Summary Report

Terbinafine hydrochloride

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

API	Active Pharmaceutical Ingredient
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
IRB	Institutional Review Board
IV	Intravenous
OTC	Over-the-counter
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ROA	Route of administration
SME	Subject matter expert
UK	United Kingdom
US	United States
USP	United States Pharmacopeia

INTRODUCTION

This report was created to assist the Food and Drug Administration (FDA) in its evaluation of the use of terbinafine hydrochloride (terbinafine HCl; UNII code: 012C11ZU6G), 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 terbinafine HCl is used in clinical research and practice to diagnose, prevent, or treat disease. Because of the broad, exploratory nature of this aim, scoping review methodology was used. Following the scoping review framework, a systematic literature review was conducted, and healthcare practitioners were consulted to identify how terbinafine HCl 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 terbinafine HCl 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

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

Terbinafine HCl was nominated for treatment of fungal infections of the skin, including athlete's foot, jock itch, and ringworm, via a topical cream, gel, ointment, suspension, and solution in strengths based on the prescriber's request, with therapeutic doses ranging from 1 to 5%.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of terbinafine HCl.[6-14]

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

- Compounded product may be the only product to effectively treat the indication for which it is intended.
- Patient need for dosage form or strength, including greater concentration, that is not available commercially.
- Patient sensitivities to dyes, fillers, preservatives, or other excipients in manufactured products.
- Need for accuracy; individual finished products vary widely in the actual API, and use of a finished product has the potential to introduce unacceptable inaccuracies into the compounded medication.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of terbinafine HCl 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 English language; and desired information, specifically product trade name, active ingredient, strength, form, route of administration (ROA), and approval status, provided in a usable format. Based on these criteria, the

medicine registers of 13 countries/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 terbinafine HCl; name variations of terbinafine HCl 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, and approval date. Information was recorded only for products with strengths, forms, and/or ROAs similar to those requested in the nominations.

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

Systematic literature review

Search strategy

A medical librarian constructed comprehensive search strategies for Ovid MEDLINE and Embase. The search strategies used a combination of controlled vocabulary terms and keywords to describe three concepts: terbinafine, topical administration or form, and substances nominated for use in combination with terbinafine (refer to Appendix 1 for full search strategies). A literature review was not conducted for topical single-ingredient terbinafine products because of the availability of FDA-approved single-ingredient terbinafine products for this ROA. Results were limited to human studies in the English language. Searches were conducted on February 13, 2021. In addition, the ECRI Guidelines Trust® repository was searched on February 13, 2021 for clinical practice guidelines that recommended the use of terbinafine and provided sufficient information on dosing and administration.

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

Study selection

Studies in which terbinafine HCl 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 terbinafine HCl was used as: an FDA-approved product in the nominated dosage form, ROA, or combination; an unspecified dosage form or ROA; or a dosage form, ROA, or combination that was not nominated. Studies in which terbinafine HCl was used to diagnose, prevent, or treat autism were excluded because of a separate project examining the use of compounded substances for patients with autism. Studies that did not meet the inclusion criteria but provided valuable information about the pharmacological or current or historical use of the substance were

noted and put in a separate group in the EndNote library. Two reviewers independently screened titles and abstracts and reviewed full-text articles. A third reviewer reconciled all disagreements.

Data extraction

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

Interviews

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

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

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

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

CURRENT AND HISTORIC USE

Results of background information

- Terbinafine HCl is available as an FDA-approved OTC product in the nominated dosage form and ROA.
- There is a current United States Pharmacopeia (USP) monograph for terbinafine HCl.
- Terbinafine HCl is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Canada, Hong Kong, Ireland, Namibia, New Zealand, Saudi Arabia, and the UK. In addition, terbinafine HCl is available as an OTC product in the nominated dosage form and ROA in Australia, Belgium, Hong Kong, Latvia, New Zealand, and the UK.

Table 1. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Status	Approval Date[b]
Terbinafine HCl	1%	Cream Solution Spray	Topical	OTC	3/9/1999
Terbinafine	1%	Gel	Topical	OTC	7/24/2006

Abbreviation: OTC, over-the-counter.

[a]Source: US FDA *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).

[b]If multiple approval dates and/or multiple strengths, then earliest date provided.

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

Active Ingredient	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date[b]
Terbinafine HCl	1%	Cream Gel Solution Spray	Cutaneous Topical	Abu Dhabi	Active	—
				Australia	Pharmacy medicine[c]	8/24/1993
				Canada	Prescription	12/31/1991
				Hong Kong	Pharmacy only[c]	5/15/2008
				Ireland	Prescription only renewable and pharmacy only[c]	7/12/1993
				Namibia	—	12/28/2003
				New Zealand	Pharmacy[c]	6/25/1992
				Saudi Arabia	Pharmacy[c]	—
				UK	Prescription only medicine and pharmacy[c]	10/3/1990

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

[a]Medicine 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, route of administration [ROA], and approval status) provided in a usable format. Information was recorded only for products with strengths, forms, and/or ROAs similar to those requested in the nominations. See *Methodology* for full explanation.

[b]If multiple approval dates and/or multiple strengths, then earliest date provided.

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

Results of literature review

Study selection

Database searches yielded 814 references; 0 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 558 titles and abstracts were screened. After screening, the full text of 165 articles was reviewed. Finally, 0 studies were included. One hundred sixty-five studies were excluded for the following reasons: wrong study design (157 studies), FDA-approved formulation (3), wrong substance (3), or duplicate study (2).

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

Characteristics of included studies

No studies were included from the literature review.

Use of terbinafine HCl

No studies were included from the literature review.

Pharmacology and historical use

There were 11 studies identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of terbinafine HCl.

Terbinafine is an allylamine antifungal agent that "selectively inhibits fungal squalene epoxidase" with "broad-spectrum activity against yeast, fungi, molds, and dermatophytes."[7,11,13] Available in oral and topical formulations, terbinafine has been used to treat skin and nail fungal infections.[11] The oral formulations are FDA approved for the treatment of onychomycosis of the toenails and fingernails due to dermatophyte infection.[15] Although terbinafine is used mostly to treat dermatophyte infections, it has shown "high in vitro activity against *Aspergillus* and other filamentous fungi."[11]

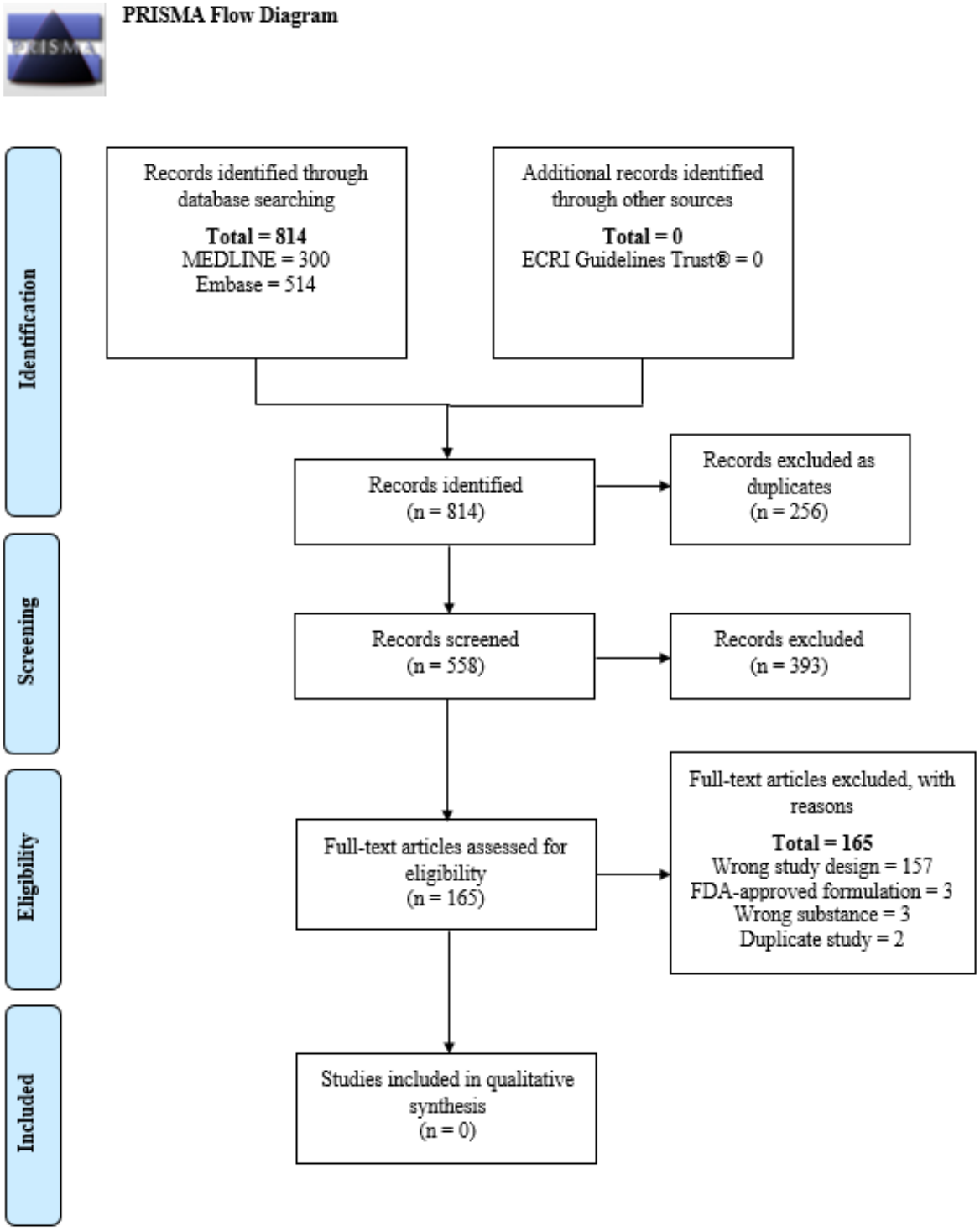
The skin is the largest organ of the body and is "home to millions of bacteria, fungi and viruses that compose the skin microbiota."[16] These microorganisms play important roles in the "protection against invading pathogens, the education of our immune system and the breakdown of natural products."[16] Bacteria constitute the largest proportion of the skin microbiota, and fungi are the least abundant.[16] The types of bacteria that colonize the skin depend on the physiology of the skin site.[16] For example, *Propionibacterium* is found predominantly in sebaceous sites, such as the face, chest, or back, whereas *Staphylococcus* and *Corynebacterium* are generally found in more humid areas, such as the bends of the elbows and feet.[16] Fungal colonization is not as dependent on the physiology of the skin site and therefore is similar across the body.[16] *Malassezia*, *Aspergillus*, *Cryptococcus*, *Rhodotorula*, and *Epicoccum* are a few of the fungi that are found on the skin.[16]

Fungal skin infections are due predominantly to *Candida albicans*, *Trichophyton*, *Epidermophyton*, *Microsporum*, and *Malassezia*.[17] Dermatophytes, which include *Trichophyton*, *Epidermophyton*, and *Microsporum*, are the most common pathogens identified in skin infections.[18] Dermatophytes need keratin for growth and therefore invade keratinized tissue, such as the skin, hair, and nails, resulting in "tinea" infections including tinea capitis, tinea barbae, tinea corporis, tinea cruris, tinea manus, tinea pedis, and tinea unguium.[17,19-21] Superficial fungal infections can be treated with either topical or oral antifungal agents. Typically, fungi infect the skin surface and "invade the stratum corneum to avoid being shed from the skin surface by desquamation."[22] Topical antifungal agents can penetrate

the stratum corneum and act as either a fungicidal agent killing the fungi or as a fungistatic agent that "renders them unable to grow or divide."[22] Systemic absorption of topical antifungal agents is minimal, so safety is less of a concern than with oral antifungal agents.[22] Topical antifungal agents are generally effective for treating tinea corporis, tinea cruris, and tinea pedis, whereas systemic treatment is typically needed for tinea capitis, tinea barbae, and tinea unguium.[23] *Malassezia* is the organism thought to be responsible for seborrheic dermatitis due to an abnormal host response and is treated with medicated shampoos.[23]

Onychomycosis is a fungal infection of the nail that causes "discoloration, thickening, and separation from the nail bed."[24] Typically, onychomycosis affects the toenails more frequently than the fingernails because of the "slower growth, reduced blood supply, and frequent confinement in dark, moist environments."[24] The prevalence increases with increasing age because of the presence of additional comorbidities such as peripheral vascular disease, immunologic disorders, and diabetes mellitus.[24] Onychomycosis is generally caused by infection with the dermatophyte *Trichophyton*, with *Candida* and nondermatophyte molds constituting a smaller portion of infections.[24] Although onychomycosis is commonly referred to as a cosmetic problem, it can be uncomfortable for patients and may lead to other infections. Treatment depends on "the severity of nail changes, the organism involved, and concerns about adverse effects and drug interactions."[24] However, treatment can be challenging because of the poor penetration of drugs through the nail, leading to patients not seeing results for a year.[24] The antifungals that belong to the azole and allylamine classes are the most frequently used oral medications.[24] A 2004 meta-analysis found that terbinafine has a 76% mycologic cure rate, itraconazole has a 59-63% cure rate, fluconazole has a 48% cure rate, and griseofulvin has a 60% cure rate.[25] Topical treatment options, such as ciclopirox and clotrimazole, are currently available, however, there is minimal evidence demonstrating that topical antifungals are effective in the treatment of onychomycosis.[24,26]

Figure 1. PRISMA flow diagram showing literature screening and selection.



Adapted from:
Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006-1012. Available from: http://www.prisma-statement.org/.

Table 3. Types of studies

No studies were included.

Table 4. Number of studies by country

No studies were included.

Table 5. Summary of included studies

No studies were included.

Table 6. Dosage by indication – US

No studies were included.

Table 7. Dosage by indication – non-US countries

No studies were included.

Table 8. Number of studies by combination

	Combination Formula	**Number of Studies**
Nominated	Terbinafine HCl 5% / DMSO 95% – topical solution	0
	Terbinafine HCl 1% / Ciclopirox 8% / Fluconazole 1% – topical solution	0
	Terbinafine HCl 4% / Fluconazole 4% / Ibuprofen 2% / Itraconazole 1% – topical solution	0
	Terbinafine HCl 4% / Ciclopirox 2% / Ibuprofen 2% / Itraconazole 1% / Urea 10% – topical gel	0

Abbreviation: DMSO, dimethyl sulfoxide.

Table 9. Compounded products – US

No studies were included.

Table 10. Compounded products – non-US countries

No studies were included.

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. Three SMEs discussed terbinafine HCl. Among these 3 SMEs were 1 medical doctor and 2 doctors of podiatric medicine. The SMEs specialized and/or were board certified in dermatology and podiatry, working in academic medical institutions and hospital settings. The SMEs had been in practice for 1 to 40 years. Additional information was collected as part of the Expanded Information Initiative, referred to as phase 3, project in which outreach was conducted to the nominators of the bulk drug substances to remedy information gaps in the initial nomination.

When treating topical fungal infections, one SME stated that the location of the fungus determines the type of product used. For example, ketoconazole shampoo works well for tinea versicolor; however, topical products are generally ineffective for onychomycosis, so systemic agents are typically preferred. Oral terbinafine is typically the drug of choice for treating onychomycosis because it has "the best efficacy of any treatment we have FDA approved for onychomycosis." Terbinafine has been associated with liver toxicity, so if a patient does not want to take an oral medication, alternatives are available, such as efinaconazole, tavaborole, and ciclopirox lacquer, that have been studied and are FDA approved for treating onychomycosis. If there is a fungus between the toes, then topical terbinafine would be effective, but this is commercially available and available OTC.

The SMEs were unsure of the reasons for the nominated combinations. One SME stated that they had not seen a fungal infection that would necessitate treatment with multiple fungal agents, saying that the combination of 2 azoles "doesn't really make sense." Another SME stated, "certainly, I hope it's not onychomycosis because there is no literature whatsoever to show that these topical creams or topical formulations of itraconazole fluconazole work in onychomycosis." Even if the formulations are intended to treat tinea pedis, the SME stated that meta-analyses have shown that terbinafine is more effective than any of the azole antifungals for tinea pedis and is available OTC.

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

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

Terbinafine HCl 4%/ciclopirox oleate 2%/ibuprofen 2%/itraconazole 1%/urea 10% will be compounded as a topical solution to treat fungal infections of the skin, 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: ethyl acetate, polysorbate 60, and mineral oil, which are components of commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include skin irritants and possible human carcinogen. Terbinafine is added for its antifungal properties, ciclopirox for its antifungal properties, ibuprofen for its anti-inflammatory properties, itraconazole for its antifungal properties, and urea for its moisturizing properties. This product is needed because it will result in a clinical difference to patients because it does not include harmful excipients found in FDA-approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Terbinafine HCl 4%/fluconazole 4%/ibuprofen 2%/itraconazole 1% will be compounded as a topical solution to treat fungal infections of the skin, 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. None of the active ingredients contained within this product are available as an FDA-approved drug intended for topical administration. Terbinafine is added for its antifungal properties, fluconazole for its skin conditioning benefits, ibuprofen for its anti-inflammatory properties, and itraconazole for its antifungal properties. This product is needed because it will result in a clinical difference to patients because it does not include harmful excipients found in FDA-approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Terbinafine HCl 1%/ciclopirox oleate 8%/fluconazole 1% will be compounded as a topical solution to treat fungal infections of the skin, 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: ethyl acetate, polysorbate 60, and mineral oil, which are components of commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include skin irritants and possible human carcinogen. Terbinafine is added for its antifungal properties, ciclopirox for its antifungal properties, and fluconazole for its skin conditioning benefits. This product is needed because it will result in a clinical difference to patients because it does not include harmful excipients found in FDA-approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

Terbinafine HCl 5%/DMSO 95% will be compounded as a topical solution to treat fungal infections of the skin, 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. None of the active ingredients contained within this product are available as an FDA-approved drug intended for topical administration. Terbinafine is added for its antifungal properties. This product is needed because it will result in a clinical difference to patients because it does not include harmful excipients found in FDA-approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

A roundtable discussion with representatives from a variety of practice settings was held to discuss the use of outsourcing facilities to obtain compounded products. Forty-three participants attended the event; refer to Table 16 for characteristics of the facilities that the participants represented. A prequestionnaire was also distributed to participants; refer to Tables 16-19 for results of the prequestionnaire.

Although a majority of the participants purchased some compounded products from an outsourcing facility, the percentage of products obtain 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 a problem with a product compounded from one outsourcing facility, minimizing the impact to the participant's facility.

Participants were asked to discuss the decision-making process used at their facility to determine what products to obtain from an outsourcing facility. One major theme that emerged from this discussion was that many of the products purchased from outsourcing facilities are used in critical care areas, such as emergency departments and operating rooms. Participants commented that outsourcing facilities are able to provide ready-to-use products that have longer beyond-use dates than products compounded in-house, allowing these products to be stocked in automated dispensing cabinets in these units. One participant commented 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 because they face a unique need in that they already have to perform a lot of manipulations to products because of a lack of concentrations or sizes available. One participant commented that "at baseline, already, we manipulate about 80% of what we dispense to patients," and another stated that "there's a number of drugs that require additional manipulation, to get them to a concentration that's appropriate for kids." One participant stated 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, such as vasopressor infusions, to prevent compounding from occurring on the floor, and another commented that "we absolutely buy as many pressor drips as we can." One participant remarked that they have received requests from anesthesiologists for products that are commercially available in vials that require manipulation before administration to be purchased as syringes from outsourcing facilities, stating that "they would prefer to have a syringe form."

Another theme regarding deciding what products to purchase from an outsourcing facility was focused on the use rate and volume of a product that is needed and the overall impact this would have on the pharmacy workload. Critical care areas, such as the emergency department and operating room, typically have a high product use rate and overall turnover, leading to several participants obtaining products intended for use in these areas from outsourcing facilities. Participants stated that they evaluate the volume of product needed and the frequency with which that volume is needed compared with the time it would take pharmacy staff to prepare this volume. One participant commented 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, although they do not obtain a lot of products from outsourcing facilities, stated that "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 complex products, such as epidurals and cardioplegia solutions, from outsourcing facilities to reduce the workload on pharmacy staff. The COVID-19 pandemic has also affected the operations of hospitals. One participant 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 stated that "without 503B, we would've been in significant trouble." One participant commented that "even though the number might be small [as a percentage of products obtained from outsourcing facilities], some of the

reasoning is quite critical, and the amount of time that it saves is very significant for . . . what we're able to do and when." Additionally, challenges with recruiting and retaining pharmacy technicians affect decision making, with one participant stating, "it is not feasible for us to meet the high volume for some common medications to repackage or compound from commercial presentations to a convenient, ready-to-use dosage form or package. The outsourcing facilities thus become a force multiplier, if you will, to offset some of the shortages in staffing."

In addition to the evaluation of the workload on pharmacy staff, the type and capabilities of the facility also affected the decision-making process. One participant commented that they do not have an established clean room and therefore perform sterile compounding in a segregated compounding area. USP <797> standards limit the beyond-use date that can be assigned to these products, and, as the participant stated, "we obviously need to provide product with much 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 used. However, the products used in a facility are often developed in-house over decades, based on physician and nurse requests and, more recently, appropriateness for an automated dispensing cabinet. As a result, one participant observed, "these practices had evolved somewhat disparately; even if we had clinical practice guidelines, nobody was putting concentrations into those guidelines and volumes into those guidelines." This has led to challenges with obtaining certain products from outsourcing facilities. As another participant said, "I think we made nine 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, although 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 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 Hospital 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 problems 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 using API only if there is a shortage, stating, “I think the FDA has really looked closely at API, and they’re slowly pushing the 503B outsourcers to a sterile-to-sterile.” Only 1 participant commented that they prefer sterile-to-sterile. Another participant stated that the companies they use are all sterile-to-sterile.

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

conditioning], so you're talking millions of dollars in investment for actually very low volume. Right now, the ROI [return on investment] isn't there." Another participant stated that the concentrations needed for ophthalmic antibiotics are not available, but the labor and risk of compounding these products in-house is not worth it.

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

Based on the responses to the prequestionnaire (refer to *Results of survey*), participants were asked questions about specific products obtained from outsourcing facilities. Several participants reported using alum (aluminum potassium) as a bladder irrigation for hemorrhagic cystitis refractory to other treatment options. Participants commented that this is high-risk compounding; they purchase alum from an outsourcing facility because they do not perform high-risk compounding in their facility. One participant commented that their policy states that high-risk compounding is not allowed except for alum. This participant wanted to move away from compounding alum in-house and stated that the addition of aluminum potassium to the bulks list might allow this to happen. Another participant had compounded alum in-house from nonsterile ingredients; however, there were challenges with crystallization after storage. A few participants commented that a sterile alum powder is available, which they purchase to compound in-house. One participant had concerns about this powder, stating, "I've talked to that company, but I've had some concerns for them because they don't sell it as a drug. The owner was selling you a chemical, we're selling you a bulk API. It's just sterile. They were fuzzy, and I never followed up, but when I asked about their process for verifying the sterility, as you would with a sterile product, we do USP <71> Sterility Testing. They couldn't really give me an answer. They just say they tested for sterility." The participants commented that alum is needed only a few times a year. However, as one participant observed, "when you need it, it's an emergency," and another noted that it "is a challenge for anybody who has the cyclophosphamide-induced hemorrhagic cystitis." As a result, one participant maintains a small inventory of alum product that is purchased from an outsourcing facility, but "more times than not, they go unused and expire." Another stated that they do not keep it in stock because there is a minimum purchase, and there are only a few patients a year for whom they need to use alum. The participant had it STAT shipped when needed. Another participant stated 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 purchased 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 if glycerin is used "it can go 3 months or something like that, so it's a huge patient satisfier to have that concentration available." The participant also commented that because they have been unable to find an outsourcing facility that compounds the concentration needed for trigeminal neuralgia, they have patients who have been waiting years for treatment. The other participant stated that they compound it in-house but said that it is not done very frequently. The participant commented that it is very difficult to sterilize because of the thickness of the product.

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

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

Although none of the participants obtained sodium phosphate or aspartic acid from outsourcing facilities for use in cardioplegic solutions, a few commented that they do obtain cardioplegic solutions from outsourcing facilities. The del Nido formulation was the product most commonly obtained. One participant commented that they compound this formulation in-house because the outsourcing facilities did not offer the volume needed at their institution. Another participant commented that although they obtain the del Nido formulation from an outsourcing facility, they also compound a proprietary formulation in-house. This participant observed that "it is complicated to do in-house. We do it on a Baxa 1200 or 2,400 . . . compounder. Then we send it up to 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 using outsourcing facilities. One participant stated that their facility does not use outsourcing facilities because "it just hasn't been financially, not just the money worth it, but just the lead time for how much time you have to give them 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 because of the "the amount of work for vetting and continually validating quality of these 503B outsourcing facilities." The participant stated that they have a robust validation process that takes several months and includes a site visit before purchase from an outsourcing facility, followed by continuous review of quality reports and warning letters. Another challenge has been the reliability of the outsourcing facility. One participant commented that "we've found 503Bs to be fairly unreliable, when we have partnered with certain ones, to be able to keep up with the volume. Everybody knows PharMEDium just closed, but we've had some other smaller 503Bs where we've had agreements for certain products to take it off our plate, and then lo and behold they're shut down, or closed, or whatever it may be." Minimum purchase amounts were also reported as a concern, with one participant stating that "what we see consistently is the 503Bs, they want us to commit to giving them a certain

volume but then will not give us a reciprocal commitment or at least will not fulfill that reciprocal commitment. That's a huge problem for us making that type of commitment, when we do ultimately have to split our volume in order to make sure that we consistently are able to take care of our patients." Another challenge was related to outsourcing facilities using API to compound narcotics. One participant commented that this often worsens drug shortages because of the quotas that the Drug Enforcement Administration places on the quantity that can be produced. The participant stated that "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

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

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

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

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

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

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

Table 11. Characteristics of survey respondents

Survey not distributed by any professional medical associations.

Table 12. Compounded products prescribed or administered

Survey not distributed by any professional medical associations.

Table 13. Reasons for using compounded products

Survey not distributed by any professional medical associations.

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

Survey not distributed by any professional medical associations.

Table 15. Obtainment of compounded topical products

Survey not distributed by any professional medical associations.

Table 16. Demographics of prequestionnaire respondents' facilities

Type of Facility	**Responses, n (N = 102)[a]**
Academic medical center	15
Acute care hospital	16
Children's hospital	8
Community hospital	11
Critical access hospital	2
Dialysis center	2
Federal government hospital	4
Health system	15
Inpatient rehabilitation center	4
Long-term acute care hospital	3
Outpatient surgery center	6
Rural hospital	2
Skilled nursing facility	0
Specialty hospital[b]	4
Trauma center	5
Urban hospital	5
Number of Beds	**Responses, n (N = 39)**
< 50	4
50-99	3
100-199	1

200-299	4
300-399	5
400-599	3
> 600	19

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

Table 17. Reasons for obtaining products from outsourcing facilities

Categories	Responses, n (N = 143)[a]
Backorders	20
Convenience	19
Cost	10
Need for concentrations not commercially available	19
Need for multi-ingredient products not commercially available	10
Need for preservative-free products	3
Need for ready-to-use products	27
No FDA-approved product available	7
No onsite compounding facility	1
Onsite compounding facility not equipped to compound all necessary products	19
Other[b]	8

[a]Respondents were allowed to select multiple categories.
[b]Respondents reported staffing shortages, need for extended dating, volume of product used, and standardization projects as additional reasons for using outsourcing facilities.

Table 18. Categories of products obtained from outsourcing facilities

Categories	Responses, n (N = 142)[a]
Cardioplegic solutions	14
Dermatologic preparations	6

Dialysate solutions	0
Fluids	8
Ophthalmic preparations	10
Patient-controlled analgesia	20
Ready-to-use anesthesia syringes	25
Ready-to-use antibiotic syringes and/or bags	14
Ready-to-use electrolyte solutions	5
Ready-to-use vasopressor solutions	18
Total parenteral nutrition solutions	16
Other[b]	6

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

Table 19. Products obtained from an outsourcing facility

Product	**Responses, n (N = 108)[a]**
Acetylcysteine	1
Adenosine	2
Aluminum potassium sulfate	2
Aspartic acid	0
Atenolol	0
Atropine	9
Baclofen	4
Betamethasone	0
Biotin	0
Bupivacaine	8
Caffeine sodium benzoate	0
Calcium chloride	1

Cholecalciferol	1
Chromium chloride	0
Clonidine	0
Dexamethasone sodium phosphate	0
Diclofenac	0
Gentamicin	0
Glycerin	1
Hydroxyzine	0
Ketamine	14
Levocarnitine	0
Lidocaine	8
Lorazepam	2
Magnesium sulfate	4
Manganese chloride	0
Methylprednisolone	0
Midazolam	15
Mupirocin	1
Norepinephrine	15
Ondansetron	0
Phytonadione	0
Potassium chloride	0
Potassium phosphate	0
Prilocaine	0
Proline	0
Propranolol	1
Ropivacaine	6

Sodium chloride	0
Sodium citrate	3
Sodium phosphate	0
Tetracaine	2
Triamcinolone acetonide	0
Tropicamide	0
None of the above	8

[a]Respondents were allowed to select multiple products.

CONCLUSION

Terbinafine HCl was nominated for inclusion on the 503B Bulks List as a topical cream, gel, ointment, suspension, or solution in concentrations ranging from 1% to 5% to treat fungal infections of the skin. Terbinafine HCl is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, Latvia, Namibia, New Zealand, Saudi Arabia, the UK, and the US.

No studies were included from the literature review.

From the interviews, topical products are generally ineffective for the treatment of onychomycosis, with oral terbinafine being the drug of choice, which is commercially available. Two of the SMEs use the commercially available topical terbinafine, and 1 has used only the oral formulation. The SMEs were unsure of the reasons for the nominated combinations.

As part of phase 3, 1 nominator provided additional information about the multi-ingredient products contained within the terbinafine HCl nomination. Terbinafine HCl will be compounded as various topical dosage forms in combination with additional APIs to treat fungal infections of the skin.

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

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. Villars V, Jones TC. Clinical efficacy and tolerability of terbinafine (Lamisil)--a new topical and systemic fungicidal drug for treatment of dermatomycoses. *Clin Exp Dermatol.* 1989;14(2):124-127.
7. Korting HC, Kiencke P, Nelles S, Rychlik R. Comparable efficacy and safety of various topical formulations of terbinafine in tinea pedis irrespective of the treatment regimen: results of a meta-analysis. *Am J Clin Dermatol.* 2007;8(6):357-364.
8. Çelebi N, Ermiş S, Özkan S. Development of topical hydrogels of terbinafine hydrochloride and evaluation of their antifungal activity. *Drug Dev Ind Pharm.* 2015;41(4):631-639.
9. Ortonne JP, Korting HC, Viguié-Vallanet C, Larnier C, Savaluny E. Efficacy and safety of a new single-dose terbinafine 1% formulation in patients with tinea pedis (athlete's foot): a randomized, double-blind, placebo-controlled study. *J Eur Acad Dermatol Venereol.* 2006;20(10):1307-1313.
10. Brown M, Evans C, Muddle A, et al. Efficacy, tolerability and consumer acceptability of terbinafine topical spray versus terbinafine topical solution: a phase IIa, randomised, observer-blind, comparative study. *Am J Clin Dermatol.* 2013;14(5):413-419.
11. Ozcan I, Abaci O, Uztan AH, et al. Enhanced topical delivery of terbinafine hydrochloride with chitosan hydrogels. *AAPS PharmSciTech.* 2009;10(3):1024-1031.
12. Sudhakar B, Varma JN, Murthy KV. Formulation, characterization and ex vivo studies of terbinafine HCl liposomes for cutaneous delivery. *Curr Drug Deliv.* 2014;11(4):521-530.
13. Tanrıverdi ST, Özer Ö. Novel topical formulations of Terbinafine-HCl for treatment of onychomycosis. *Eur J Pharm Sci.* 2013;48(4-5):628-636.
14. Hui X, Lindahl Å, Lamel S, Maibach HI. Onychopharmacokinetics of terbinafine hydrochloride penetration from a novel topical formulation into the human nail in vitro. *Drug Dev Ind Pharm.* 2013;39(9):1401-1407.
15. *Lamisil (terbinafine hydrochloride) tablets [package insert].* East Hanover, New Jersey: Novartis Pharmaceuticals Corporation;2012.
16. Byrd AL, Belkaid Y, Segre JA. The human skin microbiome. *Nat Rev Microbiol.* 2018;16(3):143-155.
17. O'Dell ML. Skin and wound infections: An overview. *Am Fam Physician.* 1998;57(10):2424-2432.
18. Hainer BL. Dermatophyte infections. *Am Fam Physician.* 2003;67(1):101-108.

19. Akhtar N, Verma A, Pathak K. Topical delivery of drugs for the effective treatment of fungal infections of skin. *Current Pharmaceutical Design.* 2015;21(20):2892-2913.

20. Kyle AA, Dahl MV. Topical therapy for fungal infections. *Am J Clin Dermatol.* 2004;5(6):443-451.

21. Weitzman I, Summerbell RC. The dermatophytes. *Clin Microbiol Rev.* 1995;8(2):240-259.

22. Kaur IP, Kakkar S. Topical delivery of antifungal agents. *Expert Opinion on Drug Delivery.* 2010;7(11):1303-1327.

23. Farage MA, Miller KW, Berardesca E, Maibach HI. Clinical implications of aging skin: Cutaneous disorders in the elderly. *American Journal of Clinical Dermatology.* 2009;10(2):73-86.

24. Westerberg D, Voyack M. Onychomycosis: current trends in diagnosis and treatment. *American Family Physician.* 2013;88(11):762-770.

25. Gupta A, Ryder J, Johnson A. Cumulative meta-analysis of systemtic antifungal agents for the treatment of onychomycosis. *British Journal of Dermatology.* 2004;150.

26. Crawford F, Hollis S. Topical treatments for fungal infections of the skin and nails of the foot. *Cochrane Database Systematic Reviews.* 2007(3):CD001434.

APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process, and other nonindexed citations and daily 1946 to February 12, 2021
- Date last searched: February 13, 2021
- Limits: Humans (search hedge); English language
- Number of results: 300

1	terbinafine/	1846
2	terbinafin$.tw.	2660
3	or/1-2	3014
4	administration, topical/	38,886
5	administration, cutaneous/	22,493
6	skin absorption/	11,855
7	topical$.tw.	108,833
8	transcutaneous$.tw.	14,873
9	epicutaneous$.tw.	2045
10	transdermal$.tw.	15,041
11	((cutanous$ or dermal$ or skin) adj3 (absorb$ or absorpt$ or appl$)).tw.	11,633
12	exp gels/	53,688
13	emulsions/	18,530
14	suspensions/	7853
15	liniments/	124
16	ointments/	12,868
17	skin cream/	1105
18	pharmaceutical solutions/	3317
19	gel?.tw.	312,713
20	emulsion?.tw.	34,454

21	suspension?.tw.	111,632
22	liniment?.tw.	148
23	ointment?.tw.	12,169
24	salve?.tw.	345
25	paste?.tw.	12,963
26	unguent$.tw.	114
27	lotion?.tw.	2385
28	cream?.tw.	19,557
29	shampoo?.tw.	1451
30	solution?.tw.	724,061
31	foam?.tw.	26,949
32	or/4-31	1,371,643
33	drug combinations/	74,273
34	ciclopirox/	407
35	c#clopirox$.tw.	582
36	dimethyl sulfoxide/	14,951
37	dmso.tw.	19,281
38	dimethylsulfox#d$.tw.	4638
39	dimethyl$ sulfox#d$.tw.	12,446
40	dimethylsulphox#d$.tw.	892
41	dimethyl$ sulphox#d$.tw.	1372
42	dimethyl$ sulfur oxid$.tw.	0
43	dimethyl sulphur oxid$.tw.	1
44	methyl$ sulfo#d$.tw.	0
45	methylsulfo#d$.tw.	0
46	methyl$ sulpho#d$.tw.	0

47	methylsulpho#d$.tw.	0
48	methylsulfinylmethan$.tw.	3
49	methyl$ sulfinylmethan$.tw.	0
50	fluconazole/	7899
51	fluc#nazol$.tw.	12,707
52	fluk#nazol$.tw.	9
53	plunazol$.tw.	0
54	prinazol$.tw.	0
55	tinazol$.tw.	2
56	ibuprofen/	9047
57	ibuprofen$.tw.	14,031
58	ibuprophen$.tw.	29
59	itraconazole/	5870
60	itr#c#nazol$.tw.	9162
61	itr#k#nazol$.tw.	12
62	o#ic#nazol$.tw.	105
63	o#ik#nazol$.tw.	0
64	exp urea/	116,964
65	carbamid$.tw.	1527
66	carbonamid$.tw.	16
67	carbonyldiamid$.tw.	4
68	karbamid$.tw.	0
69	karbonamid$.tw.	0
70	karbonyldiamid$.tw.	0
71	harnstoff.tw.	8
72	urea.tw.	85,229

73	uree.tw.	107
74	or/33-73	320,728
75	and/3,32,74	359
76	exp animals/ not humans/	4,787,714
77	75 not 76	339
78	limit 77 to english language	300

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: February 13, 2021
- Limits: Humans (search hedge); English language
- Number of results: 514

1	‘terbinafine’/mj	2111
2	‘terbinafin*’:ti,ab,tn	3787
3	#1 OR #2	4144
4	‘topical drug administration’/de	84,290
5	‘cutaneous drug administration’/de	751
6	‘transdermal drug administration’/de	9296
7	‘skin absorption’/de	8171
8	‘topical treatment’/de	13,822
9	‘topical*’:ti,ab	154,063
10	‘epicutaneous*’:ti,ab	3469
11	‘transdermal*’:ti,ab	21,958
12	((cutaneous* OR dermal* OR skin) NEAR/3 (absorb* OR absorp* OR appl*)):ti,ab	18,385
13	‘cream’/de	9825
14	‘gel’/exp	81,149
15	‘liniment’/de	257
16	‘lotion’/de	2967
17	‘ointment’/de	18,272
18	‘paste’/de	2551
19	‘salve’/de	170
20	‘suspension’/de	28,613
21	‘emulsion’/exp	47,880
22	‘shampoo’/de	2344

23	‘foam’/de	8497
24	‘cream$’:ti,ab	30,567
25	emulsion$’:ti,ab	46,571
26	‘liniment$’:ti,ab	242
27	‘lotion$’:ti,ab	4116
28	‘ointment$’:ti,ab	22,000
29	‘paste$’:ti,ab	15,477
30	‘salve$’:ti,ab	485
31	‘unguent*’:ti,ab	242
32	‘gel$’:ti,ab	367,735
33	‘suspension$’:ti,ab	148,385
34	‘shampoo$’:ti,ab	2271
35	‘solution$’:ti,ab	895,889
36	‘foam$’:ti,ab	35,394
37	#4 OR #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	1,748,637
38	‘drug combination’/de	171,941
39	‘ciclopirox’/de	1160
40	‘ciclopirox*’:ti,ab,tn	841
41	‘cyclopirox*’:ti,ab,tn	36
42	‘dimethyl sulfoxide’/de	37,500
43	‘dmso’:ti,ab,tn	28,679
44	‘dimethylsulfoxid*’:ti,ab,tn	5518
45	‘dimethyl* sulfoxid*’:ti,ab,tn	14,084
46	‘dimethylsulfoxyd*’:ti,ab,tn	14
47	‘dimethyl* sulfoxyd*’:ti,ab,tn	13
48	‘dimethylsulphoxid*’:ti,ab,tn	1107

49	‘dimethyl* sulphoxid*’:ti,ab,tn	1722
50	‘dimethylsulphoxyd*’:ti,ab,tn	2
51	‘dimethyl* sulphoxyd*’:ti,ab,tn	4
52	‘dimethyl* sulfur oxid*’:ti,ab,tn	0
53	‘dimethyl* sulphur oxid*’:ti,ab,tn	1
54	‘methyl* sulfoxid*’:ti,ab,tn	247
55	‘methylsulfoxid*’:ti,ab,tn	30
56	‘methyl* sulfoxyd*’:ti,ab,tn	1
57	‘methylsulfoxyd*’:ti,ab,tn	0
58	‘methyl* sulphoxid*’:ti,ab,tn	44
59	‘methylsulphoxid*’:ti,ab,tn	10
60	‘methyl* sulphoxyd*’:ti,ab,tn	0
61	‘methylsulphoxyd*’:ti,ab,tn	0
62	‘methylsulfinylmethan*’:ti,ab,tn	4
63	‘methyl* sulfinylmethan*’:ti,ab,tn	0
64	‘fluconazole’/de	44,777
65	‘fluconazol*’:ti,ab,tn	18,122
66	‘flucanazol*’:ti,ab,tn	38
67	‘flukonazol*’:ti,ab,tn	11
68	‘flukanazol*’:ti,ab,tn	4
69	‘plunazol*’:ti,ab,tn	2
70	‘prinazol*’:ti,ab,tn	0
71	‘tinazol*’:ti,ab,tn	3
72	‘ibuprofen’/de	51,883
73	‘ibuprofen*’:ti,ab,tn	20,059
74	‘ibuprophen*’:ti,ab,tn	60

75	‘itraconazole’/de	30,705
76	‘itraconazol*’:ti,ab,tn	12,707
77	‘itracanazol*’:ti,ab,tn	4
78	‘itriconazol*’:ti,ab,tn	1
79	‘itricanazol*’:ti,ab,tn	0
80	‘itrakonazol*’:ti,ab,tn	11
81	‘itrakanazol*’:ti,ab,tn	0
82	‘itrikonazol*’:ti,ab,tn	0
83	‘itrikanazol*’:ti,ab,tn	0
84	‘oniconazol*’:ti,ab,tn	0
85	‘onicanazol*’:ti,ab,tn	0
86	‘onikonazol*’:ti,ab,tn	0
87	‘onikanazol*’:ti,ab,tn	0
88	‘oriconazol*’:ti,ab,tn	2
89	‘oricanazol*’:ti,ab,tn	0
90	‘orikonazol*’:ti,ab,tn	0
91	‘orikanazol*’:ti,ab,tn	0
92	‘urea’/de	87,200
93	‘carbamid*’:ti,ab,tn	1677
94	‘carbonamid*’:ti,ab,tn	30
95	‘carbonyldiamid*’:ti,ab,tn	6
96	‘karbamid*’:ti,ab,tn	2
97	‘karbonamid*’:ti,ab,tn	0
98	‘karbonyldiamid*’:ti,ab,tn	0
99	‘harnstoff’:ti,ab,tn	12
100	‘urea’:ti,ab,tn	116,872

101	‘uree’:ti,ab,tn	156
102	#38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99 OR #100 OR #101	487,129
103	#3 AND #37 AND #102	663
104	[animals]/lim NOT [humans]/lim	6,168,837
105	#103 NOT #104	625
106	#103 NOT #104 AND [english]/lim	514

Appendix 2.1. Survey instrument for professional medical associations

1. How familiar are you with the following terms?

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

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

- None of the above

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

Appendix 2.2. Survey instrument for pharmacy roundtable prequestionnaire

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

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

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

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

Appendix 3. Survey distribution to professional associations

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

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