

# Summary Report

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## Dexamethasone sodium phosphate

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US Food and Drug Administration

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

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## Frequently Used Abbreviations

API	Active pharmaceutical ingredient
EU	European Union
FDA	United States Food and Drug Administration
IM	Intramuscular
IT	Intrathecal
IV	Intravenous
OTC	Over-the-counter
PEA	Percutaneous epidural adhesiolysis
PF	Preservative-free
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ROA	Route of administration
SME	Subject matter expert
SP	Sodium phosphate
TFESI	Transforaminal epidural steroid injections
UK	United Kingdom
US	United States
USP	United States Pharmacopeia

## INTRODUCTION

This report was created to assist the United States (US) Food and Drug Administration (FDA) in its evaluation of the use of dexamethasone sodium phosphate (dexamethasone SP; UNII code: AI9376Y64P), 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 dexamethasone SP is used in clinical research and practice to diagnose, prevent, or treat disease. Because of 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 dexamethasone SP has been used historically and currently.<sup>1-3</sup> 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.<sup>1,4,5</sup> Rather, the aim was to summarize the available evidence on the use of dexamethasone SP 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

Dexamethasone SP was nominated for inclusion on the 503B Bulks List by Fagron, the Specialty Sterile Pharmaceutical Society, the Outsourcing Facilities Association, and US Compounding Pharmacy. Dexamethasone SP was nominated for use in combination with additional active pharmaceutical ingredients (APIs) (refer to Table 8).

Dexamethasone SP was nominated for the treatment of allergic disorders, cerebral edema, collagen disorders, disorders of the ear, disorders of the endocrine system, disorders of the eye, disorders of the gastrointestinal tract, disorders of the hematopoietic structure, disorders of the respiratory system, disorders of the skin, edematous states, hypercalcemia of malignancy, idiopathic thrombocytopenic purpura, inflammation, inflammatory disorders of the musculoskeletal system (adjunct), mycosis fungoides, neoplastic diseases, nephrotic syndrome, palliative management of leukemias and lymphomas, rheumatic disorders, trichinosis, tuberculosis of the meninges (adjunct), and the diagnostic testing of adrenocortical hyperfunction. Dexamethasone SP will be compounded as a 0.4- to 24-mg/mL preservative-free (PF) and preserved solution for epidural, intramuscular (IM), intravenous (IV), and intrathecal (IT) injection as well as a preserved suspension with additional APIs. Dexamethasone SP will also be compounded as a topical gel and oral solution in strengths ranging from 1 to 24 mg/mL.

Additionally, dexamethasone SP was also nominated to treat unknown medical conditions, but it is generally used to treat alopecia as a topical solution and spray in strengths based on the prescriber's request; the therapeutic strength is 0.1%.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of dexamethasone SP.<sup>6-21</sup>

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

- Compounded product may be the only product to effectively treat the indication for which it is intended.
- Patients may need dosage forms or strengths, including greater concentrations, that are not available commercially. There are no FDA-approved topical products containing dexamethasone SP. There are FDA-approved forms of dexamethasone; however, the commercial strengths available and the preservatives found in the injectable products can limit their use.

- Compounding from bulk drug substances means using only the ingredients necessary to achieve the desired clinical outcomes. The API is in its purest form, without any fillers, excipients, binders, dyes, preservatives, or other materials. The PF formulation is needed for transforaminal cervical procedures.
- Individual finished products have more variance than the API, and the use of a finished product has the potential to introduce unacceptable inaccuracies into the compounded medication.
- Patients may be sensitive to dyes, fillers, preservatives, or other excipients in manufactured products.
- Prescribers or hospitals prefer various strengths, combinations with other drugs, volumes, or final product containers for administration.
- It is 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% 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 necessary; 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 dexamethasone SP products in the US and around the world. The World Health Organization, the European Medicines Agency, and globalEDGE were used to identify regulatory agencies in non-US countries. The medicine registers of non-US regulatory agencies were selected for inclusion if they met the following criteria: freely accessible; able to search and retrieve results in the English language; and desired information, specifically product trade name, active ingredient, strength, form, route of administration (ROA), and approval status, provided in a usable format. Based on these criteria, the medicine registers of 13 countries or 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 European Medicines Agency 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 or vice versa.

Each medicine register was searched for dexamethasone SP; name variations of dexamethasone SP 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 or schedule, and approval date. Information was recorded only for products with strengths, forms, or ROAs 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

dexamethasone SP. The availability of OTC products (yes/no) in the US and the ROAs of these products were recorded in a spreadsheet. Individual product information was not recorded.

### *Systematic literature review*

#### Search strategy

A medical librarian constructed 2 comprehensive search strategies for both Ovid MEDLINE and Embase. The first search strategy used a combination of controlled vocabulary terms and keywords to describe three concepts: dexamethasone SP; oral, epidural, or intrathecal administration; and therapeutic or diagnostic use. The second search strategy used a combination of controlled vocabulary terms and keywords to describe 3 concepts: dexamethasone SP; topical administration or form; and therapeutic or diagnostic use, or substances nominated for use in combination with (refer to Appendix 1 for full search strategies). A literature review was not conducted for IV or IM administration because of the availability of FDA-approved products for these ROAs. Results were limited to human studies in the English language. Searches were conducted on August 27, 2020. In addition, the ECRI Guidelines Trust<sup>®</sup> repository was searched on August 27, 2020 for clinical practice guidelines that recommended the use of dexamethasone SP and provided sufficient information on dosing and administration.

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

#### Study selection

Studies in which dexamethasone SP was used in the nominated dosage form, ROA, 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; were reviews or meta-analyses; were surveys or questionnaires (cross-sectional design); were designed to evaluate cost-effectiveness, mechanism of action, preclinical use, safety, or toxicity; or used any study design other than a randomized controlled trial conducted in a non-US country. Studies were also excluded if dexamethasone SP was used as an FDA-approved product in the nominated dosage form, ROA, or combination; was in a dosage form, ROA, or combination that was not nominated; was in an unspecified dosage form or ROA; was the wrong drug, wrong salt form, or unspecified salt form; was not used clinically; or was mentioned briefly as a rescue treatment or previously failed treatment. Studies in which dexamethasone SP was used to diagnose, prevent, or treat autism were excluded because of a separate project examining the use of compounded substances in patients 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 dexamethasone SP, setting, total number of patients, number of patients who received dexamethasone SP, patient population, indication for use of dexamethasone SP, dosage form and strength, dosage, ROA, frequency and duration of therapy, use of dexamethasone SP in a combination product, use and formulation of dexamethasone SP in a compounded product, use of dexamethasone SP compared with 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 determine how and in what circumstances dexamethasone SP 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 dexamethasone SP. 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 the complete survey and the *Results of survey* section for results of the 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 dexamethasone SP in clinical practice. The online survey was created in Qualtrics® software (refer to Appendix 3 for the 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 about the project Year 3 surveys.

The survey was posted on the project website, and the survey link was distributed to the associations that agreed to participate (refer to Appendix 4 for associations that participated and those that did not).

Participation was anonymous and voluntary. The estimated time for completion was 15 minutes, with a target of 50 responses per survey.

The University of Maryland, Baltimore Institutional Review Board and the FDA Institutional Review Board 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*

- Dexamethasone SP is available as an FDA-approved product in the nominated dosage form and ROA.
- Dexamethasone SP was available as an FDA-approved topical cream product that was discontinued, not for reasons of safety or efficacy.
- Dexamethasone SP is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for dexamethasone SP.
- Dexamethasone SP 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.

Table 1. Currently approved products—US<sup>a</sup>

<b>Active Ingredient</b>	<b>Concentration</b>	<b>Dosage Form</b>	<b>Route of Administration</b>	<b>Status</b>	<b>Approval Date<sup>b</sup></b>
Dexamethasone SP	EQ 4-10 mg/mL	Injectable	Injection	Prescription	Approved before 1/01/1982

<sup>a</sup>Source: US FDA *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).

<sup>b</sup>If multiple approval dates or multiple strengths, then earliest date provided.

Table 2. Currently approved products—select non-US countries and regions<sup>a</sup>

Active Ingredient <sup>b</sup>	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date <sup>c</sup>
Dexamethasone SP	4-10 mg/mL	Liquid, solution	Intra-articular, intrabursal, intralesional, intramuscular, intrasynovial, intravenous, local injection, periarticular, rectal, soft tissue injection, subconjunctival, subcutaneous	Abu Dhabi	Active	—
				Australia	Prescription	10/8/1991
				Belgium	Prescription	11/1/1996
				Canada	Prescription	12/31/1986
				Hong Kong	Prescription-only	3/28/1979
				Ireland	Prescription-only nonrenewable	7/28/1986
				Latvia	Prescription	6/20/1996
				Namibia	—	8/18/2004
				New Zealand	Prescription	9/20/1984
				Saudi Arabia	Prescription	—
	UK	Prescription-only	2/15/1988			
	0.4-4 mg/mL	Solution	Oral	Ireland	Prescription-only nonrenewable	2/03/2006
				UK	Prescription-only	3/08/2005
0.05%	Cream	—	Hong Kong	Prescription-only	5/18/1984	

Abbreviations: —, not provided; SP, sodium phosphate.

<sup>a</sup>Medicine registers of national regulatory agencies were searched if they met the following criteria: freely accessible; able to search and retrieve results in the English language; and desired information (product trade name, active ingredient, strength, form, ROA, and approval status) provided in a usable format.

Information was recorded only for products with strengths, forms, or ROAs similar to those requested in the nominations. See Methodology for full explanation.

<sup>b</sup>Dexamethasone SP used as the standard for name variations, including dexamethasone phosphate.

If multiple approval dates or multiple strengths, then earliest date provided.

## *Results of literature review*

### Study selection

Database searches yielded 4133 references; 18 additional references were identified by searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 3806 titles and abstracts were screened. After screening, the full text of 1946 articles was reviewed. Finally, 16 studies were included, and 1930 studies were excluded for the following reasons: wrong study design (1091 studies), wrong substance (703), nonnominated formulation (54), FDA-approved dosage form or ROA (44), unspecified dosage form or ROA (14), duplicate study (10), dexamethasone SP not used clinically (6), dexamethasone SP mentioned only briefly (2), language other than English (2), retracted articles (2), or unable to obtain full text (2).

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

### Characteristics of included studies

The 16 included studies were published between 1970 and 2020. There were 10 experimental studies, 3 observational studies, 3 descriptive studies, and 0 clinical practice guidelines. The 16 studies were conducted in the following countries: Brazil, Canada, Croatia, South Korea, Thailand, and US.

A total of 5728 patients participated in the 16 included studies. The number of patients in each study ranged from 1 to 2024.

Outcome measures differed between the included studies and included objective motor or sensory changes, straight leg raising ability, trigger points, pain relief or reduction, number of injections received, surgical rates, side effects, final daily consumption of oral morphine, plasma cortisol and glucose concentrations, hospitalization, symptom severity, functional status, electrophysiological parameters of the median nerve, and improvement or resolution of oral mucositis.

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

### Use of dexamethasone SP

A total of 826 patients received dexamethasone SP as a treatment for pain, administered as an oral suspension once or twice in a dose of 0.6 mg/kg (maximum 10 mg). Dexamethasone SP was also administered epidurally once to 5 times. The doses provided included 2-15 mg and 1.5-8 mL.

Thirty patients received dexamethasone SP for anesthesia, administered 8 mg once intrathecally.

Three hundred four patients received dexamethasone SP as a treatment for bronchiolitis, administered as an oral solution once in a dose of 1 mg/kg (maximum 12 mg).

An unspecified number of patients (17 hands) received dexamethasone SP as a treatment for carpal tunnel syndrome, administered as a gel for 10 sessions. There were 3 sessions per week for 2 weeks and then 2 sessions per week for the next 2 weeks.

A total of 359 patients received dexamethasone SP as a treatment for croup, administered as an oral suspension once or twice in a dose of 0.6 mg/kg (maximum 20 mg).

One patient received dexamethasone SP as a treatment for oral mucositis, administered as an oral rinse.

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

Dexamethasone SP was not used as a compounded product, nor was it used in a combination product (refer to Tables 8-10).

In 6 studies, the authors' concluding statement recommended the use of dexamethasone SP for anesthesia,<sup>22</sup> croup,<sup>23</sup> and pain.<sup>24-27</sup> In 1 study, the authors concluded that the use of dexamethasone SP was not recommended for the treatment of pain.<sup>28</sup> In 6 studies, the authors concluded that further studies were necessary for the use of dexamethasone in the treatment of bronchiolitis<sup>29</sup> and pain.<sup>30-34</sup> In 2 studies, the authors concluded that the efficacy of dexamethasone SP was similar to that of other study interventions used for carpal tunnel syndrome<sup>35</sup> and pain.<sup>36</sup> In 1 study, the authors did not provide a definitive conclusion for the use of dexamethasone SP.<sup>37</sup> 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 dexamethasone SP.

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.<sup>38</sup> Methylprednisolone is the methyl derivative of prednisolone, and betamethasone, dexamethasone, and triamcinolone are fluorinated derivatives of prednisolone; betamethasone is also an isomer of dexamethasone.<sup>38</sup>

The corticosteroids are grouped into 2 categories based on their particle size and aggregation in relation to red blood cells: particulates and nonparticulates.<sup>39</sup> Particulates, which include betamethasone acetate and SP (Celestone<sup>®</sup> Soluspan<sup>®</sup>), methylprednisolone acetate (Depo-Medrol<sup>®</sup>), and triamcinolone acetonide (Kenalog<sup>®</sup>), 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."<sup>39-41</sup> In contrast, nonparticulates, which include dexamethasone SP (Decadron<sup>®</sup>) and compounded betamethasone SP, because of the SP moiety, which increases solubility, are "fully soluble and clear in appearance."<sup>38,40,41</sup> Nonparticulate corticosteroids are appropriate for parenteral use and are theoretically safer for epidural use.<sup>38,41</sup> With epidural administration, there is a risk of inadvertent intravascular injection, but because the particle size of nonparticulate corticosteroids is smaller than red blood cells, "this would eliminate the risk of embolic infarction in the event of inadvertent intravascular injection."<sup>38,41</sup> However, particulates are theorized to be more efficacious because of their large particle size, leading to longer retention in the epidural space compared with nonparticulates, which "are washed out of their target region readily."<sup>41,42</sup>

Dexamethasone SP is commercially available as both a preserved and PF solution for IV, IM, intra-articular, soft-tissue, and intralesional injection.<sup>43</sup> The preserved product contains benzyl alcohol 10 mg added as a preservative.<sup>43</sup> Methylprednisolone and triamcinolone also contain benzyl alcohol as a preservative, whereas betamethasone derivatives do not.<sup>38</sup> Benzyl alcohol can function as a preservative, solvent, anesthetic, or viscosity-decreasing agent and is often used in various plants, plant products, foods, cosmetics, and medications.<sup>10</sup> Reports of allergy to benzyl alcohol are rare.<sup>10</sup> In addition, there is debate about benzyl alcohol causing neurotoxicity because "paraplegia, neural degeneration, and demyelination have been reported."<sup>38</sup> 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."<sup>38</sup> For topical corticosteroids, allergic contact dermatitis frequency is about 2.3% to 4.9% based on studies with patch-tested patients.<sup>44</sup> Patients who are allergic to a topical

corticosteroid often have cross-reactivity to the other topical corticosteroids.<sup>44</sup> Though presumably less common, this effect could also sensitize patients to corticosteroids given through other routes, such as oral, parenteral, or intralesional.<sup>44</sup>

Antenatal corticosteroids such as dexamethasone and the combination of betamethasone SP and betamethasone acetate have been used to prevent respiratory distress syndrome in preterm infants.<sup>45</sup> 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.”<sup>45</sup> According to a 2013 Cochrane Review by Brownfoot et al, dexamethasone may cause less intraventricular hemorrhage than betamethasone, although possibly with a higher rate of neonatal intensive care unit admission.<sup>45</sup> Brownfoot et al concluded that further trials are needed for the optimal type of corticosteroid to use and the optimal corticosteroid dosing, timing, and frequency of administration.<sup>45</sup> Dexamethasone can be given orally or intramuscularly, and betamethasone can be given intramuscularly, intra-amniotically, or intravenously.<sup>45</sup> 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.”<sup>46</sup> Similar to Brownfoot et al, Roberts et al noted that further information is needed for “optimal dose-to-delivery interval and the optimal corticosteroid to use.”<sup>46</sup>

Corticosteroids have also played a role “in the multimodal pain management in the treatment of chronic spinal pain (cervical and lumbar) and osteoarthritis pain.”<sup>47</sup> Transforaminal, interlaminar, and caudal injections are the most commonly used epidural techniques for “managing lumbar radicular type pain.”<sup>47</sup> 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.<sup>48</sup>

Most reported adverse effects of epidural injections are mild and transient. Ischemic complications have been reported for methylprednisolone, triamcinolone, and betamethasone but not for dexamethasone.<sup>38</sup> With the exception of 1 case, all neurological complications have been reported after particulate corticosteroid injections.<sup>40</sup> A possible hypothesis is that particulate steroids contain numerous particles that can form macroaggregates, which are bigger than red blood cells and could increase the “risk of emboli formation and small arteriole occlusion.”<sup>40</sup> A more recent hypothesis suggests that there is a “direct negative interaction between several corticosteroid particles and red blood cells.”<sup>40</sup> 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 via red blood cell aggregate formation, “with the transformation of red blood cells into spiculated red blood cells.”<sup>40</sup> On the other hand, the change in microvascular perfusion did not occur when nonparticulate corticosteroid dexamethasone SP was injected.<sup>40</sup> Although dexamethasone seems to be associated with fewer neurological complications, 1 case reported involved infarction of the terminal cone after lumbar transforaminal infiltration with dexamethasone.<sup>40</sup> However, the exact cause was hard to determine because minimal information was provided in the case report, such as the position of the needle.<sup>40</sup>

Although they are rare, in 2015 the Multi-Society Pain Workgroup published recommendations to prevent neurologic complications associated with epidural steroid injections.<sup>49</sup> These recommendations state that particulate steroids should not be used for cervical transforaminal injections, and a nonparticulate steroid should be used for lumbar transforaminal injections.<sup>49</sup> However, the recommendations also state that “there are situations in which particulate steroids could be used in the performance of lumbar transforaminal epidural steroid injections.”<sup>49</sup> The

recommendations do not address interlaminar epidural injections, and another review of epidural steroid injections states that there are “insufficient data to give a clear recommendation on which corticosteroid should be utilized” for interlaminar and caudal epidural injections.<sup>41</sup> 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 state that dexamethasone with preservatives may be used for transforaminal epidural injections because of the “paucity of evidence of neurotoxicity associated with benzyl alcohol.”<sup>50</sup> 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.”<sup>50</sup> If prescribers elect to use compounded preservative-free steroids, they “must carefully weigh the risks and benefits, as sterility assurance concerns exist.”<sup>50</sup>

In a 2018 recommendation for epidural and transforaminal corticosteroid injection from Société d’Imagerie Musculosquelettique, Fédération de Radiologie Interventionnelle, and Société Française de Radiologie, Cotten state 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.”<sup>40</sup> On the other hand, a 2015 study notes 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.<sup>30</sup> In a 2013 review of cervical epidural steroid injections for cervical spinal pain treatment, Candido and Knezevic state that dexamethasone was the only nonparticulate corticosteroid not yet implicated in spinal or brainstem infarction after cervical epidural steroid injections and suggested the use of only nonparticulate corticosteroids such as dexamethasone SP to reduce the risk of complications.<sup>42</sup> Similarly, in Cotten’s 2018 recommendation for epidural and transforaminal corticosteroid, dexamethasone SP, as the only nonparticulate corticosteroid available in France, is recommended for cervical infiltration or lumbar transforaminal infiltration.<sup>40</sup> Cotten also reports a study that cautions against using ropivacaine with dexamethasone because ropivacaine can provoke crystallization of dexamethasone.<sup>40</sup> Several studies compare dexamethasone SP with particulate steroids such as betamethasone,<sup>31</sup> methylprednisolone acetate,<sup>32</sup> or triamcinolone<sup>28,36</sup> for TFESIs in radicular pain. Three studies conclude that dexamethasone and the particulate steroid comparator used have similar effectiveness, and one study by Kennedy et al notes that the dexamethasone group had to receive slightly more injections to achieve the same outcomes as the triamcinolone group.<sup>36</sup> Another study by Kim and Brown comments 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],” which may need to be clarified by further studies.<sup>32</sup> A 2010 study by Park et al concludes that triamcinolone is more effective than dexamethasone for lumbar radiculopathy.<sup>28</sup> When radiculopathy cases are refractory to conventional TFESIs, percutaneous epidural adhesiolysis (PEA) can be used.<sup>51</sup> PEA works by washing out inflammatory cytokines and drugs while also lysing the epidural fibrosis.<sup>51</sup> A 2016 study by Cho and Park compared the efficacy of dexamethasone SP and triamcinolone acetate during PEA. Forty patients received PEA with triamcinolone acetate 80 mg, and 26 patients received PEA with dexamethasone SP 10 mg.<sup>51</sup> Cho and Park conclude that dexamethasone was noninferior to triamcinolone acetate based on success rate and percentage of the verbal numerical rating scale decrease 6 months after PEA.<sup>51</sup>

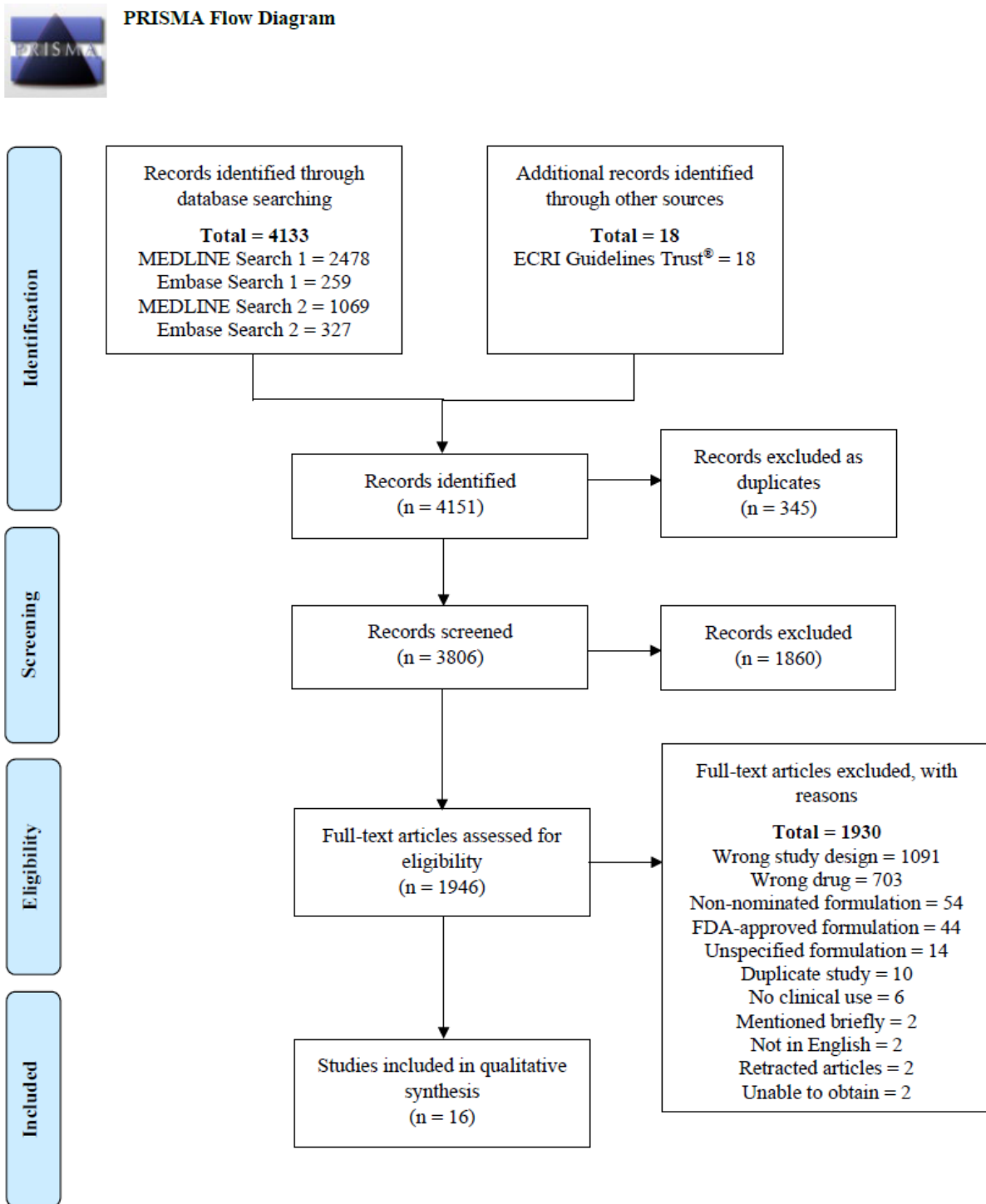
Intra-articular injections have been used to treat inflammation and pain in the knee and to provide temporary relief of “joint symptoms associated with osteoarthritis and other inflammatory

disorders.”<sup>52</sup> Hydrocortisone, methylprednisolone, dexamethasone, betamethasone, prednisolone, and triamcinolone are the most commonly used corticosteroids for intra-articular injection.<sup>52</sup> The duration of action ranges from 6 to 21 days, with hydrocortisone and dexamethasone SP providing the shortest action and triamcinolone hexacetonide the longest.<sup>52</sup> 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 although there are beneficial effects of intra-articular injections, the lowest effective dosage should be used.<sup>52</sup>

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.<sup>53</sup> Methylprednisolone acetate is the most commonly injected IT steroid and use became popular in the 1960s and 1970s. However, its use 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.”<sup>54</sup> Additionally, none of the studies evaluating the use were controlled or blinded, and it is likely that the disease spontaneously remitted in all reports.<sup>54,55</sup> There have been no studies showing the superiority of IT steroids over more conventional routes.<sup>54</sup> 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, subarachnoid hemorrhage, neurogenic bladder, brain damage, spinal cord lesions, and pachymeningitis.<sup>55</sup>

According to Sakic et al, IT steroids are frequently used for “treatment of mumps meningitis, chronic lymphocytic leukemia and central nervous involvement in lupus erythematosus.”<sup>22</sup> IT dexamethasone added to bupivacaine for elective lower limb orthopedic surgery can also prolong the duration of sensory block and decrease the amount of postoperative opioid needed; this was also similar when dexamethasone was added to a local anesthetic in peripheral nerve blocks.<sup>22</sup> In another 2007 study by Fei and Golwa, 10 patients with aneurysmal subarachnoid hemorrhage were enrolled to receive topical dexamethasone SP 10 mg and matched to a control patient who did not receive dexamethasone.<sup>56</sup> Fei and Golwa conclude that topical dexamethasone is a promising strategy to prevent cerebral vasospasm after aneurysmal subarachnoid hemorrhage.<sup>56</sup> On a similar note, phonophoresis of topically applied corticosteroids is often used for musculoskeletal inflammatory conditions.<sup>57</sup> Phonophoresis uses ultrasound to move medication through the skin to allow localized delivery and is widely used by physical therapists.<sup>57</sup> A 1995 study by Franklin et al investigated whether phonophoresis with dexamethasone SP would affect adrenal function.<sup>57</sup> Twenty-eight healthy male volunteers were randomly assigned to 1 of 4 groups: control group (8), ultrasound group (8), dexamethasone gel 0.33% group (7), and ultrasound with dexamethasone gel group (5).<sup>57</sup> Experimental treatments were applied to the volunteer’s left shoulder every other day for 2 weeks (6 treatments total).<sup>57</sup> Franklin et al conclude that phonophoresis with dexamethasone SP “does not cause dexamethasone SP to become systemic in large enough quantities to impair adrenal function.”<sup>57</sup>

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

Type of Studies	Number of Studies
Descriptive <sup>24,30,37</sup>	3
Observational <sup>25,33,34</sup>	3
Experimental <sup>22,23,26-29,31,32,35,36</sup>	10

Table 4. Number of studies by country

Country	Number of Studies
Brazil <sup>26</sup>	1
Canada <sup>23,31</sup>	2
Croatia <sup>22</sup>	1
South Korea <sup>28,30</sup>	2
Thailand <sup>35</sup>	1
US <sup>24,25,27,29,32-34,36,37</sup>	9
Total US: 9	
Total Non-US Countries: 7	

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
Pain <sup>24,25,27,32-34,36</sup>	15 mg 1.5 mL Rate: 5 mL/min	10 mg/mL	—	Epidural	1-5 times
	0.6 mg/kg (maximum 10 mg)	10 mg/mL	Suspension	Oral	Once or twice
Bronchiolitis <sup>29</sup>	1 mg/kg (maximum 12 mg)	1 mg/mL	Solution	Oral	Once
Oral mucositis <sup>37</sup>	—	—	Rinse	Oral	—

Abbreviation: —, not provided.

Table 7. Dosage by indication—non-US countries

Indication	Dosage	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Pain <sup>26,28,30,31</sup>	2-7.5 mg 3-8 mL	10 mg/mL	—	Epidural	Once or twice
Anesthesia <sup>22</sup>	8 mg	—	—	Intrathecal	Once
Carpal tunnel syndrome <sup>35</sup>	—	0.5% (60 mg)	Gel	—	4 weeks
Croup <sup>23</sup>	0.6 mg/kg (max 20 mg)	—	Suspension	Oral	Once or twice

Abbreviation: —, not provided.

Table 8. Number of studies by combination

	Combination Formula	Number of Studies
Nominated	Dexamethasone SP 0.1% / Finasteride 0.1% / Minoxidil 5% – topical solution, spray	0
	Dexamethasone SP 0.1% / Finasteride 0.1% / Minoxidil 5% / Tretinoin 0.025% – topical solution, spray	0

Abbreviation: SP, sodium phosphate.

Table 9. Compounded products—US

Indication	Publication Year	Compounding Method	Dosage Form	Final Strength
Bronchiolitis <sup>29</sup>	2007	“Research pharmacies prepared oral dexamethasone solutions (1 mg per milliliter of liquid) from generic dexamethasone phosphate injection solution.”	Solution	1 mg/mL

Table 10. Compounded products—non-US countries

*No compounded products from included non-US 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 dexamethasone SP. Among these 7 SMEs, there were 6 medical doctors and 1 nurse practitioner. The SMEs specialized or were board-certified in allergy, dermatology, oncology, neurology, physical medicine and rehabilitation, or rheumatology, working in academic medical institutions and outpatient practice. The SMEs had been in practice for 1 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.

Most of the SMEs did not use dexamethasone. One SME was familiar with the IM and IV use, especially for inflammatory conditions of the central nervous system, and reported having used the commercially available dexamethasone product as a dilutant for skin testing. Another SME said that dexamethasone is occasionally used orally in the emergency room setting for patients with asthma but that some studies show that it is just as effective as prednisone. The SME has had experience with patients who have taken dexamethasone for 2 days without improvement and still need prednisone. As a result, the SME does not use dexamethasone. One SME does not use epidural or IT steroids but commented that they might be beneficial for patients with spinal metastases and tumors.

One SME discussed the use of topical dexamethasone. There are 4 classes of steroids (class I, class II, class III, and class IV) that are grouped based on their strength. Class I steroids “are super strong, super potent,” with subsequent classes decreasing in potency. Within each class, prescribers typically have preferred steroids, and the formulation needed and insurance reimbursement determine which steroid is prescribed. The indication determines which formulation is needed; for example, ointments are more occlusive and increase moisturization and are typically preferred for atopic dermatitis. However, ointments cannot be applied to the scalp because “you can’t get ointments into your scalp if you have hair,” and patients “really don’t like them because they’re so greasy” and instead prefer creams. For patients with psoriasis of the scalp, foams and oils are preferred. If the desired formulation is not available in the preferred steroid, one SME stated they would switch to a different steroid within the same class that was available in the necessary dosage form. Regarding the combinations with minoxidil and finasteride, with or without tretinoin, for the treatment of alopecia, the SME said that they “make sense.” The “finasteride and minoxidil are for androgenic alopecia, the addition of tretinoin is going to be in order to decrease some of that scaling and increase penetration. Then the dexamethasone is really going to be for decreasing the itch.” The SME stated that this would be something that a patient would be on for a long period of time and require a patient-specific prescription. The SME has not encountered problems with excipients contained in commercially available products but continued, “I don’t have a specialty contact dermatitis clinic . . . and yes, for them, it is really important to be able to have the flexibility because they do find real allergic reactions that they need to exclude certain ingredients from, and so compounding can be really useful there.”

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 since the 1960s there have been reports of adverse events, such as arachnoiditis or other complications, associated with use, stating, “I’ve just stayed away from them.” The SME uses IV steroids and prednisolone only 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, it would be better to use a preserved product rather than a preservative-free compounded product. The SME mentioned that theoretically it would be advantageous to have betamethasone SP available as a single-agent product because it is a nonparticulate steroid and would therefore be safer for transforaminal use, but because 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 because the drug is not administered near the target nerve root. There is more variability in the steroids used for this injection technique because it is administered farther away from arteries that could cause complications, allowing prescribers the freedom to select which steroid to administer. Although a preservative-free product would be preferred, there are no guidelines indicating that one must be used, and 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 that the presence of a preservative is probably not significant when epidural steroids are administered. There is a higher risk of inadvertently injecting drug intrathecally with both transforaminal and interlaminar injections if they are performed incorrectly, with interlaminar injections having a higher risk. The SME stated that preservatives could be problematic with IT administration, commenting that some animal research 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 before injection of the steroid, and even if a preserved steroid is inadvertently administered into the intrathecal space, there is no clear evidence that this will lead to complications, with the most likely complication being nerve pain. Because of 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 a combination product with lidocaine, stating that some prescribers mix the steroid with lidocaine as a dilutant before the procedure, but 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,” continuing that there is preliminary research identifying anesthetics that are not safe.

As part of phase 3, 2 nominators provided additional information about the products that will be compounded with dexamethasone SP.

Dexamethasone SP will be compounded as a 4-mg/mL solution for IM injection to treat inflammation, administered as a 1-time dose, with the potential for additional injections in the future. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics, operating rooms, physician offices, and surgery centers. This product is needed because the commercially available product contains benzyl alcohol, which patients may be allergic to and thus eliminates potential injection sites that a practitioner may want to use, namely in the spine and surrounding areas.

Dexamethasone SP will be compounded as a 10-mg/mL solution for IM injection to treat inflammation, administered as a 1-time dose, with the potential for additional injections in the future. This product is used by practitioners as a non-patient-specific compounded product in outpatient clinics, operating rooms, physician offices, and surgery centers. This product is needed because the commercially available product

contains benzyl alcohol, which patients may be allergic to and thus eliminates potential injection sites that a practitioner may want to use, namely in the spine and surrounding areas.

Dexamethasone SP 0.1%/finasteride 0.1%/minoxidil 5%/tretinoin 0.025% will be compounded as a topical solution to treat alopecia, applied multiple times throughout the day for multiple days. This product is used by practitioners as a non-patient specific compounded product in outpatient clinics and physician offices. This product will be compounded without the following inactive ingredients: butylparaben, methylparaben, mineral oil, titanium dioxide, and trolamine, which are components of the commercially available products. These inactive ingredients are known to be harmful allergens or irritants; their hazardous concerns include allergen, classified as expected to be toxic or harmful, classified as skin irritant, human endocrine disruptor, human immune and respiratory toxicant or allergen, human skin toxicant or allergen, and possible human carcinogen. Dexamethasone SP is added for its anti-inflammatory properties, minoxidil for its ability to promote hair growth, finasteride for its dihydrotestosterone inhibitory properties, and tretinoin for its anti-inflammatory properties. This product will result in a clinical difference to patients because it does not include harmful excipients found in FDA-approved drug products and because this combination of active and inactive ingredients cannot be found in any commercially available formulations.

A roundtable discussion with representatives from a variety of practice settings was held to discuss the use of outsourcing facilities to obtain compounded products. Forty-three participants attended the event; refer to Table 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.

Although 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 a problem 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, such as 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 with 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 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 because they face a unique need in that they already perform a lot of manipulations to products because of a lack of concentrations or sizes available. One participant commented, "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, "We're trying to minimize compounding, expedite actual therapies to patients in that setting [operating room], [and] 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, such as vasopressor infusions, to prevent compounding from occurring on the floor, and another commented, "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 before administration to be purchased as syringes from outsourcing facilities, stating that "they would prefer to have a syringe form."

Another theme in deciding what products to purchase from an outsourcing facility was the use and volume of a product that is needed and the overall impact it has on the pharmacy workload. Critical care areas, such as the emergency department and operating room, typically have a high product use rate and overall turnover, leading several participants to obtain 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 with the time it would take pharmacy staff to prepare this volume. One participant commented, "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, although 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 complex products, such as epidurals and cardioplegia solutions, from outsourcing facilities to reduce the workload on pharmacy staff. The coronavirus disease 2019 pandemic has also affected the operations of hospitals, as noted by one participant who stated, "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 [percentage 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 affect 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. 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 standard 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 lack of standardization 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 in sourcing.” Additionally, although a commercial 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, “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 typically first restrict use of a drug on shortage, in order to conserve supply, before turning to an outsourcing facility. One participant commented that “most of the time, I will probably pursue restricting, conserving, and looking at all available options prior to going to an outsourcer on my end,” and another stated, “I can only think of one time in recent history where we went to an outsourcer.” One participant commented that “503Bs can't accept the additional volume if it's a true shortage. If you're not with them preshortage, you're not going to get products when you need it during the shortage,” 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, “What

the 503Bs are starting to do, some of the large ones, is that they are also conducting validation studies on API. If sterile becomes short, they quickly switch to producing through API, which ASHP [American Society of 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 problems with purchasing products compounded starting from APIs. Another participant stated that as more outsourcing facilities began using APIs, they became more comfortable with them doing so. However, one participant observed that most outsourcing facilities are switching to sterile-to-sterile and using APIs only 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 because it is used for patients with neonatal abstinence syndrome but is available only as a preservative-containing product. So there is a need for this product to be compounded from the API as a preservative-free product. One participant stated, “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. The lack of preservative-free forms is also a problem 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 because of the potential cross-reactivity for 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 needed 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. Lidocaine/epinephrine/tetracaine gel, used 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 because of 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 because of a lack of commercially available products. The participant stated that they purchase low-dose naltrexone for oral use by patients with refractory fibromyalgia and ketamine troches for patients with chronic pain. The participant continued that although 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 about 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 about 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 were problems with crystallization after storage. A few participants commented that a sterile alum powder is available, which they purchase to compound in-house. One participant had concerns about this powder, stating, “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 needed only 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 patients a year for whom they need to use alum. The participant had it stat shipped when needed. Another participant stated that “we had a meeting with the head of urology who was baffled, why they’re even ordering it. He was like, ‘this is . . . 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 when they use 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 because 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 because of the thickness of the product.

Four participants stated that they obtain sodium citrate as ready-to-use syringes for use as a locking solution for 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 available only 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).

Although 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 Although they 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 and 3 other formulations.

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

No 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 the 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 because of a need for ready-to-use products, and 20 respondents (14%) obtained drug products from outsourcing facilities because of backorders (refer to Table 16).

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

No respondents (0% of 108 responses, where respondents were allowed to select multiple drug products) obtained dexamethasone SP 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 dexamethasone sodium phosphate prescribed or administered

*No respondents to survey distributed via professional medical associations.*

Table 13. Reasons for using compounded dexamethasone sodium phosphate

*No respondents to survey distributed via professional medical associations.*

Table 14. Use of non-patient-specific compounded dexamethasone sodium phosphate

*No respondents to survey distributed via professional medical associations.*

Table 15. Demographics of prequestionnaire respondents' facilities

Type of Facility	Responses, n (N = 102) <sup>a</sup>
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 <sup>b</sup>	4
Trauma center	5
Urban hospital	5
<b>Number of Beds</b>	<b>Responses, n (N = 39)</b>
< 50	4
50-99	3
100-199	1
200-299	4
300-399	5
400-599	3
> 600	19

<sup>a</sup>Respondents were allowed to select more than 1 type of facility.

<sup>b</sup>Specialties provided include cardiology, pulmonary, vascular, home infusion, neurology, psychiatry, and oncology.

Table 16. Reasons for obtaining products from outsourcing facilities

Categories	Responses, n (N = 143) <sup>a</sup>
Backorders	20
Convenience	19
Cost	10

Need for concentrations not commercially available	19
Need for multi-ingredient products not commercially available	10
Need for preservative-free products	3
Need for ready-to-use products	27
No FDA-approved product available	7
No onsite compounding facility	1
Onsite compounding facility not equipped to compound all necessary products	19
Other <sup>b</sup>	8

<sup>a</sup>Respondents were allowed to select multiple categories.

<sup>b</sup>Respondents reported staffing shortages, need for extended dating, volume of product used, and standardization projects as additional reasons for using outsourcing facilities.

Table 17. Categories of products obtained from outsourcing facilities

<b>Categories</b>	<b>Responses, n (N = 142)<sup>a</sup></b>
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 or bags	14
Ready-to-use electrolyte solutions	5
Ready-to-use vasopressor solutions	18
Total parenteral nutrition solutions	16
Other <sup>b</sup>	6

<sup>a</sup>Respondents were allowed to select multiple categories.

<sup>b</sup>Respondents reported obtaining alum for bladder irrigation, oxytocin, anticoagulant sodium citrate solution, narcotic drips, high-cost antiseizure medications, antiviral medications, topical pain, and oral tablets or capsules.

Table 18. Products obtained from an outsourcing facility

<b>Product</b>	<b>Responses, n (N = 108)<sup>a</sup></b>
Acetylcysteine	1
Adenosine	2
Aluminum potassium sulfate	2
Aspartic acid	0
Atenolol	0
Atropine	9
Baclofen	4
Betamethasone	0
Biotin	0
Bupivacaine	8
Caffeine sodium benzoate	0
Calcium chloride	1
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

<sup>a</sup>Respondents were allowed to select multiple products.

## CONCLUSION

Dexamethasone SP was nominated for inclusion on the 503B Bulks List as a PF and preserved solution for epidural, IM, IV, and IT injection, a preserved suspension with additional APIs, a topical gel and oral solution, and a topical solution and spray to treat a variety of conditions. Dexamethasone SP is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, Latvia, Namibia, New Zealand, Saudi Arabia, UK, and the US.

From the literature review, 16 studies were included. In the included studies, dexamethasone SP was used to treat pain, bronchiolitis, oral mucositis, carpal tunnel syndrome, and croup and as part of anesthesia orally and as an epidural and IT injection. In 6 studies, the authors recommended the use of dexamethasone SP for anesthesia, croup, and pain, and 6 studies stated that additional studies were needed regarding the use of dexamethasone SP for bronchiolitis and pain. One study did not recommend the use of dexamethasone SP for the treatment of pain. Two studies concluded that dexamethasone SP was as efficacious as other study interventions used for carpal tunnel syndrome and pain, and 1 study did not provide a definitive conclusion about the use of dexamethasone SP.

From the interviews, most of the SMEs did not use dexamethasone SP; however, 1 SME stated that for patients with spinal metastases or tumors epidural or IT, dexamethasone SP might be beneficial. 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. One SME stated that the nominated combinations with minoxidil and finasteride, with or without tretinoin, would make sense for the treatment of alopecia, but this would be a long-term treatment, so the SME would write a patient-specific prescription for the patient to obtain the combination if needed.

As part of phase 3, 2 nominators provided additional information about the products that will be compounded with dexamethasone SP. Dexamethasone SP will be compounded as a 4-mg/mL and 10-mg/mL solution for IM injection to treat inflammation and as topical solution in combination with minoxidil, finasteride, and tretinoin as a multi-ingredient product to treat alopecia. These products are needed because patients may be allergic to the preservatives or excipients found in the commercially available products.

No people responded to the survey distributed via professional medical associations and available on the project website. From the prequestionnaire, 0 respondents obtained betamethasone 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 nonindexed citations and daily from 1946 to August 26, 2020
- Date last searched: August 27, 2020
- Limits: Humans (search hedge); English language
- Number of results: 2478

1	dexamethasone/	51,350
2	(dexamet?ason\$ adj3 phosphat\$).tw.	1019
3	(dexamet?ason\$ adj3 disodiumphosphat\$).tw.	1
4	(dexamet?ason\$ adj3 phsophat\$).tw.	1
5	(desamet?ason\$ adj3 phosphat\$).tw.	2
6	(desamet?ason\$ adj3 disodiumphosphat\$).tw.	0
7	(desamet?ason\$ adj3 phsophat\$).tw.	0
8	(dexamet?azon\$ adj3 phosphat\$).tw.	1
9	(dexamet?azon\$ adj3 disodiumphosphat\$).tw.	0
10	(dexamet?azon\$ adj3 phsophat\$).tw.	0
11	dexamet?ason\$ sp.tw.	2
12	desamet?ason\$ sp.tw.	0
13	dexamet?azon\$ sp.tw.	0
14	dex sp.tw.	12
15	dex p.tw.	116
16	or/1-15	51,665
17	administration, oral/	142,988
18	infusions, spinal/	160
19	exp injections, spinal/	16,124
20	epidural space/	4517

21	subarachnoid space/	4363
22	oral\$.tw.	673,336
23	spinal\$.tw.	268,695
24	intrapinal\$.tw.	5053
25	epidural\$.tw.	42,229
26	extradural\$.tw.	6766
27	extra dural\$.tw.	142
28	peridural\$.tw.	2064
29	peri dural\$.tw.	6
30	caudal\$.tw.	45,726
31	intracaudal\$.tw.	11
32	arachnoid\$.tw.	8166
33	subarachnoid\$.tw.	35,741
34	intrathecal\$.tw.	23,848
35	intra thecal\$.tw.	76
36	or/17-35	1,098,462
37	drug therapy/	30,572
38	exp diagnosis/	8,554,259
39	dt.fs.	2,229,574
40	ad.fs.	1,416,902
41	tu.fs.	2,228,423
42	di.fs.	2,571,849
43	therap\$.tw.	2,796,448
44	treat\$.tw.	5,522,658
45	diagnos\$.tw.	2,475,988
46	or/37-45	15,212,597

47	and/16,36,46	3457
48	exp animals/ not humans/	4,728,766
49	47 not 48	2716
50	limit 49 to english language	2478

## MEDLINE search strategy 2

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process, and other nonindexed citations and daily from 1946 to August 26, 2020
- Date last searched: August 27, 2020
- Limits: Humans (search hedge); English language
- Number of results: 1069

1	dexamethasone/	51,350
2	(dexamet?ason\$ adj3 phosphat\$).tw.	1019
3	(dexamet?ason\$ adj3 disodiumphosphat\$).tw.	1
4	(dexamet?ason\$ adj3 phsophat\$).tw.	1
5	(desamet?ason\$ adj3 phosphat\$).tw.	2
6	(desamet?ason\$ adj3 disodiumphosphat\$).tw.	0
7	(desamet?ason\$ adj3 phsophat\$).tw.	0
8	(dexamet?azon\$ adj3 phosphat\$).tw.	1
9	(dexamet?azon\$ adj3 disodiumphosphat\$).tw.	0
10	(dexamet?azon\$ adj3 phsophat\$).tw.	0
11	dexamet?ason\$ sp.tw.	2
12	desamet?ason\$ sp.tw.	0
13	dexamet?azon\$ sp.tw.	0
14	dex sp.tw.	12
15	dex p.tw.	116
16	or/1-15	51,665
17	administration, topical/	38,461
18	administration, cutaneous/	22,087
19	skin absorption/	11,694
20	topical\$.tw.	105,631
21	epicutaneous\$.tw.	2013
22	transdermal\$.tw.	14,628

23	((cutaneous\$ or dermal\$ or skin) adj3 (absorb\$ or absorpt\$ or appl\$)).tw.	12,286
24	emulsions/	17,971
25	exp gels/	52,045
26	liniments/	123
27	ointments/	12,796
28	skin cream/	1034
29	spray?.tw.	28,130
30	emulsion?.tw.	33,214
31	gel?.tw.	308,509
32	liniment?.tw.	145
33	ointment?.tw.	11,862
34	salve?.tw.	341
35	paste?.tw.	12,505
36	unguent\$.tw.	113
37	lotion?.tw.	2312
38	cream?.tw.	18,979
39	or/17-38	572,014
40	drug therapy/	30,572
41	ad.fs.	1,416,902
42	dt.fs.	2,229,574
43	pc.fs.	1,289,861
44	tu.fs.	2,228,423
45	therap\$.tw.	2,796,448
46	treat\$.tw.	5,522,658
47	finasteride/	2235
48	minoxidil/	1564

49	tretinoin/	22,180
50	finasterid\$.tw.	2678
51	m#nox#dil\$.tw.	1851
52	minossidil\$.tw.	0
53	(retinoi\$ adj acid\$.tw.	32,456
54	tretinoin\$.tw.	1359
55	(vitamin\$ a adj acid\$.tw.	354
56	(vitamin\$ a1 adj acid\$.tw.	0
57	or/40-56	9,119,226
58	and/16,39,57	2047
59	exp animals/ not humans/	4,728,766
60	58 not 59	1301
61	limit 60 to english language	1069

## Embase search strategy 1

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: August 27, 2020
- Limits: Humans (search hedge); English language
- Number of results: 259

1	'dexamethasone sodium phosphate'/de	2814
2	(dexamet\$ason* NEAR/3 phosphat*):ti,ab,tn	1311
3	(dexamet\$ason* NEAR/3 disodiumphosphat*):ti,ab,tn	1
4	(dexamet\$ason* NEAR/3 phsophat*):ti,ab,tn	0
5	(desamet\$ason* NEAR/3 phosphat*):ti,ab,tn	1
6	(desamet\$ason* NEAR/3 disodiumphosphat*):ti,ab,tn	0
7	(desamet\$ason* NEAR/3 phsophat*):ti,ab,tn	0
8	(dexamet\$azon* NEAR/3 phosphat*):ti,ab,tn	5
9	(dexamet\$azon* NEAR/3 disodiumphosphat*):ti,ab,tn	0
10	(dexamet\$azon* NEAR/3 phsophat*):ti,ab,tn	0
11	'dexamet\$ason* sp':ti,ab,tn	2
12	'desamet\$ason* sp':ti,ab,tn	0
13	'dexamet\$azon* sp':ti,ab,tn	0
14	'dex sp':ti,ab,tn	16
15	'dex p':ti,ab,tn	243
16	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	3536
17	'oral drug administration'/de	406,238
18	'intraspinal drug administration'/de	3460
19	'epidural drug administration'/de	8891
20	'intrathecal drug administration'/de	20,969
21	'intracaudal drug administration'/de	21
22	'epidural space'/de	6440

23	'subarachnoid space'/exp	12,959
24	'oral*':ti,ab	968,430
25	'spinal*':ti,ab	370,462
26	'intraspinal*':ti,ab	7007
27	'epidural*':ti,ab	59,747
28	'extradural*':ti,ab	9118
29	'extra dural*':ti,ab	242
30	'peridural*':ti,ab	3002
31	'peri dural*':ti,ab	12
32	'caudal*':ti,ab	59,226
33	'intracaudal*':ti,ab	23
34	'arachnoid*':ti,ab	12,342
35	'subarachnoid*':ti,ab	51,045
36	'intrathecal*':ti,ab	35,498
37	'intra thecal*':ti,ab	242
38	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37	1,783,925
39	#16 AND #38	415
40	[animals]/lim NOT [humans]/lim	6,079,990
41	#39 NOT #40	310
42	#39 NOT #40 AND [english]/lim	259

## Embase search strategy 2

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: August 27, 2020
- Limits: Humans (search hedge); English language
- Number of results: 327

1	'dexamethasone sodium phosphate'/de	2814
2	(dexamet\$ason* NEAR/3 phosphat*):ti,ab,tn	1311
3	(dexamet\$ason* NEAR/3 disodiumphosphat*):ti,ab,tn	1
4	(dexamet\$ason* NEAR/3 phsophat*):ti,ab,tn	0
5	(desamet\$ason* NEAR/3 phosphat*):ti,ab,tn	1
6	(desamet\$ason* NEAR/3 disodiumphosphat*):ti,ab,tn	0
7	(desamet\$ason* NEAR/3 phsophat*):ti,ab,tn	0
8	(dexamet\$azon* NEAR/3 phosphat*):ti,ab,tn	5
9	(dexamet\$azon* NEAR/3 disodiumphosphat*):ti,ab,tn	0
10	(dexamet\$azon* NEAR/3 phsophat*):ti,ab,tn	0
11	'dexamet\$ason* sp':ti,ab,tn	2
12	'desamet\$ason* sp':ti,ab,tn	0
13	'dexamet\$azon* sp':ti,ab,tn	0
14	'dex sp':ti,ab,tn	16
15	'dex p':ti,ab,tn	243
16	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	3536
17	'topical drug administration'/de	82,685
18	'cutaneous drug administration'/de	666
19	'transdermal drug administration'/de	9066
20	'skin absorption'/de	8056
21	'topical treatment'/de	13,044
22	'topical*':ti,ab	149,664

23	'epicutaneous*':ti,ab	3416
24	'transdermal*':ti,ab	21,409
25	((cutaneous* OR dermal* OR skin) NEAR/3 (absorb* OR absorp* OR appl*)):ti,ab	17,969
26	'cream'/de	9449
27	'gel'/exp	77,217
28	'liniment'/de	251
29	'lotion'/de	2863
30	'ointment'/de	17,925
31	'paste'/de	2521
32	'salve'/de	166
33	'cream\$':ti,ab	29,691
34	'emulsion\$':ti,ab	45,165
35	'liniment\$':ti,ab	234
36	'lotion\$':ti,ab	4006
37	'ointment\$':ti,ab	21,604
38	'paste\$':ti,ab	15,008
39	'salve\$':ti,ab	476
40	'unguent*':ti,ab	240
41	'gel\$':ti,ab	362,687
42	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41	721,020
43	#16 AND #42	518
44	[animals]/lim NOT [humans]/lim	6,079,990
45	#43 NOT #44	368
46	#43 NOT #44 AND [english]/lim	327

Appendix 2. Table 5. Summary of included studies

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
<b>Indication 1: Pain</b>					
Cho, 1970, US <sup>24</sup>	—	16 Patients with herniated intervertebral disc (gender not specified, range 24-58 y)	<ul style="list-style-type: none"> <li>Control group (7)</li> <li>Epidural block with a weak local anesthetic and steroids (9)</li> </ul> <p>The steroids mentioned were Aristocort<sup>®</sup> and Decadron<sup>®</sup></p>	Objective motor or sensory changes, straight leg raising ability, trigger points	“Epidural block consisting of 0.5% Xylocaine and steroids is recommended for use in the management of difficult patients with persistent residual low back pain following removal of lumbar disc, particularly when other modalities of treatment have been exhausted.”
Chun and Park, 2015, South Korea <sup>30</sup>	Prospective, randomized, active control trial	62 Patients who received lumbar transforaminal epidural dexamethasone injections <ul style="list-style-type: none"> <li>High-volume injectate (43.8%, mean 64 y ± 11)</li> <li>Low-volume injectate (40%, mean 68 y ± 11)</li> </ul>	<ul style="list-style-type: none"> <li>Low-volume injectate (30)</li> <li>High-volume injectate (32)</li> </ul> <p>The injectate includes dexamethasone disodium phosphate and lidocaine</p>	Incidence of patients achieving meaningful pain relief (≥50% from baseline), reduction on the visual analog scale at 4 weeks after the procedure	“Injectate at a volume of 8 mL was more effective than injectate at a volume of 3 mL for radicular pain in a lumbar transforaminal steroid injection, although both of the injectates contained the same dose of dexamethasone.” “Further studies to determine the optimal dose and volume of the dexamethasone are needed.”
Denis et al., 2015, Canada <sup>31</sup>	Randomized double-blind controlled trial	56 Patients with debilitating radicular pain <ul style="list-style-type: none"> <li>Dexamethasone sodium phosphate (44.8%, mean 47.4 y ± 14.8)</li> <li>Betamethasone (51.9%, mean 48 y ± 14.1)</li> </ul>	<ul style="list-style-type: none"> <li>Dexamethasone sodium phosphate (29)</li> <li>Betamethasone sodium phosphate and betamethasone acetate (27)</li> </ul>	Pain reduction on visual analog scale	“Pain relief and functional improvement are similar for both dexamethasone and betamethasone at 3 months. Considering its safety profile, dexamethasone could be considered as first choice for TFESI. ...More research is needed to support a recommendation of systematically using dexamethasone in TFESI.”

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Kaufmann et al., 2013, US <sup>25</sup>	Retrospective observational series	2024 Patients who underwent single lumbar TFESIs (49.7%, mean 61.4 y ± 16.3)	<ul style="list-style-type: none"> <li>• Triamcinolone acetonide</li> <li>• Betamethasone sodium phosphate/betamethasone acetate</li> <li>• Dexamethasone sodium phosphate</li> </ul> Number of patients given each medication was not specified. "As of October 2010, in response to safety concerns (spinal cord infarcts) described in literature, dexamethasone was used for all lumbar transforaminal epidural injections."	Pain numerical rating scale and Roland-Morris disability questionnaire before TFESI, at 2 weeks, and at 2 months	"This retrospective observational study suggests TFESIs are clinically effective in the treatment of lumbar radicular pain. Subjects with a shorter duration of pain are more likely to achieve a successful outcome."
Kennedy et al., 2014, US <sup>36</sup>	Multicenter, double-blind, prospective, randomized trial	78 Patients with acute unilevel disc herniation resulting in unilateral radicular pain <ul style="list-style-type: none"> <li>• Dexamethasone (65.9%, range 19-51 y)</li> <li>• Triamcinolone (65%, range 20-58 y)</li> </ul>	<ul style="list-style-type: none"> <li>• Dexamethasone phosphate (41)</li> <li>• Triamcinolone acetonide (37)</li> </ul>	Number of injections received, surgical rates, and categorical pain scores at 2 weeks, 3 months, and 6 months	"This study demonstrates that dexamethasone via a transforaminal epidural injection may not have major differences in effectiveness for lumbar radicular pain due to a herniated intervertebral disc when compared with triamcinolone."

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Kim and Brown, 2011, US <sup>32</sup>	—	60 Patients with lumbar radicular symptoms <ul style="list-style-type: none"> <li>• Dexamethasone phosphate (13%, mean 65.9 y ± 13.5)</li> <li>• Methylprednisolone acetate (20%, mean 63.7 y ± 13.1)</li> </ul>	<ul style="list-style-type: none"> <li>• Dexamethasone phosphate (30)</li> <li>• Methylprednisolone acetate (30)</li> </ul>	Pain scores (visual analog scale), side effects	“Nonparticulate [dexamethasone phosphate] seems to be close to the safety and effectiveness of particulate [methylprednisolone acetate] in the treatment of lumbar radiculopathy. There is, however, a statistically nonsignificant trend toward less pain relief and shorter duration of action that may be clarified in a larger and longer duration study.”
Lauretti et al., 2013, Brazil <sup>26</sup>	Randomized, placebo-controlled design	71 Patients with cancer (but actual number is only 58 patients because of incomplete data collection) <ul style="list-style-type: none"> <li>• Group 1 (37.5%, mean 53 y ± 14)</li> <li>• Group 2 (44.4%, mean 56 y ± 9)</li> <li>• Group 3 (40%, mean 53 y ± 11)</li> <li>• Group 4 (40%, mean 50 y ± 8)</li> <li>• Group 5 (50%, mean 52 y ± 13)</li> <li>• Group 6 (45.5%, mean 47 y ± 13)</li> </ul>	<ul style="list-style-type: none"> <li>• Group 1 as control: epidural lidocaine with saline (8)</li> <li>• Group 2: lidocaine with dexamethasone (9)</li> <li>• Group 3: epidural methadone 2.5 mg with lidocaine (10)</li> <li>• Group 4: epidural methadone 5 mg with lidocaine (10)</li> <li>• Group 5: epidural methadone 7.5 mg with lidocaine (10)</li> <li>• Group 6: epidural methadone 7.5 mg with dexamethasone (11)</li> </ul>	Pain average of the day, the final daily consumption of oral morphine, adverse effects	“Epidural methadone plus lidocaine resulted in dose-dependent analgesia, further improved by epidural dexamethasone, which also improved fatigue.”

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Murthy et al., 2014, US <sup>33</sup>	Retrospective observational study	933 Patients (2087 injections) who had received repeat single-level TFESI (44.7%, mean 61.2 y ± 15.9)	<ul style="list-style-type: none"> <li>• Triamcinolone acetonide</li> <li>• Betamethasone sodium phosphate/betamethasone acetate</li> <li>• Dexamethasone sodium phosphate</li> </ul> <p>Number of patients given each medication was not specified; dexamethasone “was used exclusively for all transforaminal epidural injections after October 2010 due to growing awareness of the potential for spinal cord infarctions related to particulate corticosteroids.”</p>	Pain numerical rating scale and Roland-Morris disability questionnaire before TFESI, at 2 weeks, and at 2 months	“Acute pain patients with an initial incomplete response who received repeat injections within 3 months demonstrated a greater, clinically significant cumulative benefit. These findings suggest a more aggressive approach in treating acute single segment lumbar radicular pain. An incomplete response at 2 weeks post injection can reasonably provoke a repeat TFESI. Because there is a paucity of literature regarding repeat TFESIs, further prospective investigation is warranted.”
Olympia et al., 2005, US <sup>27</sup>	Prospective, randomized, double-blind, placebo-controlled clinical trial	150 Children with moderate to severe pharyngitis <ul style="list-style-type: none"> <li>• Dexamethasone (46%, mean 12.7 y)</li> <li>• Placebo (38%, mean 11.3 y)</li> </ul>	<ul style="list-style-type: none"> <li>• Oral dexamethasone suspension (70)</li> <li>• Placebo (73)</li> </ul>	Hours to initial relief of sore throat and time to complete resolution of pain	“Children with moderate to severe pharyngitis had earlier onset of pain relief and shorter duration of sore throat when given oral dexamethasone.”
Park et al., 2010, South Korea <sup>28</sup>	Randomized, single center study	106 Patients with lumbar radicular pain <ul style="list-style-type: none"> <li>• Dexamethasone sodium phosphate (49.1%, mean 55.5 y ± 14.9)</li> <li>• Triamcinolone acetonide (45.3%, mean 62.5 y ± 10.8)</li> </ul>	<ul style="list-style-type: none"> <li>• Dexamethasone sodium phosphate (53)</li> <li>• Triamcinolone acetonide (53)</li> </ul>	Visual analog scale, short McGill pain questionnaire, revised Oswestry Back Disability Index	“In this study, dexamethasone and triamcinolone treatments were shown to have different effects on low back pain with sciatica, with triamcinolone being more effective than dexamethasone in lumbar radiculopathy.”

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Singh et al., 2017, US <sup>34</sup>	Retrospective cohort	721 Patients with unilateral, single-level lumbar radicular pain (46.3%, mean 50.9 y ± 11.9)	<ul style="list-style-type: none"> <li>Betamethasone sodium phosphate and betamethasone acetate (209)</li> <li>Dexamethasone sodium phosphate (512)</li> </ul>	Pain numerical rating scale, Oswestry Disability Index before TFESI at 2-week and 2-month follow-up	“Two-level TFESIs are effective in the management of radicular pain, but more research is needed to evaluate the utility of this treatment compared with single-level TFESI. Our study showed a greater improvement in pain and function as a result of 2-level TFESIs in the setting of paracentral/subarticular disk herniations.”
<b>Indication 2: Anesthesia</b>					
Sakic et al., 2019, Croatia <sup>22</sup>	Randomized, prospective, clinical study	60 Patients with proximal femoral fracture (gender not specified, range 52-95 y)	<ul style="list-style-type: none"> <li>Dexamethasone sodium phosphate with levobupivacaine (30)</li> <li>Levobupivacaine (30)</li> </ul>	Plasma cortisol and glucose concentrations, pain intensity (visual analog scale score), hospitalization	“Single shot of intrathecally administered dexamethasone with levobupivacaine received for surgical treatment of proximal femoral fractures reduces the stress response by decreasing plasma cortisol concentrations with longer lasting analgesic effect . . . hence shortening hospitalisation which explains this pattern of anesthesia as first choice method.”
<b>Indication 3: Bronchiolitis</b>					
Corneli et al., 2007, US <sup>29</sup>	Double-blind, randomized trial	598 Children with moderate to severe bronchiolitis <ul style="list-style-type: none"> <li>Dexamethasone (62.5%, mean 5.1 months ± 2.6)</li> <li>Placebo (60.5%, mean 5.1 months ± 2.8)</li> </ul>	<ul style="list-style-type: none"> <li>Dexamethasone phosphate (304)</li> <li>Placebo (294)</li> </ul>	Hospital admission after 4 hours of emergency department observation	“We found that treatment with 1 mg of oral dexamethasone per kilogram did not significantly alter the rate of hospital admission or the respiratory status after 4 hours of observation. . . . We recommend evaluation of other treatments and preventive strategies for bronchiolitis.”

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
<b>Indication 4: Carpal tunnel syndrome</b>					
Boonhong and Thienkul, 2020, Thailand <sup>35</sup>	Randomized, double-blind controlled, three-arm parallel study	33 Patients (50 hands) with mild to moderate carpal tunnel syndrome (gender not specified, range 30-75 y)	<ul style="list-style-type: none"> <li>Group 1: ultrasound with nondrug gel (16 hands)</li> <li>Group 2: phonophoresis of piroxicam (17 hands)</li> <li>Group 3: phonophoresis of dexamethasone sodium phosphate (17 hands)</li> </ul> <p>Because the groups are randomized by hands, the number of patients who received the substance is unknown.</p>	Symptom severity and functional status (Boston Carpal Tunnel Questionnaire), electrophysiological parameters of the median nerve (distal sensory latency and distal motor latency)	“This study revealed that [all 3 treatments] were not effective in improving electrodiagnostic parameters in mild to moderate [carpal tunnel syndrome] but did improve clinical symptoms and functional status without the between-group statistical differences.”
<b>Indication 5: Croup</b>					
Bjornson et al., 2004, Canada <sup>23</sup>	Double-blind trial	720 Children with mild croup (61%, mean 35 months ± 23)	<ul style="list-style-type: none"> <li>Dexamethasone phosphate (359)</li> <li>Placebo (361)</li> </ul>	Return to a medical care provider for croup within 7 days after treatment	“For children with mild croup, dexamethasone is an effective treatment. . . . Although the long-term effects of this treatment are not known, our data support the use of dexamethasone in most, if not all, children with croup.”

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
<b>Indication 6: Oral mucositis</b>					
Eggleston et al., 1998, US <sup>37</sup>	Case report	1 Patient with oral mucositis that had been present for more than 1 week (100%, 19 y)	<ul style="list-style-type: none"> <li>• Oral Decadron® rinses (1)</li> </ul> Previously tried tetracycline-soaked gauze applications and oral rinses containing lidocaine, diphenhydramine, and an antacid without improvement	Improvement/resolution of oral mucositis	“To alleviate the symptoms of [graft versus host disease], early aggressive treatment should include topical steroids, effective analgesia, a saliva substitute and/or stimulation, and meticulous oral hygiene.”

Abbreviations: —, not provided; TFESI, transforaminal epidural steroid injection.

<sup>a</sup>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)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

2. Do you prescribe or administer dexamethasone sodium phosphate to your patients?

- Yes
- No

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

- Intramuscular injection solution
- Intravenous injection solution
- Intrathecal
- Epidural
- Oral solution
- Topical gel, solution, spray
- None of the above

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

- Alopecia
- Cerebral edema
- Mycosis fungoides
- Nephrotic syndrome
- Trichinosis
- Tuberculosis of meninges
- Other (please explain) \_\_\_\_\_

5. I prescribe or administer compounded dexamethasone sodium phosphate in combination with other active pharmaceutical ingredients as a multi-ingredient product.

- Yes
- No

6. I prescribe or administer dexamethasone sodium phosphate with my patients as the following: (check all that apply)

- FDA-approved drug product
- Compounded drug product
- Other (please explain) \_\_\_\_\_

7. I use compounded dexamethasone sodium phosphate 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 dexamethasone sodium phosphate
  - Other (please explain) \_\_\_\_\_
8. Do you stock non-patient-specific compounded dexamethasone sodium phosphate at your practice?
- Yes
  - No
  - I'm not sure
9. I obtain compounded dexamethasone sodium phosphate 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)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

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

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

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

*Appendix 3.3. Survey instrument for pharmacy roundtable prequestionnaire*

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

- Fluids
  - Ophthalmic preparations
  - Patient-controlled analgesia
  - Ready-to-use anesthesia syringes
  - Ready-to-use antibiotic syringes and/or bags
  - Ready-to-use electrolyte solutions
  - Ready-to-use vasopressor solutions
  - Total parenteral nutrition solutions
  - Other, please identify \_\_\_\_\_
7. From the list below, please select the drug(s) that you obtain as either a single ingredient or multi-ingredient product from an outsourcing facility.
- Acetylcysteine
  - Adenosine
  - Aluminum potassium sulfate
  - Aspartic acid
  - Atenolol
  - Atropine
  - Baclofen
  - Betamethasone
  - Biotin
  - Bupivacaine
  - Caffeine sodium benzoate
  - Calcium chloride
  - 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*

<b>Specialty</b>	<b>Association<sup>a</sup></b>	<b>Agreed or Declined, Reason for Declining</b>
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

<sup>a</sup>Associations that declined in Year 1 or Year 2 were not contacted in Year 3.