Summary Report

Cholestyramine resin

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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 cholestyramine resin (UNII code: 4B33BGI082), 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 cholestyramine resin 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 cholestyramine resin 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 cholestyramine resin 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 NOMINATION

Cholestyramine resin was nominated for inclusion on the 503B Bulks List by Triangle Compounding Pharmacy, Inc for chronic mold exposure, skin infections from diaper rash, or wounds exposed to bile acids via oral capsules, powder for oral suspension mixture (pure powder with no filler or inactive ingredients or a 10% dilution of powder with compatible inactive ingredients), and a topical 10-35% paste, cream, and ointment.

The nominator provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of cholestyramine resin.[6-12]

The reason provided for nomination to the 503B Bulks List is because the FDA-approved products contain unwanted inactive ingredients such as “sugar or artificial sweeteners that counteract the treatment protocol.”

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of cholestyramine resin 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 cholestyramine resin; name variations of cholestyramine resin 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 cholestyramine resin. 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 strategy for Ovid MEDLINE used a combination of controlled vocabulary terms and keywords to describe two concepts: cholestyramine resin, and topical or oral administration or form. The search strategy for Embase used a combination of controlled vocabulary terms and key words to describe three concepts: cholestyramine resin, topical or oral administration or form, and therapeutic use (refer to Appendix 1 for full search strategies). Results were limited human studies in English language. Searches were conducted on August 25, 2020. In addition, the ECRI Guidelines Trust® repository was searched on August 25, 2020 for clinical practice guidelines that recommended the use of cholestyramine resin 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 cholestyramine resin 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 cholestyramine resin 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 cholestyramine resin 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 cholestyramine resin; setting; total number of patients; number of patients who received cholestyramine resin; patient population; indication for use of cholestyramine resin; dosage form and strength; dose; ROA; frequency and duration of therapy; use of cholestyramine resin in a combination product; use and formulation of cholestyramine resin in a compounded product; use of cholestyramine resin 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 cholestyramine resin 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 cholestyramine resin. 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 cholestyramine resin 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

- Cholestyramine resin is available as an FDA-approved product in the nominated dosage form and ROA.
- Cholestyramine resin is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for cholestyramine resin.
- Cholestyramine resin is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, Ireland, New Zealand, Saudi Arabia, and UK. In Hong Kong, cholestyramine powder is available as an OTC product.

Table 1. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Status	Approval Date[b]
Cholestyramine resin	EQ 4 g resin/packet or scoopful	Powder	Oral	Prescription	8/15/1996

[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[b]	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date[c]
Cholestyramine resin	4g/sachet	Powder for solution or suspension	Oral	Abu Dhabi	Active	–
				Australia	Prescription-only	8/13/1991
				Belgium	Prescription	3/7/1974
				Canada	Prescription	12/31/1993
				Ireland	Prescription-only renewable	4/1/1979
				New Zealand	Prescription	10/24/1991
				Saudi Arabia	Prescription	–
				UK	Prescription-only	7/25/1988

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]Cholestyramine resin used as the standard for name variations, including colestyramine.

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

Results of literature review

Study selection

Database searches yielded 985 references; 1 additional reference was identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 811 titles and abstracts were screened. After screening, the full text of 24 articles was reviewed. Five studies were included; after multiple reports of the same study were merged, there were 4 included studies. Nineteen studies were excluded for the following reasons: wrong study design (13 studies); wrong dosage form or ROA (3); wrong indication (2); unspecified dosage form or ROA (1).

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

Characteristics of included studies

The 4 included studies were published between 1976 and 2019. There were 2 experimental studies, 0 observational studies, 2 descriptive studies, and 0 clinical practice guidelines. The 4 studies were conducted in the following countries: Iran and US.

A total of 40 patients participated in the 4 included studies. The number of patients in each study ranged from 1 to 30.

Outcome measures differed among the included studies and included: improvement and resolution of the rash, days when clinical improvement noticed, days for complete cure, burning and pruritus severity, and erythema and secretion (subjectively evaluated).

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

Use of cholestyramine resin

Two patients received cholestyramine resin as a treatment for buttocks rash, administered as a topical 5% ointment after each bowel movement for 7 days. Eight patients received cholestyramine resin for skin inflammation around cutaneous enterostomies, administered as a topical 20% ointment for 7 to 12 days. Thirty patients received cholestyramine resin for pruritus and burning after ileostomy, administered as a topical 15% ointment approximately 1 g/day for 2 months.

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

Cholestyramine resin was used as a compounded product (topical ointment), and it was not nominated as a combination product (refer to Tables 8-10).

In all 4 studies, the authors' concluding statement recommended the use of cholestyramine resin for the treatment of buttocks rash, skin inflammation around the cutaneous enterostomies, and pruritus and burning after ileostomy.[12-15] Refer to Table 5 for summary of authors' conclusions.

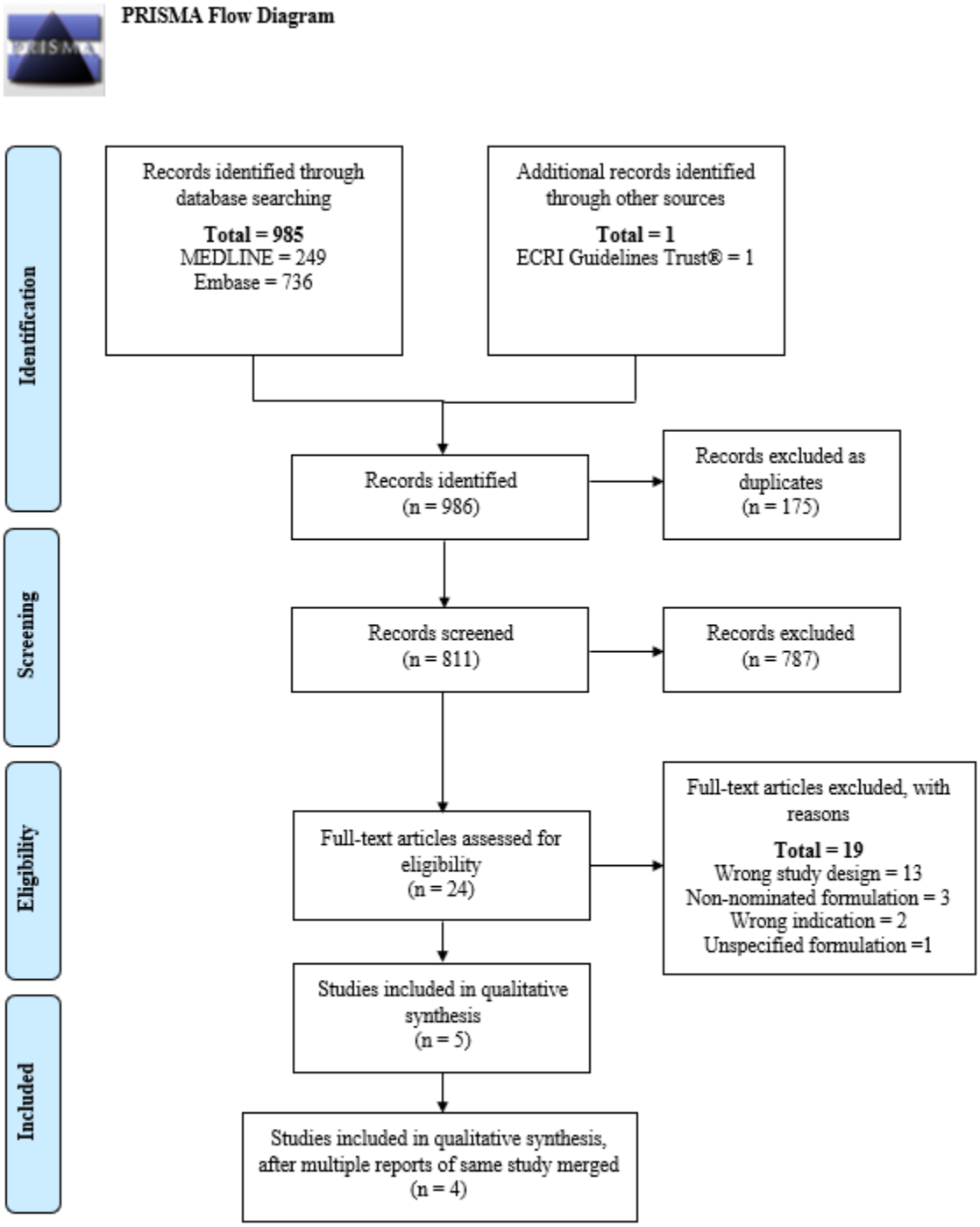
Pharmacology and historical use

In addition to the 4 included studies, 3 additional studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of cholestyramine resin.

Cholestyramine, a bile acid sequestrant, "forms a non-absorbable complex with bile acids in the intestine."[13] Bile acids have strong irritative properties and are thought to contribute to skin irritation

around the ileostomy and colostomy sites, which is a common complication after surgery.[16] Bile acids may also contribute to this complication "because of their altered intestinal metabolism after these procedures."[16] Because cholestyramine has an inhibitory effect on bile salts, cholestyramine has been tested as a topical formulation in some studies to reduce the inflammatory effects of the bile acids.[13] Some indications it has been tested for include "pain after hemorrhoidectomy, irritant diaper dermatitis, perianal skin irritation following ileoanal anastomosis, skin irritation around enterostomies, biliary fistulas, perianal irritation, and diaper rash."[13] White *et al* reported two separate cases of buttocks rashes they successfully treated with topical cholestyramine 5% ointment. White *et al* stated they have used cholestyramine ointment to treat adult ostomy sites for many years in the oncology department and found that the 5% formulation "gives a much smoother end-product that is easier to prepare and apply."[15] White *et al* also mentioned that topical cholestyramine has been used since the 1970s to treat skin breakdown related to ostomy sites and cited studies by Rodriguez *et al* and Moller *et al* showing positive results with using cholestyramine ointment.[12,15] In 1976, Rodriguez *et al* used a cholestyramine 20% ointment in Aquaphor to treat 8 patients with skin inflammation around the enterostomies while 2 patients served as the control group and received Aquaphor only.[14] The 2 patients who received Aquaphor alone did not respond to the treatment while all patients, except one lost to follow-up, who received cholestyramine were cured within 7-12 days.[14] In 1987, Moller *et al* used cholestyramine 20% ointment in 2 patients and cholestyramine 5% ointment in 4 patients for perianal inflammation.[17] Healing was achieved in all patients in 6 to 10 days.[17] Moller *et al* also found that cholestyramine 5% in polyethylene glycol base "was the only compound without a tendency to precipitate."[17] There is also an Australian case report from 1980 by Bell and Varigos about a 57 year old patient with skin irritations around biliary fistula that were not alleviated by mercurochrome and Stomahesive. This patient was then treated with cholestyramine ointment daily and within 48 hours of cholestyramine initiation, the skin inflammation almost completely subsided.[18]

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[12,15]	2
Observational	0
Experimental[13,14]	2

Table 4. Number of studies by country

Country	**Number of Studies**
Iran[13]	1
US[12,14,15]	3
	Total US: 3 Total Non-US Countries: 1

Table 5. Summary of included studies

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 1: Buttocks rash					
White *et al*, 1996, US[15]	Case report	1 Patient with reflux and regurgitation was treated with cisapride and developed a rash on the buttocks and anal irritation (100%, 2 months)	• Cholestyramine ointment (1)	Improvement in/resolution of rash	"This case shows that topical cholestyramine ointment may be a successful therapy for infants and children with rash and excoriation of the anus and buttocks due to a hyperdynamic gastrointestinal tract or when many other treatment modalities have failed. Based on cholestyramine's proven safety as an oral agent and the literature on cholestyramine for ostomy, it appears that topical cholestyramine is a safe treatment option for this indication."
White *et al*, 2003, US[12]	Case report	1 Patient who developed a severe and painful buttocks rash refractory to standard therapies (100%, 23 days)	• Cholestyramine ointment (1)	Improvement in/resolution of rash	"Cholestyramine ointment can be compounded and may provide benefit for infants who have a severe buttocks rash that is refractory to traditional therapies."
Indication 2: Skin inflammation about cutaneous enterostomies					
Rodriguez *et al*, 1976, US[14]	–	8 Patients with skin inflammation about the enterostomies (gender and age not specified)	• Cholestyramine ointment (8) • Control - Aquaphor alone (2)	Days when clinical improvement noticed, days for complete cure	"This cytotoxic effect of free bile acids could be an important mechanism contributing to the inflammation and ulceration of the skin around enterostomies. The local application of a bile acid binding resin, cholestyramine, had an impressive therapeutic benefit."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 3: Pruritus and burning after ileostomy					
Ala *et al.*, 2019, Iran[13] Ala *et al.*, 2017, Iran[19]	Double-blind, randomized clinical trial	30 Patients who underwent ileostomy • Cholestyramine (60%, mean 58 y ± 14.8) • Placebo (66.67%, mean 56.5 y ± 13.9)	• Cholestyramine ointment (15) • Placebo (15)	Burning and pruritus severity based on the visual analog scale; erythema and secretion were subjectively evaluated	"The results revealed that the topical cholestyramine formulation (15%) was well tolerated by the patients and had significant effects on the reduction of both burning and pruritus after an ileostomy."

Abbreviation: "–", not mentioned.
[a]As defined by authors.

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Buttocks rash[12,15]	Applied after each bowl movement	5%	Ointment	Topical	7 days
Skin inflammation about cutaneous enterostomies[14]	–	20%	Ointment	Topical	7-12 days

Abbreviation: "–", not mentioned.

Table 7. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Pruritus and burning after ileostomy[13]	Approximately 1 g/day	15%	Ointment	Topical	2 months

Abbreviation: "–", not mentioned.

Table 8. Number of studies by combination

No combination products were nominated

Table 9. Compounded products – US

Indication	Publication Year	Compounding Method	Dosage Form	Final Strength
Buttocks rash[12,15]	1996, 2003	3 packets of cholestyramine powder (12 g total) were dispersed in 120 mL of sterile water for irrigation. 120g of Aquaphor was placed in a 240 mL ointment jar and microwaved on medium power for approximately 15 minutes and stirred in 5-minute intervals. The cholestyramine suspension was added to the melted Aquaphor while stirring continuously. After cooling, the ointment may be dispensed.	Ointment	5%

Table 10. Compounded products – non-US countries

Indication	Compounding Method	Dosage Form	Final Strength
Pruritus and burning after ileostomy[13]	Cholestyramine ointment prepared using liquid paraffin as the levigating agent in a petrolatum base.	Ointment	15%

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. Two SMEs discussed cholestyramine resin. Between these 2 SMEs, there was 1 medical doctor and 1 nurse practitioner. The SMEs specialized and/or were board-certified in dermatology and wound care, working in academic medical centers. The SMEs had been in practice for 1 to 40 years.

One SME stated that they do not do much compounding, but they do mix lidocaine in office for surgeries. They may also prescribe some compounded drugs for cosmetic indications such as melasma and warts. One SME with experience in dermatology commented that cholestyramine resin is for bile duct related pruritus and works by "drawing out [the] bile acids." This SME had not seen cholestyramine resin used for skin infections and commented that they do not "know of a good mechanism for that." While this SME had never used topical cholestyramine before and did not know how effective it may be, they expressed that it is probably safe because it is not systemic and not likely to cause skin issues. For a patient with an itch related to bile acid back-up, they will most likely have to apply the topical product to a very large area. Although this SME also expressed that they do not know if people who use topical cholestyramine apply it broadly or only to the problem locations. This SME also does not see the need for topical cholestyramine to be stocked in the office because bile duct related pruritus is an ongoing itch problem and patients do not need to come to the office for treatment.

Another SME with experience in wound care stated that they have not used topical cholestyramine before but "it makes sense that that might work." Cholestyramine is benign when used topically and would be for fistulas and ostomy (wound drainage). Because those places tend to be a superficial injury, cholestyramine should not be highly absorbed and is probably more of a physical barrier. This SME typically uses zinc oxide-based or dimethicone-based products and noted that usually products with a lot of zinc are good. There are many different products on the market, the most important factor to this SME is that is it heavy and sticky enough so that it will stay in place as well as minimize allergens.

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

Zero people responded to the survey distributed via professional medical associations and available on the project website.

A prequestionnaire was distributed to participants of the roundtable discussion (refer to Appendix 2.3 for survey instrument).

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

Twenty-seven respondents (19% of 143 responses, where respondents were allowed to select multiple reasons) obtained drug products from outsourcing facilities due to a need for ready-to-use products and 20 respondents (14%) obtained drug products from outsourcing facilities due to backorders (refer to Table 16).

Fourteen respondents (31% of 45 total responses, where respondents were allowed to select multiple types) obtained nonsterile products from outsourcing facilities and 31 (69%) obtained sterile products from outsourcing facilities. Refer to Table 17 for the categories of products obtained from outsourcing facilities.

Cholestyramine resin was not included on the prequestionnaire (refer to Table 18).

Table 11. Characteristics of survey respondents

No respondents to survey distributed via professional medical associations

Table 12. Conditions for which cholestyramine resin prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded cholestyramine resin

No respondents to survey distributed via professional medical associations

Table 14. Use of non-patient-specific compounded cholestyramine resin

No respondents to survey distributed via professional medical associations

Table 15. Demographics of prequestionnaire respondents' facilities

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

Categories	Responses, n (N=143)[a]
Backorders	20
Convenience	19
Cost	10
Need for concentrations not commercially available	19
Need for multi-ingredient products not commercially available	10
Need for preservative-free products	3
Need for ready-to-use products	27
No FDA-approved product available	7
No onsite compounding facility	1
Onsite compounding facility not equipped to compound all necessary products	19
Other[b]	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 17. Categories of products obtained from outsourcing facilities

Categories	Responses, n (N=142)[a]
Cardioplegic solutions	14
Dermatologic preparations	6
Dialysate solutions	0
Fluids	8
Ophthalmic preparations	10
Patient-controlled analgesia	20
Ready-to-use anesthesia syringes	25
Ready-to-use antibiotic syringes and/or bags	14

Ready-to-use electrolyte solutions	5
Ready-to-use vasopressor solutions	18
Total parenteral nutrition solutions	16
Other[b]	6

[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 18. Products obtained from an outsourcing facility

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

Glycerin	1
Hydroxyzine	0
Ketamine	14
Levocarnitine	0
Lidocaine	8
Lorazepam	2
Magnesium sulfate	4
Manganese chloride	0
Methylprednisolone	0
Midazolam	15
Mupirocin	1
Norepinephrine	15
Ondansetron	0
Phytonadione	0
Potassium chloride	0
Potassium phosphate	0
Prilocaine	0
Proline	0
Propranolol	1
Ropivacaine	6
Sodium chloride	0
Sodium citrate	3
Sodium phosphate	0
Tetracaine	2
Triamcinolone acetonide	0
Tropicamide	0

None of the above	8

[a]Respondents were allowed to select multiple products.

CONCLUSION

Cholestyramine resin was nominated for inclusion on the 503B Bulks List for chronic mold exposure, skin infection from diaper rash, or wounds exposed to bile acids via oral capsules, powder oral suspension mixture, and topical 10-35% paste, cream, and ointment. Cholestyramine resin is available as an FDA-approved oral powder; it is also available as an oral powder in Abu Dhabi, Australia, Belgium, Canada, Ireland, New Zealand, Saudi Arabia, and UK. In Hong Kong, cholestyramine powder is available as an OTC product.

From the literature review, cholestyramine resin has been used for buttocks rash, skin inflammation around the cutaneous enterostomies, and pruritus/burning after ileostomy. Out of the 4 included studies, 3 studies used compounded cholestyramine resin as a topical ointment.

From the interviews conducted, neither of the SMEs had used topical cholestyramine. The SME with experience in dermatology commented that cholestyramine resin is for bile duct related pruritis. While this SME has never used topical cholestyramine before, they expressed that it is probably safe because it is not systemic and not likely to cause skin issues. The other SME with experience in wound care stated that cholestyramine is benign when used topically and would be for fistulas and ostomy (wound drainage). Because those places tend to be a superficial injury, cholestyramine should not be highly absorbed and is probably more of a physical barrier. One SME commented that they do not see the need for topical cholestyramine to be stocked in the office because bile duct related pruritus is an ongoing itch problem and patients do not need to come to the office for treatment.

Zero people responded to the survey distributed via professional medical associations and available on the project website.

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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 August 24, 2020
- Date last searched: August 25, 2020
- Limits: Humans (search hedge); English language
- Number of results: 249

1	cholestyramine resin/	2627
2	c?olest#ramin$.tw.	2484
3	resincolestiramin$.tw.	0
4	resincoles tiramin$.tw.	0
5	or/1-4	3556
6	administration, oral/	142954
7	administration, sublingual/	2958
8	oral$.tw.	673321
9	sublabial$.tw.	410
10	sublingual$.tw.	10981
11	supralingual$.tw.	19
12	capsules/	12742
13	suspensions/	7753
14	capsule?.tw.	78461
15	syrup?.tw.	5654
16	elixir?.tw.	643
17	suspension?.tw.	109158
18	administration, topical/	38451
19	administration, cutaneous/	22082
20	skin absorption/	11693

21	topical$.tw.	105631
22	epicutaneous$.tw.	2014
23	transdermal$.tw.	14620
24	((cutaneous$ or dermal$ or skin) adj3 (absorb$ or absorpt$ or appl$)).tw.	12282
25	emulsions/	17966
26	exp gels/	52025
27	liniments/	123
28	ointments/	12796
29	skin cream/	1034
30	emulsion?.tw.	33206
31	liniment?.tw.	145
32	ointment?.tw.	11863
33	salve?.tw.	341
34	paste?.tw.	12503
35	unguent$.tw.	113
36	lotion?.tw.	2309
37	cream?.tw.	18981
38	or/6-37	1147028
39	and/5,38	393
40	exp animals/ not humans/	4727814
41	39 not 40	283
42	limit 41 to english language	249

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: August 25, 2020
- Limits: Humans (search hedge); English language
- Number of results: 736

1	‘colestyramine'/mj	4178
2	‘c$olestyramin*':ti,ab,tn	3361
3	‘c$olestiramin*':ti,ab,tn	25
4	‘resincolestiramin*':ti,ab,tn	5
5	‘resincoles tiramin*':ti,ab,tn	0
6	#1 OR #2 OR #3 OR #4 OR #5	5831
7	‘sublabial drug administration'/de	63
8	‘sublingual drug administration'/de	4486
9	‘supralingual drug administration'/de	4
10	‘oral drug administration'/de	406212
11	‘oral*':ti,ab	968006
12	‘sublingual*':ti,ab	16537
13	‘sublabial*':ti,ab	547
14	‘supralingual*':ti,ab	26
15	‘drug capsule'/de	9083
16	‘elixir'/de	489
17	‘suspension'/de	27283
18	‘capsule$':ti,ab	114522
19	‘elixir$':ti,ab	974
20	‘syrup$':ti,ab	8425
21	‘suspension$':ti,ab	145053
22	‘topical drug administration'/de	82671

23	‘cutaneous drug administration'/de	664
24	‘transdermal drug administration'/de	9062
25	‘skin absorption'/de	8055
26	‘topical treatment'/de	13031
27	‘topical*':ti,ab	149606
28	‘epicutaneous*':ti,ab	3416
29	‘transdermal*':ti,ab	21395
30	((cutaneous* OR dermal* OR skin) NEAR/3 (absorb* OR absorp* OR appl*)):ti,ab	17964
31	‘cream'/de	9446
32	‘liniment'/de	251
33	‘lotion'/de	2864
34	‘ointment'/de	17920
35	‘paste'/de	2521
36	‘salve'/de	166
37	‘cream$':ti,ab	29685
38	‘emulsion$':ti,ab	45144
39	‘liniment$':ti,ab	234
40	‘lotion$':ti,ab	4007
41	‘ointment$':ti,ab	21598
42	‘paste$':ti,ab	15000
43	‘salve$':ti,ab	476
44	‘unguent*':ti,ab	240
45	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44	1848641
46	‘drug therapy'/de	744214
47	‘add on therapy'/de	18897

48	‘drug comparison':lnk	589601
49	‘drug dose':lnk	625740
50	‘drug administration':lnk	1755878
51	‘drug therapy':lnk	3926083
52	‘prevention':lnk	1177387
53	‘therap*':ti,ab	4205001
54	‘treat*':ti,ab	7995979
55	‘prevent*':ti,ab	1935556
56	‘prophyla*':ti,ab	263575
57	#46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56	13484891
58	#6 AND #45 AND #57	1214
59	[animals]/lim NOT [humans]/lim	6078717
60	#58 NOT #59	1014
61	#58 NOT #59 AND [english]/lim	736

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 cholestyramine resin to your patients?
    - Yes
    - No
3. Do you prescribe or administer cholestyramine resin by any of the following dosage forms and/or routes of administration? (check all that apply)
    - Powder for oral suspension
    - Oral capsules
    - Topical paste, cream, ointment
    - None of the above
4. I prescribe or administer cholestyramine resin for the following conditions or diseases: (check all that apply)
    - Chronic mold exposure
    - Skin infection from diaper rash or wounds exposed to bile acids (anal/rectal)
    - Other (please explain) _____
5. I prescribe or administer cholestyramine resin with my patients as the following: (check all that apply)
    - FDA-approved product
    - Compounded drug product
    - Over-the-counter drug product
    - Other (please explain) _____
6. I use compounded cholestyramine resin 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 cholestyramine resin
    - Other (please explain) _____
7. Do you stock non-patient-specific compounded cholestyramine resin at your practice?
    - Yes

- No
- I'm not sure

8. I obtain compounded cholestyramine resin 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) _____
9. 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) _____
10. 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)
    - ○ Betamethasone acetate
    - ○ Betamethasone dipropionate
    - ○ Betamethasone sodium phosphate
    - ○ Cholestyramine resin
    - ○ Cimetidine
    - ○ Clobetasol propionate
    - ○ Clotrimazole
    - ○ Cromolyn sodium
    - ○ Dexamethasone sodium phosphate
    - ○ Diclofenac sodium
    - ○ Finasteride
    - ○ Fluconazole
    - ○ Fluticasone propionate
    - ○ Hydrocortisone
    - ○ Itraconazole
    - ○ Ketoconazole
    - ○ Lidocaine hydrochloride
    - ○ Methylprednisolone acetate
    - ○ Metronidazole
    - ○ Mupirocin
    - ○ Niacinamide
    - ○ Phytonadione (vitamin K1)
    - ○ Prilocaine
    - ○ Spironolactone
    - ○ Sulfacetamide sodium monohydrate
    - ○ Terbinafine hydrochloride
    - ○ Tetracaine hydrochloride
    - ○ Triamcinolone acetonide
    - ○ Zinc oxide

- None of the above

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

Appendix 2.3. Survey instrument for pharmacy roundtable prequestionnaire

1. Please select all that apply regarding the facility with which you are affiliated.
    - Academic medical center
    - Acute care hospital
    - Children's hospital
    - Community hospital
    - Critical access hospital
    - Dialysis center
    - Federal government hospital
    - Health system
    - Inpatient rehabilitation center
    - Long-term acute care hospital
    - Outpatient surgery center
    - Rural hospital
    - Skilled nursing facility
    - Specialty hospital, please identify 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.