

Summary Report

Clobetasol propionate

Prepared for:

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

Prepared by:

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

December 2021

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

Table of Contents

INTRODUCTION	5
REVIEW OF NOMINATIONS.....	5
METHODOLOGY	6
Background information	6
Systematic literature review	6
Interviews.....	7
Survey	8
CURRENT AND HISTORIC USE	9
Results of background information.....	9
Results of literature review	11
Results of interviews.....	25
Results of survey.....	36
CONCLUSION.....	42
REFERENCES	43
APPENDICES	46
Appendix 1. Search strategies for bibliographic databases.....	46
Appendix 2.1. Survey instrument for professional medical associations	59
Appendix 2.2 Survey instrument for professional medical associations	61
Appendix 2.3. Survey instrument for pharmacy roundtable prequestionnaire	63
Appendix 3. Survey distribution to professional associations	66

Table of Tables

Table 1. Currently approved products – US	9
Table 2. Currently approved products – select non-US countries and regions	10
Table 3. Types of studies	14
Table 4. Number of studies by country	14
Table 5. Summary of included studies	15
Table 6. Dosage by indication – US	21
Table 7. Dosage by indication – non-US countries	22
Table 8. Number of studies by combination	23
Table 9. Compounded products – US	24
Table 10. Compounded products – non-US countries	24
Table 11. Characteristics of survey respondents	36
Table 12. Conditions for which clobetasol propionate prescribed or administered	36
Table 13. Reasons for using compounded clobetasol propionate	37
Table 14. Use of non-patient-specific compounded clobetasol propionate	37
Table 15. Demographics of prequestionnaire respondents’ facilities	37
Table 16. Reasons for obtaining products from outsourcing facilities	38
Table 17. Categories of products obtained from outsourcing facilities	39
Table 18. Products obtained from an outsourcing facility	39

Frequently Used Abbreviations

API	Active Pharmaceutical Ingredient
EMA	European Medicines Agency
EU	European Union
FDA	US Food and Drug Administration
GVHD	Graft-versus-host disease
IRB	Institutional Review Board
OLP	Oral lichen planus
OTC	Over-the-counter
ROA	Route of administration
SME	Subject matter expert
UK	United Kingdom
US	United States
USP	United States Pharmacopeia

INTRODUCTION

This report was created to assist the US Food and Drug Administration (FDA) in its evaluation of the use of clobetasol propionate (UNII code: 779619577M), 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 clobetasol propionate is used in clinical research and practice to diagnose, prevent, or treat disease. Due to the broad, exploratory nature of this aim, scoping review methodology was used. Following the scoping review framework, a systematic literature review was conducted and health care practitioners were consulted to identify how clobetasol propionate 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 clobetasol propionate 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

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

While the exact medical condition for which the compounded product is being requested is generally unknown, clobetasol propionate is generally used for seborrheic dermatitis, onychomycosis, tinea corporis, tinea cruris, tinea pedis, eczema, herpes labialis, psoriasis, lichen sclerosus, alopecia areata, vitiligo, vaginal lichen planus, mycosis fungoides, vaginal irritation/pain (vulvodynia), and mouth ulcers. Clobetasol propionate will be compounded into various topical dosage forms, including but not limited to gel, cream, ointment, solution, and suspension. The strength is based on a prescriber's request. Triangle Compounding Pharmacy also nominated mucosal and vaginal applications as routes of administration (ROAs).

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of clobetasol propionate.⁶⁻²⁰

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

- Although there is a commercially available FDA-approved product containing the active ingredient, the dosage form, strength, or flavor of the manufactured product may be inappropriate for the patient. Also, if FDA-approved products were used, the combination therapies would not be at therapeutic concentrations. For some patients, the mouth ulcer preparations are not effective.
- Compounding from bulk drug substances means using only the ingredients necessary to achieve the desired clinical outcomes. Thus 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 actual 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.
- Patient may have sensitivities to dyes, fillers, preservatives, or other excipients in manufactured products.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of clobetasol propionate products in the United States (US) and around the world. The World Health Organization, the European Medicines Agency (EMA), and globalEDGE were used to identify regulatory agencies in non-US countries. The medicine registers of non-US regulatory agencies were selected for inclusion if they met the following criteria: freely accessible; able to search and retrieve results in the English language; and desired information, specifically, product trade name, active ingredient, strength, form, ROA, and approval status, provided in a useable format. Based on these criteria, the medicine registers of 13 countries/regions were searched: US, Canada, European Union (EU), United Kingdom (UK), Ireland, Belgium, Latvia, Australia, New Zealand, Saudi Arabia, Abu Dhabi, Hong Kong, and Namibia. Both the EMA and the national registers of select EU countries (Ireland, UK, Belgium, and Latvia) were searched because some medicines were authorized for use in the EU and not available in a member country and vice versa.

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

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

Systematic literature review

Search strategy

A medical librarian constructed two comprehensive search strategies for both Ovid MEDLINE and Embase. The first search strategy used a combination of controlled vocabulary terms and keywords to describe 3 concepts: clobetasol propionate; topical administration or form; and substances nominated for use in combination with clobetasol propionate. The second search strategy used a combination of controlled vocabulary terms and keywords to describe 2 concepts: clobetasol propionate, and mucosal or vaginal administration (refer to Appendix 1 for full search strategies). A literature review was not conducted for topical single-ingredient clobetasol propionate products due to the availability of FDA-approved single-ingredient clobetasol propionate products for this ROA. 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 clobetasol propionate and provided sufficient information on dosing and administration.

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

Study selection

Studies in which clobetasol propionate was used in the nominated dosage form, ROA, and/or combination product to diagnose, prevent, or treat the nominated disease or condition, or other conditions not specified in the nomination, were included. Studies were excluded if they were written in a language other than English; reviews or meta-analyses; surveys or questionnaires (cross-sectional design); designed to evaluate cost-effectiveness, mechanism of action, preclinical use, safety, or toxicity; or any study design other than a randomized controlled trial conducted in a non-US country. Studies were also excluded if clobetasol propionate was used as an FDA-approved product in the nominated dosage form, ROA, or combination; used in a dosage form, ROA, or combination that was not nominated; used in an unspecified dosage form or ROA; mentioned briefly as a rescue treatment or previous failed treatment; or not used clinically. Studies in which clobetasol propionate was used to diagnose, prevent, or treat autism were excluded due to a separate project examining the use of compounded substances in individuals with autism. Studies that did not meet the inclusion criteria but provided valuable information about the pharmacological or current or historical use of the substance were noted and put in a separate group in the EndNote library. Two reviewers independently screened titles and abstracts and reviewed full-text articles. A third reviewer reconciled all disagreements.

Data extraction

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

Interviews

Semistructured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances clobetasol propionate 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 clobetasol propionate. Potential SMEs were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. Select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided verbal informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were synthesized for qualitative data analysis.

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

Survey

A survey was distributed to the members of professional medical associations to determine the use of clobetasol propionate in clinical practice. The online survey was created using Qualtrics® software (refer to Appendix 2 for complete survey). A Google™ search was conducted to identify the professional associations in the US for the relevant medical specialties. An association's website was searched to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used. An email describing the project and requesting distribution of the survey to the association's members was sent to the identified person(s). Associations that declined, did not respond, or did not provide significant data in project Years 1 and 2 were not contacted to distribute the project Year 3 surveys.

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

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

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

CURRENT AND HISTORIC USE

Results of background information

- Clobetasol propionate is available as an FDA-approved product in the nominated dosage form and ROA.
- Clobetasol propionate is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for clobetasol propionate.
- Clobetasol propionate is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, Latvia, Namibia, New Zealand, and UK. There is an EMA report on scientific conclusions and grounds for variation and amendments to the product information for clobetasol propionate by the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh).²¹ In this report, the pharmacovigilance risk assessment committee (PRAC) assessment report for clobetasol mentioned that there is “the risk of serious infections (including necrotizing fasciitis) and systemic immunosuppression (sometimes resulting in reversible Kaposi’s sarcoma lesions) when combining clobetasol propionate with other medicines affecting the immune function,” and that “a causal relationship between clobetasol propionate is a reasonable possibility” when used at doses or for durations beyond those recommended. Pertaining to osteonecrosis, the report stated that “misuse for a prolonged duration is frequent and problematic.”²¹ The PRAC concluded that the product labeling for clobetasol propionate containing products should be updated accordingly, with the CMDh agreeing with the conclusions made.²¹

Table 1. Currently approved products – US^a

Active Ingredient	Concentration	Dosage Form	Route of Administration	Status	Approval Date^b
Clobetasol propionate	0.05%	Aerosol (foam), cream, gel, lotion, ointment, shampoo, solution, spray	Topical	Prescription	2/16/1994

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

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

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

Active Ingredient ^b	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date ^c
Clobetasol propionate	0.05%	Cream, foam, gel, liquid, lotion, ointment, scalp application, shampoo, solution, spray	Cutaneous, topical	Abu Dhabi	Active	–
				Australia	Prescription-only	3/21/2013
				Belgium	Prescription	9/30/1974
				Canada	Prescription	12/31/1992
				Hong Kong	Prescription-only	6/12/1979
				Ireland	Prescription-only renewable	10/27/1983
				Latvia	Prescription	2/25/1998
				Namibia	–	12/31/1972
				New Zealand	Prescription	7/25/1991
				Saudi Arabia	Prescription	–
United Kingdom	Prescription-only	3/1/1993				

Abbreviation: –, not provided.

^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 useable format. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations. See *Methodology* section for full explanation.

^bClobetasol propionate used as standard for name variations, including clobetasoli propionas.

^cIf multiple approval dates and/or multiple strengths, then earliest date provided.

Results of literature review

Study selection

Database searches yielded 867 references; 2 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 632 titles and abstracts were screened. After screening, the full text of 209 articles was reviewed. Finally, 17 studies were included. One hundred ninety-two studies were excluded for the following reasons: wrong study design (132 studies); FDA-approved formulation (33); wrong dosage form or ROA (18); unable to obtain full text (4); clobetasol propionate only mentioned briefly (2); duplicate study (1); wrong substance (1); unspecified dosage form or ROA (1).

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

Characteristics of included studies

The 17 included studies were published between 1994 and 2020. There were 10 experimental studies, 2 observational studies, 5 descriptive studies, and 0 clinical practice guidelines. The 17 studies were conducted in the following countries: Brazil, India, Italy, Japan, Sri Lanka, Sweden, the Netherlands, and the US.

A total of 536 patients participated in the 17 included studies. The number of patients in each study ranged from 1 to 68.

Outcome measures differed among the included studies and included the following: signs and symptoms, severity, efficacy, clinical score, clinical resolution, compliance, oral examination, pain scores, adverse effects, percentage of patients attaining complete response, time from hematopoietic cell transplant, clinical history, and oral sensitivity.

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

Use of clobetasol propionate

Two hundred fifty-eight patients received clobetasol propionate for the treatment of oral lichen planus (OLP), administered as a topical cream, gel, and ointment at a concentration of 0.025-0.05% every other day to twice a day for 3 weeks to 2 months. Clobetasol propionate was also administered as an oral/mucosal lipid microsphere at a concentration of 0.025% in a 0.028 to 0.056-mg/day dose for 2 months. One hundred seventy-six patients received clobetasol propionate as a treatment of genital or oral graft-versus-host disease (GVHD), administered as an oral solution or rinse at a concentration of 0.05% in a 15 to 30-mL/day dose for 14-28 days, or as a topical solution. Ninety-eight patients received clobetasol propionate as a treatment of psoriasis, administered as a topical ointment at a concentration of 0.01-0.05% daily for 12-24 weeks. One patient received clobetasol propionate for the treatment of bullous pemphigoid, administered topically. One patient received clobetasol propionate for the treatment of Crohn's disease, administered twice daily. One patient received clobetasol propionate for the treatment of mucous membrane pemphigoid, administered as an oral/mucosal ointment at a concentration of 0.05% twice daily. One patient received clobetasol propionate for the treatment of systemic lupus erythematosus, administered as a topical/mucosal ointment.

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

Clobetasol propionate was used as a compounded product (gel, lipid microspheres, ointment), and it was also used in a combination product (refer to Tables 8-10).

In 5 studies, the authors' concluding statement recommended the use of clobetasol propionate alone and/or in combination for the treatment of OLP,^{22,23} GVHD,^{24,25} and psoriasis.²⁶ In 1 study, the authors concluded that tacrolimus may be an effective alternative to clobetasol as a first-line therapy for OLP, and may be preferred in patients with higher susceptibility to developing oral candidiasis.²⁷ In 1 study, the authors concluded that the combination of calcipotriol and clobetasol were equally effective and as well tolerated as the 308-nm excimer lamp for palmoplantar psoriasis patients.²⁸ In 2 studies, the authors concluded that further studies were necessary for the treatment of OLP.^{29,30} In 7 studies, the authors' conclusions did not address the use of clobetasol propionate.³¹⁻³⁷ In 1 study, the authors did not provide a definitive conclusion for the use of clobetasol propionate.³⁸ Refer to Table 5 for a summary of the authors' conclusions.

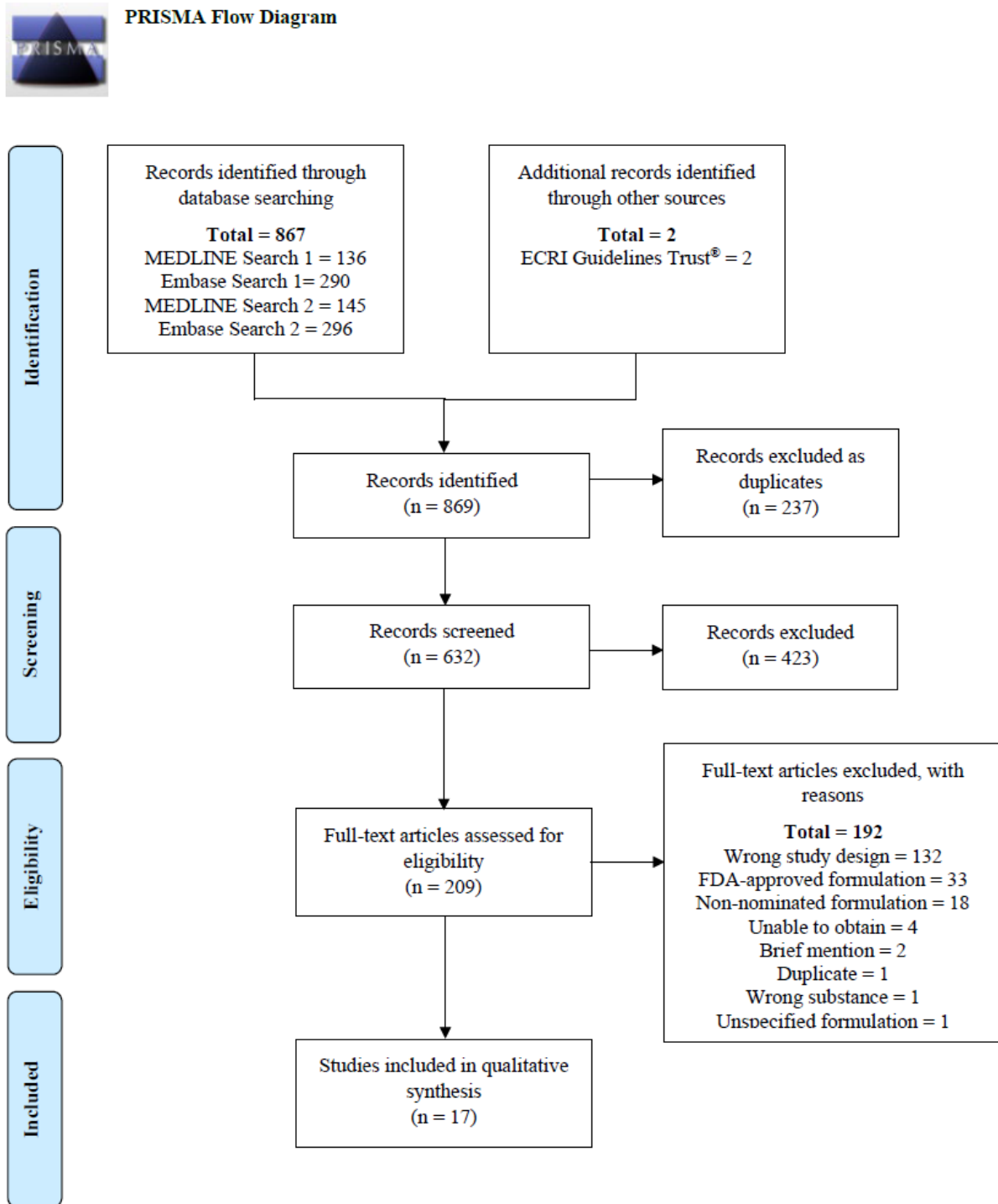
Pharmacology and historical use

Four additional studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of clobetasol propionate.

Clobetasol propionate is available in the US in several different topical formulations and is a fifth-generation corticosteroid used for OLP, psoriasis, and other steroid-responsive dermatoses.^{12,14,29} Among the available topical corticosteroids, clobetasol is the most potent for scalp psoriasis.¹¹ Traditional clobetasol dosage forms are only safe for short-term treatment of up to 4 weeks, because of potential topical side effects, such as skin atrophy and telangiectasia.¹¹ Additionally, in a 2009 case report, a 70-year-old female whose OLP was stabilized for 1.5 years with topical clobetasol gel developed Cushing's syndrome.³⁹ Based on studies with patch-tested patients, the frequency of allergic contact dermatitis is about 2.3% to 4.9% for topical corticosteroids.⁴⁰ Patients who are allergic to a topical corticosteroid often have cross-reactivity to the other topical corticosteroids.⁴⁰ While presumably less common, this could also sensitize patients to corticosteroids given through other ROA, such as oral, parenteral, or intralesional applications.⁴⁰

In studying one of the nominated topical combinations, clobetasol propionate and calcipotriol, Katoh and Kishimoto noted that they combined these ingredients as a premixed ointment in order to reduce the number of ointments patients would need to apply per day.²⁶ Refer to Table 5 for information on this study.

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 ³³⁻³⁷	5
Observational ^{31,32}	2
Experimental ^{22-30,38}	10

Table 4. Number of studies by country

Country	Number of Studies
Brazil ²⁵	1
India ^{27,28}	2
Italy ^{22,23,29}	3
Japan ²⁶	1
Sri Lanka ³⁰	1
Sweden ³⁸	1
The Netherlands ²⁴	1
Unite States (US) ³¹⁻³⁷	7
Total US: 7	
Total Non-US Countries: 10	

Abbreviation: US, United States.

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: Oral lichen planus (OLP)					
Campisi et al, 2004, Italy ²⁹	Controlled, single-blind Phase IV clinical trial	45 Patients with symptomatic OLP (26.7%, mean 61.1 y ± 12.3)	<ul style="list-style-type: none"> • Clobetasol with lipid microspheres (18) • Topical clobetasol ointment (27) 	Signs and symptoms, efficacy based on pain score, clinical score, clinical resolution, and compliance	“Our results suggest that the new topical drug delivery system (formulation A) [for clobetasol] may enhance, at least in terms of symptom remission and compliance, the effectiveness of clobetasol propionate at a dose of 0.025% in OLP therapy.” “On the basis of these preliminary positive results, the use of the latter new delivery system should be encouraged, investigated in larger [randomized controlled] trials assessed using quality of life measures and also tested with other drugs for the treatment of OLP.”
Carbone et al, 2009, Italy ²²	Randomized, controlled, double-blind study	30 Patients <ul style="list-style-type: none"> • Clobetasol 0.025% (13.3%, mean 63.06 y ± 7.93) • Clobetasol 0.05% (33.3%, mean 65.4 y ± 7.59) 	<ul style="list-style-type: none"> • Clobetasol propionate 0.025% (15) • Clobetasol propionate 0.05% (15) 	Record chart compilation, oral examination, description of symptoms and clinical signs, and photo at the beginning of therapy	“In conclusion, this study suggests that clobetasol propionate in 4% hydroxyethyl cellulose gel, independent of the concentration used, would appear to be a treatment of choice for patients with atrophic-erosive OLP, providing comparable clinical efficacy, being safe and well-tolerated. A larger concentration of the active molecules cannot further improve the therapeutic findings or optimize the obtained results in a significant manner.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Hettiarachchi et al, 2017, Sri Lanka ³⁰	Randomized, comparative, double-blind study	68 Patients with symptomatic OLP with main involvement of the bilateral buccal mucosae <ul style="list-style-type: none"> Tacrolimus group (41.2%, mean 46.65 y ± 13.15) Clobetasol (32.4%, mean 46.88 y ± 12.13) 	<ul style="list-style-type: none"> Tacrolimus (34) Clobetasol (34) 	Pain scores, clinical response	“The results suggest that tacrolimus 0.1% cream is an effective alternative to topical steroid and can be considered a first-line therapy in OLP. However, further studies are needed to confirm the effectiveness of this treatment before it is recommended for use in clinical practice.”
Lodi et al, 2007, Italy ²³	Randomized, parallel, double-blind trial	35 Outpatients with histologically proven OLP <ul style="list-style-type: none"> Clobetasol and miconazole (38.9%, mean 60.7 y ± 11.8) Clobetasol and placebo (23.5%, mean 64.9 y ± 9.9) 	<ul style="list-style-type: none"> Clobetasol propionate and miconazole (18) Clobetasol propionate and placebo (17) 	Symptoms and extension of lesions, adverse effects	“In the present randomized controlled trial, we tested the hypothesis that adding an antifungal drug (miconazole) to a topical treatment with a steroid (clobetasol propionate) may improve the treatment of patients affected by symptomatic OLP. The clobetasol propionate gel showed good efficacy in the treatment of OLP. The addition of miconazole did not improve the outcomes considered, although it prevented the onset of candidiasis secondary to local immunosuppression.”
Rodstrom et al, 1994, Sweden ³⁸	Double-blind clinical trial	40 Patients who presented with uni- or bilateral atrophic or erosive lesions on the buccal mucosa or on the tongue (25%, mean 58 y)	<ul style="list-style-type: none"> Clobetasol propionate (20) Triamcinolone acetonide (20) 	Clinical improvement in symptoms (visual analog scale), lesions were scored by a clinician	“The results demonstrate that clobetasol propionate compared with triamcinolone acetonide provides a more immediate clinical response in [erosive OLP].” “From the results of the present study it is concluded that a successful strategy for topical corticosteroid therapy for [erosive OLP] may consist of (1) a potent corticosteroid in adhesive base initially until relief of symptoms, and (2) a moderately potent corticosteroid in the same base for maintenance therapy.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Sonthalia and Singal, 2012, India ²⁷	Randomized, double-blind trial	40 Patients with histologically proven symptomatic OLP <ul style="list-style-type: none"> • Clobetasol (45%, mean 34.35 y ± 16.2) • Tacrolimus (35%, mean 35.05 y ± 13.24) 	<ul style="list-style-type: none"> • Clobetasol propionate (20) • Tacrolimus (20) 	Percentage of patients attaining complete response	“In summary, tacrolimus 0.1% ointment is an effective alternative to topical steroid and may be considered as one of the first-line therapies in the management of OLP. It may be preferred over topical steroid in patients who have an increased susceptibility to the development of oral candidiasis.”
Indication 2: Genital or oral graft-versus-host disease (GVHD)					
Lafond et al, 2011, United States (US) ³¹	Cohort	68 Patients diagnosed with genital GVHD (0%, age not specified)	<ul style="list-style-type: none"> • Grade II genital GVHD patients treated with topical clobetasol or topical tacrolimus (patients not specified) 	Time from hematopoietic cell transplant, other GVHD manifestations, gynecologic history, vulvar/vaginal findings, clinical course and treatment	“Considering that 5 of 6 (83%) affected patients in this series had acute GVHD of other organ systems, gynecologic issues should be included in the GVHD evaluation of female transplant patients. Finally, because genital [acute] GVHD was, in general, amenable to topical treatments, our findings offer hope that with appropriate diagnosis and intervention, genital [acute] GVHD can be effectively treated to improve the quality of life of female transplant survivors.”
Noce et al, 2014, Brazil ²⁵	Randomized, double-blind clinical trial	32 Patients with symptomatic oral lesions of chronic GVHD <ul style="list-style-type: none"> • Clobetasol (42.9%, range 29-60 y) • Dexamethasone (44.4%, range 27-66 y) 	<ul style="list-style-type: none"> • Clobetasol propionate (14) • Dexamethasone (18) Both groups also received nystatin	Improvement of symptoms, oral sensitivity	“In conclusion, clobetasol was significantly more effective than dexamethasone for the amelioration of symptoms and clinical aspects of oral lesions in [chronic] GVHD.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Mays et al, 2016, the Netherlands ²⁴	Phase II open label trial with an initial 2-week, randomized, double blind placebo-controlled	36 Patients with oral GVHD (55.6%, range 18-68 y)	<ul style="list-style-type: none"> • Clobetasol (not specified) • Placebo rinse (not specified) <p>After 2 weeks, all patients received an active (clobetasol) rinse until 28 days</p>	Day 28 oral GVHD response on the oral mucositis rating scale	“These controlled study data suggest that 0.05% clobetasol oral rinse is effective and safe for the treatment of [oral] GVHD even in patients who failed prior clobetasol ointment. These data support the further development of 0.05% clobetasol oral rinse for [oral] GVHD therapy.”
Shazib et al, 2020, Italy ³²	Retrospective record review	40 Patients with oral chronic GVHD (52.5%, range 24-75 y)	<p>All patients received one or more topical immunomodulatory therapies during some or all of the 24-month follow-up period:</p> <ul style="list-style-type: none"> • Dexamethasone (63*) • Tacrolimus (11) • Clobetasol (10) • Dexamethasone and tacrolimus (29) • Clobetasol and tacrolimus (10) <p>Patients also received systemic immunosuppressive therapies at baseline visit (tacrolimus, prednisone, sirolimus, or mycophenolate mofetil)</p> <p>*Number of patients who received each treatment at any time during the 24 months follow-up</p>	Clinician-reported oral mucosal scores, patient-reported sensitivity scores	“In summary, this is the first long-term follow-up study of patients with symptomatic oral [chronic] GVHD demonstrating that a significant proportion of those who initiate topical immunomodulatory therapy at the onset of the condition continue to need long-term management, for at least up to 24 months, and that these treatments appear to provide long-term clinical benefit with an excellent safety profile. Future studies are needed to determine the most effective second-line approaches to managing oral [chronic] GVHD refractory to first-line intervention.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 3: Psoriasis					
Dogra et al, 2017, India ²⁸	–	36 Patients with palmoplantar psoriasis (gender and age not specified)	<ul style="list-style-type: none"> Excimer lamp (36) Calcipotriol and clobetasol ointment (36) Patients received the excimer lamp twice weekly on one side and the topical combination once daily on the other side of the palms or soles	Percentage improvement in modified Palmoplantar Psoriasis Area and Severity Index score	“The 308-nm excimer lamp and calcipotriol–clobetasol combination were found to be equally effective and well tolerated in [palmoplantar psoriasis].”
Fatahzadeh, 2016, US ³³	Case report	1 Patient with generalized, symptomatic oral mucosal erythema resembling atrophic candidiasis synchronous with flare of chronic skin psoriasis (0%, 71 y)	<ul style="list-style-type: none"> Clobetasol propionate ointment (1) Other medications used topical nystatin ointment, hydrocortisone-iodoquinol-aloe cream 	Resolution and/or improvement in oral erythema	“Dental practitioners should be familiar with the signs and symptoms of oral psoriasis and include it in the differential diagnosis of diffuse oral mucosal erythema...Both patients and clinicians may fail to recognize the association between the skin disease and its oral counterpart when oral signs and symptoms occur in the context of long-standing cutaneous pathosis.”
Katoh and Kishimoto, 2003, Japan ²⁶	–	61 Outpatients with stable plaque psoriasis <ul style="list-style-type: none"> Calcipotriol (27%, mean 45.7 y ± 14.5) Calcipotriol and clobetasol (21%, mean 53 y ± 14.1) 	<ul style="list-style-type: none"> Calcipotriol ointment (32) Calcipotriol and clobetasol propionate ointment (29) 	Severity of psoriasis eruptions, Palmoplantar Psoriasis Area and Severity Index score	“The combination regimen was more efficacious than the monotherapy as evidenced by (1) more patients with at least 50% reduction in the eruption score after 2 weeks, (2) lower eruption score after 6 weeks and later, and (3) less adverse effects. The combined once-per-day application of 0.004% calcipotriol/0.01% clobetasol propionate as a premixed ointment is a promising regimen for psoriasis.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 4: Bullous pemphigoid					
Wardlaw et al, 2020, US ³⁴	Case report	1 Patient with esophageal involvement of bullous pemphigoid (100%, age not specified)	<ul style="list-style-type: none"> High dose proton pump inhibitors (PPIs), prolonged steroid taper, rituximab, and topical clobetasol (1) 	Improvement and/or resolution of swallowing symptoms and skin lesions	“The patient’s symptoms subsequently improved with [PPIs], topical/systemic steroids, and rituximab. Though rare esophageal manifestations of [bullous pemphigoid] exist and should be considered in patients that develop swallowing symptoms over the background of ongoing issues with this blistering skin condition.”
Indication 5: Crohn’s disease					
Aybar et al, 2010, US ³⁵	Case report	1 Patient with Crohn’s disease and frequent oral exacerbations (0%, 6 y)	<ul style="list-style-type: none"> Topical tacrolimus solution, clobetasol (1) 	Improvement/resolution of mucosal oral lesions	“In those children with isolated oral ulcerations related to Crohn’s disease we recommend using continuous topical tacrolimus early in the course, especially since there is no evidence of systemic absorption and recurrence is common if discontinued.”
Indication 6: Mucous membrane pemphigoid					
Lilly et al, 1995, US ³⁶	Case report	1 Patient with benign mucous membrane pemphigoid and advanced gingival lesions and periodontal destruction (0%, 64 y)	<ul style="list-style-type: none"> Dapsone, clobetasol ointment (1) <p>Previously was on systemic prednisolone therapy</p>	Improvement and/or resolution of exacerbation	“Benign mucous membrane pemphigoid will often first present to the dentist as a complaint of chronic oral discomfort and ulceration. The clinician should be prepared to establish a differential diagnosis and use the appropriate clinical and laboratory assessments to arrive at a final diagnosis. Once the diagnosis has been made the dentist should communicate these findings to the patient’s primary care physician and begin therapeutic management for the oral condition.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 7: Systemic lupus erythematosus					
Wester et al, 2019, US ³⁷	–	1 Patient with systemic lupus erythematosus who presented with painful oral and vaginal erosions (100%, 38 y)	<ul style="list-style-type: none"> Hydroxychloroquine, leflunomide, prednisone, dexamethasone elixir, triamcinolone ointment, clobetasol ointment (1) Clobetasol was used for vulvovaginal skin and mucosa	Improvement and/or resolution in oral and vaginal erosions	“Genital involvement of [lupus erythematosus] is very rarely reported in the literature but should be a diagnostic consideration in patients with genital lesions.”

Abbreviations: –, not provided; GVHD, graft-versus-host disease; OLP, oral lichen planus; PPI, proton pump inhibitors; US, United States.

^aAs defined by authors.

Table 6. Dosage by indication – US

Indication	Dosage	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Genital or oral graft-versus-host disease ^{31,32}	–	–	Solution	Topical	–
Bullous pemphigoid ³⁴	–	–	–	Topical	–
Crohn's disease ³⁵	Twice daily	0.05%	–	–	–
Mucous membrane pemphigoid ³⁶	Twice daily	0.05%	Ointment	Oral/mucosal	–
Psoriasis ³³	–	–	Ointment	Topical	–
Systemic lupus erythematosus ³⁷	–	–	Ointment	Topical/mucosal	–

Abbreviation: –, not provided.

Table 7. Dosage by indication – non-US countries

Indication	Dosage	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Oral lichen planus ^{22,23,27,29,30,38}	0.028-0.056 mg/day	0.025%	Lipid microspheres	Oral/mucosal	2 months
	Every other day to twice daily	0.05%	Cream, gel, ointment	Topical	3-9 weeks
	2-4 mL/day	0.025-0.05%	Ointment	Topical	2 months
Oral chronic graft-versus-host disease ^{24,25}	15-30 mL/day	0.05%	Solution, rinse	Oral	14-28 days
Psoriasis ^{26,28}	Once daily	0.01-0.05%	Ointment	Topical	12-24 weeks

Table 8. Number of studies by combination

	Combination Formula	Number of Studies
Nominated	Clobetasol propionate 0.01-0.05% / Calcipotriene 0.004-0.005% – topical cream, foam, ointment, solution ^{26,28}	2
	Clobetasol propionate 0.05% / Levocetirizine dihydrochloride 2% – topical solution	0
	Clobetasol propionate 0.05% / Niacinamide 4% – topical cream, ointment, solution	0
	Clobetasol propionate 0.05% / Pramoxine hydrochloride 1% in emu and olive oil	0
	Clobetasol propionate 0.05% / Coal tar solution 8% / Salicylic acid 6% – topical ointment	0
	Clobetasol propionate 0.05% / Hyaluronic acid sodium salt 1% / Niacinamide 4% – topical cream	0
	Clobetasol propionate 0.05% / Levocetirizine dihydrochloride 2% / Zinc pyrithione 1% – topical shampoo	0
	Clobetasol propionate 0.05% / Niacinamide 4% / Zinc pyrithione 0.2% – topical solution	0
	Clobetasol propionate 0.05% / Salicylic acid 4% / Urea 40% – topical cream	0
	Clobetasol propionate 0.05% / Ciclopirox 0.77% / Salicylic acid 3% / Tea tree oil 1% – topical shampoo	0
	Clobetasol propionate 0.05% / Ciclopirox 0.77% / Tea tree oil 1% / Zinc pyrithione 1% – topical shampoo	0
	Clobetasol propionate 0.05% / Ciclopirox 0.77% / Salicylic acid 3% / Zinc pyrithione 1% – topical shampoo	0
	Clobetasol propionate 0.05% / Coal tar solution 5% / Salicylic acid 4% / Shark cartilage 5% – topical cream	0
	Clobetasol propionate 0.05% / Levocetirizine dihydrochloride 2% / Tea tree oil 1% / Zinc pyrithione 1% – topical shampoo	0
	Clobetasol propionate 0.05% / Ciclopirox 0.77% / Salicylic acid 3% / Tea tree oil 1% / Zinc pyrithione 1% – topical shampoo	0
Clobetasol propionate 0.05% / Ibuprofen 2% / Mupirocin 5% / Salicylic acid 5% / Urea 20% – topical cream	0	

Table 9. Compounded products – US

No compounded products from included US studies

Table 10. Compounded products – non-US countries

Indication	Compounding Method	Dosage Form	Final Strength
Oral lichen planus ^{22,23,29}	“The clobetasol propionate gel was prepared by one of the authors (D.D.B.) in the hospital pharmacy, following the indications of Good Manufacturing Practice and the Italian pharmacopoeia, according to the following recipe: 0.5 g clobetasol propionate, 40 g hydroxyethyl cellulose, 20 mL alcohol (96 °C), 934 mL water, 20 mL methyl-parahydroxi-benzoate alcohol solution [prepared with 20 mL of alcohol (96 °C) and 2 g methyl-parahydroxi-benzoate].” ²³	Gel	–
	“Solid lipid microspheres were prepared using the meltable dispersion method...Cetyl alcohol (20.7 g), isopropyl myristate (8.7 g) and clobetasol propionate (0.03 g) were heated until fusion.” 200 mL of preheated (80 °C) deionized water was added to the mass and the whole mixture mechanically stirred. “Upon dispersion in the aqueous medium the molten lipid mass formed spherical oily particles. The suspension was rapidly cooled to room temperature, and the oily material solidified, enveloping the drug.” ²⁹	Lipid microspheres	0.025%
	“Hydroxyethyl cellulose was melted in boiled water and slowly turned. After a few hours, the 4% hydroxyethyl cellulose gel was mixed with an equivalent amount of clobetasol propionate ointment 0.05% (Clobesol®; Glaxo, Verona, Italy).” ²²	Ointment	0.025%
	“Clobetasol propionate was melted in 95% alcohol with a soluble additive (Abil 8851). Hydroxyethyl cellulose was melted in boiled water and slowly turned. At the temperature of 30 °C, the 4% hydroxyethyl cellulose gel was mixed with an equivalent amount of previously melt clobetasol propionate.” ²²	Ointment	0.05%

Abbreviation: –, not provided.

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. Seven SMEs discussed clobetasol propionate. All 7 SMEs were medical doctors. The SMEs specialized and/or were board-certified in allergy, dermatology, infectious disease, rheumatology, and obstetrics and gynecology, working in academic medical institutions and outpatient practice. The SMEs had been in practice for 1 to 56 years. Additional information was collected as a part of the Expanded Information Initiative, referred to as Phase 3, in which outreach was conducted to the nominators of the bulk drug substances to remedy information gaps in the initial nomination.

Three SMEs commented on the use of clobetasol to treat vulvodynia. Vulvodynia is a clinical diagnosis with a variety of different forms; “I personally divide it up into those women who have got an inflammatory component and another group of women where there’s a neuropathic component. Neuropathic, in other words, we’re into nerve-induced, not inflammatory, pain. And some of the women have significant skeletal muscle spasm and not smooth muscle spasm where they can actually get what is called vaginismus, where they actually get contraction of the skeletal muscles in the sling, in the pelvic muscles of the floor.” As a result, management depends on the different elements involved in each patient’s etiology. Vulvodynia patients who experience significant local inflammation may undergo surgery to remove the inflamed vestibule. However, not everyone undergoes surgery, and even those who eventually will undergo surgery might wait months or years before receiving the appropriate surgery.

One SME stated that they only see refractory or surgical cases of vulvodynia. Typically, topical steroids are used as an initial treatment because “when you biopsy an otherwise normal vulva and you suspect it’s vulvodynia, it still comes back with some form of inflammation, spongiotic dermatitis, something is happening there. We often are using steroids to try to decrease that inflammation.” Clobetasol is “ultrapotent, so we tend to start that.” While clobetasol is commercially available, these products have “a lot of additives in them” and these patients often have a lot of drug sensitivities and allergies. One SME described these patients as often having “more of an eczema type of skin, reactive skin,” and so prescribers have to be cautious about the products used. In these situations, “that’s when we turn to a compounding pharmacy where they can pick which base the medication’s in.”

Compounded products are often used for patients with vulvodynia and will contain gabapentin or similar agents, concentrations varying from 3% to 5%, either alone or in combination with amitriptyline; “amitriptyline and the gabapentin are really used for people whose pain is a major component, especially when it’s unprovoked pain. But [it] may be also used when it’s provoked. And both of them either used alone or in combination are often used together with baclofen. And baclofen is a muscle relaxer. So, you can get one, two, you’ve got now five possibilities of what they... Maybe 10 if you’re using different concentrations with each.” These agents are applied once or twice daily despite the paucity of studies determining the correct combination or benefits. Another SME commented that gabapentin can be compounded in concentrations up to 10%, but they predominately use gabapentin 6% in combination with amitriptyline and baclofen. The drugs used in this combination treat pain using different mechanisms.

Some products might come with additional estrogen in the form of either estradiol or estriol; “estriol is a little bit less potent than estradiol. But it’s better tolerated.” Sometimes they add estrogen or testosterone as a solo product, or they combine it with the other active ingredients. Some products contain lidocaine, but one SME cautioned that “the problem with the use of lidocaine in a topical product is that you often get reactive pain or pain that gets worse when it wears off. So, you get some relief from say burning and pain. And then you get relief for a couple of hours or a few hours and then you get worse off when you get a second round of pain. So, lidocaine is a somewhat problematic product.” Topical diazepam has also

been used, but it is not commonly applied, and “if diazepam works, you don’t know how much of it is a local effect versus how much is due to absorption and having a central effect.” One SME stated that “apart from the potential for local burning, the absorption is so low, you have no systemic side effects” continuing that these topical agents are “very relatively safe.” When asked about the efficacy for topical products, one SME said that “if they didn’t work at all, they wouldn’t sell. So, you never know how much of it is placebo effect. You’ll never know how much of it has helped.” Few studies have been published on the use of these drugs, and there is debate on whether the studies that have been completed are treating the right patient population.

However, another SME stated that they do not use clobetasol for vulvodynia and instead prefer oral gabapentin, nortriptyline, Lyrica® (pregabalin), and Cymbalta® (duloxetine); occasionally the SME will use a compounded topical gabapentin at a concentration of 6% in Aquaphor.

Two SMEs commented on the use of clobetasol for lichen planus. Patients that present with lichen planus require “a custom makeup of what they need based on what their symptoms and what their exam shows.” The commercially available clobetasol gel is often used initially to treat OLP; for vaginal lichen planus, clobetasol is applied externally with a compounded hydrocortisone product. Hydrocortisone is preferred because “the mucosa of the vaginal tissue is different than the keratinized tissue of the vulva and we use way more of it.” Since clobetasol is a more potent steroid, along with the alcohol content of the commercially available products, clobetasol is generally not used inside the vagina. One SME commented that if they suspect a patient might be allergic to the base in the commercially available product, they will have the product compounded, but stated that this is not a frequent occurrence. Another SME also stated that they “almost always use commercially available clobetasol.”

Two SMEs discussed the use of topical corticosteroids to treat psoriasis. One SME divides psoriasis treatment into 2 groups based on whether topical medications are likely to work. Patients with mild psoriasis typically receive clobetasol, and those with more moderate or severe disease will receive a topical steroid to “use on their worse spots, but I wouldn’t rely exclusively on topicals.” Another SME stated that they use clobetasol for patients with moderate to severe psoriasis or for any patients “who have some kind of dermatitis that doesn’t respond to like a milder form of hydrocortisone,” adding that clobetasol is “one of the strongest steroids.” Clobetasol is commercially available in several topical dosage forms, and 1 SME stated that patient preference will determine the formulation prescribed. The SME stated that historically, prescribers would have patients that would not respond to clobetasol therapy, although the biggest factor that leads clobetasol therapy to fail is that the patient does not apply the medication. In these instances, the addition of other medications will not likely have an effect; therefore the SME prefers to keep the regimen as simple as possible. Another SME stated that they do not use any compounded steroids.

One SME commented on the multi-ingredient products included in the nomination, stating that the ingredients are treating different conditions; clobetasol is used to decrease itch and inflammation, while the other ingredients are treating the underlying condition. For example, clobetasol and zinc pyrithione is likely designed to treat seborrheic dermatitis—and psoriasis, when combined with salicylic acid and urea—because, “you’re probably trying to decrease the scale and buildup and then getting the clobetasol sort of down into the psoriatic plaque a little bit better.” Another SME mentioned that approximately 25 years ago, a company began selling “a product called Skin Cap that contained zinc pyrithione that made psoriasis just disappear.” While the product was marketed as only containing zinc pyrithione, it actually contained clobetasol as well. Initially, it was thought that the combination of zinc pyrithione and clobetasol was more effective than clobetasol alone, and dermatologists started “to rely on this idea of compounding clobetasol with zinc.” However, the SME expressed doubt that the zinc provided any

additional benefit, referencing a study that “showed the zinc did not have any added benefit” and instead believes that due to the marketing of the product, patients were not aware that the product contained clobetasol. As a result, “the patients weren’t afraid of it, and they used it better” continuing that “if you get people to use the clobetasol, it works.”

Some of the multi-ingredient products are to treat fungal infections. The SME stated that clobetasol is likely used to decrease the itch associated with the infection, but that oftentimes, “when you look at something, you’re not sure whether it’s fungal.” Multiple potential conditions can be treated by adding clobetasol with an antifungal agent. For instance, ciclopirox combined with clobetasol is likely designed to treat onychomycosis. While oral agents are typically needed when treating onychomycosis as a result of topical products having poor efficacy, not all patients are able to tolerate the oral medications. The SME stated that there is some literature to support the use of tea tree oil when treating onychomycosis and that the salicylic acid is likely to decrease buildup and increase penetration.

The SME was unaware of literature available that supports the use of topical levocetirizine but hypothesized that it could potentially be helpful in patients with “a cutaneous mastocytosis or something like that, where you’re really trying to get at the mast cells.” Regarding the multi-ingredient products with hyaluronic acid, the SME stated that hyaluronic acid is a moisturizing agent so those products could be treating atopic dermatitis or similar conditions where the aim is to increase moisturization of the skin. The combination with calcipotriene is likely for psoriasis; however, the SME mentioned that Taclonex[®] (calcipotriene/betamethasone) is a commercially available product that combines a steroid with calcipotriene. The SME stated that clobetasol and betamethasone are both in group D1, “which would mean that if they were allergic to betamethasone, they’d probably be allergic to clobetasol.” Lastly, the SME was unsure what the multi-ingredient product that contained ibuprofen, mupirocin, salicylic acid, and urea would be used to treat. The SME stated that salicylic acid and urea are keratolytic agents that may reduce scale; mupirocin is typically used to treat *Staphylococcus* infections; and clobetasol would reduce inflammation. The SME was not sure of the reason for including ibuprofen. Further, the SME did not identify any multi-ingredient products that would be effective for alopecia areata, adding that there are rare hair-loss diseases—such as inflammatory alopecia, frontal fibrosing alopecia, or planopilaris—that can be treated with topical corticosteroids; but the SME noted that none of the multi-ingredient products nominated “are making me really think hair loss in particular.”

One SME had no experience using clobetasol.

When treating dermatologic conditions, one SME stated that they have not encountered challenges with excipients contained in commercially available products but continued by saying, “I don’t have a specialty contact dermatitis clinic...and yes, for them, it is really important to be able to have the flexibility because they do find real allergic reactions that they need to exclude certain ingredients from and so compounding can be really useful there.”

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

Clobetasol propionate 0.05% / ciclopirox oleate 0.77% will be compounded as a topical shampoo to treat seborrheic dermatitis 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 found in the commercially available products: butylated hydroxytoluene, cetearyl alcohol, chlorocresol, ethyl acetate, mineral oil, polysorbate 60, and sodium hydroxide. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include allergen, classified as expected to be toxic or harmful, human

immune and respiratory toxicant or allergen, human irritant, human respiratory irritant, human skin toxicant or allergen, possible human carcinogen. Clobetasol propionate is added for its anti-inflammatory properties and ciclopirox oleate for its antifungal properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Clobetasol propionate 0.05% / ciclopirox oleate 0.77% / salicylic acid 3% will be compounded as a topical shampoo to treat seborrheic dermatitis 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 found in the commercially available products: butylated hydroxytoluene, cetearyl alcohol, chlorocresol, ethyl acetate, mineral oil, polysorbate 60, and sodium hydroxide. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include allergen, classified as expected to be toxic or harmful, human immune and respiratory toxicant or allergen, human irritant, human respiratory irritant, human skin toxicant or allergen, possible human carcinogen. Clobetasol propionate is added for its anti-inflammatory properties, ciclopirox oleate for its antifungal properties, and salicylic acid for its keratolytic properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Clobetasol propionate 0.05% / levocetirizine dihydrochloride 2% will be compounded as a topical shampoo to treat seborrheic dermatitis 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 found in the commercially available products: butylated hydroxytoluene, cetearyl alcohol, chlorocresol, mineral oil, propylene glycol, and sodium hydroxide. 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 skin irritant, human immune and respiratory toxicant or allergen, human irritant, human respiratory irritant, human skin toxicant or allergen, possible human carcinogen. Clobetasol propionate is added for its anti-inflammatory properties and levocetirizine for its anti-itching properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Clobetasol propionate 0.05% / niacinamide 4% will be compounded as a topical cream to treat seborrheic dermatitis 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 found in commercially available products: butylated hydroxytoluene, chlorocresol, methylparaben, propylene glycol, sodium hydroxide, sodium laureth sulfate, and white petrolatum. 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 skin irritant, contamination concerns, human immune and respiratory toxicant or allergen, human irritant, human respiratory irritant, human skin toxicant or allergen, restricted in cosmetics (recommendations or requirements) use concentration or manufacturing restrictions. Clobetasol propionate is added for its anti-inflammatory properties and niacinamide for its skin conditioning benefits. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Clobetasol propionate 0.05% / niacinamide 4% will be compounded as a topical ointment to treat seborrheic dermatitis 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 found in the commercially available products: butylated hydroxytoluene, cetearyl alcohol, chlorocresol, methylparaben, mineral oil, propylene glycol, sodium hydroxide, and sodium laureth sulfate. 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 skin irritant, contamination concerns, human immune and respiratory toxicant or allergen, human irritant, human respiratory irritant, human skin toxicant or allergen, possible human carcinogen. Clobetasol propionate is added for its anti-inflammatory properties and niacinamide for its skin conditioning benefits. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Clobetasol propionate 0.05% / niacinamide 4% will be compounded as a topical solution to treat seborrheic dermatitis 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 found in the commercially available products: butylated hydroxytoluene, cetearyl alcohol, chlorocresol, methylparaben, mineral oil, propylene glycol, sodium hydroxide, sodium laureth sulfate, and white petrolatum. 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 skin irritant, contamination concerns, human immune and respiratory toxicant or allergen, human irritant, human respiratory irritant, human skin toxicant or allergen, possible human carcinogen, restricted in cosmetics (recommendations or requirements) use, concentration, or manufacturing restrictions, violation of industry recommendations—restricted in cosmetics; use, concentration, or manufacturing restrictions—not safe for use on injured or damaged skin. Clobetasol propionate is added for its anti-inflammatory properties and niacinamide for its skin conditioning benefits. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Clobetasol propionate 0.05% / calcipotriene 0.005% will be compounded as a topical aerosol—foam to treat seborrheic dermatitis 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 found in the commercially available products: butylated hydroxytoluene, cetearyl alcohol, chlorocresol, mineral oil, propylene glycol, sodium hydroxide, and sodium laureth sulfate. 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 skin irritant, contamination concerns, human irritant, human respiratory irritant, human skin toxicant or allergen, possible human carcinogen. Clobetasol propionate is added for its anti-inflammatory properties and calcipotriene for its anti-inflammatory and skin softening properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Clobetasol propionate 0.05% / calcipotriene 0.005% will be compounded as a topical solution to treat seborrheic dermatitis 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 found in the commercially available products: butylated hydroxytoluene, cetearyl alcohol, chlorocresol, mineral oil, propylene glycol, sodium hydroxide, and sodium laureth sulfate. 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 skin irritant, contamination concerns, human irritant, human respiratory irritant, human skin toxicant or allergen, possible human carcinogen. Clobetasol propionate is added for its anti-inflammatory properties and calcipotriene for its anti-inflammatory and skin softening properties. This product is needed because it will result in a clinical difference to patients as it does not include harmful excipients found in FDA-approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Several nominated formulations will no longer be compounded because the formula has been discontinued, including

- Clobetasol propionate 0.05% / pramoxine hydrochloride 1% in emu olive oil
- Clobetasol propionate 0.05% / salicylic acid 4% / urea 40%
- Clobetasol propionate 0.05% / coal tar solution 8% / salicylic acid 6%
- Clobetasol propionate 0.05% / coal tar solution 5% / salicylic acid 4% / shark cartilage 5%
- Clobetasol propionate 0.05% / ibuprofen 2% / mupirocin 5% / salicylic acid 5% / urea 20%

Additionally, several nominated formulations will no longer be compounded because hyaluronic acid, tea tree oil, and zinc pyrithione are no longer considered active ingredients, including

- Clobetasol propionate 0.05% / hyaluronic acid sodium salt 1% / niacinamide 4%
- Clobetasol propionate 0.05% / levocetirizine dihydrochloride 2% / zinc pyrithione 1%
- Clobetasol propionate 0.05% / niacinamide 4% / zinc pyrithione 0.2%
- Clobetasol propionate 0.05% / ciclopirox 0.77% / salicylic acid 3% / tea tree oil 1%
- Clobetasol propionate 0.05% / ciclopirox 0.77% / salicylic acid 3% / zinc pyrithione 1%
- Clobetasol propionate 0.05% / ciclopirox 0.77% / tea tree oil 1% / zinc pyrithione 1%
- Clobetasol propionate 0.05% / ciclopirox 0.77% / salicylic acid 3% / tea tree oil 1% / zinc pyrithione 1%
- Clobetasol propionate 0.05% / levocetirizine dihydrochloride 2% / tea tree oil 1% / zinc pyrithione 1%

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 16-18 for results of the prequestionnaire.

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

with a product compounded from 1 outsourcing facility, minimizing the impact to the participant's facility.

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

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

Another theme regarding deciding what products to purchase from an outsourcing facility was focused on the utilization and volume of a product that is needed and the overall impact this would have on the pharmacy workload. Critical care areas, like the emergency department and operating room, typically have a high product utilization and overall turnover, leading to several participants obtaining products intended for use in these areas from outsourcing facilities. Participants stated that they evaluate the volume of product needed and the frequency in which that volume is needed compared to the time it would take pharmacy staff to prepare this volume. One participant commented that "we look at the impact that it'll have on staff. If our staff are needing to batch, or if we need to mass produce these in particular to meet the patient demand, then those are the items that we're going to look to potentially move out." Another participant stated that, while they do not obtain a lot of products from outsourcing facilities, "when we do purchase from 503Bs, typically it would be if we just don't have the capacity to keep up with what the demand is." One participant also commented that they will obtain labor-intensive and more complicated products, like epidurals and cardioplegia solutions, from outsourcing facilities to reduce the workload on pharmacy staff. The coronavirus disease 2019 (COVID-19) pandemic has also impacted the operations of hospitals, as noted by 1 participant who stated that "it's just really high volume, and the bigger the hospital, the higher the volume, especially when you have one disease state in half of your

hospital” and another who expressed that “without 503B, we would’ve been in significant trouble.” One participant commented that “even though the number might be small [percent of products obtained from outsourcing facilities], some of the reasoning is quite critical, and the amount of time that it saves is very significant for beyond what we’re able to do and when.” Additionally, challenges with recruiting and retaining pharmacy technicians impact decision-making, with 1 participant stating, “It is not feasible for us to meet the high volume for some common medications to repackage or compound from commercial presentations to a convenient, ready-to-use dosage form or package. The outsourcing facilities thus become a force multiplier, if you will, to offset some of the shortages in staffing.”

In addition to the evaluation of the workload on pharmacy staff, the type and capabilities of the facility also impacted the decision-making process. One participant commented that they do not have an established cleanroom and therefore perform sterile compounding in a segregated compounding area. United States Pharmacopeia (USP) <797> standards limit the beyond-use date that can be assigned to these products and, as the participant stated, “We obviously need to provide product with much [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 forced pharmacies to consider strategies to make IV admixtures available for use on the floor. Additionally, NPSG.03.04.01 states that all medications and solutions should be adequately labeled, including in the operating room and other settings in which procedures are performed. USP <795> and <797> are applicable in operating room settings, stating that products should be labeled and used within 1 hour, which may be problematic if syringes are drawn up at the beginning of the day and cases are canceled or delayed. The participant also commented on the cost related to purchasing premade products from manufacturers, stating that “predatory pricing on premixes is present in the market.”

Standardization of products, including concentration, volume, and labeling, was also a driver for obtaining products from an outsourcing facility. However, such standardization may not always be possible. One participant stated that when evaluating similar facilities, you would expect them to have similar needs regarding the concentrations and volumes of products utilized. However, the products utilized in a facility are often developed in-house over decades based on physician and nurse requests, and, more recently, appropriateness for an automated dispensing cabinet. As a result, one participant observed, “These practices had evolved somewhat disparately; even if we had clinical practice guidelines, nobody was putting concentrations into those guidelines and volumes into those guidelines.” This has led to challenges with obtaining certain products from outsourcing facilities. As another participant said, “I think we made 9 different epidural concentrations, all driven by anesthesia, and they want what they want and 503Bs may not offer that. No one else in the country is buying that same concentration; a 503B isn’t going to go through the expense of adding that to their product list.” The participant continued that “similar with the ADCs [automated dispensing cabinets], we’ve run into situations where dextrose 50% goes on shortage and the 503Bs would be selling it in a syringe. For safety reasons and for crash cart reasons, without having to retrain thousands of nurses of where things are placed, they said, ‘No, we can’t have it, and that’s too big it won’t fit,’ we want it in this format—and then we’re stuck again because there’s no 503B offering a format during that shortage that fits where it needs to go. Then we’re stuck in sourcing.” Additionally, while a commercially available product may be available, the volume may not be

appropriate. One participant stated that “3% saline for instance, is sold in a 500 mL bag, but the clinical guideline is a 150 mL bolus. We’re either going to draw that out or we’re sending it to the ER with stickers all over it saying only give 150 [mL].” The participant continued that “it would be great if the FDA could look at the size of the container that they’re approving and whether that’s a realistic dose; is it a unit dose or isn’t it?”

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

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

A few participants commented on the need for preservative-free products, particularly in pediatric patients. The example of methadone was provided as it is used for patients with neonatal abstinence syndrome but is only available as a preservative-containing product. So, there is a need for this product to be compounded from API as a preservative-free product. One participant stated that “if there’s not a preservative-free containing option, it really should be something that should be able to be compounded from bulk ... especially for the pediatric patient population.” However, another participant from a children’s hospital stated that the need for a preservative-free option has never been a reason why they have obtained a product from an outsourcing facility. Preservative-free is also an issue for ophthalmic products; however, 1 participant observed this is more on the 503A side. One participant stated that obtaining ophthalmic products from outsourcing facilities has been a challenge and that there are products they would like to obtain from outsourcing facilities but are not able to, forcing them to compound them in-house. This participant also commented that there are 2 outsourcing facilities that compound ophthalmic products, but when they reviewed the facilities, they did not pass their internal quality standards; 1 facility had been banned from distributing products in California by the Board of Pharmacy. There is an additional challenge with obtaining cephalosporins and beta-lactams due to the potential cross-reactivity in patients with allergies. One participant stated that there are some cephalosporins they

would like to obtain from an outsourcing facility but cannot because “they would have to build a separate cleanroom with a dedicated HVAC [heating, ventilation, and air conditioning], so you’re talking millions of dollars in investment for actually very low volume. Right now, the ROI [return on investment] isn’t there.” Another participant stated that the concentrations required for ophthalmic antibiotics are not available, but the labor and risk of compounding these products in-house is not worth it.

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

Based on the responses to the prequestionnaire (refer to *Results of survey*), participants were asked questions regarding specific products obtained from outsourcing facilities. Several participants reported using alum (aluminum potassium) as a bladder irrigation for hemorrhagic cystitis refractory to other treatment options. Participants commented that this is high-risk compounding; they purchase alum from an outsourcing facility because they do not perform high-risk compounding in their facility. One participant commented that their policy states that high-risk compounding is not allowed except for alum. This participant wanted to move away from compounding alum in-house and stated that the addition of aluminum potassium to the bulks list might allow this to happen. Another participant had compounded alum in-house from nonsterile ingredients; however, there had been challenges with crystallization after storage. A few participants commented that there is a sterile alum powder available, which they purchase to compound in-house. One participant had concerns regarding this powder, stating that “I’ve talked to that company, but I’ve had some concerns for them because they don’t sell it as a drug. The owner was selling you a chemical; we’re selling you a bulk API. It’s just sterile. They were fuzzy and I never followed up, but when I asked about their process for verifying the sterility, as you would with a sterile product—we do USP [United States Pharmacopeia] <71> Sterility Testing—they couldn’t really give me an answer. They just say they tested for sterility.” The participants commented that alum is only needed a few times a year. However, as one participant observed, “When you need it, it’s an emergency,” and another noted that it “is a challenge for anybody who has the cyclophosphamide-induced hemorrhagic cystitis.” As a result, one participant maintains a small inventory of alum product that is purchased from an outsourcing facility, but “more times than not, they go unused and expire.” Another stated that they do not keep it in stock because there is a minimum purchase and there are only a few cases a year for whom they need to use alum. The participant had it stat shipped when needed. Another participant stated that “we had a meeting with the head of urology who was baffled why they’re even ordering it. He was like,

‘This is an old, really old. I don’t even know why we’re using it’ and basically approved for us to not even make it anymore for now.”

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

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

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

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

The participants also discussed challenges with utilizing outsourcing facilities. One participant stated that their facility does not use outsourcing facilities because “it just hasn’t been financially, not just the money worth it, but just the lead time for how much time you have to give them and how much you have to ... It just isn’t worth the dating that they gave us or can give us.” Another commented that they obtain very little product from outsourcing facilities due to “the amount of work for vetting and continually validating quality of these 503B outsourcing facilities.” The participant stated that they have a robust validation process that takes several months and includes a site visit prior to purchasing from an outsourcing facility, followed by continuous reviewing of quality reports and warning letters. Another challenge has been the reliability of the outsourcing facility. One participant commented that “traditionally, we’ve found 503Bs to be fairly unreliable, when we have partnered with certain ones, to be able to keep up with the volume. Everybody knows PharMEDium just closed, but we’ve had some other smaller 503Bs where we’ve had agreements for certain products to take it off our plate, and then low and behold they’re shut down, or

closed, or whatever it may be.” Minimum purchase amounts were also reported as a concern, with one participant stating that “what we see consistently is the 503Bs, they want us to commit to giving them a certain volume, but then will not give us a reciprocal commitment or at least will not fulfill that reciprocal commitment. That’s a huge problem for us making that type of commitment, when we do ultimately have to split our volume in order to make sure that we consistently are able to take care of our patients.” Another challenge was related to outsourcing facilities utilizing API to compound narcotics. One participant commented that this often worsens drug shortages due to the quotas that the Drug Enforcement Administration (DEA) places on the quantity that can be produced. The participant stated that “they [outsourcing facilities] want to buy the product that we’re trying to buy to take care of our patients today, to sell us tomorrow. We really need the FDA to say that, especially for controlled substances, that 503Bs can consistently prepare those products so that we don’t end up with a shortage year after year, after year and then chasing our tail. Also, we may actually want to tell 503Bs, they can’t buy those products or that they’re limited in the amount of their ability to buy those products to make what are essentially copies of commercially available products, because it actually induces the shortage in many ways.”

Results of survey

Zero 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 survey instrument).

Forty-three people responded to the prequestionnaire; refer to Table 15 for respondent characteristics. Amongst respondents, 35 (81% of 43 total respondents) utilized outsourcing facilities to obtain drug products, 4 (9%) did not utilize outsourcing facilities, and 4 (9%) did not respond to this question.

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

Clobetasol propionate 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 clobetasol propionate prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded clobetasol propionate

No respondents to survey distributed via professional medical associations

Table 14. Use of non-patient-specific compounded clobetasol propionate

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 one 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

Abbreviation: FDA, US Food and Drug Administration.

^aRespondents were allowed to select multiple categories.

^bRespondents reported staffing shortages, need for extended dating, volume of product used, standardization projects as additional reasons for utilizing 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/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
Calcium chloride	1
Caffeine sodium benzoate	0
Cholecalciferol	1
Chromium chloride	0
Clonidine	0
Dexamethasone sodium phosphate	0
Diclofenac	0
Gentamicin	0
Glycerin	1
Hydroxyzine	0
Ketamine	14
Levocarnitine	0
Lidocaine	8
Lorazepam	2
Magnesium sulfate	4
Manganese chloride	0
Methylprednisolone	0
Midazolam	15
Mupirocin	1
Norepinephrine	15
Ondansetron	0
Phytonadione	0
Potassium chloride	0
Potassium phosphate	0

Prilocaine	0
Proline	0
Propranolol	1
Ropivacaine	6
Sodium chloride	0
Sodium citrate	3
Sodium phosphate	0
Tetracaine	2
Triamcinolone acetonide	0
Tropicamide	0
None of the above	8

^aRespondents were allowed to select multiple products.

CONCLUSION

Clobetasol propionate was nominated for inclusion on the 503B Bulks List as mucosal and vaginal products, as well as various topical dosage forms to treat unknown medical conditions; generally, clobetasol propionate is used for seborrheic dermatitis, onychomycosis, tinea corporis, tinea cruris, tinea pedis, eczema, herpes labialis, psoriasis, lichen sclerosus, alopecia areata, vitiligo, vaginal lichen planus, mycosis fungoides, vaginal irritation/pain (vulvodynia), and mouth ulcers. Clobetasol propionate is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, Latvia, Namibia, New Zealand, and UK, and the US.

The literature review included 17 studies. In the 17 included studies, clobetasol was used as a topical product to treat OLP (6 studies), GVHD (4), psoriasis (3), bullous and mucous membrane pemphigoid (2), Crohn's disease (1), and systemic lupus erythematosus (1). Three of the studies utilized a compounded formulation of clobetasol to treat oral lichen planus and 2 studies used a multi-ingredient product containing clobetasol and calcipotriene to treat psoriasis.

Six of the 7 SMEs interviewed had experience using clobetasol. The SMEs reported using clobetasol for various conditions including lichen planus, vulvodynia, and psoriasis; however, none of the SMEs routinely utilize a compounded formulation; 2 SMEs will prescribe a compounded product if the patient has allergies to the commercially available product. One SME discussed the multi-ingredient products included in the nomination stating that they were likely used to treat various conditions but that the clobetasol was added to reduce itch and inflammation.

As part of Phase 3, 1 nominator provided additional information regarding the multi-ingredient products contained within the clobetasol propionate nomination. Clobetasol 0.05% will be combined as various multi-ingredient topical products to treat seborrheic dermatitis.

Zero people responded to the survey distributed via professional medical associations and available on the project website. Clobetasol propionate was not included on the prequestionnaire.

REFERENCES

1. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *Int J Soc Res Method.* 2005;8(1):19-32.
2. Colquhoun HL, Levac D, O'Brien KK, et al. Scoping reviews: time for clarity in definition, methods, and reporting. *J Clin Epidemiol.* 2014;67(12):1291-1294.
3. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. *Implement Sci.* 2010;5:69.
4. Peters MDJ, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. *Int J Evid Based Healthc.* 2015;13(3):141-146.
5. Munn Z, Peters MDJ, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review?: guidance for authors when choosing between a systematic or scoping review approach. *BMC Med Res Methodol.* 2018;18(1):143.
6. Corazza M, Borghi A, Minghetti S, Toni G, Virgili A. Clobetasol propionate vs. mometasone furoate in 1-year proactive maintenance therapy of vulvar lichen sclerosus: results from a comparative trial. *J Eur Acad Dermatol Venereol.* 2016;30(6):956-961.
7. Gottlieb AB, Ford RO, Spellman MC. The efficacy and tolerability of clobetasol propionate foam 0.05% in the treatment of mild to moderate plaque-type psoriasis of nonscalp regions. *J Cutan Med Surg.* 2003;7(3):185-192.
8. Helgesen AL, Warloe T, Pripp AH, et al. Vulvovaginal photodynamic therapy vs. topical corticosteroids in genital erosive lichen planus: a randomized controlled trial. *Br J Dermatol.* 2015;173(5):1156-1162.
9. Ho N, Pope E, Weinstein M, Greenberg S, Webster C, Krafchik BR. A double-blind, randomized, placebo-controlled trial of topical tacrolimus 0.1% vs. clobetasol propionate 0.05% in childhood vitiligo. *Br J Dermatol.* 2011;165(3):626-632.
10. Jarratt MT, Clark SD, Savin RC, et al. Evaluation of the efficacy and safety of clobetasol propionate spray in the treatment of plaque-type psoriasis. *Cutis.* 2006;78(5):348-354.
11. Langasco R, Tanriverdi ST, Özer Ö, et al. Prolonged skin retention of clobetasol propionate by bio-based microemulsions: a potential tool for scalp psoriasis treatment. *Drug Dev Ind Pharm.* 2018;44(3):398-406.
12. Lebwohl M, Sherer D, Washenik K, et al. A randomized, double-blind, placebo-controlled study of clobetasol propionate 0.05% foam in the treatment of nonscalp psoriasis. *Int J Dermatol.* 2002;41(5):269-274.
13. Lenane P, Macarthur C, Parkin PC, et al. Clobetasol propionate, 0.05%, vs hydrocortisone, 1%, for alopecia areata in children: a randomized clinical trial. *JAMA Dermatol.* 2014;150(1):47-50.
14. Mazzotta A, Esposito M, Carboni I, Schipani C, Chimenti S. Clobetasol propionate foam 0.05% as a novel topical formulation for plaque-type and scalp psoriasis. *J Dermatolog Treat.* 2007;18(2):84-87.
15. Naldi L, Diphorn J. Seborrhoeic dermatitis of the scalp. *BMJ Clin Evid.* 2015;2015.
16. Olsen EA, Cornell RC. Topical clobetasol-17-propionate: review of its clinical efficacy and safety. *J Am Acad Dermatol.* 1986;15(2 Pt 1):246-255.
17. Tan J, Thomas R, Wang B, et al. Short-contact clobetasol propionate shampoo 0.05% improves quality of life in patients with scalp psoriasis. *Cutis.* 2009;83(3):157-164.

18. Tosti A, Iorizzo M, Botta GL, Milani M. Efficacy and safety of a new clobetasol propionate 0.05% foam in alopecia areata: a randomized, double-blind placebo-controlled trial. *J Eur Acad Dermatol Venereol.* 2006;20(10):1243-1247.
19. Virgili A, Borghi A, Toni G, Minghetti S, Corazza M. First randomized trial on clobetasol propionate and mometasone furoate in the treatment of vulvar lichen sclerosus: results of efficacy and tolerability. *Br J Dermatol.* 2014;171(2):388-396.
20. Voigtländer V. A clinical comparison of betamethasone 17,21-dipropionate and clobetasol propionate creams in dermatology. *J Int Med Res.* 1977;5(2):128-131.
21. Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human (CMD-h). *CMDh Scientific conclusions and grounds for variation, amendments to the Product Information, and timetable for the implementation.* London, UK: European Medicines Agency; 2020. PSUSA/00000799/202002.
22. Carbone M, Arduino PG, Carozzo M, et al. Topical clobetasol in the treatment of atrophic-erosive oral lichen planus: a randomized controlled trial to compare two preparations with different concentrations. *J Oral Pathol Med.* 2009;38(2):227-233.
23. Lodi G, Tarozzi M, Sardella A, et al. Miconazole as adjuvant therapy for oral lichen planus: a double-blind randomized controlled trial. *Br J Dermatol.* 2007;156(6):1336-1341.
24. Mays JW, Curtis LM, Bassim C, et al. A randomized phase 2 placebo controlled trial of clobetasol rinse for treatment of oral chronic graft-versus-host disease. *Blood.* 2016;128(22).
25. Noce CW, Gomes A, Shcaira V, et al. Randomized double-blind clinical trial comparing clobetasol and dexamethasone for the topical treatment of symptomatic oral chronic graft-versus-host disease. *Biol Blood Marrow Transplant.* 2014;20(8):1163-1168.
26. Katoh N, Kishimoto S. Combination of calcipotriol and clobetasol propionate as a premixed ointment for the treatment of psoriasis. *Eur J Dermatol.* 2003;13(4):382-384.
27. Sonthalia S, Singal A. Comparative efficacy of tacrolimus 0.1% ointment and clobetasol propionate 0.05% ointment in oral lichen planus: a randomized double-blind trial. *Int J Dermatol.* 2012;51(11):1371-1378.
28. Dogra S, Thakur A, Narang T. Comparison of efficacy of excimer lamp vs. calcipotriol-clobetasol propionate ointment combination in the treatment of palmoplantar psoriasis. *Br J Dermatol.* 2017;177:102-103.
29. Campisi G, Giandalia G, De Caro V, Di Liberto C, Arico P, Giannola LI. A new delivery system of clobetasol-17-propionate (lipid-loaded microspheres 0.025%) compared with a conventional formulation (lipophilic ointment in a hydrophilic phase 0.025%) in topical treatment of atrophic/erosive oral lichen planus. a Phase IV, randomized, observer-blinded, parallel group clinical trial. *Br J Dermatol.* 2004;150(5):984-990.
30. Hettiarachchi P, Hettiarachchi RM, Jayasinghe RD, Sitheequ M. Comparison of topical tacrolimus and clobetasol in the management of symptomatic oral lichen planus: a double-blinded, randomized clinical trial in Sri Lanka. *J Investig Clin Dent.* 2017;8(4).
31. Lafond S, Klepac Pulanic T, Turner M, et al. Genital graft versus host disease: acute versus early onset chronic disease. *Biol Blood Marrow Transplant.* 2011;17(2):S344.
32. Shazib MA, Muhlbauer J, Schweiker R, Li S, Cutler C, Treister N. Long-term utilization patterns of topical therapy and clinical outcomes of oral chronic graft-versus-host disease. *Biol Blood Marrow Transplant.* 2020;26(2):373-379.

33. Fatahzadeh M. Manifestation of psoriasis in the oral cavity. *Quintessence Int.* 2016;47(3):241-247.
34. Wardlaw S, Raza A, Boumitri C. An unexpected cause of dysphagia in a patient hospitalized for nephrectomy. *Am J Gastroenterol.* 2020;115(SUPPL):S1006.
35. Aybar A, Malkani A, Safta A. Continuous topical tacrolimus therapy in oral manifestation of crohn's disease. *Am J Gastroenterol.* 2010;105:S386-S387.
36. Lilly JP, Spivey JD, Fotos PG. Benign mucous membrane pemphigoid with advanced periodontal involvement: diagnosis and therapy. *J Periodontol.* 1995;66(8):737-741.
37. Wester A, Seamens A, Champion R. Genital plaques in a patient with SLE. *J Am Acad Dermatol.* 2019;81(4):AB216.
38. Rodstrom PO, Hakeberg M, Jontell M, Nordin P. Erosive oral lichen planus treated with clobetasol propionate and triamcinolone acetonide in Orabase: a double-blind clinical trial. *J Dermatolog Treat.* 1994;5(1):7-10.
39. Pramick M, Whitmore SE. Cushing's syndrome caused by mucosal corticosteroid therapy. *Int J Dermatol.* 2009;48(1):100-101.
40. Chew AL, Maibach HI. Multiple corticosteroid orally elicited allergic contact dermatitis in a patient with multiple topical corticosteroid allergic contact dermatitis. *Cutis.* 2000;65(5):307-311.

APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy 1

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process, and other non-indexed citations and daily 1946 to February 8, 2021
- Date last searched: February 9, 2021
- Limits: Humans (search hedge); English language
- Number of results: 136

1	clobetasol/	1402
2	clobetasol\$.tw.	1138
3	or/1-2	1854
4	administration, topical/	38,869
5	administration, cutaneous/	22,469
6	skin absorption/	11,852
7	topical\$.tw.	108,716
8	transcutaneous\$.tw.	14,869
9	epicutaneous\$.tw.	2046
10	transdermal\$.tw.	15,012
11	((cutaneous\$ or dermal\$ or skin) adj3 (absorb\$ or absorpt\$ or appl\$)).tw.	11,619
12	exp gels/	53,632
13	emulsions/	18,505
14	suspensions/	7852
15	liniments/	124
16	ointments/	12,863
17	skin cream/	1100
18	pharmaceutical solutions/	3315
19	gel?.tw.	312,538
20	emulsion?.tw.	34,396

21	suspension?.tw.	111,529
22	liniment?.tw.	148
23	ointment?.tw.	12,161
24	salve?.tw.	345
25	paste?.tw.	12,936
26	unguent\$.tw.	114
27	lotion?.tw.	2383
28	cream?.tw.	19,536
29	shampoo?.tw.	1451
30	solution?.tw.	723,147
31	foam?.tw.	26,918
32	or/4-31	1,370,200
33	drug combinations/	74,222
34	niacinamide/	12,600
35	amid\$ pp.tw.	4
36	nicotinamid\$.tw.	21,885
37	niacetamid\$.tw.	0
38	niacinamid\$.tw.	520
39	niacin amid\$.tw.	3
40	nicamid\$.tw.	0
41	nicosedin\$.tw.	0
42	nicotamid\$.tw.	14
43	(nicotinic adj2 amid\$.tw.	115
44	nicotinoylamid\$.tw.	1
45	ni#otinsaureamid\$.tw.	0
46	nikotamin\$.tw.	0

47	vitamin\$ b3.tw.	444
48	vitamin\$ b 3.tw.	54
49	vitamin\$ pp.tw.	164
50	mupirocin/	1253
51	mupirocin\$.tw.	1871
52	pseudomonic acid\$.tw.	89
53	hyaluronic acid/	22,086
54	hyaluron\$.tw.	37,502
55	levocetirizin\$.tw.	415
56	ciclopirox/	407
57	c#clopirox\$.tw.	581
58	tea tree oil/	447
59	((melaleuca or tea or ti) adj2 oil).tw.	761
60	(zinc adj2 (omadine or perythione or pyridinethione or pyrithione)).tw.	311
61	salicylic acid/	6717
62	salicylates/	13,086
63	salicylic acid\$.tw.	13,177
64	carboxyphenol.tw.	6
65	hydroxybenzoic acid\$.tw.	2726
66	ibuprofen/	9038
67	ibuprofen\$.tw.	14,010
68	ibuprophen\$.tw.	29
69	pramocain\$.tw.	6
70	pramoxin\$.tw.	48
71	calcipotri\$.tw.	1204
72	coal tar/	2334

73	((coal or doak) adj tar).tw.	1319
74	exp urea/	116,910
75	carbamid\$.tw.	1521
76	carbonamid\$.tw.	16
77	carbonyldiamid\$.tw.	4
78	karbamid\$.tw.	0
79	karbonamid\$.tw.	0
80	karbonyldiamid\$.tw.	0
81	harnstoff.tw.	8
82	urea.tw.	85,107
83	uree.tw.	107
84	(shark\$ adj cartilag\$).tw.	202
85	ae 941.tw.	31
86	ae941.tw.	1
87	or/33-86	365,021
88	and/3,32,87	150
89	exp animals/ not humans/	4,785,606
90	88 not 89	143
91	limit 90 to english language	136

MEDLINE search strategy 2

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process, and other non-indexed citations and daily 1946 to February 8, 2021
- Date last searched: February 9, 2021
- Limits: Humans (search hedge); English language
- Number of results: 145

1	clobetasol/	1402
2	clobetasol\$.tw.	1138
3	or/1-2	1854
4	administration, buccal/	995
5	administration, intravaginal/	4938
6	administration, mucosal/	268
7	administration, intranasal/	14,938
8	administration, rectal/	2551
9	buccal\$.tw.	28,339
10	intravaginal\$.tw.	5737
11	vaginal\$.tw.	103,087
12	mucosa\$.tw.	238,120
13	mucous\$.tw.	23,321
14	transmucosa\$.tw.	1931
15	transmucous\$.tw.	12
16	intranasal\$.tw.	27,648
17	nasal\$.tw.	119,977
18	rectal\$.tw.	90,872
19	nasal sprays/	570
20	suppositories/	3930
21	“vaginal creams, foams, and jellies”/	1296
22	suppositor\$.tw.	4456

23	semi solid\$.tw.	2395
24	foam?.tw.	26,918
25	jelly.tw.	5204
26	jellies.tw.	290
27	or/4-26	619,909
28	and/3,27	158
29	exp animals/ not humans/	4,785,606
30	28 not 29	158
31	limit 30 to english language	145

Embase search strategy 1

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: February 9, 2021
- Limits: Humans (search hedge); English language
- Number of results: 290

1	'clobetasol propionate'/mj	1228
2	'clobetasol'/mj	436
3	'clobetasol*':ti,ab,tn	1893
4	#1 OR #2 OR #3	2637
5	'topical drug administration'/de	84,147
6	'cutaneous drug administration'/de	748
7	'transdermal drug administration'/de	9274
8	'skin absorption'/de	8166
9	'topical treatment'/de	13,785
10	'topical*':ti,ab	153,843
11	'epicutaneous*':ti,ab	3475
12	'transdermal*':ti,ab	22,001
13	((cutaneous* OR dermal* OR skin) NEAR/3 (absorb* OR absorp* OR appl*)):ti,ab	18,371
14	'cream'/de	9805
15	'gel'/exp	80,973
16	'liniment'/de	256
17	'lotion'/de	2962
18	'ointment'/de	18,247
19	'paste'/de	2550
20	'salve'/de	170
21	'suspension'/de	28,505
22	'emulsion'/exp	47,778

23	'shampoo'/de	2339
24	'foam'/de	8468
25	'cream\$':ti,ab	30,525
26	'emulsion\$':ti,ab	46,525
27	'liniment\$':ti,ab	241
28	'lotion\$':ti,ab	4112
29	'ointment\$':ti,ab	21,977
30	'paste\$':ti,ab	15,463
31	'salve\$':ti,ab	486
32	'unguent*':ti,ab	242
33	'gel\$':ti,ab	368,046
34	'suspension\$':ti,ab	148,248
35	'shampoo\$':ti,ab	2270
36	'solution\$':ti,ab	894,699
37	'foam\$':ti,ab	35,343
38	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37	1,746,954
39	'drug combination'/de	170,429
40	'nicotinamide'/exp	16,724
41	'amid* pp':ti,ab,tn	7
42	'nicotinamid*':ti,ab,tn	26,492
43	'niacetamid*':ti,ab,tn	0
44	'niacinamid*':ti,ab,tn	819
45	'nicamid*':ti,ab,tn	1
46	'nicosedin*':ti,ab,tn	0
47	'nicotamid*':ti,ab,tn	26
48	(nicotinic NEAR/2 acid*):ti,ab,tn	9649

49	'nicotinoylamid*':ti,ab,tn	2
50	'nicotinsaureamid*':ti,ab,tn	6
51	'nikotinsaureamid*':ti,ab,tn	2
52	'nikotamin*':ti,ab,tn	0
53	'vitamin* b3':ti,ab,tn	525
54	'vitamin* b 3':ti,ab,tn	20
55	'vitamin* pp':ti,ab,tn	297
56	'pseudomonic acid'/de	7169
57	'mupirocin*':ti,ab,tn	2661
58	'pseudomonic acid*':ti,ab,tn	128
59	'hyaluronic acid'/de	45,511
60	'hyaluron*':ti,ab,tn	51,099
61	'levocetirizine'/de	1877
62	'levocetirizin*':ti,ab,tn	727
63	'ciclopirox'/de	1157
64	'ciclopirox*':ti,ab,tn	840
65	'cyclopirox*':ti,ab,tn	36
66	'tea tree oil'/de	1320
67	((melaleuca OR tea OR ti) NEAR/2 oil):ti,ab,tn	981
68	'pyrithione zinc'/de	835
69	(zinc NEAR/2 (omadine OR perythione OR pyridinethione OR pyrithione)):ti,ab,tn	401
70	'salicylic acid'/de	26,885
71	'salicylic acid*':ti,ab,tn	15,633
72	'carboxyphenol':ti,ab,tn	9
73	'hydroxybenzoic acid*':ti,ab,tn	3400
74	'ibuprofen'/de	51,807

75	'ibuprofen*':ti,ab,tn	20,019
76	'ibuprophen*':ti,ab,tn	60
77	'pramocaine'/de	337
78	'pramocain*':ti,ab,tn	10
79	'pramoxin*':ti,ab,tn	75
80	'calcipotriol'/de	4227
81	'calcipotri*':ti,ab,tn	1888
82	'coal tar'/de	2959
83	((coal OR doak) NEAR/1 tar):ti,ab,tn	1929
84	'urea'/de	87,086
85	'carbamid*':ti,ab,tn	1675
86	'carbonamid*':ti,ab,tn	30
87	'carbonyldiamid*':ti,ab,tn	6
88	'karbamid*':ti,ab,tn	2
89	'karbonamid*':ti,ab,tn	0
90	'karbonyldiamid*':ti,ab,tn	0
91	'harnstoff':ti,ab,tn	12
92	'urea':ti,ab,tn	116,756
93	'uree':ti,ab,tn	156
94	'shark cartilage'/de	10
95	'shark cartilage extract'/de	23
96	'shark cartilage extract ae 941'/de	11
97	(shark* NEAR/1 cartilag*):ti,ab,tn	264
98	'ae 941':ti,ab,tn	238
99	'ae941':ti,ab,tn	32
100	#39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70	527,150

	OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99	
101	#4 AND #38 AND #100	344
102	[animals]/lim NOT [humans]/lim	6,165,344
103	#101 NOT #102	328
104	#101 NOT #102 AND [english]/lim	290

Embase search strategy 2

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: February 9, 2021
- Limits: Humans (search hedge); English language
- Number of results: 296

1	'clobetasol propionate'/mj	1228
2	'clobetasol'/mj	436
3	'clobetasol*':ti,ab,tn	1893
4	#1 OR #2 OR #3	2637
5	'buccal drug administration'/de	704
6	'rectal drug administration'/de	8782
7	'intranasal drug administration'/de	15,076
8	'intravaginal drug administration'/de	6547
9	'mucosal drug administration'/de	472
10	'buccal*':ti,ab	36,469
11	'intravaginal*':ti,ab	8155
12	'vaginal*':ti,ab	161,410
13	'mucosa*':ti,ab	343,731
14	'mucous*':ti,ab	39,430
15	'transmucosa*':ti,ab	2583
16	'transmucous*':ti,ab	28
17	'intranasal*':ti,ab	37,667
18	'nasal*':ti,ab	168,494
19	'rectal*':ti,ab	144,916
20	'nose spray'/de	3314
21	'suppository'/de	6153
22	'transmucosal drug delivery system'/de	142

23	'agents used intravaginally'/exp	310,022
24	'suppositor*':ti,ab	7250
25	'semi solid*':ti,ab	3319
26	'foam\$':ti,ab	35,343
27	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26	1,192,445
28	#4 AND #27	347
29	[animals]/lim NOT [humans]/lim	6,165,344
30	#28 NOT #29	331
31	#28 NOT #29 AND [english]/lim	296

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 clobetasol propionate to your patients?

- Yes
- No

3. Do you prescribe or administer clobetasol propionate 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
- Vaginal products
- None of the above

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

- Alopecia areata
- Eczema
- Herpes labialis
- Lichen sclerosus
- Mouth ulcers
- Mycosis fungoides
- Onychomycosis
- Psoriasis
- Seborrheic dermatitis
- Tinea corporis, cruris, pedis
- Vaginal irritation/pain (vulvodynia)
- Vaginal lichen planus
- Vitiligo
- Other (please explain) _____

5. I prescribe or administer compounded clobetasol propionate in combination with other active pharmaceutical ingredients as a multi-ingredient product.

- Yes
- No

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

- FDA-approved drug products
 - Compounded drug products
 - Over-the-counter products
 - Other (please explain) _____
7. I use compounded clobetasol propionate 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 clobetasol propionate
 - Other (please explain) _____
8. Do you stock non-patient-specific compounded clobetasol propionate at your practice?
- Yes
 - No
 - I'm not sure
9. I obtain compounded clobetasol propionate 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
 - Calcium chloride
 - Caffeine sodium benzoate
 - Cholecalciferol
 - Chromium chloride
 - Clonidine
 - Dexamethasone sodium phosphate
 - Diclofenac
 - Gentamicin
 - Glycerin
 - Hydroxyzine
 - Ketamine
 - Levocarnitine
 - Lidocaine
 - Lorazepam
 - Magnesium sulfate
 - Manganese chloride
 - Methylprednisolone
 - Midazolam
 - Mupirocin
 - Norepinephrine
 - Ondansetron
 - Phytonadione
 - Potassium chloride
 - Potassium phosphate
 - Prilocaine
 - Proline
 - Propranolol
 - Ropivacaine
 - Sodium chloride
 - Sodium citrate

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

Appendix 3. Survey distribution to professional associations

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

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