

Summary Report

Cromolyn sodium

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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 United States (US) Food and Drug Administration (FDA) in its evaluation of the use of cromolyn sodium (UNII code: Q2WXR110PK), 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 cromolyn sodium 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 cromolyn sodium has been used historically and currently.¹⁻³ Assessments of study quality and risk of bias were not performed because the aim of this report was not to make specific recommendations on the use of this substance in clinical practice.^{1,4,5} Rather, the aim was to summarize the available evidence on the use of cromolyn sodium 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

Cromolyn sodium was nominated for inclusion on the 503B Bulks List by Triangle Compounding Pharmacy, Inc.

Cromolyn sodium was nominated for the treatment of allergies, inflammatory response, histamine release, and mast cell activation via capsules, liquids, gels, ointments, creams, solutions, and suspensions for oral, mucosal, nasal, and topical administration.

The nominator provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of cromolyn sodium.⁶⁻⁹

The reasons provided for nomination to the 503B Bulks List included 1) the preferred formulation for systemic effect is an oral capsule instead of the nasal spray and 2) the commercial product is a diluted nasal spray, but prescriptions are typically for higher doses of oral capsules or topical creams, and the nasal spray is not ideal when compounding topical creams.

METHODOLOGY

Background information

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

Each medicine register was searched for cromolyn sodium; name variations of cromolyn sodium 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; route of administration (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 cromolyn sodium. The availability of OTC products (yes/no) in the US and the ROAs of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

Search strategy

A medical librarian constructed comprehensive search strategies for Ovid MEDLINE and Embase. The search strategies used a combination of controlled vocabulary terms and keywords to describe three concepts: cromolyn sodium; oral, nasal, mucosal, or topical administration or form; therapeutic or preventative use for allergy, asthma, or bronchospasm (refer to Appendix 1 for full search strategies). Results were limited to human studies in the English language. Searches were conducted on August 31, 2020. In addition, the ECRI Guidelines Trust[®] repository was searched on August 31, 2020, for clinical practice guidelines that recommended the use of cromolyn sodium and provided sufficient information on dosing and administration.

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

Study selection

Studies in which cromolyn sodium 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 cromolyn sodium was used as an FDA-approved product in the nominated dosage form, ROA, or combination; a dosage form, ROA, or combination that was not nominated; an unspecified dosage form or ROA; cromolyn sodium not used clinically; or cromolyn sodium was mentioned briefly as a rescue treatment or a previously failed treatment. Studies in which cromolyn sodium 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 cromolyn sodium; setting; total number of patients; number of patients who received cromolyn sodium; patient population; indication for the use of cromolyn sodium; dosage form and strength; dose; ROA; frequency and duration of therapy; use of cromolyn sodium in a combination product; use and formulation of

cromolyn sodium in a compounded product; use of cromolyn sodium 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 cromolyn sodium was used in a clinical setting. The systematic literature review and indications from the nomination were reviewed to identify medical specialties that would potentially use cromolyn sodium. 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 3 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 cromolyn sodium in clinical practice. The online survey was created using Qualtrics[®] software (refer to Appendix 3 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 4 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

- Cromolyn sodium is available as an FDA-approved product in the nominated dosage form and ROA. Cromolyn sodium is also available as a 10% solution for inhalation and a 4% ophthalmic solution.
- Cromolyn sodium was available as an FDA-approved oral 100 mg capsule that was discontinued, not for reasons of safety or efficacy.
- Cromolyn sodium is available as an OTC nasal product in the US.
- There is a current United States Pharmacopeia (USP) monograph for cromolyn sodium.
- Cromolyn sodium is available in the nominated dosage form and ROA in Abu Dhabi, Canada, Namibia, New Zealand, and UK.

Table 1. Currently approved products – US^a

Active Ingredient	Concentration	Dosage Form	Route of Administration	Status	Approval Date^b
Cromolyn sodium	100 mg/5 mL	Concentrate	Oral	Prescription	2/29/1996

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

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

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

Active Ingredient	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date ^b
Cromolyn sodium	100 mg	Capsule	Oral	Abu Dhabi	Active	–
				Canada	Prescription	12/31/1981
				New Zealand	Prescription	11/20/1977
				UK	Prescription-only	5/01/2005
Cromolyn sodium	20 mg/mL	Solution	Oral	Abu Dhabi	Active	–
Cromolyn sodium	2-4%	Spray	Nasal	Abu Dhabi	Active	–
				Australia	Pharmacy medicine ^c	10/21/1991
				Namibia	–	8/18/2004
				New Zealand	Pharmacy-only ^c	8/17/2006

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 usable 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.

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

^cPharmacy-only medications may only be sold in a pharmacy, and a pharmacist must make or supervise the sale.

Results of literature review

Study selection

Database searches yielded 4990 references; 1 additional reference was identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 3380 titles and abstracts were screened. After screening, the full text of 947 articles was reviewed. Ninety-seven studies were included; after multiple reports of the same study were merged, there were 88 included studies. Eight hundred fifty studies were excluded for the following reasons: wrong study design (615 studies); wrong dosage form or ROA (90); unspecified dosage form or ROA (78); FDA approved product (39); cromolyn sodium not used clinically (12); unable to obtain full text (10); cromolyn sodium only mentioned briefly (5); wrong substance (1).

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

Characteristics of included studies

The 88 included studies were published between 1971 and 2019. There were 76 experimental studies, 1 observational study, 11 descriptive studies, and 0 clinical practice guidelines. The 88 studies were conducted in the following countries: Australia, Canada, Denmark, France, Germany, Hungary, Iran, Italy, Japan, Norway, Singapore, Spain, Sweden, the Netherlands, UK, and US.

A total of 3987 patients participated in the 88 included studies. The number of patients in each study ranged from 1 to 409.

Outcome measures differed among the included studies and included: resolution/relief of clinical signs, daily diary of symptoms, use of other therapy, histological examination of biopsy, appearance of nasal mucosa, wheal, flare areas, blood flow on Doppler, tolerance to allergen challenge, side effects, nasal airways resistance ratio, serum immunoglobulin levels, number and characteristics of stools, liver function test, renal function test, urinalysis, prick testing, patient preference for treatment, clinical and sigmoidoscopic activity, rectal biopsy, sigmoidoscopy, daily stool frequency.

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

Use of cromolyn sodium

Nine hundred forty-one patients received cromolyn sodium for allergy treatment and/or prevention, administered as a nasal capsule, metered nebulizer, powder for insufflator or solution in doses ranging from 15 mg/day to 40 mg/day per nostril for 2 to 16 weeks. Cromolyn sodium was also administered as an oral capsule in doses ranging from 100 mg/day to 1600 mg/day for 1 to 18 months, as a topical 0.2% to 4% cream or solution for one time to 3 days, and as a vaginal 4% cream in a dose of 5 mL once.

Five hundred seventy-one patients received cromolyn sodium as treatment for atopic dermatitis/atopic eczema, administered as an oral capsule in doses ranging from 30 mg/kg/day to 40 mg/kg/day or 400 mg/day to 800 mg/day. Cromolyn sodium was also administered as an oral 2% to 4% aqueous solution in doses ranging from 400 mg/day to 1600 mg/day for 8 weeks. Topically, cromolyn sodium has been administered as a topical 0.21% to 10% cream, lotion, nebulizer solution, emulsion, and ointment for 2-64 weeks. One study specified a topical 0.21% cream in a dose of 80 mg/m²/day for 1

month while another study provided a mean dosing of $80.8 \text{ g/m}^2 \pm 55.55$ to $91.5 \text{ g/m}^2 \pm 50.37$ for a topical 4% emulsion that was given for 12 weeks.

One hundred eighty-five patients received cromolyn sodium as a treatment for Crohn's disease and/or ulcerative colitis, administered as an oral capsule or tablet in doses ranging from 800 mg/day to 2000 mg/day for 4 weeks-6 months or as an enema in a dose of 1200 mg/day for 2 weeks.

Two hundred seventy-two patients received cromolyn sodium as a treatment for irritable bowel syndrome (IBS), administered as an oral capsule in doses ranging from 450 mg/day to 2000 mg/day for 4 to 52 weeks.

Eight patients received cromolyn sodium as a treatment for mastocytosis, administered as an oral capsule in a dose of 400 mg/day for 1 to 26 months or as a topical 4% cream.

Eight patients received cromolyn sodium as a treatment for pyoderma gangrenosum, administered as a topical 1% to 4% solution for 2 to 52 weeks.

One hundred one patients received cromolyn sodium as a treatment for pruritus/urticaria, administered as an oral capsule in doses ranging from 405 mg/day to 800 mg/day for 4 to 8 weeks. Cromolyn sodium was also administered as topical 1% to 4% cream or emulsion in a dose of 4 mL for one time to 4 weeks.

Twenty-six patients received cromolyn sodium as a treatment for chronic proctitis, administered as an oral capsule in a dose of 300 mg/day for 4 weeks or as a rectal enema in a dose of 400 mg/day for 4 weeks.

Ten patients received cromolyn sodium as a treatment for exercise-induced asthma, administered as an oral capsule in doses ranging from 200 mg/day to 800 mg/day for 2 days.

Two patients received cromolyn sodium as a treatment for mast cell activation syndrome, administered as an oral douche. The dose and duration of treatment were unspecified.

Thirteen patients received cromolyn sodium as a treatment for recalcitrant idiopathic vulvar vestibulitis, administered as a topical 4% cream for 3 months.

Five patients received cromolyn sodium as a treatment for recombinant human insulin-induced lipatrophy, administered as an unspecified topical 4% product for 4 to 20 weeks.

Fifteen patients received cromolyn sodium as a treatment for recurrent aphthous ulcers, administered as a mucosal or oral tablet in a dose of 800 mg/day for 30 days.

Thirteen patients received cromolyn sodium as a treatment for urticaria pigmentosa, administered as an oral capsule in doses ranging from 200 mg/day to 800 mg/day for 4 weeks

Twelve patients received cromolyn sodium as a treatment for varioliform gastritis, administered as an oral liquid in doses ranging from 200 mg/day to 400 mg/day for 28 days.

Forty-nine patients received cromolyn sodium as a treatment for vasomotor rhinitis, administered as a capsule via the nasal route in a dose of 20 mg/day per nostril for 6 weeks.

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

Cromolyn sodium was used as a compounded product (cream and capsule), but it was not used in a combination product (refer to Tables 8-10).

In 45 studies, the authors' concluding statement recommended the use of cromolyn sodium for the treatment and/or prevention of allergy,¹⁰⁻³¹ atopic dermatitis/atopic eczema,³²⁻⁴⁰ irritable bowel

syndrome,⁴¹⁻⁴³ mastocytosis,⁴⁴⁻⁴⁷ pyoderma gangrenosum,⁴⁸⁻⁵⁰ pruritus/urticaria,⁵¹⁻⁵³ mast cell activation syndrome,⁵⁴ recombinant human insulin-induced lipodystrophy,⁵⁵ recurrent aphthous ulcers,⁵⁶ urticaria pigmentosa,⁵⁷ and varioliform gastritis.⁵⁸ In 12 studies, the authors concluded that the use of cromolyn sodium was not recommended for the treatment and/or prevention of allergy,⁵⁹⁻⁶³ atopic dermatitis/atopic eczema,⁶⁴⁻⁶⁶ Crohn's disease and/or ulcerative colitis,⁶⁷⁻⁷⁰ and pruritus/urticaria.⁷¹ In 3 studies, the authors concluded that the efficacy of cromolyn sodium was similar to that of other study interventions for the treatment and/or prevention of allergy⁷² and atopic dermatitis/atopic eczema.^{73,74} In 7 studies, the authors concluded that further studies were necessary for the use of cromolyn sodium in treatment and/or prevention of allergy,^{75,76} atopic dermatitis/atopic eczema,^{77,78} irritable bowel syndrome,⁷⁹ pyoderma gangrenosum,⁸⁰ and recalcitrant idiopathic vulvar vestibulitis.⁸¹ In 1 study, the authors concluded that the use of cromolyn sodium is favorable for nasal symptoms of allergic rhinoconjunctivitis and suggested further studies of cromolyn sodium for eye symptoms.⁸² In 15 studies, the authors did not provide a definitive conclusion for the use of cromolyn sodium.⁸³⁻¹⁰¹ In 5 studies, the authors' conclusions did not address the use of cromolyn sodium.¹⁰²⁻¹⁰⁶ Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

Additional studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of cromolyn sodium.

Cromolyn sodium was developed in the late 1950s and 1960s, and became available in Great Britain in 1968 for prophylaxis of asthma.⁷⁶ Cromolyn sodium entered the US market in 1973 as a treatment for asthma.¹⁰⁷ The mechanism of action is not entirely understood but its primary mechanism is to act as a mast cell stabilizer by inhibiting mast cell degranulation caused by immunoglobulin E (IgE) antibody reactions and other nonimmunological substances.¹⁰⁷ Cromolyn sodium has “anti-allergic, anti-pruritic and anti-inflammatory properties” and works by “[inhibiting] the release of inflammatory mediators from [sensitized] mast cells.”³³ Cromolyn sodium is “lipid insoluble and poorly absorbed from the gastrointestinal tract after oral administration” and therefore the effects are “primarily topical” and must be considered when determining how to deliver the drug to the target organ.^{108,109} Cromolyn sodium is commercially available as a 4% ophthalmic solution to treat vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis, a 5.2 mg/spray nasal spray for treatment and prevention of nasal symptoms of hay fever and other nasal allergies, a 10 mg/mL solution for inhalation for the prophylaxis of bronchial asthma, and a 100 mg/5mL oral concentrate for the management of mastocytosis.¹¹⁰⁻¹¹³

When administered prior to exposure to an allergen, cromolyn sodium has been found to be effective for several “type I immediate hypersensitivity reactions, including allergic rhinitis, allergic ocular disorders, systemic mastocytosis, and gastrointestinal allergy.”^{107,114} Cromolyn sodium has an added benefit of blocking both immediate and late allergic reactions, whereas bronchodilators and corticosteroids only inhibit the immediate reaction or the late reaction.^{108,114} Cromolyn sodium has been shown to be effective in nonallergic disorders including ulcerative colitis, recurrent aphthous ulcers, and interstitial cystitis.¹¹⁵

Studies have evaluated the use of cromolyn sodium in patients with food allergies; however, results have been mixed.^{109,115,116} Cavagni and Caffarelli conducted a literature review of studies and concluded that “avoidance of the offending food is the treatment of choice” and that use of cromolyn sodium should only be considered if avoidance is difficult, the offending food is contained in many foods, there is hypersensitivity to many foods, or to increase efficacy of an elimination diet.¹¹⁷ Similarly, Businco et al emphasized that avoidance of the offending food should remain the primary

treatment and that use of cromolyn sodium should only be used “when symptoms persist even after a well-controlled food avoidance.”¹¹⁸ A more recent overview of diagnosing and treating food allergies and intolerances conducted by Patriarca et al in 2009 reiterated the challenges that people may face with avoidance diets and stated that while “there are no controlled studies certifying its efficacy” cromolyn sodium may be used prophylactically.¹¹⁹

Cromolyn sodium has also been studied for use in ulcerative colitis and irritable bowel syndrome. Zhang et al reviewed the role of mast cells in irritable bowel syndrome stating that “recent discoveries of MCs [mast cells] in the pathophysiology of IBS [irritable bowel syndrome] have revealed numerous potential therapeutic targets.”¹²⁰ While the studies that have been conducted have methodological flaws, Spanier et al completed a systematic review of alternative therapies in the treatment of irritable bowel syndrome and found that oral cromolyn appears to be as effective as elimination diets and stated that cromolyn is “a reasonable choice before elimination diets are initiated.”¹²¹ Similarly, Park and Camilleri conducted a systematic review to evaluate the role of food allergy in the etiology and management of patients with irritable bowel syndrome. Based on the published evidence, the authors proposed an algorithm for managing irritable bowel syndrome due to food hypersensitivity, indicating that cromolyn sodium may be considered if symptoms are unresolved after a trial of an exclusion diet.¹²² However, additional studies should be completed to identify the clinical benefit and the patients that would benefit from this treatment.^{120,122}

Pyoderma gangraenosum is a rare, chronic inflammatory ulcerative skin disease that is characterized by ulcers with “heaped up and undermined borders and a necrotic base.”¹²³ Systemic treatment with high-dose corticosteroids is typically the first-line therapy, followed by dapsone, clofazimine, azathioprine, and recently cyclosporine A.¹²³ However, these therapies are associated with severe side-effects limiting their use. Lip was the first to report the successful treatment of 5 patients with chronic leg ulcers with the contents of 1 to 6 cromolyn sodium capsules sprinkled on the ulcer and wrapped with a non-adhesive dressing.¹²⁴ de Cock and Thorne reported the successful use of a 2% aqueous solution of cromolyn sodium in 2 patients, Massone treated 1 patient with a 2% cromolyn sodium solution applied 3 times daily for 1 hour, and Langenbach had success with a 4% formulation in 1 patient.¹²⁵⁻¹²⁷ Tamir et al also reported positive results after treating 5 patients with a 1% topical solution of cromolyn sodium with initial improvement seen after 3 to 7 days and complete healing after 5 to 8 weeks.¹²⁸ Rongioletti et al published the results of a case report in which a patient with blastomycosis-like pyoderma, a “vegetating tissue reaction, often secondary to a bacterial infection occurring in patients with a compromised immune system.”¹²⁹ The patient failed initial treatment with antibiotics and curettage. Because they were aware of cromolyn sodium’s success in the treatment of chronic leg ulcers, the authors treated the patient for 1 month with a topical 4% cromolyn sodium preparation, after which the lesion healed.¹²⁹ However, there have been no controlled trials evaluating the efficacy.^{123,130}

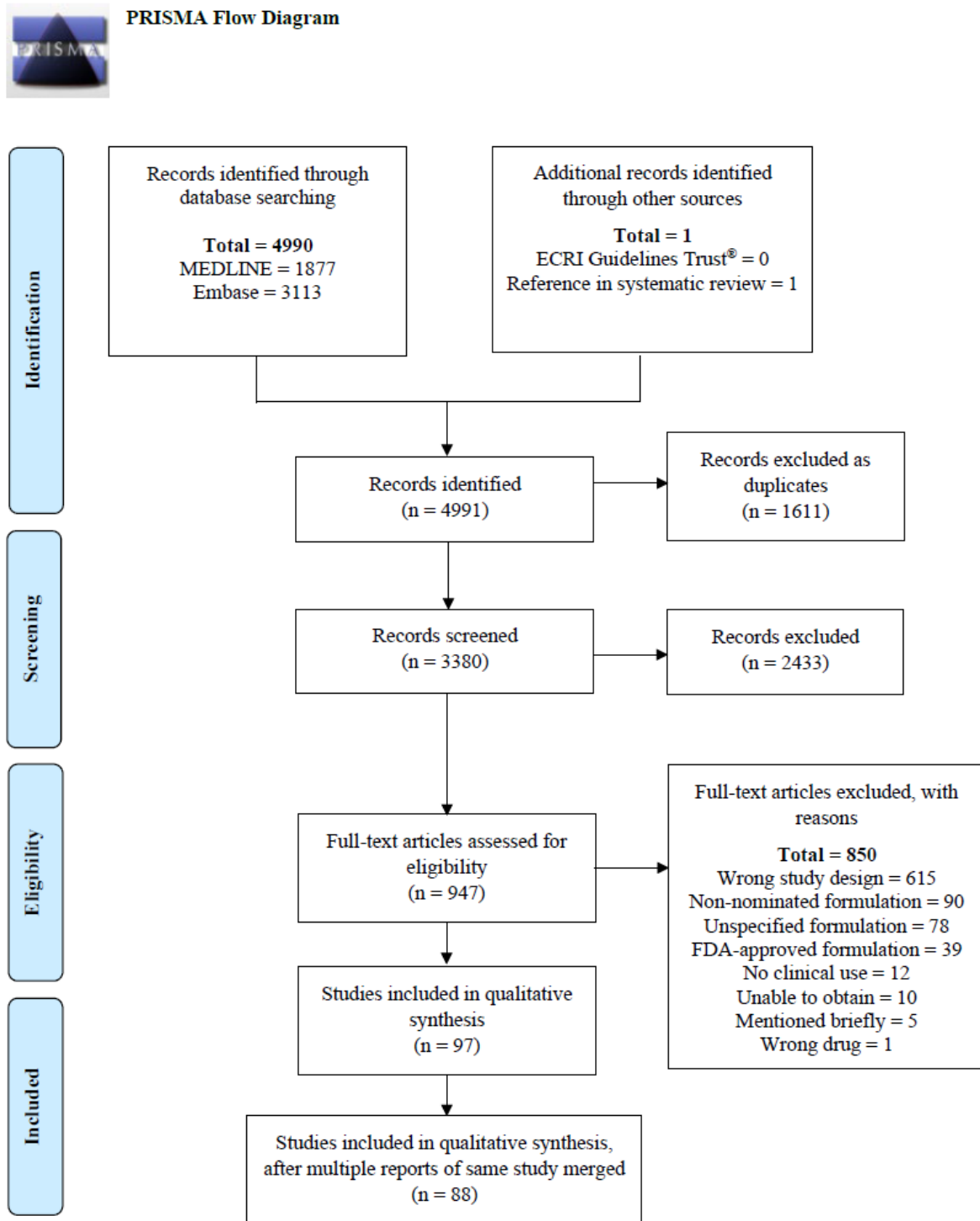
Mastocytosis is a “heterogenous group of disorders characterized by abnormal growth and accumulation of mast cells in one or more organ systems.”¹³¹ Mastocytosis is categorized into 3 groups: cutaneous, systemic, and localized mast cell tumors.¹³² In cutaneous mastocytosis (CM), mast cells accumulate only in the skin and can be further divided into maculopapular cutaneous mastocytosis (also called urticaria pigmentosa), diffuse cutaneous mastocytosis, and localized mastocytoma of the skin.¹³² CM is typically diagnosed in childhood, with urticaria pigmentosa the most common presentation, accounting for 70% to 90% of cases.¹³³ Systemic mastocytosis (SM) is more commonly diagnosed in adults and involves the accumulation of mast cells in 1 or more internal organs with or without skin involvement and includes indolent SM, smoldering SM, aggressive SM, SM with an associated hematologic neoplasm, and mast cell leukemia.¹³² Symptoms are “thought to

be due to the release of histamine from mast cells” and can vary depending on the organ system or systems involved.^{134,135} Treatment typically includes use of H₁ and H₂ antagonists to block the effect of histamine, or a mast cell stabilizer like cromolyn sodium.^{134,135} A 2019 review of treatment options for mast cell activation syndrome and mastocytosis includes the use of cromolyn at starting doses of 100 mg orally daily titrated to 200 mg 4 times daily, with patients with severe gastrointestinal symptoms potentially needing doses of 1000 to 1200 mg daily.¹³⁶ Additionally, the review includes the use of a 1% to 4% sodium cromolyn cream or ointment for management of cutaneous symptoms.¹³⁶ The 2011 “Guidelines for the Diagnosis and Treatment of Cutaneous Mastocytosis in Children” also recommends the use of a water-soluble cromolyn sodium cream.¹³³ There is a commercially available oral formulation of cromolyn that is approved for management of patients with mastocytosis, but there is no topical formulation.¹¹⁰

Allen published a formula for a cromolyn sodium topical gel that contains 1 g of cromolyn sodium, carbopol 941 as a gelling agent, triethanolamine to adjust the viscosity, benzalkonium chloride, edetate disodium, water, and ethanol.¹³⁷ Pesko published a formula for a cromolyn sodium 10% topical lotion that contains 20 g of cromolyn sodium mixed with water and then incorporated into anhydrous lanolin.¹³⁸ Zur reviewed the various topical formulations that have been reported in the literature to identify the optimal formulation to treat atopic dermatitis and other skin allergies.¹³⁹ Cromolyn sodium is hydrophilic and has minimal passive diffusion into the lipophilic stratum corneum. As a result, the ingredients and methods used are important to “ensure sufficient penetration of the active ingredient into the skin and achieve good clinical results.”¹³⁹ When preparing the topical product, Zur states that cromolyn sodium should be completely dissolved in water, an appropriate base should be selected, and then the solution should be incorporated into the base using an electronic mortar and pestle.¹³⁹ Zur includes a formulation for a 4% cromolyn sodium cream using 4 g of cromolyn sodium, sodium benzoate, water, and Basiscream BAK.¹³⁹

Studies were also found in which cromolyn sodium was used for indications that were not nominated. Safaeian et al conducted a study in which 40 mg/4mL of a cromolyn sodium 4% solution and 50 mL of a 0.5% Marcaine[®] solution were used as a bladder instillation in 10 women with interstitial cystitis. After receiving 4 weekly bladder instillations with the solution, patients had a significant improvement in their O’Leary-Sant Interstitial Cystitis Symptom and Problem Index, the Urogenital Distress Inventory, and the Visual Analog Scale for Urgency and Pain.¹⁴⁰ Based on these positive results, the authors indicated that a double-blind cross-over study was pending; however, no record of this study was identified.¹⁴⁰ Sato et al conducted a study in which 30 patients with IgA nephropathy were randomly divided into 2 groups; one group received 1200 mg/day of oral cromolyn sodium and the second, control group received no treatment. After 16 weeks of treatment, patients who received cromolyn sodium had a significant reduction in proteinuria compared to the control group. However, no significant changes were noted in the creatinine clearance, serum albumin, serum IgA, and IgA circulating immune complex. The authors concluded that cromolyn sodium “may reduce proteinuria in some patients with IgA nephropathy over a short course of therapy” but stated that additional studies were needed to determine the effectiveness of cromolyn sodium.¹⁴¹ Toppet et al administered a 1-time dose of the commercially available cromolyn sodium by inhalation in 9 children and nasal administration in 9 children, all with severe sickle-cell disease.¹⁴² The percentage of sickle cells was measured prior to the treatment, 1 hour after, and 24 hours after the dose. In both treatment groups the percentage of sickle cells significantly decreased, indicating that cromolyn sodium is “a good candidate for antisickling treatment, and its activity both in vitro and ex vivo is associated with a very low toxicity.”¹⁴²

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 ^{10,48-50,54,55,80,94,99,102,104,105}	11
Observational ¹⁰⁶	1
Experimental ^{11-47,51-53,56-79,81-93,95-98,100,101,103}	76

Table 4. Number of studies by country

Country	Number of Studies
Australia ^{29,41,61,83}	4
Canada ^{14,18,23,24,31}	4
Denmark ^{71,77,91,96,103}	5
France ⁵⁸	1
Germany ^{53,57}	2
Hungary ⁶⁰	1
Iran ^{51,52,93}	3
Italy ^{25,28,34,42,43}	5
Japan ^{17,36,37,85,88}	5
Norway ⁶⁹	1
Singapore ⁷⁸	1
Spain ^{12,79}	2
Sweden ^{16,66,75,82,87,97}	6
The Netherlands ²⁶	1
United Kingdom ^{11,13,15,22,30,32,33,35,39,56,59,62,63,65,67,68,70,72,73,84,86,89,90,92,95,98,100,101}	24
United States ^{10,19-21,27,38,40,44-50,54,55,64,76,80,81,94,99,102,104-106}	22
Multiple Countries <ul style="list-style-type: none"> • Norway, United Kindgom⁷⁴ 	1
Total US: 22	
Total Non-US Countries: 66	

Table 5. Summary of included studies

Refer to Appendix 2

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Treatment or prevention of allergy ^{10,19-21,27,76,102}	15-30 mg/day/nostril	5-20 mg 2%	Capsule, metered nebulizer, solution	Nasal	4-6.86 weeks
	–	25-50 mg	Capsule	Oral	1-18 months
	1-4 times daily	4%	Cream, solution	Topical	Once – 3 days
	5 cc (1 vaginal applicator full)	4%	Cream	Vaginal	Once
Mastocytosis ^{44-47,94,99,104,105}	400 mg/day	100 mg	Capsule	Oral	1-26 months
	–	4%	Cream	Topical	–
Pyoderma gangrenosum ^{48-50,80,106}	–	1-4%	Solution	Topical	2-52 weeks
Atopic dermatitis ^{38,40,64}	30-40 mg/kg/day	–	Capsule	Oral	9 days
	80 mg/m ² /day	0.21%	Cream	Topical	1 month
Mast cell activation syndrome ⁵⁴	–	100-200 mg	Douche	Oral	–
Recalcitrant idiopathic vulvar vestibulitis ⁸¹	3 times daily	4%	Cream	Topical	3 months
Recombinant human insulin-induced lipoatrophy ⁵⁵	2 times daily	4%	–	Topical	4-20 weeks

Abbreviation: –, not provided.

Table 7. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Treatment or prevention of allergy ^{11-14,16-18,22-26,28-31,53,59-63,72,75,82-86,98,103}	15-40 mg/day/nostril	10-20 mg 2-4%	Capsule, powder for insufflator, solution	Nasal	2-16 weeks
	100-1600 mg/day	25-150 mg	Capsule	Oral	4 weeks
	Once daily	0.2-4%	Cream	Topical	Once
Atopic dermatitis/atopic eczema ^{32-37,39,65,66,73,74,77,78,87-90}	400-800 mg/day	100 mg	Capsule	Oral	4-6 weeks
	400-1600 mg/day	2-4%	Aqueous solution	Oral	8 weeks
	1-3 times daily	1-10%	Cream, lotion, nebulizer solution, ointment	Topical	2-64 weeks
	Mean 80.8 g/m ² ± 55.55 to mean 91.5 g/m ² ± 50.37	4%	Emulsion	Topical	12 weeks
Crohn's disease ⁷⁰ and/or ulcerative colitis ^{67-69,91,92}	1200 mg/day	600 mg	Enema	–	2 weeks
	800-2000 mg/day	200 mg	Capsule, tablet	Oral	4 weeks – 6 months
Irritable bowel syndrome ^{41-43,79,93}	450-2000 mg/day	50-200 mg	Capsule	Oral	4-52 weeks
Pruritus/urticaria ^{15,51,52,71}	405-800 mg/day	135-200 mg	Capsule	Oral	4-8 weeks
	4 mL Twice daily	1-4%	Cream, emulsion	Topical	Once – 4 weeks
Chronic proctitis ^{95,100,101}	300 mg/day	100 mg	Capsule	Oral	4 weeks
	400 mg/day	200 mg	Enema	Rectal	4 weeks

Exercise-induced asthma ⁹⁶	200-800 mg/day	100 mg	Capsule	Oral	2 days
Recurrent aphthous ulcers ⁵⁶	800 mg/day	200 mg	Tablet	Mucosal, oral	30 days
Urticaria pigmentosa ⁵⁷	200-800 mg/day	100 mg	Capsule	Oral	4 weeks
Varioliform gastritis ⁵⁸	200-400 mg/day	–	Liquid	Oral	28 days
Vasomotor rhinitis ⁹⁷	20 mg/day/nostril	10 mg	Capsule	Nasal	6 weeks

Abbreviation: –, not provided.

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
Allergy ¹⁰	1991	“A 4% cromolyn cream was compounded by dissolving powdered cromolyn sodium into an inert water-based cream. HEB cream contains purified water mineral oil, white petrolatum, stearyl alcohol, cetyl alcohol, sodium lauryl sulfate, methylparaben, and propyl paraben as preservatives.”	Cream	4%
Atopic dermatitis ³⁸	1998	Cromolyn inhalation solution (Intal) 20 mg/2 mL mixed with Velvachol cream. Then 80 mg (8 mL) of Intal inhalation solution was mixed into 1 oz of Velvachol cream.	Cream	0.21%
Recalcitrant idiopathic vulvar vestibulitis ⁸¹	2001	“Cromolyn cream consisted of a 4% preparation of cromolyn powder mixed in a hydrophilic cream base.”	Cream	4%
Recombinant human insulin-induced lipotrophy ⁵⁵	2008	“Topical 4% sodium cromolyn was prepared in petrolatum solvent.”	–	4%

Abbreviation: –, not provided.

Table 10. Compounded products – non-US countries

Indication	Compounding Method	Dosage Form	Final Strength
Chronic kidney disease-associated pruritus ⁵²	“[Cromolyn sodium] was formulated into capsules (size 2) using 135 mg of cromolyn powder plus 30 mg lactose powder as filler.”	Capsule	135 mg
Irritable bowel syndrome ⁷⁹	“[Disodium cromoglycate] was prepared at the hospital pharmacy as a powder mix on a starch base containing no lactose, and delivered in opaque gelatine capsules.”	Capsule	200 mg

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. Six SMEs discussed cromolyn sodium. The 6 SMEs were medical doctors who specialized and/or were board-certified in allergy, dermatology, oncology, and primary care, working in academic medical institutions and private practice. The SMEs had been in practice for 1 to 52 years.

Three SMEs discussed the use of cromolyn sodium for patients with mast cell activation syndromes and mastocytosis. Mast cell activation is “a syndrome of chronic inappropriate activation of some portion of the body’s mast cells” and “the mast cell produces more than a thousand different very potent mediators, each of which has a huge range of effects in the body.” A range of symptoms is seen in these patients depending on which mast cells are activated. Typically, this involves inflammation, “allergic issues,” and dystrophisms, which are the “inappropriate growth or development in various tissues.” Patients may have gastrointestinal symptoms like nausea, vomiting, and diarrhea; “brain organic syndrome” (forgetfulness); a short memory span; anxiety; the inability to concentrate; and potentially even depression. Some patients may have dental, gingival, and oral mucosal problems, hair loss, and “some women have extraordinary difficulties in the genital tract with very painful vulvitis, chronic refractory vaginitis, very painful dyspareunia, painful intercourse, or severe, abnormal, uterine bleeding/excessive menstruation.”

Cromolyn is a “main stage drug” and “first-line therapy” that has been shown to inhibit mast cell activation and can be “a very helpful drug in mast cell disease.” Cromolyn blocks the release of mast cells but the mechanism by which it works is not clearly understood. There is some thought that “it binds some receptors on mast cells” as well as neutrophils, but the exact receptor it binds to is still unknown. Another SME stated that it is “thought to stabilize mast cells and therefore decrease their activation or degranulation. So, when you treat mast cell activation syndrome, we use drugs to block the mediators that are released, like antihistamines, to block the histamine receptors, but that's already too late; the mast cells have already degranulated and released over 200 chemicals. If we can decrease the degranulation, obviously that's a better result.”

Patients are typically maintained on cromolyn indefinitely, or “as long as the drug is still working,” at doses ranging from 200 mg to 1200 mg taken anywhere from 2 to 6 times a day. The 3 SMEs stated that they use all of the commercially available formulations of cromolyn leading to “profound effects” on a patient’s symptoms. One SME stated that they will use the commercially available products in “novel ways.” For patients with oral mucosal problems, they said, “I tell them to take some oral cromolyn and do an oral rinse, a mouthwash with cromolyn” and for patients with hair loss the SME has the patients “try mixing some cromolyn into their shampoo. The SME will also use the liquid cromolyn and have patients “apply it as a vaginal douche or a cromolyn soaped tampon, or a compounded cromolyn and vaginal suppository” to help control genital tract issues and will have patients with skin related effects mix the liquid cromolyn “into a jar of whatever skin cream they already know they tolerate and mix it up” to formulate a cream to apply to the affected areas.

One SME commented that they would prefer to start patients on a compounded formulation of cromolyn, but it is not always covered by a patient’s insurance and even though it is often cheaper than the commercially available product, patients prefer to start with the commercially available product. The SME said that “these patients unpredictably are very reactive to these drugs, these additives.” Patients may tolerate one manufacturer’s product but when switched to a different manufacturer, patients “suddenly have a mast cell flare.” Prescribers have to be very cautious because of these sensitivities and will “therefore resort to compounded cromolyn to avoid the problem.” Another SME does not use a compounded formulation frequently, stating that “the reason we’re getting it compounded almost always

is because the patient is reacting to some excipient in one or more of the commercially available formulations.” The SME said that, “[i]t’s very common for these patients, particularly the more severely afflicted mast cell patients to react to the . . . for their dysfunctional mast cells to be further triggered, to activate even further by various excipients in the medication products. Very common for mast cell patients to react adversely to medication products, but when such reactions happen, it’s almost never because of the drug and instead, it’s almost always because of some excipient.” One SME uses a compounded 1% to 4% topical cream, ointment, and solution for cutaneous mastocytosis, typically in children. The SME also mentioned that it can be compounded as a tablet or capsule instead of a liquid.

However, there are “some drawbacks” to cromolyn. First, it is not significantly absorbed, with one SME stating that only “about 1%” is actually absorbed,” and therefore it must be applied “directly to the tissue where the mast cells are that you’d like to gain control [over].” Additionally, the commercially available products “are insanely expensive, utterly unjustifiably expensive, and that creates barriers for access for some patients.” One SME stated that the oral formulation is packaged as a “sterile single-use ampule” which does not make logical sense since the product is for oral use. In other countries cromolyn is much cheaper and is available as an oral tablet or capsule. One SME commented that there are “no great publications so far in terms of control, studies where there would be a control arm or a placebo arm and then the sodium cromolyn” but “the sodium cromolyn is [a] medication that we would like to have as an FDA-approved medication in all regards because it’s been extremely helpful.”

One SME said that “we had it available as a compound for the last 25 years or more, before I was even a fellow. And I think it’s really important to know that it has made a big difference in the quality of life of all the patients with mastocytosis and mast cell activation syndrome. So, I’m a little bit puzzled by the fact that we have not been able to make strides and have it FDA approved because the fact that it’s not makes in some patients really difficult for them to acquire. It’s expensive and not everybody can actually be on it just because of that. So, there is a tremendous unmet need at this moment.”

One SME has not used topical cromolyn but discussed the potential use of cromolyn for patients with atopic dermatitis. Typically, atopic dermatitis is treated with topical steroids as “the foundational therapy” and once it is under control “switching to sort of a moisturization regimen with maybe occasional topical steroids.” There are additional anti-inflammatory topical agents that could be used but “beyond that, you’re starting to talk about systemic medications.” The SME was not sure where cromolyn would fit in the treatment approach for atopic dermatitis compared to the other topical agents that are available but stated, “[t]here is some literature on helping prevent itch and stuff in atopic dermatitis, so I think there is some potential use there.”

One SME stated that they will occasionally use cromolyn for patients with asthma.

Two SMEs stated that they do not use cromolyn, with one stating that it has to be taken 4 times a day and “we have so much better medications with the steroids that it’s kind of useless now.”

One SME said that it would be useful to have cromolyn stocked in-office.

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 obtained varied from less than 1% to the majority of compounded products used at one participant’s facility. A participant stated, “we have this method that we use where if we can buy it commercially ready to administer, we do that. If we can’t buy it in that format, then we buy it in a

vial, for example, that can be snapped into a Mini-Bag Plus, because we're a Baxter house, as a second preference. If we can't buy it in either of those two formats and we can get it from a 503B, then we do that. And our last resort is compounding internally." Two participants commented that they will not outsource a product unless 2 outsourcing facilities that they contract with are able to compound the product. This redundancy will allow for a quick flip to the other outsourcing facility if there is an issue with a product compounded from 1 outsourcing facility, minimizing the impact to the participant's facility.

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

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

Another theme regarding deciding what products to purchase from an outsourcing facility was focused on the utilization and volume of a product that is needed and the overall impact this would have on the pharmacy workload. Critical care areas, like the emergency department and operating room, typically have a high product utilization and overall turnover, leading to several participants obtaining products intended for use in these areas from outsourcing facilities. Participants stated that they evaluate the volume of product needed and the frequency with which that volume is needed compared to the time it would take pharmacy staff to prepare this volume. One participant commented that "we look at the impact that it'll have on staff. If our staff are needing to batch, or if we need to mass produce these in particular to meet the patient demand, then those are the items that we're going to look to potentially move out." Another participant stated that, while they do not obtain a lot of products from outsourcing facilities, "when we do purchase from 503Bs, typically it would be if we just don't have the capacity to keep up

with what the demand is.” One participant also commented that they will obtain labor-intensive and more complicated products, like epidurals and cardioplegia solutions, from outsourcing facilities to reduce the workload on pharmacy staff. The coronavirus disease 2019 (COVID-19) pandemic has also impacted the operations of hospitals, as noted by 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 [more] extensive beyond-use dating than we can provide.” Several participants also commented that they do not perform high-risk compounding in-house and therefore, all of these products are outsourced. There are challenges with midsize hospitals being able “to operationalize testing compounds we make for extended stability.” One participant stated, “We might make our own syringes if we could get extended dating, but I believe my operations colleagues don’t always know how to do this and adhere to the letter of the law.”

One participant also commented on the impact that The Joint Commission has had on pushing pharmacies to obtain products from outsourcing facilities. The 2018 medication management standard MM.05.01.07 was intended to move IV admixture preparation out of the nursing unit. This forced pharmacies to consider strategies to make IV admixtures available for use on the floor. Additionally, NPSG.03.04.01 states that all medications and solutions should be adequately labeled, including in the operating room and other settings in which procedures are performed. USP <795> and <797> are applicable in operating room settings, stating that products should be labeled and used within 1 hour, which may be problematic if syringes are drawn up at the beginning of the day and cases are canceled or delayed. The participant also commented on the cost related to purchasing premade products from manufacturers, stating that “predatory pricing on premixes is present in the market.”

Standardization of products, including concentration, volume, and labeling, was also a driver for obtaining products from an outsourcing facility. However, such standardization may not always be possible. One participant stated that when evaluating similar facilities, you would expect them to have similar needs regarding the concentrations and volumes of products 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 9 different epidural concentrations, all driven by anesthesia, and they want what they want, and 503Bs may not offer that. No one else in the country is buying that same concentration; a 503B isn’t going to go through the expense of adding that to their product list.” The participant also said 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 insourcing.” 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 APIs. If sterile becomes short, they quickly switch to producing through APIs, which the ASHP [American Society of Health-System Pharmacists] and the FDA allow.” This “adds a lot of flexibility so they can bounce back and forth and really try to insulate us from shortages.”

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

A few participants commented on the need for preservative-free products, particularly in pediatric patients. The example of methadone was provided as it is used for patients with neonatal abstinence syndrome but is only available as a preservative-containing product. So, there is a need for this product to be compounded from API as a preservative-free product. One participant stated that “if there’s not a preservative-free containing option, it really should be something that should be able to be compounded from bulk . . . especially for the pediatric patient population.” However, another participant from a children’s hospital said that they have never needed to use an outsourcing facility for preservative-free products. 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 are 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. 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 nonsterile for clinic use.” As a result, the inpatient pharmacy is often asked to take on this role but “you don’t have the space or the staff to do that.”

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

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

Four participants stated that they obtain sodium citrate as ready-to-use syringes for use as a locking solution in patients undergoing dialysis, with 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 to [*sic*] for pH and potassium testing. Obviously, then we’re confined to <797> beyond-use dates versus longer beyond-use dates that we get from the 503B.” Another participant commented that cardioplegic solutions are managed by the perfusion department, not the pharmacy, and they use the del Nido formulation as well as 3 other formulations.

The participants also discussed challenges with utilizing outsourcing facilities. One participant stated that their facility does not use outsourcing facilities because “it just hasn’t been financially, not just the money worth it, but just the lead time for how much time you have to give them and how much you have to. . . . It just isn’t worth the dating that they gave us or can give us.” Another commented that they obtain very little product from outsourcing facilities due to “the amount of work for vetting and continually validating quality of these 503B outsourcing facilities.” The participant stated that they have a robust validation process that takes several months and includes a site visit prior to purchasing from an outsourcing facility, followed by continuous reviewing of quality reports and warning letters. Another challenge has been the reliability of the outsourcing facility. One participant commented that “[t]raditionally, 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 utilizing API to compound narcotics. One participant commented that this often worsens drug shortages due to the quotas that the Drug Enforcement Administration places on the quantity that can be produced. The participant stated that "they [outsourcing facilities] want to buy the product that we're trying to buy to take care of our patients today, to sell us tomorrow. We really need the FDA to say that, especially for controlled substances, that 503Bs can consistently prepare those products so that we don't end up with a shortage year after year after year and then chasing our tail. Also, we may actually want to tell 503Bs they can't buy those products or that they're limited in the amount of their ability to buy those products to make what are essentially copies of commercially available products because it actually induces the shortage in many ways."

Results of survey

One person responded to the survey distributed via professional medical associations and available on the project website; refer to Table 11 for respondent characteristics.

The respondent used cromolyn sodium as a nasal product to treat allergies and chronic rhinorrhea (refer to Table 12).

The respondent used cromolyn sodium as an FDA-approved product, compounded drug product, and OTC drug product. The respondent used compounded cromolyn sodium due to lack of commercial products in an appropriate dosage form, strength or combination, patient allergies, and other patient conditions preventing use of commercial products. Refer to Table 13 for reasons for using compounded cromolyn sodium. Explanation for using compounded cromolyn sodium due to patient allergies included that "some patients are extremely sensitive and require a compounded form. They have specifically come to me for these treatments in the past."

The respondent does not stock non-patient-specific compounded cromolyn sodium at their practice.

A prequestionnaire was distributed to participants of the roundtable discussion (refer to Appendix 3.3 for survey instrument).

Forty-three people responded to the prequestionnaire; refer to Table 15 for respondent characteristics. Among 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.

Cromolyn sodium was not included on the prequestionnaire (refer to Table 18).

Table 11. Characteristics of survey respondents

Terminal Clinical Degree	Responses, n (N = 1)
Doctor of Medicine (MD)	0
Doctor of Osteopathic Medicine (DO)	0
Doctor of Medicine in Dentistry (DMD/DDS)	0
Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)	0
Naturopathic Doctor (ND)	1
Nurse Practitioner (NP)	0
Physician Assistant (PA)	0
Practice Setting	Responses, n (N = 1)
Physician office or private practice	1
Outpatient clinic	0
Hospital or health system	0
Academic medical center	0
Emergency room	0
Operating room	0

Table 12. Conditions for which cromolyn sodium prescribed or administered

Condition	Responses, n (N = 2)^a
Allergies	1
Atopic dermatitis	0
Atopic eczema	0
Other ^b	1

^aSurvey respondents were allowed to select multiple conditions.

^bRespondent reported using cromolyn sodium for chronic rhinorrhea.

Table 13. Reasons for using compounded cromolyn sodium

Reason	Responses, n (N = 3)^a
Commercial product not available in desired dosage form, strength, or combination	1
Patient allergies prevent use of commercial products ^b	1
Patient conditions prevent use of commercial products	1
No commercial products	0

^aSurvey respondents were allowed to select multiple reasons.

^bRespondent stated “Some patients are extremely sensitive and require a compounded form. They have specifically come to me for these treatments in the past.

Table 14. Use of non-patient-specific compounded cromolyn sodium

Do you stock non-patient-specific compounded cromolyn sodium at your practice?	Responses, n (N = 1)
Yes	0
No	1
Not sure	0
No response	
How do you obtain your stock of non-patient-specific compounded cromolyn sodium?	
Compound yourself at practice	0
Product compounded by in-house pharmacy	0
Purchase from compounding pharmacy	0
Purchase from outsourcing facility	0
No response	1

Table 15. Demographics of prequestionnaire respondents' facilities

Type of Facility	Responses, n (N = 102) ^a
Academic medical center	15
Acute care hospital	16
Children's hospital	8
Community hospital	11
Critical access hospital	2
Dialysis center	2
Federal government hospital	4
Health system	15
Inpatient rehabilitation center	4
Long-term acute care hospital	3
Outpatient surgery center	6
Rural hospital	2
Skilled nursing facility	0
Specialty hospital ^b	4
Trauma center	5
Urban hospital	5
Number of Beds	Responses, n (N = 39)
< 50	4
50-99	3
100-199	1
200-299	4
300-399	5
400-599	3
> 600	19

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

^bSpecialties provided include cardiology, pulmonary, vascular, home infusion, neurology, psychiatry, oncology.

Table 16. Reasons for obtaining products from outsourcing facilities

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

^aRespondents were allowed to select multiple categories.

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

Table 17. Categories of products obtained from outsourcing facilities

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

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

^aRespondents were allowed to select multiple categories.

^bRespondents reported obtaining alum for bladder irrigation, oxytocin, anticoagulant sodium citrate solution, narcotic drips, high-cost 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
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^aRespondents were allowed to select multiple products.

CONCLUSION

Cromolyn sodium was nominated for inclusion on the 503B Bulks List as capsules, liquids, gels, ointments, creams, solutions, and suspensions for oral, mucosal, nasal, and topical administration to treat allergies, inflammatory response, histamine release, and mast cell activation. Cromolyn sodium is available in the nominated dosage form and ROA in Abu Dhabi, Canada, Namibia, New Zealand, the UK, and the US.

From the literature review, 88 studies were included. Cromolyn sodium was used for the treatment and prevention of allergies, mastocytosis, pyoderma gangrenosum, atopic dermatitis, mast cell activation syndrome, recalcitrant idiopathic vulvar vestibulitis, recombinant human insulin-induced lipodystrophy, atopic eczema, Crohn's disease, ulcerative colitis, irritable bowel syndrome, pruritis, urticaria, and chronic proctitis as various oral, topical, nasal, vaginal, and rectal products. Cromolyn sodium was used as a compounded cream and capsule. In 45 studies the authors recommended the use of cromolyn sodium; 12 studies did not recommend use, 3 studies found that the efficacy of cromolyn sodium was similar to the study intervention, 8 studies stated that further studies were needed, 15 studies did not provide a definitive conclusion, and 5 studies did not address the use of cromolyn sodium.

Six SMEs discussed the use of cromolyn. While 3 SMEs did not use cromolyn, 3 SMEs stated that it is a first-line agent for treating patients with mast cell activation syndromes and mastocytosis. The SMEs that used cromolyn typically use the commercially available formulations but stated that these patients often have sensitivities to excipients found in commercially available products that warrant the use of a compounding formulation. Patients are typically maintained on cromolyn indefinitely and 1 SME stated that it would be beneficial to maintain an in-office stock.

From the survey responses, 1 out of 1 respondent used cromolyn sodium. The respondent used cromolyn sodium as a nasal product for allergies and chronic rhinorrhea. Commercial products not being available in the desired dosage form, strength, or combination, patient allergies prevent use of the commercially available products, and patient conditions prevent the use of commercially available products were the reasons for using a compounded cromolyn sodium product over an FDA-approved product. The respondent did not stock non-patient-specific compounded cromolyn sodium at their practice. Cromolyn sodium 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 August 28, 2020
- Date last searched: August 31, 2020
- Limits: Humans (search hedge); English language
- Number of results: 1877

1	cromolyn sodium/	4074
2	chromogl#cat\$.tw.	116
3	cromogl#cat\$.tw.	2941
4	cromogl#ci\$.tw.	35
5	cromolyn\$.tw.	1349
6	or/1-5	5658
7	exp administration, oral/	146,507
8	administration, topical/	38,461
9	administration, mucosal/	260
10	administration, intranasal/	14,673
11	skin absorption/	11,694
12	inhal\$.tw.	109,465
13	oral\$.tw.	673,859
14	buccal\$.tw.	27,567
15	sublabial\$.tw.	412
16	sublingual\$.tw.	10,994
17	supralingual\$.tw.	20
18	topical\$.tw.	105,698
19	cutaneous\$.tw.	152,146
20	transcutaneous\$.tw.	14,467

21	epicutaneous\$.tw.	2014
22	transdermal\$.tw.	14,643
23	((cutaneous\$ or dermal\$ or skin) adj3 (absorb\$ or absorpt\$ or appl\$)).tw.	11,287
24	mucosal\$.tw.	120,449
25	mucous\$.tw.	22,983
26	transmucosa\$.tw.	1895
27	transmucous\$.tw.	12
28	intranasal\$.tw.	26,913
29	nasal\$.tw.	116,469
30	capsules/	12,745
31	aerosols/	30,555
32	nasal sprays/	529
33	oral sprays/	91
34	emulsions/	17,973
35	exp gels/	52,068
36	suspensions/	7756
37	liniments/	123
38	ointments/	12,796
39	exp tablets/	24,629
40	skin cream/	1034
41	pharmaceutical solutions/	3305
42	capsule?.tw.	78,520
43	microcapsule?.tw.	5215
44	tablet?.tw.	52,232
45	pill?.tw.	21,577
46	liquid?.tw.	402,210

47	syrup?.tw.	5656
48	elixir?.tw.	644
49	lozenge?.tw.	1139
50	troche?.tw.	165
51	emulsion?.tw.	33,235
52	suspension?.tw.	109,228
53	aerosol\$.tw.	45,170
54	spray?.tw.	28,148
55	gel?.tw.	308,603
56	liniment?.tw.	145
57	ointment?.tw.	11,868
58	salve?.tw.	341
59	paste?.tw.	12,511
60	unguent\$.tw.	113
61	lotion?.tw.	2313
62	cream?.tw.	18,992
63	(nose adj2 drop?).tw.	250
64	or/7-63	2,326,729
65	drug therapy/	30,572
66	de.fs.	2,992,723
67	dt.fs.	2,230,036
68	ad.fs.	1,417,133
69	tu.fs.	2,228,819
70	di.fs.	2,572,312
71	pc.fs.	1,290,187
72	therap\$.tw.	2,798,841

73	treat\$.tw.	5,527,202
74	prevent\$.tw.	1,427,059
75	prophyla\$.tw.	165,367
76	exp hypersensitivity/	344,843
77	bronchial spasm/	4310
78	allerg\$.tw.	186,781
79	hypersensitiv\$.tw.	73,917
80	asthma\$.tw.	157,370
81	((bronchial\$ or bronch?o\$ or bronchus) adj2 (constrict\$ or spasm\$)).tw.	917
82	bronch?ospas\$.tw.	5407
83	bronchismus\$.tw.	1
84	bronch?ostric\$.tw.	2
85	(mast cell\$ adj2 (activat\$ or degranulat\$)).tw.	8587
86	mastocytos\$.tw.	3692
87	or/65-86	12,774,419
88	and/6,64,87	2608
89	exp animals/ not humans/	4,729,286
90	88 not 89	2161
91	limit 90 to english language	1877

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: August 31, 2020
- Limits: Humans (search hedge); English language
- Number of results: 3113

1	'chromoglycate disodium'/mj	7778
2	'chromoglicat*':ti,ab,tn	8
3	'chromoglycat*':ti,ab,tn	179
4	'chromoglicat*':ti,ab,tn	197
5	'chromoglycat*':ti,ab,tn	3583
6	'chromoglici*':ti,ab,tn	30
7	'chromoglyci*':ti,ab,tn	41
8	'chromolyn*':ti,ab,tn	2130
9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	9915
10	'buccal drug administration'/exp	5159
11	'oral drug administration'/de	406,274
12	'topical drug administration'/de	82,708
13	'cutaneous drug administration'/de	668
14	'intranasal drug administration'/de	14,927
15	'mucosal drug administration'/de	442
16	'transdermal drug administration'/de	9067
17	'topical treatment'/de	13,057
18	'skin absorption'/de	8056
19	'inhal*':ti,ab	163,723
20	'oral*':ti,ab	968,782
21	'buccal*':ti,ab	35,379
22	'sublabial*':ti,ab	548

23	'sublingual*':ti,ab	16,547
24	'supralingual*':ti,ab	26
25	'topical*':ti,ab	149,731
26	'cutaneous*':ti,ab	218,158
27	'transcutaneous*':ti,ab	19,539
28	'transdermal*':ti,ab	21,414
29	((cutaneous* OR dermal* OR skin) NEAR/3 (absorb* OR absorpt* OR appl*)):ti,ab	17,971
30	'mucosal*':ti,ab	172,434
31	'mucous*':ti,ab	38,743
32	'transmucosa*':ti,ab	2536
33	'transmucous*':ti,ab	27
34	'intranasal*':ti,ab	36,681
35	'nasal*':ti,ab	163,509
36	'aerosol'/de	63,670
37	'cream'/de	9455
38	'drug capsule'/de	9084
39	'drug solution'/de	3109
40	'elixir'/de	489
41	'gel'/exp	77,280
42	'liniment'/de	251
43	'lotion'/de	2863
44	'lozenge'/de	1211
45	'microcapsule'/de	11,529
46	'nose drops'/de	771
47	'nose spray'/de	3184
48	'ointment'/exp	18,651

49	'oral spray'/de	219
50	'paste'/de	2521
51	'salve'/de	165
52	'suspension'/de	27,320
53	'syrup'/de	27,320
54	'tablet'/exp	48,560
55	'pill'/de	9962
56	'aerosol*':ti,ab	68,247
57	'cream\$':ti,ab	29,703
58	'capsule\$':ti,ab	114,590
59	'liquid\$':ti,ab	477,709
60	'solution\$':ti,ab	869,969
61	'emulsion\$':ti,ab	45,186
62	'liniment\$':ti,ab	234
63	'lotion\$':ti,ab	4006
64	'lozenge\$':ti,ab	1553
65	'microcapsule\$':ti,ab	6468
66	'elixir\$':ti,ab	974
67	'spray*':ti,ab	53,173
68	'ointment\$':ti,ab	21,613
69	'paste\$':ti,ab	15,009
70	'pill\$':ti,ab	31,525
71	'salve\$':ti,ab	476
72	'suspension\$':ti,ab	145,128
73	'syrup\$':ti,ab	8430
74	'tablet\$':ti,ab	93,362

75	'troche\$:ti,ab	247
76	'unguent*:ti,ab	240
77	(nose NEAR/2 drop\$):ti,ab	415
78	'gel\$:ti,ab	362,752
79	#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 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78	4,107,248
80	'drug therapy'/de	744,687
81	'add on therapy'/de	18,912
82	'drug dose':lnk	625,874
83	'drug administration':lnk	1,757,254
84	'drug therapy':lnk	3,929,231
85	'prevention':lnk	1,178,117
86	'therap*:ti,ab	4,208,504
87	'treat*:ti,ab	8,002,301
88	'prevent*:ti,ab	1,937,390
89	'prophyla*:ti,ab	263,747
90	'hypersensitivity'/exp	694,962
91	'bronchospasm'/exp	27,995
92	'mastocytosis'/exp	7406
93	'allerg*:ti,ab	298,936
94	'hypersensitiv*:ti,ab	102,167
95	'asthma*:ti,ab	242,316
96	((bronchial* OR bronch\$o* OR bronchus) NEAR/2 (constrict* OR spas*)):ti,ab	1702
97	'bronch\$ospas*:ti,ab	8837
98	'bronchismus*:ti,ab	1

99	'bronch\$strict*':ti,ab	11
100	('mast cell*' NEAR/2 (activat* OR degranulat*)):ti,ab	11,433
101	'mastocytos*':ti,ab	5691
102	#80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99 OR #100 OR #101	13,770,649
103	#9 AND #79 AND #102	4726
104	[animals]/lim NOT [humans]/lim	6,081,128
105	#103 NOT #104	4114
106	#103 NOT #104 AND [english]/lim	3113

Appendix 2. Table 5. Summary of included studies

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 1: Allergy (treatment and/or prevention)					
Bosso et al, 1991, US ¹⁰	Case report	1 Patient with immunoglobulin E (IgE) mediated hypersensitivity to seminal fluid (0%, 23 y)	<ul style="list-style-type: none"> • Pretreatment with cromolyn cream prior to intercourse 	Resolution/relief of clinical signs	“In conclusion, we have described a patient with documented IgE-mediated, immediate local and cutaneous hypersensitivity to SF, in whom 4% cromolyn cream applied intravaginally 30 minutes before challenge and intercourse successfully prevented both reactions.”
Brain et al, 1974, UK ¹¹	Double-blind crossover study	29 Patients with perennial rhinitis (52%, mean 25.6 y)	<ul style="list-style-type: none"> • Sodium cromoglycate (SCG) (29) • Placebo (29) 	Daily diary of symptoms and use of other therapy	“This trial has clearly demonstrated that a 2 per cent solution of SCG is significantly better than placebo in a group of patients suffering from perennial rhinitis.”
Caballero et al, 1978, Spain ¹²	Double-blind, controlled trial	15 Patients with perennial rhinitis (gender and age not provided)	<ul style="list-style-type: none"> • SCG (10) • Placebo (5) 	Patient-recorded clinical symptoms, histological examination of biopsy before trial and at 4 and 8 weeks	“The conclusion, therefore, is that SCG is a very useful drug for the treatment of severe perennial rhinitis but particularly so in those who are classified as allergic.”
Capel and McKelvie, 1971, UK ¹³	Double-blind trial	44 Patients with grass-pollen rhinitis (hay fever) (64%, male mean age 25 y, female mean age 30 y)	<ul style="list-style-type: none"> • Disodium cromoglycate (DSCG) (23) • Placebo (21) 	Patient-recorded clinical symptoms; clinician interview every 2 weeks	“In a double-blind trial of nasal insufflation of [DSCG] for hayfever (grass-pollen rhinitis) nine of twenty-two patients taking the drug were helped compared with one of nineteen who took lactose - a statistically significant difference.”
Chandra et al, 1982, Canada ¹⁴	Double-blind, controlled crossover study	47 Patients with seasonal allergic rhinitis (40%, range 9-41 y)	<ul style="list-style-type: none"> • SCG (47) • Placebo (47) 	Patient-reported severity of symptoms and overall assessment	“It is concluded that intranasal [SCG] administration is an efficacious preventive and therapeutic approach in the management of patients with seasonal allergic rhinitis.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Chatterjee et al, 1974, UK ⁷²	Randomized, comparative trial	19 Patients with seasonal allergic or perennial rhinitis (65%, range 8-43 y)	<ul style="list-style-type: none"> • SCG (9) • Beclomethasone dipropionate (10) 	Patient-recorded symptoms; appearance of nasal mucosa prior to and at the end of the trial	“From the patient daily symptoms scores [both] beclomethasone dipropionate and [SCG] led to an improvement, particularly during the second week of treatment. The physician's overall assessment leads to the conclusion that both treatments offer benefit.”
Cullen and Turner, 1973, Australia ⁸³	Double-blind controlled trial	72 Patients with seasonal allergic rhinitis (25%, range 17-81 y)	<ul style="list-style-type: none"> • DSCG (38) • Placebo (34) 	Patient-reported daily symptoms and antihistamine use	“In summary, these results of the present trial indicate that daily nasal symptoms of allergic seasonal rhinitis... were significantly benefited by the instillation of a 2% solution of DSCG without significant benefit to the eye or sinus regions. However, comparisons of these two trials in Western Australia suggests that DSCG when administered as a powder by nasal insufflation may be more effective in ameliorating the effects of allergic rhinitis than when administered by instillation as a 2% nasal solution.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Edwards et al, 2011, UK ¹⁵	Randomized, double-blind vehicle controlled intra-subject design trial	35 Healthy volunteers with 15 non-atopic and 20 atopic (gender and age not provided)	<ul style="list-style-type: none"> • Study 1: 16 subjects received either 4% SCG or reversed osmosis purified water delivered using iontophoresis at various sites on the upper and lower forearm prior to injection of histamine • Study 2: 12 subjects applied 4% SCG emulsion and matching vehicle to two areas of each forearm prior to injection of histamine • Study 3: 7 subjects applied 1%, 2% or 4% SCG emulsion and matching vehicle to upper and lower forearms prior to injection of histamine 	Wheal, flare areas, and blood flow on Doppler, planimetry to calculate wheal areas, severity of itch	“We conclude that the 4% SCG cutaneous emulsion used in these studies will be useful in skin diseases such atopic dermatitis (eczema) and cutaneous mastocytosis where itching is a predominant feature.”
Engstrom, 1971, Sweden ⁷⁵	–	13 Children with seasonal allergic rhinitis (69.2%, range 7-14 y)	<ul style="list-style-type: none"> • DSCG (13) • Placebo (13) 	Tolerance to allergen challenge	“It was thus shown that DSCG exerts a protective action against the effect of nasal allergen challenge. The results, however, seem favourable enough to encourage further studies on the clinical efficacy of the drug in seasonal allergic rhinitis during the pollen season.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Engstrom et al, 1971, Sweden ⁸²	Double blind clinical trial	38 Children with allergic rhinoconjunctivitis due to birch pollen allergen (78.9%, range 7-17 y)	<ul style="list-style-type: none"> • DSCG (20) • Placebo (18) 	Reduction of nasal and eye symptoms	“From the results obtained in this study it is reasonable to conclude that nasal application of DSCG is a valuable alternative to antihistamines, corticosteroids, and decongestants in controlling the nasal symptoms of allergic rhinoconjunctivitis...However, local application seems to be necessary to obtain effect; the eye symptoms can not be controlled by insufflation in the nose alone. Further studies of the effect of local instillation of DSCG in the eyes would be of interest.”
Fagerberg and Zetterstrom, 1975, Sweden ¹⁶	Double-blind, cross-over study	23 Patients who had symptoms of perennial rhinitis severe enough to demand treatment of some sort for at least 1 year <ul style="list-style-type: none"> • Active placebo (41.67%, range 27.5 y) • Placebo-active (63.64%, range 16-54 y) 	<ul style="list-style-type: none"> • Active placebo (12) • Placebo-active (11) Active drug is DSCG	Assessment of the symptoms (sneezing, blocking, running, and itching); use of other treatments such as antihistamines; side effects	“It is concluded that a therapeutic trial of [SCG] is worth considering in patients with perennial rhinitis, irrespective of the results of [radioallergosorbent test] and intracutaneous skin tests.”
Frankland et al, 1975, UK ⁵⁹ Frankland and Walker, 1975, UK ⁶³	–	60 Patients who had a history of seasonal allergic rhinitis and had positive skin prick tests to grass pollen extracts <ul style="list-style-type: none"> • Betamethasone (60%, mean 28 y) • SCG (53.3%, mean 26 y) 	<ul style="list-style-type: none"> • Betamethasone valerate (30) • SCG (30) 	Assessment of the symptoms (eye irritation, nasal irritation, sneezing, nasal discharge, nasal obstruction, chest symptoms); patients' subjective assessment of their treatment; use of additional drugs such as antihistamine or nasal decongestants	“This study indicates that intranasal betamethasone valerate at a dose level of 400 mcg/day is an effective therapy in the treatment of seasonal allergic rhinitis...Although [SCG] applied locally did provide some relief of the patient's symptoms, betamethasone valerate in the majority of cases was able to control these symptoms and was therefore clinically superior.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Hasegawa et al, 1976, Japan ¹⁷	Double-blind crossover trial	16 Patients with a history of rhinitis (56.25%, range 15-43 y)	<ul style="list-style-type: none"> • SCG (16) • Placebo (16) 	Nasal airways resistance ratio, assessed symptoms of attacks of sneezing and itching, watery secretion, and the color and swelling of the mucous membrane	“The protective effect of SCG occurred equally in those patients who were sensitive to Japanese cedar pollen and house dust, thus it would appear that it should be effective clinically in both seasonal and perennial rhinitis.”
Knight et al, 1976, Canada ¹⁸	Double-blind	77 Patients with ragweed allergic rhinitis, conducted at two different sites Toronto: <ul style="list-style-type: none"> • DSCG (47.1%, range 10-59 y) • Placebo (38.1%, range 14-52 y) Hamilton: <ul style="list-style-type: none"> • DSCG (21.1%, range 14-47 y) • Placebo (45%, range 16-53 y) 	<ul style="list-style-type: none"> • DSCG (36) • Placebo (41) 	Symptoms (number of sneezing episodes, degree of nasal obstruction, degree of watery rhinorrhea, itching of the eyes and nose, sinus pain, general feeling of well-being), number of antihistamine tablets taken	“Overall, we have concluded from these studies that [DSCG] powder given in a dose of 10 mg into each nostril 4 times daily prior to and during the ragweed pollen season may be more effective in controlling symptoms of ragweed-allergic rhinitis in some patients than a lactose placebo.”
Kocoshis and Gryboski, 1979, US ¹⁹	Double-blind clinical trial	14 Children with milk allergy and concomitant allergies to one or more foods (gender not provided, range 2-15 y)	<ul style="list-style-type: none"> • Cromolyn (13) • Placebo (9) Crossover to other treatment occurred if the initial agent was ineffective	Number and characteristics of the stools, complete blood count, serum immunoglobulin levels, liver function, renal function tests, urinalysis	“Our data show a statistically significant protective effect of cromolyn on the symptoms of gastrointestinal food allergy.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Kuhn et al, 1976, US ²⁰	3 center collaborative study, double-blind placebo-controlled parallel group design	114 Patients with a history of ragweed hay fever and strongly positive skin test (gender not provided, range 9-54 y)	<ul style="list-style-type: none"> • Cromolyn sodium (not provided) • Placebo (not provided) 	Patients scored daily symptoms (sneezing, nasal congestion, rhinorrhea); use of chlorpheniramine	“[Cromolyn sodium] appears to be effective in the management of ragweed-allergic rhinitis.”
Leiferman et al, 1975, US ²¹	Double-blind investigation	26 Patients with symptoms of ragweed pollinosis for several years <ul style="list-style-type: none"> • Control (61.5%, range 14-53 y) • Treatment (69.2%, range 17-66 y) 	<ul style="list-style-type: none"> • Cromolyn sodium (13) • Control (13) 	Daily diary summarizing symptoms and medication, severity of symptoms (sneezing, coughing, stuffy or runny nose, red, itchy eyes, and asthmas)	“The results suggest that treatment with cromolyn sodium enhanced IgE antibody response to pollen exposure and significantly reduced the severity of hay fever symptoms in patients with high preseasonal levels of IgE antibody to ragweed.”
Ludman, 1999, US ¹⁰²	Case report	1 Patient (0%, 23 y)	<ul style="list-style-type: none"> • Cromolyn (1) 	Resolution and/or improvement of symptoms of irritation	“While [seminal plasma protein allergy] is not a common problem, it is serious enough to warrant consideration when evaluating a woman for vulvovaginitis, atopic reactions, or dyspareunic. Referral to an immunologist for further testing is recommended if [seminal plasma protein allergy] is suspected.”
Manners, 1975, UK ²²	Single-blind group comparative study	46 Patients (gender not provided, range 11-54 y)	<ul style="list-style-type: none"> • SCG solution (24) • SCG powder (22) 	Diary card used to record degree of nasal discharge, obstruction, sneezing and itching; nasal mucus collection for estimation of eosinophilia	“From the results described in the present paper, it is concluded that during periods of high grass pollen counts in Great Britain, SCG, used either as a spray or as a powder, is an acceptable means of treating hay fever.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
McDowell and Spitz, 1977, US ⁷⁶	Double-blind crossover study	17 Patients with chronic perennial allergic rhinitis (range 17-71 y)	<ul style="list-style-type: none"> • Cromolyn sodium (17) • Placebo (17) 	Daytime and nighttime occurrences and severity of such symptoms as itchy, runny, or stuffy nose, mouth breathing, postnasal drip and itchy eyes or throat; number of episodes of nose blowing and sneezing	“While the results of this study are not conclusive, the improvement of 6 of the 14 patients who completed the study indicates that this method of treatment warrants further investigation.”
Monro et al, 1984, UK ⁸⁴	Double-blind	9 Patients with severe migraine before food challenge (33.3%, range 30-64 y)	<ul style="list-style-type: none"> • SCG (9) • Placebo (9) 	Symptoms scored on a scale of 1-4 related to daily activities, frequency, duration, and severity	“The observation that these patients are protected by oral SCG does suggest that an allergic gatekeeper mechanism in the gut triggers the production of symptoms, with immune complexes acting as a messenger. Further research to identify the specificity of the mixed immune complexes in these patients is in progress.”
Mygind and Thomsen, 1975, Denmark ¹⁰³	–	10 Patients with allergic rhinitis and hypersensitivity to grass pollen (gender and age not provided)	<ul style="list-style-type: none"> • DSCG (10) • ICI 74,917 (10) • Placebo (10) 	Number of sneezes and drips from the nose	“In conclusion, measures of nasal secretion and irritation after challenge with allergen showed a protective effect when subjects were pretreated with ICI 74,917. The results justify trials to evaluate ICI 74,917 in the treatment of allergic rhinitis.”
Nizami and Baboo, 1977, Canada ²³ Nizami, 1976, Canada ³¹	Randomized, double-blind, crossover study	92 Patients (46.7%, mean 26 y)	<ul style="list-style-type: none"> • SCG (92) • Placebo (92) 	Symptoms (sneezing, running nose, blockage of nose, eye symptoms, sinus pains), number of antihistamines per day	“In our study SCG was well accepted by the patients and in the dosage used it was quite effective.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Nizami et al, 1977, Canada ²⁴	Preliminary double-blind, placebo controlled, crossover study	16 Patients (12.5%, range 5-67 y)	<p>First 2 weeks about half the patients on cromolyn 50 mg 4x/day while other half on placebo for 1 week (crossover to cromolyn or placebo the next week).</p> <p>Subsequent weeks were done in a similar 2 week crossover design with dose changes depending on if there was an allergic reaction (dose increase to 100 mg or 150 mg 4x/day) or no reaction (dose reduced to 25 mg 4x/day). Once the most effective dose was found, patients were continued on that dose for 1-3 months.</p>	Daily symptoms, medications taken, allergic reactions, delayed reactions	“Though the number of patients studied so far is too small to draw any final conclusions, more than 60% of our patients had remission in their food allergy symptoms with oral cromolyn. The dose needed for a particular patient has to be adjusted according to the amount of allergen exposure.”
Okuda et al, 1984, Japan ⁸⁵	Intergroup, double-blind comparative	302 Patients with perennial nasal allergy (gender and age not provided)	<ul style="list-style-type: none"> • Group 1: N-(3,4-dimethoxycinnamoyl) anthranilic acid (N-5') and DSCG-placebo (100) • Group 2: N-5'-placebo and DSCG (102) • Group 3: N-5' placebo and DSCG-placebo (100) 	Total number of sneeze and of nose blowing episodes, side effects	“N-5' showed a level of anti-nasal allergy efficacy approximately comparable to that of DSCG. However, its efficacy was manifested somewhat more slowly than with DSCG and, upon reviewing all the results, its efficacy on nasal obstruction was somewhat inferior to that of DSCG although statistically, not significantly so.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Ortolani et al, 1983, Italy ²⁵	Double-blind crossover study	24 Adult patients with adverse reactions to foods and food additives <ul style="list-style-type: none"> • Active to placebo group (33.3%, range 15-53 y) • Placebo to active group (33.3%, range 26-67 y) 	<ul style="list-style-type: none"> • SCG (24) • Placebo (24) 	Assessment of symptom severity, opinion by both patient and doctor on the success or failure of the trial	“Oral [SCG] appears to be both effective and well tolerated in the treatment of food allergies, particularly when used in conjunction with a maintenance elimination diet.”
Osváth et al, 1986, Hungary ⁶⁰	Matched, self-controlled trial	17 Patients with food allergies (gender not provided, range 2-14 y)	<ul style="list-style-type: none"> • DSCG (17) • Ketotifen (17) 	Organ-symptoms ameliorated, urticaria, atopic dermatitis, abdominal pain, allergic symptoms, number of eosinophils	“Symptoms of food allergy can be well prevented in children through ketotifen therapy more than by DSCG.”
Pelikan and Pelikan-Filipek, 1989, the Netherlands ²⁶	Double-blind placebo-matched crossover	38 Patients with perennial allergic rhinitis who developed a nasal response to ingestion challenge with certain foods (gender not provided, range 14-60 y)	<ul style="list-style-type: none"> • Cromolyn sodium (38) • Placebo (38) 	Types of nasal response to food ingestion challenge, scratch tests, appearance of the nasal mucosa, nasal, and other complaints	“It can be concluded that cromolyn in a daily oral dose of 200 mg four times prevented the immediate and late nasal responses to ingested food.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Phillips et al, 1996, US ²⁷	—	<p>2-part study: First part to determine whether immediate pretreatment of the skin with cromolyn could modify the allergic response and part 2 to determine the effect of pretreatment of the skin with a 4% cromolyn cream or solution on this response</p> <p>Part 1: 20 Patients known to be allergic to at least two standard antigens (gender and age not provided)</p> <p>Part 2: 10 Patients known to be allergic to at least two standard antigens used in prick testing (gender and age not provided)</p>	<p>Part 1: cromolyn or placebo was applied to the left and right forearms in a randomized, blinded manner</p> <ul style="list-style-type: none"> • Cromolyn sodium cream (20) • Placebo cream (20) <p>Part 2: cromolyn cream was applied to one forearm and solution to be applied to the other forearm</p> <ul style="list-style-type: none"> • Cromolyn sodium cream (10) • Cromolyn sodium solution (10) 	Prick testing, wheal and flare size, level of itching	<p>“Topical cromolyn is remarkably free of adverse side-effects. Because of the risk of prolonged use of topical steroid preparations, particularly in children, it would seem worth pursuing the potential benefits of topical cromolyn. The present results suggest that pretreatment with topical cromolyn can modulate itch, and wheal and flare responses in the skin.”</p>
Resta et al, 1982, Italy ²⁸	<p>Double-blind group comparative study</p> <p>Second study was a double-blind crossover study</p>	<p>39 Patients with allergic rhinitis</p> <p>First study:</p> <ul style="list-style-type: none"> • SCG solution (44.4%, range 7-50 y) • SCG powder (50%, range 17-47 y) • Placebo (54.5%, range 8-48 y) <p>Second study:</p> <ul style="list-style-type: none"> • 20 patients with maximal nasal blockage (gender and age not provided) 	<p>First study:</p> <ul style="list-style-type: none"> • SCG solution (18) • SCG powder (10) • Placebo (11) <p>Second study</p> <ul style="list-style-type: none"> • SCG solution (20) • SCG powder (20) 	Subjective assessment for each nasal symptom, rhinorrhea, number of sneezes a day, number of hours per day when the nose was blocked, nasal itching, resistance to air flow in the nasal cavities	<p>“The conclusions are that both [SCG] powder and solution are effective in the treatment of allergic rhinitis and both formulations have a very low incidence of minor side effects. We suggest that the powder formulation should be the choice in those patients in whom excessive running is the main symptom and that solution is used in those with predominantly nasal obstruction. Two further points which favour the solution are that first, the total daily dose of [SCG] is lower than the powder and secondly the delivery system is efficient and acceptable to patients.”</p>

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Sunderman and Crawford, 1973, Australia ²⁹	Double-blind crossover trial	68 Patients with intractable chronic perennial rhinitis (gender not provided, mean 35 y)	<ul style="list-style-type: none"> • SCG BP (68) • Placebo (68) 	Improvement in symptoms (nasal secretions, degree of blocking or nasal airways resistance, symptom scores, side effects)	“SCG BP is an effective addition to the range of therapies available for [chronic allergic rhinitis].”
Tandon and Strahan, 1980, Australia ⁶¹	Double-blind crossover trial	14 Patients with perennial rhinitis due to animal dander (28.6%, range 13-45 y)	<ul style="list-style-type: none"> • Beclomethasone dipropionate aerosol with a placebo capsule (14) • SCG with nasal insufflator with a placebo aerosol (14) 	Symptom score card for sneezing, nasal discharge, nasal obstruction, post-nasal drip; patient preference for the treatment combination	“In patients with perennial allergic rhinitis, if intranasal [SCG] does not produce an adequate response, there is good reason to believe that intranasal beclomethasone dipropionate will produce an improvement in a majority of such patients. Therefore, intranasal beclomethasone dipropionate is a significant [advancement] in the management of patients with troublesome perennial rhinitis.”
Taylor and Shivalkar, 1972, UK ⁸⁶ Taylor and Shivalkar, 1971, UK ⁹⁸	—	49 University students with seasonal allergic rhinitis (gender not provided, range 18-27 y)	<ul style="list-style-type: none"> • Group 1: lactose powder as placebo (15) • Group 2: lactose powder plus DSCG (17) • Group 3: lactose powder plus DSCG and nasal sprays of isotonic saline (10) 	Changes in nasal airways resistance, symptom score, number of sneezes, nasal discharge, number of paper handkerchiefs, nasal obstruction	“[DSCG] did not facilitate the induction of local desensitization although it blocked the unpleasant symptoms of nasal challenge. Diminished sensitivity persisted at least for several months and test groups had significantly lower symptom scores during the pollen season when compared with control subjects.”
Thorne and Bradbeer, 1972, UK ³⁰	Double-blind crossover	35 Patients with perennial rhinitis for at least two years (gender and age not provided)	<ul style="list-style-type: none"> • DSCG (35) • Placebo (35) 	Patient preference, daily symptom scores, clinical assessment, ventilation tests performed through the nose	“In a double blind crossover trial of two months duration nasal insufflations of DSCG and lactose were found to be superior to insufflations of pure lactose in the treatment of patients with perennial allergic rhinitis.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Wilson and Walker, 1976, UK ⁶²	–	20 patients with a history of seasonal allergic rhinitis <ul style="list-style-type: none"> • Betamethasone valerate (80%, mean 33 y) • SCG (70%, mean 28 y) 	<ul style="list-style-type: none"> • Betamethasone valerate (10) • SCG (10) 	Daily record card for their assessment of symptoms such as eye irritation, nasal irritation, sneezing, nasal discharge, and nasal obstruction; mean daily symptom scores	“This study indicates that intranasal betamethasone valerate is an effective treatment for seasonal rhinitis.”
Indication 2: Atopic dermatitis/atopic eczema					
Ariyanayagam et al, 1985, UK ³²	Double-blind, group comparison trial	46 Patients with chronic atopic eczema (54%, range for adults 16-65 y; range for children 2-14 y)	Patients randomly assigned to: <ul style="list-style-type: none"> • Topical SCG (not provided) • Placebo (not provided) 	Daily record of pruritus, sleeplessness, severity on 3-point scale; clinician rated severity of eczema, serum immunoglobulin E (IgE), urine SCG	“These results together with follow-up studies suggest that topical SCG as a long-term measure may be useful in the management of mild or moderately severe eczema, reducing the frequency of acute exacerbations.”
Atherton et al, 1982, UK ⁷³	Placebo-controlled double blind crossover trial	29 Children with atopic eczema (62%, range 2-10 y)	<ul style="list-style-type: none"> • Oral SCG (29) • Placebo (29) 	Parent-reported daily itch, nighttime sleep disturbance, number of antihistamine doses, number of corticosteroid ointment applications; clinician evaluation; parent- and clinician-rated overall effect for well-being and eczema severity	“The results of this study do not confirm previous anecdotal reports of effectiveness of [SCG] in children with atopic eczema. They are however not incompatible with the possibility of benefit in particular individuals.”
Berth-Jones et al, 2015, UK ³³	Randomized, double-blind, parallel group study	206 Children with atopic dermatitis <ul style="list-style-type: none"> • SCG (45%, mean 5.2 y ± 2.73) • Control (52.4%, mean 5.5 y ± 2.86) 	<ul style="list-style-type: none"> • SCG emulsion (103) • Vehicle (103) 	Change in SCORAD score (SCORing Atopic Dermatitis)	“It is concluded that this 4% SCG cutaneous emulsion provides an effective, clinically useful and safe treatment for atopic dermatitis in children with demonstrable steroid-sparing benefit.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Burks and Sampson, 1988, US ⁶⁴	Double-blind, placebo-controlled crossover trial	10 Children with atopic dermatitis and egg hypersensitivity (50%, mean 7.6 y ± 3.2)	<ul style="list-style-type: none"> • Cromolyn (10) • Placebo (10) 	Investigator-scored reaction to food challenge; parent-recorded daily symptoms	“From this study it can be concluded that oral cromolyn sodium is of no therapeutic benefit in children with atopic dermatitis and documented food hypersensitivity.”
Businco et al, 1986, Italy ³⁴	Double-blind crossover trial	31 Children with atopic dermatitis due to food allergy (45%, range 6 months-10 y)	<ul style="list-style-type: none"> • SCG (31) • Placebo (31) 	Clinician assessment of eczema severity; parent-recorded itching, sleep disturbance, weeping and redness of skin	“[SCG] does seem to reduce the exacerbations of atopic dermatitis caused by food allergens.”
Croner et al, 1981, Sweden ⁸⁷	Double-blind group comparative study	19 Children with moderate or severe atopic eczema (gender not provided, mean 6.6 y ± 4.2)	<ul style="list-style-type: none"> • SCG ointment (12) • Placebo ointment (7) 	Parent-reported day- and nighttime itch, sleep, and severity of dermatitis	“SCG has thus shown a slightly higher steroid sparing effect than the vehicle alone and further studies using SCG in a more modern type of ointment might be rewarding; however, the general impression of the investigators in this trial is that there is no such success to be expected for SCG in atopic eczema as in the treatment of bronchial asthma.”
Edwards et al, 2015, UK, Norway ⁷⁴	Randomized clinical trial	<p>177 Children with atopic dermatitis</p> <ul style="list-style-type: none"> • SCG (52.5%, mean 5.4 y ± 3.6) • Vehicle (54.2%, mean 4.6 y ± 3.1) 	<ul style="list-style-type: none"> • SCG emulsion (118) • Vehicle (59) <p>Patients allowed to continue topical corticosteroids, immunomodulators or wet-wrapping during trial. After 12 weeks of randomized control trial, patients available for entry into open phase in which topical SCG was administered in unblinded fashion (157)</p>	Change in SCORAD score	“In conclusion, this formulation of [SCG] represents a potentially useful and safe and well tolerated treatment for atopic dermatitis in children, during a long-treatment period. Although the trial failed to demonstrate differences between the 4% SCG emulsion and the vehicle during the first 3 months of this trial, the inclusions of the results of this trial in a meta-analysis of all three trials does not alter the analysis of this trial.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Graham et al, 1984, UK ⁶⁵	Double-blind crossover trial	29 Children who had chronic atopic eczema (gender not provided, range 3-12 y)	<ul style="list-style-type: none"> • Oral SCG (22) • Placebo (22) 	Daily subjective recording of pruritus, sleeplessness, the severity and area of eczema, and hydrocortisone and antihistamine usage	“Although there was a significant improvement in the patients' eczema whilst on strict elimination diets, these are obviously quite unsuitable for long-term use. However, by tailoring a diet for each individual child the improvement was maintained. When SCG was superimposed on this diet in the double-blind crossover trial against placebo no additional benefit was seen.”
Haider, 1977, UK ³⁵	Double-blind randomized group-comparative trial	42 Children with chronic atopic eczema <ul style="list-style-type: none"> • SCG (57.1%, range 0.42-13 y) • Placebo (61.9%, range 1-14 y) 	<ul style="list-style-type: none"> • SCG (21) • Placebo (21) 	Improvement in inflammation, lichenification, and cracking, severity of itching during the day and night, and the degree of sleep disturbance	“SCG may be a safe alternative to topical steroids in the treatment of atopic eczema in children”
Hiratsuka et al, 1996, Japan ⁸⁸	Double-blind, randomized-group, comparative trial	43 Patients with atopic dermatitis (51.2%, range 5.2-14.6 y)	<ul style="list-style-type: none"> • SCG solution (21) • Beclomethasone dipropionate ointment (22) 	Scores for skin, itching, and sleep disturbance; complications; spontaneous immunoglobulin production by peripheral blood B cells or surface IgE+ B cells	“Topical steroid treatment increases in vitro spontaneous IgE production by B cells. This indicates that topical steroids may decrease inflammation; however, a large-scale study on the effect of topical steroids on IgE production in vitro and in vivo may be necessary.”
Kimata and Hiratsuka, 1994, Japan ³⁶	Double-blind, placebo-controlled, randomized group-comparative trial	53 Patients with moderate to severe atopic dermatitis <ul style="list-style-type: none"> • Topical SCG (52%, range 4-14 y) • Topical placebo (45.8%, range 4-13 y) 	<ul style="list-style-type: none"> • Topical SCG and oral oxatomide (25) • Topical placebo and oral oxatomide (24) 	Diary-card scores for itching and sleep disturbance; severity of atopic dermatitis (inflammation, lichenification, cracking)	“These results suggest that [SCG] solution may be very effective in combination with anti-allergic medication in the treatment of moderate to severe [atopic dermatitis] in children.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Kimata and Igarashi, 1990, Japan ³⁷	Double-blind, randomized-group, comparative trial	45 Patients with moderate to severe atopic dermatitis <ul style="list-style-type: none"> • Cromolyn (52%, range 0.8-3 y) • Solution (50%, range 0.9-3 y) 	<ul style="list-style-type: none"> • Cromolyn (25) • Solution (20) 	Severity of atopic dermatitis (inflammation, lichenification, cracking), scores of sleep and itching	“Topically applied cromolyn solution was found to be very effective, improving dermatitis, itching and sleep disturbance, with no untoward effects.”
Kjellman and Gustafsson, 1986, Sweden ⁶⁶	Double-blind group comparative study design	40 Children with atopic eczema <ul style="list-style-type: none"> • SCG (55%, range 1-18 y) • Placebo (40%, range 1-12 y) 	<ul style="list-style-type: none"> • 4% SCG cream (20) • Placebo cream (20) 	State of the eczema (redness, vesiculation and crusting, excoriations and lichenification, areas affected), bacterial cultures, pyoderma, itch, sleep disturbance, and overall severity of the eczema, family and clinician's opinions of the efficacy of the trial cream, number of daily applications of hydrocortisone	“The trial showed that there is great need for improved information, family support and topical as well as general treatment in childhood atopic eczema, but topical SCG did not relieve the patients' eczema.”
Lindskov and Knudsen, 1983, Denmark ⁷⁷	Double-blind cross-over trial	24 Patients with active atopic dermatitis (50%, range 4-37 y)	<ul style="list-style-type: none"> • DSCG (24) • Placebo (24) 	Severity of day and night itching, general severity of eczema on a visual analogue scale, blood samples for serum total IgE, skin prick tests for number of allergens	“We have not been able to confirm the favourable results of DSCG in atopic dermatitis...Oral DSCG give few side effects, and in our opinion further clinical studies are necessary in order to estimate its priority in the treatment of atopic dermatitis.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Moore et al, 1998, US ³⁸ Moore et al, 1997, US ⁴⁰	Double-blind, placebo-controlled, crossover study	21 Pediatric patients with moderate to severe atopic dermatitis <ul style="list-style-type: none"> Group 1 (55.6%, 33 months ± 20.43) Group 2 (33.3%, 54.14 months ± 47.26) 	<ul style="list-style-type: none"> Group 1: received cromolyn first for 1 month and then placebo the next month (9) Group 2: received placebo first for 1 month and then cromolyn the next month (12) 	Severity score based on extent and skin involvement, skin test, radioallergosorbent test positivity, eosinophil levels, IgE concentrations, presence of concomitant rhinitis or asthma	“Treatment with topical cromolyn in a hydrophilic emollient vehicle has a significant anti-inflammatory effect on moderate-to-severe atopic dermatitis. We have now incorporated this treatment into our clinical practice.”
Pike and Atherton, 1988, UK ⁸⁹	Double-blind, placebo-controlled trial	36 Patients (gender not specified, range 1-14 y)	<ul style="list-style-type: none"> SCG (not provided) Placebo (not provided) 	Diary card data, eczema severity scores and doctor's and parental judgments of efficacy	“This lack of effect may indicate that SCG concentration at its site of action is still inadequate in spite of improved absorption, that mast cells are of limited relevance in [atopic dermatitis] or that cutaneous mast cells are relatively unresponsive to SCG, a possibility that is underlined by recent evidence of mast cell heterogeneity.”
Stainer et al, 2005, UK ³⁹	Double-blind, randomized, placebo-controlled trial	114 Patients with atopic dermatitis (59.6%, range 1.8-11.9 y)	<ul style="list-style-type: none"> SCG lotion (58) Placebo lotion (56) 	Change in SCORAD score	“These results show a clinically useful benefit of this SCG lotion in children with moderately severe [atopic dermatitis].”
Thirumoorthy et al, 1983, Singapore ⁷⁸	Double blind clinical trial	20 Patients with atopic dermatitis (40%, range 1-42 y)	<ul style="list-style-type: none"> Placebo cream (20) SCG cream (20) <p>One cream was randomized for the left side while the other was the right side</p>	Severity of eczema, physical signs of pruritis	“Only long-term controlled studies can confirm the steroid sparing effect of SCG. Future studies should incorporate a steroid preparation in the [SCG] cream so that deterioration from steroid withdrawal does not occur and it is also likely then that patients will agree to participate in long-term studies. A search for a higher concentration of SCG in a suitable base needs to be continued.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Thirumoorthy and Greaves, 1978, UK ⁹⁰	–	11 Patients (72.7%, range 13-38 y)	<ul style="list-style-type: none"> • DSCG ointment (11) • Placebo ointment (11) One ointment was randomized for the left side while the other was the right side	Amount of itching on both sides; clinical response of the two sides were assessed weekly by the clinician and the patient	“Although numbers were small in this study the results suggest that at any rate in the formulation we used, DSCG is unlikely to be of therapeutic value in severe atopic eczema. The possibility remains, however, that topical DSCG may be of value in milder forms of eczema and possibly in reducing the incidence of relapses.”
Indication 3: Crohn's disease and/or ulcerative colitis					
Binder et al, 1981, Denmark ⁹¹	Controlled clinical study	141 Patients with ulcerative colitis, 25 patients with Crohn's disease (47.5%, age not provided)	<ul style="list-style-type: none"> • DSCG (83) • Placebo (83) 	Clinical and sigmoidoscopic activity at each visit	“No beneficial effect of DSCG as compared with placebo was found, as the DSCG and the placebo group showed the same number of relapses in patients with a clinically inactive ulcerative colitis at the start of trial and the same number of patients improving, deteriorating, and maintaining steady state in patients with clinically active ulcerative colitis at the start of trial.”
Buckell et al, 1978, UK ⁶⁷	Double-blind crossover trial	26 Patients with ulcerative colitis resistant to medical treatment (61%, range 12-72 y)	<ul style="list-style-type: none"> • DSCG (26) • Placebo (26) 	Clinical assessment of bowel frequency, rectal bleeding, urgency, incontinence, general well-being, body weight and ability to work, sigmoidoscopic appearance, rectal biopsy	“It is possible that the use of a larger oral dose of [DSCG], a longer treatment period, rectal administration, or any combination of these three may allow a beneficial therapeutic effect to be demonstrated in patients with chronic persistent colitis. However, the absence of improvement in this study is not encouraging.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Dronfield and Langman, 1978, UK ⁶⁸	Comparative trial	54 Patients with ulcerative colitis <ul style="list-style-type: none"> • Sulphasalazine (48%, mean 38.7 y) • High-dose SCG (56%, mean 37.0 y) • Low-dose SCG (50%, mean 30.4 y) 	Patients initially randomized to either sulphasalazine or low-dose SCG, 9 sulphasalazine patients and 4 high-dose SCG patients were crossed over after relapse on the alternative treatment, and 5 patients switched from low to high-dose SCG when it became available. <ul style="list-style-type: none"> • Sulphasalazine (33) • High-dose SCG (25) • Low-dose SCG (12) 	Incidence of relapse, sigmoidoscopy and rectal biopsy	“These results suggest that oral [SCG] is considerably less effective than sulphasalazine in maintaining remission, and by analogy with results in other trials may be no more effective than placebo tablets.”
Hovdenak et al, 1986, Norway ⁶⁹	Double-blind study	43 Patients with active ulcerative proctosigmoiditis <ul style="list-style-type: none"> • DSCG (52.4%, range 21-71 y) • Placebo (47.8%, range 21-58 y) 	<ul style="list-style-type: none"> • DSCG (21) • Placebo (22) 	Bowel frequency, rectal bleeding, general well-being, abdominal pain, severity and extent of the disease	“It is concluded that DSCG did not improve symptoms or inflammatory changes in ulcerative proctosigmoiditis”
Williams et al, 1980, UK ⁷⁰	Double-blind cross-over trial	18 Outpatients with Crohn's disease (33.3%, range 20-70 y)	<ul style="list-style-type: none"> • DSCG (18) • Placebo (18) 	Daily stool frequency, consistency, amount, presence of blood or mucus; general well-being, abdominal pain	“We concluded that DSCG given orally in a dose of 1.2 g daily is unhelpful in the management of patients with moderately active or quiescent Crohn's disease.”
Willoughby et al, 1979, UK ⁹²	–	120 Patients with ulcerative colitis (61.7%, range 18-81 y)	<ul style="list-style-type: none"> • DSCG (not provided) • Sulphasalazine (not provided) • DSCG and sulphasalazine (not provided) 	Relapse, colitic symptoms	“The mode of action of [sulphasalazine] is unknown but it is unlikely to be the same as that of DSCG. There was therefore the possibility that a combination of these two drugs might prove beneficial but this has not been borne out.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 4: Irritable bowel syndrome (IBS)					
Bolin, 1980, Australia ⁴¹	Randomized, double-blind trial	20 Patients with persistent diarrhea diagnosed as IBS (65%, range 33-71 y)	<ul style="list-style-type: none"> • SCG (20) • Placebo (20) 	Daily symptom record, patient- and clinician-rated severity at end of treatment periods	“The finding of symptomatic improvement in 40% of the patients who had in the past tried a multitude of symptomatic measures, suggests that oral SCG has a role to play in treating persistent diarrhoea without an obvious organic cause.”
Ebrahimi Daryani et al, 2009, Iran ⁹³	Randomized, placebo-controlled, double-blinded crossover study	16 Patients with irritable bowel syndrome (IBS) (25%, mean 40.3 y ± 10.9)	<ul style="list-style-type: none"> • Cromolyn (16) • Placebo (16) 	Weekly assessment of symptoms, side effects	“In conclusion, long term, high dose treatment with cromolyn seems to be partially effective for treatment of abdominal pain in patients with IBS while main symptoms (diarrhea or constipation) may not decrease during treatment period.”
Lobo et al, 2017, Spain ⁷⁹	–	<p>16 Healthy subjects (56%, mean 32.1 y ± 2.3)</p> <p>43 Patients with diarrhea-predominant IBS</p> <ul style="list-style-type: none"> • No treatment (32%, mean 37.4 y ± 2.1) • DSCG (39%, mean 42.5 y ± 3.8) 	<ul style="list-style-type: none"> • Healthy subjects (16) • IBS with no treatment (25) • IBS with DSCG (18) 	Jejunal mast cell activation and specific innate immune signaling pathways in IBS	“Oral DSCG modulates mucosal immune activity and improves gut symptoms in [diarrhea-predominant] IBS patients. Future placebo-controlled clinical trials are needed for confirmation of clinical benefit of DSCG for [diarrhea-predominant] IBS.”
Lunardi et al, 1991, Italy ⁴²	Double-blind cross-over trial	20 Patients with IBS due to food intolerance (10%, mean 33.5 y)	<ul style="list-style-type: none"> • SCG (18) • Placebo (18) 	Severity of each symptom on a daily card	“We therefore conclude that in patients with IBS and proven food intolerance a long treatment period with a high dose of oral [SCG] may be useful.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Stefanini et al, 1995, Italy ⁴³	Multicenter study	409 Patients with diarrheic type of IBS <ul style="list-style-type: none"> Elimination diet (43%, mean 37.6 y ± 13.5) Cromolyn sodium (47%, mean 36.7 y ± 12.6) 	<ul style="list-style-type: none"> Elimination diet (209) Cromolyn sodium (200) 	Severity of symptoms, presence of each intestinal symptom (abdominal distention, abdominal pain, flatulence, etc.) and type of treatment recorded on diary card; global assessment of intestinal symptoms by physician; side effects	“These results confirm the high prevalence of adverse reactions to foods in diarrheic irritable bowel syndrome and the usefulness of cromolyn sodium treatment in these patients.”
Indication 5: Mastocytosis					
Bankova et al, 2013, US ⁹⁴ Bankova et al, 2012, US ⁹⁹	Case report	1 Patient with diffuse cutaneous mastocytosis and vaccination-induced bullous eruption (100%, 5 months old)	Diagnosed at 3 months of age with diffuse cutaneous mastocytosis, started on H1- and H2-antagonists and topical SCG at that time; bullous eruptions after vaccinations at 5 months of age treated with oral steroids; 2 subsequent episodes of blistering associated with vaccination and viral illness treated with oral and topical sodium cromolyn	Resolution/relief of clinical signs	“Protocols for premedication with steroids, antihistamines, and leukotriene receptor antagonists have been successful in prevention of complications. Mast cell stabilizers such as cromolyn improve disease control. In our experience, steroids are the preferred therapy for cases with blister formation, as has been previously reported in the literature.”
Chan et al, 2012, US ¹⁰⁴	Case reports	2 Patients with mastocytosis (0%, age 2 months and 6 y)	<ul style="list-style-type: none"> 6-Year-old female: topical and oral cromolyn (in addition to antihistamines) 2-Month-old female: topical cromolyn (in addition to antihistamines) 	Resolution/relief of clinical signs	“Childhood mast cell disorders can present with significant morbidity. Baseline H1 and H2 blockers are not always effective in controlling symptoms. Treatment is especially difficult in [diffuse cutaneous mastocytosis] when large skin surface areas are affected.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Kinneman et al, 2013, US ¹⁰⁵	-	1 Patient with a history of eczema and 4-week history of cheek flushing admitted after a diffuse flushing reaction, becoming difficult to arouse, and appearance of wheals on his trunk that evolved into large bulla (100%, 6 months)	<ul style="list-style-type: none"> • H1 and H2 receptor blockers, hydrocortisone cream, cromolyn cream, and prednisolone 	Resolution of bullous mastocytosis	“Even though our case would be classified as cutaneous mastocytosis, there is clearly a systemic component as shown by the activated circulating basophils, which supports of the high risk of anaphylaxis in these patients. Further work is necessary to evaluate abnormal circulating cells in mastocytosis.”
Soter et al, 1979, US ⁴⁴ Soter et al, 1978, US ⁴⁶ Soter et al, 1978, US ⁴⁷	Double-blind crossover study	8 Patients with systemic mastocytosis (50%, range 23-76 y)	<ul style="list-style-type: none"> • DSCG (4*) • Placebo (5) *1 patient only received placebo	Improvement in pruritus, whealing, flushing, diarrhea, abdominal pain, and disorders of cognitive function; symptoms recorded daily in diary by the patients, physicians graded clinical manifestations, skin-biopsy specimens and 24-hour urine collections	“Although it is poorly absorbed after administration by mouth, [DSCG] is of clinical benefit to patients with systemic mastocytosis.”
Wasserman et al, 1979, US ⁴⁵	Double-blind protocol	6 Patients (gender and age not provided)	<ul style="list-style-type: none"> • DSCG (not provided) • Placebo (not provided) 	Symptoms recorded daily; improvement in symptoms (pruritus, diarrhea, abdominal pain)	“Although the oral administration of DSCG is effective in ameliorating a variety of clinical manifestations of mastocytosis, its site of action may extend beyond the mast cell.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 6: Pyoderma gangrenosum					
Anderson et al, 1994, US ⁴⁸	Case report	2 Patients with pyoderma gangrenosum, which progressed despite oral steroids and azathioprine (case 1) and 'standard' therapy impractical (case 2) <ul style="list-style-type: none"> Case 1 (0%, 23 y) Case 2 (100%, 62 y) 	<ul style="list-style-type: none"> Case 1: Topical cromolyn sprayed on area Case 2: Contents of cromolyn ampule applied directly to ulcerated 	Resolution of lesions	“Pyoderma gangrenosum is often a very difficult disorder to treat. The majority of systemic therapeutic modalities have significant and potentially long-lasting side effects. Topical 4% cromolyn sodium followed by occlusion with a hydrocolloid dressing may be an effective treatment alternative or adjunctive therapy.”
Cave and Burakoff, 1987, US ⁸⁰	Case reports	2 Patients with ulcerative colitis admitted for pyoderma gangrenosum (50%, ages 30 and 40 y)	<ul style="list-style-type: none"> Female: pyoderma gangrenosum lesion unresponsive to intravenous antibiotics, administered topical DSCG Male: initial treatment for pyoderma gangrenosum was topical DSCG 	Resolution of lesions	“Objective evidence for the efficacy of DSCG in the treatment of [pyoderma gangrenosum] will probably require a multicenter study because of the rarity of the condition. In the meanwhile the use of [DSCG] should be considered in the initial therapy for [pyoderma gangrenosum] in patients with inflammatory bowel disease.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Hughes et al, 2000, US ¹⁰⁶	Retrospective analysis	7 Patients with inflammatory bowel disease (IBD) and peristomal pyoderma gangrenosum (57.1%, range 36-83 y)	<p>Only patient cases who used topical cromolyn sodium provided:</p> <ul style="list-style-type: none"> • Patient 1: effective therapies included topical clobetasol, topical cromolyn sodium, and infliximab. Ineffective therapies included sulfasalazine, metronidazole, triamcinolone acetonide • Patient 2: effective therapies included dapsone, mycophenolate mofetil. Ineffective therapies included prednisone, topical cromolyn sodium, clobetasol propionate 	Resolution of peristomal pyoderma gangrenosum	“Our experiences demonstrate that although [peristomal pyoderma gangrenosum] has been most often reported in patients with IBD, it may occur in the absence of IBD.”
Saffouri et al, 1984, US ⁴⁹	Case report	1 Patient with a history of ulcerative colitis and pyoderma gangrenosum (0%, 35 y)	<ul style="list-style-type: none"> • DSCG (1) 	Resolution and/or improvement of pyoderma gangrenosum	“The pyoderma gangrenosum was treated successfully with topical application of [DSCG].”
Smith et al, 1987, US ⁵⁰	Case report	1 Patient with 3 small punctate lesions with surrounding erythema developed on the right shin (100%, 87 y)	<ul style="list-style-type: none"> • Cromolyn sodium (1) 	Resolution and/or improvement of pyoderma gangrenosum	“We consider that the addition of 2% cromolyn sodium may be a safe, inexpensive, and effective adjunct to the management of pyoderma gangrenosum and may be of particular value when used in combination with an occlusive hydrocolloid dressing.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 7: Pruritus/urticaria					
Feily et al, 2012, Iran ⁵¹	Randomized, double-blind, prospective study	60 Patients with end-stage renal disease (63%, mean 53 y ± 11.4)	<ul style="list-style-type: none"> • Cromolyn sodium cream (30) • Placebo (30) 	Pruritus levels using visual analogue scale (VAS), side effects	“According to our study cromolyn sodium cream 4% was more effective than placebo in reducing pruritus in uremic patients. We suggest to our colleagues to consider this treatment when facing a patient suffering from this symptom.”
Thormann et al, 1980, Denmark ⁷¹	Double-blind crossover trial	15 Patients with chronic urticaria (gender not specified, range 19-58 y)	<ul style="list-style-type: none"> • Placebo (15) • SCG (15) 	Clinical assessments, symptom severity score	“We may conclude that oral SCG had no significant effect on our patients suffering from chronic urticaria.”
Vessal et al, 2010, Iran ⁵²	Double-blind placebo-controlled study	40 Patients on hemodialysis with pruritus <ul style="list-style-type: none"> • Placebo (43%, mean 57.47 y +/- 13.6) • Cromolyn (58%, mean 56.90 y +/- 15.49) 	<ul style="list-style-type: none"> • Placebo (19) • Cromolyn sodium capsules (21) 	Severity of pruritus on VAS, serum tryptase levels	“Cromolyn sodium can significantly reduce the severity of pruritus in [hemodialysis] patients, but this effect is not due to a decrease in serum tryptase level.”
Vieira Dos Santos et al, 2010, Germany ⁵³	Randomized single-blind manner	60 Patients with dermal inflammation (range 23-42 y) <ul style="list-style-type: none"> • Allergic (40%) • Histamine-induced (17.5%) 	All patients received each cream randomized to four areas on each forearm (two sites per arm) and covered with an occlusive dressing before undergoing skin-prick tests: <ul style="list-style-type: none"> • SCG 0.2% (60) • SCG 1% (60) • SCG 4% (60) • Placebo (60) 	Pruritus, flare, skin temperature, weal volume	“SCG is effective in reducing pruritus but has no effect on weals, supporting the proposition that, in the skin, SCG inhibits sensory C-fibre nerve activation rather than preventing mast cell degranulation. We suggest that topical SCG treatment, delivered in an appropriate vehicle, may be beneficial for symptomatic relief of pruritus in patients with cutaneous mastocytosis and other pruritic dermatoses.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 8: Chronic proctitis					
Heatley et al, 1975, UK ⁹⁵ Heatley et al, 1974, UK ¹⁰¹ Heatley et al, 1977, UK ¹⁰⁰	Double-blind crossover study	26 Patients with chronic proctitis (34.6%, range 18-74 y)	<ul style="list-style-type: none"> • DSCG (26) • Placebo (26) 	Frequency of bowel motions each day, occurrence of rectal bleeding, for an overall assessment by patients indicated clinical progress by choosing excellent, good, fair, bad, or terrible	“Patients who responded to DSCG had significantly more eosinophils in their rectal biopsies than those who failed to respond and in some instances the counts were very high. The findings support the hypothesis that an allergic reaction is important in the pathogenesis of proctitis.”
Indication 9: Exercise-induced asthma					
Dahl and Henriksen, 1980, Denmark ⁹⁶	–	10 Patients with exercise-induced asthma (50%, range 13-40 y)	<ul style="list-style-type: none"> • Inhaled SCG capsule (10) • Inhaled placebo capsule (10) • Oral SCG capsule (10) • Oral placebo capsule (10) 	Peak expiratory flow rate after exercise	“Only [SCG] inhalations protected against exercise-induced asthma. The effect of [SCG] seems to be a local action of mucosal surfaces.”
Indication 10: Mast cell activation syndrome					
Afrin et al, 2019, US ⁵⁴	Case report	5 Patients with mast cell activation syndrome with chronic dyspareunia, vaginitis, and/or dysfunctional uterine bleeding (0%, range 34-61 y)	<ul style="list-style-type: none"> • Case 1: Topical/vaginal cromolyn • Case 2: Oral cromolyn • Case 4: Oral cromolyn • Case 5: Topical/vaginal cromolyn <p>*Only cases that used cromolyn were included</p>	Resolution/relief of clinical signs	“In at least some patients with chronic, otherwise idiopathic dyspareunia, [dysfunctional uterine bleeding], or genital tract inflammation, systemic histamine receptor antagonists or the topical application of diphenhydramine or cromolyn may prove helpful, possibly via targeting an underlying [mast cell activation syndrome].”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 11: Recalcitrant idiopathic vulvar vestibulitis					
Nyirjesy et al, 2001, US ⁸¹	Prospective, double blind, randomized, placebo-controlled study	26 Patients with recalcitrant idiopathic vulvar vestibulitis (0%, range 24-49 y)	<ul style="list-style-type: none"> • Cromolyn cream (13) • Placebo cream (13) 	Symptoms (burning, irritation), signs (erythema, extent of erythema, tenderness), dyspareunia	“Cromolyn cream did not confer a significant benefit in patients with vulvar vestibulitis. The large placebo response suggests the need for large well controlled studies of other treatment modalities.”
Indication 12: Recombinant human insulin-induced lipoatrophy					
Lopez et al, 2008, US ⁵⁵	–	5 Patients with severe local insulin-induced lipoatrophy (40%, age not specified)	<ul style="list-style-type: none"> • Sodium cromolyn (5) 	Occurrence of new lipoatrophic sites, improvements in old lesions	“Tryptase-positive/chymase-positive mast cells, known to be sensitive to sodium cromolyn, may contribute to the destructive immune process mediated in response to exogenous insulin. Mast cell stabilizing therapy with topical cromolyn may reverse early and prevent new lipoatrophic lesions.”
Indication 13: Recurrent aphthous ulcers					
Dolby and Walker, 1975, UK ⁵⁶	Random, double blind trial with crossover	15 Patients with recurrent aphthous ulcer (gender and age not provided)	<ul style="list-style-type: none"> • Cromoglycic acid tablet (15) • Placebo (15) 	Patient-recorded discomfort or pain during trial period	“[Cromoglycic acid] would appear to have few contra-indications, thus offering an advantage over topical corticosteroid therapy which clinicians may be reluctant to prescribe in young patients or patients with cardiovascular disease or peptic ulceration. From the results of the trial it would appear to be of considerable value in the symptomatic treatment of [recurrent aphthous ulcer].”
Indication 14: Urticaria pigmentosa					
Czarnetzki and Behrendt, 1981, Germany ⁵⁷	Blind trial	13 Patients with urticaria pigmentosa (sex, age not provided)	<ul style="list-style-type: none"> • Oral DSCG (13) • Placebo (13) 	Resolution/relief of pruritus, whealing, and gastrointestinal therapy	“Oral DSCG thus appears to be a useful alternative for patients with urticaria pigmentosa.”

Author, Year, Country	Study Type ^a	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 15: Varioliform gastritis					
Andre et al, 1982, France ⁵⁸	Randomized placebo-controlled double-blind trial	18 Patients with varioliform gastritis <ul style="list-style-type: none"> • SCG (sex not provided, mean 55 y) • Placebo (sex not provided, mean 54 y) 	<ul style="list-style-type: none"> • SCG 200 mg/day (6) • SCG 400 mg/day (6) • Placebo (6) <p>Note that 6 additional patients were treated with cimetidine. However, since these patients were not part of the trial, this additional information is not presented here.</p>	Endoscopic assessment (with biopsies) before and after treatment, patient-rated result (complete cure, considerable improvement, failure)	It is “important to differentiate [varioliform gastritis] from other types of gastritis, as treatment with [SCG] appears to be effective.”
Indication 16: Vasomotor rhinitis					
Löfkvist et al, 1977, Sweden ⁹⁷	Double-blind cross-over study	49 Patients with vasomotor rhinitis (gender not provided, range 16-65 y)	<ul style="list-style-type: none"> • Group 1: SCG for 6 weeks, 1 week without medication and then placebo for 6 weeks (24) • Group 2: placebo for 6 weeks, 1 week without medication and then SCG for 6 weeks (25) 	Daily diary card for symptoms (blocking, running, sneezing, and itching)	“Although a substantial number of results were obtained, no significant difference between the effects of SCG and placebo treatment, on variables measured, was detected. However, some patients experienced relief with, and preferred, the treatment with SCG.”

Abbreviations: –, not provided; DSCG, disodium cromoglycate; IBS, irritable bowel syndrome; IgE, immunoglobulin E; SCG, sodium cromoglycate or sodium cromoglycate; VAS, visual analogue scale.

^aAs defined by authors.

Appendix 3.1. 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 cromolyn sodium to your patients?

- Yes
- No

3. Do you prescribe or administer cromolyn sodium by any of the following dosage forms and/or routes of administration? (check all that apply)

- Nasal products
- Oral products
- Rectal products
- Topical products
- Vaginal products
- None of the above

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

- Allergies
- Atopic dermatitis
- Atopic eczema
- Other (please explain) _____

5. I prescribe or administer cromolyn sodium with my patients as the following: (check all that apply)

- FDA-approved drug products
- Compounded drug products
- Over-the-counter products
- Other (please explain)

6. I use compounded cromolyn sodium 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 cromolyn sodium
 - Other (please explain) _____
7. Do you stock non-patient-specific compounded cromolyn sodium at your practice?
- Yes
 - No
 - I'm not sure
8. I obtain compounded cromolyn sodium 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 3.2. Survey instrument for professional medical associations

1. How familiar are you with the following terms?

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

2. Do you prescribe or administer any of the following as a compounded topical product? (please check all that apply)

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

- None of the above
3. Do you prescribe the compounded topical products that you selected in in combination with other active pharmaceutical ingredients as a multi-ingredient product?
 - Yes
 - No
 - I'm not sure
 4. Why do you use the compounded topical products that you selected? (please check all that apply)
 - Commercial products are not available in the dosage form, strength, or combination I need (please explain) _____
 - Patient allergies prevent me from using commercially available products (please explain) _____
 - Patient conditions prevent me from using commercially available products (please explain) _____
 - I am not aware of any commercially available products containing these products
 - Other (please explain) _____
 5. Do you stock non-patient-specific compounded products at your practice?
 - Yes
 - No
 - I'm not sure
 6. I obtain compounded products from the following: (please check all that apply)
 - Compound myself at my practice
 - Have the product compounded by an in-house pharmacy
 - Purchase, or have a patient purchase, from a compounding pharmacy
 - Purchase, or have a patient purchase, from an outsourcing facility
 - Other (please explain) _____
 7. What is your practice setting? (please check all that apply)
 - Physician office/private practice
 - Outpatient clinic
 - Hospital/health system
 - Academic medical center
 - Emergency room
 - Operating room
 - Other (please describe) _____
 8. What degree do you hold? (please check all that apply)
 - Doctor of Medicine (MD)
 - Doctor of Osteopathic Medicine (DO)
 - Doctor of Medicine in Dentistry (DMD/DDS)
 - Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
 - Naturopathic Doctor (ND)
 - Nurse Practitioner (NP)
 - Physician Assistant (PA)
 - Other (please describe) _____

Appendix 3.3. Survey instrument for pharmacy roundtable prequestionnaire

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

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

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

Appendix 4. 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.