Summary Report

Methylprednisolone acetate

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

API	Active pharmaceutical ingredient
EMA	European Medicines Agency
EU	European Union
FDA	US Food and Drug Administration
IRB	Institutional Review Board
IM	Intramuscular
IT	Intrathecal
IV	Intravenous
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 Food and Drug Administration (US FDA) in its evaluation the use of methylprednisolone acetate (UNII code: 43502P7F0P), 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 methylprednisolone acetate 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 methylprednisolone acetate 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 methylprednisolone acetate and thereby assist the FDA to determine whether there is a need for the inclusion of this substance on the 503B Bulks List.

REVIEW OF NOMINATIONS

Methylprednisolone acetate was nominated for inclusion on the 503B Bulks List by Fagron, the Specialty Sterile Pharmaceutical Society (SSPS), and US Compounding Pharmacy. Methylprednisolone acetate was nominated for use in combination with additional active pharmaceutical ingredients (API) (refer to Table 8).

Methylprednisolone acetate was nominated for the treatment of adrenal insufficiency, allergic disorders, allergic rhinitis, asthma, bursitis, collagen disease, contact dermatitis due to poison ivy, Crohn's disease, disorders of the eye, disorders of the hematopoietic structure, disorders of the respiratory system, disorders of the skin, epicondylitis, ganglion of aponeurosis, inflammation and immune response caused by various conditions, inflammatory disorders of the musculoskeletal system, leukemia, malignant lymphoma, multiple sclerosis, mycosis fungoides, nephrotic syndrome, osteoarthritis, rheumatoid arthritis, tenosynovitis, trichinosis, tuberculosis of the meninges, ulcerative colitis, carcinoma of the breast, disorders of the optic nerve, fever due to malignancy, giant cell arteritis, primary intracranial tumor, multiple myeloma, and prostate cancer.

Methylprednisolone acetate will be compounded as a 40 to 80 mg/mL solution for intramuscular (IM) injection diluted into potential diluents such as sterile water for injection, sodium chloride, and dextrose. Methylprednisolone will also be compounded as a 40 mg/mL and 80 mg/mL injection. Additionally, methylprednisolone acetate will be compounded as a 40 mg/mL and 80 mg/mL preservative-free suspension for intrathecal (IT) injection, a 50 mg/mL and 100 mg/mL preserved suspension for IM and soft tissue injection, and as a 40 mg/mL and 80 mg/mL preserved suspension in combination with lidocaine for IM and soft tissue injection.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of methylprednisolone acetate.[6-11]

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

- There are available FDA-approved products with methylprednisolone. However, there are serious dose-dependent side effects that can occur with corticosteroids. This can be avoided by compounding specific strengths for correct dosing and reduce the time needed for therapy.

- The preservative-free formulation is commonly preferred for intrathecal administration. There is also a preference for a product that is "pre-mixed with lidocaine to lessen pain without risk of contamination from not mixing under aseptic conditions."
- Patient need for dosage form or strength, including greater concentration, that is not available commercially.
- Prescriber or hospital preference for various strengths, combinations with other drugs, volumes, and/or final product containers for administration.
- Unsafe to expose the direct compounding area to hundreds of vials or ampoules and hundreds of aseptic manipulations during the compounding of a typical size batch for outsourcing facilities; a single vessel compounded from bulk API is safer and more efficient than unmanageable amounts of small vials.
- As required by Current Good Manufacturing Practices, bulk API powders can be formulated to 100 percent potency, but finished products cannot; commercially available finished products have an inherent variance in potency, creating an uncertain final concentration for the new product.
- In order to use the most advanced technology available to provide the greatest level of sterility assurance and quality, bulk starting material is required; it is not feasible financially, nor from a processing standpoint, to use finished pharmaceutical dosage forms with advanced isolated robotic equipment or other advanced aseptic processing equipment.
- Manufacturer backorder.

METHODOLOGY

Background information

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

Each medicine register was searched for methylprednisolone acetate; name variations of methylprednisolone acetate were entered if the initial search retrieved no results. The following information from the search results of each register was recorded in a spreadsheet: product trade name, active ingredient, strength, form, ROA, status and/or schedule, and approval date. Information was recorded only for products with strengths, forms, and/or 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 methylprednisolone acetate. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

Search strategy

A medical librarian constructed two comprehensive search strategies for both Ovid MEDLINE and Embase. The first search strategy used a combination of controlled vocabulary terms and keywords to describe two concepts: methylprednisolone acetate, and epidural or intrathecal administration. The second search strategy used a combination of controlled vocabulary terms and keywords to describe three concepts: methylprednisolone acetate; lidocaine; and intramuscular, intraarticular, or soft tissue administration (refer to Appendix 1 for full search strategies). A literature review was not conducted for single-ingredient injectable methylprednisolone products due to the availability of FDA-approved single-ingredient methylprednisolone products in this ROA/form. Results were limited to human studies in English language. Searches were conducted on September 5, 2020. In addition, the ECRI Guidelines Trust® repository was searched on September 5, 2020 for clinical practice guidelines that recommended the use of methylprednisolone acetate 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 de-duplicated results were uploaded to Covidence (Veritas Health Innovation) for screening.

Study selection

Studies in which methylprednisolone acetate 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 methylprednisolone acetate 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; in an unspecified dosage form or ROA; wrong drug or salt form; methylprednisolone acetate not used clinically; or methylprednisolone acetate mentioned briefly as a rescue treatment or previously failed treatment. Studies in which methylprednisolone acetate 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 methylprednisolone acetate, setting; total number of patients; number of patients who received methylprednisolone acetate; patient population, indication for use of methylprednisolone acetate, dosage form and strength, dose, ROA, frequency and duration of therapy, use of methylprednisolone acetate in a combination product, use and formulation of methylprednisolone acetate in a compounded product, use of methylprednisolone acetate compared to FDA-approved drugs or other treatments, outcome measures, and authors' conclusions. One reviewer extracted data from the included studies; a second reviewer checked the data extraction.

Interviews

Semistructured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances methylprednisolone acetate was used in a clinical setting. The systematic literature review and indications from the nominations were reviewed to identify medical specialties that would potentially use methylprednisolone acetate. 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 methylprednisolone acetate 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 for project Year 3 surveys.

The survey was posted on the project website and the survey link was distributed to the associations that agreed to participate (refer to Appendix 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

- Methylprednisolone acetate is available as an FDA-approved product in the nominated dosage form and ROA.
- Methylprednisolone acetate is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for methylprednisolone acetate.
- Methylprednisolone acetate is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, Latvia, Namibia, New Zealand, Saudi Arabia, and UK. There is an EMA report on scientific conclusions and grounds for variation and amendments to the product information for methylprednisolone by the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh).[12] In this report, the pharmacovigilance risk assessment committee (PRAC) Assessment report for methylprednisolone that leukocytosis, thrombotic events, epidural lipomatosis, and chorioretinopathy should be added as adverse reactions and a warning to appropriately monitor for hepatobiliary disorders should be included for products containing methylprednisolone for systemic use.[12] Additionally, hepatitis and increased liver enzymes should be included in the parenteral methylprednisolone product information while just increased liver enzymes should be included in the oral methylprednisolone product information.[12] The PRAC concluded that the product labeling for oral and parenteral products containing methylprednisolone should be updated accordingly, with the CMDh agreeing with the conclusions made.[12]

Table 1. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Status	Approval Date[b]
Methylprednisolone acetate	20-80 mg/mL	Injectable	Injection	Prescription	Approved prior to 1/01/1982

[a]Source: US FDA *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).
[b]If multiple approval dates and/or multiple strengths, then earliest date provided.

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

Active Ingredient[b]	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date[c]
Methylprednisolone acetate	20-80 mg/mL	Solution, suspension	Intraarticular, injection intralesional, intramuscular, intrasynovial, intravenous, periarticular, rectal, tendon sheath	Abu Dhabi	Active	–
				Australia	Prescription-only	8/02/1991
				Belgium	Prescription	4/20/1963
				Canada	Prescription	12/31/1960
				Hong Kong	Prescription-only	8/15/1978
				Ireland	Prescription-only non-renewable	4/01/1978
				Latvia	Prescription	12/20/2016
				Namibia	–	2/22/1971
				New Zealand	Prescription	6/16/1976
				Saudi Arabia	Prescription	–
				UK	Prescription-only	3/07/1989
Methylprednisolone acetate / Lidocaine	40 mg/mL / 10 mg/mL	Solution, suspension	Intraarticular, intrabursal, injection, intralesional, intrasynovial, periarticular, tendon sheath	Canada	Prescription	12/31/1973
				Belgium	Prescription	4/30/1975
				Hong Kong	Prescription-only	8/15/1978
				Ireland	Prescription-only non-renewable	3/02/1981

				Namibia	–	7/24/1974
				New Zealand	Prescription	1/24/1978
				UK	Prescription-only	3/03/1981

Abbreviation: –, not provided.

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

[b]Methylprednisolone acetate used as the standard for name variations, including methylprednisolone, methylprednisolone acetas. Lidocaine used as the standard for name variations, including lidocaine HCl.

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

Results of literature review

Study selection

Database searches yielded 1132 references; 0 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 822 titles and abstracts were screened. After screening, the full text of 237 articles was reviewed. Fifty-seven studies were included; after multiple reports of the same study were merged, there were 52 included studies. One hundred eighty studies were excluded for the following reasons: wrong study design (138 studies); wrong dosage form or ROA (33); duplicate study (3); unspecified dosage form or ROA (3); methylprednisolone acetate only mentioned briefly (2); FDA-approved formulation (1).

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

Characteristics of included studies

The 52 included studies were published between 1961 and 2020. There were 39 experimental studies, 5 observational studies, 8 descriptive studies, and 0 clinical practice guidelines. The 52 studies were conducted in the following countries: Denmark, Egypt, Finland, Germany, India, Iran, Israel, Italy, Japan, Mexico, Pakistan, South Africa, the Netherlands, Turkey, United Kingdom, and US.

A total of 2926 patients participated in the 52 included studies. The number of patients in each study ranged from 1 to 292.

Outcome measures differed among the included studies and included: pain relief, adverse events, absence of tenderness, Finkelstein test, injection accuracy, range of motion, patient's self-assessment, clinical assessment, treatment failure, favorable response rate, time duration, adherence, cytokine levels, back-to-work time, corticosteroid concentration, blood electrolytes, time to recovery/recurrence, neurologic index, cerebrospinal fluid cell albumin. Blood brain barrier integrity, steroid dissipation, symptoms of post lumbar puncture syndrome, headache.

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

Use of methylprednisolone acetate

One thousand four hundred twenty-two patients received methylprednisolone acetate as a treatment for painful inflammatory conditions, administered via various injections (intra-articular, intrathecal, intra-bursal, epidural, peri-articular, subacromial) in doses ranging from 10-200 mg one to three times. Other dosing schedules included methylprednisolone for 20-240 mg/week. Duration of treatment ranged from once to 4 weeks. One study stated an average range of 4.3-5.6 weeks. One hundred fifty-eight patients received methylprednisolone acetate as a treatment for multiple sclerosis, administered intrathecally in doses ranging from 12.5-160 mg/week. Another dosing schedule was methylprednisolone given as a series of 6 injections (16-100 mg) over 2–3 weeks with a booster of 100 mg given every 2-3 months as needed. While another dosing schedule was methylprednisolone 80 mg for the first 3 injections over 2-3 days, and then repeated at 2–4 week intervals. Duration of treatment ranged from once to 7.5 years. One hundred twenty-nine patients received methylprednisolone acetate for reduction/prevention of post lumbar puncture syndrome, or post-pneumoencephalography and myelography symptoms, administered intrathecally as a one-time 40 mg dose.

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

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

In 17 studies, the authors' concluding statement recommended the use of methylprednisolone acetate for the treatment of painful inflammatory conditions,[13-25] multiple sclerosis,[26] and reduction/prevention of post lumbar puncture syndrome, or post-pneumoencephalography and myelography symptoms.[27-29] In 5 studies, the authors concluded that the use of methylprednisolone acetate was not recommended for the treatment of painful inflammatory conditions[30-33] and multiple sclerosis.[34] In 6 studies, the authors concluded that the efficacy of methylprednisolone acetate was similar to that of other study interventions for the treatment of painful inflammatory conditions.[35-40] In 15 studies, the authors concluded that further studies were necessary for the treatment of painful inflammatory conditions[41-52] and multiple sclerosis.[53-55] In 4 studies, the authors did not provide a definitive conclusion for the use of methylprednisolone acetate.[56-59] In 5 studies, the authors' conclusions did not address the use of methylprednisolone acetate.[60-64] 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 methylprednisolone acetate.

Synthetic corticosteroids, which include methylprednisolone, betamethasone, dexamethasone, and triamcinolone "are derivatives of prednisolone, which is an analogue of cortisol" and therefore provide varying levels of anti-inflammatory effects.[65] Methylprednisolone is the methyl derivative of prednisolone and betamethasone, dexamethasone, and triamcinolone are fluorinated derivatives of prednisolone; betamethasone is also an isomer of dexamethasone.[65]

The corticosteroids are grouped into 2 categories based on their particle size and aggregation in relation to red blood cells, particulates and non-particulates.[66] Particulates, which include betamethasone acetate and sodium phosphate (Celestone® Soluspan®), methylprednisolone acetate (Depo-Medrol®), and triamcinolone acetonide (Kenalog®), have particle sizes or aggregates that are larger than red blood cells and contain "corticosteroid esters that are insoluble in iodinated contrast, local anesthetic, and saline material."[66-68] In contrast, non-particulates, which include dexamethasone sodium phosphate (Decadron®) and compounded betamethasone SP, due to the SP moiety which increases the solubility, are "fully soluble and clear in appearance."[65,67,68] Non-particulate corticosteroids are appropriate for parenteral use and are theoretically safer for epidural use.[65,68] With epidural administration, there is a risk of inadvertent intravascular injection but since the particle size of non-particulate corticosteroids is smaller than red blood cells "this would eliminate the risk of embolic infarction in the event of inadvertent intravascular injection."[65,68] However, particulates are theorized to be more efficacious due to their large particle size leading to longer retention in the epidural space compared to non-particulates which "are washed out of their target region readily."[68,69]

Methylprednisolone acetate is commercially available as a preserved suspension for IM, intra-articular, soft-tissue, and intralesional injection.[70] The product contains benzyl alcohol as a preservative and polyethylene glycol as a vehicle, both of which are potential neurotoxins.[70,71] Benzyl alcohol can function as a preservative, solvent, anesthetic, and/or viscosity-decreasing agent and is often used in various plants, plant products, foods, cosmetics, and medications.[72] Reports of allergy to benzyl alcohol are relatively rare.[72] In addition, there is debate about benzyl alcohol causing neurotoxicity as "paraplegia, neural degeneration, and demyelination have been reported."[65]

However, all the reported cases had an immediate onset of symptoms that is "more consistent with an embolic event than with demyelinating sequelae following an injection."[65] Benzyl alcohol was replaced with myristyl-gamma-picolinium chloride due to the potential neurotoxic effect of benzyl alcohol and polyethylene glycol.[71] On the product labeling for methylprednisolone acetate suspension, the manufacturer cautioned against mixing or diluting with other solutions because of possible physical incompatibilities.[70,73] However, methylprednisolone acetate is "often mixed with local anesthetic or contrast agent at the time of injection."[73] Local anesthetics can also cause neurologic injuries, which is a risk that can be potentially additive.[73] Adverse events mentioned in the literature for the combination of methylprednisolone acetate and lidocaine injection include acute ischemia and anaphylaxis.[74,75]

Antenatal corticosteroids such as dexamethasone, and the combination of betamethasone SP and betamethasone acetate, have been used to prevent respiratory distress syndrome (RDS) in preterm infants.[76] The combination of betamethasone SP and betamethasone acetate is used to "maximize the drug's efficiency while reducing the number of injections given to the mother."[76] According to a 2013 Cochrane Review by Brownfoot et al, dexamethasone may have less intraventricular hemorrhage compared to that of betamethasone, although possibly with a higher rate of neonatal intensive care unit admission.[76] Brownfoot et al concluded that further trials are still needed for the optimal type of corticosteroid to use as well as the optimal corticosteroid dosing, timing, and frequency of administration.[76] Dexamethasone can be given orally or intramuscularly while betamethasone can be given intramuscularly, intra-amniotically, or intravenously.[76] The updated 2017 Cochrane Review by Roberts et al supports "the continued use of a single course of antenatal corticosteroids to accelerate fetal lung maturation in women at risk of preterm birth" and also found no difference in efficacy between betamethasone and dexamethasone except for "less maternal chorioamnionitis occurring with betamethasone."[77] Similar to Brownfoot et al, Roberts et al noted further information is still needed for "optimal dose-to-delivery interval and the optimal corticosteroid to use."[77]

Corticosteroids have also played a role "in the multimodal pain management in the treatment of chronic spinal pain (cervical and lumbar) and osteoarthritis pain."[78] Epidural steroids have been used since 1952 to treat radicular types of pain.[79] Transforaminal, interlaminar, and caudal injections are the most commonly used epidural techniques for "managing lumbar radicular type pain."[78] In 2021, the American Society of Interventional Pain Physicians released evidence-based guidelines for the use of epidural interventions in the management of chronic pain.[80]

Most reported adverse effects of epidural injections are mild and transient. Ischemic complications have been reported for methylprednisolone, triamcinolone, and betamethasone, but not with dexamethasone.[65] With the exception of 1 case, all neurological complications have been reported after particulate corticosteroid injections.[67] A possible hypothesis is that particulate steroids contain numerous particles that can form macro-aggregates, which are bigger than red blood cells and could increase the "risk of emboli formation and small arteriole occlusion."[67] A more recent hypothesis suggests that there is a "direct negative interaction between several corticosteroid particles and red blood cells."[67] In a study done on mice, 3 particulate corticosteroids (methylprednisolone acetate, triamcinolone acetonide, and prednisolone acetate) injected intra-arterially immediately led to a massive effect on microvascular perfusion due to red blood cell aggregate formation "with the transformation of red blood cells into spiculated red blood cells.[67] On the other hand, the change in microvascular perfusion did not occur when non-particulate corticosteroid dexamethasone SP was injected.[67] While dexamethasone seems to be associated with less neurological complications, 1 case reported involved infarction of the terminal cone after lumbar transforaminal infiltration with

dexamethasone.[67] However, the exact cause was hard to determine due to minimal information provided in the case report such as the position of the needle.[67]

While complications are rare, in 2015 the Multi-Society Pain Workgroup published recommendations to prevent neurologic complications associated with epidural steroid injections.[81] These recommendations stated that particulate steroids should not be used for cervical transforaminal injections and a nonparticulate steroid should be used for lumbar transforaminal injections.[81] However, the recommendations also stated that "there are situations in which particulate steroids could be used in the performance of lumbar transforaminal epidural steroid injections."[81] The recommendations did not address interlaminar epidural injections and another review of epidural steroid injections stated that there is "insufficient data to give a clear recommendation on which corticosteroid should be utilized" for interlaminar and caudal epidural injections.[68] The Spine Intervention Society released a position statement on best practices for epidural steroid injections in the event of a shortage of preservative-free dexamethasone. These recommendations stated that dexamethasone with preservatives may be used for transforaminal epidural injections due to "paucity of evidence of neurotoxicity associated with benzyl alcohol."[82] The recommendations also state that other particulate steroids can be considered for lumbar transforaminal injections and "because the risk is indistinguishable, either particulate or nonparticulate steroids may be used in the performance of interlaminar or caudal epidural injections at the spinal level."[82] If prescribers elect to use compounded preservative-free steroids, they "must carefully weigh the risks and benefits, as sterility assurance concerns exist."[82]

In a 2018 recommendation for epidural and transforaminal corticosteroid injection from Société d'imagerie musculosquelettique (SIMS), Fédération de radiologie interventionnelle (FRI), and Société franc ̧aise de radiologie (SFR), Cotten et al stated that knowledge about the neurological complications while using particulate corticosteroids in transforaminal injections "has led to a change in practices in several countries, as well the recommendation of using dexamethasone SP for transforaminal injections."[67] On the other hand, a 2015 study noted that there has not been evidence that dexamethasone is less effective than particulate steroids in transforaminal epidural steroid injections (TFESIs) for radicular pain; however, evidence for dexamethasone's efficacy for TFESIs remains limited.[83] In a 2013 review about cervical epidural steroid injections for cervical spinal pain treatment, Candido and Knezevic stated that dexamethasone was the only non-particulate corticosteroid not yet implicated in spinal or brain stem infarction following cervical epidural steroid injections and suggested the use of only non-particulate corticosteroids such as dexamethasone SP to reduce the risk of complications.[69] Similarly, in Cotten et al's 2018 recommendation for epidural and transforaminal corticosteroid, dexamethasone SP, as the only non-particulate corticosteroid available in France, was recommended for cervical infiltration or lumbar transforaminal infiltration.[67] Cotten et al also reported a study that cautioned against using ropivacaine with dexamethasone because ropivacaine can provoke crystallization of dexamethasone.[67] There were several studies that compared dexamethasone SP to particulate steroids such as betamethasone,[84] methylprednisolone acetate,[85] or triamcinolone[86,87] for TFESIs in radicular pain. Three studies concluded that dexamethasone and the particulate steroid comparator used had a similar effectiveness, with one study by Kennedy et al that noted the dexamethasone group had to receive slightly more injections to achieve the same outcomes as the triamcinolone group.[86] Another study by Kim and Brown commented that there did "seem to be some statistically non-significant trend toward [dexamethasone SP] being slightly less effective and of shorter duration than [methylprednisolone acetate]," of which may need to be clarified by further studies.[85] While a 2010 study by Park et al, concluded that triamcinolone was more effective than dexamethasone for lumbar radiculopathy.[87] When there are

radiculopathy cases that are refractory to conventional TFESIs, percutaneous epidural adhesiolysis (PEA) can be used.[88] PEA works by washing out inflammatory cytokines and drugs while also lysing the epidural fibrosis.[88] In a 2016 study by Cho et al, the efficacy of dexamethasone SP and triamcinolone acetate during PEA were compared. Forty patients received PEA with triamcinolone acetate 80 mg while 26 patients received PEA with dexamethasone SP 10 mg.[88] Cho et al concluded that dexamethasone was non-inferior to triamcinolone acetate based on success rate and percentage of the verbal numerical rating scale decrease 6 months after PEA.[88]

Intra-articular injections have been used to treat inflammation and pain in the knee and to provide temporary relief of "joint symptoms associated with osteoarthritis and other inflammatory disorders."[89] Hydrocortisone, methylprednisolone, dexamethasone, betamethasone, prednisolone, and triamcinolone are the most commonly used corticosteroids for intra-articular injection.[89] The duration of action ranges from 6-21 days, with hydrocortisone and dexamethasone sodium phosphate providing the shortest action and triamcinolone hexacetonide the longest.[89] However, the effect of these injections on articular cartilage is a concern. A 2015 literature review found that "Corticosteroids have a time- and dose-dependent effect on articular cartilage, with beneficial effects occurring at low doses and duration and detrimental effects at high doses and durations" concluding that while there are beneficial effects of intra-articular injections, the lowest effective dose should be used.[89]

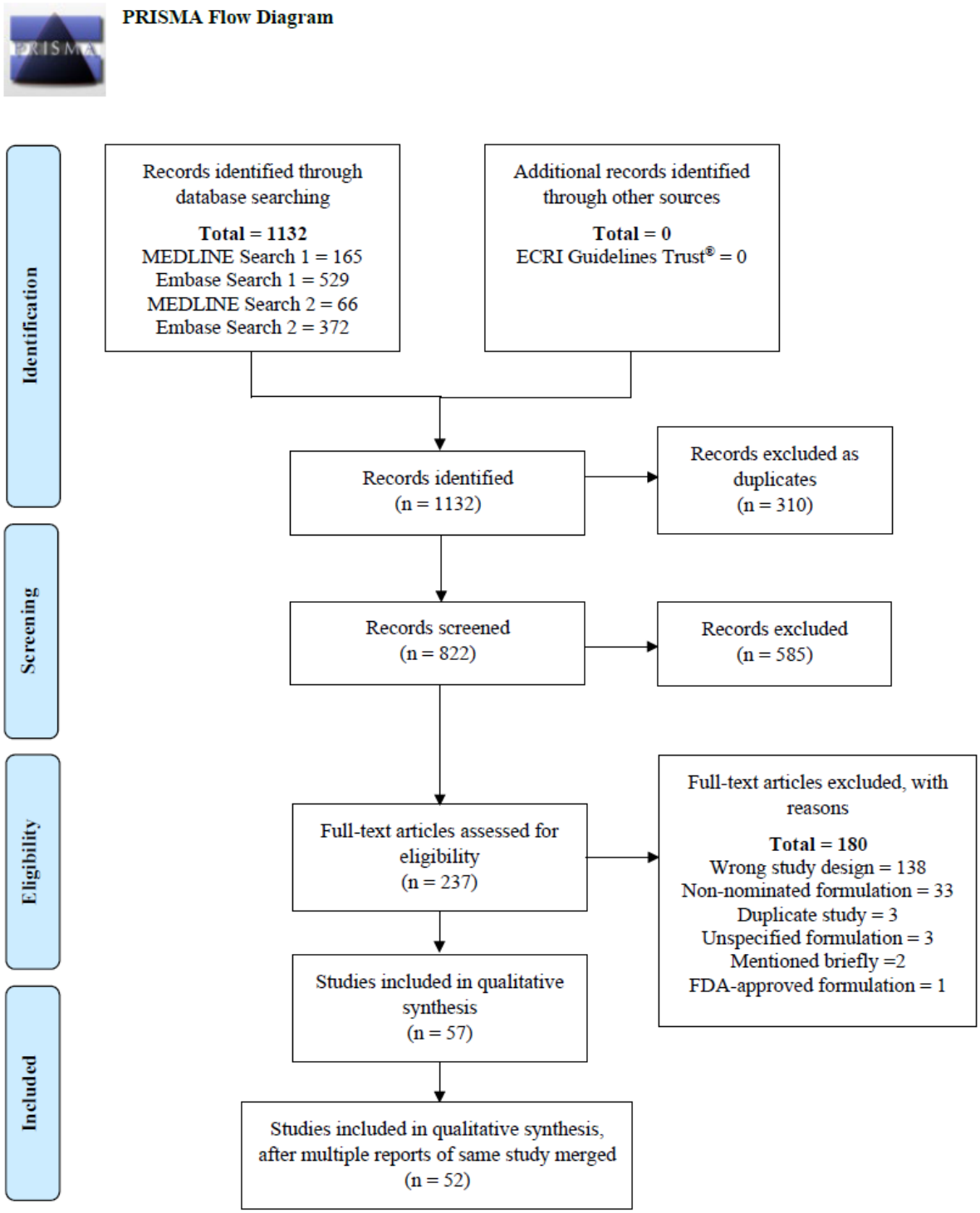
Steroids were first reported as being used intrathecally in 1953 when Kamen and Erdman reported positive results after using IT hydrocortisone and IM adrenocorticotropic hormone in a patient with relapsing-remitting multiple sclerosis.[73] Methylprednisolone acetate is the most frequently injected IT steroid and use became popular in the 1960s and 1970s. However, the use in patients with multiple sclerosis remains controversial with advocates claiming "benefits including reduction of spasticity, improvement of gait and sphincter control, and more rapid remission of symptoms" while critics state that use fails "to show improvement or showed only transient possible benefit."[90] Additionally, none of the studies evaluating the use were controlled or blinded and there was the likelihood that the disease spontaneously remitted in all reports.[71,90] There have been no studies showing the superiority of IT steroids over other, more conventional, routes.[90] IT methylprednisolone acetate has also been used since 1960 after introduction by Sehgal and Gardner frot the treatment of lumbar radiculopathy.[91] A case report by Cohen published in 1979 discussed the development of conus medullaris syndrome in a woman after long-term intrathecal steroid injections and stated that "a more cautious approach than that previously advocated in the treatment of benign disease."[91] IT administration has also been associated with adverse effects including subarachnoid blocks, inadvertent subarachnoid injection leading to transient sensory levels, pleocytosis, transient urinary incontinence, arachnoiditis, aseptic meningitis, cerebral hemorrhage, subarachnoid hemorrhage, neurogenic bladder, conus syndrome, brain damage, spinal cord lesions, and pachymeningitis.[31,71,91-93] According to Munts et al, these reported adverse events were mostly reported in multiple sclerosis patients who had repeated administrations.[31] The product labeling for methylprednisolone includes a contraindication for intrathecal administration and that there has been "severe medical events [associated with administration] by this route."[70,73]

Nelson and Landau summarized 2 publications evaluating the use of IT methylprednisolone acetate for the treatment of postherpetic neuralgia.[93] Postherpetic neuralgia occurs in about 10% of patients with herpes zoster and is accompanied by intractable severe pain.[93] There are no effective therapies and most treatment options are associated with "unpleasant or dangerous side effects."[93] The rationale for using IT steroids "hinges on the question of whether inflammation of dorsal root ganglia or central pain pathways are present in patients with PHN [postherpetic neuralgia]."[93] Nelson and Landau stated

that “the rationale for intrathecal methylprednisolone for postherpetic neuralgia treatment is fallacious” stating that “efficacy of this new therapy is unproved” and that “all evidence indicates that this treatment should not be used.”[93]

Bernat in 1981 and Nelson and Landau in 2001 recommended against the use of IT steroids for any indications with Bernat stating that “that there is no evidence that the intrathecal route of steroid administration offers any advantage over a higher steroid dosage by a more conventional route.”[71,90] There are also concerns with the potential of the additives in steroid formulations, including polyethylene glycol, benzyl alcohol, and benzalkonium chloride, to be neurotoxic.[71,90]

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[26,32,42,45,54,55,59,64]	8
Observational[16,23,57,58,62]	5
Experimental[13-15,17-22,24,25,27-31,33-41,43,44,46-53,56,60,61,63]	39

Table 4. Number of studies by country

Country	**Number of Studies**
Denmark[24,43]	2
Egypt[20]	1
Finland[30,48,49]	3
Germany[63]	1
India[35,60]	2
Iran[22,37,38,46,50,61]	6
Israel[17]	1
Italy[41]	1
Japan[21]	1
Mexico[39]	1
Pakistan[13,14]	2
South Africa[18]	1
The Netherlands[31,52]	2
Turkey[36]	1
United Kingdom[15,44,56]	3
US[16,19,23,25-29,32-34,40,42,45,47,51,53-55,57-59,62,64]	24
	Total US: 24 Total Non-US Countries: 28

Table 5. Summary of included studies

Refer to Appendix 2

Table 6. Dosage by indication – US

Indication	Dosage	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Painful inflammatory conditions[16,19,23,25,32,33,40,42,45,47,51,57,62]	10-200 mg	40-80 mg/mL	Suspension	Intra-articular, intrathecal, injection	1-3 times
	120 mg/week	40 mg/mL	Suspension	Intra-articular, intrabursal	3 weeks
Multiple sclerosis[26,34,53-55,58,59,64]	12.5-160 mg/week	40 mg/mL	Suspension	Intrathecal	Once-22 months
	Series of 6 injections (16-100 mg) given over 2-3 weeks; booster 100 mg given every 2-3 months if needed	40 mg/mL	Suspension	Intrathecal	–
	80 mg for first 3 injections over 2-3 days then repeated at 2-4 week intervals	40 mg/mL	–	Intrathecal	Mean 3.4 y (range 2 months to 7.5 y)
Reduction/prevention of post lumbar puncture syndrome, or post-pneumoencephalography and myelography symptoms[27-29]	40 mg	40 mg/mL	–	Intrathecal	Once

Abbreviation: –, not provided; y, year.

Table 7. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Painful inflammatory conditions[13-15,17,18,20-22,24,30,31,35-39,41,43,44,46,48-50,52,56,60,61,63]	12-80 mg	40 mg/mL	Solution, suspension	Intra-articular, intrathecal, injection, peri-articular, subacromial	1-3 times
	240 mg/week	–	–	Intrathecal, epidural	4 weeks
	20 mg/week	–	–	Injection	3 weeks
	10 mg per 2 weeks (average 31 mg over an average period of 3.1 weeks)	40 mg/mL	Suspension	Injection	Average range 4.3-5.6 weeks

Abbreviation: –, not provided.

Table 8. Number of studies by combination

	Combination Formula	Number of Studies
Nominated	Methylprednisolone acetate 40-80 mg/mL / Lidocaine 1-2% – intra-articular, intrathecal, intrabursal, epidural, peri-articular, subacromial injection[13-22,24,25,30,33,35-52,56,60-63]	37

Table 9. Compounded products – US

No compounded products from included studies

Table 10. Compounded products – non-US countries

No compounded products from included studies

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. Seven SMEs discussed methylprednisolone acetate. Among these 7 SMEs, there were 6 medical doctors and 1 nurse practitioner. The SMEs specialized and/or were board-certified in allergy, oncology, neurology, ophthalmology, physical medicine and rehabilitation, and rheumatology working in academic medical institutions and outpatient practice. The SMEs had been in practice for 10 to 52 years. Additional information was collected as part of the Expanded Information Initiative project, referred to as Phase 3, in which outreach was conducted to the nominators of the bulk drug substances to remedy information gaps in the initial nomination.

Three SMEs commented that they do not use methylprednisolone. When treating asthma, 1 SME stated that since methylprednisolone is an injection it is typically only used "if they're in the ER or in the hospital with [an] asthma flare, if they're bad and they can't tolerate PO [oral] prednisone." The SME said this would not be administered in an outpatient clinic and that "they would be going to the ER for that." One SME does not use epidural or IT steroids but commented that they might be beneficial in patients with spinal metastases and tumors.

One SME does use methylprednisolone for intraarticular steroid injections for osteoarthritis and inflammatory arthritis. The SME commented that the choice of steroid used is dependent upon what the clinic stocks stating, "those are interchangeable for me." The SME has not encountered any patients that were allergic to the commercially available formulation and did not see a need for a preservative-free formulation.

One SME mentioned that preservative-free corticosteroids are a "huge need" in ophthalmology because there are several inflammatory anterior segment conditions and "some people develop allergies to preservatives." Benzalkonium chloride is associated with "a lot of neurotoxicity and epithelial toxicity" but also that "there are just some people that are sensitive to preservatives or have inflammation." The SME stated that it can be challenging to determine whether inflammation is due to a patient's underlying disease or if it is the result of an allergy to a preservative. As a result, it may be beneficial to have a PF product for patients so that there is not "another level of complexity" adding into the treatment plan. However, it is harder to obtain PF products, so a commercially available product is often started initially and then switched "if I thought there was a problem." The SME mentioned that, while not the majority, there are some patients who "have such a fragile ocular surface" and are started immediately on a PF product. The SME uses compounded PF methylprednisolone

One SME commented on the use of IT steroids for multiple sclerosis but has never used them for this indication. The SME stated that they have been used off-label "just as a one-off" but there has been literature published since the 1960s reporting adverse events associated with use, such as arachnoiditis or other complications. The SME stated, "I've just stayed away from them." The SME only uses IV steroids and prednisolone when treating patients with multiple sclerosis, commenting that if a patient does not tolerate a steroid, they will use a different medication.

One SME discussed the use of epidural steroid injections. There are 2 main types of epidural injections, transforaminal and interlaminar. With a transforaminal epidural injection, the epidural space is approached from the side and allows for the drug to be administered close to the inflamed nerve. The SME stated that preservative-free dexamethasone is the only steroid that should be used but that, even in the event of a shortage, a preserved product would be preferred over a preservative-free compounded product. The SME mentioned that theoretically it would be advantageous to have betamethasone sodium phosphate available as a single agent product since it is a nonparticulate steroid and would therefore be

safer for transforaminal use —but since the product would have to be compounded this would be a barrier to use. Interlaminar epidural injections are administered through the middle of the back and are less precise than transforaminal injections as the drug is not administered near the target nerve root. There is more variability in the steroids used for this injection technique as it is administered farther from arteries that could cause complications, allowing prescribers the freedom to select which steroid to administer. While a preservative-free would be preferred, there are no guidelines indicating that one must be used. The SME stated that using a commercially available preserved product would still be preferable to using a compounded preservative-free product.

Regarding the need for a preservative-free product to be compounded, the SME stated the presence of a preservative would likely not be significant when administering epidural steroids. There is a higher risk with both transforaminal and interlaminar injections of inadvertently injecting the drug intrathecally, with interlaminar injections presenting a higher risk. The SME stated that preservatives could be problematic with IT administration commenting that there is some animal research that shows that preservatives may result in major complications if injected intrathecally. However, the SME stated that if the procedure is performed correctly, the needle should not enter the IT space. Typically, a dye is injected first to ensure proper placement of the needle prior to the injection of the steroid; even if a preserved steroid is inadvertently administered into the intrathecal space, there is no clear guidance that this will lead to complications, with the most likely complication being nerve pain. Due to variability in technique and the risk of potential complications as a result, the SME stated that it is better to use a commercially available product, because a contaminated product, even if administered perfectly, could still cause harm.

The SME did not see any clinical reason for steroids to be compounded for epidural use, stating that they have never needed to inject anything that is not commercially available. The SME also did not see a need for there to be a combination product with lidocaine, stating that while some prescribers will mix the steroid with lidocaine as a dilutant prior to the procedure, there is no need for this to be available as a premixed product. Additionally, the SME said that "we don't know as much about anesthetics mixed in as we thought," and went on to say that there is preliminary research identifying anesthetics that are not safe. Another SME commented that they do not see a pharmacologic reason why a compounded methylprednisolone with lidocaine as a combination would be advantageous, stating that though they have seen patients have adverse events due to joint injections, most cases resulted from a combination of a local anesthetic with methylprednisolone, not a compounded product.

As part of Phase 3, 2 nominators provided additional information regarding the products that will be compounded using methylprednisolone acetate.

Methylprednisolone acetate will be compounded as an 80-mg/mL PF solution for IV injection to treat inflammation brought on by a variety of conditions. This product is used by practitioners as a non–patient-specific compounded product in outpatient clinics and surgery centers. This product is needed because the commercially available products contain either benzyl alcohol or myristyl-gamma-picolinum chloride as preservatives and are contraindicated for spinal/intrathecal injections.

Methylprednisolone acetate will be compounded as a 40-mg/mL, 50 mg/mL, 80=mg/mL, and 100-mg/mL PF suspension for intra-articular injection and other ROAs to treat inflammatory disorders of the musculoskeletal system. This product is needed because a PF formulation will allow for use in sensitive or allergic patients.

Methylprednisolone acetate will be compounded as a 40-mg/mL and 80=mg/mL suspension in combination with lidocaine with a ROA that depends on the application for treatment of inflammatory disorders of the musculoskeletal system. This product is needed because the addition of lidocaine will

lessen the pain on administration without increasing the risk of contamination from not mixing under aseptic conditions.

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 API. If sterile becomes short, they quickly switch to producing through API, 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 APIs by outsourcing facilities. One commented that as long as they are conducting end-product sterility and stability testing and the product meets quality standards, they are not concerned with the starting ingredients. As long as buyers are familiar with regulations and know what to look for, another participant commented, there should not be any issues with purchasing products compounded starting from 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

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

A prequestionnaire was distributed to participants of the roundtable discussion (refer to Appendix 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) used outsourcing facilities to obtain drug products, 4 (9%) did not use outsourcing facilities, and 4 (9%) did not respond to this question.

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

Zero respondents (0% of 108 responses, where respondents were allowed to select multiple drug products) obtained methylprednisolone from a 503B outsourcing facility (refer to Table 18).

Table 11. Characteristics of survey respondents

No respondents to survey distributed via professional medical associations

Table 12. Conditions for which methylprednisolone acetate prescribed or administered

No respondents to survey distributed via professional medical associations

Table 13. Reasons for using compounded methylprednisolone acetate

No respondents to survey distributed via professional medical associations

Table 14. Use of non-patient-specific compounded methylprednisolone acetate

No respondents to survey distributed via professional medical associations

Table 15. Demographics of prequestionnaire respondents' facilities

Type of Facility	**Responses, n (N = 102)[a]**
Academic medical center	15
Acute care hospital	16
Children's hospital	8
Community hospital	11
Critical access hospital	2
Dialysis center	2
Federal government hospital	4
Health system	15
Inpatient rehabilitation center	4
Long-term acute care hospital	3
Outpatient surgery center	6
Rural hospital	2
Skilled nursing facility	0

Specialty hospital[b]	4
Trauma center	5
Urban hospital	5
Number of Beds	**Responses, n (N = 39)**
< 50	4
50-99	3
100-199	1
200-299	4
300-399	5
400-599	3
> 600	19

[a]Respondents allowed to select multiple facilities.
[b]Specialties provided include cardiology, pulmonary, vascular, home infusion, neurology, psychiatry, oncology.

Table 16. Reasons for obtaining products from outsourcing facilities

Categories	Responses, n (N = 143)[a]
Drug shortages	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 on-site compounding facility	1
On-site compounding facility not equipped to compound all necessary products	19
Other[b]	8

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

Table 17. Categories of products obtained from outsourcing facilities

Categories	Responses, n (N = 142)[a]
Cardioplegic solutions	14
Dermatologic preparations	6
Dialysate solutions	0
Fluids	8
Ophthalmic preparations	10
Patient-controlled analgesia	20
Ready-to-use anesthesia syringes	25
Ready-to-use antibiotic syringes and/or bags	14
Ready-to-use electrolyte solutions	5
Ready-to-use vasopressor solutions	18
Total parenteral nutrition solutions	16
Other[b]	6

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

Table 18. Products obtained from an outsourcing facility

Product	Responses, n (N = 108)[a]
Acetylcysteine	1
Adenosine	2
Aluminum potassium sulfate	2
Aspartic acid	0
Atenolol	0
Atropine	9

Baclofen	4
Betamethasone	0
Biotin	0
Bupivacaine	8
Calcium chloride	1
Caffeine sodium benzoate	0
Cholecalciferol	1
Chromium chloride	0
Clonidine	0
Dexamethasone sodium phosphate	0
Diclofenac	0
Gentamicin	0
Glycerin	1
Hydroxyzine	0
Ketamine	14
Levocarnitine	0
Lidocaine	8
Lorazepam	2
Magnesium sulfate	4
Manganese chloride	0
Methylprednisolone	0
Midazolam	15
Mupirocin	1
Norepinephrine	15
Ondansetron	0
Phytonadione	0

Potassium chloride	0
Potassium phosphate	0
Prilocaine	0
Proline	0
Propranolol	1
Ropivacaine	6
Sodium chloride	0
Sodium citrate	3
Sodium phosphate	0
Tetracaine	2
Triamcinolone acetonide	0
Tropicamide	0
None of the above	8

[a]Respondents were allowed to select multiple products.

CONCLUSION

Methylprednisolone acetate was nominated for inclusion on the 503B Bulks List as a solution for IM injection, a preservative-free suspension for IT injection, a preserved suspension for IM and soft tissue injection, and as a preserved suspension in combination with lidocaine for IM and soft tissue injection to treat a variety of conditions. Methylprednisolone acetate is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, Latvia, Namibia, New Zealand, Saudi Arabia, the UK, and the US.

From the literature review, 52 studies were included. In the included studies methylprednisolone acetate was used as an intra-articular, IT, intrabursal, periarticular, subacromial, and epidural injection to treat painful inflammatory conditions, multiple sclerosis, and to reduce or prevent post-lumbar puncture syndrome or post-pneumoencephalography and myelography symptoms. In 17 studies, the authors recommended the use of methylprednisolone acetate, in 5 studies the use of methylprednisolone acetate was not recommended, 6 studies found that the efficacy of methylprednisolone acetate was similar to that of other study interventions, 15 studies stated that further studies were necessary, studies did not provide definitive conclusions for the use, and studies did not provide recommendations on the use of methylprednisolone acetate.

From the interviews, 3 SMEs did not use methylprednisolone; however, 1 SME stated that potentially for patients with spinal metastases or tumors epidural or IT steroids might be beneficial. One SME uses methylprednisolone for intraarticular steroid injections for osteoarthritis and inflammatory arthritis but stated that the steroids are interchangeable and that the agent used is largely dependent on what the clinic stocks. The SME has not encountered any patients that were allergic to the commercially available formulation and did not see a need for a preservative-free formulation. One SME discussed the use of epidural steroid injections but did not see a clinical need for a compounded product to be available. One SME mentioned that IT steroids have been used for the treatment of multiple sclerosis, but there have been reports of adverse events and therefore the SME does not use IT steroids.

As part of Phase 3, 2 nominators provided additional information regarding the products that will be compounded using methylprednisolone acetate. Methylprednisolone acetate will be compounded as an 80 mg/mL PF solution for IV injection to treat inflammation; a 40 mg/mL, 50 mg/mL, 80 mg/mL, and 100 mg/mL PF suspension for intra-articular injection and other ROAs to treat inflammatory disorders of the musculoskeletal injection; and as a 40 mg/mL and 80 mg/mL suspension for injection in combination with lidocaine for treatment of inflammatory disorders of the musculoskeletal system.

Zero people responded to the survey distributed via professional medical associations and available on the project website. From the prequestionnaire, 0 respondents obtained methylprednisolone from a 503B outsourcing facility.

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APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy 1

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process, and other non-indexed citations and daily 1946 to September 4, 2020
- Date last searched: September 5, 2020
- Limits: Humans (search hedge); English language
- Number of results: 165

1	methylprednisolone acetate/	745
2	(methyl prednisolon$ adj3 acetat$).tw.	65
3	(methylprednisolon$ adj3 acetat$).tw.	764
4	(metil prednisolon$ adj3 acetat$).tw.	0
5	(metilprednisolon$ adj3 acetat$).tw.	0
6	or/1-5	1187
7	infusions, spinal/	160
8	exp injections, spinal/	16,135
9	epidural space/	4518
10	subarachnoid space/	4365
11	(spinal$ adj2 (administ$ or infus$ or inject$)).tw.	2375
12	intraspinal$.tw.	5062
13	epidural$.tw.	42,285
14	extradural$.tw.	6772
15	extra dural$.tw.	142
16	peridural$.tw.	2064
17	peri dural$.tw.	6
18	caudal$.tw.	45,772
19	intracaudal$.tw.	11
20	arachnoid$.tw.	8173

21	subarachnoid$.tw.	35,780
22	intrathecal$.tw.	23,883
23	intra thecal$.tw.	76
24	transforamin$.tw.	3170
25	trans foramin$.tw.	18
26	or/7-25	167,905
27	and/6,26	195
28	exp animals/ not humans/	4,731,219
29	27 not 28	180
30	limit 29 to english language	165

MEDLINE search strategy 2

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process, and other non-indexed citations and daily 1946 to September 4, 2020
- Date last searched: September 5, 2020
- Limits: Humans (search hedge); English language
- Number of results: 66

1	methylprednisolone acetate/	745
2	(methyl prednisolon$ adj3 acetat$).tw.	65
3	(methylprednisolon$ adj3 acetat$).tw.	764
4	(metil prednisolon$ adj3 acetat$).tw.	0
5	(metilprednisolon$ adj3 acetat$).tw.	0
6	or/1-5	1187
7	lidocaine/	24,436
8	lidocain$.tw.	21,762
9	lignocain$.tw.	2924
10	or/7-9	33,417
11	injections, intramuscular/	31,034
12	injections, intra-articular/	7929
13	injections, subcutaneous/	32,739
14	infusions, subcutaneous/	1090
15	infus$.tw.	271,819
16	inject$.tw.	743,934
17	(soft tissue? adj2 (administ$ or therap$ or treat$ or deliver$)).tw.	2768
18	intramuscular$.tw.	52,593
19	intra muscular$.tw.	719
20	intraarticular$.tw.	5507
21	articular$.tw.	64,070
22	intrabursa$.tw.	194

23	bursa$.tw.	10,967
24	intrasynovial$.tw.	285
25	synovial$.tw.	38,825
26	periarticular$.tw.	3674
27	subcutaneous$.tw.	166,794
28	percutaneous$.tw.	145,652
29	or/11-28	1,377,596
30	and/6,10,29	74
31	exp animals/ not humans/	4,731,219
32	30 not 31	72
33	limit 32 to english language	66

Embase search strategy 1

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: September 5, 2020
- Limits: Humans (search hedge); English language
- Number of results: 529

1	'methylprednisolone acetate'/de	3632
2	('methyl prednisolon*' NEAR/3 acetat*):ti,ab,tn	109
3	(methylprednisolon* NEAR/3 acetat*):ti,ab,tn	984
4	('metil prednisolon*' NEAR/3 acetat*):ti,ab,tn	0
5	(metilprednisolon* NEAR/3 acetat*):ti,ab,tn	4
6	#1 OR #2 OR #3 OR #4 OR #5	3903
7	'intraspinal drug administration'/de	3462
8	'epidural drug administration'/de	8893
9	'intrathecal drug administration'/de	20,970
10	'intracaudal drug administration'/de	21
11	'epidural space'/de	6445
12	'subarachnoid space'/exp	12,975
13	'transforaminal epidural injection'/de	27
14	'transforaminal epidural steroid injection'/de	66
15	'spinal*':ti,ab	370,841
16	'intraspinal*':ti,ab	7010
17	'epidural*':ti,ab	59,791
18	'extradural*':ti,ab	9121
19	'extra dural*':ti,ab	242
20	'peridural*':ti,ab	3002
21	'peri dural*':ti,ab	12
22	'caudal*':ti,ab	59,269

23	'intracaudal*':ti,ab	23
24	'arachnoid*':ti,ab	12,352
25	'subarachnoid*':ti,ab	51,095
26	'intrathecal*':ti,ab	35,526
27	'intra thecal*':ti,ab	242
28	'transforamin*':ti,ab	4031
29	'trans foramin*':ti,ab	39
30	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29	551,434
31	#6 AND #30	638
32	[animals]/lim NOT [humans]/lim	6,084,657
33	#31 NOT #32	597
34	#31 NOT #32 AND [english]/lim	529

Embase search strategy 2

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: September 5, 2020
- Limits: Humans (search hedge); English language
- Number of results: 372

1	'methylprednisolone acetate'/de	3632
2	('methyl prednisolon*' NEAR/3 acetat*):ti,ab,tn	109
3	(methylprednisolon* NEAR/3 acetat*):ti,ab,tn	984
4	('metil prednisolon*' NEAR/3 acetat*):ti,ab,tn	0
5	(metilprednisolon* NEAR/3 acetat*):ti,ab,tn	4
6	#1 OR #2 OR #3 OR #4 OR #5	3903
7	'lidocaine'/de	76,119
8	'lidocain*':ti,ab,tn	30,482
9	'lignocain*':ti,ab,tn	4079
10	#7 OR #8 OR #9	80,141
11	'intramuscular drug administration'/de	71,727
12	'intraarticular drug administration'/exp	7426
13	'periarticular drug administration'/exp	248
14	'subcutaneous drug administration'/de	100,833
15	'soft tissue drug administration'/de	31
16	'injection'/exp	247,815
17	'inject*':ti,ab	1,104,263
18	'infusion*':ti,ab	358,445
19	('soft tissue$' NEAR/2 (administ* OR therap* OR treat* OR deliver*)):ti,ab	3601
20	'intramuscular*':ti,ab	75,808
21	'intra muscular*':ti,ab	1286
22	'intraarticular*':ti,ab	27,951

23	'articular*':ti,ab	90,532
24	'intrabursa*':ti,ab	270
25	'bursa*':ti,ab	12,822
26	'intrasynovial*':ti,ab	370
27	'synovial*':ti,ab	55,528
28	'periarticular*':ti,ab	6056
29	'subcutaneous*':ti,ab	251,599
30	'percutaneous*':ti,ab	222,960
31	#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	2,079,850
32	#6 AND #10 AND #31	410
33	[animals]/lim NOT [humans]/lim	6,084,657
34	#32 NOT #33	400
35	#32 NOT #33 AND [english]/lim	372

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: Painful inflammatory conditions					
Ahmad et al., 2013, Pakistan[13]	–	60 Patients with pain in heel for a minimum period of 12 weeks and who were not satisfied with the treatment received during that period (56.7%, mean 48.267 y ± 8.5)	• Methylprednisolone and lignocaine injection (30) • Dexamethasone phosphate and lignocaine injection (30)	Pain relief, adverse events	"Local methylprednisolone injection is superior to local dexamethasone injection in providing short term pain relief to the patients with plantar fasciitis."
Akhtar et al., 2020, Pakistan[14]	Single blinded randomized controlled trial	134 Patients who presented with wrist pain and diagnosed with de Quervain's disease • Methylprednisolone acetate and xylocaine with thumb spica cast (29.9%, mean 40.73 y ± 9.20) • Thumb spica cast (26.1%, mean 41.44 y ± 8.5)	• Thumb spica cast with methylprednisolone acetate and lidocaine hydrochloride (67) • Thumb spica cast (67)	Reduction in the severity of pain on visual analogue scale (VAS), absence of tenderness on the radial side of the wrist, negative Finkelstein test	"Patients treated with methylprednisolone injection with casting showed good results in pain relief, negative Finkelstein test and minimum to no complications. The patients also showed good compliance with corticosteroid injection with casting."
Bhayana et al., 2018, India[60]	Randomized clinical controlled trial	60 Patients with rotator cuff syndrome • Ultrasound guided (43.3%, mean 44.53 y ± .92) • Landmark guided (66.6%, mean 42.03 y ± 9.9)	• Ultrasound (30) • Landmark guided (30) Both groups received methylprednisolone acetate with lignocaine	Clinical assessment, accuracy of injection, pain score (VAS), Constant score with goniometer evaluation for range of motion, patient's self-assessment proforma, post injection side effects	"In our study we found [ultrasound] guided injection to be more accurate, however, it did not provide any significant advantage in terms of clinical outcome or safety profile when compared to patients receiving steroid injections using [landmark guided] approach. However, it was found that combining exercise with [corticosteroid injections] improves the effectiveness of injection. We conclude that in subacromial impingement secondary to rotator cuff disease, clinical outcome and safety profile of [ultrasound guided injection] and [landmark guided injection] are comparable."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Bourne, 1984, UK[15] Bourne and Bourne, 2000, UK[94]	Randomized single-blind trial	57 Patients who failed to respond to previous treatments for chronic backache (gender and age not specified)	• Triamcinolone acetonide plus lignocaine hydrochloride (19) • Methylprednisolone plus lignocaine hydrochloride (15) • Lignocaine hydrochloride (23)	Pain relief	"The results show that injections of triamcinolone acetonide or methylprednisolone in small doses with lignocaine were more successful in the treatment of chronic backache than injections of lignocaine alone."
Bulgen et al., 1984, UK[56]	–	42 Patients with previously untreated frozen shoulder (33.3%, mean 55.8 y, range 44-74 y)	• Methylprednisolone acetate plus lignocaine hydrochloride (11) • Mobilization (11) • Ice (12) • Non-treatment (8)	Pain relief, range of shoulder motion, clinical assessment	"This study has shown that there is little long-term advantage in any of our treatment regimens over no treatment, but that steroid injections may benefit pain and range of movement in the early stages."
Callegari et al., 2011, Italy[41]	Prospective, open-label, randomized, single-center study	30 Patients with trigger finger • Methylprednisolone acetate, lidocaine, and hyaluronic acid (40%, mean 52.9 y, range 35-69 y) • Open surgery (27%, mean 52.1 y, range 40-70 y)	• Ultrasound-guided injection of methylprednisolone acetate, lidocaine, and hyaluronic acid (15) • Open surgery (15)	Proportion of patients with a satisfactory outcome (resolution of symptoms)	"Ultrasound-guided injection of corticosteroids and [hyaluronic acid] appears a safe and feasible option in the treatment of [trigger finger]. While open surgery remains the reference treatment in terms of symptom resolution, the reduced need for physiotherapy and additional medications, suggesting lower costs, and in particular the short recovery time associated with ultrasound-guided injection of corticosteroids and [hyaluronic acid] may support a further evaluation of the use of this infiltrative therapy for the treatment of [trigger finger]."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Curtis et al., 2000, US[42]	–	2 Patients with painful nodules in the lower back and lateral iliac crest areas (0%, ages 35 y and 53 y)	• Methylprednisolone acetate with lidocaine hydrochloride (2)	Pain relief	"Randomized trials on this subject are needed. In the meantime, physicians should keep back mice in mind when presented with atypical and unaccountable symptoms in the lower abdomen, inguinal region or legs."
Dardas et al., 2017, US[16]	Retrospective case series	292 Patients with repeated corticosteroid injections for trigger fingers (36%, mean 60 y ± 11)	• Methylprednisolone acetate with lidocaine (292) 284 patients received second injections and 62 patients received a third injection	Treatment failure (subsequent injection or surgical release of the A1 pulley of the affected digit)	"Thirty-nine percent of second and third corticosteroid injections for trigger finger yield long-term relief. Although most patients ultimately require surgical release, 50% of patients receiving repeat trigger injections realize 1 year or more of symptomatic relief. Repeat injections of trigger fingers should be considered in patients who prefer nonsurgical treatment."
Emad et al., 2011, Iran[61]	–	70 Patients with pain in the gluteal muscles (gender and age not specified)	Methylprednisolone acetate and lidocaine plus: • Stretching of the muscle immediately after injection (35) • No muscle stretching (35)	Pain intensity (VAS, Numeric Pain Intensity Scale and Brief Pain Inventory Scale)	"On the whole, the effect of muscle stretch immediately after Lidocaine and Methylprednisolone acetate solution injection on decreasing trigger points pain has more persistent treatment effects (minimum two months) as compared with the common method (without stretch). Therefore, muscle stretch immediately after injection may reduce repeated injections and decline their secondary side effects. So, it could be considered as a suitable method in trigger point's treatment."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Goyal et al., 2020, India[35]	Randomized controlled study	67 Patients with subacromial impingement syndrome • Ketorolac (41.2%, mean 51.7 y ± 13.22) • Methylprednisolone acetate and lignocaine (30.3%, mean 52.7 y ± 11.81)	• Subacromial ketorolac (34) • Methylprednisolone acetate and lignocaine (33)	Pain (VAS), shoulder pain and disability score, and range of motion	"In this study, ketorolac had equivalent results as compared to corticosteroids, when used in subacromial infiltrations. Though methylprednisolone showed slightly better clinical outcomes, the difference between them was statistically insignificant (p>0.05). With the risk of potential side effects of corticosteroids, ketorolac could be considered as a viable alternative in the treatment of [subacromial impingement syndrome]."
Guner et al., 2013, Turkey[36]	Prospective randomized controlled study	61 Patients diagnosed with plantar fasciitis (23%, mean 41.4 y ± 12.23)	• Methylprednisolone acetate with lidocaine (30) • Tenoxicam with lidocaine (31)	Pain relief, patient satisfaction	"In the current study, the tenoxicam injection was not significantly more effective than the corticosteroid injection for the treatment of plantar fasciitis; rather, both methods were effective and successful in treating the condition. The tenoxicam therapy appears to provide pain relief, but its effectiveness in the long term should be explored in future studies."
Gunter and Schwellnus, 2004, South Africa[18]	Randomized controlled trial	18 Patients with recent onset iliotibial band friction syndrome (gender and age not specified)	• Methylprednisolone acetate with lignocaine hydrochloride (9) • Lignocaine hydrochloride (9)	Total daily pain and total pain during running	"In conclusion, the results of this study show that the infiltration of the lateral femoral condyle area deep to the iliotibial tract with corticosteroid decreased pain during running after 14 days. Therefore the practical recommendation for treating runners is that local corticosteroid infiltration is effective and safe in the early (first 14 days) treatment of recent onset [iliotibial band friction syndrome]."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Habib et al., 2006, Israel[17]	–	42 Patients with carpal tunnel syndrome • Classic approach (19.0%, mean 43.3 y ± 12.6) • Novel approach (23.8%, mean 41 ± 11.3)	• Classic approach with 35 mg methylprednisolone and 0.5 mL lidocaine (21) • Novel approach with 12 mg methylprednisolone and 0.15 mL lidocaine (21)	Favorable response rate, time duration, pain level	"In conclusion, local corticosteroid injection using the novel approach for the treatment of carpal tunnel syndrome is helpful, and the favorable response rates are comparable to those using the classic approach after 1, 3, 6, and 12 weeks. The novel approach is much less time consuming and is not more painful."
Henriksen et al., 2015, Denmark[43]	Randomized, blinded, placebo-controlled clinical trial	100 Patients who had radiographic confirmation of clinical osteoarthritis of the knee, clinical signs of localized inflammation in the knee, and knee pain during walking (39%, mean 63.4 y ± 9.3)	• Methylprednisolone acetate with lidocaine hydrochloride (50) • Isotonic saline with lidocaine (50)	Change in pain score	"No additional benefit results from adding an intra-articular injection of 40 mg of corticosteroid before exercise in patients with painful [osteoarthritis] of the knee. Further research is needed to establish optimal and potentially synergistic combinations of conservative treatments."
Holt et al., 2013, UK[44]	Single-blind randomized pilot trial	40 Patients with a clinical diagnosis of rotator cuff tendinopathy or adhesive capsulitis • Methylprednisolone acetate with lidocaine (42%, mean 61.5 y ± 9.8) • Lidocaine (29%, mean 56.0 y ± 11.3)	• Methylprednisolone acetate with lidocaine (19) • Lidocaine (21)	Pain relief, shoulder function, adherence to allocated treatment	"The lessons learned from this pilot will usefully inform the design of a large, definitive efficacy trial in primary care. It will be important to optimize recruitment and maintain a high rate of follow-up over 52 weeks in the larger, main trial that we plan. Such a trial is necessary to confirm the benefits of corticosteroid injection, a commonly used treatment for shoulder pain, and to exclude adverse longer-term outcomes."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Imran et al., 2013, US[19]	Randomized, double-blind, placebo-controlled trial	30 Patients with acute or recurrent subdeltoid or trochanteric bursitis (gender and age not specified)	• Methylprednisolone acetate and lidocaine (15) • Lidocaine and saline (15)	Improvement in bursal pain (VAS)	"Three of four VAS outcomes exceeded 50% improvement in the experimental group, whereas with the control group no VAS outcomes exceeded (31%). Periarticular corticosteroid plus lidocaine in addition to full dose of celecoxib enhances short term benefits of treatment for bursitis."
Jacobs, 2019, US[45]	Case report	1 Patient with Bertolotti's Syndrome (0%, 15 y)	• Methylprednisolone acetate with lidocaine (1)	Pain relief	"More studies are needed to evaluate the long-term efficacy of interventional spine procedures vs. surgical management for patients with Bertolotti's syndrome."
Jahangiri et al., 2014, Iran[46]	Double-blind randomized clinical trial	60 Patients with osteoarthritis of the first carpometacarpal joint (27%, mean 63.6 y ± 9.7)	• Placebo injections of saline followed by methylprednisolone acetate with lidocaine (30) • Dextrose with lidocaine (30)	Pain intensity (VAS)	"Both [local corticosteroid] and [dextrose] can relieve pain and suppress inflammatory processes…Further research with a large sample size is needed to compare possible complications of [local corticosteroid] vs [dextrose] injections in the management of [osteoarthritis]."
Kannus et al., 1990, Finland[30]	Prospective, randomized, double-blind study	60 Patients with musculoskeletal overuse injury • Methylprednisolone acetate and bupivacaine (100%, mean 29.2 y) • Methylprednisolone acetate and lidocaine (100%, mean 29.9 y)	• Methylprednisolone acetate and bupivacaine (30) • Methylprednisolone acetate and lidocaine (30)	Pain (VAS)	"In conclusion, long-acting bupivacaine is recommended as an anesthetic substance in local steroid injections of musculoskeletal overuse injuries. A ready-made steroid bupivacaine mixture may be the most reasonable alternative because of its simpler use and better aseptics compared with self-made mixtures."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Kershen et al., 2018, US[62]	Retrospective review	77 Patients suspected or confirmed with facet-mediated lumbar pain (37.7%, mean 51.1 y) A total of 100 procedures with 205 total facet joints injected	• 0.25% bupivacaine (29 procedures) • 0.5% bupivacaine (39 procedures) • Lidocaine (32 procedures) • Lidocaine and methylprednisolone (92 procedures) • Lidocaine and betamethasone (4 procedures) • Lidocaine and triamcinolone acetonide (4 procedures)	Pain (numeric pain rating scale), image analysis	"Both intra-articular and periarticular facet injections provide similar and statistically significant immediate and 1-week postinjection relief of facet-mediated pain."
Khallaf et al., 2018, Egypt[20]	–	40 Patients with adhesive capsulitis • Genohumoral approach (40%, mean 49.6 y ± 8.6) • Subacromial subdeltoid approach (40%, mean 45.1 y ± 8.4)	• Genohumoral joint approach (20) • Subacromial subdeltoid approach (20) Both groups received methylprednisolone with lidocaine	Pain relief, shoulder range of motion	"Intraarticular steroid injection of the shoulder joint followed by exercises in patients with adhesive capsulitis decreases pain, improves function and [range of motion] with a more favorable response by the [genohumoral] approach. Ultrasound-guided injection is an accurate, easy and cost-effective approach."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Kikuchi et al., 1999, Japan[21]	Randomized, blinded study	25 Patients with postherpetic neuralgia for greater than one year • Epidural (50%, mean 65 y ± 9) • Intrathecal (38.5%, mean 65 y ± 9)	• Epidural methylprednisolone acetate and lidocaine (12) • Intrathecal methylprednisolone acetate and lidocaine (13)	Pain (VAS), cytokine levels	"In summary, intrathecal [methylprednisolone acetate] provided better analgesia than did epidural [methylprednisolone acetate] in patients with intractable [postherpetic neuralgia]. The analgesic effect lasted more than 24 weeks without side effects. Therefore, we conclude that intrathecal administration of [methylprednisolone acetate] may be indicated for treatment of intractable [postherpetic neuralgia]."
Koyonos et al., 2009, US[47]	Randomized, prospective, double-blind study	58 Patients (59 knees) with knee osteoarthritis who had arthroscopic meniscectomy in which chondromalacia was confirmed • Saline group (73.3%, mean 52 y ± 9) • Steroid group (65.5%, mean 49 y ± 11)	• Saline with lidocaine (30 knees) • Methylprednisolone with lidocaine (29 knees)	Treatment satisfaction, duration of pain medication use, back-to-work time, active range of motion, subjective questionnaire scores	"In patients with [osteoarthritis] of the knee, who are inherently at greater risk for poorer outcomes following meniscectomy, adding an intra-articular corticosteroid injection to postoperative care is safe and effective at decreasing pain and improving function for the first 6 weeks after surgery. Additional high quality clinical trials are necessary to further characterize the benefits, indications, and durability of intra-articular corticosteroid injections in the setting of [osteoarthritis] and in that of postoperative care."
Luukkainen et al., 2002, Finland[48]	Double blind, controlled study	24 Patients with chronic sacroiliac joint pain • Methylprednisolone and lidocaine (23.1%, mean 50.3 y, range 38-68 y) • Sodium chloride and lidocaine (36.4%, mean 49.3 y, range 32-70 y)	• Methylprednisolone acetate and lidocaine (13) • Sodium chloride and lidocaine (11)	Pain (VAS)	"These results indicate that the periarticular injection of methylprednisolone may be effective in the treatment of low back pain in the region of the [sacroiliac joint] also in non-spondylarthropathic patients. However, since the number of patients in our study was low, these results must be regarded as very preliminary. Further studies are needed with larger patient series and also with longer follow-up times."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Luukkainen et al., 1999, Finland[49]	Double blind, controlled study	20 Patients with seronegative spondylarthropathy and clinical sacroiliitis • Methylprednisolone acetate and lignocaine (40%, mean 42 y ± 10) • Sodium chloride and lignocaine (70%, mean 40 y ± 11)	• Methylprednisolone acetate and lignocaine (10) • Sodium chloride and lignocaine (10)	Pain (VAS and pain index of sacroiliac joint)	"The results of this study indicate that the periarticular injection of methylprednisolone may be effective in the treatment of clinical sacroiliitis in patients with seronegative spondylarthropathy. However, because the number of patients in our study was low, these results must be regarded as preliminary."
Mardani-Kivi et al., 2014, Iran[50]	Prospective trial	67 Patients with de Quervain tenosynovitis • Corticosteroid injection only (14.7%, mean 45 y ± 12) • Corticosteroid injection and thumb spica cast (21.2%, mean 42 y ± 13)	• Corticosteroid injection only (34) • Corticosteroid injection and thumb spica cast (33)	Treatment success rate (presence or absence of pain on the radial side of the wrist, tenderness at the first dorsal compartment, and Finkelstein test results)	"The combined technique of corticosteroid injection and thumb spica casting was better than injection alone in the treatment of de Quervain tenosynovitis in terms of treatment success and functional outcomes... We recommend conducting further clinical trial studies without these limitations and comparing [corticosteroid injection] + [thumb spica cast] and [corticosteroid injection] alone with different dosages and combinations."
Mardani-Kivi et al., 2015, Iran[22]	Prospective randomized clinical trial	84 Patients acute symptomatic plantar fasciitis • Corticosteroid injection (17.6%, mean 44.68 y ± 9.20) • Extracorporeal shock wave therapy (14.7%, mean 43.91 y ± 7.96)	• Corticosteroid injection (41) • Extracorporeal shock wave therapy (43)	Pain intensity (VAS), success and recurrence rates	"In conclusion, although the [corticosteroid injection] technique had significantly better treatment outcomes, both [corticosteroid injection] and [extracorporeal shock wave therapy] could be preferred as the primary treatment of patients with acute plantar fasciitis."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Mitchell et al., 2018, Germany[63]	Randomized controlled study	40 Patients with trochanteric pain syndrome • Conventional anatomic landmark palpation guidance (7%, mean 51.5 y ± 15.4) • Ultrasound guidance (0%, mean 49.2 y ± 12.0)	• Conventional anatomic landmark palpation guidance (20) • Ultrasound guidance (20) All patients received lidocaine and methylprednisolone	Procedural pain (VAS), pain at outcome, therapeutic duration, time-to-next intervention, and costs	"[Ultrasound]-guided and anatomic landmark injection of the trochanteric bursa have similar 2-week and 6-month outcomes; however, US guidance is considerably more expensive and less cost effective. Anatomic landmark-guided injection remains the method of choice, but should be routinely performed using a sufficiently long needle [at least a 2 in (50.8 mm)]. [Ultrasound] guidance should be reserved for extreme obesity or injection failure."
Munts et al., 2010, the Netherlands[31]	Double-blind randomized placebo-controlled parallel-group trial	21 Patients with chronic complex regional pain syndrome (23.8%, mean 46 y ± 11)	• Methylprednisolone acetate (10) • Placebo (11)	Change in pain (pain intensity numeric rating scale)	"In conclusion, a single bolus administration of [intrathecal methylprednisolone] is not efficacious in chronic [complex regional pain syndrome] patients, which may indicate that spinal immune activation does not play an important role in this phrase of the syndrome."
Nagpal and Eckmann, 2013, US[32]	Case report	1 Patient with chronic lower back pain (0%, age not specified)	• Methylprednisolone acetate (1)	Pain relief	"This case report reviews the value of intrathecal steroid injections for refractory pain due to nerve root irritation and demonstrates the ability of epidural catheters to violate the dura mater unintentionally, validating fluoroscopic guidance with contrast enhancement as an essential component of this procedure."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Nalamachu et al., 2006, US[51]	Randomized, parallel-group, open-label, single-center, active-controlled, prospective pilot study	40 Patients with carpal tunnel syndrome • Lidocaine patch (35%, mean 48.4 y ± 10.3) • Methylprednisolone acetate and lidocaine (25%, mean 47.5 y ± 13.9)	• Lidocaine patch (20) • Methylprednisolone acetate and lidocaine (20)	Pain intensity, pain relief, and pain interference (Brief Pain Inventory, Patient and Global Clinical Impression of Improvement), satisfaction (Global Assessment of Treatment Satisfaction)	"This pilot trial demonstrated that the lidocaine patch 5% was efficacious in reducing pain associated with [carpal tunnel syndrome] and was well tolerated. The lidocaine patch 5% may offer patients with [carpal tunnel syndrome] effective, noninvasive treatment for the management of their symptoms. Further controlled trials are warranted."
Raeissadat et al., 2020, Iran[37]	Randomized clinical trial	75 Patients who had symptoms of plantar fasciitis for at least 3 months (46.6%, mean 41.04 y ± 8.96)	• Methylprednisolone and lidocaine (37) • Hyaluronic acid and lidocaine (38)	Pain (VAS), foot ankle ability index, pressure pain threshold, functional foot index, plantar fascia thickness, patient satisfaction	"Both corticosteroid and hyaluronic acid were effective modalities for plantar fasciitis and can improve pain and function with no superiority in 24th-week follow-ups, although [corticosteroid] seems to have a faster trend of improvement in the short term."
Rizk et al., 1991, US[33]	Randomized, single-blind study	48 Patients with adhesive capsulitis (58.3%, mean 55 y, range 40-70 y)	• Intra-articular methylprednisolone and lidocaine (16) • Intrabursal methylprednisolone and lidocaine (16) • Intra-articular lidocaine (8) • Intrabursal lidocaine (8)	Shoulder range of motion and pain	"In our patients treated after a mean interval of 13 weeks from the onset of shoulder pain, a series of three injectios into the shoulder joint or subacromial bursa did not appear to influence the course of adhesive capsulitis."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Safari et al., 2020, Iran[38]	Randomized, controlled, single-blind study	24 Patients with coccydynia • Methylprednisolone acetate with lidocaine (33.3%, mean 38.7 y ± 16.1) • Celecoxib (16.7%, mean 37.9 y ± 14.2)	• Methylprednisolone acetate with lidocaine (12) • Celecoxib (12)	Pain severity	"Corticosteroid injection for coccydynia treatment at least has the same advantages of oral [nonsteroidal anti-inflammatory drug] medication. Regarding its single-dose administration and reasonable price, it can be considered as an alternative modality in treatment of this disease if the target patient is selected correctly."
Sehgal and Gardner, 1963, US[23]	–	45 Patients with neurological disorders (gender and age not specified)	• Methylprednisolone acetate (45)	Concentration of corticosteroid, blood electrolytes, pleocytosis	"It is safe to use methylprednisolone acetate in some neurologic disorders when it is given intrathecally."
Sehgal et al., 1962, US[57]	–	100 Patients with persistent sciatica who underwent Pantopaque myelography (63%, range 24-74 y))	• Subarachnoid corticosteroid injection (100) Did not specify how many patients received methylprednisolone among other corticosteroids	Pain relief	"1. The intrathecal injection of Pantopaque in some cases is followed by early or late meningeal reactions, of mild to severe degree, in some instances progressing to chronic adhesive arachnoiditis. 2. Intrathecal injections of small amounts of a suspension of methylprednisolone acetate reduced the radicular pain accompanying such meningeal reactions in 60 of 100 patients. 3. No adverse effects of this therapy have been noted in the treatment of chronic low back and sciatic pain that sometimes follows Pantopaque myelography."
Sonne et al., 1985, Denmark[24]	Double-blind controlled study	29 Patients with lower back pain of at least one month duration (27%, mean 57 y)	• Methylprednisolone and lignocaine (14) • Isotonic saline (15)	Pain scores, clinical improvement	"Our finding of a significantly better effect in the methylprednisolone treated group, indicates that certain inflammatory changes in the lumbar ligaments could be the origin of pain in some patients with persistent low-back pain. This may constitute evidence of the efficacy of corticosteroids, Biopsy performed before and following blockade treatment with corticosteroids may provide proof."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
vanVeen et al., 2015, the Netherlands[52]	Randomized, double-blind, placebo-controlled trial	55 Patients with ulnar neuropathy at the elbow • Methylprednisolone and lidocaine (60%, mean 56 y) • Placebo (36%, mean 53 y)	• Methylprednisolone acetate and lidocaine (30) • Placebo (25)	Subjective change in symptoms	"In conclusion, we could not demonstrate a positive effect of [ultrasound]-guided corticosteroid injection in [ulnar neuropathy of the elbow] compared with placebo. As patients included in the study had symptoms for a long period of time, it may be of interest to investigate the effect of corticosteroid injection in patients with a shorter duration of symptoms."
Vega-Morales et al., 2012, Mexico[39] Vega-Morales et al., 2011, Mexico[95]	Randomized, double-blind, placebo-controlled trial	58 Patients with anserine bursitis • Methylprednisolone and lidocaine (25%, mean 53.4 y ± 12.5) • Distilled water and lidocaine (20%, 54.4 y ± 10)	• Methylprednisolone and lidocaine (28) • Distilled water and lidocaine (30)	Western Ontario and McMaster Universities Arthritis Index, adverse events	"The infiltration with methylprednisolone in anserine syndrome is not superior to placebo in patients taking diclofenac measured by the [Western Ontario and McMaster Universities Arthritis Index] scale at 4 weeks. The incidence of adverse events did not show any differences either."
Witt et al., 1991, US[25]	Prospective study	95 Patients with de Quervain tenosynovitis (23%, mean 44 y)	• Methylprednisolone acetate and lidocaine (95)	Time to recovery or recurrence, wrist tenderness, Finkelstein test	"In conclusion, a combination of injection of steroids and immobilization in a splint is an effective method for the treatment of de Quervain tenosynovitis. Anatomical variations, including a septated first dorsal compartment, were present in a high percentage of wrists in which nonoperative treatment failed and operative release was subsequently performed. Surgeons should be aware of this association so that an adequate decompression can be carried out."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Wu et al., 2012, US[40] Wu et al., 2012, US[96]	Prospective randomized double-blinded pilot study	14 Amputees with intractable residual and/or phantom limb pain who failed in the conventional treatments • Clostridium Botulinum type A neurotoxin (57.1%, mean 47 y, range 20-75 y) • Lidocaine and Depomedrol (85.7%, mean 50 y, range 37-65 y)	• Clostridium Botulinum type A neurotoxin (7) • Lidocaine and Depomedrol (7)	Pain relief	"Both Botox and Lidocaine/Depomedrol injections resulted in immediate improvement of [residual limb pain] (not [phantom limb pain]) and pain tolerance, which lasted for 6 months in amputees who failed in conventional treatments."
Indication 2: Multiple sclerosis					
Baker, 1967, US[26]	–	30 Patients with multiple sclerosis (26.7%, mean 41 y, range 20-57 y)	• Intrathecal methylprednisolone acetate (30) Total of 709 intrathecal injections administered to the 30 patients (average 23.6 injections/patient, average 7 injections/patient-year)	Neurologic index (severity of disease)	"Thirty patients with multiple sclerosis were given intrathecal injections of methylprednisolone acetate for periods of several months to over seven years. Generally, injections were repeated at two- to four-week intervals. Based on an objective neurologic rating, 25 patients improved. There were no serious side effects from either methylprednisolone or the lumbar punctures."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Baumhefner et al., 1989, US[53]	–	9 Patients with multiple sclerosis (100%, range 28-57 y)	• Methylprednisolone acetate (2) • Methylprednisolone sodium succinate (2) • Methylprednisolone acetate and methylprednisolone sodium succinate (5)	Intra-blood brain barrier IgG synthesis rate, isoelectric focusing, cerebrospinal fluid cell counting, cerebrospinal fluid cell albumin, blood brain barrier integrity	"From the present study we have concluded that there is no advantage of [methylprednisolone sodium succinate] or intrathecal [methylprednisolone acetate] over [adrenocorticotropic hormone] in the suppression of the [central nervous system] inflammatory response in [multiple sclerosis], and the well documented risk of serious adversities with intrathecal [methylprednisolone acetate] prohibit its present use in the clinical treatment of [multiple sclerosis]. However, if a pure preparation of [methylprednisolone acetate] became available without preservatives or suspending agents, further investigations with this agent intrathecally in combination with systemic [adrenocorticotropic hormone] might be indicated."
Beck, 1967, US[58]	–	15 Patients with multiple sclerosis (60%, range 25-63 y)	• Methylprednisolone acetate (15) A total of 86 injections of intrathecal methylprednisolone acetate were given	Improvement based on percentage of decrease in muscle and bladder spasticity	"The improvement rate of 46.6% appears to warrant continued studies along these lines. No major side effects were encountered and no minor side effects persisted to warrant discontinuing therapy. An optimistic inclusive approach to therapy of multiple sclerosis is encouraged."
Boines, 1961, US[54]	–	12 Patients with multiple sclerosis (33.3%, range 28-50 y)	• Methylprednisolone Acetate (12)	Improvement in symptoms, pain relief	"Good to excellent improvement followed intrathecal injection of methylprednisolone acetate in 9 of 12 patients with multiple sclerosis. These results correspond to those reported with intrathecal steroids referred to in the introductory paragraphs. My findings suggest that further studies should be made to determine the place of intrathecal steroid therapy."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Boines, 1964, US[64]	–	35 Patients with multiple sclerosis (gender and age not specified) The resulting study group only involved 19 patients with multiple sclerosis to carry out assays for 17-hydroxycorticosteroid	• Methylprednisolone acetate (35)	Steroid dissipation	"All assays and values for 17-hydroxycorticosteroids varied remarkably from patient to patient, and from time to time in the same patient when serial tests were done. Whatever the reasons for these variations--clinical improvement in terms of lessened muscle spasm, improved urinary bladder control, and improved eye and locomotor function appeared to be independent of measurable steroid concentrations."
De Vito and Mannarelli, 1966, US[59]	–	13 Patients with typical multiple sclerosis (69%, range 25-63 y)	• Intrathecal methylprednisolone acetate and intravenous polarizing solutions (13)	Improvement in cranial nerve involvement, muscle strength, balance, muscle band bladder spasticity	"One can conclude from this study that intrathecal methylprednisolone acetate does not prevent exacerbations of multiple sclerosis and it would appear from this small series that it does not influence the acute fulminating type...A major factor which must be considered in evaluating the results of the intrathecal methylprednisolone acetate is whether the results are due primarily to the antiallergic effect or anti-inflammatory effect of the medication or secondarily to the effects of the vehicle upon the adjacent roots...The relative safety of the combination of the polarizing solution and the intrathecal methylprednisolone acetate is well demonstrated in this small study."
Goldstein et al., 1970, US[34] Goldstein et al., 1962, US[97] Goldstein et al., 1962, US[98]	–	38 Patients with multiple sclerosis (gender and age not specified)	• Methylprednisolone acetate (38)	Cerebrospinal fluid gamma globulin, clinical improvement of symptoms, steroid concentration	"It is our conclusion that although the intrathecal administration of methylprednisolone acetate is an interesting experimental procedure, in view of the lowering of the [cerebrospinal fluid] gamma globulin, it is not indicated in the routine treatment of patients with multiple sclerosis."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Ringer, 1968, US[55]	–	8 Patients with multiple sclerosis (25%, range 27-72 y)	• Methylprednisolone acetate (8)	Improvement with symptoms, side effects	"I believe that physiotherapy is important as an adjunct to methylprednisolone therapy - this must be insisted upon since the exercises force the patient to assume an active role in his battle with multiple sclerosis. While further investigation is required to confirm the usefulness of the intrathecal technic, I am satisfied that it will ultimately be accepted by many physicians."
Indication 3: Reduction/prevention of post lumbar puncture syndrome, or post-pneumoencephalography and myelography symptoms					
Kulick, 1965, US[27]	–	200 Patients who received lumbar puncture • Saline (50%, mean 52 y) • Steroid polyglycol saline (48%, mean 47 y) • Polyglycol saline (48%, mean 50 y) • No injection (52%, mean 47 y)	• Saline (50) • Methylprednisolone acetate and polyglycol vehicle with saline (50) • Polyglycol vehicle and saline (50) • Routine lumbar puncture (50)	Symptoms of postlumbar puncture syndrome (headache, back pain, pain on neck flexion or straight leg raising)	"It is concluded that the intrathecal instillation of methylprednisolone acetate is of substantial clinical value in prevention of symptoms following lumbar punctures."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Kulick, 1966, US[28]	–	Part 1: 120 Patients who received fractional air pneumoencephalography • Saline (47%, mean 45 y) • Methylprednisolone acetate (36.7%, mean 44 y) • Vehicle (43.3%, mean 46 y) • No injection (40%, mean 47 y) Part 2: 120 Patients who received Pantopaque myelography • Saline (40%, mean 48 y) • Methylprednisolone acetate (40%, mean 44 y) • Vehicle (53.3%, mean 50 y) • No injection (46.7%, mean 48 y)	Part 1: • Saline (30) • Methylprednisolone acetate with polyglycol vehicle and saline (30) • Polyglycol vehicle and saline (30) • No injection (30) Part 2: Saline (30) • Methylprednisolone acetate with polyglycol vehicle and saline (30) • Polyglycol vehicle and saline (30) • No injection (30)	Incidence of symptoms for post-procedural syndrome	"It is concluded that intrathecal instillation of methylprednisolone is of significant clinical value in alleviation of symptoms following air pneumoencephalography and Pantopaque myelography."
McLennan et al., 1973, US[29]	–	60 Patients who underwent myelography or pneumoencephalography (gender and age not specified)	• Saline (41) • Depo-Medrol (19)	Headache, intensity of headache	"Intrathecal Depo-Medtrol instillation immediately following myelography and pneumoencephalography is effective in preventing headache. The mechanism of action is unknown, Many difficulties with analysis of headache in a heterogenous patient population were considered."

Abbreviations: –, not provided; VAS, visual analogue scale.
[a]As 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)	○	○	○
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	○	○	○
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	○	○	○

2. Do you prescribe or administer methylprednisolone acetate to your patients?
    - Yes
    - No
3. Do you prescribe or administer methylprednisolone acetate by any of the following dosage forms and/or routes of administration? (check all that apply)
    - Intramuscular injection
    - Intra-articular injection
    - Intrathecal
    - Soft tissue injection
    - None of the above
4. I prescribe or administer methylprednisolone acetate for the following conditions or diseases: (check all that apply)
    - Adrenal insufficiency
    - Allergic rhinitis
    - Asthma
    - Bursitis
    - Contact dermatitis
    - Crohn's disease
    - Epicondylitis
    - Giant cell arteritis
    - Leukemia
    - Multiple sclerosis
    - Multiple myeloma
    - Mycosis fungoides
    - Nephrotic syndrome
    - Osteoarthritis, rheumatoid arthritis
    - Prostate cancer
    - Trichinosis
    - Ulcerative colitis
    - Other (please explain) _____

5. I prescribe or administer compounded methylprednisolone acetate in combination with other active pharmaceutical ingredients as a multi-ingredient product.
    - Yes
    - No
6. I prescribe or administer methylprednisolone acetate with my patients as the following: (check all that apply)
    - FDA-approved drug product
    - Compounded drug product
    - Over-the-counter drug product
    - Other (please explain) _____
7. I use compounded methylprednisolone acetate 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 methylprednisolone acetate
    - Other (please explain) _____
8. Do you stock non–patient-specific compounded methylprednisolone acetate at your practice?
    - Yes
    - No
    - I'm not sure
9. I obtain compounded methylprednisolone acetate from the following: (check all that apply)
    - Compound myself at my practice
    - Have the product compounded by an in-house pharmacy
    - Purchase, or have a patient purchase, from a compounding pharmacy
    - Purchase, or have a patient purchase, from an outsourcing facility
    - Other (please explain) _____
10. What is your practice setting? (check all that apply)
    - Physician office/private practice
    - Outpatient clinic
    - Hospital/health system
    - Academic medical center
    - Emergency room
    - Operating room
    - Other (please describe) _____
11. What degree do you hold? (check all that apply)
    - Doctor of Medicine (MD)
    - Doctor of Osteopathic Medicine (DO)
    - Doctor of Medicine in Dentistry (DMD/DDS)
    - Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
    - Naturopathic Doctor (ND)
    - Nurse Practitioner (NP)
    - Physician Assistant (PA)
    - Other (please describe) _____

Appendix 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)	○	○	○
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	○	○	○
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	○	○	○

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

- None of the above

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

Appendix 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 on-site compounding facility
    - On-site compounding facility not equipped to compound all necessary products
    - Other, please explain _____
5. Please select the type(s) of products obtained from an outsourcing facility.
    - Nonsterile products
    - Sterile products
6. Please select the category(ies) of products obtained from an outsourcing facility.
    - Cardioplegic solutions
    - Dermatologic preparations
    - Dialysate solutions

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

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

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

Appendix 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

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