Summary Report

Ketoconazole

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

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

INTRODUCTION

This report was created to assist the Food and Drug Administration (FDA) in their evaluation of the use of ketoconazole (UNII code: R9400W927I), 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 ketoconazole is used in clinical research and practice to diagnose, prevent, or treat disease. Due to the broad, exploratory nature of this aim, scoping review methodology was used. Following the scoping review framework, a systematic literature review was conducted and healthcare practitioners were consulted to identify how ketoconazole has been used historically and currently.[1-3] Assessment 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 ketoconazole 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

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

Ketoconazole was nominated for the treatment of fungal infections and seborrheic dermatitis via various topical dosage forms and strengths based on the prescriber's request. Additionally, 25-200 mg oral capsules, and topical, mucosal, and vaginal solutions, suspensions, shampoos, and gels in concentrations from 2-10% will be compounded.

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

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

- While there may be commercially available FDA-approved medications containing the active ingredient, the dosage form, strength, or flavor may be inappropriate for the patient.
- Patient sensitivities to dyes, fillers, preservatives, or other excipients in manufactured products.
- Individual finished products have a considerable variance in the actual API and the use of a finished product has the potential to introduce unacceptable inaccuracies into the compounded medication.

METHODOLOGY

Background information

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

Systematic literature review

Search strategy

A medical librarian constructed comprehensive search strategies for Ovid MEDLINE and Embase. The search strategies used a combination of controlled vocabulary terms and keywords to describe two concepts: ketoconazole, and topical, mucosal or vaginal administration or form (refer to Appendix 1 for full search strategies). A literature review was not conducted for oral products due to the availability of FDA-approved oral ketoconazole products. Results were limited to human studies in English language. Searches were conducted on September 6, 2020. In addition, the ECRI Guidelines Trust® repository was searched on September 6, 2020 for clinical practice guidelines that recommended the use of ketoconazole 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 ketoconazole 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, pre-clinical 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 ketoconazole was used as: an FDA-approved product in the nominated dosage form, ROA, or combination; in an unspecified or non-nominated dosage form, ROA, or combination; or mentioned briefly as a rescue treatment or previously failed treatment. Studies in which ketoconazole 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 ketoconazole; setting; total number of patients; number of patients who received ketoconazole; patient population; indication for use of ketoconazole; dosage form and strength; dose; ROA; frequency and duration of therapy; use of ketoconazole in a combination product; use and formulation of ketoconazole in a compounded product; use of ketoconazole 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

Semi-structured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances ketoconazole 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 ketoconazole. 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 ketoconazole 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

- Ketoconazole is available as an FDA-approved product in the nominated dosage form and ROA.
- Ketoconazole was available as an FDA-approved 100 mg/5 mL oral suspension that was discontinued, not for reasons of safety or efficacy.
- Ketoconazole is available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for ketoconazole.
- Ketoconazole is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, EU, Hong Kong, Ireland, Latvia, Namibia, New Zealand, Saudi Arabia, and UK. Ketoconazole oral capsules were available in the EU but were withdrawn October of 2013 due to risk of liver injury.

Table 1. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Status	Approval Date[b]
Ketoconazole	200 mg	Tablet	Oral	Prescription	06/15/1999
	2%	Aerosol, cream, gel, shampoo	Topical	Prescription	08/31/1990

[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]
Ketoconazole	1%, 2%	Application, cream, gel, shampoo	Topical	Abu Dhabi	Active	–
				Australia	Schedule 2	08/28/1991
				Canada	Prescription	12/30/1990
				Hong Kong	Pharmacy only	03/10/1989
				Ireland	Prescription	11/10/1987
				Latvia	Prescription	12/05/1996
				Namibia	–	09/18/1986
				New Zealand	Pharmacy	06/22/1989
				Saudi Arabia	Prescription	–
				UK	Prescription	12/03/1983

Ketoconazole	200 mg	Tablet	Oral	Abu Dhabi	Active	–
				Belgium	Prescription	11/18/2014
				Canada	Prescription	03/02/1998
				EU	Authorized	11/18/2014
				Ireland	Prescription	–
				Latvia	Prescription	11/19/2014
				Namibia	–	08/18/2004
				New Zealand	Prescription	04/07/1982
				UK	Prescription	11/19/2014
Ketoconazole / Clobetasol propionate / Neomycin sulfate	–	Cream	Topical	Hong Kong	Prescription	03/21/2003

Abbreviation: "– ", not mentioned.

[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, ROA, and approval status) provided in a useable format. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations. See Methodology for full explanation.

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

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

Results of literature review

Study selection

Database searches yielded 2166 references; 3 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 1492 titles and abstracts were screened. After screening, the full text of 99 articles was reviewed. Finally, 4 studies were included. Ninety-five studies were excluded for the following reasons: wrong study design (56 studies); used as an FDA-approved formulation (31); unspecified dosage form or ROA (5); duplicate study (1); ketoconazole not used clinically (1); language other than English (1).

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

Characteristics of included studies

The 4 included studies were published between 2002 and 2019. There were 4 experimental studies, 0 observational studies, 0 descriptive studies, and 0 clinical practice guidelines. The 4 studies were conducted in the following countries: Argentina, Egypt, Iran, and Mexico.

A total of 308 patients participated in the 4 included studies. The number of patients in each study ranged from 51 to 126.

Outcome measures differed among the included studies and included: resolution of infection, mean number of colonies, clinical effectiveness, mycological effectiveness, therapeutic effectiveness, tolerability, therapeutic successes, posttreatment effectiveness, Tongue Lesion Index (TLI), Oral Lesion Index (OLI), and mycological analysis.

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

Use of ketoconazole

Fifty patients received ketoconazole as an experimental treatment and 52 patients received ketoconazole as a comparator treatment for vulvovaginal candidiasis, administered vaginally in doses ranging from 50 mg to 400 mg. Duration of treatment ranged from 3 days to 7 days. Fifteen patients received ketoconazole as an experimental treatment for Candida-associated denture stomatitis, administered as a fine layer topically for an unspecified duration of therapy. Eleven patients received ketoconazole as a comparator treatment for chronic oral candidiasis, administered topically until resolution of infection or 45 days, whichever occurs first.

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

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

In 1 study, the authors' concluding statement recommended the use of topical ketoconazole for treatment of Candida-associated denture stomatitis. In 1 study, the authors' concluded that ketoconazole flakes in situ gel is a promising delivery option for the treatment of vaginal candidiasis. In 2 studies, the authors' conclusions did not address the use of ketoconazole. Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

In addition to the 4 included studies, additional studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of ketoconazole.

The skin is the largest organ of the body and is "home to millions of bacteria, fungi and viruses that compose the skin microbiota."[17] These microorganisms play important roles in the "protection against invading pathogens, the education of our immune system and the breakdown of natural products."[17] Bacteria constitute the largest proportion of the skin microbiota and fungi are the least abundant.[17] The types of bacteria that colonize the skin are dependent upon the physiology of the skin site.[17] For example, *Propionibacterium* is predominately found in sebaceous sites, like the face, chest, or back, while *Staphylococcus* and *Corynebacterium* are generally found in more humid areas, like the bends of the elbow and feet.[17] Fungal colonization is not as dependent on the physiology of the skin site and therefore is similar across the body.[17] *Malassezia*, *Aspergillus*, *Cryptococcus*, *Rhodotorula*, and *Epicoccum* are a few of the fungi that are found on the skin.[17]

Fungal skin infections are predominately due to *Candida albicans*, *Trichophyton*, *Epidermophyton*, *Microsporum*, and *Malassezia*.[18] Dermatophytes, which include *Trichophyton*, *Epidermophyton*, and *Microsporum*, are the most common pathogens identified in skin infections.[19] Dermatophytes require keratin for growth and therefore invade keratinized tissue, like 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.[18,20-22] Superficial fungal infections can be treated with either topical or oral anti-fungal agents. Typically, fungi will infect with skin surface and "invade the stratum corneum to avoid being shed from the skin surface by desquamation."[23] Topical anti-fungal agents can penetrate the stratum corneum and act as either a fungicidal agent killing the fungi or as a fungistatic agent which "renders them unable to grow or divide."[23] Systemic absorption of topical anti-fungal agents is minimal so safety is less of a concern compared to oral anti-fungal agents.[23] Topical anti-fungal 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.[24] *Malassezia* is the organism thought to be responsible for seborrheic dermatitis due to the result of an abnormal host response and is treated by using medicated shampoos.[24]

Wounds can be categorized as either acute, caused by external damage to the skin, or chronic, a result of "endogenous mechanisms associated with a predisposing condition that ultimately compromises the integrity of dermal and epidermal tissue."[25] When tissue is exposed this creates an environment that is "conducive to microbial colonization and proliferation."[25] Colonization can be a result of normal skin flora, the environment, or "endogenous sources involving mucous membranes."[25] Even with microbial colonization, most wounds will heal within several weeks and the "indiscriminate prescribing of systemic and topical antibiotics has contributed to the development of multi-resistant bacteria."[26,27] However, this colonization can complicate wound healing, especially in elderly, diabetic, and obese patients.[17] Due to the polymicrobial nature of wound colonization, wounds are at risk of becoming infected.[25] The International Wound Infection Institute's Wound Infection in Clinical Practice principles of best practice states that a holistic approach should be taken when treating wound infections.[28] The primary objective in managing a wound is to reduce the risk of injection while "optimizing local conditions to encourage healing."[26] This can be accomplished through "surgical debridement to remove devitalized tissue, restoration of local tissue perfusion, and use of systemic and topical antimicrobial agents to clear or prevent infection."[26,28]

While most wound infections are the result of bacteria, some wounds are at an increased risk for fungal infections. A 2010 retrospective study found that 23% of clinical specimens taken from

patients with chronic wounds were positive for fungi.[29] Burn patients have one of the highest risks for developing fungal infections due to the combination of damaged skin and immune dysfunction.[30] A 2008 review of 15 burn centers found that 6.3% of patients presenting with a burn had a positive fungal culture.[30] The use of topical and systemic antimicrobial agents has also contributed to the increase in fungal infections seen in burn patients.[31] *Candida albicans* is reported as the most common fungal pathogen causing infection in burn patients.[31] As a result, prophylaxis with nystatin has shown to be effective in preventing infection.[31,32] However, the broad use of antifungal agents in patients not at high risk of infection may lead to increased resistance.[32] A 2020 Cochrane systematic review assessed "the effect of topical interventions on wound healing in people with facial burns of any depth."[33] They found that "the evidence about the effectiveness of topical treatments for facial burns is low to very low."[33] Kalan et al evaluated 100 nonhealing diabetic foot ulcers (DFUs) and found that 80% contained fungi.[34] When topical antifungal agents are used they should be in "used in conjunction with good wound care practice."[28]

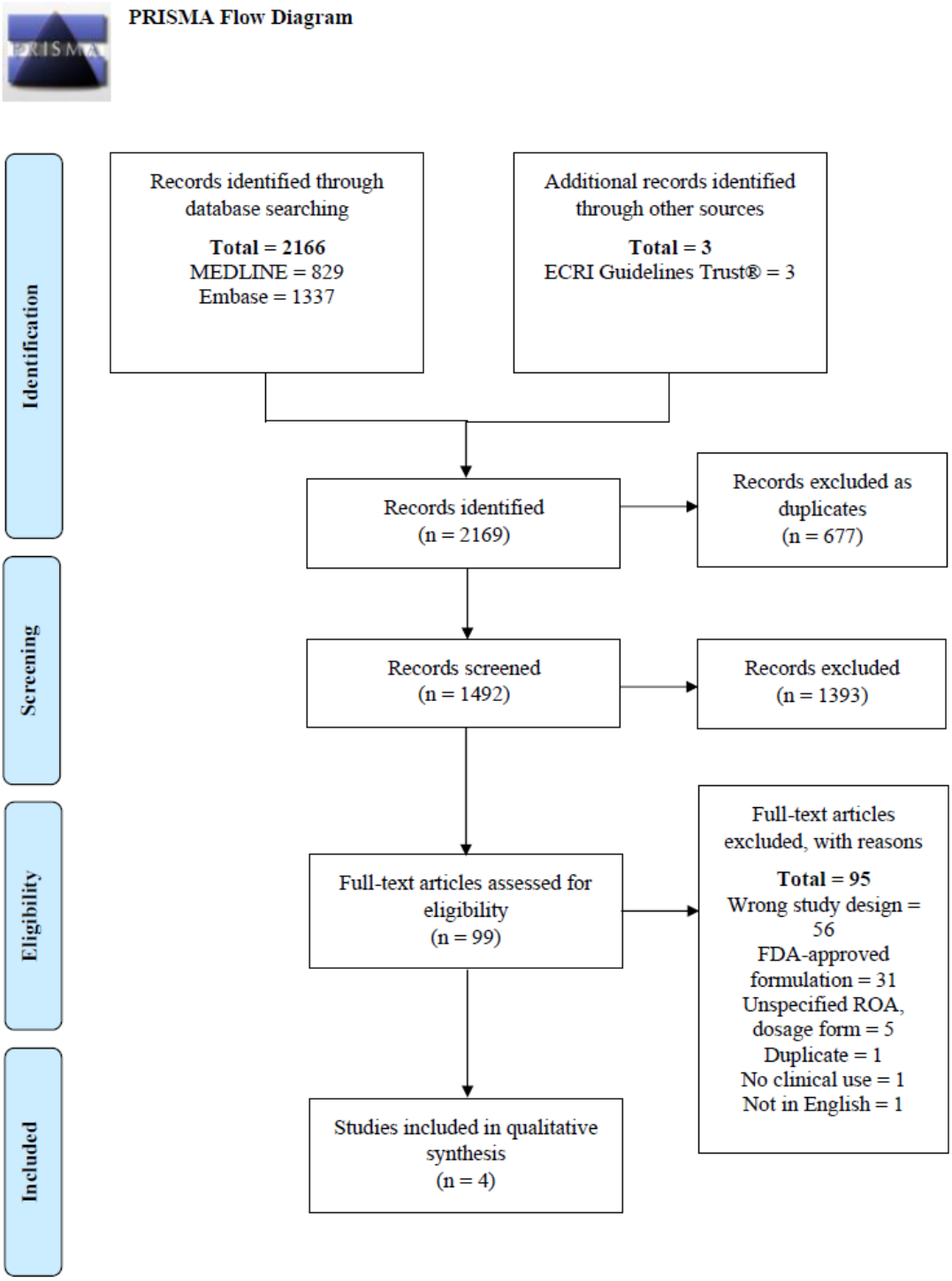
Fungal wound infections have also been associated with wounded warrior patients with the number increasing since the beginning of the war in Afghanistan.[35] The Joint Trauma System Clinical Practice guideline for invasive fungal infection in war wounds recommends that in patients with at least 3 risk factors for invasive fungal infection topical antifungal therapy should be initiated using Dakins.[35]

Oral ketoconazole was first approved in the US in July of 1981 and was the only oral antifungal agent available until fluconazole was introduced in 1990.[13] Ketoconazole is an imidazole derivative antifungal agent that inhibits the biosynthesis of ergosterol, the main sterol present in the membranes of fungi.[36] Ketoconazole has a wide spectrum of activity against commonly encountered fungal pathogens including Aspergillus species, *Blastomyces dermatitidis*, Candida species, *Cryptococcus neoformans*, *Coccidioides immitis*, *Histoplasma capsulatum*, and *Paracoccidioides brasiliensis*.[36] Ketoconazole became the standard of care for treatment of various systemic fungal infections.[37] However, several "clinically relevant shortcomings" became apparent including variable absorption, lack of an intravenous formulation, due to being mostly fungistatic it was less effective in immunocompromised patients, dose related side effects, symptomatic and potentially fatal drug-induced hepatitis, endocrine disturbances at high doses, and unpredictable drug interactions.[37] With the increasing number of reports of hepatoxicity and other serious adverse effects, France suspended the use in July 2011 which then led to the EMA performing an evaluation and recommending that its marketing authorizations be suspended.[13] The Australian government also announced that it would be deregistered and discontinued December of 2013.[13] The FDA announced amendments to the ketoconazole product labeling in July of 2013 to include recommendations against use in patients with liver disease, provided recommendations for monitoring of liver function, and recommended that it only be prescribed for life-threatening endemic mycoses when there is no other suitable alternative.[13,38] FDA provided an additional safety announcement in 2016 warning against the use of oral ketoconazole for treatment of skin and nail fungal infections due to the risk of "serious liver damage, adrenal gland problems, and harmful interactions with other medicines that outweigh its benefit in treating these conditions."[39]

While ketoconazole is no longer recommended for oral use, there are several commercially available topical dosage forms that are commonly used to treat various topical fungal infections including tinea corporis, tinea cruris, tinea pedis, tinea versicolor, cutaneous candidiasis, and seborrheic dermatitis.[40] The topical dosage forms are not associated with the same adverse effects as the oral formulation.[39]

Vulvovaginal candidiasis is one of the most prevalent infections with, on average, 75% of women are estimated to acquire at least once in their lifetime.[41] Patients typically present with external dysuria, vulvar pruritus, pain, swelling, redness, and vaginal discharge.[42] Candida albicans is the predominate source of infection making up approximately 80%-92% of cases.[41] The 2015 Centers for Disease Control (CDC) Sexually Transmitted Disease Treatment Guidelines recommends s short-course of a topical antifungal agent, including clotrimazole, miconazole, or tioconazole, as the treatment of choice resulting in resolution of infection in 80%-90% of patients.[42] The CDC guidelines do not mention the use of ketoconazole for vulvovaginal candidiasis.[42]

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



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

Table 3. Types of studies

Types of Studies	**Number of Studies**
Descriptive	0
Observational	0
Experimental[43-46]	4
Clinical practice guideline	0

Table 4. Number of studies by country

Country	**Number of Studies**
Argentina[46]	1
Egypt[43]	1
Iran[45]	1
Mexico[44]	1
	Total US: 0 Total Non-US Countries: 4

Table 5. Summary of included studies

Indication 1: Vulvovaginal candidiasis					
Author, Year, Country	**Study Type[a]**	**Patient Population (% male, age)**	**Intervention/Comparator (# of patients)**	**Primary Outcome Measure**	**Authors' Conclusions**
Abd Ellah, *et al*., 2019, Egypt[43]	Pilot, randomized controlled trial	100 Patients with vulvovaginal candidiasis (0%, range 20-60 y)	• Group 1 (50): Ketoconazole flakes-loaded *in situ* gel • Group 2 (50): Terconazole vaginal cream	Resolution of infection	The ketoconazole flakes *in situ* gel were as effective as terconazole in improving the patient complaints and complete eradication of infection and could be considered as a highly promising ketoconazole delivery option for treatment of vaginal candidiasis.
Herrera-Arellano, *et al*., 2009, Mexico[44]	Randomized, double-blind and controlled clinical trial	101 Patients with vulvovaginal candidiasis (0%, range 17-54 y)	• Group 1 (49): *Solanum chrysotrichum* vaginal suppositories • Group 2 (52): Ketoconazole vaginal suppositories	Clinical effectiveness, mycological effectiveness, therapeutic effectiveness, tolerability, therapeutic successes, posttreatment effectiveness	*Solanum chrysotrichum* exhibits the same clinical effectiveness as ketoconazole, but with lower percentages of mycological eradication.
Indication 2: Candida-associated denture stomatitis					
Author, Year, Country	**Study Type[a]**	**Patient Population (% male, age)**	**Intervention/Comparator (# of patients)**	**Primary Outcome Measure**	**Authors' Conclusions**
Khozeimeh, *et al*., 2010, Iran[45]	Randomized clinical trial	30 Patients with Candida-associated denture stomatitis (sex not provided, range 56-90 y)	• Group 1 (15): Ketoconazole tablets • Group 2 (15): Ketoconazole ointment	Mean number of colonies	Topical ketoconazole 2% was effective in reducing the number of Candida colonies and has minimal side effects in long-term administration compared to ketoconazole tablets.

Indication 3: Chronic oral candidiasis					
Author, Year, Country	**Study Type[a]**	**Patient Population (% male, age)**	**Intervention/Comparator (# of patients)**	**Primary Outcome Measure**	**Authors' Conclusions**
Lopez-De-Blanc, *et al*., 2002, Argentina[46]	Double-blind trial, randomized in 4 parallel groups	51 Patients with erythematous chronic candidiasis (51%, age not provided)	• Group 1 (10): 3% Fenticonazole in Orabase® • Group 2 (20): 2% Fenticonazole in Orabase® • Group 3 (10): Nystatin 100,000 units in Orabase® • Group 4 (11): 2% Ketoconazole in Orabase®	Tongue Lesion Index (TLI), Oral Lesion Index (OLI), mycological analysis	Fenticonazole proved to be as effective as nystatin and ketoconazole in topical treatment of oral candidiasis.

[a]As defined by authors.

Table 6. Dosage by indication – US

No studies were included

Table 7. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Vulvovaginal candidiasis[43,44]	50 mg daily	50 mg/5 mL	Gel	Vaginal	3 days
	400 mg daily	400 mg	Suppository		7 days
Candida-associated denture stomatitis[45]	Fine layer twice daily	2%	Ointment	Topical	–
Chronic oral candidosis[46]	–	2%	Cream	Topical	Until resolution of infection or 45 days

Abbreviation: "–", not mentioned.

Table 8. Number of studies by combination

	Combination Formula	Number of Studies
Nominated	Ketoconazole 2% / Betamethasone dipropionate 0.05% – topical cream	0
	Ketoconazole 2% / Hydrocortisone 2.5% – topical cream	0
	Ketoconazole 2% / Niacinamide 4% – topical cream	0
	Ketoconazole 2% / Spironolactone 5% – topical cream	0
	Ketoconazole 2% / Fluocinolone acetonide 0.01% / Sodium sulfacetamide 10% – topical cream	0
	Ketoconazole 2% / Hydrocortisone 2.5% / Iodoquinol 1% – topical cream	0
	Ketoconazole 2% / Minoxidil 7% / Tretinoin 0.05% – topical solution	0
	Ketoconazole 2% / Salicylic acid 2% / Zinc pyrithione 1% – topical shampoo	0

Table 9. Compounded products – US

No compounded products from included studies

Table 10. Compounded products – non-US countries

Indication	Compounding Method	Dosage Form	Final Strength
Vulvovaginal candidiasis[43,44]	Ketoconazole was added to different concentrations of β-CD in 5 mL of simulated vaginal fluid in the presence and absence of polyvinylpyrrolidone (PVP) 40,000. These mixtures were shaken in a water bath at 30 ± 0.5 °C for 7 days to reach equilibrium state and then filtered. Co-ground mixtures were prepared by grinding ketoconazole, β-CD (1:1 M) in the presence and absence of PVP 40,000 using a mortar and pestle for 30 minutes. The obtained mixtures were sieved to obtain a particle size range of 125-250 μm using USP sieve series. Aqueous solutions of gellan gum were prepared by continuous stirring of gellan gum in water for 15-20 minutes at boiling temperature, followed by cooling at room temperature. The ketoconazole co-ground mixture (1% w/v) was added to different concentrations of gellan gum solutions. The gel-flakes were prepared using drop-stir technique via dropping of gellan gum solution containing 1% ketoconazole co-ground mixture into different concentrations of chitosan solutions (1% acetic acid solution). This dropwise addition was done under continuous vigorous magnetic stirring. PF-127 was dissolved in cold water and the solution was refrigerated overnight. The ketoconazole gel-flakes were incorporated into different concentrations of PF-127 solutions under stirring.	Flakes-loaded *in situ* gel	50 mg/5 mL
	400 mg ketoconazole and 600 mg vehicle; formulated with Pluracol E 600®, Tween 80®, EDTA, sterile water, Suppocire®, and Suppoweiss®	Suppository	400 mg
Candida-associated denture stomatitis[45]	Ketoconazole in Orabase® ointment prepared by the pharmaceutical research laboratory	Ointment	2%

Results of interviews

One hundred eighty-four SMEs were contacted for interviews; 64 agreed to be interviewed, and 120 declined or failed to respond to the interview request. Six SMEs discussed ketoconazole. Amongst these 6 SMEs, there were 2 medical doctors, 1 nurse practitioner, and 3 doctors of podiatric medicine. The SMEs specialized and/or were board-certified in dermatology, infectious diseases, and wound, ostomy, and continence care working in academic medical institutions and private practice. The SMEs had been in practice for 1 to 56 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 will determine the type of product used. Similarly, the dosage form selected also plays a role with one SME stating that creams are typically effective for the bottom of the foot while gels are preferred for in between the toes. For example, ketoconazole shampoo works well for tinea versicolor, however, topical products are generally ineffective for onychomycosis so systemic agents are typically preferred. Itraconazole was the "first antifungal that was FDA approved for the treatment of onychomycosis" but as an oral formulation. Fluconazole has also been used but it "never received FDA approval for this indication." When treating onychomycosis, oral terbinafine is typically the drug of choice because it has "the best efficacy of any treatment we have FDA approved for onychomycosis." If a patient does not want to take an oral medication, there are alternatives available, like efinaconazole, tavaborole, and ciclopirox laquer, that have been studied and are FDA approved for treating onychomycosis. Regarding the combination products included in the nomination, one 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. One SME commented that "for a lot of these skin conditions on the feet, that you'd be amazed what soap and water does."

When a topical antifungal is needed most of the SMEs used the commercially available formulations, ketoconazole and clotrimazole. However, one SME stated that "90% of the time I do not use an azole, I use ciclopirox. When I use azoles, it's only because insurance coverage for the patient is directing me to do so." When an azole is used the SME uses either ketoconazole or clotrimazole. There were concerns about the effectiveness of these products with one SME stating "the two that are available are older and they don't do as great a job as we want to, so that's why they're the first in step therapy and patients generally fail them, so yes, we do need something that is better. Fluconazole because of its activity against Candida certainly would be a welcome addition." Another SME commented that clotrimazole is "an extremely weak, relatively ineffective antifungal." When ketoconazole and clotrimazole fail, the SME turns to topical naftifine, ciclopirox, or luliconazole. Another SME also stated that there are systemic infections in which itraconazole would be preferred to ketoconazole but was unaware of any fungal skin infections that would need to be treated topically with itraconazole. The SME was not aware of tinea versicolor developing resistance to ketoconazole stating that it is "probably not a huge concern."

When treating wounds, the SMEs do not use antifungals because, as one SME stated, "we're often dealing with the bacterial issues and biofilms which the fungus can be part of that biofilm, but the bacteria is really the problem." With another SME stating, "to date, we have found essentially no efficacy" continuing that "putting on prescription antibiotics and prescription antifungals, there's really very, very little evidence to support that that does much in terms of healing wounds." When treating a wound in which there is a true infection, or suspected infection, "the best way to approach it is going to be a

systemic antibiotic." One SME said the fungi that topical antifungal agents treat do not live at high temperature so they are not going to invade beyond the dermis stating that "if you had a true wound infection that was fungal, it would be a fungus that you'd need an oral systemic antifungal for." Another SME stated "there is a lot of buzz conversation that wounds may be delayed in healing because of the presence of fungi. I haven't grasped that mentality yet, but some people do apply a shotgun type of approach to try to kill both bacteria and fungi." Another SME stated that the topical products they use in wound care are typically to treat superficial wounds commenting that "there are still full thickness ones but they're just not extremely deep wounds, typically."

When caring for incontinent patients, one SME uses "a fair amount" of topical antifungals, especially in the acute care setting. Due to the use of antibiotics the SME encounters "tons of fungus" that can be located "all over." Additionally, in heavier patients there is more skin-to-skin contact which can lead to the growth of yeast and fungi. However, the SME does not use compounded products and instead only uses commercially available products. The SME stated that they will apply multiple different products individually to a wound to create a "layered effect" but does not compound them together into a single product. In an out-patient setting patients will have "to do the dressing changes typically more often than when they come to see us in clinic" and occasionally home health nurses might be involved to assist with dressing changes. In this setting having a single product available might be easier than having a patient "layer up." Another SME commented that if a patient is being treated for a fungal infection this would not likely be something to be treated in office stating that it would probably be something that a patient would use for an extended period.

One SME commented on a few of the nominated combination products. The SME said that the combination of ketoconazole, sulfacetamide, and fluocinolone "does make a lot of sense" for the treatment of seborrheic dermatitis. Sulfacetamide is commonly used to treat seborrheic dermatitis, ketoconazole would be added "with the thought that some of that is being caused by pityrosporum," and fluocinolone would help to reduce the inflammation, redness, and itch. Regarding the spironolactone-ketoconazole formulation, the SME stated that this is likely used to treat acne. However, the SME was not sure of the effectiveness of topical spironolactone as it is normally used orally to treat acne. The SME commented that "a lot of acne is multi-factorial" so "combining them might be convenient," but also added that these products are available separately and that "I'm not sure that any of those combinations are going to be better than just using what we always use, that's commercially available." The SME also mentioned that purchasing the products individually is likely cheaper than having something compounded.

Two SMEs discussed the toxicity issues associated with using ketoconazole orally with one SME stating that there have been reports of liver failure. One SME stated that ketoconazole first became available in 1980, however, it is rarely used today. The SME stated that while ketoconazole is a valuable drug but "due to its toxicity faced with the safety" it is "almost not available today." The SME continued that the only rare indication is when there is a multi-drug resistant Candida species and ketoconazole is "the only azole it may be susceptible to is ketoconazole, otherwise we don't use it."

One SME commented that fluconazole-resistant vaginal *Candida albicans* is "an enormous problem" stating that they have seen over 100 women with the infection. Fluconazole resistance is suspected when a patient does not clinically improve and they remain positive on the potassium hydroxide (KOH) test but not all patients that do not improve on fluconazole have a resistant infection. The SME stated that fluconazole resistance is diagnosed by conducting susceptibility testing with a minimum inhibitory concentration (MIC). If the fungus is susceptible to another azole, then the SME will select that agent but there is frequently cross-resistance to other azoles with "more than half the patients with fluconazole

resistance C. albicans, there's cross resistance to ketoconazole and itraconazole and there's frequently cross-resistance to the other topical azoles, clotrimazole or miconazole." The SME mentioned 2 new drugs coming to market, ibrexafungerp and oteseconazole, that are active against fluconazole resistant organisms, however, they are not commercially available at this time (ibrexafungerp was approved by FDA in June of 2021 for treatment of vulvovaginal candidiasis). When the SME encounters class resistance they use compounded boric acid suppositories.

For topical preparations, one SME stated that they have not encountered challenges with excipients contained in commercially available products but continued that "I don't have a specialty contact dermatitis clinic…and yes, for them, it is really important to be able to have the flexibility because they do find real allergic reactions that they need to exclude certain ingredients from and so compounding can be really useful there." Another SME stated that they rarely use compounded products dermatologically but frequently use them for gynecological indications, including candida vaginitis, bacterial vaginosis, trichomonas, and symptomatic relief, because there is a limited number of products available. The SME stated that the location in which the product is being applied is important continuing that the introitus and the vestibule are hyper-innervated areas that do not tolerate a lot of products so "you have to be very gentle, very cautious" because you can induce burning, irritation, and soreness very easily that can lead to distress and pain. However, the vagina which "has stratified squamous epithelium, which is thick and lots of secretions has a much higher tolerance for compounded products."

Regarding combination products, one SME is "very anti-combination of a steroid and an antifungal." The SME referenced the commercially available clotrimazole-betamethasone product that is currently available stating that it "can cause a lot of harm." The SME continued that "steroids can mildly reduce the fungal growth, but when you take it away, you get what's called tinea incognito" additionally, "many antifungals…are naturally anti-inflammatory. you don't need a steroid on top of it." However, another SME stated that there is a need for a combination antifungal and steroid and that the product that is available is low potency. In the instances when the SME wants to use this combination, they have the patient apply them separately at different times of the day. Another SME had concerns regarding combination compounded products stating that "we don't even know if they chemically can be mixed. If they're stable when they're mixed together or if there's some sort of interaction between them. And there could be actually some antagonism when drugs are mixed."

As part of Phase 3, one of the nominators provided additional information regarding the multi-ingredient products contained within the ketoconazole nomination.

Ketoconazole 2% / 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: butylated hydroxytoluene, ethanol, propylene glycol, sodium hydroxide, and sodium laureth sulfate. These inactive ingredients are known to be harmful allergens or irritants with concerns including allergen, classified as expected to be toxic or harmful, classified as skin irritant, contamination concerns, human irritant, human respiratory irritant, violation of industry recommendations - restricted in cosmetics; use, concentration, or manufacturing restrictions - not safe for use on injured or damaged skin. Ketoconazole is added for its antifungal 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.

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

Ketoconazole 2% / salicylic acid 2% / zinc pyrithione 1% will be compounded as a topical shampoo to treat 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: butylated hydroxytoluene, ethanol, propylene glycol, and sodium hydroxide. These inactive ingredients are known to be harmful allergens or irritants with concerns including allergen, classified as expected to be toxic or harmful, classified as skin irritant, human irritant, human respiratory irritant, violation of industry recommendations - restricted in cosmetics; use, concentration, or manufacturing restrictions - not safe for use on injured or damaged skin. Ketoconazole is added 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.

Ketoconazole 2% / hydrocortisone 2.5% / iodoquinol 1% will be compounded as a topical cream to treat topical fungal infections applied multiple times through the day for multiple days. This product is used by practitioners as a non-patient specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylated hydroxytoluene, butylparaben, silicon dioxide, benzalkonium chloride, butylene glycol, cetearyl alcohol, chlorocresol, hexylene glycol, isopropyl palmitate, methylparaben, mineral oil, polyethylene glycol, polysorbate 20, potassium hydroxide, propylene glycol, sodium hydroxide, sodium lauryl sulfate, titanium dioxide, trolamine, and white petrolatum. These inactive ingredients are known to be harmful allergens or irritants with concerns including allergen, classified as expected to be toxic or harmful, classified as irritant, classified as skin irritant, highly comedogenic, human endocrine disruptor, human immune and respiratory toxicant or allergen, human irritant, human respiratory irritant, human skin toxicant or allergen, human toxicant or allergen, persistent or bioaccumulative, possible human carcinogen, restricted in cosmetics (recommendations or requirements) - use, concentration, or manufacturing restrictions, violation of industry recommendations - restricted in cosmetics; use, concentration, or manufacturing

restrictions - not safe for use on injured or damaged skin (only for products for use on damaged skin). Iodoquinol is added for its capability to harm bacteria and fight infections. 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.

Betamethasone dipropionate 0.05% / ketoconazole 2%, fluocinolone acetonide 0.01% / ketoconazole 2% / sodium sulfacetamide 10%, ketoconazole 2% / minoxidil 7% / tretinoin 0.05%, and ketoconazole 2% / spironolactone 5% will not be pursued as they have been discontinued.

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

While 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 an issue 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, 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 five-minute gown and glove. If we don't have somebody in the IV [intravenous] room, if you're doing 797 right, it's five minutes. It's four minutes to tube it. It's three 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 presser 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, while they do not obtain a lot of products from outsourcing facilities, stated that "when we do purchase from 503B's, 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 COVID-19 pandemic has also impacted the operations of hospitals with one 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 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 impacted 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. United States Pharmacopeia (USP) <797> standards limit the beyond-use-date that can be assigned to these products and, as the participant stated, "we obviously need to provide product with much extensive beyond use dating than we can provide." Several participants also commented that they do not perform high-risk compounding in-house and therefore, all of these products are outsourced. There are challenges with mid-size 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 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 with one-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 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, 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 pre-shortage, you're not going to get products when you need it during the shortage" continuing that "typically in a shortage, you learn to live without them. You have to." Additionally, in the event of the shortage being the result of lack of an API, outsourcing facilities are likely to be equally affected and unable to provide assistance. However, one participant stated that they first began working with outsourcing facilities because of shortages. This participant commented that "what the 503Bs are starting to do, some of the large ones, is that they are also conducting validation studies on API. If sterile becomes short, they quickly switch to producing through API, which ASHP [American Society of 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 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 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. Preservative free is also an issue for ophthalmic products, however, one participant observed this is more on the 503A side. One participant stated that obtaining ophthalmic products from outsourcing facilities has been a challenge and that there are products they would like to obtain from outsourcing facilities but are not able to, forcing them to compound them in-house. This participant also commented that there are 2 outsourcing facilities that compound ophthalmic products but when they reviewed the facilities, they did not pass their internal quality standards; one facility had been banned from distributing products in California by the Board of Pharmacy. There is an additional challenge with obtaining cephalosporins and beta-lactams 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 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 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 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 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 are doing the non-sterile 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 non-sterile 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 noting 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 three 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 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 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 12-24 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 2,400, either one, 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 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 "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 503B's 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 503B's where we've had agreements for certain products to take it off our plate, and then low and behold they're shut down, or closed, or whatever it may be." Minimum purchase amounts were also reported as a concern with one participant stating that "what we see consistently is the 503Bs, they want us to commit to giving them a certain volume, but then will not give us a reciprocal commitment or at least will not fulfill that reciprocal commitment. That's a huge problem for us making that type of commitment, when we do ultimately have to split our volume in order to make sure that we consistently are able to take care of our patients." Another challenge was related to outsourcing facilities utilizing API to compound narcotics. One participant commented that this often worsens drug shortages due to the quotas that the Drug Enforcement Administration (DEA) places on the quantity that can be produced. The participant stated that "they [outsourcing facilities] want to buy the product that we're trying to buy to take care of our patients today, to sell us tomorrow. We really need the FDA to say that, especially for controlled substances, that 503Bs can consistently prepare those products so that we don't end up with a shortage year after year, after year and then chasing our tail. Also, we may actually want to tell 503Bs, they can't buy those products or that they're limited in the amount of their ability to buy those products to make what are essentially copies of commercially available products, because it actually induces the shortage in many ways."

Results of survey

Thirty-three people responded to the survey distributed via professional medical associations and available on the project website; refer to Table 11 for respondent characteristics.

Among respondents, 11 (17% of 64 responses, where respondents were allowed to select multiple products) used ketoconazole as a compounded topical product (refer to Table 12). Fourteen (100% of 14 responses) respondents reported utilizing compounded topical products in combination with other active pharmaceutical ingredients as a multi-ingredient product.

Ten (50% of 20 responses, where respondents were allowed to select multiple reasons) respondents reported using compounded topical products due to lack of commercial products in an appropriate dosage

form, strength or combination, patient allergies preventing use of commercially available products (1, 5%), other patient conditions preventing use of commercial products (3, 15%), or no commercially available products (3, 15%). Three (15%) respondents used compounded topical products because 'oral medications are contraindicated due to comorbidities', 'very good for medication use, patient compliance is improved with need to apply medication,' and 'decreased systemic effects and higher concentrations at specific areas of need.' Refer to Table 13 for reasons for using compounded topical products.

The majority of respondents (11 of 13 responses, 85%) did not stock non-patient-specific compounded products at their practice. Respondents reported obtaining compounded topical products by purchasing, or having the patient purchase, the product from a compounding pharmacy (12 of 14 responses, where respondents were allowed to select multiple avenues, 86%) or outsourcing facility (2, 14%). Refer to Table 14 for how respondents obtained compounded products.

A prequestionnaire was distributed to participants of the roundtable discussion (refer to Appendix 2.4 for survey instrument).

Forty-three people responded to the prequestionnaire; refer to Table 16 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 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.

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

Table 11. Characteristics of survey respondents

Terminal Clinical Degree	Responses, n (N=29)
Doctor of Medicine (MD)	0
Doctor of Osteopathic Medicine (DO)	0
Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)	2
Physician Assistant (PA)	0
Doctor of Podiatric Medicine (DPM)	27
No Response	6
Practice Setting	**Responses, n (N=35)[a]**
Physician office or private practice	23
Outpatient clinic	6
Hospital or health system	3
Academic medical center	1
Emergency room	0
Operating room	2
No response	6

[a]Some respondents reported more than one practice setting.

Table 12. Compounded topical products prescribed or administered

Condition	Responses, n (N=64)[a]
Clotrimazole	15
Fluconazole	6
Itraconazole	9
Ketoconazole	11
Metronidazole	4
Mupirocin	9
Zinc oxide	3

None of the above	15
No Response	4

[a]Survey respondents allowed to select multiple products.

Table 13. Reasons for using compounded topical products

Reason	Responses, n (N=20)[a,b]
Commercial product not available in desired dosage form, strength, or combination	10
Patient allergies prevent use of commercial products	1
Patient conditions prevent use of commercial products	3
No commercial products	3
Other[b]	3

[a]Survey respondents allowed to select multiple reasons.
[b]Respondents stated 'oral medications are contraindicated due to comorbidities', 'very good for medication use, patient compliance is improved with need to apply medication,' and 'decreased systemic effects and higher concentrations at specific areas of need.'

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

Do you stock non-patient-specific compounded topical products at your practice?	Responses, n (N=13)
Yes	2
No	11
Not sure	0
No response	20

Table 15. Obtainment of compounded topical products

How do you obtain compounded topical products?	Responses, n (N=14)[a]
Compound yourself at practice	0
Product compounded by in-house pharmacy	0
Purchase from compounding pharmacy	12

Purchase from outsourcing facility	2
No response	21

[a]Survey respondents allowed to select methods.

Table 16. Demographics of prequestionnaire respondents' facilities

Type of Facility	**Responses, n (N=102)[a]**
Academic medical center	15
Acute care hospital	16
Children's hospital	8
Community hospital	11
Critical access hospital	2
Dialysis center	2
Federal government hospital	4
Health system	15
Inpatient rehabilitation center	4
Long-term acute care hospital	3
Outpatient surgery center	6
Rural hospital	2
Skilled nursing facility	0
Specialty hospital[b]	4
Trauma center	5
Urban hospital	5
Number of Beds	**Responses, n (N=38)**
< 50	4
50-99	3
100-199	1
200-299	3

300-399	5
400-599	3
> 600	18

[a]Respondents allowed to select more than one type of facility.
[b]Specialties provided include cardiology, pulmonary, vascular, home infusion, neurology, psychiatry, 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]	6

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

Table 18. Categories of products obtained from outsourcing facilities

Categories	**Responses, n (N=142)[a]**
Cardioplegic solutions	14
Dermatologic preparations	6
Dialysate solutions	0

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

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

Table 19. Products obtained from an outsourcing facility

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

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

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

[a]Respondents were allowed to select multiple products.

CONCLUSION

Ketoconazole was nominated for inclusion on the 503B Bulks List as various topical, mucosal, and vaginal dosage forms and oral capsules, to treat fungal infections and seborrheic dermatitis. Ketoconazole is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, EU, Hong Kong, Ireland, Latvia, Namibia, New Zealand, Saudi Arabia, UK, and US.

From the literature review, ketoconazole is used for treatment of vulvovaginal candidiasis, Candida-associated denture stomatitis, and chronic oral candidiasis.

From the interviews, ketoconazole is commonly used topically to treat seborrheic dermatitis, however, there is a commercially available product. The ketoconazole, sulfacetamide, and fluocinolone is likely used to treat seborrheic dermatitis and would make sense since sulfacetamide is commonly used to treat seborrheic dermatitis, ketoconazole would be added as an antifungal, and fluocinolone would help to reduce the inflammation, redness, and itch. The spironolactone-ketoconazole formulation is likely to treat acne, but one SME questioned the effectiveness of topical spironolactone. As part of Phase 3, one of the nominators provided additional information regarding the multi-ingredient products contained within the ketoconazole nomination. Ketoconazole will be compounded as a topical cream and shampoo in combination with additional APIs to treat seborrheic dermatitis and fungal infections.

From the survey responses, 11 out of 33 respondents used compounded topical ketoconazole.

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APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process, and other non-indexed citations and daily 1946 to September 4, 2020
- Date last searched: September 6, 2020
- Limits: Humans (search hedge); English language
- Number of results: 829

1	ketoconazole/	5594
2	keto#an#zol$.tw.	4
3	keto#on#zol$.tw.	7787
4	ketozol$.tw.	1
5	oxoc#nazol$.tw.	0
6	or/1-5	9247
7	administration, topical/	38468
8	administration, buccal/	979
9	administration, cutaneous/	22105
10	administration, intravaginal/	4858
11	administration, mucosal/	260
12	skin absorption/	11700
13	topical$.tw.	105809
14	transcutaneous$.tw.	14480
15	epicutaneous$.tw.	2014
16	transdermal$.tw.	14651
17	((cutanous$ or dermal$ or skin) adj3 (absorb$ or absorpt$ or appl$)).tw.	11306
18	buccal$.tw.	27583
19	intravaginal$.tw.	5620
20	vaginal$.tw.	100503

21	mucosal$.tw.	120551
22	mucous$.tw.	22994
23	transmucosa$.tw.	1897
24	transmucous$.tw.	12
25	emulsions/	17992
26	exp gels/	52139
27	liniments/	123
28	ointments/	12796
29	vaginal creams, foams and jellies/	1276
30	skin cream/	1037
31	pharmaceutical solutions/	3306
32	emulsion?.tw.	33269
33	gel?.tw.	308738
34	liniment?.tw.	145
35	ointment?.tw.	11878
36	salve?.tw.	341
37	paste?.tw.	12526
38	unguent$.tw.	113
39	lotion?.tw.	2315
40	cream?.tw.	19012
41	or/7-40	821691
42	and/6,41	1079
43	exp animals/ not humans/	4731219
44	42 not 43	956
45	limit 44 to english language	829

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: September 6, 2020
- Limits: Humans (search hedge); English language
- Number of results: 1337

1	‘ketoconazole'/mj	7296
2	‘ketocanazol*':ti,ab,tn	9
3	‘ketoconazol*':ti,ab,tn	10099
4	‘ketokanazol*':ti,ab,tn	0
5	‘ketokonazol*':ti,ab,tn	77
6	‘ketocanozol*':ti,ab,tn	2
7	‘ketokanozol*':ti,ab,tn	0
8	‘ketoconozol*':ti,ab,tn	11
9	‘ketokonozol*':ti,ab,tn	0
10	‘ketozol*':ti,ab,tn	2
11	‘oxocanazol*':ti,ab,tn	0
12	‘oxoconazol*':ti,ab,tn	0
13	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	13109
14	‘buccal drug administration'/de	676
15	‘topical drug administration'/de	82882
16	‘cutaneous drug administration'/de	668
17	‘intravaginal drug administration'/de	6506
18	‘mucosal drug administration'/de	446
19	‘topical treatment'/de	13093
20	‘skin absorption'/de	8061
21	‘topical*':ti,ab	150020
22	‘transcutaneous*':ti,ab	19554

23	‘transdermal*':ti,ab	21443
24	((cutaneous* OR dermal* OR sin) NEAR/3 (absorb* OR absorpt* OR appl*)):ti,ab	4644
25	‘buccal*':ti,ab	35419
26	‘intravaginal*':ti,ab	7978
27	‘vaginal*':ti,ab	157596
28	‘mucosal*':ti,ab	172576
29	‘mucous*':ti,ab	38780
30	‘transmucosa*':ti,ab	2537
31	‘transmucous*':ti,ab	27
32	‘cream'/de	9475
33	‘drug solution'/de	3113
34	‘gel'/exp	77471
35	‘liniment'/de	251
36	‘lotion'/de	2869
37	‘ointment'/exp	18658
38	‘paste'/de	2523
39	‘salve'/de	166
40	‘transmucosal drug delivery system'/de	126
41	‘cream$':ti,ab	29753
42	‘emulsion$':ti,ab	45254
43	‘liniment$':ti,ab	234
44	‘lotion$':ti,ab	4012
45	‘ointment$':ti,ab	21624
46	‘paste$':ti,ab	15024
47	‘salve$':ti,ab	476
48	‘unguent*':ti,ab	240

49	‘gel$':ti,ab	363006
50	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49	1114166
51	#13 AND #50	1920
52	[animals]/lim NOT [humans]/lim	6084657
53	#51 NOT #52	1737
54	#51 NOT #52 AND [english]/lim	1337

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 ketoconazole to your patients?
    - Yes
    - No
3. I prescribe or administer ketoconazole with my patients as the following: (check all that apply)
    - FDA-approved drug product
    - Compounded drug product
    - Over-the-counter drug product
4. Do you prescribe or administer compounded ketoconazole by any of the following dosage forms and/or routes of administration? (check all that apply)
    - Oral products
    - Topical products
    - Vaginal products
    - None of the above
5. I prescribe or administer compounded ketoconazole for the following conditions or diseases: (check all that apply)
    - Oral fungal infections
    - Topical fungal infections
    - Vaginal fungal infections
    - Other (please explain) _____
6. I prescribe or administer compounded ketoconazole in combination with other active pharmaceutical ingredients as a multi-ingredient product.
    - Yes
    - No
7. I use compounded ketoconazole 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 ketoconazole

- Other (please explain) _____

8. Do you stock non-patient-specific compounded ketoconazole at your practice?
    - Yes
    - No
    - I'm not sure
9. I obtain compounded ketoconazole 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)	○	○	○
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)
    - o Clotrimazole
    - o Fluconazole
    - o Itraconazole
    - o Ketoconazole
    - o Metronidazole
    - o Mupirocin
    - o Zinc oxide
    - o None of the above
3. Do you prescribe the compounded topical products that you selected in combination with other active pharmaceutical ingredients as a multi-ingredient product?
    - o Yes
    - o No
    - o I'm not sure
4. Why do you use the compounded topical products that you selected? (please check all that apply)
    - o Commercial products are not available in the dosage form, strength, or combination I need (please explain) _____
    - o Patient allergies prevent me from using commercially available products (please explain) _____
    - o Patient conditions prevent me from using commercially available products (please explain) _____
    - o I am not aware of any commercially available products containing these products
    - o Other (please explain) _____
5. Do you stock non-patient-specific compounded products at your practice?
    - o Yes
    - o No
    - o I'm not sure
6. I obtain compounded products from the following: (please check all that apply)
    - o Compound myself at my practice
    - o 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 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 2.4. 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 specialtiy(ies)
    - Trauma center
    - Urban hospital
2. Please select the number of beds in the facility with which you are affiliated.
    - < 50
    - 50-99
    - 100-199
    - 200-299
    - 300-399
    - 400-599
    - > 600
3. Do you use an outsourcing facility (503b facility) to obtain any products used in your facility? A list of FDA registered outsourcing facilities can be found at https://www.fda.gov/drugs/human-drug-compounding/registered-outsourcing-facilites.
    - Yes
    - No
4. Why do you use an outsourcing facility to obtain product(s)? Please select all that apply
    - Backorders
    - Convenience
    - Cost
    - Need for concentrations not commercially available
    - Need for preservative-free products
    - Need for ready-to-use products
    - No FDA-approved products available
    - No onsite compounding facility
    - Onsite compounding facility not equipped to compound all necessary products
    - Other, please explain _____
5. Please select the type(s) of products obtained from an outsourcing facility.
    - Nonsterile products
    - Sterile products
6. Please select the category(ies) of products obtained from an outsourcing facility.
    - Cardioplegic solutions
    - Dermatologic preparations
    - Dialysate solutions

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

7. From the list below, please select the drug(s) that you obtain as either a single ingredient or multi-ingredient product from an outsourcing facility.
    - Acetylcysteine
    - Adenosine
    - Aluminum potassium sulfate
    - Aspartic acid
    - Atenolol
    - Atropine
    - Baclofen
    - Betamethasone
    - Biotin
    - Bupivacaine
    - 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.