

Summary Report

Betamethasone dipropionate

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US Food and Drug Administration

Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List

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Frequently Used Abbreviations

API	Active pharmaceutical ingredient
EU	European Union
FDA	United States 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 US Food and Drug Administration (FDA) in its evaluation of the use of betamethasone dipropionate (UNII code: 826Y60901U), 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 betamethasone dipropionate 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 health care practitioners were consulted to identify how betamethasone dipropionate 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 betamethasone dipropionate 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

Betamethasone dipropionate was nominated for inclusion on the 503B Bulks List by the Outsourcing Facilities Association, Sincerus Florida, LLC, and Triangle Compounding Pharmacy, Inc. Betamethasone dipropionate 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, betamethasone dipropionate is generally used to treat various inflammatory skin conditions such as allergies, dermatitis, eczema, rash, and psoriasis. The nominated formulations are various topical dosage forms including gel, cream, ointment, solution, and suspension. The strength is based on prescriber's request.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of betamethasone dipropionate.⁶⁻¹⁶

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

- Although there are commercially available FDA-approved products containing the active ingredient, the dosage form, strength, or flavor of the manufactured product may be inappropriate for the patient.
- For certain conditions, betamethasone dipropionate may be better absorbed than other topical steroids. Other betamethasone salt forms may not be appropriate for the desired dosage form for reasons such as solubility.
- 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 any fillers, excipients, binders, dyes, preservatives, or other materials.
- Individual finished products have more variance than the API, and the use of a finished product has the potential to introduce unacceptable inaccuracies into the compounded medication.
- Compounded product may be the only product to effectively treat the indication for which it is intended.
- Patients may be sensitive to dyes, fillers, preservatives, or other excipients in manufactured products.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of betamethasone dipropionate products in the United States (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 betamethasone dipropionate; name variations of betamethasone dipropionate 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 betamethasone dipropionate. 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: betamethasone dipropionate, 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 betamethasone dipropionate products because of the availability of FDA-approved topical single-ingredient betamethasone dipropionate products. Results were limited to human studies in the English language. Searches were conducted on February 9, 2021. In addition, the ECRI Guidelines Trust[®] repository was searched on February 9, 2021 for clinical practice guidelines that recommended the use of betamethasone dipropionate 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 betamethasone dipropionate 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 betamethasone dipropionate was used as an FDA-approved product in the nominated dosage form, ROA, or combination; was used in a dosage form, ROA, or combination that was not nominated; was used in an unspecified dosage form or ROA; was the wrong drug or salt form of betamethasone; was mentioned briefly as a rescue treatment or as a previously failed treatment; or was not used clinically. Studies in which betamethasone dipropionate was used to diagnose, prevent, or treat autism were excluded because of a separate project examining the use of compounded substances for 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 betamethasone dipropionate, setting, total number of patients, number of patients who received betamethasone dipropionate, patient population, indication for use of betamethasone dipropionate, dosage form and strength, dosage, ROA, frequency and duration of therapy, use of betamethasone dipropionate in a combination product, use and formulation of betamethasone dipropionate in a compounded product, use of betamethasone dipropionate 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 betamethasone dipropionate 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 betamethasone dipropionate. 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 the 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 betamethasone dipropionate in clinical practice. The online survey was created with Qualtrics® software (refer to Appendix 2 for the 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

- Betamethasone dipropionate is available as an FDA-approved product in the nominated dosage form and ROA.
- Betamethasone dipropionate is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for betamethasone dipropionate.
- Betamethasone dipropionate is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, Namibia, New Zealand, Saudi Arabia, and UK.

Table 1. Currently approved products— US^a

Active Ingredient	Concentration	Dosage Form	Route of Administration	Status	Approval Date ^b
Betamethasone dipropionate	EQ 0.05%	Cream, cream (augmented), gel (augmented), lotion, lotion (augmented), ointment, ointment (augmented), spray	Topical	Prescription	7/27/1983

^aSource: US FDA *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).

^bIf multiple approval dates or multiple strengths, then earliest date provided.

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

Active Ingredient	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date ^b
Betamethasone dipropionate	0.05%	Cream, lotion, ointment, solution	Cutaneous, topical	Abu Dhabi	Active	—
				Australia	Prescription-only	10/8/1991
				Belgium	Prescription	4/30/1974
				Canada	Prescription	12/31/1975
				Namibia	—	12/31/1972
				New Zealand	Prescription	6/10/1976
				Saudi Arabia	Prescription	—
				UK	Prescription-only	6/10/1986

Abbreviations: —, not provided; UK, United Kingdom.

^aMedicine registers of national regulatory agencies were searched if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information (product trade name, active ingredient, strength, form, ROA, and approval status) provided in a 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.

^bIf multiple approval dates or multiple strengths, then earliest date provided.

Results of literature review

Study selection

Database searches yielded 400 references; 3 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 360 titles and abstracts were screened. After screening, the full text of 158 articles was reviewed. Finally, 1 study was included, and 157 studies were excluded for the following reasons: wrong study design (122 studies), wrong substance (15), FDA-approved product (15), nonnominated formulation (2), unable to obtain full text (2), or betamethasone dipropionate mentioned only briefly (1).

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

Characteristics of included studies

The 1 included experimental study from India was published in 2000.

A total of 59 patients participated in the included study.

Outcome measures differed between the included studies and included adverse effects and improvement in symptoms.

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

Use of betamethasone dipropionate

Fifty-nine patients received betamethasone dipropionate as treatment for dermatosis, administered as a 0.05% ointment.

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

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

In the 1 included study, the authors' concluding statement mentioned that the betamethasone dipropionate combination with mupirocin was safe and effective.¹⁷ Refer to Table 5 for 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 betamethasone dipropionate.

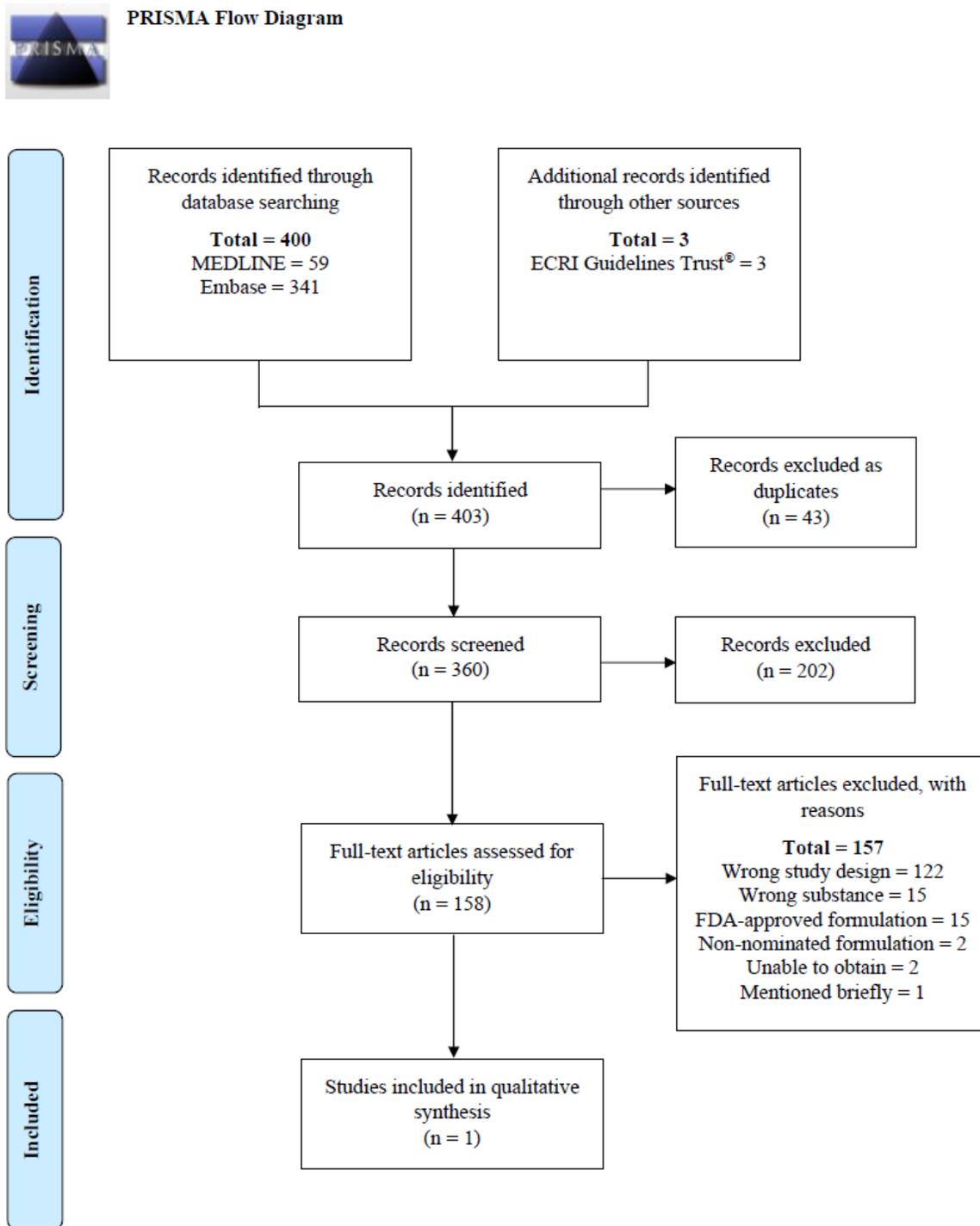
Betamethasone dipropionate is a “synthetic fluorinated corticosteroid for topical dermatologic use.”¹⁸ Several studies used topical betamethasone dipropionate in a non-nominated combination with other APIs. One combination mentioned was with tazarotene, a 3rd-generation retinoid derivative, and betamethasone dipropionate cream for plaque psoriasis.¹⁹ Two studies mentioned a topical ointment combination with betamethasone dipropionate and salicylic acid, with some specifying the commercial product Diprosalic®.^{20,21} The salicylic acid helps betamethasone penetrate through the epidermis via its keratolytic action.²⁰ Another combination mentioned is a gentamicin sulfate and betamethasone dipropionate for hidradenitis suppurativa.²² One study used a topical combination cream consisting of betamethasone dipropionate with chiniform (Diproform®).²³ There is also a

compounded all-purpose nipple ointment for treating sore nipples developed by Dr. Jack Newman that contains at least 3 different ingredients, which can be substituted, such as mupirocin, miconazole, and betamethasone dipropionate.²⁴ Mupirocin is for bacterial coverage, miconazole for fungal coverage, and betamethasone for an anti-inflammatory effect.²⁴ At least 1 case of corticosteroid excess occurred in an infant after continual use of a nipple ointment for 2 months.²⁴

Two studies used a nominated combination containing mupirocin 2% and betamethasone dipropionate 0.05% ointment (Supirocin-B[®]) for treatment of infected dermatoses.^{17,25} One was a postmarketing study in India for this combination ointment, in which 251 patient clinical case records were analyzed.²⁵ Savant et al reported that 5 patients experienced adverse effects: 2 experienced mild irritation, and 3 experienced a burning sensation.²⁵ One patient also had worsening of skin lesions.²⁵ Savant et al concluded that the Supirocin-B[®] ointment “seems to be safe and effective in the treatment of infected dermatoses.”²⁵

In a 2018 France case report, a woman with plaque psoriasis presented with plaques that had an annular inflammatory pattern after she had used a compounded topical preparation that consisted of resorcinol 1 g, salicylic acid 3 g, 0.05% tretinoin cream 30 g, and betamethasone dipropionate 90 g cream daily for 4 months.²⁶ The authors stated that there is a lack of evidence-based literature to support the use of compounded topical preparations for plaque psoriasis.²⁶ They also commented that tretinoin was not efficacious for psoriasis when used as monotherapy.²⁶ Resorcinol and tretinoin are known irritants that “may have been harmful by the induction of a Koebner’s phenomenon responsible for the annular enlargement of plaques.”²⁶

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

Type of Studies	Number of Studies
Descriptive	0
Observational	0
Experimental ¹⁷	1

Table 4. Number of studies by country

Country	Number of Studies
India ¹⁷	1
Total US: 0	
Total Non-US Countries: 1	

Table 5. Summary of included studies

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Saple et al, 2000, India ¹⁷	—	59 Patients who had primary infection complicated by dermatoses or dermatoses infected secondarily (gender and age not specified)	<ul style="list-style-type: none"> Mupirocin and betamethasone dipropionate ointment (59) 	Improvement in symptoms, adverse effects	“From the analysis of 59 patients, it was noted that this ointment was found to be safe and very effective by dermatologist in the treatment of infected dermatoses in 94.9% of the patients. Similarly 89.8% of the patients reported more than 70% improvement in their symptoms after 7 days of treatment. No adverse effects were reported during the treatment period by any of the patients except worsening of skin lesions by one patient.”

Abbreviation: —, not provided.

^aAs defined by authors.

Table 6. Dosage by indication—US

No US studies were included.

Table 7. Dosage by indication—non-US countries

Indication	Dosage	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Infected dermatoses ¹⁷	—	0.05%	Ointment	Topical	—

Abbreviation: —, not provided.

Table 8. Number of studies by combination

	Combination Formula	Number of Studies
Nominated	Betamethasone dipropionate 0.05% / Ketoconazole 2% – topical cream	0
	Betamethasone dipropionate 0.05% / Minoxidil 5-7% – topical solution	0
	Betamethasone dipropionate 0.05% / Mupirocin 2% – topical ointment ¹⁷	1
	Betamethasone dipropionate 0.05% / Niacinamide 4% – topical cream	0
	Betamethasone dipropionate 0.05% / Minoxidil 5% / Niacinamide 2% / Pentoxifylline 0.5% – topical solution	0
	Betamethasone dipropionate 0.05% / Menthol 2% / Pramoxine 1% / Tranilast 0.5% – topical lotion, solution	0
	Betamethasone dipropionate 0.05% / Ascorbyl Palmitate 2% / Hyaluronic acid sodium salt 0.2% / Hydroquinone 8% / Kojic acid 6% / Niacinamide 2% / Potassium azeloyl diglycinate 8% – topical emulsion	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

One hundred ninety-nine SMEs were contacted for interviews; 63 agreed to be interviewed, and 136 declined or failed to respond to the interview request. Five SMEs discussed betamethasone dipropionate. The 5 SMEs were medical doctors who specialized or were board-certified in allergy, dermatology, obstetrics and gynecology, or rheumatology, working in academic medical institutions and outpatient practice. The SMEs had been in practice for 1 to 52 years. Additional information was collected as part of the Expanded Information Initiative (referred to as phase 3) project 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. 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, one SME stated they would switch to a different steroid within the same class that was available in the necessary dosage form.

One SME discussed the multi-ingredient products included in the nomination. The SME stated that some prescribers combine a steroid with minoxidil when treating patients with androgenic alopecia because minoxidil “can be irritating and cause itch.” Betamethasone with ketoconazole would probably be used to treat fungal infections that are also itchy. Additionally, “some fungal infections can look like things like nummular dermatitis, and so if you give that to a patient, you’re treating sort of both possibilities.” Betamethasone with mupirocin would be used to treat *Staphylococcus* infections or atopic dermatitis. Atopic dermatitis can be infected with *Staphylococcus*, which can drive atopic lesions, so the combination would treat both the atopic dermatitis and the colonization. Betamethasone, menthol, pramoxine, and tranilast would be used to treat itch, with menthol providing more immediate relief and betamethasone treating the underlying inflammatory condition that is leading to the itch; pramoxine is a numbing agent, and tranilast also treats itch by inhibiting histamine release from mast cells. Betamethasone, ascorbyl palmitate, hyaluronic acid, hydroquinone, kojic acid 6%, niacinamide 2%, and potassium azeloyl diglycinate would be used to treat melasma. Hydroquinone and kojic acid are bleaching agents, with hydroquinone “trying to decrease melanin production”; betamethasone provides some additional bleaching and removes uneven pigment, and hyaluronic acid acts as a moisturizer. The SME did not think ascorbyl palmitate and potassium azeloyl diglycinate were acting as active ingredients. The SME stated 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 SME was concerned about the selection of betamethasone in this formulation, stating that melasma is often on the face, and because betamethasone is a more potent steroid, there is a risk of skin atrophy; hydrocortisone is more common because it is not as potent. For the other combinations, betamethasone would be a reasonable choice, but the prescriber would have to evaluate the “area of the body you’re planning on putting it on and for how long you’re using it.”

One SME stated that there would not be a need to stock these formulations in-office because a patient would use them “for weeks if not months.” The 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 stated that they use betamethasone ointment when treating lichen planus, lichen simplex chronicus, and lichen sclerosus.

Two SMEs stated they have never used betamethasone dipropionate. Another SME commented that they have prescribed betamethasone dipropionate but not as a compounded product.

As part of phase 3, 1 nominator provided additional information about the multi-ingredient products contained within the betamethasone dipropionate nomination.

Betamethasone dipropionate 0.05%/minoxidil 5% will be compounded as a topical solution to treat alopecia, 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: chlorocresol, sodium hydroxide, 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 classified as expected to be toxic or harmful; human endocrine disruptor; human irritant; human skin toxicant or allergen; 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. Betamethasone dipropionate is added for its anti-inflammatory properties and minoxidil for its ability to promote hair growth. 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.

Betamethasone dipropionate 0.05% / minoxidil 5% / niacinamide 2% / pentoxifylline 0.5% will be compounded as a topical solution to treat alopecia, 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: chlorocresol, sodium hydroxide, 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 classified as expected to be toxic or harmful; human endocrine disruptor; human irritant; human skin toxicant or allergen; 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. Betamethasone dipropionate is added for its anti-inflammatory properties, minoxidil for its ability to promote hair growth, niacinamide for its skin conditioning benefits, and pentoxifylline to promote circulation. 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.

Betamethasone dipropionate 0.05% / minoxidil 7% will be compounded as a topical solution to treat alopecia, 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: chlorocresol, sodium hydroxide, 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

classified as expected to be toxic or harmful; human endocrine disruptor; human irritant; human skin toxicant or allergen; 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. Betamethasone dipropionate is added for its anti-inflammatory properties and minoxidil for its ability to promote hair growth. 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 than 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, "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], [and] 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, “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 it has 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 several participants to obtain products intended for use in these areas from outsourcing facilities. Participants stated that they compare the volume of product needed and the frequency in which that volume is needed 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 complex 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 1 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 said, “Without 503B, we would’ve been in significant trouble.” One participant commented that “even though the number might be small [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 1 participant stating, “It is not feasible for us to meet the high volume for some common medications to repackage or compound from commercial presentations to a convenient, ready-to-use dosage form or package. The outsourcing facilities thus become a force multiplier, if you will, to offset some of the shortages in staffing.”

In addition to pharmacy staff workload, 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 they outsource all these products. 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 lack of standardization has led to challenges with obtaining certain products from outsourcing facilities. As another participant said, “I think we made 9 different epidural concentrations, all driven by anesthesia, and they want what they want, and 503Bs may not offer that. No one else in the country is buying that same concentration; a 503B isn’t going to go through the expense of adding that to their product list.” The participant continued, “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 on 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, “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 preshortage, you’re not going to get products when you need it during the shortage,” continuing that “typically in a shortage, you learn to live without them. You have to.” Additionally, in the event of the shortage being the result of lack of an API, outsourcing facilities are likely to be equally affected and unable to provide assistance. However, one participant stated that they first began working with outsourcing facilities because of shortages. This participant commented, “What the 503Bs are starting to do, some of the large ones, is that they are also conducting validation studies on API. If sterile becomes short, they quickly switch to producing through API, which ASHP [American Society of Health-System Pharmacists] and the FDA allows.” This “adds a lot of flexibility so they can bounce back and forth and really try to insulate us from shortages.”

A few participants commented on the use of 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 for 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 that “if there’s not a preservative-free containing option, it really should be something that should be able to be compounded from bulk, . . . especially for the pediatric patient population.” However, another participant from a children’s hospital stated that the need for a preservative-free option has never been a reason why they have obtained a product from an outsourcing facility. The lack of preservative-free forms is also an issue for ophthalmic products; however, 1 participant observed this is more on the 503A side. One participant stated that obtaining ophthalmic products from outsourcing facilities has been a challenge and that there are products they would like to obtain from outsourcing facilities but are not able to, forcing them to compound them in-house. This participant also commented that there are 2 outsourcing facilities that compound ophthalmic products, but when they reviewed the facilities, they did not pass their internal quality standards; 1 facility had been banned from distributing products in California by the Board of Pharmacy. There is an additional challenge with obtaining cephalosporins and beta-lactams 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, used 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 1 stating, “I think that there is a large opportunity for more nonsterile products to be produced by 503Bs.” Another stated that as their facility grows and acquires more outpatient clinics, they receive a lot of questions 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 had compounded alum in-house from nonsterile ingredients; however, there were problems 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 the cyclophosphamide-induced hemorrhagic cystitis.” As a result, one participant maintains a small inventory of alum product that is purchased from an outsourcing facility, but “more times than not, they go unused and expire.” Another stated that they do not keep it in stock because there is a minimum purchase, and there are only a few 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 an old, really old. I don’t even know why we’re using it,’ and basically approved for us to not even make it anymore for now.”

Two participants commented on the use of glycerin at their facility. One stated that they purchase it from a 503A because they were not able to find an outsourcing facility that provides this product. The participant commented that glycerin is used in 3 different concentrations at their facility, 1 for ophthalmic use, 1 for neurologic use in trigeminal neuralgia, and 1 for instilling into “a very specific kind of pump that’s used to deliver a very specific kind of chemotherapy.” When there are breaks in the chemotherapy regimen, the pump has to be filled with something, and 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 1 commenting that “our nephrologists like it in place of heparin for some patients to keep the ports patent or so they don’t have to go to alteplase or some of the other drugs.” There is a commercially available product; however, it is 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 do obtain cardioplegic solutions from outsourcing facilities. The del Nido formulation was the product most commonly obtained. One

participant commented that they compound this formulation in-house because the outsourcing facilities do 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, “It is complicated to do in-house. We do it on a Baxa 1200 or 2400, either one, compounder. Then we send it up [*sic*] for pH and potassium testing. Obviously, then we’re confined to <797> beyond-use dates versus longer beyond-use dates that we get from the 503B.” Another participant commented that cardioplegic solutions are managed by the perfusion department, not pharmacy, and they use del Nido solution and 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 API 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

No people responded to the survey distributed via professional medical associations and available on the project website; refer to Table 11 for respondent characteristics.

A prequestionnaire was distributed to participants of the roundtable discussion (refer to Appendix 2.3 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.

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

Table 11. Characteristics of survey respondents

No respondents to survey distributed via professional medical associations.

Table 12. Conditions for which betamethasone dipropionate prescribed or administered

No respondents to survey distributed via professional medical associations.

Table 13. Reasons for using compounded betamethasone dipropionate

No respondents to survey distributed via professional medical associations.

Table 14. Use of non-patient-specific compounded betamethasone dipropionate

No respondents to survey distributed via 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

^aRespondents were allowed to select more than 1 type of facility.

^bSpecialties 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

^aRespondents were allowed to select multiple categories.

^bRespondents 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

^aRespondents were allowed to select multiple categories.

^bRespondents 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

^aRespondents were allowed to select multiple products.

CONCLUSION

Betamethasone dipropionate was nominated for inclusion on the 503B Bulks List as various topical dosage forms to treat inflammatory skin conditions. Betamethasone dipropionate is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, Namibia, New Zealand, Saudi Arabia, the UK, and the US.

From the literature review, 1 study was included. Betamethasone dipropionate was used as a topical ointment to treat infected dermatoses. Betamethasone dipropionate was used in combination with mupirocin but was not used as a compounded product. The authors concluded that the betamethasone dipropionate combination with mupirocin was safe and effective.

From the interviews, 2 SMEs do not use betamethasone dipropionate, and another SME uses only the commercially available formulation. One SME has used betamethasone ointment to treat lichen planus, lichen simplex chronicus, and lichen sclerosus. Another SME discussed the use of the multi-ingredient combination products included in the nomination.

As part of phase 3, 1 nominator provided additional information about the multi-ingredient products contained within the betamethasone dipropionate nomination. Betamethasone will be compounding in combination with minoxidil with or without niacinamide and pentoxifylline as a topical solution to treat alopecia. Betamethasone dipropionate is included in the formulations for its anti-inflammatory properties.

No people responded to the survey distributed via professional medical associations and available on the project website. Betamethasone dipropionate 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 8, 2021
- Date last searched: February 9, 2021
- Limits: Humans (search hedge); English language
- Number of results: 59

1	betamethasone/	5991
2	bet?ade#amet\$.tw.	0
3	bet?amet?a#on\$.tw.	5092
4	bet?a met?a#on\$.tw.	137
5	or/1-4	7899
6	administration, topical/	38,869
7	administration, cutaneous/	22,469
8	skin absorption/	11,852
9	topical\$.tw.	108,698
10	transcutaneous\$.tw.	14,868
11	epicutaneous\$.tw.	2046
12	transdermal\$.tw.	15,012
13	((cutaneous\$ or dermal\$ or skin) adj3 (absorb\$ or absorpt\$ or appl\$)).tw.	11,618
14	exp gels/	53,632
15	emulsions/	18,505
16	suspensions/	7852
17	liniments/	124
18	ointments/	12,863
19	skin cream/	1100
20	pharmaceutical solutions/	3315

21	gel?.tw.	312,507
22	emulsion?.tw.	34,387
23	suspension?.tw.	111,519
24	liniment?.tw.	148
25	ointment?.tw.	12,161
26	salve?.tw.	345
27	paste?.tw.	12,933
28	unguent\$.tw.	114
29	lotion?.tw.	2383
30	cream?.tw.	19,534
31	shampoo?.tw.	1451
32	solution?.tw.	723,049
33	or/6-32	1,347,275
34	drug combinations/	74,222
35	minoxidil/	1588
36	m#nox#dil\$.tw.	1912
37	minossidil\$.tw.	0
38	niacinamide/	12,600
39	amid\$ pp.tw.	4
40	nicotinamid\$.tw.	21,884
41	niacetamid\$.tw.	0
42	niacinamid\$.tw.	520
43	niacin amid\$.tw.	3
44	nicamid\$.tw.	0
45	nicosedin\$.tw.	0
46	nicotamid\$.tw.	14

47	(nicotinic adj2 amid\$.tw.	115
48	nicotinoylamid\$.tw.	1
49	ni#otinsaureamid\$.tw.	0
50	nikotamin\$.tw.	0
51	vitamin\$ b3.tw.	444
52	vitamin\$ b 3.tw.	54
53	vitamin\$ pp.tw.	164
54	pentoxifylline/	4194
55	ox?pentifyllin\$.tw.	75
56	ox?pentiphyllin\$.tw.	0
57	pentox#fil#n\$.tw.	12
58	pentox#fyll#n\$.tw.	4555
59	pentox#phyll#n\$.tw.	152
60	menthol/	2011
61	ment?ol\$.tw.	3268
62	levoment?ol\$.tw.	5
63	mupirocin/	1253
64	mupirocin\$.tw.	1871
65	pseudomonic acid\$.tw.	89
66	ketoconazole/	5629
67	ketoc#n#zol\$.tw.	7875
68	ketok#n#zol\$.tw.	31
69	ketozol\$.tw.	1
70	oxoc#nazol\$.tw.	0
71	hyaluronic acid/	22,086
72	hyaluron\$.tw.	37,488

73	hydroquinones/	4500
74	hydrochin\$.tw.	17
75	hydroquin\$.tw.	6130
76	pramocain\$.tw.	6
77	pramoxin\$.tw.	48
78	tranilast\$.tw.	627
79	((ascorb\$ or vitamin\$ c) adj2 palmit\$).tw.	328
80	ascorbylpalmit\$.tw.	3
81	palmitoylascorb\$.tw.	8
82	azeloglycin\$.tw.	1
83	azeloyl.tw.	8
84	(koji\$ adj2 acid\$).tw.	926
85	or/35-84	105,198
86	and/5,33,85	69
87	exp animals/ not humans/	4,785,606
88	86 not 87	59
89	limit 88 to english language	59

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: February 9, 2021
- Limits: Humans (search hedge); English language
- Number of results: 341

1	'betamethasone dipropionate'/de	2841
2	'bet\$adesamet*':ti,ab,tn	0
3	'bet\$adexamet*':ti,ab,tn	1
4	'bet\$amet\$ason*':ti,ab,tn	7733
5	'bet\$amet\$azon*':ti,ab,tn	79
6	'bet\$a met\$ason*':ti,ab,tn	96
7	'bet\$a met\$azon*':ti,ab,tn	1
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	9876
9	'topical drug administration'/de	84,147
10	'cutaneous drug administration'/de	748
11	'transdermal drug administration'/de	9274
12	'skin absorption'/de	8166
13	'topical treatment'/de	13,785
14	'topical*':ti,ab	153,843
15	'epicutaneous*':ti,ab	3475
16	'transdermal*':ti,ab	22,001
17	((cutaneous* OR dermal* OR skin) NEAR/3 (absorb* OR absorp* OR appl*)):ti,ab	18,371
18	'cream'/de	9805
19	'gel'/exp	80,973
20	'liniment'/de	256
21	'lotion'/de	2962
22	'ointment'/de	18,247

23	'paste'/de	2550
24	'salve'/de	170
25	'suspension'/de	28,505
26	'emulsion'/exp	47,778
27	'shampoo'/de	2339
28	'cream\$':ti,ab	30,525
29	'emulsion\$':ti,ab	46,525
30	'liniment\$':ti,ab	241
31	'lotion\$':ti,ab	4112
32	'ointment\$':ti,ab	21,977
33	'paste\$':ti,ab	15,463
34	'salve\$':ti,ab	486
35	'unguent*':ti,ab	242
36	'gel\$':ti,ab	368,046
37	'suspension\$':ti,ab	148,248
38	'shampoo\$':ti,ab	2270
39	'solution\$':ti,ab	894,699
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	1,716,722
41	'drug combination'/de	170,429
42	'minoxidil'/de	7851
43	'minoxidil*':ti,ab,tn	2602
44	'minoxydil*':ti,ab,tn	2
45	'manoxidil*':ti,ab,tn	0
46	'manoxydil*':ti,ab,tn	0
47	'minossidil*':ti,ab,tn	0
48	'nicotinamide'/exp	16,724

49	'amid* pp':ti,ab,tn	7
50	'nicotinamid*':ti,ab,tn	26,492
51	'niacetamid*':ti,ab,tn	0
52	'niacinamid*':ti,ab,tn	819
53	'nicamid*':ti,ab,tn	1
54	'nicosedin*':ti,ab,tn	0
55	'nicotamid*':ti,ab,tn	26
56	(nicotinic NEAR/2 acid*):ti,ab,tn	9649
57	'nicotinoylamid*':ti,ab,tn	2
58	'nicotinsaureamid*':ti,ab,tn	6
59	'nikotinsaureamid*':ti,ab,tn	2
60	'nikotamin*':ti,ab,tn	0
61	'vitamin* b3':ti,ab,tn	525
62	'vitamin* b 3':ti,ab,tn	20
63	'vitamin* pp':ti,ab,tn	297
64	'pentoxifylline'/de	13,885
65	'ox\$pentifyllin*':ti,ab,tn	107
66	'ox\$pentiphyllin*':ti,ab,tn	1
67	'pentoxifilin*':ti,ab,tn	29
68	'pentoxifilen*':ti,ab,tn	0
69	'pentoxyfilin*':ti,ab,tn	9
70	'pentoxyfilen*':ti,ab,tn	0
71	'pentoxifyllin*':ti,ab,tn	5809
72	'pentoxifyllen*':ti,ab,tn	1
73	'pentoxyfyllin*':ti,ab,tn	143
74	'pentoxyfyllen*':ti,ab,tn	0

75	'pentoxiphyllin*':ti,ab,tn	116
76	'pentoxiphyllen*':ti,ab,tn	0
77	'pentoxyphyllin*':ti,ab,tn	149
78	'pentoxyphyllen*':ti,ab,tn	0
79	'menthol'/de	5403
80	'ment\$ol*':ti,ab,tn	4489
81	'levoment\$ol*':ti,ab,tn	16
82	'pseudomonic acid'/de	7169
83	'mupirocin*':ti,ab,tn	2661
84	'pseudomonic acid*':ti,ab,tn	128
85	'ketoconazole'/de	29,661
86	'ketocanazol*':ti,ab,tn	9
87	'ketoconazol*':ti,ab,tn	10,241
88	'ketokanazol*':ti,ab,tn	0
89	'ketokonazol*':ti,ab,tn	79
90	'ketocanozol*':ti,ab,tn	2
91	'ketokanozol*':ti,ab,tn	0
92	'ketoconoazol*':ti,ab,tn	11
93	'ketokonozol*':ti,ab,tn	0
94	'ketozol*':ti,ab,tn	2
95	'oxocanazol*':ti,ab,tn	0
96	'oxoconazol*':ti,ab,tn	0
97	'hyaluronic acid'/de	45,511
98	'hyaluron*':ti,ab,tn	51,099
99	'hydroquinone'/de	6743
100	'hydrochin*':ti,ab,tn	39

101	'hydroquin*':ti,ab,tn	7661
102	'pramocaine'/de	337
103	'pramocain*':ti,ab,tn	10
104	'pramoxin*':ti,ab,tn	75
105	'tranilast'/de	1569
106	'tranilast*':ti,ab,tn	844
107	'ascorbyl palmitate'/de	398
108	((ascorb* OR 'vitamin* c') NEAR/2 palmit*):ti,ab,tn	404
109	'ascorbylpalmit*':ti,ab,tn	14
110	'palmitoylascorb*':ti,ab,tn	11
111	'azeloglycin*':ti,ab,tn	2
112	'azeloyl*':ti,ab,tn	9
113	'kojic acid'/de	1737
114	(koji* NEAR/2 acid*):ti,ab,tn	1212
115	#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	354,547
116	#8 AND #40 AND #115	398
117	[animals]/lim NOT [humans]/lim	6,165,344
118	#116 NOT #117	381
119	#116 NOT #117 AND [english]/lim	341

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)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

2. Do you prescribe or administer betamethasone dipropionate to your patients?

- Yes
- No

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

- Topical products including but not limited to cream, emulsion, gel, ointment, solution, suspension
- None of the above

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

- Inflammatory skin conditions such as dermatitis, eczema, rash, allergies, and psoriasis
- Other (please explain) _____

5. I prescribe or administer betamethasone dipropionate in combination with other active pharmaceutical ingredients as a multi-ingredient product.

- Yes
- No

6. I prescribe or administer betamethasone dipropionate with my patients as the following: (check all that apply)

- FDA-approved drug product
- Compounded drug product
- Over-the-counter drug product
- Other (please explain) _____

7. I use compounded betamethasone dipropionate because: (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 betamethasone dipropionate

- Other (please explain) _____
- 8. Do you stock non-patient-specific compounded betamethasone dipropionate at your practice?
 - Yes
 - No
 - I'm not sure
- 9. I obtain compounded betamethasone dipropionate from the following: (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) _____
- 10. What is your practice setting? (check all that apply)
 - Physician office/private practice
 - Outpatient clinic
 - Hospital/health system
 - Academic medical center
 - Emergency room
 - Operating room
 - Other (please describe) _____
- 11. What degree do you hold? (check all that apply)
 - Doctor of Medicine (MD)
 - Doctor of Osteopathic Medicine (DO)
 - Doctor of Medicine in Dentistry (DMD/DDS)
 - Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
 - Naturopathic Doctor (ND)
 - Nurse Practitioner (NP)
 - Physician Assistant (PA)
 - Other (please describe) _____

Appendix 2.2. Survey instrument for professional medical associations

1. How familiar are you with the following terms?

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

2. Do you prescribe or administer any of the following as a compounded topical product? (please check all that apply)

- Betamethasone acetate
- Betamethasone dipropionate
- Betamethasone sodium phosphate
- Cholestyramine resin
- Cimetidine
- Clobetasol propionate
- Clotrimazole
- Cromolyn sodium
- Dexamethasone sodium phosphate
- Diclofenac sodium
- Finasteride
- Fluconazole
- Fluticasone propionate
- Hydrocortisone
- Itraconazole
- Ketoconazole
- Lidocaine hydrochloride
- Methylprednisolone acetate
- Metronidazole
- Mupirocin
- Niacinamide
- Phytonadione (vitamin K1)
- Prilocaine
- Spironolactone
- Sulfacetamide sodium monohydrate
- Terbinafine hydrochloride
- Tetracaine hydrochloride
- Triamcinolone acetonide
- Zinc oxide

- None of the above
3. Do you prescribe the compounded topical products that you selected in in combination with other active pharmaceutical ingredients as a multi-ingredient product?
 - Yes
 - No
 - I'm not sure
 4. Why do you use the compounded topical products that you selected? (please check all that apply)
 - Commercial products are not available in the dosage form, strength, or combination I need (please explain) _____
 - Patient allergies prevent me from using commercially available products (please explain) _____
 - Patient conditions prevent me from using commercially available products (please explain) _____
 - I am not aware of any commercially available products containing these products
 - Other (please explain) _____
 5. Do you stock non-patient-specific compounded products at your practice?
 - Yes
 - No
 - I'm not sure
 6. I obtain compounded products from the following: (please check all that apply)
 - Compound myself at my practice
 - Have the product compounded by an in-house pharmacy
 - Purchase, or have a patient purchase, from a compounding pharmacy
 - Purchase, or have a patient purchase, from an outsourcing facility
 - Other (please explain) _____
 7. What is your practice setting? (please check all that apply)
 - Physician office/private practice
 - Outpatient clinic
 - Hospital/health system
 - Academic medical center
 - Emergency room
 - Operating room
 - Other (please describe) _____
 8. What degree do you hold? (please check all that apply)
 - Doctor of Medicine (MD)
 - Doctor of Osteopathic Medicine (DO)
 - Doctor of Medicine in Dentistry (DMD/DDS)
 - Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
 - Naturopathic Doctor (ND)
 - Nurse Practitioner (NP)
 - Physician Assistant (PA)
 - Other (please describe) _____

Appendix 2.3. Survey instrument for pharmacy roundtable prequestionnaire

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

- Fluids
 - Ophthalmic preparations
 - Patient-controlled analgesia
 - Ready-to-use anesthesia syringes
 - Ready-to-use antibiotic syringes and/or bags
 - Ready-to-use electrolyte solutions
 - Ready-to-use vasopressor solutions
 - Total parenteral nutrition solutions
 - Other, please identify _____
7. From the list below, please select the drug(s) that you obtain as either a single ingredient or multi-ingredient product from an outsourcing facility.
- Acetylcysteine
 - Adenosine
 - Aluminum potassium sulfate
 - Aspartic acid
 - Atenolol
 - Atropine
 - Baclofen
 - Betamethasone
 - Biotin
 - Bupivacaine
 - 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 or 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

^aAssociations that declined in Year 1 or Year 2 were not contacted in Year 3.