

Summary Report

Fluticasone propionate

Prepared for:

US Food and Drug Administration

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

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Frequently Used Abbreviations

API	Active Pharmaceutical Ingredient
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 its evaluation of the use of fluticasone propionate (UNII code: O2GMZ0LF5W), 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 fluticasone propionate is used in clinical research and practice to diagnose, prevent, or treat disease. Due to the broad, exploratory nature of this aim, scoping review methodology was used. Following the scoping review framework, a systematic literature review was conducted and health care practitioners were consulted to identify how fluticasone propionate 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 fluticasone propionate and thereby assist the FDA to determine whether there is a need for the inclusion of this substance on the 503B Bulks List.

REVIEW OF NOMINATIONS

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

While the exact medical condition for which the compounded product is being requested is generally unknown, fluticasone propionate is generally used for dermatitis. The nominated formulation is a topical cream. One nominator stated that the strength is based on the prescriber's request, while the other provided 0.005% to 0.1% as a range.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of fluticasone propionate.⁶⁻¹⁵

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

- There are commercially available FDA-approved products containing fluticasone as nasal and inhaled preparations. However, these preparations cannot be used topically or as a source to compound topical preparations because the dosing and excipients would interfere with the compounding process.
- Compounding from bulk drug substances means using only the ingredients necessary to achieve the desired clinical outcomes. The API is in its purest form without any fillers, excipients, fillers, binders, dyes, preservatives, or other materials.
- Individual finished products have more variance than the actual API, and the use of a finished product has the potential to introduce unacceptable inaccuracies into the compounded medication.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of fluticasone propionate products in the United States (US) and around the world. The World Health Organization, the European Medicines Agency (EMA), and globalEDGE were used to identify regulatory agencies in non-US countries. The medicine registers of non-US regulatory agencies were selected for inclusion if they met the following criteria: freely accessible; able to search and retrieve results in 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 fluticasone propionate; name variations of fluticasone propionate were entered if the initial search retrieved no results. The following information from the search results of each register was recorded in a spreadsheet: product trade name; active ingredient; strength; form; ROA; status and/or schedule; approval date. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations.

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

Systematic literature review

Search strategy

A literature review was not conducted for topical single-ingredient fluticasone propionate products due to the availability of FDA-approved single-ingredient fluticasone propionate products for this ROA. The search strategies for the substance that fluticasone propionate was nominated for use in combination with, niacinamide, were used because niacinamide was also nominated for topical administration. A medical librarian constructed comprehensive search strategies for Ovid MEDLINE and Embase. The search strategies used a combination of controlled vocabulary terms and keywords to describe three concepts: niacinamide; topical administration or form; and therapeutic use (refer to Appendix 1 for full search strategies). Results were limited to human studies in English language. Searches were conducted on February 17, 2021. In addition, the ECRI Guidelines Trust[®] repository was searched on February 17, 2021 for clinical practice guidelines that recommended the use of topical fluticasone propionate and provided sufficient information on dosing and administration.

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

Study selection

Studies in which fluticasone propionate was used in the nominated dosage form, ROA, and/or combination product to diagnose, prevent, or treat the nominated disease or condition, or other conditions not specified in the nomination, were included. Studies were excluded if they were written in a language other than English; reviews or meta-analyses; surveys or questionnaires (cross-sectional design); designed to evaluate cost-effectiveness, mechanism of action, preclinical use, safety, or toxicity; or any study design other than a randomized controlled trial conducted in a non-US country. Studies were also excluded if fluticasone propionate was used as an FDA-approved product in the nominated dosage form, ROA, or combination; or a dosage form, ROA, or combination that was not nominated. Studies in which fluticasone propionate was used to diagnose, prevent, or treat autism were excluded due to a separate project examining the use of compounded substances in individuals

with autism. Studies that did not meet the inclusion criteria but provided valuable information about the pharmacological or current or historical use of the substance were noted and put in a separate group in the EndNote library. Two reviewers independently screened titles and abstracts and reviewed full-text articles. A third reviewer reconciled all disagreements.

Data extraction

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

Interviews

Semistructured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances fluticasone propionate was used in a clinical setting. The systematic literature review and indications from the nominations were reviewed to identify medical specialties that would potentially use fluticasone propionate. Potential SMEs were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. Select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided verbal informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were synthesized for qualitative data analysis.

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

Survey

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

- Fluticasone propionate is available as an FDA-approved product in the nominated dosage form and ROA. Fluticasone propionate is also available as a topical lotion and ointment.
- Fluticasone propionate is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for fluticasone propionate.
- Fluticasone propionate is available in the nominated dosage form and ROA in Abu Dhabi, Hong Kong, Latvia, Namibia, Saudi Arabia, and UK.

Table 1. Currently approved products – US^a

Active Ingredient	Concentration	Dosage Form	Route of Administration	Status	Approval Date^b
Fluticasone propionate	0.05%	Cream	Topical	Prescription	5/14/2004

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

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

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

Active Ingredient ^b	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date ^c
Fluticasone propionate	0.05%	Cream	Topical	Abu Dhabi	Active	–
				Hong Kong	Prescription-only	6/9/1994
				Latvia	Prescription	3/15/2000
				Namibia	–	12/28/2003
				Saudi Arabia	Prescription	–
				UK	Prescription-only	10/31/2012

Abbreviation: –, not provided.

^aMedicine registers of national regulatory agencies were searched if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information (product trade name, active ingredient, strength, form, ROA, and approval status) provided in a useable format. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations. See Methodology for full explanation.

^bFluticasone propionate used as the standard for name variations, including fluticasone propionas.

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

Results of literature review

Study selection

Database searches yielded 1266 references; 0 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 1014 titles and abstracts were screened. After screening, the full text of 372 articles was reviewed. Finally, 0 studies were included. Three hundred seventy-two studies were excluded for the following reasons: wrong study design (257 studies); wrong substance (74); non-nominated dosage form or ROA (15); unspecified dosage form or ROA (8); unable to obtain full text (7); fluticasone propionate only mentioned briefly (5); duplicate study (2); FDA-approved product (2); language other than English (2).

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

Characteristics of included studies

No studies were included from the literature review.

Use of fluticasone propionate

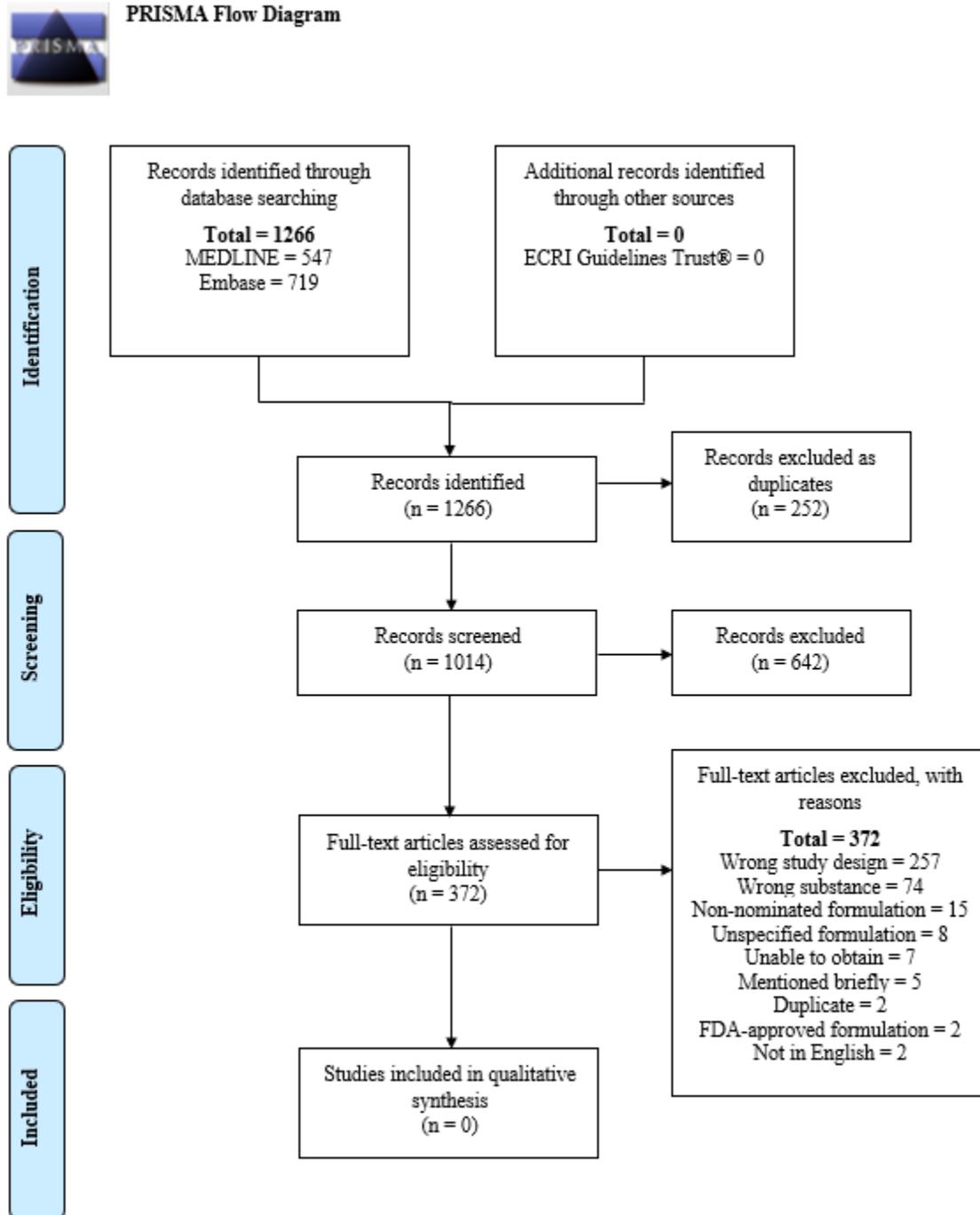
No studies were included from the literature review.

Pharmacology and historical use

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

Fluticasone propionate is a medium potency glucocorticoid (class III) that is used for the topical treatment of various inflammatory skin disorders, especially atopic dermatitis. Fluticasone propionate is commercially available as a topical cream, lotion, and ointment.¹⁰

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



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

Table 3. Types of studies

No studies were included

Table 4. Number of studies by country

No studies were included

Table 5. Summary of included studies

No studies were included

Table 6. Dosage by indication – US

No studies were included

Table 7. Dosage by indication – non-US countries

No studies were included

Table 8. Number of studies by combination

	Combination Formula	Number of Studies
Nominated	Fluticasone propionate 0.05% / Niacinamide 4% – topical cream	0

Table 9. Compounded products – US

No studies were included

Table 10. Compounded products – non-US countries

No studies were included

Results of interviews

One hundred ninety-nine SMEs were contacted for interviews; 63 agreed to be interviewed, and 136 declined or failed to respond to the interview request. One SME discussed fluticasone propionate. The SME was a medical doctor specializing and/or board-certified in dermatology, working in an academic medical institution. The SME had been in practice for 1 year. 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.

Atopic dermatitis is usually a chronic disease and as such usually requires lifelong treatment. One exception is if atopic dermatitis starts in childhood, some may grow out of it; however, some children will continue with the same severity, or it could worsen when they go through adolescence. The SME stated that “so almost everybody will use it chronically; they'll use it for more than a year. But their trajectory may change over years.” The preferred treatment for atopic dermatitis would be “great moisturization and skin care.” For moderate to severe atopic dermatitis, topical steroids will be added. There are also several alternatives to topical steroids, such as crisaborole or topical tacrolimus. Dupilumab, an injectable, is usually reserved for severe atopic dermatitis.

Although the SME thinks there are other choices for topical steroids, using fluticasone would be a valid choice, as the SME points out, “If people prefer fluticasone for some reason, I think [it is] potentially something that some people may want to use.” Another reason to have options is due to the risk of patients developing allergic contact dermatitis to certain steroids. Fluticasone may not be a good alternative because it is in the group that patients most commonly develop allergic contact dermatitis to, and there is cross-reactivity between some commonly used steroids and fluticasone; however, it is possible that a patient would not have a reaction to fluticasone but be reactive to other steroids. All steroids work through the same mechanisms, so they have similar side effects, such as cutaneous atrophy and allergic contact dermatitis. To minimize the risk of cutaneous atrophy, the strength of the steroid should be tailored to the anatomic site and to the treatment duration the patient. While treatment is usually lifelong, most patients will have flare-ups occasionally in different areas of the body so usually patients are not using steroids in one area for a long time. Once the patient is back to baseline, reliance on good skincare should be done to prevent future flare-ups. For using topical compounded steroids specifically, according to this SME, “the fact that [it is] being compounded, I [do not] think adds necessarily to that concern, as long as [it is] being compounded at the right strength and appropriately sterile, or whatever standard they use.”

Regarding the need for products to be compounded without certain excipients, the 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.”

As part of Phase 3, one nominator provided additional information regarding the multi-ingredient product contained within the fluticasone propionate nomination.

Fluticasone propionate 0.05% / niacinamide 4% will be compounded as a topical cream 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: methylparaben and propylene glycol, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include the following: allergen, classified as expected to be

toxic or harmful, classified as skin irritant, endocrine disruptor, human immune and respiratory toxicant or allergen, human respiratory irritant, human skin toxicant or allergen, and possible human carcinogen. Fluticasone is added for its anti-itching 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.

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

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

Another theme regarding deciding what products to purchase from an outsourcing facility focused on the use 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 use 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 Another participant who did not obtain a lot of products from outsourcing facilities stated that “when we do purchase from 503Bs, typically it would be if we just don't have the capacity to keep up with what the demand is.” One participant also commented that they will obtain labor intensive and more complicated products, like epidurals and cardioplegia solutions, from outsourcing facilities to reduce the workload on pharmacy staff. The coronavirus disease 2019 (COVID-19) pandemic has also impacted the operations of hospitals as reflected in comments of 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 evaluating the workload on pharmacy staff, the type and capabilities of the facility also impacted the decision-making process. One participant commented that they do not have an established cleanroom and therefore perform sterile compounding in a segregated compounding area. United States Pharmacopeia (USP) <797> standards limit the beyond-use date that can be assigned to these products and, as the participant stated, “we obviously need to provide product with much extensive beyond use dating than we can provide.” Several participants also commented that they do not perform high-risk compounding in-house and therefore, all of these products are outsourced. There are challenges with midsize hospitals being able “to operationalize testing compounds we make for extended stability.” One participant stated, “we might make our own syringes if we could get extended dating, but I believe my operations colleagues don't always know how to do this and adhere to the letter of the law.”

One participant also commented on the impact that The Joint Commission has had on pushing pharmacies to obtain products from outsourcing facilities. The 2018 medication management standard MM.05.01.07 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 rooms and other settings in which procedures are performed. USP <795> and <797> are applicable in operating room settings, stating that products should be labeled and used within 1-hour, which may be problematic if

syringes are drawn up at the beginning of the day and cases are canceled or delayed. The participant also commented on the cost related to purchasing premade products from manufacturers stating that “predatory pricing on premixes is present in the market.”

Standardization of products, including concentration, volume, and labeling, was also a driver for obtaining products from an outsourcing facility. However, such standardization may not always be possible. One participant stated that when evaluating similar facilities, you would expect them to have similar needs regarding the concentrations and volumes of products used. However, the products used in a facility are often developed in-house over decades based on physician and nurse requests, and more recently, appropriateness for an automated dispensing cabinet. As a result, one participant observed, “these practices had evolved somewhat disparately, even if we had clinical practice guidelines, nobody was putting concentrations into those guidelines and volumes into those guidelines.” This has led to challenges with obtaining certain products from outsourcing facilities. As another participant said, “I think we made nine different epidural concentrations, all driven by anesthesia, and they want what they want, and 503Bs may not offer that. No one else in the country is buying that same concentration; a 503B isn't going to go through the expense of adding that to their product list.” The participant pointed out that “similar with the ADCs [automated dispensing cabinets], we've run into situations where dextrose 50% goes on shortage and the 503Bs would be selling it in a syringe. For safety reasons and for crash cart reasons, without having to retrain thousands of nurses of where things are placed, they said, ‘no, we can't have it, and that's too big! It won't fit!’ We want it in this format, and then we're stuck again because there's no 503B offering a format during that shortage that fits where it needs to go. Then we're stuck in sourcing.” Additionally, while a commercially available product may be available, the volume may not be appropriate. One participant stated that “3% saline for instance, is sold in a 500-mL bag, but the clinical guideline is a 150-mL bolus. We're either going to draw that out or we're sending it to the ER with stickers all over it saying only give 150 [mL].” The participant continued that “it would be great if the FDA could look at the size of the container that they're approving and whether that's a realistic dose: is it a unit dose or isn't it?”

Participants had differing opinions on the use of outsourcing facilities to obtain drugs during a shortage. Several participants stated that they will typically first restrict use of a drug on shortage, in order to conserve supply, before turning to an outsourcing facility. One participant commented that “most of the time, I will probably pursue restricting, conserving, and looking at all available options prior to going to an outsourcer on my end,” and another stated, “I can only think of one time in recent history where we went to an outsourcer.” One participant commented that “503Bs can't accept the additional volume if it's a true shortage. If you're not with them preshortage, you're not going to get products when you need it during the shortage.” The participant added that “typically in a shortage, you learn to live without them. You have to.” Additionally, if the shortage is due to a scarce 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 APIs by outsourcing facilities. One commented that as long as they are conducting end-product sterility and stability testing and the product meets quality standards, they are not concerned with the starting ingredients. As long as buyers are familiar with regulations and know what to look for, another participant commented, there should not be any issues with purchasing products compounded starting from APIs. Another participant stated that as more outsourcing facilities

began using APIs, they became more comfortable with them doing so. However, one participant observed that most outsourcing facilities are switching to sterile-to-sterile and only using APIs if there is a shortage, stating, “I think the FDA has really looked closely at APIs, 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 APIs 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 was never the reason they 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 cleanroom with a dedicated HVAC [heating, ventilation, and air conditioning], so you're talking millions of dollars in investment for actually very low volume. Right now, the ROI [return on investment] isn't there.” Another participant stated that the concentrations required for ophthalmic antibiotics are not available, but the labor and risk of compounding these products in-house is not worth it.

A few participants commented on purchasing nonsterile products from outsourcing facilities. LET (lidocaine-epinephrine-tetracaine) gel, for use as a topical anesthetic, was the most commonly obtained product along with buffered lidocaine to put in J-Tips. Another participant stated that they obtain diclofenac suppositories from an outsourcing facility due to the high cost of indomethacin suppositories. One participant commented that most of the products they outsource are nonsterile products, generally for oral or topical administration due to a lack of commercially available products being available. The participant stated that they purchase low dose naltrexone for oral use in patients with refractory fibromyalgia and ketamine troches for patients with chronic pain. The participant continued that while the evidence does not support many of the ingredients used in topical pain products, “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 [that] 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 nonsterile ingredients; however, there had been challenges with crystallization after storage. A few participants commented that there is a sterile alum powder available, which they purchase to compound in-house. One participant had concerns regarding this powder, stating that “I’ve talked to that company, but I’ve had some concerns for them because they don’t sell it as a drug. The owner was selling you a chemical; we’re selling you a bulk API. It’s just sterile. They were fuzzy and I never followed up but, when I asked about their process for verifying the sterility, as you would with a sterile product, we do USP <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 to 24 hours depending on storage which results in waste.

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

While none of the participants obtained sodium phosphate or aspartic acid from outsourcing facilities for use in cardioplegic solutions, a few commented that they do obtain cardioplegic solutions from outsourcing facilities. The del Nido formulation was the product most commonly obtained. One participant commented that they compound this formulation in-house because the outsourcing facilities

did not offer the volume needed at their institution. Another participant commented that while they do obtain the del Nido formulation from an outsourcing facility, they also compound a proprietary formulation in-house. This participant observed that “it is complicated to do in-house. We do it on a Baxa 1200 or 2400, either one, compounder. Then we send it up for pH and potassium testing. Obviously, then we're confined to 797 beyond-use dates versus longer beyond-use-dates that we get from the 503B.” Another participant commented that cardioplegic solutions are managed by the perfusion department, not pharmacy, and they use del Nido solution as well as 3 other formulations.

The participants also discussed challenges with using outsourcing facilities. One participant stated that their facility does not use outsourcing facilities because “it just hasn't been financially, not just the money worth it, but just the lead time for how much time you have to give them and how much you have to... It just isn't worth the dating that they gave us or can give us.” Another commented that they obtain very little product from outsourcing facilities 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 FDA quality reports and warning letters. Another challenge has been the reliability of the outsourcing facility. One participant commented that “Traditionally, we've found 503Bs to be fairly unreliable, when we have partnered with certain ones, to be able to keep up with the volume. Everybody knows PharMEDium just closed, but we've had some other smaller 503Bs where we've had agreements for certain products to take it off our plate, and then lo and behold they're shut down, or closed, or whatever it may be.” Minimum purchase amounts were also reported as a concern with one participant stating that “what we see consistently is the 503Bs, they want us to commit to giving them a certain volume, but then will not give us a reciprocal commitment or at least will not fulfill that reciprocal commitment. That's a huge problem for us making that type of commitment, when we do ultimately have to split our volume in order to make sure that we consistently are able to take care of our patients.” Another challenge was related to outsourcing facilities using APIs to compound narcotics. One participant commented that this often worsens drug shortages 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

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

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

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

Twenty-seven respondents (19% of 143 responses, where respondents were allowed to select multiple reasons) obtained drug products from outsourcing facilities 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.

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

Table 11. Characteristics of survey respondents

Survey not distributed by any professional medical associations

Table 12. Compounded products prescribed or administered

Survey not distributed by any professional medical associations

Table 13. Reasons for using compounded products

Survey not distributed by any professional medical associations

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

Survey not distributed by any professional medical associations

Table 15. Obtainment of compounded topical products

Survey not distributed by any professional medical associations

Table 16. Demographics of prequestionnaire respondents' facilities

Type of Facility	Responses, n (N = 102) ^a
Academic medical center	15
Acute care hospital	16
Children's hospital	8
Community hospital	11
Critical access hospital	2
Dialysis center	2
Federal government hospital	4

Health system	15
Inpatient rehabilitation center	4
Long-term acute care hospital	3
Outpatient surgery center	6
Rural hospital	2
Skilled nursing facility	0
Specialty hospital ^b	4
Trauma center	5
Urban hospital	5
Number of Beds	Responses, n (N = 39)
< 50	4
50-99	3
100-199	1
200-299	4
300-399	5
400-599	3
> 600	19

^aRespondents allowed to select more than one type of facility.

^bSpecialties 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	8

^aRespondents allowed to select multiple categories.

^bRespondents reported staffing shortages, need for extended dating, volume of product used, standardization projects as additional reasons for utilizing outsourcing facilities.

Table 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

^aRespondents allowed to select multiple categories.

^bRespondents 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

^aRespondents were allowed to select multiple products.

CONCLUSION

Fluticasone propionate was nominated for inclusion on the 503B Bulks List as a 0.005% to 0.1% topical cream and while the exact medical condition for which the compounded product is being requested is generally unknown, fluticasone propionate is generally used for dermatitis. Fluticasone propionate is available in the nominated dosage form and ROA in Abu Dhabi, Hong Kong, Latvia, Namibia, Saudi Arabia, the UK, and the US.

No studies were included from the literature review.

From the interviews, atopic dermatitis treatment is typically focused on providing moisturization. Topical steroids may be added for moderate to severe disease. Patients generally only use topical steroids while they are experiencing a flare-up, after which a return to ensuring good skincare is done. Fluticasone propionate may be a reasonable choice but is in the groups of steroids that patients most commonly develop allergic contact dermatitis.

As part of Phase 3, one nominator provided additional information regarding the multi-ingredient product contained within the fluticasone propionate nomination. Fluticasone propionate 0.05% / niacinamide 4% will be compounded as a topical cream to treat dermatitis. This product will be compounded without methylparaben and propylene glycol as inactive ingredients, which are known to be harmful allergens or irritants. Fluticasone propionate is added for its anti-itching properties and niacinamide for its skin conditioning benefits.

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

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APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process, and other non-indexed citations and daily 1946 to February 15, 2021
- Date last searched: February 17, 2021
- Limits: Humans (search hedge); English language
- Number of results: 547
- Note: See search strategy methodology for explanation as to why searches for niacinamide were used

1	niacinamide/	12,605
2	amid\$ pp.tw.	4
3	nicotinamid\$.tw.	21,934
4	niacetamid\$.tw.	0
5	niacinamid\$.tw.	521
6	niacin amid\$.tw.	3
7	nicamid\$.tw.	0
8	nicosedin\$.tw.	0
9	nicotamid\$.tw.	14
10	(nicotinic adj2 amid\$.tw.	115
11	nicotinoylamid\$.tw.	1
12	ni#otinsaureamid\$.tw.	0
13	nikotamin\$.tw.	0
14	vitamin\$ b3.tw.	447
15	vitamin\$ b 3.tw.	54
16	vitamin\$ pp.tw.	164
17	or/1-16	31,012
18	administration, topical/	38,889
19	administration, cutaneous/	22,495

20	skin absorption/	11,855
21	topical\$.tw.	108,892
22	transcutaneous\$.tw.	14,884
23	epicutaneous\$.tw.	2047
24	transdermal\$.tw.	15,053
25	((cutaneous\$ or dermal\$ or skin) adj3 (absorb\$ or absorpt\$ or appl\$)).tw.	11,638
26	exp gels/	53,703
27	emulsions/	18,535
28	suspensions/	7853
29	liniments/	124
30	ointments/	12,869
31	skin cream/	1105
32	pharmaceutical solutions/	3318
33	gel?.tw.	312,791
34	emulsion?.tw.	34,471
35	suspension?.tw.	111,680
36	liniment?.tw.	148
37	ointment?.tw.	12,175
38	salve?.tw.	345
39	paste?.tw.	12,971
40	unguent\$.tw.	114
41	lotion?.tw.	2387
42	cream?.tw.	19,567
43	shampoo?.tw.	1451
44	solution?.tw.	724,460
45	foam?.tw.	26,959

46	spray?.tw.	29,279
47	or/18-46	1,393,811
48	drug combinations/	74,281
49	drug therapy/	30,745
50	ad.fs.	1,440,913
51	dt.fs.	2,279,437
52	de.fs.	3,038,277
53	tu.fs.	2,266,830
54	pc.fs.	1,320,022
55	therap\$.tw.	2,912,001
56	treat\$.tw.	5,728,068
57	prevent\$.tw.	1,481,240
58	prophyl\$.tw.	170,862
59	or/48-58	11,330,971
60	and/17,47,59	987
61	exp animals/ not humans/	4,788,182
62	60 not 61	600
63	limit 62 to english language	547

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: February 17, 2021
- Limits: Humans (search hedge); English language
- Number of results: 719
- Note: See search strategy methodology for explanation as to why searches for niacinamide were used

1	'nicotinamide'/de	16,352
2	'amid* pp':ti,ab,tn	7
3	'nicotinamid*':ti,ab,tn	26,488
4	'niacetamid*':ti,ab,tn	0
5	'niacinamid*':ti,ab,tn	817
6	'nicamid*':ti,ab,tn	1
7	'nicosedin*':ti,ab,tn	0
8	'nicotamid*':ti,ab,tn	26
9	(nicotinic NEAR/2 acid*):ti,ab,tn	9655
10	'nicotinoylamid*':ti,ab,tn	2
11	'nicotinsaureamid*':ti,ab,tn	6
12	'nikotinsaureamid*':ti,ab,tn	2
13	'nikotamin*':ti,ab,tn	0
14	'vitamin* b3':ti,ab,tn	528
15	'vitamin* b 3':ti,ab,tn	20
16	'vitamin* pp':ti,ab,tn	297
17	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	43,433
18	'topical drug administration'/de	84,340
19	'cutaneous drug administration'/de	756
20	'transdermal drug administration'/de	9303
21	'skin absorption'/de	8173

22	'topical treatment'/de	13,841
23	'topical*':ti,ab	154,166
24	'epicutaneous*':ti,ab	3472
25	'transdermal*':ti,ab	21,973
26	((cutaneous* OR dermal* OR skin) NEAR/3 (absorb* OR absorp* OR appl*)):ti,ab	18,393
27	'cream'/de	9831
28	'gel'/exp	81,210
29	'liniment'/de	257
30	'lotion'/de	2968
31	'ointment'/de	18,280
32	'paste'/de	2552
33	'salve'/de	170
34	'suspension'/de	28,635
35	'emulsion'/exp	47,909
36	'shampoo'/de	2344
37	'foam'/de	8507
38	'aerosol'/de	65,844
39	'cream\$':ti,ab	30,590
40	'emulsion\$':ti,ab	46,594
41	'liniment\$':ti,ab	242
42	'lotion\$':ti,ab	4119
43	'ointment\$':ti,ab	22,009
44	'paste\$':ti,ab	15,484
45	'salve\$':ti,ab	485
46	'unguent*':ti,ab	242
47	'gel\$':ti,ab	367,818

48	'suspension\$:ti,ab	148,453
49	'shampoo\$:ti,ab	2271
50	'foam\$:ti,ab	35,415
51	'spray\$:ti,ab	38,973
52	#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 OR #50 OR #51	1,015,468
53	'drug combination'/de	172,266
54	'drug therapy'/de	793,878
55	'drug dose':lnk	629,758
56	'drug administration':lnk	1,797,602
57	'drug therapy':lnk	4,019,840
58	'prevention':lnk	1,199,296
59	'therap*':ti,ab	4,363,252
60	'treat*':ti,ab	8,276,184
61	'prevent*':ti,ab	2,007,332
62	'prophyl*':ti,ab	272,296
63	#53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62	13,822,305
64	#17 AND #52 AND #63	1035
65	[animals]/lim NOT [humans]/lim	6,170,289
66	#64 NOT #65	822
67	#64 NOT #65 AND [english]/lim	719

Appendix 2.1. Survey instrument for professional medical associations

1. How familiar are you with the following terms?

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

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

Appendix 2.2. Survey instrument for pharmacy roundtable prequestionnaire

1. Please select all that apply regarding the facility with which you are affiliated.
 - Academic medical center
 - Acute care hospital
 - Children's hospital
 - Community hospital
 - Critical access hospital
 - Dialysis center
 - Federal government hospital
 - Health system
 - Inpatient rehabilitation center
 - Long-term acute care hospital
 - Outpatient surgery center
 - Rural hospital
 - Skilled nursing facility
 - Specialty hospital, please identify 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 on-site compounding facility
 - On-site compounding facility not equipped to compound all necessary products
 - Other, please explain _____
5. Please select the type(s) of products obtained from an outsourcing facility.
 - Nonsterile products
 - Sterile products
6. Please select the category(ies) of products obtained from an outsourcing facility.
 - Cardioplegic solutions
 - Dermatologic preparations
 - Dialysate solutions

- Fluids
 - Ophthalmic preparations
 - Patient-controlled analgesia
 - Ready-to-use anesthesia syringes
 - Ready-to-use antibiotic syringes and/or bags
 - Ready-to-use electrolyte solutions
 - Ready-to-use vasopressor solutions
 - Total parenteral nutrition solutions
 - Other, please identify _____
7. From the list below, please select the drug(s) that you obtain as either a single ingredient or multi-ingredient product from an outsourcing facility.
- Acetylcysteine
 - Adenosine
 - Aluminum potassium sulfate
 - Aspartic acid
 - Atenolol
 - Atropine
 - Baclofen
 - Betamethasone
 - Biotin
 - Bupivacaine
 - Calcium chloride
 - Caffeine sodium benzoate
 - Cholecalciferol
 - Chromium chloride
 - Clonidine
 - Dexamethasone sodium phosphate
 - Diclofenac
 - Gentamicin
 - Glycerin
 - Hydroxyzine
 - Ketamine
 - Levocarnitine
 - Lidocaine
 - Lorazepam
 - Magnesium sulfate
 - Manganese chloride
 - Methylprednisolone
 - Midazolam
 - Mupirocin
 - Norepinephrine
 - Ondansetron
 - Phytonadione
 - Potassium chloride
 - Potassium phosphate
 - Prilocaine
 - Proline
 - Propranolol
 - Ropivacaine
 - Sodium chloride
 - Sodium citrate

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

Appendix 3. Survey distribution to professional associations

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

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