selection

Database searches yielded 1559 references; 0 additional references were identified from searching ECRI Guidelines Trust®. After duplicates were removed, 1166 titles and abstracts were screened. After screening, the full text of 258 articles was reviewed. Fifty-eight studies were included; after multiple reports of the same study were merged, there were 54 included studies. Two hundred studies were excluded for the following reasons: wrong study design (151 studies); nonnominated ROA, form, or combination (29); zinc oxide only mentioned briefly (9); language other than English (4); wrong substance (4); zinc oxide not used clinically (2); zinc oxide was used for sun protection (1).

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

Characteristics of included studies

The 54 included studies were published between 1947 and 2020. There were 37 experimental studies, 5 observational studies, and 12 descriptive studies. The 54 studies were conducted in the following countries: Australia, China, Denmark, India, Iran, Italy, Lebanon, Mexico, the Netherlands, Pakistan, Panama, Sweden, Thailand, UK, and US.

A total of 4630 patients participated in the 54 included studies. The number of patients in each study ranged from 1 to 1134.

Outcome measures differed among the included studies and included the following: time to wound closure, disappearance of necrotic tissue, size of ulcer, area of necrosis, skin damage scores, evolution of healing, intensity of reaction, wound or ulcer area, healing rate, time to remove and reapply skin protectants, severity of oral mucositis, scar formation, transepidermal water loss, pain, drainage and odor control, pain control, prevention of infection, time to ambulation and discharge, postoperative problems, mass regression, occurrence of new lesions, ulcer healing, wound improvement, adverse events, skin color, counts of desquamating corneocytes and parakeratotic cells, bacteriology of the surface, topical delivery of zinc oxide, reduction in sodium lauryl sulphate, skin damage, occurrence of diaper dermatitis, rash severity, severity of dermatitis, resolution of erythroderma and dermatitis, improvement in rash, dermatitis score, recurrence, occurrence perineal dermatitis, intertrigo severity, clinical efficacy, hospitalization duration, mean cost, satisfaction of nursing, resolution of vulvar symptoms, cure rates of warts, change in number and size of warts, reduction of actinic keratosis, tumor border, and incidence of adenolymphangitis attacks

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

Use of zinc oxide

One thousand seven hundred seventy-two patients received topical zinc oxide for wound healing in concentrations ranging from 3% to 15%. Duration of treatment ranged from once to up to 9 months. Eight hundred sixty-nine patients received topical zinc oxide as a skin protectant in concentrations ranging from 7.5% to 40.0%. Duration of treatment ranged from once to 8 weeks. One hundred forty-three patients received topical zinc oxide as a treatment for warts in concentrations ranging from 15% to 20%. Duration of treatment ranged from 4 weeks to 3 months, or until cure. Two patients received topical zinc oxide as a one-time treatment for actinic keratosis, removed after 1 week of application.

One hundred twenty patients received topical zinc oxide as a treatment for adenolymphangitis, administered when the affected limb was injured or injected for a period of 12 months.

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

Zinc oxide was not used as a compounded product, nor was it used in a nominated combination product (refer to Tables 8-10).

In 19 studies, the authors' concluding statement recommended the use of topical zinc oxide for use as a skin protectant and in wound healing, in addition to the treatment of actinic keratosis.[8-26] In 1 study, the authors concluded that topical zinc oxide had limited use in wound healing and should only be used in situations where necrosis is limited to the skin and does not involve deeper tissues.[27] In 11 studies, the authors concluded that the use of topical zinc oxide was not recommended for use as a skin protectant, in wound healing, or as treatment for warts.[28-38] In 6 studies, the authors concluded that further studies were necessary for the use of topical zinc oxide as a skin protectant and in wound healing, in addition to the treatment of warts.[39-44] In 15 studies, the authors' concluding statement did not address the use of topical zinc oxide as a skin protectant or in wound healing, in addition to the treatment of adenolymphangitis.[45-59] In 2 studies, the authors did not provide a conclusive recommendation for the use of topical zinc oxide for wound healing.[60,61] Refer to Table 5 for the summary of authors' conclusions.

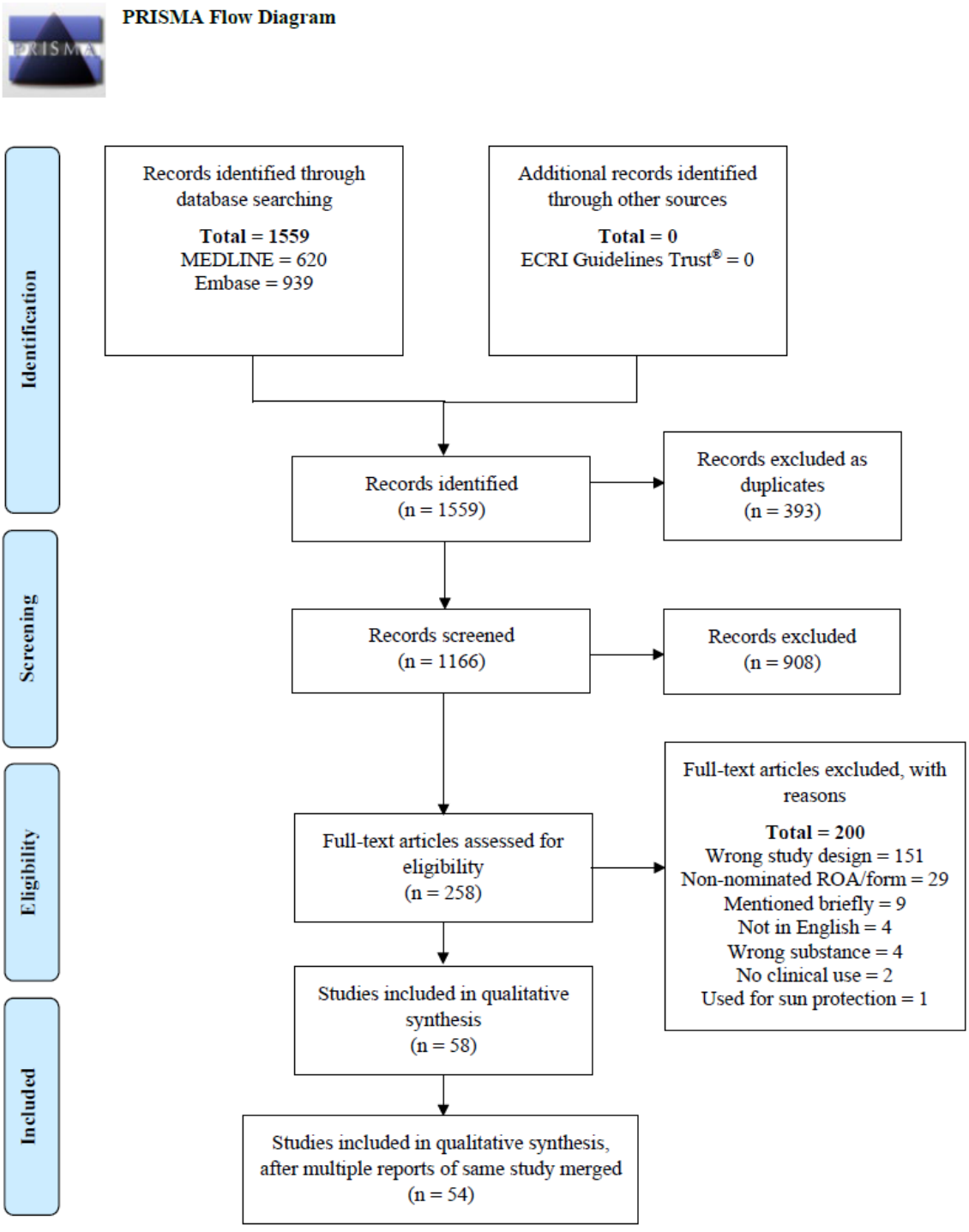
Pharmacology and historical use

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

While zinc oxide was nominated for use as a sunblock agent, the decision was made to exclude this indication from the literature review due to the already established use of zinc oxide in various sunscreen agents. From a rule proposed in 2019 from the FDA regarding "Sunscreen Drug Products for Over-the-Counter Human Use," zinc oxide is one of the OTC sunscreen monograph products generally recognized as safe and effective at concentrations up to 25%.[62] Past use of zinc oxide has typically resulted in products with an opaque, white color due to large particle size, but this has been reduced in recent years due to manufacturing of zinc oxide in smaller particle sizes, or as "nanomaterials."[62] However, in the 2019 proposed rule, the FDA has not proposed conditions of use that distinguish nanomaterials from other dosage forms of zinc oxide.[62]

Three formulations containing the method of preparation of compounded products containing zinc oxide were obtained through the literature search; they were entitled "Diaper Rash Cream with Miconazole," "Riley Butt Cream," and "Cohen's Rectal Ointment."[63-65] The first was specified to be "used in the treatment of mild skin irritations, including diaper rash."[63] The "Riley Butt Cream" had the same indications as the diaper rash cream but provided information that "zinc oxide is a mild astringent and is used topically as a soothing and protective application in eczema and mild skin disorders."[64] The rectal ointment was reported to have "been used in the treatment of hemorrhoids and other rectal irritations," and used zinc oxide paste, or Lassar's paste.[65] The Lassar's paste was described to contain 2% salicylic acid in a zinc oxide paste and "is used in the treatment of dermatomycoses and as an astringent and protectant."[65]

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[14,19,24,41,46,47,49,53-56,61]	12
Observational[15,40,45,51,52]	5
Experimental[8-13,16-18,20-23,25-39,42-44,48,50,57-60]	37

Table 4. Number of studies by country

Country	Number of Studies
Australia[16,58]	2
China[33]	1
Denmark[39]	1
India[18,44,57]	3
Iran[21,34]	2
Italy[12,59]	2
Lebanon[42]	1
Mexico[29,30,48]	3
The Netherlands[9,32]	2
Pakistan[38]	1
Sweden[8,10,13,17,27,37,60]	7
Thailand[22,23,43]	3
UK[11,25,31]	3
US[14,15,19,20,24,26,28,36,40,41,45-47,49-56,61]	22
Multiple Countries • Panama and US[35]	1
	Total US[a]: 23 Total Non-US Countries[a]: 32

Abbreviations: UK, United Kingdom; US, United States.
[a]Study 35 was counted in both the US and non-US totals.

Table 5. Summary of included studies

See Appendix 2

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Skin protectant[20,35,36,40,41,49-56]	–	10-40%	Cream, ointment, paste	Topical	2 days-4 weeks
	–	–	Diaper		24 hours-4 weeks
	Apply 0.2-5 mg/cm²	7.5-40%	Ointment		Once
	Apply 0.05 mL	25%	Paste		
	Apply at each diaper changing and after bathing	–	Ointment		7 days
	Apply weekly	–	Ointment		–
Wound healing[14,15,19,26,28,45-47,61]	–	–	Paste	Topical	As long as possible 2 months Up to 3 months
	Apply 1-2 mg/cm²	15%	Paste		Once
	Apply every 4-7 days	–	Wrap		–
	Change dressing every 2-5 days	–	Dressing, paste		10-84 days
Actinic keratosis[24]	Apply once	–	Gauze	Topical	Remove after 1 week

Abbreviation: –, not provided.

Table 7. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Wound healing[8-13,16-18,27,29-31,39,44,48,59,60]	–	–	Paste	Topical	2-3 weeks
	Apply 1-3 times daily	–	Cream, oil, ointment, paste	Topical	14 days-3 months
		5%			
	Apply every 1-2 weeks	–	Paste	Topical	8-12 weeks
	Apply every 1-3 days	–	Ointment	Topical	Once-8 weeks
		3%	Mesh		90 days
	Apply at each dressing change	–	Paste	Topical	Until ulcer heals-12 weeks
	Change dressings every 1-3 days	400 mcg/cm²	Compress, gauze	Topical	5 weeks-up to 9 months
	Change dressing 1-3 times per week	–	Tape		
Skin protectant[21-23,25,32-35,37,58]	–	15.25-32.00%	Cream, ointment	Topical	Once-14 days
	Apply twice daily	–	Ointment, plaster		3 days-3 weeks
	Apply at diaper change and after bath	7.5%	Cream		7 days-8 weeks
		–	Ointment		
Warts[38,42,43]	Apply 2-3 times per day	15-20%	Ointment, paste	Topical	4 weeks-3 months Until cure
Adenolymphangitis[57]	Apply to affected limb when injured or injected	–	Ointment	Topical	12 months

Abbreviation: –, not provided.

Table 8. Number of studies by combination

	Combination Formula	Number of Studies
Nominated	Zinc oxide 10% / Benzoin tincture 6% / Hydrocortisone 1% / Miconazole nitrate 1% – topical ointment	0
	Zinc oxide 5% / Pentoxifylline 0.5% / Tranilast 1% / Triamcinolone acetonide 0.1% – topical gel	0
	Zinc oxide 5% / Niacinamide 4% / Tacrolimus 0.03-0.1% – topical ointment	0

Table 9. Compounded products – US

No compounded products from reported studies

Table 10. Compounded products – non-US countries

No compounded products from reported studies

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 zinc oxide. Among these 5 SMEs, there was 1 medical doctor, 3 doctors of podiatric medicine, and 1 nurse practitioner. The SMEs specialized and/or were board-certified in dermatology; infectious disease; and wound, ostomy, and continence; working in academic medical institutions, private practice, and inpatient practice. The SMEs had been in practice for 1 to 40 years.

Several SMEs commented that zinc oxide is typically used as a skin protectant or barrier cream. Two SMEs commented on the use of zinc oxide as part of an Unna boot, which "is an impregnated gauze that is either zinc oxide or calamine lotion." One SME commented that it is one of the "oldest treatments in the book for venous leg ulcers," as well as being used on wounds and as a dressing for orthopedic injuries. The Unna boot provides compression, and the zinc oxide is "supposed to have both antimicrobial and healing properties."

Zinc oxide can also be used for a draining wound to "protect the surrounding skin from exudate from the wound." The zinc oxide is applied to the periwound skin because "the dressing would absorb as much as it could, but it might not absorb all the drainage" which "would be hard on the skin." However, one SME mentioned that a wound has to have a "really copious drainage for me to think about it and most wounds where I'm having a nurse take care of it, or a family member, they change the dressing often enough that I'm not concerned." One SME who specializes in wound, ostomy, and continence care uses either a zinc oxide–based or dimethicone-based product for patients with fistulas or ostomies to "contain that drainage and limit the access to the skin."

There are several formulations available and the one used is important. If a pouching system is used—as one SME stated, "We feel like we do a better job of protecting the skin if we can put a pouch on it"—ointments and other products that are greasy cannot be used because the pouch would not stick to the area. Heavier and stickier formulations "stay in place" providing more protection to the skin. Consideration of excipients is also important because oftentimes the product is being applied to broken skin which may lead to "absorption and reaction possibilities." However, the SME has not had any issues with patients having allergies to excipients in the commercially available zinc formulations.

Regarding the nominated combinations, one SME stated that zinc oxide could be used with a topical steroid, such as triamcinolone, on the irritated periwound skin, especially in venous leg ulcers, as "there's a lot of inflammation that's going on within that ulcer and that's part of [where] the exudate is from and where the drainage is coming from. If you can calm that down a little bit with a topical rather than systemic corticosteroid, then you actually help the patient tolerate their dressing more so they're not itching and ready to just scratch it off."

Zinc oxide can also be used as a vehicle to mix other active ingredients. While zinc oxide is used frequently, the SMEs did not see a reason for a compounded formulation. One SME said that "you can go out to a drugstore and pick up a tube of it for a couple of pennies" and another replied that "I think there are plenty of zinc oxide creams out there, I'm not sure why you'd want to compound it necessarily."

Three SMEs expressed concerns about the lack of evidence for the efficacy of compounded combination products. A SME who specialized 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 about the 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."

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, 3 (5% of 64 responses, where respondents were allowed to select multiple products) used zinc oxide as a compounded topical product (refer to Table 12). Fourteen respondents (100% of 14 responses) 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 3.3 for survey instrument).

Forty-three people responded to the prequestionnaire; refer to Table 16 for respondent characteristics. Among 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.

Zinc oxide 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

Zinc oxide was nominated for inclusion on the 503B Bulks List as various topical products in strengths per the prescriber's request for use as a mild astringent and topical protectant with some antiseptic action, in addition to being used in bandages, pastes, ointments, dental cements, and as a sunblock.

From the literature review, 54 studies were included. Zinc oxide was used topically in various dosage forms for wound healing, as a skin protectant, to treat warts and actinic keratosis, and to treat adenolymphangitis. None of the studies included utilized a compounded formulation nor any of the nominated combinations.

From the interviews, zinc oxide is commonly used as a skin protectant and barrier cream, especially in patients with wounds that have drainage that can damage the surrounding skin. However, the SMEs did not see a need for zinc oxide to be compounded as there are several commercially available products.

From the survey responses, 3 out of 33 respondents used zinc oxide. Zinc oxide was not included on the prequestionnaire.

REFERENCES

1. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *Int J Soc Res Method.* 2005;8(1):19-32.
2. Colquhoun HL, Levac D, O'Brien KK, et al. Scoping reviews: time for clarity in definition, methods, and reporting. *J Clin Epidemiol.* 2014;67(12):1291-1294.
3. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. *Implement Sci.* 2010;5:69.
4. Peters MDJ, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. *Int J Evid Based Healthc.* 2015;13(3):141-146.
5. Munn Z, Peters MDJ, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. *BMC Med Res Methodol.* 2018;18(1):143.
6. Nash JF. Human safety and efficacy of ultraviolet filters and sunscreen products. *Dermatol Clin.* 2006;24(1):35-51.
7. Smijs TG, Pavel S. Titanium dioxide and zinc oxide nanoparticles in sunscreens: focus on their safety and effectiveness. *Nanotechnol Sci Appl.* 2011;4:95-112.
8. Agren MS, Stromberg HE. Topical treatment of pressure ulcers. A randomized comparative trial of Varidase and zinc oxide. *Scandinavian Journal of Plastic & Reconstructive Surgery.* 1985;19(1):97-100.
9. Baatenburg de Jong H, Admiraal H. Comparing cost per use of 3M Cavilon No Sting Barrier Film with zinc oxide oil in incontinent patients. *J Wound Care.* 2004;13(9):398-400.
10. Brandrup F, Menne T, Agren MS, Stromberg HE, Holst R, Frisen M. A randomized trial of two occlusive dressings in the treatment of leg ulcers. *Acta Dermato-Venereologica.* 1990;70(3):231-235.
11. Cameron J, Hoffman D, Wilson J, Cherry G. Comparison of two peri-wound skin protectants in venous leg ulcers: a randomised controlled trial. *J Wound Care.* 2005;14(5):233-236.
12. Dini V, Salibra F, Brilli C, Romanelli M. Instrumental evaluation of the protective effects of a barrier film on surrounding skin in chronic wounds. *Wounds.* 2008;20(9):254-257.
13. Eriksson G, Eklund AE, Liden S, Zetterquist S. Comparison of different treatments of venous leg ulcers: a controlled study using stereophotogrammetry. *Curr Ther Res.* 1984;35(4):678-684.
14. Gao AL, Cole JG, Stoecker WV. Unna boot central gauze technique for chronic venous leg ulcers. *Dermatol Online J.* 2017;23(1):15.
15. Grube BJ, Engrav LH, Heimbach DM. Early ambulation and discharge in 100 patients with burns of the foot treated by grafts. *J Trauma.* 1992;33(5):662-664.
16. Stacey MC, Jopp-Mckay AG, Rashid P, Hoskin SE, Thompson PJ. The influence of dressings on venous ulcer healing--a randomised trial. *Eur J Vasc Endovasc Surg.* 1997;13(2):174-179.
17. Stromberg HE, Agren MS. Topical zinc oxide treatment improves arterial and venous leg ulcers. *Br J Dermatol.* 1984;111(4):461-468.
18. Walton RT, Fritschi EP, Umapathy VA. Treatment of plantar ulcers in leprosy patients in the community with adhesive zinc tape. *Lepr Rev.* 1986;57(1):53-56.
19. Yee BE, Paravar T. Getting to the bottom of it: ulcerating gluteal plaques in dermatomyositis. *JAAD Case Rep.* 2020;6(10):961-963.

20. Baldwin S, Odio MR, Haines SL, O'Connor RJ, Englehart JS, Lane AT. Skin benefits from continuous topical administration of a zinc oxide/petrolatum formulation by a novel disposable diaper. *J Eur Acad Dermatol Venereol.* 2001;15(suppl 1):5-11.

21. Bayat Shah Parast F, Montaseri S, Soltanian M, Pourarian S, Montaseri H. Comparison of the effects of aloe vera gel & zinc oxide ointment on Dipper rash in children aged 6 to 18 months referred to healthcare centers in Firouzabad 2015-2016. *Annals of Tropical Medicine and Public Health.* 2018;13(Special Issue):SX748.

22. Chaithirayanon S. Comparative study between talcum and zinc oxide cream for the prevention of irritant contact diaper dermatitis in infants. *J Med Assoc Thai.* 2016;99(suppl 8):S1-S6.

23. Samakayanusorn N, Chaithirayanon S, Chalermchai T, Ophaswongs S, Siriwat N, Udompataikul M. Comparison of rice starch powder and zinc oxide cream for the prevention of irritant diaper dermatitis. *J Med Assoc Thail.* 2017;100(10):S1-S6.

24. Maloney K, Arshanapalli A, Tung-Hahn E, O'Sullivan K, Tung R. Short contact 5-fluorouracil with zinc oxide occlusive dressing and cryotherapy for field and focal treatment of actinic keratoses—adjunct to excision of upper extremity squamous cell carcinomas in organ transplant recipients. *J Am Acad Dermatol.* 2019;81(4):AB124.

25. Anthony D, Barnes E, Malone-Lee J, Pluck R. A clinical study of Sudocrem in the management of dermatitis due to the physical stress of incontinence in a geriatric population. *J Adv Nurs.* 1987;12(5):599-603.

26. Xhauflaire-Uhoda E, Vroome V, Cauwenbergh G, Pierard GE. Dynamics of skin barrier repair following topical applications of miconazole nitrate. *Skin Pharmacol Physiol.* 2006;19(5):290-294.

27. Apelqvist J, Larsson J, Stenstrom A. Topical treatment of necrotic foot ulcers in diabetic patients: a comparative trial of DuoDerm and MeZinc. *Br J Dermatol.* 1990;123(6):787-792.

28. Marshall W. Factors in healing of congestive ulcers of the leg and their treatment by the author's method. *Med Times N Y.* 1947;75(6):154-156.

29. Salazar JJ, Serrano GG, Leon-Quintero GI, Torres-Mendoza BM. Use of topical ketanserin for the treatment of ulcers in leprosy patients. *Indian J Lepr.* 2001;73(2):103-110.

30. Salgado RM, Cruz-Castaneda O, Elizondo-Vazquez F, et al. Maltodextrin/ascorbic acid stimulates wound closure by increasing collagen turnover and TGF-beta1 expression in vitro and changing the stage of inflammation from chronic to acute in vivo. *J Tissue Viability.* 2017;26(2):131-137.

31. Travers JP, Dalziel KL, Makin GS. Assessment of a new one-layer adhesive bandaging method in maintaining prolonged limb compression and effects on venous ulcer healing. *Phlebology.* 1992;7(2):59-63.

32. Nijhuis WA, Houwing RH, Van der Zwet WC, Jansman FG. A randomised trial of honey barrier cream versus zinc oxide ointment. *Br J Nurs.* 2012;21(20):9-10, 12.

33. Qiao XP, Ge YZ. Clinical effect of hydrocolloid dressings in prevention and treatment of infant diaper rash. *Exp Ther.* 2016;12(6):3665-3669.

34. Sajjadian N, Hashemian F, Kadivar M, Sohani S, Taheri PA. Efficacy of topical sucralfate versus topical zinc oxide in diaper dermatitis: a randomized, double blind study. *Iranian J Dermatol.* 2012;15(61):85-88.

35. Spraker MK, Gisoldi EM, Siegfried EC, et al. Topical miconazole nitrate ointment in the treatment of diaper dermatitis complicated by candidiasis. *Cutis.* 2006;77(2):113-120.

36. Tucker SB, Flannigan SA, Ross CE. Inhibition of cutaneous paresthesia resulting from synthetic pyrethroid exposure. *Int J Dermatol.* 1984;23(10):686-689.

37. Wallengren J. Tea tree oil attenuates experimental contact dermatitis. *Arch Dermatol Res.* 2011;303(5):333-338.

38. Niazi BR, Farid Ur R. Efficacy of 20% zinc oxide paste versus 15% salicylic acid - 15% lactic acid combination in treatment of common viral warts. *J Pakistan Assoc Dermatol.* 2018;28(3):333-336.

39. Agren MS, Ostenfeld U, Kallehave F, et al. A randomized, double-blind, placebo-controlled multicenter trial evaluating topical zinc oxide for acute open wounds following pilonidal disease excision. *Wound Repair Regen.* 2006;14(5):526-535.

40. Driver DS. Perineal dermatitis in critical care patients. *Crit Care Nurs.* 2007;27(4):42-46; quiz 47.

41. Young DL, Chakravarthy D, Drower E, Reyna R. Skin care product evaluation in a group of critically ill, premature neonates: a descriptive study. *J Wound Ostomy Continence Nurs.* 2014;41(6):519-527.

42. Khattar JA, Musharrafieh UM, Tamim H, Hamadeh GN. Topical zinc oxide vs. salicylic acid-lactic acid combination in the treatment of warts. *Int J Dermatol.* 2007;46(4):427-430.

43. Songsantiphap C, Asawanonda P. Topical 15% zinc oxide ointment significantly reduces the size of common warts after four weeks: a randomized, triple-blinded, placebo-controlled trial. *J Clin Aesthet Dermatol.* 2019;12(9):26-31.

44. Chaitanya N, Badam R, Aryasri AS, et al. Efficacy of improvised topical zinc (1%) ora-base on oral mucositis during cancer chemo-radiation—a randomized study. *J Nutr Sci Vitaminol.* 2020;66(2):93-97.

45. Kitahama A, Elliott LF, Kerstein MD, Menendez CV. Leg ulcer: conservative management or surgical treatment? *JAMA.* 1982;247(2):197-199.

46. Logue ME, Elwood H, Smidt A. Congenital juvenile xanthogranuloma with ulceration: a pediatric case report. *Dermatol Online J.* 2017;23(7):15.

47. Parry MF. Genital ulceration due to foscarnet: case report and literature review. *Infect Dis Clin Pract.* 1994;3(6):453-454.

48. Zeron HM, Krotzsch Gomez FE, Munoz RE. Pressure ulcers: a pilot study for treatment with collagen polyvinylpyrrolidone. *Int J Dermatol.* 2007;46(3):314-317.

49. Champion RW, Hebert AA, Crawford HP, Lester LJ. Cutaneous manifestations of cobalamin C deficiency. *J Am Acad Dermatol.* 2011;64(2):AB87.

50. Conley P, McKinsey D, Ross O, Ramsey A, Feeback J. Does skin care frequency affect the severity of incontinence-associated dermatitis in critically ill patients? *Nursing.* 2014;44(12):27-32.

51. Daly JW, Ellis GF. Treatment of vaginal dysplasia and carcinoma in situ with topical 5-fluorouracil. *Obstet Gynecol.* 1980;55(3):350-352.

52. Goldowsky SJ, Carney WI. The postphlebitic state. *Am J Surg.* 1954;88(2):304-307.

53. Graham JA, Hansen KK, Rabinowitz LG, Esterly NB. Pyoderma gangrenosum in infants and children. *Pediatr Dermatol.* 1994;11(1):10-17.

54. Kao L, Wermuth M. Perineal dermatitis after citronella lamp oil ingestion. *Clin Toxicol.* 2010;48(6):645.

55. Quatrano NA, Shvartsbeyn M, Meehan SA, Pomerantz R, Pomeranz MK. Extragenital bullous lichen sclerosus. *Dermatol Online J.* 2015;21(12).

56. Solheim K, Elas D, Stockdale C. Treatment of hailey-hailey disease of the vulva: a retrospective case series. *J Lower Genital Tract Dis.* 2015;19(3):S21.

57. Joseph A, Mony P, Prasad M, John S, Srikanth, Mathai D. The efficacies of affected-limb care with penicillin diethylcarbamazine, the combination of both drugs or antibiotic ointment, in the prevention of acute adenolymphangitis during bancroftian filariasis. *Ann Trop Med Parasitol.* 2004;98(7):685-696.

58. Concannon P, Gisoldi E, Phillips S, Grossman R. Diaper dermatitis: a therapeutic dilemma. Results of a double-blind placebo controlled trial of miconazole nitrate 0.25%. *Pediatr Dermatol.* 2001;18(2):149-155.

59. de Giorgi V, Sestini S, Mannone F, et al. The use of silicone gel in the treatment of fresh surgical scars: a randomized study. *Clin Exp Dermatol.* 2009;34(6):688-693.

60. Eriksson G. Comparison of two occlusive bandages in the treatment of venous leg ulcers. *Br J Dermatol.* 1986;114(2):227-230.

61. Gordon R, Grant L. Management of ulcerated AIDS-related Kaposi's sarcoma lesions. *J Wound Ostomy Continence Nurs.* 1996;23(2):115-118.

62. Gottlieb S. Sunscreen drug products for over-the-counter human use. *Federal Register.* 2019;84(38):6204-6275.

63. Allen LV Jr. Diaper rash cream with miconazole. *Int J Pharm Compd.* 2009;13(1):68.

64. Allen LV Jr. Riley butt cream. *Int J Pharm Compd.* 2009;13(4):339.

65. Allen LV Jr. Cohen's rectal ointment. *Int J Pharm Compd.* 2010;14(3):244.

66. Mirastschijski U, Martin A, Jorgensen LN, Sampson B, Agren MS. Zinc, copper, and selenium tissue levels and their relation to subcutaneous abscess, minor surgery, and wound healing in humans. *Biol Trace Elem Res.* 2013;153(1-3):76-83.

67. Sajjadian N, Kadivar M. Comparing the efficacy of topicalsucralfate versus topical zinc oxide in diaper dermatitis, a randomized double blind study. *Archives of Disease in Childhood.* 2012;97:A111-A112.

68. Hashemian F, Sohani S, Kadivar M, Sajjadian N, Atashbiz M. Comparing the efficacy of topical sucralfate versus topical zinc oxide in diaper dermatitis: a randomized, double blind study. *Eur J Pediatr Dermatol.* 2010;20(1):31.

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 November 13, 2020
- Date last searched: November 16, 2020
- Limits: Humans (search hedge); English language
- Number of results: 620

1	zinc oxide/	7006
2	((cinc or zinc$ or zink$) adj2 (oxid$ or oxyd$ or white)).tw.	8365
3	oxozinc.tw.	4
4	cincox#d$.tw.	0
5	zincox#d$.tw.	14
6	zinkox#d$.tw.	3
7	or/1-6	12,325
8	administration, topical/	38,635
9	administration, cutaneous/	22,229
10	skin absorption/	11,763
11	topical$.tw.	106,931
12	transcutaneous$.tw.	14,629
13	transdermal$.tw.	14,784
14	((cutaneous$ or dermal$ or skin) adj3 (absorb$ or absorpt$ or appl$)).tw.	12,439
15	exp gels/	52,763
16	liniments/	123
17	ointments/	12,816
18	skin cream/	1053
19	suspensions/	7797
20	liniment?.tw.	146

21	ointment?.tw.	12,029
22	salve?.tw.	343
23	paste?.tw.	12,675
24	unguent$.tw.	113
25	lotion?.tw.	2344
26	cream?.tw.	19,212
27	gel?.tw.	309,819
28	suspension?.tw.	109,953
29	or/8-28	633,159
30	drug therapy/	30,655
31	ad.fs.	1,427,973
32	de.fs.	3,013,416
33	dt.fs.	2,251,361
34	pc.fs.	1,304,112
35	tu.fs.	2,245,738
36	therap$.tw.	2,841,008
37	treat$.tw.	5,605,870
38	prevent$.tw.	1,446,650
39	prophyl$.tw.	167,724
40	hydrocortisone/	72,301
41	miconazole/	2023
42	niacinamide/	12,523
43	pentoxifylline/	4177
44	tacrolimus/	16,095
45	exp triamcinolone/	9473
46	((benjamin or benzoin$ or sumatra) adj3 (gum? or sap? or tincture?)).tw.	62

47	h#drocorticosteroid$.tw.	16
48	h#dro#ortisat$.tw.	2
49	h#dro#ortison$.tw.	16,451
50	h#dro#ortisyl.tw.	1
51	h#dro#orton$.tw.	16
52	mic?ona#ol$.tw.	2746
53	mic?ona#il$.tw.	0
54	mik?ona#ol$.tw.	1
55	mik?ona#il$.tw.	0
56	amide pp.tw.	2
57	nicotinamid$.tw.	21,494
58	niacetamid$.tw.	0
59	niacinamid$.tw.	512
60	nicamid$.tw.	0
61	nicosedin$.tw.	0
62	nicotami#$.tw.	14
63	nicotinami#$.tw.	21,512
64	(nicotinic adj2 amid$).tw.	115
65	nicotinoylami#$.tw.	13
66	nicotinsaureamid$.tw.	0
67	vitamin$ b3.tw.	424
68	vitamin$ pp.tw.	164
69	ox?pentifyllin$.tw.	75
70	ox?pentiphyllin$.tw.	0
71	pentox#fil#n$.tw.	12
72	pentox#fyll#n$.tw.	4519

73	pentox#phyll#n$.tw.	152
74	ta#rolimus$.tw.	16,375
75	tsukubaenolid$.tw.	0
76	tranilast$.tw.	614
77	t?iamcinolon$.tw.	7799
78	tramcinolon$.tw.	3
79	triancinolon$.tw.	8
80	or/30-79	11,177,541
81	and/7,29,80	874
82	exp animals/ not humans/	4,756,396
83	81 not 82	696
84	limit 83 to english language	620

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: November 16, 2020
- Limits: Humans (search hedge); English language
- Number of results: 939

1	‘zinc oxide’/de	11,694
2	((cinc OR zinc* OR zink*) NEAR/2 (oxid* OR oxyd* OR white)):ti,ab,tn	8281
3	‘oxozinc’:ti,ab,tn	5
4	‘cincoxid*’:ti,ab,tn	0
5	‘cincoxyd*’:ti,ab,tn	0
6	‘zincoxid*’:ti,ab,tn	184
7	‘zincoxyd*’:ti,ab,tn	2
8	‘zinkoxid*’:ti,ab,tn	4
9	‘zinkoxyd*’:ti,ab,tn	3
10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	15,538
11	‘topical drug administration’/de	83,427
12	‘cutaneous drug administration’/de	690
13	‘transdermal drug administration’/de	9155
14	‘skin absorption’/de	8112
15	‘topical treatment’/de	13,381
16	‘topical*’:ti,ab	151,721
17	‘transcutaneous*’:ti,ab	19,751
18	‘transdermal*’:ti,ab	21,705
19	((cutaneous* OR dermal* OR skin) NEAR/3 (absorb* OR absorp* OR appl*)):ti,ab	18,151
20	‘cream’/de	9636
21	‘gel’/exp	78,968
22	‘liniment’/de	250

23	‘lotion’/de	2906
24	‘ointment’/de	18,068
25	‘paste’/de	2535
26	‘salve’/de	169
27	‘suspension’/de	27,880
28	‘cream$’:ti,ab	30,075
29	‘liniment$’:ti,ab	237
30	‘lotion$’:ti,ab	4049
31	‘ointment$’:ti,ab	21,776
32	‘paste$’:ti,ab	15,199
33	‘salve$’:ti,ab	483
34	‘unguent*’:ti,ab	242
35	‘gel$’:ti,ab	365,171
36	‘suspension$’:ti,ab	146,543
37	#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 OR #36	846,045
38	‘drug therapy’/de	763,224
39	‘drug dose’:lnk	627,704
40	‘drug administration’:lnk	1,775,400
41	‘drug therapy’:lnk	3,970,993
42	‘prevention’:lnk	1,188,149
43	‘treat*’:ti,ab	8,120,483
44	‘therap*’:ti,ab	4,274,777
45	‘prevent*’:ti,ab	1,966,600
46	‘prophyl*’:ti,ab	267,091
47	‘gum benzoin’/de	33
48	‘hydrocortisone’/de	143,127

49	‘miconazole’/de	10,351
50	‘nicotinamide’/de	16,144
51	‘pentoxifylline’/de	13,789
52	‘tacrolimus’/de	81,550
53	‘tranilast’/de	1554
54	‘triamcinolone’/de	16,137
55	‘triamcinolone acetonide’/de	15,577
56	((benjamin OR benzoin* OR sumatra) NEAR/3 (gum$ OR sap$ OR tincture$)):ti,ab,tn	111
57	‘hydrocorticosteroid*’:ti,ab,tn	56
58	‘hydrocortisat*’:ti,ab,tn	10
59	‘hydrocortison*’:ti,ab,tn	27,672
60	‘hydrocortisyl’:ti,ab,tn	15
61	‘hydrocorton*’:ti,ab,tn	165
62	‘hidrocorticosteroid*’:ti,ab,tn	0
63	‘hidrocortisat*’:ti,ab,tn	0
64	‘hidrocortison*’:ti,ab,tn	22
65	‘hidrocortisyl’:ti,ab,tn	0
66	‘hidrocorton*’:ti,ab,tn	0
67	‘hydrokortison*’:ti,ab,tn	7
68	‘mic$onasol*’:ti,ab,tn	1
69	‘mic$onazol*’:ti,ab,tn	3564
70	‘mic$onasil*’:ti,ab,tn	0
71	‘mic$onazil*’:ti,ab,tn	0
72	‘mik$onasol*’:ti,ab,tn	0
73	‘mik$onazol*’:ti,ab,tn	4
74	‘mik$onasil*’:ti,ab,tn	0

75	‘mik$onazil*’:ti,ab,tn	0
76	‘amide pp’:ti,ab,tn	2
77	‘nicotinamid*’:ti,ab,tn	26,109
78	‘niacetamid*’:ti,ab,tn	0
79	‘niacinamid*’:ti,ab,tn	809
80	‘nicamid*’:ti,ab,tn	1
81	‘nicosedin*’:ti,ab,tn	0
82	‘nicotamid*’:ti,ab,tn	26
83	‘nicotamin*’:ti,ab,tn	0
84	‘nicotinamin*’:ti,ab,tn	21
85	‘nicotinamid*’:ti,ab,tn	26,109
86	(nicotinic NEAR/2 acid*):ti,ab,tn	9618
87	‘nicotinoylamin*’:ti,ab,tn	21
88	‘nicotinoylamid*’:ti,ab,tn	2
89	‘nicotinsaureamid*’:ti,ab,tn	6
90	‘nikotamin*’:ti,ab,tn	0
91	‘vitamin* b3’:ti,ab,tn	513
92	‘vitamin* pp’:ti,ab,tn	295
93	‘ox$pentifyllin*’:ti,ab,tn	107
94	‘ox$pentiphyllin*’:ti,ab,tn	1
95	‘pentoxifilin*’:ti,ab,tn	29
96	‘pentoxifilen*’:ti,ab,tn	0
97	‘pentoxyfilin*’:ti,ab,tn	9
98	‘pentoxyfilen*’:ti,ab,tn	0
99	‘pentoxifyllin*’:ti,ab,tn	5747
100	‘pentoxifyllen*’:ti,ab,tn	1

101	‘pentoxyfyllin*’:ti,ab,tn	140
102	‘pentoxyfyllen*’:ti,ab,tn	0
103	‘pentoxiphyllin*’:ti,ab,tn	116
104	‘pentoxiphyllen*’:ti,ab,tn	0
105	‘pentoxyphyllin*’:ti,ab,tn	149
106	‘pentoxyphyllen*’:ti,ab,tn	0
107	‘tacrolimus*’:ti,ab,tn	32,959
108	‘takrolimus*’:ti,ab,tn	7
109	‘tsukubaenolid*’:ti,ab,tn	5
110	‘tranilast*’:ti,ab,tn	836
111	‘tiamcinolon*’:ti,ab,tn	4
112	‘triamcinolon*’:ti,ab,tn	11,190
113	‘tramcinolon*’:ti,ab,tn	12
114	‘triancinolon*’:ti,ab,tn	20
115	#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 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 OR #100 OR #101 OR #102 OR #103 OR #104 OR #105 OR #106 OR #107 OR #108 OR #109 OR #110 OR #111 OR #112 OR #113 OR #114	13,672,580
116	#10 AND #37 AND #115	1325
117	[animals]/lim NOT [humans]/lim	612,0526
118	#116 NOT #117	1157
119	#116 NOT #117 AND [english]/lim	939

Appendix 2. 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: Wound healing					
Agren et al, 2006, Denmark[39] Mirastschijski et al, 2013, Denmark[66]	Randomized, double-blind, placebo-controlled multicenter trial	64 Patients who underwent operation for pilonidal abscess or chronic pilonidal disease • Zinc oxide (81.8%, median 26 y [IQR (interquartile range) 22-31]) • Placebo (83.9%, median 25 y [IQR 21-32])	• Zinc oxide mesh (33) • Placebo (31)	Time to wound closure	"Zinc oxide was not associated with increased pain by the visual analog scale, cellular abnormalities by histopathological examination of wound biopsies, or other harmful effects. Larger clinical trials will be required to show definitive effects of topical zinc oxide on wound healing and infection."
Agren and Stromberg, 1985, Sweden[8]	Randomized, open trial	28 Patients with 1 or more necrotic pressure ulcers (28.6%, range 46-92 y)	Topical treatment with either: • Zinc oxide (14) • Varidase (14)	Disappearance of necrotic tissue	"Nevertheless, we conclude from our controlled study that Varidase and zinc oxide, in the form and dosage used here, are about equally effective in promoting the removal of necrotic tissue from ulcers."
Apelqvist et al, 1990, Sweden[27]	Open randomized controlled study	44 Patients with diabetes and necrotic foot ulcers • Adhesive zinc oxide tape (MeZinc; 45.5%, mean 63 y ± 13) • Adhesive occlusive hydrocolloid dressing (DuoDerm; 72.7%, mean 62 y ± 18)	• MeZinc (22) • DuoDerm (22)	Size of ulcer, area of necrosis	"In conclusion, from this study we cannot recommend the use of adhesive hydrocolloid dressings such as DuoDerm for the treatment of necrotic ulcers on the feet of diabetics. Although an adhesive zinc oxide tape reduced the initial necrotic area in many of our diabetic patients, this treatment is not without risk and should be used for necrosis that is limited to the skin and does not involve deeper tissue."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Baatenburg de Jong and Admiraal, 2004, the Netherlands[9]	Single-center open-label prospective randomized study	39 Patients with at least moderate skin damage from incontinence • Cavilon No Sting Barrier Film (NSBF; 26.3%, mean 85.1 y ± 7.2) • Zinc oxide oil (40%, mean 83.3 y ± 7.8)	• Cavilon NSBF (not reported) • Zinc oxide oil (not reported)	Skin damage scores	"Both products resulted in an improvement in skin condition after 14 days, but Cavilon NSBF was found to be more cost-effective."
Brandrup et al, 1990, Sweden[10]	Prospective, randomized trial Patch-testing	31 Patients with leg ulcers • MeZinc® (31.3%, mean 73 y ± 14) • Duoderm® (13.3%, mean 77 y ± 9) 1103 Patients with eczema (gender and age not specified)	Leg ulcer study: • Mezinc® patch (16) • Duoderm® (15) Patch testing study: • Mezinc® (1103)	Evolution of healing, intensity of reaction	"Both dressings were well tolerated by leg ulcer patients and there appeared to be no major differences in the efficacy of the two occlusive dressings."
Cameron et al, 2005, UK[11]	Randomized controlled trial	35 Patients with venous leg ulceration with maceration and/or irritation of periwound area • Cavilon No Sting Barrier Film (NSBF; 22.2%, mean 73.4 y ± 10.2) • Zinc paste (41.2%, mean 72.9 y ± 10.4)	• Cavilon NSBF (18) • Zinc paste (17)	Wound area, healing rate, time to remove and reapply skin protectants	"Although both products were found to be effective barrier preparations, the benefits of NSBF in terms of reduced treatment time, patient comfort and ease of use are important factors to be considered when managing the peri-ulcer skin."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Chaitanya et al, 2020, India[44]	Randomized study	75 Patients receiving chemotherapy or radiotherapy for oral cancers • Zinc (65%, mean 55.4 y ± 12.4) • Control (65%, mean 53.96 y ± 14) • Improvised zinc (65%, mean 46.12 y ± 12.96)	• Topical zinc oxide paste (25) • Improvised preparations containing zinc oxide, amla, tulsi, and curcumin (25) • Control (25)	Severity of oral mucositis	"Zinc is beneficial in decreasing the severity of radiation-induced mucositis and oral discomfort. These results should be confirmed by additional evaluation in randomized studies with a larger number of patients. It was concluded that improvised zinc administration during head and neck radiation therapy produced significant benefit in relieving radiation-induced oral mucositis."
de Giorgi et al, 2009, Italy[59]	Randomized controlled trial	110 Patients who had undergone outpatient surgery (50%, range 23-81 y)	• Silicone gel and zinc oxide (65) • Zinc oxide cream (45)	Scar formation	"In conclusion, our study demonstrates that silicone gel is able to reduce the formation of keloid and hypertrophic scars and the signs/symptoms associated during the healing process (paraesthesia, pulling sensation, alterations in colour). Indeed, although the pathogenetic hypotheses are numerous and require further investigation, the clinical data show that silicone gel favours the reduction of scar tissue thickness, making the scar softer, smoother and flatter. This limits scar damage to a minimum and definitely improves the aesthetic results."
Dini et al, 2008, Italy[12]	Randomized controlled trial	40 Patients requiring treatment of chronic venous leg ulcers or pressure ulcers (32.5%, mean 69 y ± 4)	• Cavilon No Sting Barrier Film (NSBF; not reported) • Zinc oxide ointment (not reported)	Transepidermal water loss (TEWL)	"The results of this study showed that TEWL measurements are the most important biophysical parameters for evaluating the efficiency of the human skin water barrier and that the NSBF and zinc oxide ointment helped improve the surrounding skin barrier. As an additional benefit, the NSBF was easy to apply—therefore reducing patient discomfort and suffering."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Eriksson, 1986, Sweden[60]	Randomized open trial	34 Patients with chronic venous leg ulcers (26.5%) • Male patients (mean 66.9 y) • Female patients (mean 74.3 y)	• Hydrocolloid dressing plus compression (not reported) • Double-layer bandage, consisting of inner stocking with zinc oxide paste and an elastic outer bandage (not reported)	Healing rate	"No statistically significant difference was found between the results of the two treatments."
Eriksson et al, 1984, Sweden[13]	Randomized controlled studies	53 Patients with venous leg ulcers (24.5%, mean 70.1 y) 9 Patients were excluded from period 2 of the trial due to healing of ulcers or other unrelated reasons	Period 1: • Saline (not reported) • Dextranomer beads (not reported) Phase 2: • Skin-tec® (not reported) • Metallina® dressings (not reported) • Double-layer bandage with inner stocking and zinc paste paired with an elastic outer bandage (not reported)	Pain, ulcer area, and volume	"In conclusion, the double-layer bandage is recommended as routine treatment and can be introduced right from the beginning as further studies have shown."
Gao et al, 2017, US[14]	Case synopses	3 Patients with venous leg ulcers (0%, range 79-88 y)	• 3-Layer Unna boot with a central gauze soaked with saline so only the peripheral rim of the ulcer is exposed to zinc oxide paste (3)	Healing rate	"The three patients in this pilot study showed rapid healing for venous leg ulcers with central gauze modification of Unna boot therapy."
Gordon and Grant, 1996, US[61]	Case	1 Patient with AIDS-related Kaposi's sarcoma referred for ulcerated lesions (100%, 42 y)	• Zinc oxide and glycerol-impregnated wrap (1)	Drainage and odor control, pain control, prevention of infection	–

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Grube et al, 1992, US[15]	–	100 Patients with burns of the foot, ankle, or distal leg treated by grafts (gender not specified, mean 28.8 y ± 16.9)	• Unna boots* (92) The study results only apply to patients who were treated with Unna boots *While there is no mention of "zinc oxide" in this report, other sources say Unna boots typically contain zinc oxide paste	Time to ambulation and discharge, postoperative problems	"Unna boot application permits immediate ambulation, avoids frequent dressing changes, permits a brief or no hospital stay, and provides excellent graft take with prompt return to work."
Kitahama et al, 1982, US[45]	–	65 Patients with chronic leg ulcers (50.8%, range 25-98 y)	• Pressure dressings with boric acid, petrolatum-base ointment (46) • Skintight plaster-of-Paris boots overnight until edema disappeared, followed by gauze saturated with calamine, glycerin, and zinc oxide with plaster of Paris applied over gauze rolls (7)	Healing rate	"Nonsurgical treatment of venous stasis ulcer is inexpensive and effective."
Logue et al, 2017, US[46]	Case report	1 Patient presenting with congenital juvenile xanthogranuloma (JXG) with ulceration (0%, 2 weeks)	• Petrolatum ointment with occasional use of topical miconazole and zinc oxide as barriers (1)	Mass regression, occurrence of new skin lesions	"This case highlights a rare presentation of JXG. Biopsy may be necessary to differentiate from other more worrisome entities, but the overall prognosis is benign and necessary intervention is typically minimal."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Marshall, 1947, US[28]	–	139 Patients with congestive, indolent ulcers (gender and age not specified)	• Zinc oxide ointment plus allantoin and sulfanilamide ointment (54) • Allantoin and sulfanilamide ointment (22) • Subcutaneous kutapressin and zinc oxide dressings (27) • Allantoin and sulfanilamide ointment plus subcutaneous kutapressin (36)	Healing rate	"Fifty-four patients were treated with zinc oxide ointment U.S.P. [United States Pharmacopeia] and pressure dressings and only two showed appreciable improvement in the ulcer area after a period of 12 weeks."
Parry, 1994, US[47]	Case report	1 Patient presenting with genital ulceration due to foscarnet (100%, 49 y)	• Topical protective dressing of zinc oxide paste and lidocaine ointment (1)	Ulcer healing	"Clinicians should be aware of the frequent occurrence of genital ulceration due to foscarnet therapy. With appropriate management, resolution of such ulcerations may be achieved without terminating therapy."
Salazar et al, 2001, Mexico[29]	Prospective, comparative, and quasi-experimental study	66 Patients affected by leprosy with skin ulcerations due to a variety of causes • Ketanserin (KTS) gel (51.5%, mean 58.75 y ± 9.06) • Control (57.6%, mean 57.48 y ± 8.86)	• Ketanserin gel (33) • Topically applied clioquinol and/or zinc oxide paste (33)	Ulcer healing, side effects	"The apparent efficacy of KTS as coadjuvant treatment of ulcers in these patients has provided good results in our study, for which reason we consider it a good alternative for patients with chronic ulcers resistant to other treatments. With the addition of this drug, these patients may be kept and treated within their own social and cultural parameters and those of health workers without any problems."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Salgado et al, 2017, Mexico[30]	Bi-institutional, open, prospective, longitudinal, experimental pilot study	21 Patients with venous ulcers (23.8%, range 39-90 y) While 21 patients were recruited, the demographic table only specifies 20 patients; no mention is made of missing patient	Oral diosmin/hesperidin plus topical administration of either: • Maltodextrin and ascorbic acid (11) • Zinc oxide ointment (9)	Wound improvement, adverse events	"In conclusion, the present observations indicate that maltodextrin–ascorbic acid treatment favors wound repair in vitro and in vivo."
Stacey et al, 1997, Australia[16]	Randomized clinical trial	113 Patients with venous ulceration (40.7%, range 31-92 y)	• Vicopaste—a zinc oxide impregnated paste bandage (43) • Acoband—a zinc oxide impregnated stockinette (44) • Kaltostat—a calcium alginate fiber dressing (46) Number of affected limbs was provided per group rather than number of patients; 113 patients had 133 ulcerated limbs	Healing rate	"The use of a paste bandage significantly improved the healing of chronic venous ulcers when used in combination with compression bandaging, and compared to an alginate dressing and a zinc oxide impregnated stockinette."
Stromberg and Agren, 1984, Sweden[17]	Randomized, double-blind study	37 Patients with arterial or venous leg ulcers (35.1%, range 66-95 y)	• Zinc oxide (18) • Placebo (19)	Healing rate	"Whatever function zinc has during wound healing in human beings, our findings seem to show that topical zinc oxide in the form and dosage used in this investigation is a valuable adjunct in the treatment of leg ulcers."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Travers et al, 1992, UK[31]	–	27 Patients with venous ulcers • Panelast Acryl (gender not specified, mean 54 y ± 3) • Three-layer bandaging technique (gender not specified, mean 59 y ± 4) This study also had 11 patients with bilateral varicose veins in a separate, nonrandomized analysis; as a result, they are not included in this table	• Panelast Acryl—1-layer acrylic adhesive bandage (15) • 3-Layer bandage technique—zinc oxide paste bandage followed by a nonadhesive compression bandage and tubular overlay (12)	Healing rate	"Adhesive bandaging produced more effective sustained compression than non-adhesive crepe. Adhesive bandaging was as effective as the currently used three layer bandaging technique in healing venous ulcers and was quicker to apply."
Walton et al, 1986, India[18]	Randomized controlled trial	43 Patients with leprosy presenting with plantar ulcers (gender and age not specified)	• Zinc oxide impregnated adhesive plaster (22) • Conventional antiseptic soaked gauze dressings (21)	Area of ulcer	"It is concluded that zinc tape is at least as effective as ordinary dressings in healing ulcers. It is more acceptable to patients than untidy, dirty bandages and so deserves more widespread use."
Xhauflaire-Uhoda et al, 2006, US[26]	Double-blind, randomized intraindividual study	15 Volunteers undergoing controlled tape stripping and sustained surfactant challenge at 5 test sites (gender not specified, range 34-48 y)	Each patient had 5 test sites: • Untreated (15) • Zinc oxide and miconazole paste 1 mg/cm² (15) • Zinc oxide and miconazole paste 2 mg/cm² (15) • Zinc oxide paste 1 mg/cm² (15) • Zinc oxide paste 2 mg/cm² (15)	TEWL	"We conclude that the occlusive effect of a paste helped mitigate SBF [skin barrier function] defect. The adjunction of miconazole nitrate improved the efficacy."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Yee and Paravar, 2020, US[19]	Case report	1 Patient presenting with plaques and ulcerations associated with dermatomyositis (0%, 77 y)	• Zinc oxide paste (1) Patient also received body application of fluocinonide, gabapentin, prednisone, and azathioprine	Resolution of ulcers	"Although this patient's clinical improvement may have been primarily attributed to increased immunosuppression targeting her dermatomyositis, the concomitant initiation of zinc oxide addressed a potential exacerbating factor of recurrent friction and irritation in the area."
Zeron et al, 2007, Mexico[48]	Clinical, prospective, blind, randomized, and comparative study	24 Patients with pressure ulcers • Collagen-polyvinylpyrrolidone (Clg-pvp) (16.7%, mean 79.83 y) • Control (25%, mean 78.33 y)	All patients received cleaning of ulcers with soap and application of zinc oxide paste in addition to either: • Clg-pvp injection (12) • Control (12)	Ulcer size	"With conventional soap cleaning, zinc oxide paste and clg-pvp application, it was found that after the 3-week treatment the mean ulcer diameter was less than in the group treated with conventional soap cleaning, zinc oxide paste and placebo; however, it would be desirable to carry out further studies with a longer follow-up period and a greater number of patients for a more reliable statistical forecast."
Indication 2: Skin protectant					
Anthony et al, 1987, UK[25]	Double-blind controlled trial	67 Patients in geriatric wards who required incontinence pads (15.6%, range 65-105 y) 10 Patients died or were withdrawn from the study, resulting in 57 patients completing the study	• Sudocrem (29) • Zinc cream (28) Sudocrem also contains zinc oxide	Skin color, counts of desquamating corneocytes and parakeratotic cells, bacteriology of the surface	"The study supports the view that Sudocrem is a safe and effective preparation for use in the management of incontinence-associated dermatitis. Our findings indicate that it may promote the healing of such lesions as well as producing an antiseptic effect. A more important observation is the indication that the normal skin of an incontinent patient does not deteriorate when managed with Sudocrem or zinc cream."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Baldwin et al, 2001, US[20]	Randomized, double-blind trial Randomized, blinded clinical trial Randomized, double-blind, parallel group comparison trial	Study A: 67 Patients who were routine users of disposable diapers (gender not specified, mean 15.2 months) Study B: 19 Volunteers who received demarcation of skin sites on the upper arm (0%, age not specified) Study C: 304 Patients who were routine users of disposable diapers (50%, mean 9.9 months)	Study A: • Single zinc oxide/petrolatum (ZnO/Pet) diaper for 3 hours (27) • Multiple ZnO/Pet diapers according to parental changing habits over 24 hours (40) Study B: • 7.5% ZnO/Pet formulation, 0.2 mg/cm² (19) • 7.5% ZnO/Pet formulation, 5.0 mg/cm² (19) • 40% ZnO/Pet formulation, 0.2 mg/cm² (19) • 40% ZnO/Pet formulation, 5.0 mg/cm² (19) • Pet formulation, 0.2 mg/cm² (19) • Pet formulation, 5.0 mg/cm² (19) • Control—no pretreatment with a formulation (19) After pretreatment, all sites received occlusive patch with irritant sodium lauryl sulphate (SLS) Study C: • ZnO/Pet formulation–containing diaper (not reported) • Control diaper (not reported)	Topical delivery of zinc oxide, reduction in SLS skin damage, occurrence of diaper dermatitis, rash severity	"The results demonstrated the clinical benefits associated with continuous topical administration of a zinc oxide/petrolatum-based formulation by this novel diaper."
Bayat Shah Parast et al, 2018, Iran	Single-blind randomized clinical trial	40 Patients 6-18 months with diaper dermatitis • Aloe vera gel (60%, age not specified) • Zinc oxide ointment (35%, age not specified)	• Aloe vera gel (not reported) • Zinc oxide ointment (not reported)	Severity of dermatitis, adverse events	"Studies have shown that aloe vera gel and zinc oxide ointment impact on the improvement of diaper dermatitis is the same, it is suggested that due to the availability of aloe vera gel in the treatment of diaper dermatitis used."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Chaithirayanon, 2016, Thailand[22]	Experimental, prospective randomized controlled trial study	50 Patients with normal skin on the diaper area • Talcum powder (72%, mean 8.7 months ± 2.4) • Zinc oxide cream (44%, mean 8.8 months ± 2.1)	• Talcum powder (25) • Zinc oxide cream (25)	Occurrence of diaper dermatitis, clinical severity, side effects	"The topical zinc oxide cream has been proven to have better effectiveness in the diaper dermatitis prevention in infants than talcum powder."
Champion et al, 2011, US[49]	–	1 Patient with history of cobalamin C (CblC) deficiency presenting for generalized desquamative dermatitis (100%, 14 months)	• Hydrocortisone cream, zinc oxide, and Eucerin (1)	Resolution of erythroderma and dermatitis	"The infant was restarted on his dietary and medical regimen with skin treatments that included hydrocortisone 2.5% cream, zinc oxide 40%, and Eucerin. Dramatic improvement of the erythroderma occurred within 24 hours. While generalized exfoliative dermatitis has been noted to occur with dietary restriction of branched chain amino acids, this patient's course supports the conclusion that his cutaneous manifestations were the physiologic consequence of an inborn error of metabolism and not secondary to dietary restriction. CblC deficiency coupled with poor parental compliance resulted in dermatologic sequelae significant enough to result in hospitalization for this infant. Parental education of cutaneous manifestations of poor disease control have been implemented to reduce future disease flares."
Concannon et al, 2001, Australia[58]	Placebo-controlled, randomized, double-blind, parallel-group trial	202 Patients with diaper dermatitis • Miconazole nitrate (53.5%, range 2-13 months) • Ointment base (52.5%, range 2-13 months)	Zinc oxide and petrolatum ointment base with either: • Miconazole nitrate (101) • Placebo (101)	Improvement in rash	"Treatment with miconazole nitrate 0.25% was as safe as with ointment base alone. Miconazole nitrate 0.25% ointment is a safe and effective treatment for diaper dermatitis in infants."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Conley et al, 2014, US[50]	Randomized prospective study	99 Patients who were incontinent or had a fecal diversion device or urinary catheter for more than 2 days • Protocol every 6 hours (gender not specified, mean 75 y) • Protocol every 12 hours (gender not specified, mean 67 y)	All patients received the same skin protocol containing a cleanser with aloe vera, water, and cleansing lotion either: • Every 6 hours (55) • Every 12 hours (44) Patients with erythema received skin protectant with zinc oxide and menthol	Dermatitis score	"The researchers studied a defined skin care protocol using a cleanser with aloe vera and a cleansing lotion, followed by application of either a moisture barrier with silicone or skin protectant with zinc oxide and menthol, undertaken at two different frequencies. Data revealed the incidence of moderate IAD [incontinence-associated dermatitis] was decreased in the experimental group (receiving the skin protocol every 6 hours and p.r.n.)."
Daly and Ellis, 1980, US[51]	–	17 Patients with vaginal lesions ranging from moderate dysplasia to carcinoma in situ (0%, range 33-78 y)	• All patients received intravaginal 5-fluorouracil (5-FU); zinc oxide ointment was applied to vulva and perineum to minimize external irritation (17)	Recurrence	"Topical application of 5-FU in the vagina may prove to be a useful method of therapy for patients with vaginal dysplastic lesions, especially after radiation therapy."
Driver, 2007, US[40]	Observational performance study	308 Patients recruited from the intensive care unit (ICU) 16 Patients from Phase 1 had fecal incontinence 16 Patients from Phase 2 had fecal incontinence	Phase 1: • Patients who were fecal incontinent received a no-rinse cleanser and zinc oxide barrier (16) Phase 2: • Dimethicone cleanser and barrier (16)	Occurrence perineal dermatitis	"Despite the limitations of this performance study, outcomes improved for patients who were consistently treated with a 1-step product that both cleans and protects the skin. These preliminary results are promising and warrant further studies to verify the findings."
Goldowsky and Carney, 1954, US[52]	–	35 Patients with a history of deep thrombophlebitis (34.3%, mean 53-56 y*) *Mean age was provided for female patients (53 y) and male patients (56 y) separately	• Elastic bandages, gentian violet aqueous solution, and zinc oxide ointment (35)	Healing rate	"Such benefits as may accrue from other methods of management in all probability depend upon the accompanying compression, bedrest or other attendant follow-up measures."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Graham et al, 1994, US[53]	Case report	1 Patient presenting with pyoderma gangrenosum (100%, 3 weeks)	• Prednisone, intralesion triamcinolone, saline soaks, and topical application of Bactroban ointment and zinc oxide paste (1)	Resolution of ulcers	"In infants, therefore, diagnosis may be more difficult due to the absence of diseases commonly associated with this disorder, and the tendency for ulcers to appear in an area where young children are frequently afflicted with more benign cutaneous lesions."
Kao and Wermuth, 2010, US[54]	Case report	1 Patient with perineal dermatitis after citronella lamp oil ingestion (0%, 42 y)	• Soft soap washes, zinc oxide, and desonide ointment that was replaced by bacitracin ointment as lesions improved	Resolution of lesions	"Large volume hydrocarbon ingestion may result in diarrhea and subsequent desquamating dermatitis in the perineal region. Close and early skin monitoring is warranted. If diarrhea develops, limiting dermal contact with early rectal tube placement should be considered.'
Nijhuis et al, 2012, the Netherlands[32]	Multicenter, randomized cross-comparative study	31 Patients with symmetrical intertrigo (10%, mean 81.7 y ± 7.9)	• Honey barrier cream (31) • Zinc oxide ointment (31)	Intertrigo severity looking at erythema, moisture, and skin damage	"The present study demonstrates that honey barrier cream is as effective as the standard treatment, with the advantage of not needing to be cleansed from the skin, which is required with zinc oxide ointment. Moreover, honey barrier cream reduces pruritus complaints and is comfortable for patients. Nevertheless, the efficacy of the honey barrier cream has to be confirmed in a larger study population with special attention to its antibacterial and antifungal properties."
Qiao and Ge, 2016, China[33]	–	210 Patients with diaper rash (50.5%, mean 5.7 months ± 1.2)	• Hydrocolloid dressings (70) • Mupirocin plaster and topical pearl powder (70) • Zinc oxide plaster (70)	Clinical efficacy, incidence of adverse events, time to resolution, hospitalization duration, mean cost, satisfaction of nursing	"In conclusion, it is crucial to identify the cause(s) for infant diaper rash, provide treatment and appropriate nursing measures, to prevent diaper rash from recurring. Hydrocolloid dressings, combined with individualized nursing, are an effective treatment for infant diaper rash and worthy of future clinical application."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Quatrano et al, 2015, US[55]	Case synopsis	1 Patient presenting with lichen sclerosus (0%, 65 y)	• Topical glucocorticoids and zinc oxide	Resolution of vulvar symptoms	"In our case, the extragenital lesions became asymptomatic after a short course of topical glucocorticoids and subsequent treatment was with emollients alone."
Sajjadian et al, 2012, Iran[34] Sajjadian and Kadivar, 2012, Iran[67] Hashemian et al, 2010, Iran[68]	Double-blind randomized clinical trial	46 Patients receiving treatment for diaper dermatitis (45.7%, mean 4.4 months ± 6.5)	Topical application of either: • Sucralfate (25) • Zinc oxide (21)	Diaper severity scores	"The complete healing time in the sucralfate group was significantly shorter than the zinc oxide group, showing that sucralfate seems to be more effective than zinc oxide in the treatment of diaper rash. Since sucralfate in topical formulations acts as a physical barrier with proved safety and no noticeable absorption, it may be used as a potential treatment for diaper dermatitis."
Samakayanusorn et al, 2017, Thailand[23]	Experimental, investigator-blinded, prospective randomized controlled trial	100 Patients receiving prevention for diaper dermatitis • Rice starch powder (48.2%, mean 13.2 months ± 5.7) • Zinc oxide (51.8%, mean 12.1 months ± 5.5)	• Rice starch powder (50) • Zinc oxide cream (50)	Diaper dermatitis severity scoring scale	"Additional information that rice starch powder could prevent diaper dermatitis with the same efficiency as zinc oxide cream, but with no effect on the duration of disease was presented. Thus, rice starch powder is an alternative substance for preventing diaper dermatitis."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Solheim et al, 2015, US[56]	Retrospective case series	5 Patients diagnosed with Hailey-Hailey disease (0%, age not specified)	Initial treatment included topical steroid, vulvar skin care guidelines, baking soda soaks, skin protectant (such as "A&D ointment" or zinc oxide), and additional treatment (such as crotamiton, clotrimazole, or Polysporin) 3 patients were followed long-term, and treatment included • Zinc oxide ointment (3) • Oral fluconazole as needed (1) • Betamethasone-clotrimazole ointment (2) • Nystatin-triamcinolone ointment (1)	Successful remission	"Treatment of Hailey-Hailey disease must be tailored to the individual patient. Adherence to vulvar skin care guidelines is critical for the remission of Hailey-Hailey disease. Treatment is long-term and may be complicated by episodes of fungal and bacterial superinfection and lichen simplex chronicus."
Spraker et al, 2006, Panama and US[35]	Double-blind, vehicle-controlled, parallel-group study	236 Patients with moderate-to-severe diaper dermatitis • Miconazole nitrate (46%, mean 7.67 months ± 4.87) • Zinc oxide (46%, mean 9.59 months ± 6.89)	• Miconazole nitrate ointment (112) • Zinc oxide and petrolatum vehicle control (124)	Overall cure	"In summary, this study showed that miconazole nitrate 0.25% ointment was well tolerated and significantly more effective than zinc oxide/petrolatum vehicle control for treatment of DD [diaper dermatitis] complicated by candidiasis."
Tucker et al, 1984, US[36]	Pilot studies	5 Participants receiving diluted fenvalerate topically to both earlobes (gender and age not specified)	Each participant was own control • Lilly® Zinc Oxide Paste (5) • Butylated hydroxyanisole in petrolatum (5) • Kerodex® 51 (5) • Squibb® Mineral Oil (5) • White® A&D Ointment (5) • Nature's Bounty® Natural Vitamin E Oil (5)	Dermal sensations	"Vitamin E oil (dl-alpha tocopheryl acetate) proved the most efficacious."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Wallengren, 2011, Sweden[37]	–	21 Patients with contact allergy to nickel (9.5%, range 25-73 y)	All patients were tested with nickel 2-5% in petrolatum, benzalkonium chloride in water, and petrolatum alone Afterwards, patients received interventions and were tested for allergic contact dermatitis to nickel, irritant contact dermatitis to benzalkonium chloride, and in immediate reactions to histamine and benzoic acid. The interventions were: • Ichthammol (21) • Zinc oxide (21) • Camphor (21) • Levomenthol (21) • Tea tree oil 20% or 50% (21) • Clobetasol butyrate (21)	Clinical scoring system, planimetry, visual analog score	"In summary, under occlusion, tea tree oil seems to be a more effective anti-eczematic agent than zinc oxide and clobetasol butyrate, which is superior to ichthammol and zinc oxide in topical treatment of urticarial reactions."
Young et al, 2014, US[41]	Open-label, descriptive study	29 Patients in the neonatal intensive care unit (NICU; 58.6%, mean gestation 31.7 weeks)	All patients received the standard cleanser, either undiluted or diluted for a no-rinse application. Patients also received other interventions depending on specific needs: • Standard moisturizer (29) • Silicone moisturizer (8) • Zinc oxide (3)	Neonatal Skin Condition Score (NSCS), Skin Erythema Scale (SES), pain	"Use of a product line, including 2 cleansers, 2 moisturizers, and a skin protectant with zinc oxide, did not increase overall skin condition or erythema when used in a critically ill, premature neonatal population. No significant difference was found between pain in subjects at study enrollment and completion. Additional research is needed to determine if these products would perform better or worse than others, designed for the same purpose."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 3: Warts					
Khattar et al, 2007, Lebanon[42]	Randomized, double-blind controlled trial	44 Patients receiving treatment for warts • Zinc oxide (45.5%, mean 25.8 y ± 8.1) • Salicylic acid and lactic acid (54.5%, mean 21.2 y ± 3.8)	• Zinc oxide ointment (22) • Salicylic acid and lactic acid (22)	Cure rates of warts, side effects	"Zinc oxide is simple to apply and painless, and therefore may be promising for the treatment of children. Further studies are needed to clarify the role of zinc. Other methods, such as subcutaneous or intralesional routes, may prove to have a more rapid effect. The period of treatment may need to be extended to improve the results."
Niazi and Farid Ur, 2018, Pakistan[38]	Randomized controlled trial	210 Patients suffering from common warts • Zinc oxide (9.5%, mean 26.89 y ± 12.461) • Salicylic acid and lactic acid (14.3%, mean 27.04 y ± 13.592)	• Zinc oxide ointment (105) • Salicylic acid and lactic acid combination (105)	Change in number and size of warts	"Topically applied 15% salicylic acid-15% lactic acid combination is superior in efficacy to 20% zinc oxide paste in treatment of common viral warts."
Songsantiphap and Asawanonda, 2019, Thailand[43]	Randomized, triple-blind, placebo-controlled trial	16 Patients with at least two similar palmar warts or verruca vulgaris (43.7%, median 29 y [Interquartile range 24.5-40])	All patients received both interventions • Zinc oxide ointment (16) • Hydrophilic cream placebo (16)	Diameter and surface area, volume, physician's global assessment, participant satisfaction, application and adherence, safety, and adverse events	"According to our study results, topical 15% zinc oxide might be effective reducing the size of common warts as monotherapy. Therefore, we believe that when used on difficult-to-treat warts prior to or as an adjunct to other treatments, it might increase the chance of wart clearance. Future studies involving the combination of topical zinc oxide 15% with other treatments, studies with a longer duration and larger sample sizes, and a cost effectiveness study might be warranted."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 4: Actinic keratosis					
Maloney et al, 2019, US[24]	Cases	2 Patients with history of organ transplant presenting for surgical management of cutaneous squamous cell carcinomas, surrounded by localized hyperkeratotic and diffuse flat actinic keratosis (100%, age not specified)	• Targeted liquid nitrogen, followed by occlusion with 5-fluorouracil and zinc oxide wrap (2)	Reduction of actinic keratosis (AK), tumor border	"In both patients, a clinical reduction of AKs and a more distinct tumor border was noted. Neither reported adverse reactions. In chronic wounds, zinc oxide has been shown to promote healing and decrease inflammation. Field and focal treatment of background actinically damaged skin prior to excision of a skin cancer can help define the otherwise poorly marginated neoplasms. Ultimately, this may improve histopathological accuracy and reduce the required margin to clear the tumor. This in-office combination method of treating field and focal actinic damage can increase patient comfort and compliance without adding to the burden of at-home healthcare tasks."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 5: Adenolymphangitis (ADL)					
Joseph et al, 2004, India[57]	Double-blind, placebo-controlled, clinical study	150 Patients who had suffered at least 2 adenolymphangitis (ADL) attacks in the preceding year • Placebo (26.7%, mean 49.8 y ± 12.5) • Topical antibiotic (26.7%, mean 49.9 y ± 11.1) • Diethylcarbamazine (DEC; 20%, mean 50.7 y ± 18.1) • Penicillin (26.7%, mean 47.9 y ± 15.1) • DEC and penicillin (26.7%, mean 47.3 y ± 15.6)	Daily administration of: • 2 placebo tablets plus topical antibiotic framycetin (30) Daily administration of placebo zinc oxide ointment, plus either • 2 placebo tablets (30) • 1 DEC tablet and 1 placebo tablet (30) • 1 penicillin tablet and 1 placebo tablet (30) • 1 DEC tablet and 1 penicillin tablet (30)	Incidence of ADL attacks	"It is recommended that a combination of penicillin prophylaxis and affected-limb care be incorporated into filariasis-control programmes [sic], to decrease morbidity."

Abbreviations: –, not provided; IQR, interquartile range; 5-FU, 5-fluorouracil; ADL, adenolymphangitis; AK, actinic keratosis; CblC, cobalamin C; clg-pvp, collagen-polyvinylpyrrolidone; DD, diaper dermatitis; DEC, diethylcarbamazine; JXG, juvenile xanthogranuloma; KTS, ketanserin; NICU, neonatal intensive care unit; NSBF, No Sting Barrier Film; NSCS, Neonatal Skin Condition Score; SBF, skin barrier function; SES, Skin Erythema Scale; SLS, sodium lauryl sulphate; TEWL, transepidermal water loss; UK, United Kingdom; US, United States; USP, United States Pharmacopeia; ZnO/Pet, zinc oxide/petrolatum.
[a]As defined by authors.

Appendix 3.1. 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 3.2. 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 3.3. 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 4. 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.