

# Summary Report

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## Betamethasone sodium phosphate

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

INTRODUCTION .....	5
REVIEW OF NOMINATIONS.....	5
METHODOLOGY .....	6
Background information .....	6
Systematic literature review .....	6
Interviews.....	7
Survey .....	8
CURRENT AND HISTORIC USE .....	9
Results of background information.....	9
Results of literature review .....	11
Results of interviews.....	22
Results of survey.....	29
CONCLUSION.....	35
REFERENCES .....	36
APPENDICES .....	39
Appendix 1. Search strategies for bibliographic databases.....	39
Appendix 2.1. Survey instrument for professional medical associations .....	45
Appendix 2.2. Survey instrument for professional medical associations .....	47
Appendix 2.3. Survey instrument for pharmacy roundtable prequestionnaire .....	49
Appendix 3. Survey distribution to professional associations .....	52

## Table of Tables

Table 1. Currently approved products – US .....	9
Table 2. Currently approved products – select non-US countries and regions .....	10
Table 3. Types of studies .....	17
Table 4. Number of studies by country .....	17
Table 5. Summary of included studies .....	18
Table 6. Dosage by indication – US .....	20
Table 7. Dosage by indication – non-US countries .....	20
Table 8. Number of studies by combination .....	21
Table 9. Compounded products – US .....	21
Table 10. Compounded products – non-US countries .....	21
Table 11. Characteristics of survey respondents .....	29
Table 12. Conditions for which betamethasone sodium phosphate prescribed or administered .....	29
Table 13. Reasons for using compounded betamethasone sodium phosphate .....	29
Table 14. Use of non-patient-specific compounded betamethasone sodium phosphate .....	29
Table 15. Demographics of prequestionnaire respondents’ facilities .....	30
Table 16. Reasons for obtaining products from outsourcing facilities .....	31
Table 17. Categories of products obtained from outsourcing facilities .....	31
Table 18. Products obtained from an outsourcing facility .....	32

## Frequently Used Abbreviations

API	Active pharmaceutical ingredient
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
IRB	Institutional Review Board
IM	Intramuscular
IT	Intrathecal
IV	Intravenous
OTC	Over-the-counter
ROA	Route of administration
SME	Subject matter expert
SP	Sodium phosphate
UK	United Kingdom
US	United States

## INTRODUCTION

This report was created to assist the United States (US) Food and Drug Administration (FDA) in its evaluation of the use of betamethasone sodium phosphate (betamethasone SP; UNII code: 7BK02SCL3W), 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 betamethasone SP is used in clinical research and practice to diagnose, prevent, or treat disease. Due to the broad, exploratory nature of this aim, scoping review methodology was used. Following the scoping review framework, a systematic literature review was conducted and healthcare practitioners were consulted to identify how betamethasone 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 betamethasone 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

Betamethasone SP was nominated for inclusion on the 503B Bulks List by Fagron, the Specialty Sterile Pharmaceutical Society (SSPS), and US Compounding Pharmacy.

Betamethasone SP was nominated for treatment of allergic disorders, bursitis, cerebral edema, 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, exacerbations of multiple sclerosis (acute), gouty arthritis (acute, adjunct), inflammation, inflammatory disorders of the musculoskeletal system (adjunct), leukemia, malignant lymphoma, nephrotic syndrome, osteoarthritis, rheumatoid arthritis, systemic lupus erythematosus, tenosynovitis (adjunct), trichinosis, tuberculosis of the meninges (adjunct), complication of prematurity, disorders relating to short gestation and/or low birthweight, multiple myeloma, and primary intracranial tumor (adjunct).

Betamethasone SP is compounded as a 3 to 24 mg/mL preservative-free solution for intramuscular (IM) and intravenous (IV) injection diluted into potential diluents such as sterile water for injection, sodium chloride, and dextrose. Betamethasone SP is also compounded in combination with betamethasone acetate as a 6 mg/mL (3 mg/mL acetate with 3 mg/mL SP) and a 12 mg/mL preservative-free suspension for intrathecal (IT) injection and as a 7 mg/mL (3 mg/mL acetate with 4 mg/mL SP) preserved suspension for IM and soft tissue injections (refer to Table 8).

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of betamethasone SP.<sup>6-11</sup>

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

- Betamethasone SP is a component of an FDA-approved product with betamethasone acetate. The approved product contains the preservative benzalkonium chloride, to which an estimated 10% of the population is allergic. There is a need for preservative-free formulations.
- Prescriber or hospital preference for various strengths, combinations with other drugs, volumes, and/or final product containers for administration.
- Unsafe to expose the direct compounding area to hundreds of vials or ampoules and hundreds of aseptic manipulations during the compounding of a typically sized batch for outsourcing facilities; a single vessel compounded from bulk API is safer and more efficient than unmanageable numbers 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 utilize the most advanced technology available to provide the greatest level of sterility assurance and quality, bulk starting material is required; it is not feasible financially, nor from a processing standpoint, to use finished pharmaceutical dosage forms with advanced isolated robotic equipment or other advanced aseptic processing equipment.
- Manufacturer backorder.

## METHODOLOGY

### *Background information*

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

Each medicine register was searched for betamethasone SP; name variations of betamethasone 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 and/or schedule; and approval date. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations.

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

### *Systematic literature review*

#### Search strategy

A medical librarian constructed comprehensive search strategies for Ovid MEDLINE and Embase. The search strategies used a combination of controlled vocabulary terms and keywords to describe two concepts: betamethasone acetate or betamethasone SP, and intravenous, intramuscular, intra-articular or IT administration (refer to Appendix 1 for full search strategies). The same search strategies were utilized for both betamethasone acetate and betamethasone SP because these substances were nominated for the same ROA, either alone or in combination with one another. Results were limited to human studies in the English language. Searches were conducted on August 26, 2020. In addition, the ECRI Guidelines Trust® repository was searched on August 26, 2020, for clinical practice guidelines that recommended the use of betamethasone (salt form not specified) and provided sufficient information on dosing and administration.

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

### Study selection

Studies in which betamethasone SP was used in the nominated dosage form, ROA, and/or combination product to diagnose, prevent or treat the nominated disease or condition, or other conditions not specified in the nomination, were included. Studies were excluded if they were written in a language other than English; reviews or meta-analyses; surveys or questionnaires (cross-sectional design); designed to evaluate cost-effectiveness, mechanism of action, preclinical use, safety, or toxicity; or any study design other than a randomized controlled trial conducted in a non-US country. Studies were also excluded if betamethasone SP was used as an FDA-approved product in the nominated dosage form, ROA, or combination; a dosage form, ROA, or combination that was not nominated; in an unspecified dosage form or ROA; betamethasone SP not used clinically; or betamethasone SP mentioned briefly as a rescue treatment or a previously failed treatment. Studies in which betamethasone SP was used to diagnose, prevent, or treat autism were excluded due to a separate project examining the use of compounded substances in individuals with autism. Studies that did not meet the inclusion criteria but provided valuable information about the pharmacological or current or historical use of the substance were noted and put in a separate group in the EndNote library. Two reviewers independently screened titles and abstracts and reviewed full-text articles. A third reviewer reconciled all disagreements.

### Data extraction

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

### *Interviews*

Semistructured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances betamethasone 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 betamethasone 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 2 for complete survey and *Results*

*of survey* section for results of prequestionnaire). The roundtable lasted 60 minutes and was conducted via Zoom, audio recorded, and professionally transcribed. The transcriptions and notes were synthesized for qualitative data analysis.

### *Survey*

A survey was distributed to the members of professional medical associations to determine the use of betamethasone SP in clinical practice. The online survey was created using Qualtrics® software (refer to Appendix 2 for complete survey). A Google™ search was conducted to identify the professional associations in the US for the relevant medical specialties. An association's website was searched to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used. An email describing the project and requesting distribution of the survey to the association's members was sent to the identified person(s). Associations that declined, did not respond, or did not provide significant data in project Years 1 and 2 were not contacted to distribute the project Year 3 surveys.

The survey was posted on the project website and the survey link was distributed to the associations that agreed to participate (refer to Appendix 3 for associations that participated and those that did not).

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

The University of Maryland, Baltimore Institutional Review Board (IRB) and the FDA IRB reviewed the interview and survey methods and found both to be exempt. The Office of Management and Budget approved this project.

## CURRENT AND HISTORIC USE

### *Results of background information*

- Betamethasone SP is available as an FDA-approved combination product in the nominated dosage form and ROA.
- Betamethasone SP was available as a 3 mg/mL FDA-approved injection product that was discontinued, not for reasons of safety or efficacy.
- Betamethasone SP is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for betamethasone SP.
- Betamethasone SP is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, Namibia, New Zealand, 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>
Betamethasone sodium phosphate / Betamethasone acetate	EQ 3 mg base/mL / 3 mg/mL	Injectable	Injection	Prescription	Approved prior to 1/01/1982

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

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

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

Active Ingredient	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date <sup>b</sup>
Betamethasone sodium phosphate	4 mg/mL	Solution	Injection, intralesional, intramuscular, intravenous, subconjunctival	Abu Dhabi	Active	–
				Namibia	–	8/18/2004
				UK	Prescription-only	9/22/1992
Betamethasone sodium phosphate / Betamethasone acetate	3-4 mg/mL / 3 mg/mL 5.7 mg/mL	Solution, suspension	Intra-articular, intrabursal, intracavitary, intracutaneous, intradermal, intralesional, intramuscular, periarticular	Abu Dhabi	Active	–
				Australia	Prescription-only	10/8/1991
				Belgium	Prescription	3/01/1967
				Canada	Prescription	12/31/1965
				New Zealand	Prescription	12/31/1969

Abbreviation: –, not provided.

<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 English language; and desired information (product trade name, active ingredient, strength, form, ROA, and approval status) provided in a useable format. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations. See Methodology for full explanation.

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

## *Results of literature review*

### Study selection

Database searches yielded 1296 references; 3 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 1125 titles and abstracts were screened. After screening, the full text of 403 articles was reviewed. Finally, 6 studies were included. Three hundred ninety-seven were excluded for the following reasons: wrong study design (207 studies); wrong substance (85); FDA-approved formulation (67); wrong dosage form or ROA (35); unspecified dosage form or ROA (2); unable to obtain (1).

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

### Characteristics of included studies

The 6 included studies were published between 1987 and 2013. There were 6 experimental studies, 0 observational studies, 0 descriptive studies, and 0 clinical practice guidelines. The 6 studies were conducted in the following countries: Austria, Chile, France, Italy, Sweden, and UK.

A total of 1114 patients participated in the 6 included studies. The number of patients in each study ranged from 12 to 398.

Outcome measures differed among the included studies and included: Pain intensity, consumption of non-steroidal anti-inflammatory agents, frequency of respiratory distress syndrome, use of oxygen, neonatal mortality, maximum respiratory rate, partial pressure of carbon dioxide and oxygen, arterial pH, forced expiratory volume in one second, forced vital capacity, cumulative dose-response curves, peak expiratory flow, fetal heart rate, characteristics, and biophysical activities.

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

### Use of betamethasone SP

Two hundred twelve patients received betamethasone SP as a treatment for pain and nausea, administered intrathecally in a 2 mL dose. Betamethasone SP was also administered as a 12 mg intravenous solution once. Four hundred ninety-six patients received betamethasone SP as prevention for respiratory distress syndrome, administered intramuscularly in doses ranging from 4-24 mg/day for one time to 2 days. Twelve patients received betamethasone SP as a treatment for asthma, administered intramuscularly 8 mg/day for 10 days. Twenty-two patients received betamethasone SP as enhancement for fetal lung maturity, administered intramuscularly 12 mg/day for 2 days.

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

Betamethasone SP was not used as a compounded product. It was nominated to be used in a combination product, but none were found from the included studies (refer to Tables 8-10).

In 1 study, the authors concluded that IT steroids significantly reduce pain after lumbar disc surgery, but the benefits are probably outweighed by the risks.<sup>12</sup> Another study concluded that betamethasone reduced immediate post-operative pain but not chronic pain; there was an increased risk for wound bleeding but the authors concluded that the benefits outweigh the risk for the complication.<sup>13</sup> For 1 study, the authors concluded that the use of antenatal thyrotropin-releasing hormone and corticosteroids compared to corticosteroids did not reduce the frequency of respiratory distress

syndrome or improve preterm neonatal outcomes.<sup>14</sup> In 1 study, the authors' concluding statement recommended the use of betamethasone SP for the prevention of respiratory distress syndrome.<sup>15</sup> In 2 studies, the authors did not provide a definitive conclusion for the use of betamethasone SP.<sup>16,17</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 betamethasone 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>18</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>18</sup>

The corticosteroids are grouped into 2 categories based on their particle size and aggregation in relation to red blood cells, particulates, and non-particulates.<sup>19</sup> Particulates, which include betamethasone acetate and sodium phosphate (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>19-21</sup> In contrast, non-particulates, which include dexamethasone sodium phosphate (Decadron<sup>®</sup>) and compounded betamethasone SP, due to the SP moiety which increases the solubility, are “fully soluble and clear in appearance.”<sup>18,20,21</sup> Nonparticulate corticosteroids are appropriate for parenteral use and are theoretically safer for epidural use.<sup>18,21</sup> With epidural administration, there is a risk of inadvertent intravascular injection, but since 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>18,21</sup> However, particulates are theorized to be more efficacious due to their large particle size leading to longer retention in the epidural space compared to non-particulates, which “are washed out of their target region readily.”<sup>21,22</sup>

Betamethasone SP is commonly used in combination with betamethasone acetate. Betamethasone SP has a short half-life of 36 to 72 hours and provides immediate activity, while betamethasone acetate has a longer half-life and provides sustained activity.<sup>7</sup> This combination of betamethasone SP and betamethasone acetate is commercially available as Celestone<sup>®</sup> Soluspan<sup>®</sup> and is approved for intra-articular, intrabursal, intralesional, intramuscular, and soft tissue injection; it should not be administered intravenously.<sup>23</sup> Celestone<sup>®</sup> Soluspan<sup>®</sup> can be mixed with paraben-free lidocaine if there is a need for a local anesthetic effect; parabens can lead to flocculation of the steroid.<sup>23</sup> Celestone<sup>®</sup> Soluspan<sup>®</sup> does contain the preservative benzalkonium chloride.<sup>23</sup>

Antenatal corticosteroids such as dexamethasone and the combination of betamethasone SP and betamethasone acetate have been used to prevent respiratory distress syndrome (RDS) in preterm infants.<sup>7</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>7</sup> According to a 2013 Cochrane Review by Brownfoot et al, dexamethasone may cause less intraventricular hemorrhage compared to that of betamethasone, although possibly with a higher rate of neonatal intensive care unit admission.<sup>7</sup> Brownfoot et al concluded that further trials are still needed for the optimal type of corticosteroid to use as well as the optimal corticosteroid dosing, timing, and frequency of administration.<sup>7</sup> Dexamethasone can be given orally or intramuscularly while betamethasone can be

given intramuscularly, intra-amniotically, or intravenously.<sup>7</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>24</sup> Similar to Brownfoot et al, Roberts et al noted further information is still needed for “optimal dose-to-delivery interval and the optimal corticosteroid to use.”<sup>24</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>25</sup> Transforaminal, interlaminar, and caudal injections are the most commonly used epidural techniques for “managing lumbar radicular type pain.”<sup>25</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>26</sup>

Most reported adverse effects of epidural injections are mild and transient. Ischemic complications have been reported for methylprednisolone, triamcinolone, and betamethasone, but not with dexamethasone.<sup>18</sup> With the exception of 1 case, all neurological complications have been reported after particulate corticosteroid injections.<sup>20</sup> A possible hypothesis is that particulate steroids contain numerous particles that can form macro-aggregates, which are bigger than red blood cells and could increase the “risk of emboli formation and small arteriole occlusion.”<sup>20</sup> A more recent hypothesis suggests that there is a “direct negative interaction between several corticosteroid particles and red blood cells.”<sup>20</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 due to red blood cell aggregate formation “with the transformation of red blood cells into spiculated red blood cells.”<sup>20</sup> On the other hand, the change in microvascular perfusion did not occur when nonparticulate corticosteroid dexamethasone SP was injected.<sup>20</sup> While 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>20</sup> However, the exact cause was hard to determine due to minimal information provided in the case report, such as the position of the needle.<sup>20</sup>

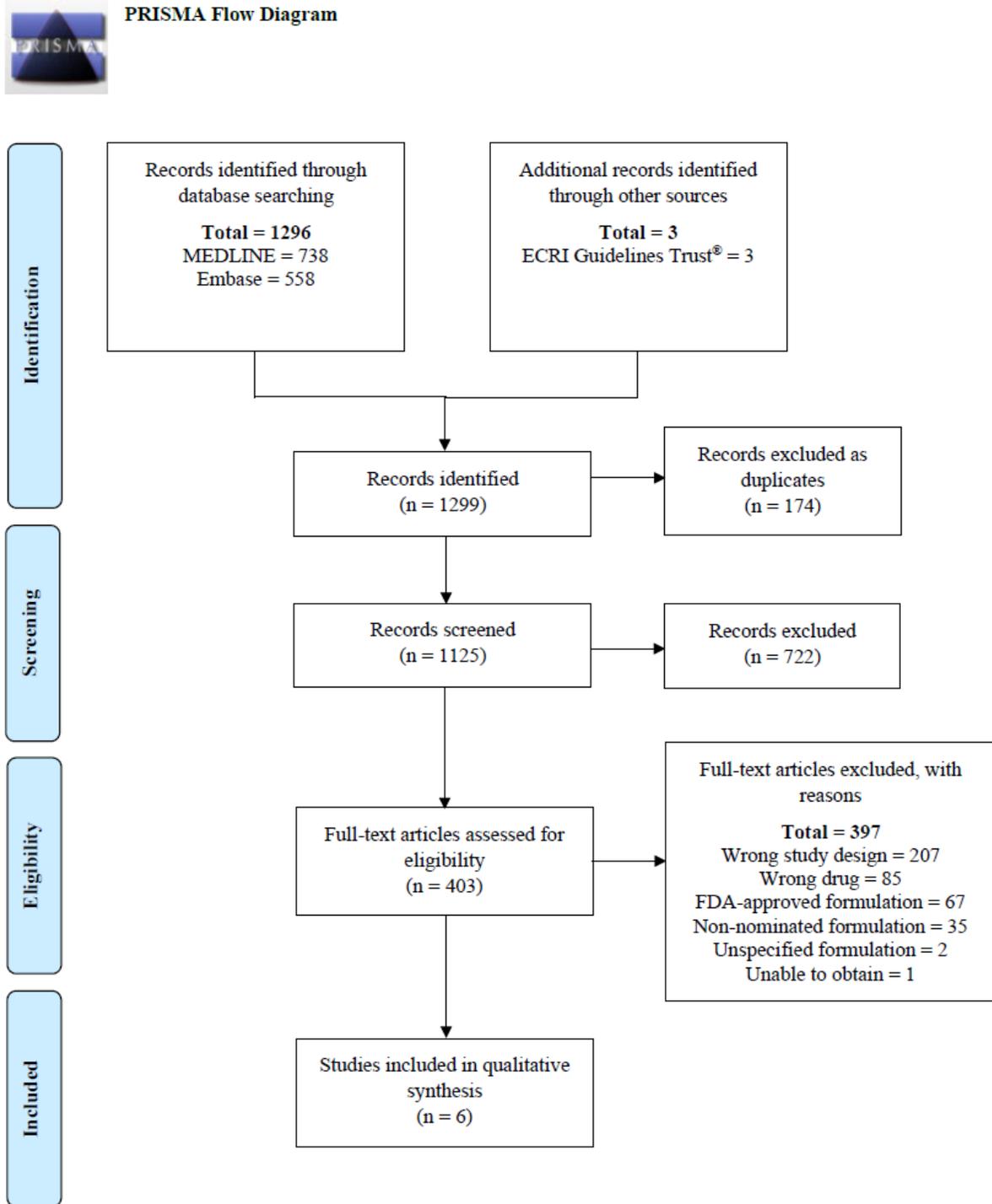
In 2015, the Multi-Society Pain Workgroup published recommendations to prevent the rare neurologic complications associated with epidural steroid injections.<sup>27</sup> These recommendations stated that particulate steroids should not be used for cervical transforaminal injections and a nonparticulate steroid should be used for lumbar transforaminal injections.<sup>27</sup> However, the recommendations also stated that “there are situations in which particulate steroids could be used in the performance of lumbar transforaminal epidural steroid injections.”<sup>27</sup> The recommendations did not address interlaminar epidural injections and another review of epidural steroid injections stated that there is “insufficient data to give a clear recommendation on which corticosteroid should be utilized” for interlaminar and caudal epidural injections.<sup>21</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 stated that dexamethasone with preservatives may be used for transforaminal epidural injections due to the “paucity of evidence of neurotoxicity associated with benzyl alcohol.”<sup>28</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>28</sup> If prescribers elect to use compounded preservative-free steroids, they “must carefully weigh the risks and benefits, as sterility assurance concerns exist.”<sup>28</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 et al stated that knowledge about the neurological complications of 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>20</sup> On the other hand, a 2015 study noted that there has not been evidence that dexamethasone is less effective than particulate steroids in transforaminal epidural steroid injections (TFESIs) for radicular pain; however, evidence for dexamethasone's efficacy for TFESIs remains limited.<sup>29</sup> In a 2013 review about cervical epidural steroid injections for cervical spinal pain treatment, Candido and Knezevic stated that dexamethasone was the only nonparticulate corticosteroid not yet implicated in spinal or brain stem infarction following cervical epidural steroid injections and suggested the use of only nonparticulate corticosteroids such as dexamethasone SP to reduce the risk of complications.<sup>22</sup> Similarly, because dexamethasone SP was the only nonparticulate corticosteroid available in France, Cotten et al recommended it for cervical infiltration or lumbar transforaminal infiltration.<sup>20</sup> Cotten et al also reported a study that cautioned against using ropivacaine with dexamethasone because ropivacaine can provoke crystallization of dexamethasone.<sup>20</sup> There were several studies that compared dexamethasone SP to particulate steroids such as betamethasone,<sup>30</sup> methylprednisolone acetate,<sup>31</sup> or triamcinolone<sup>32,33</sup> for TFESIs in radicular pain. Three studies concluded that dexamethasone and the particulate steroid comparator used had a similar effectiveness, with one study by Kennedy et al noting that the dexamethasone group had to receive a slightly higher number of injections to achieve the same outcomes as the triamcinolone group.<sup>32</sup> Another study by Kim and Brown commented that there did "seem to be some statistically non-significant trend toward [dexamethasone SP] being slightly less effective and of shorter duration than [methylprednisolone acetate]," which may need to be clarified by further studies.<sup>31</sup> A 2010 study by Park et al concluded that triamcinolone was more effective than dexamethasone for lumbar radiculopathy.<sup>33</sup> When there are radiculopathy cases that are refractory to conventional TFESIs, percutaneous epidural adhesiolysis (PEA) can be used.<sup>34</sup> PEA works by washing out inflammatory cytokines and drugs while also lysing the epidural fibrosis.<sup>34</sup> In a 2016 study by Cho et al, the efficacy of dexamethasone SP and triamcinolone acetate during PEA were compared. Forty patients received PEA with triamcinolone acetate 80 mg while 26 patients received PEA with dexamethasone SP 10 mg.<sup>34</sup> Cho et al concluded that dexamethasone was non-inferior to triamcinolone acetate based on success rate and percentage of the verbal numerical rating scale decrease 6 months after PEA.<sup>34</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>35</sup> Methylprednisolone acetate is the most frequently injected IT steroid and its use became popular in the 1960s and 1970s. However, the 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>36</sup> Additionally, none of the studies evaluating the use were controlled or blinded, so it is possible that the disease spontaneously remitted in all reports.<sup>36,37</sup> There have been no studies showing the superiority of IT steroids over other, more conventional routes.<sup>36</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>37</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>38</sup> Hydrocortisone, methylprednisolone, dexamethasone, betamethasone, prednisolone, and triamcinolone are the most commonly used corticosteroids for intra-articular injection.<sup>38</sup> The duration of action ranges from 6-21 days, with hydrocortisone and dexamethasone sodium phosphate providing the shortest action and triamcinolone hexacetonide the longest.<sup>38</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 durations and detrimental effects at high doses and durations,” concluding that while there are beneficial effects of intra-articular injections, the lowest effective dose should be used.<sup>38</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

<b>Types of Studies</b>	<b>Number of Studies</b>
Descriptive	0
Observational	0
Experimental <sup>12-17</sup>	6

Table 4. Number of studies by country

<b>Country</b>	<b>Number of Studies</b>
Austria <sup>12</sup>	1
Chile <sup>14</sup>	1
France <sup>16</sup>	1
Italy <sup>17</sup>	1
Sweden <sup>13</sup>	1
UK <sup>15</sup>	1
Total US: 0	
Total Non-US Countries: 6	

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 and nausea</b>					
Langmayr et al, 1995, Austria <sup>12</sup>	Double-blind, placebo-controlled prospective study	26 Patients who underwent surgery for a herniated lumbar disc <ul style="list-style-type: none"> <li>• Betamethasone (76.9%, mean 44 y)</li> <li>• Normal saline (76.9%, mean 40 y)</li> </ul>	<ul style="list-style-type: none"> <li>• Solu-Celestan® (betamethasone) (13)</li> <li>• Normal saline (13)</li> </ul>	Pain intensity (visual analogue pain scale), consumption of non-steroidal anti-inflammatory agents	“Intrathecal application of steroids provides short-lasting, statistically significant pain reduction after lumbar disc surgery. Benefits of intrathecal steroids are probably outweighed by the risks associated with violation of the dural barrier.”
Simsa et al, 2013, Sweden <sup>13</sup>	–	398 Patients (94.7%, mean 52 y ± 12)	<ul style="list-style-type: none"> <li>• Betapred® (betamethasone) (199)</li> <li>• Placebo (199)</li> </ul>	Post-operative pain assessed using a visual analogue scale	“In conclusion, betamethasone reduces immediate post-operative pain but did not affect chronic pain after 1 year or nausea. This was at the cost of an increased risk for patient-reported wound bleeding, but we consider the benefits to outweigh this complication.”
<b>Indication 2: Prevention of respiratory distress syndrome (RDS)</b>					
Collaborative Santiago Surfactant Group, 1998, Chile <sup>14</sup>	Randomized, multicenter, double-blind, placebo-controlled trial	370 Female patients with singleton pregnancies <33 weeks of gestation <ul style="list-style-type: none"> <li>• Thyrotropin-releasing hormone (0%, maternal age 27.7 y ± 6.8)</li> <li>• Placebo (0%, maternal age 28.2 y ± 6.9)</li> </ul>	<ul style="list-style-type: none"> <li>• Thyrotropin-releasing hormone (190)</li> <li>• Placebo (180)</li> </ul> <p>All patients received betamethasone phosphate</p>	Frequency of RDS, use of oxygen, neonatal mortality	“The combination of antenatal thyrotropin-releasing hormone and corticosteroids does not reduce the frequency of [RDS] or improve the outcome of preterm neonates compared with the use of corticosteroids alone.”

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Gamsu et al, 1989, UK <sup>15</sup>	Prospective, randomized, double-blind, multicenter trial	251 Females enrolled gave birth to 262 liveborn infants (0%, age not specified)	<ul style="list-style-type: none"> <li>• Betamethasone phosphate (126)</li> <li>• Placebo (125)</li> </ul>	Signs of respiratory distress, maximum respiratory rate, partial pressure of carbon dioxide and oxygen, arterial pH	“The UK Multicentre Trial contributes further evidence of the effectiveness of antenatal corticosteroids in the prevention of RDS in preterm infants. Its use should be restricted to women in whom glucocorticoids are not contraindicated because of maternal disease, severe hypertension or infection, including amnionitis, and it is most appropriately administered when delivery is likely to occur between 26 and 34 weeks gestation and within 8 days of treatment.”
<b>Indication 3: Asthma</b>					
Grandordy et al, 1987, France <sup>16</sup>	Double-blind randomized crossover design	<p>12 Patients with chronic severe asthma (66.7%, range 24-55 y)</p> <p>There were 2 parts to this study; only the first part is reported because betamethasone was used as an injection</p>	<ul style="list-style-type: none"> <li>• Betamethasone SP injection with placebo tablets (12)</li> <li>• Prednisolone tablets with placebo injection (12)</li> </ul>	Forced expiratory volume in one second (FEV1), forced vital capacity, cumulative dose-response curves, peak expiratory flow	“There was a significant increase in FEV1 while they were taking betamethasone but no prednisolone. Individual analysis of the data showed that FEV1 increased with betamethasone in nine patients and remained stable or decreased in three...There was no significant difference between the bronchodilator responses to cumulative doses of inhaled salbutamol when they were measured immediately before, on the last day of treatment with each steroid, and between steroid treatment periods.”

Indication 4: Enhancement of fetal lung maturity					
Rotmensch et al, 1999, Italy <sup>17</sup>	Prospective randomized trial	46 Pregnant women at risk for preterm delivery <ul style="list-style-type: none"> <li>• Betamethasone (0%, maternity age 28.4 y ± 4.3)</li> <li>• Dexamethasone (0%, maternity age 27.7 y ± 4.4)</li> </ul>	<ul style="list-style-type: none"> <li>• Bentelan® (betamethasone) (22)</li> <li>• Dexamethasone (24)</li> </ul>	Fetal heart rate characteristics and biophysical activities	“Both betamethasone and dexamethasone induce a profound, albeit transient, suppression of fetal heart rate characteristics and biophysical activities in the preterm fetus. However, the effect of betamethasone is more pronounced. Awareness of these phenomena might prevent unwarranted iatrogenic delivery of preterm fetuses.”

Abbreviations: –, not provided; FEV1, forced expiratory volume in one second; RDS, respiratory distress syndrome.

<sup>a</sup>As defined by authors.

Table 6. Dosage by indication – US

*No US studies from included studies*

Table 7. Dosage by indication – non-US countries

Indication	Dosage	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Pain <sup>12</sup> and nausea <sup>13</sup>	2 mL	–	–	Intrathecal	–
	12 mg	4 mg/mL	Solution	Intravenous	Once
Prevention of respiratory distress syndrome <sup>14,15</sup>	4-24 mg/day	4 mg/mL	–	Intramuscular	Once – 2 days
Asthma <sup>16</sup>	8 mg/day	–	–	Intramuscular	10 days
Enhancement of fetal lung maturity <sup>17</sup>	12 mg/day	–	–	Intramuscular	2 days

Abbreviation: –, not provided.

Table 8. Number of studies by combination

	<b>Combination Formula</b>	<b>Number of Studies</b>
Nominated	Betamethasone SP 3-4 mg/mL / Betamethasone acetate 3 mg/mL – intrathecal, intramuscular, soft tissue injection	0

Abbreviation: SP, sodium phosphate

Table 9. Compounded products – US

*No US studies from included studies*

Table 10. Compounded products – non-US countries

*No compounded products from included studies*

## *Results of interviews*

One hundred ninety-nine SMEs were contacted for interviews; 63 agreed to be interviewed, and 136 declined or failed to respond to the interview request. Eight SMEs discussed betamethasone acetate. Among these 8 SMEs, there were 5 medical doctors, 2 doctors of podiatric medicine, and 1 nurse practitioner. The SMEs specialized and/or were board-certified in allergy, dermatology, infectious disease, oncology, neurology, physical medicine and rehabilitation, and rheumatology, working in academic medical institutions, outpatient practice, and inpatient practice. The SMEs had been in practice for 10 to 52 years. Additional information was collected as part of the Expanded Information Initiative project, referred to as Phase 3, in which outreach was conducted to the nominators of the bulk drug substances to remedy information gaps in the initial nomination.

Most of the SMEs did not have any experience using betamethasone as an injection. One SME commented that they have only used the topical formulation of betamethasone and another SME stated that they do not use epidural or IT steroids but commented that they might be beneficial in patients with spinal metastases and tumors. Three SMEs mentioned that they do intra-articular, periarticular, and peritendinous injections of steroids for joint pain, or for psoriatic plaques or other inflammatory skin lesions if topical medications are not providing relief; however, they preferred either methylprednisolone or triamcinolone. One SME commented that they prefer the combination of betamethasone acetate and SP because it has both a short-acting and long-acting steroid. The SME uses this formulation “quite a bit” when treating patients with heel pain or plantar fasciitis.

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

One SME discussed the use of epidural steroid injections. There are 2 main types of epidural injections: transforaminal and interlaminar. In 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 in the event of a shortage a commercially available preserved product would be preferred over a preservative-free compounded product. The SME mentioned that theoretically it would be advantageous to have betamethasone sodium phosphate available as a single-agent product since it is a nonparticulate steroid and would therefore be safer for transforaminal use, but since the product would have to be compounded this would be a barrier to use. Interlaminar epidural injections are administered through the middle of the back and are less precise than transforaminal injections as the drug is not administered near the target nerve root. There is more variability in the steroids used for this technique as the injections are farther away from arteries that could cause complications; this allows prescribers the freedom to select which steroid to administer. While a preservative-free formulation would be preferred, there are no guidelines that indicate that one must be used, and the SME stated again that using a commercially available preserved product would still be preferable to using a compounded preservative-free product.

Regarding the need for a preservative-free product to be compounded, the SME stated the presence of a preservative is likely not significant when administering epidural steroids. There is a higher risk of inadvertently injecting a drug intrathecally with both transforaminal and interlaminar injections if the procedures are performed incorrectly, with interlaminar injections having a higher risk. The SME stated that preservatives could be problematic with IT administration, commenting that there is some animal

research that shows that preservatives may result in major complications if injected intrathecally. However, the SME stated that if the procedure is performed correctly, the needle should not enter the IT space. Typically, a dye is injected first to ensure proper placement of the needle prior to the injection of the steroid. Even if a preserved steroid is inadvertently administered into the IT space, there is no clear guidance that this will lead to complications (the most likely of which is nerve pain). Due to variability in technique and the risk of potential complications as a result, the SME stated that it is better to use a commercially available product because a contaminated product, even if administered perfectly, could still cause harm.

The SME did not see any clinical reason for steroids to be compounded for epidural use, stating that they have never needed to inject anything that is not commercially available. The SME also did not see a need for there to be a combination product with lidocaine, stating that some prescribers will mix the steroid with lidocaine as a dilutant prior to the procedure but there is no need for this to be available as a premixed product. Additionally, the SME said, “[W]e don’t know as much about anesthetics mixed in as we thought,” adding that there is preliminary research identifying anesthetics that are not safe.

As part of Phase 3, 1 nominator provided additional information regarding the products that are compounded using betamethasone SP.

Betamethasone SP is compounded as a 3 mg/mL solution for IM injection to treat inflammation administered once a day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in emergency rooms, offices, outpatient clinics, and other clinical settings. This product is needed because there is no betamethasone SP product commercially available. The commercially available betamethasone contains betamethasone acetate and betamethasone SP as well as the preservative benzalkonium chloride, to which patients can be allergic.

Betamethasone SP is compounded as a 4 mg/mL solution for IM injection to treat inflammation, administered once a day for multiple days. This product is used by practitioners as a non-patient-specific compounded product in emergency rooms, offices, outpatient clinics, and other clinical settings. This product is needed because there is no betamethasone SP product commercially available. The commercially available betamethasone contains betamethasone acetate and betamethasone SP as well as the preservative benzalkonium chloride, which patients can be allergic.

A roundtable discussion with representatives from a variety of practice settings was held to discuss the use of outsourcing facilities to obtain compounded products. Forty-three participants attended the event; refer to Table 15 for characteristics of the facilities that the participants represented. A prequestionnaire was also distributed to participants; refer to Tables 15-18 for results of the prequestionnaire.

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

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

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

Another theme regarding deciding what products to purchase from an outsourcing facility was focused on the utilization and volume of a product that is needed and the overall impact this would have on the pharmacy workload. Critical care areas, like the emergency department and operating room, typically have a high product utilization and overall turnover, leading to several participants obtaining products intended for use in these areas from outsourcing facilities. Participants stated that they evaluate the volume of product needed and the frequency with which that volume is needed compared to the time it would take pharmacy staff to prepare this volume. One participant commented that “we look at the impact that it’ll have on staff. If our staff are needing to batch, or if we need to mass produce these in particular to meet the patient demand, then those are the items that we’re going to look to potentially move out.” Another participant stated that, while they do not obtain a lot of products from outsourcing facilities, “when we do purchase from 503Bs, typically it would be if we just don’t have the capacity to keep up with what the demand is.” One participant also commented that they will obtain labor-intensive and more complicated products, like epidurals and cardioplegia solutions, from outsourcing facilities to reduce the workload on pharmacy staff. The coronavirus disease 2019 (COVID-19) pandemic has also impacted the operations of hospitals, as noted by one participant who stated that “it’s just really high volume, and the bigger the hospital, the higher the volume, especially when you have one disease state in half of your hospital” and another who expressed that “without 503B, we would’ve been in significant trouble.” One participant commented that “even though the number might be small [percent of products obtained from

outsourcing facilities], some of the reasoning is quite critical, and the amount of time that it saves is very significant for beyond what we're able to do and when." Additionally, challenges with recruiting and retaining pharmacy technicians impact decision-making, with one participant stating "it is not feasible for us to meet the high volume for some common medications to repackage or compound from commercial presentations to a convenient, ready-to-use dosage form or package. The outsourcing facilities thus become a force multiplier, if you will, to offset some of the shortages in staffing."

In addition to evaluating the workload on pharmacy staff, the type and capabilities of the facility also impacted the decision-making process. One participant commented that they do not have an established cleanroom and therefore perform sterile compounding in a segregated compounding area. United States Pharmacopeia (USP) <797> standards limit the beyond-use date that can be assigned to these products and, as the participant stated, "We obviously need to provide product with much [more] extensive beyond-use dating than we can provide." Several participants also commented that they do not perform high-risk compounding in-house and therefore, all of these products are outsourced. There are challenges with midsize hospitals being able "to operationalize testing compounds we make for extended stability." One participant stated, "We might make our own syringes if we could get extended dating, but I believe my operations colleagues don't always know how to do this and adhere to the letter of the law."

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

Standardization of products, including concentration, volume, and labeling, was also a driver for obtaining products from an outsourcing facility. However, such standardization may not always be possible. One participant stated that when evaluating similar facilities, you would expect them to have similar needs regarding the concentrations and volumes of products used. However, the products used in a facility are often developed in-house over decades based on physician and nurse requests, and more recently, appropriateness for an automated dispensing cabinet. As a result, one participant observed, "these practices had evolved somewhat disparately. Even if we had clinical practice guidelines, nobody was putting concentrations into those guidelines and volumes into those guidelines." This has led to challenges with obtaining certain products from outsourcing facilities. As another participant said, "I think we made 9 different epidural concentrations, all driven by anesthesia, and they want what they want, and 503Bs may not offer that. No one else in the country is buying that same concentration; a 503B isn't going to go through the expense of adding that to their product list." The participant also said that "similar with the ADCs [automated dispensing cabinets], we've run into situations where dextrose 50% goes on shortage and the 503Bs would be selling it in a syringe. For safety reasons and for crash cart reasons, without having to retrain thousands of nurses of where things are placed, they said, 'no, we can't have it, and that's too big, it won't fit, we want it in this format' and then we're stuck again because there's no 503B offering a format during that shortage that fits where it needs to go. Then we're stuck insourcing." Additionally, while a commercially available product may be available, the volume may not be appropriate. One participant stated that "3% saline, for instance, is sold in a 500 mL bag, but the clinical guideline is a 150 mL bolus. We're either going to draw that out or we're sending it to the ER

with stickers all over it saying only give 150 [mL].” The participant continued that “it would be great if the FDA could look at the size of the container that they’re approving and whether that’s a realistic dose: is it a unit dose, or isn’t it?”

Participants had differing opinions on the use of outsourcing facilities to obtain drugs during a shortage. Several participants stated that they will typically first restrict use of a drug on shortage, in order to conserve supply, before turning to an outsourcing facility. One participant commented that “most of the time, I will probably pursue restricting, conserving, and looking at all available options prior to going to an outsourcer on my end,” and another stated, “I can only think of one time in recent history where we went to an outsourcer.” One participant commented that “503Bs can’t accept the additional volume if it’s a true shortage. If you’re not with them pre-shortage, you’re not going to get products when you need it during the shortage” continuing that “typically in a shortage, you learn to live without them. You have to.” Additionally, in the event of the shortage being the result of lack of an API, outsourcing facilities are likely to be equally affected and unable to provide assistance. However, one participant stated that they first began working with outsourcing facilities because of shortages. This participant commented that “what the 503Bs are starting to do, some of the large ones, is that they are also conducting validation studies on API. If sterile becomes short, they quickly switch to producing through API, which [the] ASHP [American Society of Health-System Pharmacists] and the FDA allow.” This “adds a lot of flexibility so they can bounce back and forth and really try to insulate us from shortages.”

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

A few participants commented on the need for preservative-free products, particularly in pediatric patients. The example of methadone was provided as it is used for patients with neonatal abstinence syndrome but is only available as a preservative-containing product. So, there is a need for this product to be compounded from API as a preservative-free product. One participant stated that “if there’s not a preservative-free containing option, it really should be something that should be able to be compounded from bulk... especially for the pediatric patient population.” However, another participant from a children’s hospital said that they have never needed to use an outsourcing facility for preservative-free products. Preservative-free is also an issue for ophthalmic products; however, one participant observed this is more on the 503A side. One participant stated that obtaining ophthalmic products from outsourcing facilities has been a challenge and that there are products they would like to obtain from outsourcing facilities but are not able to, forcing them to compound them in-house. This participant also commented that there are 2 outsourcing facilities that compound ophthalmic products, but when they reviewed the facilities, they did not pass their internal quality standards; one facility had been banned from distributing products in California by the Board of Pharmacy. There is an additional challenge with obtaining cephalosporins and beta-lactams due to the potential cross-reactivity in patients with allergies. One participant stated that there are some cephalosporins they would like to obtain from an outsourcing facility but cannot because “they would have to build a separate cleanroom with a dedicated HVAC [heating, ventilation, and air conditioning], so you’re talking millions of dollars in investment for actually

very low volume. Right now, the ROI [return on investment] isn't there." Another participant stated that the concentrations required for ophthalmic antibiotics are not available, but the labor and risk of compounding these products in-house are not worth it.

A few participants commented on purchasing nonsterile products from outsourcing facilities. LET (lidocaine-epinephrine-tetracaine) gel, for use as a topical anesthetic, was the most commonly obtained product along with buffered lidocaine to put in J-Tips. Another participant stated that they obtain diclofenac suppositories from an outsourcing facility due to the high cost of indomethacin suppositories. One participant commented that most of the products they outsource are nonsterile products, generally for oral or topical administration due to a lack of commercially available products. The participant stated that they purchase low-dose naltrexone for oral use in patients with refractory fibromyalgia and ketamine troches for patients with chronic pain. The participant continued that while the evidence does not support many of the ingredients used in topical pain products, "there are select patients. It's very rare that taking that cream away from them actually causes more harm than good." A few participants commented that there is a gap in the market for nonsterile products, with one stating, "I think that there is a large opportunity for more nonsterile products to be produced by 503Bs." Another stated that as their facility grows and acquires more outpatient clinics, they receive a lot of questions regarding obtaining products for office use. The participant noted that they often have to refer these clinics to outsourcing facilities but stated "there's not many 503Bs [that] are doing the nonsterile for clinic use." As a result, the inpatient pharmacy is often asked to take on this role but "you don't have the space or the staff to do that."

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

Two participants commented on the use of glycerin at their facility. One stated that they purchase it from a 503A because they were not able to find an outsourcing facility that provides this product. The participant commented that glycerin is used in 3 different concentrations at their facility, 1 for ophthalmic

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

Four participants stated that they obtain sodium citrate as ready-to-use syringes for use as a locking solution in patients undergoing dialysis, with one commenting that “our nephrologists like it in place of heparin for some patients to keep the ports patent or so they don’t have to go to alteplase or some of the other drugs.” There is a commercially available product; however, it is only available as a 500 mL bag and the dose needed is typically less than 30 mL. If the syringes are prepared in-house, then the beyond-use date is limited to 12 to 24 hours depending on storage, which results in waste.

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

While none of the participants obtained sodium phosphate or aspartic acid from outsourcing facilities for use in cardioplegic solutions, a few commented that they do obtain cardioplegic solutions from outsourcing facilities. The del Nido formulation was the product most commonly obtained. One participant commented that they compound this formulation in-house because the outsourcing facilities did not offer the volume needed at their institution. Another participant commented that while they do obtain the del Nido formulation from an outsourcing facility, they also compound a proprietary formulation in-house. This participant observed that “it is complicated to do in-house. We do it on a Baxa 1200 or 2400, either one, compounder. Then we send it up to [*sic*] for pH and potassium testing. Obviously, then we’re confined to <797> beyond-use dates versus longer beyond-use dates that we get from the 503B.” Another participant commented that cardioplegic solutions are managed by the perfusion department, not the pharmacy, and they use the del Nido formulation as well as 3 other formulations.

The participants also discussed challenges with utilizing outsourcing facilities. One participant stated that their facility does not use outsourcing facilities because “it just hasn’t been financially, not just the money worth it, but just the lead time for how much time you have to give them and how much you have to.... It just isn’t worth the dating that they gave us or can give us.” Another commented that they obtain very little product from outsourcing facilities due to “the amount of work for vetting and continually validating quality of these 503B outsourcing facilities.” The participant stated that they have a robust validation process that takes several months and includes a site visit prior to purchasing from an outsourcing facility, followed by continuous reviewing of quality reports and warning letters. Another challenge has been the reliability of the outsourcing facility. One participant commented that “[t]raditionally, we’ve found 503Bs to be fairly unreliable, when we have partnered with certain ones, to be able to keep up with the volume. Everybody knows PharMEDium just closed, but we’ve had some other smaller 503Bs where we’ve had agreements for certain products to take it off our plate, and then lo and behold they’re shut down, or closed, or whatever it may be.” Minimum purchase amounts were also reported as a concern with one participant stating that “what we see consistently is the 503Bs, they want us to commit to giving them a certain volume, but then will not give us a reciprocal commitment or at least will not fulfill that reciprocal commitment. That’s a huge problem for us making that type of commitment, when we do ultimately have to split our volume in order to make sure that we consistently are able to take care of our patients.”

Another challenge was related to outsourcing facilities utilizing API to compound narcotics. One participant commented that this often worsens drug shortages due to the quotas that the Drug Enforcement Administration places on the quantity that can be produced. The participant stated that “they [outsourcing facilities] want to buy the product that we’re trying to buy to take care of our patients today, to sell us tomorrow. We really need the FDA to say that, especially for controlled substances, that 503Bs can consistently prepare those products so that we don’t end up with a shortage year after year after year and then chasing our tail. Also, we may actually want to tell 503Bs they can’t buy those products or that they’re limited in the amount of their ability to buy those products to make what are essentially copies of commercially available products because it actually induces the shortage in many ways.”

### *Results of survey*

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

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

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

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

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

Zero respondents (0% of 108 responses, where respondents were allowed to select multiple drug products) obtained betamethasone 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 betamethasone sodium phosphate prescribed or administered

*No respondents to survey distributed via professional medical associations*

Table 13. Reasons for using compounded betamethasone sodium phosphate

*No respondents to survey distributed via professional medical associations*

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

*No respondents to survey distributed via professional medical associations*

Table 15. Demographics of prequestionnaire respondents' facilities

<b>Type of Facility</b>	<b>Responses, n (N = 102)<sup>a</sup></b>
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 one type of facility.

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

Table 16. Reasons for obtaining products from outsourcing facilities

<b>Categories</b>	<b>Responses, n (N = 143)<sup>a</sup></b>
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, standardization projects as additional reasons for utilizing 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 and/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 anti-seizure medications, antiviral medications, topical pain, and oral tablets/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
Calcium chloride	1
Caffeine sodium benzoate	0
Cholecalciferol	1
Chromium chloride	0
Clonidine	0
Dexamethasone sodium phosphate	0
Diclofenac	0
Gentamicin	0

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

None of the above	8
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<sup>a</sup>Respondents were allowed to select multiple products.

## CONCLUSION

Betamethasone SP was nominated for inclusion on the 503B Bulks List as a preservative-free solution for IM and IV injection and in combination with betamethasone SP as a preservative-free suspension for IT injection and as a preserved suspension for IM and soft tissue injection to treat a variety of conditions. Betamethasone SP is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, Namibia, New Zealand, the UK, and the US.

From the literature review, 6 studies were included. In the included studies, betamethasone SP was used to treat pain and nausea, to prevent respiratory distress syndrome, to treat asthma, and to enhance fetal lung maturity as an IT, IM, and IV injection. In 1 study, the authors stated that while IT steroids significantly reduce pain after lumbar disc surgery, the benefits are probably outweighed by the risks. Another study found that betamethasone reduced immediate post-operative pain but not chronic pain and while there was an increased risk for wound bleeding, the benefits outweighed the risks. One study recommended the use of betamethasone SP for the prevention of respiratory distress syndrome, while another study concluded that the use of antenatal thyrotropin-releasing hormone and corticosteroids compared to corticosteroids did not reduce the frequency of respiratory distress syndrome or improve preterm neonatal outcomes. Two studies did not provide definitive conclusions regarding the use of betamethasone SP.

Most of the SMEs interviewed did not have experience with injecting betamethasone. The SMEs who performed steroid injections typically used either methylprednisolone or triamcinolone. One SME discussed the use of epidural steroid injections but did not see a clinical need for a compounded product. 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.

Zero 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.

## REFERENCES

1. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *Int J Soc Res Method.* 2005;8(1):19-32.
2. Colquhoun HL, Levac D, O'Brien KK, et al. Scoping reviews: time for clarity in definition, methods, and reporting. *J Clin Epidemiol.* 2014;67(12):1291-1294.
3. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. *Implement Sci.* 2010;5:69.
4. Peters MDJ, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. *Int J Evid Based Healthc.* 2015;13(3):141-146.
5. Munn Z, Peters MDJ, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review?: guidance for authors when choosing between a systematic or scoping review approach. *BMC Med Res Methodol.* 2018;18(1):143.
6. Blankenbaker DG, De Smet AA, Stanczak JD, Fine JP. Lumbar radiculopathy: treatment with selective lumbar nerve blocks--comparison of effectiveness of triamcinolone and betamethasone injectable suspensions. *Radiology.* 2005;237(2):738-741.
7. Brownfoot FC, Gagliardi DI, Bain E, Middleton P, Crowther CA. Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev.* 2013(8):CD006764.
8. Habib G, Artul S, Chernin M, Hakim G, Jabbour A. The effect of intra-articular injection of betamethasone acetate/betamethasone sodium phosphate at the knee joint on the hypothalamic-pituitary-adrenal axis: a case-controlled study. *J Investig Med.* 2013;61(7):1104-1107.
9. Habib G, Safia A. The effect of intra-articular injection of betamethasone acetate/betamethasone sodium phosphate on blood glucose levels in controlled diabetic patients with symptomatic osteoarthritis of the knee. *Clin Rheumatol.* 2009;28(1):85-87.
10. Leopold SS, Redd BB, Warne WJ, Wehrle PA, Pettis PD, Shott S. Corticosteroid compared with hyaluronic acid injections for the treatment of osteoarthritis of the knee: a prospective, randomized trial. *J Bone Joint Surg Am.* 2003;85(7):1197-1203.
11. Salem, II, Najib NM. Pharmacokinetics of betamethasone after single-dose intramuscular administration of betamethasone phosphate and betamethasone acetate to healthy subjects. *Clin Ther.* 2012;34(1):214-220.
12. Langmayr JJ, Obwegeser AA, Schwarz AB, Laimer I, Ulmer H, Ortler M. Intrathecal steroids to reduce pain after lumbar disc surgery a double-blind, placebo-controlled prospective study. *Pain.* 1995;62(3):357-361.
13. Simsa J, Magnusson N, Hedberg M, Lorentz T, Gunnarsson U, Sandblom G. Betamethasone in hernia surgery: a randomized controlled trial. *Eur J Pain.* 2013;17(10):1511-1516.
14. Collaborative Santiago Surfactant Group. Collaborative trial of prenatal thyrotropin-releasing hormone and corticosteroids for prevention of respiratory distress syndrome. *Am J Obstet Gynecol.* 1998;178(1 Pt 1):33-39.
15. Gamsu HR, Mullinger BM, Donnai P, Dash CH. Antenatal administration of betamethasone to prevent respiratory distress syndrome in preterm infants: report of a UK multicentre trial. *Br J Obstet Gynaecol.* 1989;96(4):401-410.

16. Grandordy B, Belmatoug N, Morelle A, De Lauture D, Marsac J. Effect of betamethasone on airway obstruction and bronchial response to salbutamol in prednisolone resistant asthma. *Thorax*. 1987;42(1):65-71.
17. Rotmensch S, Liberati M, Vishne TH, Celentano C, Ben-Rafael Z, Bellati U. The effect of betamethasone and dexamethasone on fetal heart rate patterns and biophysical activities: a prospective randomized trial. *Acta Obstet Gynecol Scand*. 1999;78(6):493-500.
18. Benedetti EM, Siriwetcharak R, Stanec J, Rosenquist RW. Epidural steroid injections: complications and management. *Tech Reg Anesth Pain Manag*. 2009;13(4):236-250.
19. Derby R, Lee SH, Date ES, Lee JH, Lee CH. Size and aggregation of corticosteroids used for epidural injections. *Pain Med*. 2008;9(2):227-234.
20. Cotten A. Epidural and transforaminal corticosteroid injections: towards reduced risks of neurological complications. *Diagn Interv Imaging*. 2018;99(4):187-188.
21. Schneider B, Varghis N, Kennedy DJ. Ideal corticosteroid choice for epidural steroid injections: a review of safety and efficacy. *Curr Phys Med Rehabil Rep*. 2015;3(2):151-158.
22. Candido KD, Knezevic N. Cervical epidural steroid injections for the treatment of cervical spinal (neck) pain. *Curr Pain Headache Rep*. 2013;17(2):314.
23. Celestone® Soluspan® [Package insert]. Schering Corporation. 2007.
24. Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev*. 2017;2017(3):CD004454.
25. Knezevic N, Jovanovic F, Voronov D, Candido K. Do corticosteroids still have a place in the treatment of chronic pain?. *Front Pharmacol*. 2018;9:1229.
26. Manchikanti L, Knezevic N, Navani A, Christo P, Limerick G, Calodney A. Epidural interventions in the management of chronic spinal pain: American Society of Interventional Pain Physicians (ASIPP) comprehensive evidence-based guidelines. *Pain Physician*. 2021;24:S27-S208.
27. Rathmell J, Benzon H, Dreyfuss P, et al. Safeguards to prevent neurologic complications after epidural steroid injections: consensus opinions from a multidisciplinary working group and national organizations. *Anesthesiology*. 2015;122(5):974-984.
28. Duszynski B. Spine Intervention Society position statement on best practices for epidural steroid injections in the setting of a preservative-free dexamethasone shortage. *Pain Med*. 2019;20(7):1277-1280.
29. Chun EH, Park HS. Effect of high-volume injectate in lumbar transforaminal epidural steroid injections: a randomized, active control trial. *Pain Physician*. 2015;18(6):519-525.
30. Denis I, Claveau G, Filiatrault M, Fugere F, Fortin L. Randomized double-blind controlled trial comparing the effectiveness of lumbar transforaminal epidural injections of particulate and nonparticulate corticosteroids for lumbosacral radicular pain. *Pain Med*. 2015;16(9):1697-1708.
31. Kim D, Brown J. Efficacy and safety of lumbar epidural dexamethasone versus methylprednisolone in the treatment of lumbar radiculopathy: a comparison of soluble versus particulate steroids. *Clin J Pain*. 2011;27(6):518-522.
32. Kennedy DJ, Plastaras C, Casey E, et al. Comparative effectiveness of lumbar transforaminal epidural steroid injections with particulate versus nonparticulate corticosteroids for lumbar

- radicular pain due to intervertebral disc herniation: a prospective, randomized, double-blind trial. *Pain Med.* 2014;15(4):548-555.
33. Park CH, Lee SH, Kim BI. Comparison of the effectiveness of lumbar transforaminal epidural injection with particulate and nonparticulate corticosteroids in lumbar radiating pain. *Pain Med.* 2010;11(11):1654-1658.
  34. Cho S, Park HS. Percutaneous epidural adhesiolysis with epidural steroid injection: a non-inferiority test of non-particulate steroids versus particulate steroids. *Pain Med.* 2016;17(9):1612-1619.
  35. Nelson DA, Landau WM. Intraspinial steroids: history, efficacy, accidentality, and controversy with review of United States Food and Drug Administration reports. *Neurosurg Q.* 2001;11(4):276-289.
  36. Bernat J. Intraspinial steroid therapy. *Neurology.* 1981;31:168-171.
  37. Nelson D, Landau W. Intraspinial steroids: history, efficacy, accidentality, and controversy with review of United States Food and Drug Administration reports. *J Neurol Neurosurg Psychiatry.* 2001;70(4):433-443.
  38. Wernecke C, Braun J, Dragoo J. The effect of intra-articular corticosteroids on articular cartilage: a systematic review. *Orthop J Sports Med.* 2015;3(5):2325967115581163.

## APPENDICES

### *Appendix 1. Search strategies for bibliographic databases*

#### MEDLINE search strategy

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process, and other nonindexed citations and daily 1946 to August 25, 2020
- Date last searched: August 26, 2020
- Limits: Humans (search hedge); English language
- Number of results: 738

1	betamethasone/	5933
2	(betadexamethason\$ adj3 acetat\$.tw.	0
3	(betamet?ason\$ adj3 acetat\$.tw.	122
4	(betamet?azon\$ adj3 acetat\$.tw.	0
5	(beta met?ason\$ adj3 acetat\$.tw.	3
6	(betadexamethason\$ adj3 phosphat\$.tw.	0
7	(betamet?ason\$ adj3 phosphat\$.tw.	290
8	(betamet?azon\$ adj3 phosphat\$.tw.	0
9	(beta met?ason\$ adj3 phosphat\$.tw.	6
10	or/1-9	6034
11	exp administration, intravenous/	143,188
12	infusions, parenteral/	26,253
13	injections/	42,600
14	injections, intramuscular/	31,026
15	injections, intra-articular/	7923
16	infusions, spinal/	159
17	exp injections, spinal/	16,122
18	epidural space/	4516
19	subarachnoid space/	4363
20	inject\$.tw.	743,208

21	infusion\$.tw.	245,146
22	(parenteral\$ adj2 (administ\$ or therap\$ or treat\$ or deliver\$)).tw.	12,232
23	intravenous\$.tw.	341,230
24	intra venous\$.tw.	576
25	intravascular\$.tw.	47,874
26	intra vascular\$.tw.	304
27	intramuscular\$.tw.	52,556
28	intra muscular\$.tw.	719
29	intraarticular\$.tw.	5504
30	intra articular\$.tw.	15,853
31	intrabursa\$.tw.	194
32	intra bursa\$.tw.	19
33	intrasynovial\$.tw.	284
34	intra synovial\$.tw.	28
35	periarticular\$.tw.	3662
36	peri articular\$.tw.	436
37	spinal\$.tw.	268,808
38	intraspinal\$.tw.	5054
39	epidural\$.tw.	42,241
40	extradural\$.tw.	6768
41	extra dural\$.tw.	142
42	peridural\$.tw.	2065
43	peri dural\$.tw.	6
44	caudal\$.tw.	45,736
45	intracaudal\$.tw.	11
46	arachnoid\$.tw.	8166

47	subarachnoid\$.tw.	35,759
48	intrathecal\$.tw.	23,858
49	intra thecal\$.tw.	76
50	or/11-49	1,669,037
51	and/10,50	1323
52	exp animals/ not humans/	4,728,467
53	51 not 52	901
54	limit 53 to english language	738

## Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: August 26, 2020
- Limits: Humans (search hedge); English language
- Number of results: 558

1	'betamethasone acetate'/de	332
2	'betamethasone sodium phosphate'/de	1392
3	'betamethasone acetate plus betamethasone sodium phosphate'/de	415
4	(betadexamethason* NEAR/3 acetat*):ti,ab,tn	0
5	(betamet\$ason* NEAR/3 acetat*):ti,ab,tn	186
6	(betamet\$azon* NEAR/3 acetat*):ti,ab,tn	3
7	('beta met\$ason*' NEAR/3 acetat*):ti,ab,tn	0
8	(betadexamethason* NEAR/3 phosphat*):ti,ab,tn	0
9	(betamet\$ason* NEAR/3 phosphat*):ti,ab,tn	409
10	(betamet\$azon* NEAR/3 phosphat*):ti,ab,tn	5
11	('beta met\$ason*' NEAR/3 phosphat*):ti,ab,tn	9
12	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	2123
13	'parenteral drug administration'/de	2165
14	'intramuscular drug administration'/de	71,723
15	'intraarticular drug administration'/exp	7419
16	'periarticular drug administration'/exp	248
17	'intravascular drug administration'/de	330
18	'intravenous drug administration'/exp	393,259
19	'injection'/exp	247,778
20	'intraspinal drug administration'/de	3460
21	'epidural drug administration'/de	8889
22	'intrathecal drug administration'/de	20,969

23	'intracaudal drug administration'/de	21
24	'epidural space'/de	6438
25	'subarachnoid space'/exp	12,957
26	'inject*':ti,ab	1,102,682
27	'infusion*':ti,ab	358,185
28	(parenteral* NEAR/2 (administ* OR therap* OR treat* OR deliver*)):ti,ab	18,351
29	'intravenous*':ti,ab	491,748
30	'intra venous*':ti,ab	1458
31	'intravascular*':ti,ab	68,796
32	'intra vascular*':ti,ab	693
33	'intramuscular*':ti,ab	75,728
34	'intra muscular*':ti,ab	1286
35	'intraarticular*':ti,ab	27,906
36	'intra articular*':ti,ab	21,215
37	'intrabursa*':ti,ab	270
38	'intra bursa*':ti,ab	30
39	'intrasynovial*':ti,ab	369
40	'intra synovial*':ti,ab	51
41	'periarticular*':ti,ab	6040
42	'peri articular*':ti,ab	792
43	'spinal*':ti,ab	370,408
44	'intraspinal*':ti,ab	7005
45	'epidural*':ti,ab	59,737
46	'extradural*':ti,ab	9118
47	'extra dural*':ti,ab	242
48	'peridural*':ti,ab	3002

49	'peri dural*':ti,ab	12
50	'caudal*':ti,ab	59,219
51	'intracaudal*':ti,ab	23
52	'arachnoid*':ti,ab	12,340
53	'subarachnoid*':ti,ab	51,036
54	'intrathecal*':ti,ab	35,492
55	'intra thecal*':ti,ab	242
56	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55	2,570,468
57	#12 AND #56	846
58	[animals]/lim NOT [humans]/lim	6,079,317
59	#57 NOT #58	680
60	#57 NOT #58 AND [english]/lim	558

*Appendix 2.1. Survey instrument for professional medical associations*

1. How familiar are you with the following terms?

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

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

- Yes
- No

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

- Intramuscular injection
- Intravenous injection
- Intrathecal suspension
- Soft tissue injection (ex: tendon, bursa, intra-articular)
- None of the above

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

- Allergic disorder
- Bursitis
- Cerebral edema
- Leukemia
- Multiple myeloma
- Multiple sclerosis
- Nephrotic syndrome
- Osteoarthritis, rheumatoid arthritis
- Primary intracranial tumor
- Systemic lupus erythematosus
- Tenosynovitis
- Trichinosis
- Tuberculosis of meninges
- Other (please explain) \_\_\_\_\_

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

- Yes
- No

6. I prescribe or administer betamethasone 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 betamethasone 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 betamethasone sodium phosphate
  - Other (please explain) \_\_\_\_\_
8. Do you stock non-patient-specific compounded betamethasone sodium phosphate at your practice?
- Yes
  - No
  - I'm not sure
9. I obtain compounded betamethasone 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 2.2. Survey instrument for professional medical associations*

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	<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 2.3. Survey instrument for pharmacy roundtable prequestionnaire*

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

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

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

*Appendix 3. Survey distribution to professional associations*

<b>Specialty</b>	<b>Association<sup>a</sup></b>	<b>Agreed/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 and/or Year 2 were not contacted in Year 3.