Summary Report

Hydrocortisone

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Frequently Used Abbreviations

API	Active pharmaceutical ingredient
EU	European Union
FDA	US Food and Drug Administration
IV	Intravenous
OTC	Over-the-counter
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ROA	Route of administration
SME	Subject matter expert
UK	United Kingdom
US	United States
USP	United States Pharmacopeia

INTRODUCTION

This report was created to assist the United States (US) Food and Drug Administration (FDA) in its evaluation of the use of hydrocortisone (UNII code: WI4X0X7BPJ), 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 hydrocortisone is used in clinical research and practice to diagnose, prevent, or treat disease. Because of 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 hydrocortisone 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 hydrocortisone 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

Hydrocortisone was nominated for inclusion on the 503B Bulks List by David Smith, the Outsourcing Facilities Association, Sincerus Florida, LLC, and Triangle Compounding Pharmacy, Inc. Hydrocortisone was nominated for use in combination with additional active pharmaceutical ingredients (APIs) (refer to Table 8).

Although the exact medical condition for which the compounded product is being requested is generally unknown, hydrocortisone is generally used for acne, allergic states, dermatological diseases, endocrine disorders, gastrointestinal diseases, hematologic disorders, hyperhidrosis, inflammation associated with topical bacterial and fungal infections, melasma, neoplastic diseases, nervous system diseases, ophthalmic diseases, pruritus, renal diseases, respiratory diseases, and rheumatic disorders. Hydrocortisone was also nominated to treat adrenal insufficiency, allergies, eczema, melasma, and psoriasis.

Hydrocortisone will be compounded as various topical dosage forms based on the prescriber's request, including creams, gels, ointments, solutions, and suspensions in strengths based on the prescriber's request, typically ranging from 0.5% to 4%. Hydrocortisone will also be compounded as various oral dosage forms with strengths based on the prescriber's request. Additionally, hydrocortisone will be compounded as capsules, creams, gels, ointments, suspensions, and suppositories for oral and topical administration. Strengths include 0.25% to 10%, 0.5 to 10 mg, 0.5 to 10 mg/mL, and 50 to 500 mg.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of hydrocortisone.[6-16]

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

- The compounded product may be the prescriber's preference or the only product to effectively treat the indication for which it is intended.
- Patients may need dosage forms or strengths, including greater concentrations, that are not available commercially.
- Patients may be sensitive to dyes, fillers, preservatives, or other excipients in manufactured products.
- Hydrocortisone will be compounded in combination with other APIs to treat conditions such as melasma and inflammation or pruritus associated with conditions.

- Compounding from bulk drug substances means using only the ingredients necessary to achieve the desired clinical outcomes. The API is in its purest form, without fillers, excipients, binders, dyes, preservatives, or other materials.
- Individual finished products have more variance than the actual API, and the use of a 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 hydrocortisone products in the US and around the world. The World Health Organization, the European Medicines Agency, and globalEDGE were used to identify regulatory agencies in non-US countries. The medicine registers of non-US regulatory agencies were selected for inclusion if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information, specifically product trade name, active ingredient, strength, form, route of administration (ROA), and approval status, provided in a usable format. Based on these criteria, the medicine registers of 13 countries or 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 European Medicines Agency 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 or vice versa.

Each medicine register was searched for hydrocortisone; name variations of hydrocortisone 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 or schedule, and approval date. Information was recorded only for products with strengths, forms, or ROAs 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 hydrocortisone. The availability of OTC products (yes/no) in the US and the ROAs 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: hydrocortisone, topical administration or form, and substances nominated for use in combination with (refer to Appendix 1 for full search strategies). A literature review was not conducted for topical single-ingredient hydrocortisone products because of the availability of FDA-approved single-ingredient products for this ROA. Results were limited to human studies in the English language. Searches were conducted on February 10, 2021. In addition, the ECRI Guidelines Trust® repository was searched on February 10, 2021 for clinical practice guidelines that recommended the use of hydrocortisone and provided sufficient information on dosing and administration.

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

Study selection

Studies in which hydrocortisone was used in the nominated dosage form, ROA, 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; were reviews or meta-analyses; were surveys or questionnaires (cross-sectional design); were designed to evaluate cost-effectiveness, mechanism of action, preclinical use, safety, or toxicity; or used any study design other than a randomized controlled trial conducted in a non-US country. Studies were also excluded if hydrocortisone was used as an FDA-approved product in the nominated dosage form, ROA, or combination; was in a dosage form, ROA, or combination that was not nominated; was in an unspecified dosage form or ROA; was not used clinically; or was mentioned briefly as a rescue treatment or previously failed treatment. Studies in which hydrocortisone was used to diagnose, prevent, or treat autism were excluded because of a separate project examining the use of compounded substances in patients 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 hydrocortisone, setting, total number of patients, number of patients who received hydrocortisone, patient population, indication for use of hydrocortisone, dosage form and strength, dose, ROA, frequency and duration of therapy, use of hydrocortisone in a combination product, use and formulation of hydrocortisone in a compounded product, use of hydrocortisone compared with FDA-approved drugs or other treatments, outcome measures, and 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 determine how and in what circumstances hydrocortisone 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 hydrocortisone. Potential SMEs were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. Select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided verbal informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were synthesized for qualitative data analysis.

In addition to interviews with individual SMEs, a roundtable discussion with pharmacists was held. Participants were identified through outreach to professional associations that would potentially purchase compounded products from outsourcing facilities. A prequestionnaire was distributed to those who agreed to participate, to collect information about the types of facilities at which participants worked and the products they purchased from outsourcing facilities (refer to Appendix 2 for the complete survey and the *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 hydrocortisone in clinical practice. The online survey was created in Qualtrics® software (refer to Appendix 2 for complete survey). A Google™ search was conducted to identify the professional associations in the US for the relevant medical specialties. An association's website was searched to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used. An email describing the project and requesting distribution of the survey to the association's members was sent to the identified person(s). Associations that declined, did not respond, or did not provide significant data in project Years 1 and 2 were not contacted about the project Year 3 surveys.

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

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

The University of Maryland, Baltimore Institutional Review Board and the FDA Institutional Review Board 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

- Hydrocortisone is available as an FDA-approved product in the nominated dosage form and ROA.
- Hydrocortisone was available as an FDA-approved EQ10 mg base/5 mL oral suspension, 0.5% topical aerosol, 1% topical gel, and 0.5% topical paste product that was discontinued, not for reasons of safety or efficacy.
- Hydrocortisone is available as various topical OTC products in the US.
- There is a current United States Pharmacopeia (USP) monograph for hydrocortisone.
- Hydrocortisone is available in the nominated dosage form and ROA in all foreign medical registries searched.

Table 1. Currently approved products—US[a]

Active Ingredient[b]	Concentration	Dosage Form	Route of Administration	Status	Approval Date[c]
Hydrocortisone	0.5-20 mg	Granule, tablet	Oral	Prescription	Approved before 1/01/1982
Hydrocortisone	0.1-2.5%	Cream, lotion, ointment, solution	Topical	Prescription	Approved before 1/01/1982

[a]Source: US FDA *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).
[b]Hydrocortisone was used as the standard for name variations, including hydrocortisone acetate, hydrocortisone butyrate, hydrocortisone probutate, and hydrocortisone valerate.
[c]If multiple approval dates or multiple strengths, then earliest date provided.

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

Active Ingredient[b]	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date[c]
Hydrocortisone	0.5-20 mg	Capsule, granules, tablet	Oral	Abu Dhabi	Active	—
				Australia	Prescription-only	10/21/1991
				Belgium	Prescription	6/30/1961
				Canada	Prescription	12/31/1954
				EU	Authorized	11/03/2011
				Hong Kong	Prescription-only	2/16/1994
				Ireland	Prescription-only	4/01/1978
				Latvia	Prescription	3/23/2010
				Namibia	—	12/27/1987
				New Zealand	Prescription	5/11/1995
				Saudi Arabia	Pharmacy[d]	—
				UK	Prescription-only	2/23/1989
Hydrocortisone	0.1-2.5%	Cream, emulsion, gel, lotion, ointment, solution, spray	Cutaneous, topical	Abu Dhabi	Active	—
				Australia	Pharmacist only[d], pharmacy-only[e] medicine; prescription-only	8/02/1991

				Belgium	Prescription	11/28/1984
				Canada	Prescription	12/18/2000
				Hong Kong	Pharmacy-only[e]	4/26/1979
				Ireland	Pharmacy,[e] prescription-only	10/14/1977
				Latvia	Prescription	10/01/1997
				Namibia	—	12/28/1975
				New Zealand	Pharmacy,[e] prescription, restricted	4/10/1974
				Saudi Arabia	Pharmacy[e]	—
				UK	Pharmacy,[e] prescription-only	9/28/1973

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 usable format. Information was recorded only for products with strengths, forms, or ROAs similar to those requested in the nominations. See Methodology for full explanation.

[b]Hydrocortisone was used as the standard for name variations, including hydrocortisonum, hydrocortisoni acetas, hydrocortisone acetate, hydrocortisone 17-butyrate, hydrocortisoni butyras, hydrocortisone butyrate, hydrocortisone propin, hydrocortisone sodium succinate, hydrocortisone sodium phosphate ester, and hydrocortisone valerate.

[c]If multiple approval dates or multiple strengths, then earliest date provided.

[d]Pharmacist-only medications may be sold to the public from a pharmacist without a prescription.

[e]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; 2 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 1256 titles and abstracts were screened. After screening, the full text of 361 articles was reviewed. Finally, 5 studies were included. A total of 356 studies were excluded for the following reasons: wrong study design (237 studies), nonnominated formulation (79), FDA-approved formulation (26), unable to obtain full text (5), unspecified dosage form or ROA (3), wrong substance (3), duplicate study (2), and language other than English (1).

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

Characteristics of included studies

The 5 included studies were published between 1993 and 2018. There were 5 experimental studies, 0 observational studies, 0 descriptive studies, and 0 clinical practice guidelines. The 5 studies were conducted in the following countries: Italy, UK, and US.

A total of 526 patients participated in the 5 included studies. The number of patients in each study ranged from 18 to 283.

Outcome measures differed between the included studies and included pain, total remission, resting and squeeze anal pressure, symptoms, concurrent use of analgesics, Melasma Area and Severity Index scores, pruritus, side effects or discomfort, effectiveness, and convenience of applications.

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

Use of hydrocortisone

A total of 197 patients received hydrocortisone and lidocaine as a treatment for anal fissures, administered as a topical gel or ointment for 3-6 weeks. Forty-four patients received hydrocortisone and lidocaine as a treatment for hemorrhoidal thrombosis, administered as a topical gel for 2 weeks. Eighteen patients received hydrocortisone and hydroquinone as a treatment for melasma, administered as a topical cream. Twenty-five patients received hydrocortisone and lidocaine as a treatment for pruritus ani, administered as a topical spray for 1 week.

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

Hydrocortisone was not used as a compounded product, but it was used in combination products (refer to Tables 8-10).

In 1 study, the authors' concluding statement recommended the use of hydrocortisone and lidocaine for the treatment of pruritus ani.[17] In 4 studies, the authors did not provide a definitive conclusion for the use of hydrocortisone.[18-21] Refer to Table 5 for a 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 hydrocortisone.

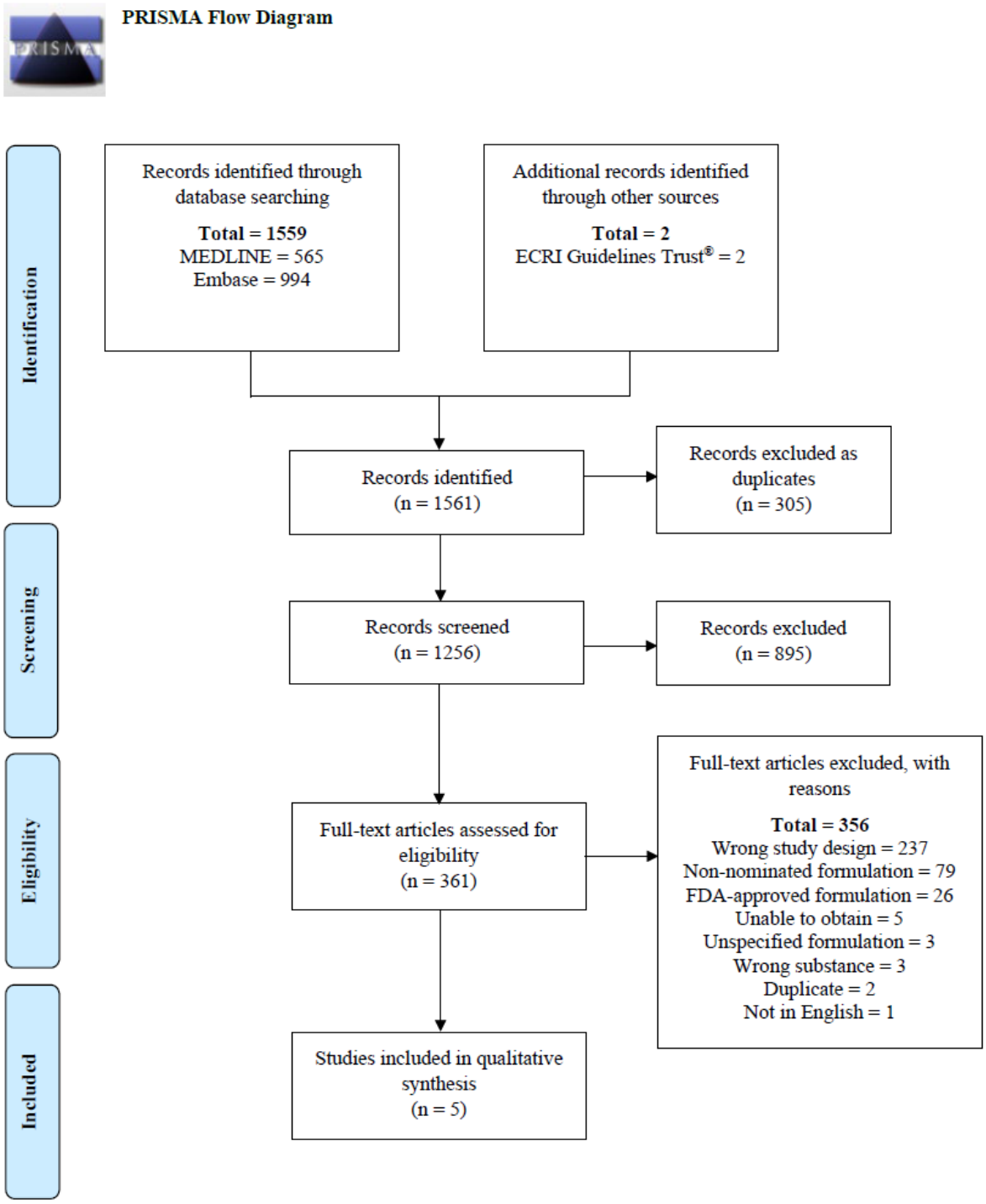
Cortisone was synthesized in the 1940s.[22] Then in 1948, cortisone was used for a patient with rheumatic arthritis, and the response achieved led to interest in continuing cortisone research.[22] There was a cortisone famine caused by the great demand that was resolved, in 1951, when mass production of hydrocortisone became possible.[22] Topical hydrocortisone, as a corticosteroid, is used as an anti-inflammatory agent for various acute and chronic dermatoses.[23] Based on studies with patch-tested patients, the allergic contact dermatitis frequency is about 2.3-4.9% for topical corticosteroids.[24] Patients who are allergic to a topical corticosteroid often have cross-reactivity to the other topical corticosteroids.[24] Though presumably less common, this cross-reactivity could also sensitize patients to corticosteroids given through other ROAs such as oral, parenteral, or intralesional.[24]

Several studies used topical hydrocortisone in one of the nominated combinations with hydroquinone and tretinoin for the treatment of melasma. In 1998, a study by Kang et al used hydrocortisone 1%, hydroquinone 5%, and tretinoin 0.1% for 25 Korean patients with melasma for 4 months.[25] Patients applied about 0.3 g of the topical combination cream on the lesions twice a week instead of a daily application to minimize the side effects of erythema or peeling.[25] Kang et al conclude that the topical combination cream could be "used repeatedly for a duration of 1 month every 6 months . . . and the side effects of long-term treatment of [tretinoin or hydroquinone] would be prevented."[25] In 2002, Sarkar et al studied using serial glycolic acid peels with a topical modified Kligman's formula (hydrocortisone acetate 1%, hydroquinone 5%, tretinoin 0.05%) cream for Indian patients with melasma.[14] Twenty patients received the topical cream with glycolic acid peel, and the other 20 received only the topical cream as the control group.[14] Sarkar et al conclude that superficial chemical peels are good adjunct to topical therapy for melasma.[14] In a 2012 study by Fleming and Bashir, hydrocortisone 1%, hydroquinone 5%, and tretinoin 0.1% cream was used to treat facial hyperpigmentation in 41 patients who used the cream nightly for 90 days.[26] Fleming and Bashir conclude that "patients reported improvement in both hyperpigmentation and quality of life."[26] Also, in a 2013 study by Chaudhary and Dayal, the combination of hydrocortisone 1%, hydroquinone 2%, and tretinoin 0.05% topical cream was used with glycolic acid peeling for melasma.[7] Twenty patients received the topical combination only (control group), and the other 20 patients received the topical combination with serial glycolic acid peeling.[7] Chaudhary and Dayal conclude that that using the topical combination with glycolic acid peeling "significantly enhances the therapeutic efficacy of glycolic acid peeling," making this combination a "highly effective, safe and promising therapeutic option in treatment of melasma."[7] Additionally, a 2014 study by Tourlaki et al used hydrocortisone butyrate 0.1%, hydroquinone 4%, and retinoic acid 0.03% cream for patients with melasma for 10 days, followed by laser treatment.[27] Tourlaki et al conclude that the combination cream and the laser were useful for patients with melasma who were resistant to the combination cream alone; however, the long-term efficacy is limited.[27] A 2020 case series by Piquero-Casals et al also mentioned use of a compounded gel-cream that consisted of hydrocortisone 1%, hydroquinone 4%, and 0.025% tretinoin for 16 weeks for 4 patients with melasma.[28]

Other nominated topical combinations mentioned include hydrocortisone acetate micronized powder 10% and lidocaine HCl 0.1-2% (optional) compounded in aquasonic 100 gel or aquaphor, aquabase, Eucerin, or hydrocream base as a phonophoresis therapy that offers an alternative to injections for indications such as "polyarthritis, tendinitis, bursitis, painful 'trigger points' and other inflammatory

conditions."[29] A 1976 study used a gentamicin and hydrocortisone cream for patients with various inflammatory dermatoses.[30]

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	0
Observational	0
Experimental[17-21]	5

Table 4. Number of studies by country

Country	**Number of Studies**
Italy[18,19,21]	3
UK[17]	1
US[20]	1
	Total US: 1 Total Non-US Countries: 4

Table 5. Summary of included studies

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 1: Anal fissures					
Antropoli et al, 1999, Italy[18]	Prospective, randomized, double-blind, multicenter design	283 Patients (gender not specified, mean 47 y ± 10.7)	• Nifedipine gel (141) • Hydrocortisone acetate and lidocaine gel (142)	Presence of pain, total remission, resting and squeeze anal pressure	"Our study clearly demonstrates that the therapeutic use of nifedipine, which at present is used only in cardiovascular pathologies, should be extended with local use to the conservative treatment of anal fissures."
Perrotti et al, 2002, Italy[21]	Prospective, randomized, double-blind study	110 Patients with chronic anal fissure • Nifedipine group (78.2%, mean 43.2 y ± 15.4) • Hydrocortisone group (65.5%, mean 45.5 y ± 13.9)	• Nifedipine and lidocaine ointment (55) • Hydrocortisone and lidocaine ointment (55)	Reduction in mean anal resting pressure, pain relief, and healing of chronic anal fissure	"Our study clearly demonstrates that the therapeutic use of topical nifedipine and lidocaine ointment should be extended to the conservative treatment of chronic anal fissure."
Indication 2: Hemorrhoidal thrombosis					
Perrotti et al, 2000, Italy[19]	Prospective, randomized study	90 Patients (gender not specified, mean 34 y ± 10.8)	• Nifedipine and lidocaine gel (46) • Hydrocortisone acetate and lidocaine gel (44)	Symptoms, pain, concurrent use of analgesics	"Our study clearly demonstrates that the use of Nifedipine, which at present is for treatment of cardiovascular disorders, should be extended to the conservative treatment of acute thrombosed haemorrhoids, using a topical application."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 3: Melasma					
Schlessinger et al, 2018, US[20]	—	18 Patients (0%, age not specified)	• Glycolic acid peel on one side of the face and 1064-nm Q-switched laser on the other side All areas were pretreated with a hydroquinone and hydrocortisone cream.	Melasma Area and Severity Index scores, pain visual analog scores	"Participants were equally pleased with both treatments. Superficial chemical peels and [neodymium-doped yttrium aluminum garnet] laser appear to be equally effective in the treatment of melasma."
Indication 4: Pruritus ani					
Allenby et al, 1993, UK[17]	Double blind placebo-controlled crossover study 2 studies were reported, but only the placebo-controlled study was described because the other study was not a randomized foreign study	25 Patients with a history of pruritus ani ranging from several months to several years (52%, range 27-81 y)	• Placebo (25) • Perinal (hydrocortisone and lignocaine) (25) Patients were randomly assigned to placebo or Perinal for 1 week and then switched to the remaining option for the next week.	Pruritus assessed based on analog scale, side effects or discomfort, effectiveness, convenience of applications	"Most patients presenting with pruritus ani have no identifiable lesion to treat or other underlying pathology. Furthermore, many patients who undergo surgery for potentially implicated anorectal conditions continue to have symptoms. For these reasons it is common practice to assist patients to minimise their symptoms, and in this respect it is concluded that Perinal has a very useful role to play in breaking the vicious cycle of itching and scratching."

Abbreviation: —, not provided.
[a]As defined by authors.

Table 6. Dosage by indication—US

Indication	Dosage	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Melasma[20]	—	2.5%	Cream	Topical	—

Abbreviation: —, not provided.

Table 7. Dosage by indication—non-US countries

Indication	Dosage	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Anal fissures[18,21]	—	1%	Gel	Topical	3 weeks
	6 g/day	1%	Ointment	Topical	6 weeks
Hemorrhoidal thrombosis[19]	—	1.5%	Gel	Topical	2 weeks
Pruritus ani[17]	0.2-0.3 mL/day	0.2%	Spray	Topical	1 week

Abbreviation: —, not provided.

Table 8. Number of studies by combination

	Combination Formula	Number of Studies
Nominated	Hydrocortisone 1% / Aluminum chloride hexahydrate 20%	0
	Hydrocortisone 2.5% / Gentamicin 0.1%	0
	Hydrocortisone 0.5-2.5% / Hydroquinone 4% – topical cream[20]	1
	Hydrocortisone 2.5% / Ketoconazole 2%	0
	Hydrocortisone 0.2-2.5% / Lidocaine 1-1.5% – topical gel, ointment, spray[17-19,21]	4

	Hydrocortisone 2.5% / Clindamycin 1% / Niacinamide 4%	0
	Hydrocortisone 2% / Clindamycin 1% / Tretinoin 0.05%	0
	Hydrocortisone 1-4% / Hydroquinone 4-8% / Tretinoin 0.025-0.05%	0
	Hydrocortisone 2.5% / Levocetirizine dihydrochloride 2% / Menthol 1%	0
	Hydrocortisone 2.5% / Levocetirizine dihydrochloride 2% / Tranilast 0.5%	0
	Hydrocortisone 1% / Benzoin tincture 6% / Miconazole nitrate 1% / Zinc Oxide 10%	0
	Hydrocortisone 2% / Clindamycin 1% / Niacinamide 2% / Tretinoin 0.025%	0
	Hydrocortisone / Glycolic acid / Triamcinolone / Tretinoin	0
	Hydrocortisone 0.5% / Hydroquinone 4-8% / Kojic acid 4-6% / Tretinoin 0.025-0.05%	0
	Hydrocortisone 1% / Lidocaine HCl monohydrate 3% / Nifedipine 4% / Witch Hazel 5%	0
	Hydrocortisone 0.5% / Ascorbyl palmitate 2% / Green tea extract 2% / Hydroquinone 6% / Kojic acid 6%	0
	Hydrocortisone 0.5% / Ascorbyl Palmitate 2% / Hydroquinone 4% / Kojic acid 6% / Tretinoin 0.025%	0
	Hydrocortisone 0.5% / Ascorbyl palmitate 1% / Kojic acid 4% / Lactic acid 10% / Potassium azeloyl diglycinate 10%	0
	Hydrocortisone 0.5% / Clindamycin 1% / Niacinamide 2% / Spironolactone 2% / Tretinoin 0.025%	0
	Hydrocortisone 1% / Clioquinol 1% / Coal tar solution 2% / Metronidazole 2% / Salicylic acid 2%	0
	Hydrocortisone 0.5% / Ascorbyl Palmitate 2% / Hyaluronic acid sodium salt 0.5% / Hydroquinone 4%/ Kojic acid 4% / Tretinoin 0.05%	0

Table 9. Compounded products—US

No compounded products from included studies.

Table 10. Compounded products—non-US countries

No compounded products from included studies.

Results of interviews

A total of 199 SMEs were contacted for interviews; 63 agreed to be interviewed, and 136 declined or failed to respond to the interview request. Seven SMEs discussed hydrocortisone. The 7 SMEs were medical doctors who specialized or were board-certified in allergy, dermatology, infectious disease, or rheumatology, working in academic medical institutions. The SMEs had been in practice for 1 to 56 years. Additional information was collected as part of the Expanded Information Initiative project, referred to as phase 3, in which outreach was conducted to the nominators of the bulk drug substances to remedy information gaps in the initial nomination.

There are 4 classes of steroids (class I, class II, class III, and class IV) that are grouped based on their strength. Class I steroids "are super strong, super potent," with subsequent classes decreasing in potency. One SME stated that triamcinolone is a higher-potency steroid, so it should not be applied to the face, only "from the neck down." Within each class, prescribers typically have preferred steroids, and the formulation needed and insurance reimbursement determine which steroid is prescribed. The indication determines which formulation is needed; for example, ointments are more occlusive and increase moisturization and are typically preferred for atopic dermatitis. However, ointments cannot be applied to the scalp because "you can't get ointments into your scalp if you have hair," and patients "really don't like them because they're so greasy" and instead prefer creams. For patients with psoriasis of the scalp, foams and oils are preferred. If the desired formulation is not available in the preferred steroid, 1 SME stated they would switch to a different steroid within the same class that was available in the necessary dosage form.

Hydrocortisone is a lower-potency steroid that can be used for patients with a mild rash, mild eczema, eczema on the face, or any facial rashes. The SMEs all had experience using hydrocortisone, with 1 SME stating that the cream and ointment are "probably the 2 more common ones that we use." However, most used the commercially available OTC formulations and were not familiar with any of the nominated combinations. One SME stated that if a patient does not respond to hydrocortisone, they switch to a more potent steroid.

Although the SMEs did not have experience using any of the combinations, 1 SME discussed the combinations. Another SME commented that they use hydrocortisone in combination with Aquaphor or another emollient because it makes it easier for the patient to use if it is a combination. The combinations with hydroquinone, kojic acid, and tretinoin would be to treat melasma. The SME stated that using hydrocortisone in this formulation would be reasonable because melasma is commonly on the face, so a milder steroid should be used. The SME also said that compounding products for melasma is "a very reasonable thing to do because a lot of these things aren't necessarily available as a standalone." Additionally, being able to titrate hydroquinone is important because "if you overdo it, you can get sort of paradoxical darkening."

The combinations with clindamycin and spironolactone are for acne, with the hydrocortisone to reduce inflammation, clindamycin would target bacterial causes for acne, and tretinoin is "really going to be the workhorse" where "you're going to be changing the follicle keratinization and trying to get rid of those plugs." Spironolactone would be used if "you think that there's some hormonal component."

The combinations with hydrocortisone, levocetirizine, tranilast, and menthol would be used for itch. Another SME thought that the combinations with levocetirizine were "interesting" because patients with eczema often "get itchy, they scratch" and "that's what's causing the rash, it's the rash cycle." A topical formulation may be beneficial, but the SME was unsure of the effectiveness. The SME was also unsure

about the inclusion of menthol, stating, “I don’t know that I would have done menthol,” and was not familiar with tranilast.

Aluminum chloride hexahydrate is used as an antiperspirant, and the SME said that hydrocortisone might be included because “sometimes people get itchy with this antiperspirant.” The SME stated that hyperhidrosis is “a real problem,” and a combination of hydrocortisone with aluminum chloride might decrease irritation.

The benzoin tincture, hydrocortisone, miconazole, and zinc oxide are probably used for foot fungus, as is the hydrocortisone/ketoconazole combination. The SME said that the miconazole and benzoin are antimicrobial, hydrocortisone will relieve itch, and the zinc oxide will “dry up your feet.” The SME was unsure about the gentamicin and hydrocortisone combination, stating that it could be “for a lot of things.” Coal tar with hydrocortisone would probably be used for psoriasis. The SME commented that salicylic acid acts as a keratolytic, and metronidazole might be included if there is a microbial colonization that is causing a foul odor. Hydrocortisone with lidocaine probably would also be used for itch but includes a numbing agent as well. Lastly, hydrocortisone with nifedipine would probably be used for anal pruritus if “you think that there are hemorrhoids.”

The SME said that the use of hydrocortisone for these indications would make sense, stating that “it is good to have available a lower-potency [steroid] in case you’re trying to treat something in an unusual location.” However, the SME mentioned that if you “were to decouple them, then you could choose whichever steroid you wanted separately from whatever else you were trying to treat with” but also said that “having the combination in one product can be convenient for patients.”

One SME has not encountered challenges with excipients contained in commercially available products but continued, “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.”

One SME discussed the use of hydrocortisone for patients with extensive vulvitis. The SME said that in these patients “it’s not enough just to give fluconazole,” continuing that “you’ve got to give a topical agent to be applied to the vulva, and it’s usually a steroid. So it could be a 1 to 5% steroid, and usually 1% hydrocortisone, 2%, 3%, it relieves it.” Mycolog® (nystatin and triamcinolone) is the most widely used topical antifungal steroid for vulval inflammation, but there is no generic, so it is “not cheap.” The SME stated that “if you want to use something cheap, you’ve got to use hydrocortisone.” The SME also stated that “there are virtually no commercially available topical steroids for the vagina, and there’s a major need for it.” This lack is problematic when patients have desquamative inflammatory vaginitis, which is an inflammatory process that involves the vagina, the vestibule, and sometimes the vulva, which respond to steroids. However, no topical steroids are available for intravaginal use. The SME used a compounding pharmacy to prepare a hydrocortisone 10% cream. Although this is not a common condition, it is a chronic condition necessitating daily therapy.

As part of phase 1, nominator provided additional information about the multi-ingredient products contained in the hydrocortisone nomination.

Hydrocortisone 2.5%/ketoconazole 2%/iodoquinol 1% will be compounded as a topical cream to treat topical fungal infections, applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylated hydroxytoluene, butylparaben, silicon dioxide, benzalkonium chloride, butylene glycol, cetearyl alcohol, chlorocresol, hexylene glycol, isopropyl palmitate, methylparaben, mineral oil, polyethylene glycol,

polysorbate 20, potassium hydroxide, propylene glycol, sodium hydroxide, sodium lauryl sulfate, titanium dioxide, trolamine, and white petrolatum, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants. Their hazardous concerns include allergen; classified as expected to be toxic or harmful; classified as irritant; classified as skin irritant; highly comedogenic; human endocrine disruptor; human immune and respiratory toxicant or allergen; human irritant; human respiratory irritant; human skin toxicant or allergen; human toxicant or allergen; persistent or bioaccumulative; possible human carcinogen; restricted in cosmetics (recommendations or requirements), use, concentration, or manufacturing restrictions; violation of industry recommendations, restricted in cosmetics; and use, concentration, or manufacturing restrictions, not safe for use on injured or damaged skin (only for products for use on damaged skin). Iodoquinol is added for its ability to harm bacteria and fight infections. The reason for including hydrocortisone and ketoconazole was not provided. This product will result in a clinical difference to patients because it does not include harmful excipients found in FDA-approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Hydrocortisone 0.5%/hydroquinone 4%/tretinoin 0.025% will be compounded as a topical emulsion to treat melasma, applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylated hydroxytoluene, butylparaben, ethanol, silicon dioxide, benzalkonium chloride, butylene glycol, cetearyl alcohol, chlorocresol, hexylene glycol, methylparaben, mineral oil, polyethylene glycol, potassium hydroxide, propylene glycol, sodium hydroxide, titanium dioxide, trolamine, and white petrolatum, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants. Their hazardous concerns include allergen; classified as expected to be toxic or harmful; classified as irritant; classified as skin irritant; determined safe for use in cosmetics; subject to concentration or use limitations, safe for use in cosmetics with some qualifications; human endocrine disruptor; human immune and respiratory toxicant or allergen; human irritant; human respiratory irritant; human skin toxicant or allergen; human toxicant or allergen; persistent or bioaccumulative; possible human carcinogen; restricted in cosmetics (recommendations or requirements), use, concentration, or manufacturing restrictions; violation of industry recommendations, restricted in cosmetics; and use, concentration, or manufacturing restrictions, not safe for use on injured or damaged skin (only for products for use on damaged skin). Hydrocortisone is added for its anti-inflammatory properties, hydroquinone for its skin-lightening properties, and tretinoin for its anti-inflammatory properties. This product will result in a clinical difference to patients because it does not include harmful excipients found in FDA-approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Hydrocortisone 0.5%/hydroquinone 6%/tretinoin 0.025% will be compounded as a topical emulsion to treat melasma, applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylated hydroxytoluene, butylparaben, ethanol, silicon dioxide, benzalkonium chloride, butylene glycol, cetearyl alcohol, chlorocresol, hexylene glycol, methylparaben, mineral oil, polyethylene glycol, potassium hydroxide, propylene glycol, sodium hydroxide, titanium dioxide, trolamine, and white petrolatum, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants. Their hazardous concerns include allergen; classified as expected to be toxic or harmful; classified as irritant; classified as skin irritant; determined safe for use in cosmetics; subject to concentration or use limitations, safe for use in cosmetics with some qualifications; human endocrine

disruptor; human immune and respiratory toxicant or allergen; human irritant; human respiratory irritant; human skin toxicant or allergen; human toxicant or allergen; persistent or bioaccumulative; possible human carcinogen; restricted in cosmetics (recommendations or requirements), use, concentration, or manufacturing restrictions; violation of industry recommendations, restricted in cosmetics; and use, concentration, or manufacturing restrictions, not safe for use on injured or damaged skin (only for products for use on damaged skin). Hydrocortisone is added for its anti-inflammatory properties, hydroquinone for its skin-lightening properties, and tretinoin for its anti-inflammatory properties. This product will result in a clinical difference to patients because it does not include harmful excipients found in FDA-approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Hydrocortisone 0.5%/hydroquinone 6%/tretinoin 0.05% will be compounded as a topical emulsion to treat melasma, applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylated hydroxytoluene, butylparaben, ethanol, silicon dioxide, benzalkonium chloride, butylene glycol, cetearyl alcohol, chlorocresol, hexylene glycol, methylparaben, mineral oil, polyethylene glycol, potassium hydroxide, propylene glycol, sodium hydroxide, titanium dioxide, trolamine, and white petrolatum, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants. Their hazardous concerns include allergen; classified as expected to be toxic or harmful; classified as irritant; classified as skin irritant; determined safe for use in cosmetics; subject to concentration or use limitations, safe for use in cosmetics with some qualifications; human endocrine disruptor; human immune and respiratory toxicant or allergen; human irritant; human respiratory irritant; human skin toxicant or allergen; human toxicant or allergen; persistent or bioaccumulative; possible human carcinogen; restricted in cosmetics (recommendations or requirements), use, concentration, or manufacturing restrictions; violation of industry recommendations, restricted in cosmetics; and use, concentration, or manufacturing restrictions, not safe for use on injured or damaged skin (only for products for use on damaged skin). Hydrocortisone is added for its anti-inflammatory properties, hydroquinone for its skin-lightening properties, and tretinoin for its anti-inflammatory properties. This product will result in a clinical difference to patients because it does not include harmful excipients found in FDA-approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Hydrocortisone 0.5%/hydroquinone 8%/tretinoin 0.05% will be compounded as a topical emulsion to treat melasma, applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylated hydroxytoluene, butylparaben, ethanol, silicon dioxide, benzalkonium chloride, butylene glycol, cetearyl alcohol, chlorocresol, hexylene glycol, methylparaben, mineral oil, polyethylene glycol, potassium hydroxide, propylene glycol, sodium hydroxide, titanium dioxide, trolamine, and white petrolatum, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants. Their hazardous concerns include allergen; classified as expected to be toxic or harmful; classified as irritant; classified as skin irritant; determined safe for use in cosmetics; subject to concentration or use limitations, safe for use in cosmetics with some qualifications; human endocrine disruptor; human immune and respiratory toxicant or allergen; human irritant; human respiratory irritant; human skin toxicant or allergen; human toxicant or allergen; persistent or bioaccumulative; possible human carcinogen; restricted in cosmetics (recommendations or requirements), use, concentration, or manufacturing restrictions; violation of industry recommendations, restricted in cosmetics; and use,

concentration, or manufacturing restrictions, not safe for use on injured or damaged skin (only for products for use on damaged skin). Hydrocortisone is added for its anti-inflammatory properties, hydroquinone for its skin-lightening properties, and tretinoin for its anti-inflammatory properties. This product will result in a clinical difference to patients because it does not include harmful excipients found in FDA-approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Hydrocortisone 0.5%/hydroquinone 8%/tretinoin 0.025% will be compounded as a topical emulsion to treat melasma, applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylated hydroxytoluene, butylparaben, ethanol, silicon dioxide, benzalkonium chloride, butylene glycol, cetearyl alcohol, chlorocresol, hexylene glycol, methylparaben, mineral oil, polyethylene glycol, potassium hydroxide, propylene glycol, sodium hydroxide, titanium dioxide, trolamine, and white petrolatum, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants. Their hazardous concerns include allergen; classified as expected to be toxic or harmful; classified as irritant; classified as skin irritant; determined safe for use in cosmetics; subject to concentration or use limitations, safe for use in cosmetics with some qualifications; human endocrine disruptor; human immune and respiratory toxicant or allergen; human irritant; human respiratory irritant; human skin toxicant or allergen; human toxicant or allergen; persistent or bioaccumulative; possible human carcinogen; restricted in cosmetics (recommendations or requirements), use, concentration, or manufacturing restrictions; violation of industry recommendations, restricted in cosmetics; and use, concentration, or manufacturing restrictions, not safe for use on injured or damaged skin (only for products for use on damaged skin). Hydrocortisone is added for its anti-inflammatory properties, hydroquinone for its skin-lightening properties, and tretinoin for its anti-inflammatory properties. This product will result in a clinical difference to patients because it does not include harmful excipients found in FDA-approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Hydrocortisone 2.5%/hydroquinone 4%/tretinoin 0.025% will be compounded as a topical emulsion to treat melasma, applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylated hydroxytoluene, butylparaben, ethanol, silicon dioxide, benzalkonium chloride, butylene glycol, cetearyl alcohol, chlorocresol, hexylene glycol, methylparaben, mineral oil, polyethylene glycol, potassium hydroxide, propylene glycol, sodium hydroxide, titanium dioxide, trolamine, and white petrolatum, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants. Their hazardous concerns include allergen; classified as expected to be toxic or harmful; classified as irritant; classified as skin irritant; determined safe for use in cosmetics; subject to concentration or use limitations, safe for use in cosmetics with some qualifications; human endocrine disruptor; human immune and respiratory toxicant or allergen; human irritant; human respiratory irritant; human skin toxicant or allergen; human toxicant or allergen; persistent or bioaccumulative; possible human carcinogen; restricted in cosmetics (recommendations or requirements), use, concentration, or manufacturing restrictions; violation of industry recommendations, restricted in cosmetics; and use, concentration, or manufacturing restrictions, not safe for use on injured or damaged skin (only for products for use on damaged skin). Hydrocortisone is added for its anti-inflammatory properties, hydroquinone for its skin-lightening properties, and tretinoin for its anti-inflammatory properties. This product will result in a clinical difference to patients because it does not include harmful excipients found

in FDA-approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Hydrocortisone 1%/hydroquinone 8%/tretinoin 0.05% will be compounded as a topical emulsion to treat melasma, applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylated hydroxytoluene, butylparaben, ethanol, silicon dioxide, benzalkonium chloride, butylene glycol, cetearyl alcohol, chlorocresol, hexylene glycol, methylparaben, mineral oil, polyethylene glycol, potassium hydroxide, propylene glycol, sodium hydroxide, titanium dioxide, trolamine, and white petrolatum, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants. Their hazardous concerns include allergen; classified as expected to be toxic or harmful; classified as irritant; classified as skin irritant; determined safe for use in cosmetics; subject to concentration or use limitations, safe for use in cosmetics with some qualifications; human endocrine disruptor; human immune and respiratory toxicant or allergen; human irritant; human respiratory irritant; human skin toxicant or allergen; human toxicant or allergen; persistent or bioaccumulative; possible human carcinogen; restricted in cosmetics (recommendations or requirements), use, concentration, or manufacturing restrictions; violation of industry recommendations, restricted in cosmetics; and use, concentration, or manufacturing restrictions, not safe for use on injured or damaged skin (only for products for use on damaged skin). Hydrocortisone is added for its anti-inflammatory properties, hydroquinone for its skin-lightening properties, and tretinoin for its anti-inflammatory properties. This product will result in a clinical difference to patients because it does not include harmful excipients found in FDA-approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Hydrocortisone 0.5%/hydroquinone 6% will be compounded as a topical emulsion to treat melasma, applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylated hydroxytoluene, butylparaben, ethanol, silicon dioxide, benzalkonium chloride, butylene glycol, cetearyl alcohol, chlorocresol, hexylene glycol, methylparaben, mineral oil, polyethylene glycol, potassium hydroxide, propylene glycol, sodium hydroxide, titanium dioxide, trolamine, and white petrolatum, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants. Their hazardous concerns include allergen; classified as expected to be toxic or harmful; classified as irritant; classified as skin irritant; determined safe for use in cosmetics; subject to concentration or use limitations, safe for use in cosmetics with some qualifications; human endocrine disruptor; human immune and respiratory toxicant or allergen; human irritant; human respiratory irritant; human skin toxicant or allergen; human toxicant or allergen; persistent or bioaccumulative; possible human carcinogen; restricted in cosmetics (recommendations or requirements), use, concentration, or manufacturing restrictions; violation of industry recommendations, restricted in cosmetics; and use, concentration, or manufacturing restrictions, not safe for use on injured or damaged skin (only for products for use on damaged skin). Hydrocortisone is added for its anti-inflammatory properties and hydroquinone for its skin-lightening properties. This product will result in a clinical difference to patients because it does not include harmful excipients found in FDA-approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Hydrocortisone 1%/clioquinol 1%/coal tar solution 2%/metronidazole 2%/salicylic acid 2% will be compounded as a topical cream to treat rosacea, applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient

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

Hydrocortisone 2.5%/ketoconazole 2% will be compounded as a topical cream to treat topical fungal infections, applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylated hydroxytoluene, butylparaben, silicon dioxide, benzalkonium chloride, butylene glycol, cetearyl alcohol, chlorocresol, hexylene glycol, isopropyl palmitate, methylparaben, mineral oil, polyethylene glycol, polysorbate 20, potassium hydroxide, propylene glycol, sodium hydroxide, sodium lauryl sulfate, titanium dioxide, trolamine, and white petrolatum, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include allergen; classified as expected to be toxic or harmful; classified as irritant; classified as skin irritant; highly comedogenic; human endocrine disruptor; human immune and respiratory toxicant or allergen; human irritant; human respiratory irritant; human skin toxicant or allergen; human toxicant or allergen; persistent or bioaccumulative; possible human carcinogen; restricted in cosmetics (recommendations or requirements), use, concentration, or manufacturing restrictions; violation of industry recommendations, restricted in cosmetics; and use, concentration, or manufacturing restrictions, not safe for use on injured or damaged skin (only for products for use on damaged skin). Ketoconazole is added for its antifungal properties and hydrocortisone for its anti-inflammatory properties. This product will result in a clinical difference to patients because it does not include harmful excipients found in FDA-approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

A roundtable discussion with representatives from a variety of practice settings was held to discuss the use of outsourcing facilities to obtain compounded products. Forty-three participants attended the event; refer to Table 15 for characteristics of the facilities that the participants represented. A prequestionnaire was also distributed to participants; refer to Tables 15-18 for results of the prequestionnaire.

Although 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 allows for a quick flip to the other outsourcing facility if there is a problem 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, such as 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 with products compounded in-house, allowing these products to be stocked in automated dispensing cabinets in these units. One participant commented, "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 because they face a unique need in that they already perform a lot of manipulations to products because of 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, "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, such as 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 before administration to be purchased as syringes from outsourcing facilities, stating that "they would prefer to have a syringe form."

Another theme in deciding what products to purchase from an outsourcing facility was the use and volume of a product that is needed and the overall impact on the pharmacy workload. Critical care areas, such as the emergency department and operating room, typically have a high product use rate 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 with which that volume is needed compared with the time it would take pharmacy staff to prepare this volume. One participant commented, "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, although 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 obtain labor-intensive and more complicated products, such as epidurals and cardioplegia solutions, from outsourcing facilities to reduce the workload on pharmacy staff. The coronavirus disease 2019 pandemic has also affected the operations of hospitals, as noted by one participant who stated, "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 [as a percentage 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 affect decision making, with one 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 evaluating the workload on pharmacy staff, the type and capabilities of the facility also affected 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. 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 [more] 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 standard 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 used. However, the products used 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 also said 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, although a commercial 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 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 pre-shortage, 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 allow." 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 APIs 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 problems with purchasing products compounded starting from APIs. Another participant stated that as more outsourcing facilities began using APIs, they became more comfortable with them doing so. However, one participant observed that most outsourcing facilities are switching to sterile-to-sterile and using APIs only 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 because it is used for patients with neonatal abstinence syndrome but is available only as a preservative-containing product. So there is a need for this product to be compounded from the API as a preservative-free product. One participant stated, "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 said that they have never needed to use an outsourcing facility for preservative-free products. The lack of preservative-free forms is also a problem for ophthalmic products; however, one 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; one 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 because of potential cross-reactivity for 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 needed for ophthalmic antibiotics are not available, but the labor and risk of compounding these products in-house are not worth it.

A few participants commented on purchasing nonsterile products from outsourcing facilities. 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 because of 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 because of a lack of commercially available products. The participant stated that they purchase low-dose naltrexone for oral use by patients with refractory fibromyalgia and ketamine troches for patients with chronic pain. The participant continued that although the evidence does not support many of the ingredients used in topical pain products, "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 one 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 about 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 about 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 compounded alum in-house from nonsterile ingredients; however, there were challenges with crystallization after storage. A few participants commented that a sterile alum powder is available, which they purchase to compound in-house. One participant had concerns about this powder, stating, "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 needed only 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 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 patients a year for whom they need to use alum. The participant had it stat shipped when needed. Another participant stated, "We had a meeting with the head of urology, who was baffled, why they're even ordering it. He was like, 'this is . . . 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 when they use 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 because 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 because of the thickness of the product.

Four participants stated that they obtain sodium citrate as ready-to-use syringes for use as a locking solution for patients undergoing dialysis, with one 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 available only 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).

Although none of the participants obtained sodium phosphate or aspartic acid from outsourcing facilities for use in cardioplegic solutions, a few commented that they 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 although they 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 to [*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 the pharmacy, and they use the del Nido formulation as well as 3 other formulations.

The participants also discussed challenges with using 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. . . . 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 because of "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 before they can purchase 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, "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 lo 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 using APIs to compound narcotics. One participant commented that this often worsens drug shortages because of the quotas that the Drug Enforcement Administration places on the quantity that can be produced. The participant stated that 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

The survey was not approved for distribution by any professional medical associations.

A prequestionnaire was distributed to participants of the roundtable discussion (refer to Appendix 2.2 for the survey instrument).

Forty-three people responded to the prequestionnaire; refer to Table 15 for respondent characteristics. Among respondents, 35 (81% of 43 total respondents) used outsourcing facilities to obtain drug products, 4 (9%) did not use 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 because of a need for ready-to-use products, and 20 respondents (14%) obtained drug products from outsourcing facilities because of backorders (refer to Table 16).

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 17 for the categories of products obtained from outsourcing facilities.

Hydrocortisone was not included on the prequestionnaire (refer to Table 18).

Table 11. Characteristics of survey respondents

Survey not distributed by any professional medical associations.

Table 12. Conditions for which hydrocortisone prescribed or administered

Survey not distributed by any professional medical associations.

Table 13. Reasons for using compounded hydrocortisone

Survey not distributed by any professional medical associations.

Table 14. Use of non-patient-specific compounded hydrocortisone

Survey not distributed by any professional medical associations.

Table 15. 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 1 type of facility.
[b]Specialties provided include cardiology, pulmonary, vascular, home infusion, neurology, psychiatry, and oncology.

Table 16. 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

[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 using outsourcing facilities.

Table 17. 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 or capsules.

Table 18. 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
Caffeine sodium benzoate	0
Calcium chloride	1
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

Hydrocortisone was nominated for inclusion on the 503B Bulks List as various topical and oral dosage forms with strengths based on the prescriber's request and as oral and topical capsules, creams, gels, ointments, suspensions, and suppositories to treat a variety of medical conditions. Hydrocortisone is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, the EU, Hong Kong, Ireland, Latvia, Namibia, New Zealand, Saudi Arabia, the UK, and the US.

From the literature review, 5 studies were included. In the included studies, hydrocortisone was used to treat melasma, anal fissures, hemorrhoidal thrombosis, and pruritus ani as a topical cream, gel, ointment, or spray. Studies were found in which hydrocortisone was used in combination with hydroquinone and lidocaine, which were nominated multi-ingredient combination products; no studies were found where hydrocortisone was used as a compounded product. One of the studies recommended the use of hydrocortisone and lidocaine for treatment of pruritus ani, and 4 studies did not provide a definitive conclusion for the use of hydrocortisone.

From the interviews, the SMEs all had experience using hydrocortisone but the typically use the commercially available OTC products. None of the SMEs had experience with any of the nominated combinations.

As part of phase 3, 1 nominator provided additional information about the multi-ingredient products contained within the hydrocortisone nomination. Hydrocortisone will be compounded in combination with additional APIs as various topical products to treat fungal infections, rosacea, and melasma. Hydrocortisone is included in the formulations for its anti-inflammatory properties.

The survey was not approved for distribution by any professional medical associations. Hydrocortisone was not included on the prequestionnaire.

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APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process, and other nonindexed citations and daily from 1946 to February 9, 2021
- Date last searched: February 10, 2021
- Limits: Humans (search hedge); English language
- Number of results: 565

1	hydrocortisone/	72,676
2	17 hydroxycorticosterone.tw.	78
3	compound f.tw.	173
4	h#dro#ortis$.tw.	16,609
5	or/1-4	78,231
6	administration, topical/	38,880
7	administration, cutaneous/	22,485
8	skin absorption/	11,854
9	topical$.tw.	108,790
10	transcutaneous$.tw.	14,874
11	epicutaneous$.tw.	2046
12	transdermal$.tw.	15,024
13	((cutanous$ or dermal$ or skin) adj3 (absorb$ or absorpt$ or appl$)).tw.	11,624
14	exp gels/	53,656
15	emulsions/	18,512
16	suspensions/	7853
17	liniments/	124
18	ointments/	12,865
19	skin cream/	1105
20	pharmaceutical solutions/	3316

21	gel?.tw.	312,628
22	emulsion?.tw.	34,428
23	suspension?.tw.	111,582
24	liniment?.tw.	148
25	ointment?.tw.	12,167
26	salve?.tw.	345
27	paste?.tw.	12,942
28	unguent$.tw.	114
29	lotion?.tw.	2385
30	cream?.tw.	19,546
31	shampoo?.tw.	1451
32	solution?.tw.	723,580
33	or/6-32	1,348,139
34	drug combinations/	74,245
35	aluminum chloride/	1197
36	alum$ chlorid$.tw.	1553
37	((ascorb$ or vitamin$ c) adj2 palmit$).tw.	330
38	ascorbylpalmit$.tw.	3
39	palmitoylascorb$.tw.	8
40	azeloglycin$.tw.	1
41	azeloyl.tw.	8
42	((benzoin or sumatra) adj2 (absolute or gum or resin or tincture)).tw.	61
43	clindamycin/	5771
44	chlo?lincocin$.tw.	4
45	clind#m#cin$.tw.	10,965
46	clinim#cin$.tw.	4

47	clioquinol/	981
48	chlor?iodoquin$.tw.	5
49	cli?quinol$.tw.	603
50	iodoch?or? hydroxycholin$.tw.	0
51	iodoch?or?hydroxycholin$.tw.	0
52	iodoch?or? hydroxyquin$.tw.	2
53	iodoch?or?hydroxyquin$.tw.	96
54	iodoch?or?xyquin$.tw.	22
55	iodohydroxych?or?quin$.tw.	1
56	isoch?or?xychinolin$.tw.	0
57	quiniodochlor$.tw.	2
58	coal tar/	2334
59	((coal or doak) adj tar).tw.	1319
60	gentamicins/	18,423
61	gentam#cin$.tw.	27,938
62	((glycol?ic or hydroxyacetic or hydroxyethanoic) adj2 acid$).tw.	7727
63	green tea$.tw.	8945
64	hyaluronic acid/	22,090
65	hyaluron$.tw.	37,524
66	hydroquinones/	4503
67	hydrochin$.tw.	17
68	hydroquin$.tw.	6133
69	ketoconazole/	5629
70	ketoc#n#zol$.tw.	7875
71	ketok#n#zol$.tw.	31
72	ketozol$.tw.	1

73	oxoc#nazol$.tw.	0
74	(koji$ adj2 acid$).tw.	928
75	lactic acid/	42,927
76	(lactic$ adj2 acid$).tw.	39,523
77	milchsaure.tw.	2
78	milk acid$.tw.	133
79	levocetirizin$.tw.	415
80	lidocaine/	24,651
81	lidocain$.tw.	22,161
82	lignocain$.tw.	2954
83	liquocain$.tw.	0
84	menthol/	2011
85	ment?ol$.tw.	3271
86	levoment?ol$.tw.	5
87	metronidazole/	12,905
88	metr#nida$.tw.	16,373
89	miconazole/	2031
90	mic?ona#ol$.tw.	2762
91	mik?ona#ol$.tw.	1
92	niacinamide/	12,603
93	amid$ pp.tw.	4
94	nicotinamid$.tw.	21,909
95	niacetamid$.tw.	0
96	niacinamid$.tw.	520
97	niacin amid$.tw.	3
98	nicamid$.tw.	0

99	nicosedin$.tw.	0
100	nicotamid$.tw.	14
101	(nicotinic adj2 amid$).tw.	115
102	nicotinoylamid$.tw.	1
103	ni#otinsaureamid$.tw.	0
104	nikotamin$.tw.	0
105	vitamin$ b3.tw.	446
106	vitamin$ b 3.tw.	54
107	vitamin$ pp.tw.	164
108	nifedipine/	15,614
109	m#fedipin$.tw.	1
110	n#fedipin$.tw.	19,653
111	salicylic acid/	6717
112	((hydroxybenzoic or salicylic) adj2 acid$).tw.	15,821
113	spironolactone/	6822
114	espironola#ton$.tw.	6
115	spironola#ton$.tw.	6006
116	spirothiobarbit$.tw.	1
117	anthranilic acid$.tw.	1391
118	tranilast$.tw.	628
119	tretinoin/	22,341
120	retinoic acid$.tw.	32,688
121	trentin$.tw.	218
122	tretinoin$.tw.	1383
123	vitamin$ a acid$.tw.	354
124	vitamin a1 acid$.tw.	0

125	exp triamcinolone/	9534
126	fluox#prednisolon$.tw.	1
127	t?iamcinolon$.tw.	7910
128	tramcinolon$.tw.	3
129	t?ancinolon$.tw.	0
130	hamamelis/	43
131	hamameli$.tw.	195
132	(witch adj2 hazel).tw.	50
133	(zinc adj2 (omadine or perythione or pyridinethione or pyrithione)).tw.	311
134	or/34-133	452,610
135	and/5,33,134	886
136	exp animals/ not humans/	4,786,326
137	135 not 136	714
138	limit 137 to english language	565

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: February 10, 2021
- Limits: Humans (search hedge); English language
- Number of results: 994

1	‘hydrocortisone’/mj	54,567
2	‘17 hydroxycorticosterone’:ti,ab,tn	180
3	‘compound f’:ti,ab,tn	346
4	‘hidrocortis*’:ti,ab,tn	24
5	‘hidrokortis*’:ti,ab,tn	0
6	‘hydrocortis*’:ti,ab,tn	27,977
7	‘hydrokortis*’:ti,ab,tn	7
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	71,366
9	‘topical drug administration’/de	84,198
10	‘cutaneous drug administration’/de	749
11	‘transdermal drug administration’/de	9283
12	‘skin absorption’/de	8169
13	‘topical treatment’/de	13,793
14	‘topical*’:ti,ab	153,930
15	‘epicutaneous*’:ti,ab	3475
16	‘transdermal*’:ti,ab	22,013
17	((cutaneous* OR dermal* OR skin) NEAR/3 (absorb* OR absorp* OR appl*)):ti,ab	18,377
18	‘cream’/de	9810
19	‘gel’/exp	81,063
20	‘liniment’/de	257
21	‘lotion’/de	2964
22	‘ointment’/de	18,258

23	‘paste’/de	2550
24	‘salve’/de	170
25	‘suspension’/de	28,563
26	‘emulsion’/exp	47,835
27	‘shampoo’/de	2340
28	‘cream$’:ti,ab	30,545
29	‘emulsion$’:ti,ab	46,560
30	‘liniment$’:ti,ab	242
31	‘lotion$’:ti,ab	4114
32	‘ointment$’:ti,ab	21,988
33	‘paste$’:ti,ab	15,469
34	‘salve$’:ti,ab	486
35	‘unguent*’:ti,ab	242
36	‘gel$’:ti,ab	368,162
37	‘suspension$’:ti,ab	148,336
38	‘shampoo$’:ti,ab	2271
39	‘solution$’:ti,ab	895,285
40	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39	1,717,718
41	‘drug combination’/de	170,854
42	‘aluminum chloride’/de	3962
43	‘alum* chlorid*’:ti,ab,tn	2599
44	‘ascorbyl palmitate’/de	398
45	((ascorb* OR ‘vitamin* c’) NEAR/2 palmit*):ti,ab,tn	404
46	‘ascorbylpalmit*’:ti,ab,tn	14
47	‘palmitoylascorb*’:ti,ab,tn	11
48	‘azeloglycin*’:ti,ab,tn	2

49	‘azeloyl’:ti,ab,tn	9
50	‘gum benzoin’/de	34
51	((benzoin OR sumatra) NEAR/2 (absolute OR gum OR resin OR tincture)):ti,ab,tn	113
52	‘clindamycin’/de	52,843
53	‘chlo$lincocin*’:ti,ab,tn	1
54	‘clindamicin*’:ti,ab,tn	88
55	‘clindamycin*’:ti,ab,tn	14,748
56	‘clindomicin*’:ti,ab,tn	0
57	‘clindomycin*’:ti,ab,tn	7
58	‘clinimicin*’:ti,ab,tn	0
59	‘clinimycin*’:ti,ab,tn	10
60	‘clioquinol’/de	3136
61	‘chlor$iodoquin*’:ti,ab,tn	8
62	‘cli$quinol*’:ti,ab,tn	823
63	‘iodochor hydroxycholin*’:ti,ab,tn	0
64	‘iodochorhydroxycholin*’:ti,ab,tn	0
65	‘iodochor hydroxyquin*’:ti,ab,tn	3
66	‘iodochorhydroxyquin*’:ti,ab,tn	180
67	‘iodochorxyquin*’:ti,ab,tn	43
68	‘iodohydroxychorquin*’:ti,ab,tn	1
69	‘isochorxychinolin*’:ti,ab,tn	0
70	‘quiniodochlor*’:ti,ab,tn	4
71	‘coal tar’/de	2959
72	((coal OR doak) NEAR/1 tar):ti,ab,tn	1929
73	‘gentamicin’/de	111,973
74	‘gentamicin*’:ti,ab,tn	33,033

75	‘gentamycin*’:ti,ab,tn	4811
76	‘glycolic acid’/de	3576
77	((glycol$ic OR hydroxyacetic OR hydroxyethanoic) NEAR/2 acid*):ti,ab,tn	9434
78	‘sinecatechins’/de	4792
79	‘sinecatechin’/de	10
80	‘green tea*’:ti,ab,tn	11,409
81	‘hyaluronic acid’/de	45,543
82	‘hyaluron*’:ti,ab,tn	51,129
83	‘hydroquinone’/de	6744
84	‘hydrochin*’:ti,ab,tn	39
85	‘hydroquin*’:ti,ab,tn	7665
86	‘ketoconazole’/de	29,672
87	‘ketocanazol*’:ti,ab,tn	9
88	‘ketoconazol*’:ti,ab,tn	10,246
89	‘ketokanazol*’:ti,ab,tn	0
90	‘ketokonazol*’:ti,ab,tn	79
91	‘ketocanozol*’:ti,ab,tn	2
92	‘ketokanozol*’:ti,ab,tn	0
93	‘ketoconozol*’:ti,ab,tn	11
94	‘ketokonozol*’:ti,ab,tn	0
95	‘ketozol*’:ti,ab,tn	2
96	‘oxocanazol*’:ti,ab,tn	0
97	‘oxoconazol*’:ti,ab,tn	0
98	‘kojic acid’/de	1739
99	(koji* NEAR/2 acid*):ti,ab,tn	1213
100	‘lactic acid’/de	87,157

101	(lactic* NEAR/2 acid*):ti,ab,tn	51,331
102	‘milchsaure’:ti,ab,tn	6
103	‘milk acid*’:ti,ab,tn	161
104	‘levocetirizine’/de	1878
105	‘levocetirizin*’:ti,ab,tn	728
106	‘lidocaine’/de	77,579
107	‘lidocain*’:ti,ab,tn	31,062
108	‘lignocain*’:ti,ab,tn	4125
109	‘liquocain*’:ti,ab,tn	0
110	‘menthol’/de	5405
111	‘ment$ol*’:ti,ab,tn	4492
112	‘levoment$ol*’:ti,ab,tn	16
113	‘metronidazole’/de	70,819
114	‘metranida*’:ti,ab,tn	64
115	‘metronida*’:ti,ab,tn	23,979
116	‘miconazole’/de	10,417
117	‘mic$onasol*’:ti,ab,tn	1
118	‘mic$onazol*’:ti,ab,tn	3589
119	‘mik$onasol*’:ti,ab,tn	0
120	‘mik$onazol*’:ti,ab,tn	4
121	‘nicotinamide’/exp	16,732
122	‘amid* pp’:ti,ab,tn	7
123	‘nicotinamid*’:ti,ab,tn	26,503
124	‘niacetamid*’:ti,ab,tn	0
125	‘niacinamid*’:ti,ab,tn	819
126	‘nicamid*’:ti,ab,tn	1

127	‘nicosedin*’:ti,ab,tn	0
128	‘nicotamid*’:ti,ab,tn	26
129	(nicotinic NEAR/2 acid*):ti,ab,tn	9650
130	‘nicotinoylamid*’:ti,ab,tn	2
131	‘nicotinsaureamid*’:ti,ab,tn	6
132	‘nikotinsaureamid*’:ti,ab,tn	2
133	‘nikotamin*’:ti,ab,tn	0
134	‘vitamin* b3’:ti,ab,tn	525
135	‘vitamin* b 3’:ti,ab,tn	20
136	‘vitamin* pp’:ti,ab,tn	297
137	‘nifedipine’/de	49,586
138	‘mefedipin*’:ti,ab,tn	0
139	‘mifedipin*’:ti,ab,tn	1
140	‘nefedipin*’:ti,ab,tn	14
141	‘nifedipin*’:ti,ab,tn	24,182
142	‘salicylic acid’/de	26,899
143	‘salicylic acid*’:ti,ab,tn	15,641
144	‘carboxyphenol’:ti,ab,tn	9
145	‘hydroxybenzoic acid*’:ti,ab,tn	3402
146	‘spironolactone’/de	32,546
147	‘espironolacton*’:ti,ab,tn	25
148	‘espironolatton*’:ti,ab,tn	0
149	‘spironolacton*’:ti,ab,tn	9803
150	‘spironolatton*’:ti,ab,tn	1
151	‘spirothiobarbit*’:ti,ab,tn	4
152	‘tranilast’/de	1569

153	‘anthranilic acid*’:ti,ab,tn	2026
154	‘tranilast*’:ti,ab,tn	844
155	‘retinoic acid’/de	43,057
156	‘retinoic acid*’:ti,ab,tn	39,294
157	‘trentin*’:ti,ab,tn	289
158	‘tretinoin*’:ti,ab,tn	2117
159	‘vitamin* a acid’:ti,ab,tn	466
160	‘vitamin* a1 acid’:ti,ab,tn	0
161	‘triamcinolone’/de	16,304
162	‘triamcinolone acetonide’/de	15,741
163	‘fluoxyprednisolon*’:ti,ab,tn	3
164	‘fluoxiprednisolon*’:ti,ab,tn	1
165	‘tiamcinolon*’:ti,ab,tn	4
166	‘triamcinolon*’:ti,ab,tn	11,323
167	‘tramcinolon*’:ti,ab,tn	12
168	‘triancinolon*’:ti,ab,tn	21
169	‘hamamelis’/de	211
170	‘hamameli*’:ti,ab,tn	238
171	(witch NEAR/2 hazel):ti,ab,tn	66
172	‘zinc oxide’/de	11,962
173	(zinc NEAR/2 (omadine OR perythione OR pyridinethione OR pyrithione)):ti,ab,tn	401
174	#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 OR #115 OR #116 OR #117 OR #118 OR #119 OR #120 OR #121 OR #122 OR #123 OR #124 OR #125 OR #126 OR #127 OR #128 OR #129 OR #130 OR #131 OR #132 OR #133 OR #134 OR #135 OR #136 OR #137 OR #138 OR #139 OR #140 OR #141 OR #142 OR #143 OR #144 OR #145 OR #146 OR #147 OR #148 OR	965,658

	#149 OR #150 OR #151 OR #152 OR #153 OR #154 OR #155 OR #156 OR #157 OR #158 OR #159 OR #160 OR #161 OR #162 OR #163 OR #164 OR #165 OR #166 OR #167 OR #168 OR #169 OR #170 OR #171 OR #172 OR #173	
175	#8 AND #40 AND #174	1549
176	[animals]/lim NOT [humans]/lim	6,167,026
177	#175 NOT #176	1346
178	#175 NOT #176 AND [english]/lim	994

Appendix 2.1. Survey instrument for professional medical associations

1. How familiar are you with the following terms?

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

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

- None of the above

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

Appendix 2.2. 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-facilites.
    - 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
    - Caffeine sodium benzoate
    - Calcium chloride
    - Cholecalciferol
    - Chromium chloride
    - Clonidine
    - Dexamethasone sodium phosphate
    - Diclofenac
    - Gentamicin
    - Glycerin
    - Hydroxyzine
    - Ketamine
    - Levocarnitine
    - Lidocaine
    - Lorazepam
    - Magnesium sulfate
    - Manganese chloride
    - Methylprednisolone
    - Midazolam
    - Mupirocin
    - Norepinephrine
    - Ondansetron
    - Phytonadione
    - Potassium chloride
    - Potassium phosphate
    - Prilocaine
    - Proline
    - Propranolol
    - Ropivacaine
    - Sodium chloride
    - Sodium citrate

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

Appendix 3. Survey distribution to professional associations

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

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