Summary Report

# Phytonadione

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# Frequently Used Abbreviations

| | |
|---|---|
| ADC | Automated dispensing cabinet |
| API | Active Pharmaceutical Ingredient |
| ASHP | American Society of Health-System Pharmacists |
| ED | Emergency department |
| EGFR | Epidermal growth factor receptor |
| EMA | European Medicines Agency |
| EU | European Union |
| FDA | US Food and Drug Administration |
| IRB | Institutional Review Board |
| IV | Intravenous |
| OR | Operating room |
| OTC | Over-the-counter |
| PT | Prothrombin time |
| ROA | Route of administration |
| SME | Subject matter expert |
| TPN | Total parenteral nutrition |
| 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 phytonadione (also known as vitamin K; UNII codes: A034SE7857 and S5Z3U87QHF), 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 phytonadione 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 phytonadione has been used historically and currently.[1-3] Assessment of study quality and risk of bias were not performed because the aim of this report was not to make specific recommendations on the use of this substance in clinical practice.[1,4,5] Rather, the aim was to summarize the available evidence on the use of phytonadione 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

Phytonadione was nominated for inclusion on the 503B Bulks List by Athenex Pharma Solutions and Fagron. Phytonadione was nominated for use in combination with additional Active Pharmaceutical Ingredients (API) (refer to Table 8).

Phytonadione was nominated for treatment and prevention of coumarin toxicity, hemorrhage, hemorrhagic disease of the newborn, hypoprothrombinemia, nutritional supplementation, osteoporosis, and vitamin K deficiency via a 0 to 20 mg/50 mL or 21 to 50 mg/100 mL intravenous (IV) solution in 5% dextrose or normal saline and a 0.5 to 10 mg prefilled syringe for IV or subcutaneous administration. In addition, phytonadione was nominated for reduction of infraorbital dark circles and wrinkles of the lower eyelids via a 2% topical product in combination with retinol, vitamin C, and vitamin E.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of phytonadione.[6-10]

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

- Compounded drug product may be the only product to effectively treat the indication for which it is intended to treat.
- May be necessary to compound strength or dosage form that is not commercially available.
- Patient sensitivity to manufactured product dyes, fillers, preservatives, and other excipients.
- Manufacturer backorders.
- Topical application of phytonadione, retinol, vitamin C and vitamin E is generally safer than bleaching and other alternative treatments for infraorbital dark circles and wrinkles of the lower eyelids since made of natural vitamins.
- No FDA-approved topical phytonadione cream.

## METHODOLOGY

### *Background information*

The national medicine registers of 13 countries and regions were searched to establish the availability of phytonadione products in the United States (US) and around the world. The World Health Organization, the European Medicines Agency (EMA), and globalEDGE were used to identify regulatory agencies in

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

Each medicine register was searched for phytonadione; name variations of phytonadione 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 phytonadione. 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: phytonadione, and topical administration or form (refer to Appendix 1 for full search strategies). A literature review was not conducted for injectable phytonadione products due to the availability of FDA-approved products for this ROA. Results were limited to human studies in English language. Searches were conducted September 8, 2020. In addition, the ECRI Guidelines Trust® repository was searched September 8, 2020 for clinical practice guidelines that recommended the use of phytonadione and provided sufficient information on dosing and administration.

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

#### Study selection

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

### *Interviews*

Semistructured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances phytonadione 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 phytonadione. Potential SMEs were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. Select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided oral informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were synthesized for qualitative data analysis.

In addition to interviews with individual SMEs, a roundtable discussion with pharmacists was held. Participants were identified through outreach to professional associations that would potentially purchase compounded products from outsourcing facilities. A prequestionnaire was distributed to those who agreed to participate to collect information about the types of facilities at which participants worked and the products they purchased from outsourcing facilities (refer to Appendix 2 for complete survey and *Results of survey* section for results of prequestionnaire). The roundtable lasted 60 minutes and was conducted via Zoom, audio recorded, and professionally transcribed. The transcriptions and notes were synthesized for qualitative data analysis.

### *Survey*

A survey was distributed to the members of professional medical associations to determine the use of phytonadione 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*

- Phytonadione is available as an FDA-approved injectable solution. Phytonadione is also available as an FDA-approved oral tablet.
- Phytonadione is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for phytonadione.
- Phytonadione is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, Namibia, New Zealand, Saudi Arabia, and the UK.

Table 1. Currently approved products – US[a]

| Active Ingredient | Concentration | Dosage Form | Route of Administration | Status | Approval Date[b] |
|---|---|---|---|---|---|
| Phytonadione | 1 mg/0.5 mL | Injectable | Injection | Prescription | Approved prior to 1/1/1982 |
| Phytonadione | 10 mg/mL | Injectable | Injection | Prescription | 7/25/1983 |

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

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

| Active Ingredient[b] | Concentration | Dosage Form | Route of Administration | Approved for Use | | |
|---|---|---|---|---|---|---|
| | | | | Country | Status | Approval Date[c] |
| Phytonadione | 1 mg/0.5 mL<br>10 mg/mL | Emulsion<br>Solution | Intravenous<br>Intramuscular<br>Subcutaneous | Abu Dhabi | Active | – |
| | | | | Australia | Not scheduled, not considered by committee | 10/9/1997 |
| | | | | Belgium | Medical prescription | 4/30/1961 |
| | | | | Canada | Prescription | 12/31/1989 |
| | | | | Hong Kong | Prescription only | 5/9/1988 |
| | | | | Ireland | Prescription-only, non-renewable | 4/6/1990 |
| | | | | Namibia | – | 11/11/2010 |
| | | | | New Zealand | General sale | 10/22/1993 |
| | | | | Saudi Arabia | Prescription | – |
| | | | | UK | Prescription-only medicine | 6/20/1996 |

Abbreviations: –, not provided; UK, United Kingdom.

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

[b]Includes products with active ingredient listed as phytomenadione or vitamin K1.

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

*Results of literature review*

## Study selection

Database searches yielded 225 references; 1 additional reference was identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 226 titles and abstracts were screened. After screening, the full text of 44 articles was reviewed. Ten studies were included; after multiple reports of the same study were merged, there were 6 included studies. Thirty-four studies were excluded for the following reasons: wrong study design (31 studies); FDA-approved formulation (2); and wrong substance (1).

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

## Characteristics of included studies

The 6 included studies were published between 2002 and 2020. 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: Germany, Hungary, Japan, and US.

A total of 231 patients participated in the 6 included studies. The number of patients in each study ranged from 10 to 126.

Outcome measures differed among the included studies and included: incidence of grade ≥ 2 skin rash, change of the vitamin K1 to placebo ratio, number of acneiform eruptions, capillary resistance, and bruises rated by patient and dermatologist.

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

## Use of phytonadione

Thirty-eight patients received phytonadione for bruising/purpura, administered topically twice daily as a 0.5-5% cream or ointment for 1-2 weeks. One hundred seventeen patients received phytonadione as prophylaxis and/or treatment for cetuximab or panitumumab-induced skin toxicity, administered topically twice daily as a 0.1% cream or ointment for 4-8 weeks.

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

Phytonadione was used as a compounded product (ointment), and it used in a combination product (refer to Tables 8-10).

In 2 studies, the authors concluded that the use of phytonadione was not recommended for the prophylaxis and/or treatment for cetuximab or panitumumab-induced skin toxicity[11] and bruising/purpura.[12] In 2 studies, the authors concluded that further studies were necessary for the prophylaxis for cetuximab or panitumumab-induced skin toxicity[13] and bruising/purpura.[14] In 1 study, the authors concluded that phytonadione did not prevent bruising after laser treatment but applying phytonadione post laser treatment reduced the severity of bruising.[15] In 1 study, authors did not provide a definitive conclusion for the use of phytonadione.[16] Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

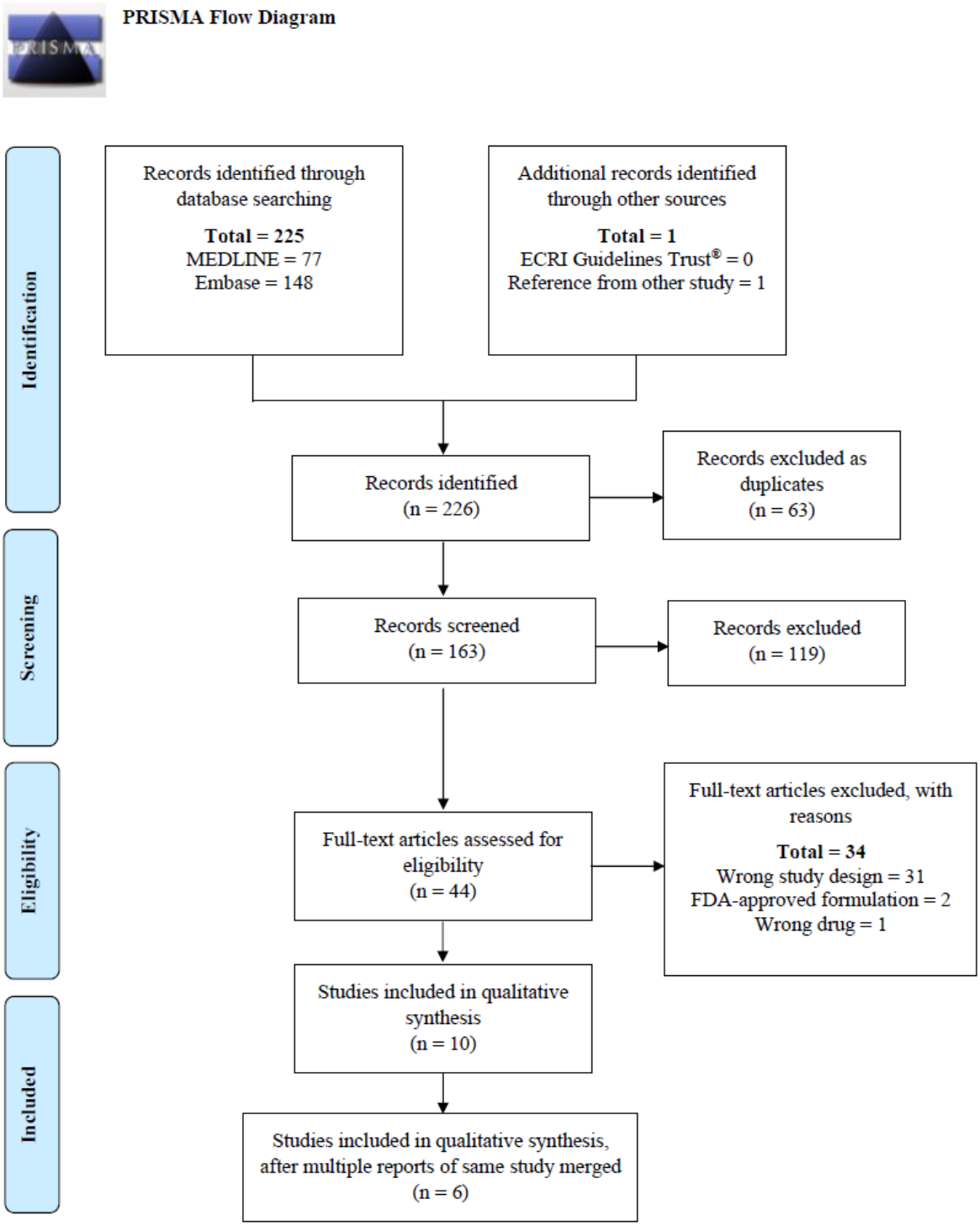
In addition to the 6 included studies, 9 additional studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of phytonadione.

Phytonadione, also known as vitamin K1 or phytomenadione, is found in green plants and becomes metabolized to vitamin K2 via vitamin K3 in humans.[8,13,15] Drugs such as cetuximab that inhibit the epidermal growth factor receptor (EGFR) may cause skin toxicities because EGFR is on "tumor cells, keratinocytes, cells of eccrine and sebaceous glands and in the epithelium of hair."[16] There was EGFR activation and "downstream signaling in human keratinocytes [when] exposed to [vitamin K3]."[16,17] According to a 2013 review of the treatment options for skin rash caused by EGFR-targeted therapies, Orvirk et al stated that "topical vitamin K1 treatment has demonstrated significant clinical efficacy in the absence of any toxicity, with the limited evidence favoring a prophylactic treatment approach."[18] At the time of that review, there were no completed randomized, controlled trials. Since then, a 2018 double-blinded, vehicle-controlled, randomized trial called EVITA (Evaluation of VITAmin K) by Hofheinz et al used vitamin K1 0.1% cream with doxycycline.[16] Hofheinz et al concluded that their "primary end point of decreasing grade $\geq$ 2 skin rash was not met [but] using vitamin K1 cream [prophylactically did decrease] the severity of acne-like skin rash according to [the scoring developed by Wollenberg and Moosmann called WoMo]."[16] Another randomized, double-blind, placebo-controlled study was conducted by Hashimoto et al in 2020 and concluded that topical vitamin K1 ointment was not effective for cetuximab or panitumumab-induced skin toxicities.[13] There were additional studies conducted between 2010-2017 that mentioned use of topical vitamin K1 for prophylaxis and/or cetuximab-induced skin toxicity that did not meet the literature review inclusion criteria.[19-24] Most of these additional studies concluded that topical vitamin K1 exhibited promising data.[19-24] Another combination with topical vitamin K used for cetuximab-induced skin toxicity was a vitamin K 0.1% and urea cream.[25]

Topical vitamin K is also used for the prevention and treatment of purpura even though there has been "no direct evidence to prove their efficacy," and the mechanism of action of topical vitamin K on treating purpura is unclear.[14,15] A 2002 study by Shah et al evaluated 22 patients for prevention and clearing of laser-induced purpura.[15] Half of the patients applied vitamin K 5% cream to half of their face and a placebo alone to the other half (pre-treatment group) while the other group followed the same application after laser treatment (post-treatment group).[15] Shah et al concluded that vitamin K pretreatment did not prevent bruising while "vitamin K cream after laser treatment did reduce the severity of bruising."[15] Another study by Kovacs et al, came to a similar conclusion using a topical vitamin K 0.5% cream and found that the clearing of bruising could not be confirmed in their study.[14] Another combination with topical vitamin K used in studies for purpura included a vitamin K 1% and retinol 0.3% cream.[12,26]

One study was found using the nominated topical formulation. In a 2004 study by Mitsuishi et al, a topical gel with phytonadione 2%/retinol 0.1%,/vitamins C and E 0.1% was used in 57 healthy volunteers with dark under-eye circles and wrinkles for 8 weeks.[8] Phytonadione was chosen due to some reports of it being able to reduce bruising after laser treatment.[8] Retinol was used due to its established safety for facial applications in the cosmetic field.[8] Vitamin E can decrease wrinkles while vitamin C has improved melasma and senile freckles in a human skin study.[8] Mitsuishi et al concluded that the topical combination gel was "fairly or moderately effective in reducing dark under-eye circles, especially in cases of [hemostasis]…[and] also slightly decreased wrinkles."[8]

Figure 1. PRISMA flow diagram showing literature screening and selection.




Adapted from:
Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006-1012. Available from: http://www.prisma-statement.org/.

Table 3. Types of studies

| **Types of Studies** | **Number of Studies** |
|---|---|
| Descriptive | 0 |
| Observational | 0 |
| Experimental[11-16] | 6 |

Table 4. Number of studies by country

| **Country** | **Number of Studies** |
|---|---|
| Germany[16] | 1 |
| Hungary[14] | 1 |
| Japan[11,13] | 2 |
| US[12,15] | 2 |
| | Total US: 2<br>Total Non-US Countries: 4 |

Table 5. Summary of included studies

| Author, Year, Country | Study Type[a] | Patient Population (% male, age) | Intervention/Comparator (No. of patients) | Primary Outcome Measure | Authors' Conclusions |
|---|---|---|---|---|---|
| **Indication 1: Bruising/purpura** | | | | | |
| Kovacs et al, 2004, Hungary[14] | Double-blind, placebo-controlled study | 10 Healthy individuals (20%, range 28-63 y) | • Vitamin K cream (not provided)<br>• Placebo (not provided) | Capillary resistance | "Our finding that vitamin K cream had no effect on [capillary resistance] ...showing that topical vitamin K was not effective in preventing laser-induced bruising…Contradictory data on the efficacy of vitamin K preparations might be caused by the differences in the concentration and vehicle in the different studies. Therefore, further investigations may be necessary to prove whether vitamin K cream is effective in treating bruising." |
| Leu et al, 2010, US[12] | Double-blinded randomized controlled trial | 16 Healthy volunteers (37.5%, range 21-65 y) | • Vitamin K 5% (16)<br>• Vitamin K and retinol 0.3% (16)<br>• Arnica 20% (16)<br>• White petrolatum (16)<br>All patients received the 4 interventions which were randomized to different bruises | Dermatologist rated the bruises via a visual analogue scale in standardized photographs after bruise creation and at week 1 and 2 | "Topical 20% arnica ointment may be able to reduce bruising more effectively than placebo and more effectively than low-concentration vitamin K formulations, such as 1% vitamin K with 0.3% retinol." |

| Author, Year, Country | Study Type[a] | Patient Population (% male, age) | Intervention/Comparator (No. of patients) | Primary Outcome Measure | Authors' Conclusions |
|---|---|---|---|---|---|
| Shah et al, 2002, US[15] | Double-blind, randomized, placebo-controlled study | 22 Patients who received or are going to receive laser treatment (gender and age not specified) | Each patient applied vitamin K cream to half of their face and vehicle alone to the other half. They were randomized to:<br>• Pretreatment group – before laser treatment (11)<br>• Posttreatment group – after laser treatment (11) | Bruising rated by patient and physician via visual analogue scale | "Although pretreatment with vitamin K did not prevent bruising after laser treatment, use of vitamin K cream after laser treatment did reduce the severity of bruising, particularly in the initial days of application." |
| **Indication 2: Prophylaxis and/or treatment for cetuximab or panitumumab-induced skin toxicity** | | | | | |
| Hofheinz et al, 2018, Germany[16]<br>Gaiser et al, 2018, Germany[27]<br>Gaiser et al, 2019, Germany[28] | Double-blind, vehicle-controlled, randomized phase II trial | 126 Patients who received cetuximab and FOLFIRI<br>• Doxycycline and vitamin K1 (70%, range 44-83 y)<br>• Doxycycline and vehicle (66.7%, range 24-84 y) | • Doxycycline and vitamin K1 cream (66)<br>• Doxycycline and vehicle (60) | Incidence of grade ≥ 2 skin rash | "The primary end point of decreasing grade 2 skin rash was not met. However, using vitamin K1 cream as part of prophylactic treatment decreased the severity of acne-like skin rash according to [the scoring developed by Wollenberg and Moosmann called WoMo], an alternative and more thorough skin toxicity scoring tool." |
| Hashimoto et al, 2020, Japan[13] | Randomized, double-blind, placebo-controlled phase II study | 29 Patients who developed acneiform eruptions after they received cetuximab or panitumumab (72.4%, range 31-78 y) | • Vitamin K1 ointment (29)<br>• Placebo ointment (29)<br>1 Ointment was applied to the right or left area while the other ointment was applied to the remaining area | Change of the vitamin K1 to placebo ratio, number of acneiform eruptions | "[Vitamin K] ointment was not effective against acneiform eruptions induced by treatment with cetuximab or panitumumab...The reassessment of number of administrations and [vitamin K1] concentration in the ointment, as well as the endpoint of skin lesions, are required before designing further studies." |

| Author, Year, Country | Study Type[a] | Patient Population (% male, age) | Intervention/Comparator (No. of patients) | Primary Outcome Measure | Authors' Conclusions |
|---|---|---|---|---|---|
| Ishikawa et al, 2015, Japan[11]<br>Nakajo et al, 2016, Japan[29]<br>Tsushima et al, 2015, Japan[30] | Multi-center, self-controlled, double-blinded randomized phase III trial | 28 Patients who received cetuximab (75%, range 48-87 y) | • Vitamin K1 containing moisturizing cream (28)<br>• Moisturizing cream (28)<br>One cream was randomized to the left or right side and the other cream was applied to the remaining side. | Incidence of grade ≥ 2 skin toxicity within 4 weeks | "Topical application of the [vitamin K1] cream was not effective in reducing the incidence of [cetuximab]-related skin reactions." |

Abbreviation: –, not provided.
[a]As defined by authors.
[b]Phytonadione is also vitamin K or K1; for accuracy, the substance name that the study authors used is presented in this table.

Table 6. Dosage by indication – US

| Indication | Dosage | Concentration | Dosage Form | Route of Administration | Duration of Treatment |
|---|---|---|---|---|---|
| Bruising/purpura[12,15] | Twice daily | 1-5% | Cream, ointment | Topical | 2 weeks |

Table 7. Dosage by indication – non-US countries

| Indication | Dosage | Concentration | Dosage Form | Route of Administration | Duration of Treatment |
|---|---|---|---|---|---|
| Prophylaxis and/or treatment for cetuximab or panitumumab-induced skin toxicity[11,13,16] | Twice daily | 0.1% | Cream, ointment | Topical | 4-8 weeks |
| Bruising/purpura[14] | Twice daily | 0.5% | Cream | Topical | 1 week |

Table 8. Number of studies by combination

| | Combination Formula[a] | Number of Studies |
|---|---|---|
| Nominated | Phytonadione 2% / Retinol 0.1% / Vitamin C not specified / Vitamin E not specified – topical cream | 0 |
| Others found in literature | Vitamin K 1% / Retinol 0.3%[12] | 1 |

[a]Phytonadione is also vitamin K or K1; for accuracy, the substance name that the study authors used is presented in this table.

Table 9. Compounded products – US

| Indication | Publication Year | Compounding Method | Dosage Form | Final Strength |
|---|---|---|---|---|
| Bruising/purpura[12] | 2010 | "All of the four topical agents were prepared by a licensed compounding pharmacy." | Ointment | 1%, 5% |

Table 10. Compounded products – non-US countries

| Indication | Compounding Method[a] | Dosage Form | Final Strength |
|---|---|---|---|
| Prophylaxis and/or treatment for cetuximab or panitumumab-induced skin toxicity[13] | The ointment was "prepared by thoroughly blending [vitamin K1] (100 mg) with white petrolatum (100 g). After the coloring fluid was prepared by dissolving the required amount of yellow food-grade coloring agent in purified water (2.5 mL)." | Ointment | 0.1% |

[a]Phytonadione is also vitamin K or K1; for accuracy, the substance name that the study authors used is presented in this table.

*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. Nine SMEs discussed phytonadione, including 1 medical doctor and 8 pharmacists. The SMEs specialized and/or were board-certified in dermatology and nutrition, working in academic medical institutions, inpatient practice, and outsourcing facilities. The SMEs had been in practice for 1 to 43 years.

One SME discussed the use of phytonadione in dermatology. While the SME had never used phytonadione to reduce dark circles and wrinkles around the eye, the SME theorized that phytonadione was being used to increase "the natural coagulability" and decrease "sort of bruising, or what's thought to be bruising under the eyes." The SME was not able to comment on the effectiveness, but mentioned that it was likely "super safe."

Eight SMEs discussed the use of phytonadione as a nutritional supplement. Every newborn receives an IM injection of vitamin K at birth to prevent hemorrhagic disease of the newborn. Breast milk is deficient in vitamin K and so the dose at birth "gives them a really good start." There is a need for this product to be preservative-free due to an increase in the number of parents that want their child to only receive preservative-free products. While there is a preservative-free product available, when that product is on backorder it becomes "a huge issue." The alternative would be to provide oral vitamin K, but the oral products are either "little microgram tablets that you get over the counter, or you have 5 mg tablets, and we need 1 [mg]. As a result, you either "have to give very small doses every day for a month or bigger doses a couple times over the next few weeks, so compliance is an issue, and the dosage form is an issue."

Vitamin K is a component of commercially available IV pediatric multivitamin products that is added to total parenteral nutrition (TPN) solutions. Supplemental vitamin K is often added to TPN solutions for neonatal and pediatric patients with liver complications or if a patient has an unrepaired atresia. Treatment of an atresia is usually surgery, but while the patient is waiting to undergo surgery, they can become deficient in vitamin K because they are unable to synthesize it. They will require supplementation in their TPN; however, 1 SME mentioned that they had only encountered 1 patient with a true vitamin K deficiency due to not having the flora required to synthesize it, but after the patient underwent surgery, the problem was resolved. The cause of other patients' vitamin K deficiency is typically an underlying liver disease.

Vitamin K is also a component of the commercially available adult multivitamin products for TPN solutions which is "usually more than adequate for most patients." As a result, vitamin K is rarely supplemented in adult TPN solutions with 1 SME providing the example that out of 100 adult TPN bags "maybe only 1 or 2" would require additional vitamin K to be added. Historically, older formulations of adult multivitamin products did not contain vitamin K and so there would be a need to supplement vitamin K in a patient's TPN. The vitamin K was either administered as "a low dose, a daily vitamin K added to PN [parenteral nutrition] or a once-a-week supplementation." However, now that newer multivitamin formulations contain vitamin K there is not a need for supplemental vitamin K to be added. One SME mentioned that "it's possible, you'd have patients with deficiency. My experience and understanding is that's also probably pretty uncommon." Another SME commented that typically in adults, vitamin K deficiency is due to an underlying condition; for example, in surgical patients or patients with liver disease.

Vitamin K is also used in patients with coagulation disorders. One of the big indicators that a patient has a vitamin K deficiency is a prolonged prothrombin time (PT) outside the context of liver disease, which increases a patient's risk of bleeding. However, the SME stated that "if you had somebody definitely that

was thrombocytopenic, and they have an elevated PT, everybody always, traditionally, will give them vitamin K regardless if they think they're vitamin K deficient."

While vitamin K is a component of commercially available multivitamin products, multivitamins are "the most problematic we have throughout the last several decades" regarding drug shortages. Several SMEs commented that the major exception to adding supplemental vitamin K to a TPN would be in the event of a multivitamin shortage. There is a commercially available product that can be used while the multivitamin is on shortage, but it has a concentration that is challenging to draw up the required dose for nutritional supplementation. The American Society of Parenteral and Enteral Nutrition recommends a daily dose of 150 mcg for adults, but the commercially available products are 2 mg/mL and 10 mg/mL. To overcome this challenge, some prescribers may provide a higher dose administered once weekly during these shortages, but this could be concerning if a patient is on an anticoagulant as the higher dose of vitamin K has the potential to reverse the anticoagulant. Having a lower concentration available would be beneficial during these shortage situations. Two SMEs also commented that the commercially available products are ampules that complicate the preparation of a TPN solution because a filter needle must be used. Additionally, for patients on a home TPN this would be challenging because "it's probably not really very feasible for patients to break an ampule in the home setting."

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

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

Participants were asked to discuss the decision-making process used at their facility to determine what products to obtain from an outsourcing facility. One major theme that emerged from this discussion was that many of the products purchased from outsourcing facilities are used in critical care areas, such as emergency departments (EDs) and operating rooms (ORs). 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 (ADCs) 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 ADC, stating that "operationally, if you have a stat medication or something that needs to be delivered within 10 to 15 minutes, if you're looking at us doing it, you're looking at a five-minute gown and glove. If we don't have somebody in the IV [intravenous] room, if you're doing 797 right, it's five minutes. It's four minutes to tube it. It's three minutes to make it, and then you have a dosage system or a camera system, a few minutes more. We are not able to meet that need or they're just contaminating the IV room if they are trying to do it."

Having ready-to-use products available also minimizes the need for compounding and product manipulations to occur on the floor. This can be especially beneficial in children's hospitals as they face a unique need in that they are already having to perform a lot of manipulations to products due to a lack of concentrations or sizes available. One participant commented that "at baseline, already, we manipulate about 80% of what we dispense to patients" and another stated that "there's a number of drugs that require additional manipulation, to get them to a concentration that's appropriate for kids." One participant stated that "we're trying to minimize compounding, expedite actual therapies to patients in that setting [operating room], minimize manipulations as much as possible." Similarly in the ED, 1 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, "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 the decision of what products to purchase from an outsourcing facility was focused on the use and volume of a product that is needed and the overall impact this would have on the pharmacy workload. Critical care areas, like the ED and OR, typically have a high product utilization and overall turnover leading to several participants obtaining products intended for use in these areas from outsourcing facilities. Participants stated that they evaluate the volume of product needed and the frequency in which that volume is needed compared to the time it would take pharmacy staff to prepare this volume. One participant commented that "we look at the impact that it'll have on staff. If our staff are needing to batch, or if we need to mass produce these in particular to meet the patient demand, then those are the items that we're going to look to potentially move out." Another participant, while they do not obtain a lot of products from outsourcing facilities, stated that "when we do purchase from 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, such as epidurals and cardioplegia solutions, from outsourcing facilities to reduce the workload on pharmacy staff. The COVID-19 pandemic has also impacted the operations of hospitals with 1 participant who stated that "it's just really high volume, and the bigger the hospital, the higher the volume, especially when you have one disease state in half of your hospital" and another who expressed that "without 503B, we would've been in significant trouble." One participant commented that "even though the number might be small [percent of products obtained from outsourcing facilities], some of the reasoning is quite critical, and the amount of time that it saves is very significant for beyond what we're able to do and when." Additionally, challenges with recruiting and retaining pharmacy technicians impact decision-making with one participant stating "it is not feasible for us to meet the high volume for some common medications to repackage or compound from commercial presentations to a convenient, ready-to-use dosage form or package. The outsourcing facilities thus become a force multiplier, if you will, to offset some of the shortages in staffing."

In addition to the evaluation of the workload on pharmacy staff, the type and capabilities of the facility also impacted the decision-making process. One participant commented that they do not have an established 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 extensive beyond-use dating than we can provide." Several participants also commented that they do not perform high-risk compounding in-house and therefore, all of these products are outsourced. There are challenges with mid-size hospitals being able "to operationalize testing compounds we make for extended stability."

One participant stated, “we might make our own syringes if we could get extended dating, but I believe my operations colleagues don’t always know how to do this and adhere to the letter of the law.”

One participant also commented on the impact that The Joint Commission has had on encouraging 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 labeled adequately, including in OR and other settings in which procedures are performed. USP <795> and <797> are applicable in OR 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, it was expected that they had 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 ADC. As a result, 1 participant observed, “these practices had evolved somewhat disparately, even if we had clinical practice guidelines, nobody was putting concentrations into those guidelines and volumes into those guidelines.” This has led to challenges with obtaining certain products from outsourcing facilities. As another participant said, “I think we made nine different epidural concentrations, all driven by anesthesia, and they want what they want and 503Bs may not offer that. If no one else in the country is buying that same concentration, a 503B isn’t going to go through the expense of adding that to their product list.” The participant continued that “similar with the ADCs, we’ve run into situations where dextrose 50% goes on shortage, and the 503Bs would be selling it in a syringe. For safety reasons and for crash cart reasons, without having to retrain thousands of nurses of where things are placed, they said, ‘no, we can’t have it, and that’s too big it won’t fit.’ We want it in this format, and then we’re stuck again because there’s no 503B offering a format during that shortage that fits where it needs to go. Then we’re stuck in sourcing.” Additionally, while a commercially available product may be available, the volume may not be appropriate. One participant stated that “3% saline for instance, is sold in a 500 mL bag, but the clinical guideline is a 150 mL bolus. We’re either going to draw that out or we’re sending it to the ER with stickers all over it saying only give 150 [mL].” The participant continued that “it would be great if the FDA could look at the size of the container that they’re approving and whether that’s a realistic dose: Is it a unit dose or isn’t it?”

Participants had differing opinions on the use of outsourcing facilities to obtain drugs during a shortage. Several participants stated that they will typically first restrict use of a drug on shortage, 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.” 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, 1 participant stated that they first began working with outsourcing facilities because of shortages. This participant commented that “what the 503Bs are starting to do, some of the large ones, is that they are also conducting validation studies on

API. If sterile becomes short, they quickly switch to producing through API, which ASHP [American Society of Hospital Pharmacists] and the FDA allows." This "adds a lot of flexibility so they can bounce back and forth and really try to insulate us from shortages."

A few participants commented on the use of API by outsourcing facilities. One commented that as long as they are conducting end-product sterility and stability testing and the product meets quality standards, they are not concerned with the starting ingredients. As long as buyers are familiar with regulations and know what to look for, another participant commented, there should not be any issues with purchasing products compounded starting from API. Another participant stated that as more outsourcing facilities began using API, they became more comfortable with them doing so. However, 1 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. There is a need for this product to be compounded from API as a preservative-free product. One participant stated that "if there's not a preservative-free containing option, it really should be something that should be able to be compounded for bulk... especially for the pediatric patient population." However, another participant from a children's hospital stated that the need for a preservative-free option has never been a reason why they have obtained a product from an outsourcing facility. Preservative-free is also an issue for ophthalmic products; however, 1 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; 1 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 is not worth it.

A few participants commented on purchasing nonsterile products from outsourcing facilities. Lidocaine-epinephrine-tetracaine (LET) 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 availability of commercial 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; "however, there are select patients. It's very rare that taking that cream away from them actually causes more harm than good." A few participants commented that there is a gap in the market for nonsterile products with 1 stating, "I think that there is a large opportunity for more nonsterile products to be produced by 503Bs." Another stated that as their

facility grows and acquires more outpatient clinics, they receive a lot of questions regarding obtaining products for office use. The participant noted that they often have to refer these clinics to outsourcing facilities but stated, “There’s not many 503Bs are doing the 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 non-sterile ingredients; however, there had been challenges with crystallization after storage. A few participants commented that there is a sterile alum powder available, which they purchase to compound in-house. One participant had concerns regarding this powder, stating that “I’ve talked to that company, but I’ve had some concerns for them because they don’t sell it as a drug. The owner was selling you a chemical, we’re selling you a bulk API. It’s just sterile. They were fuzzy and I never followed up but, when I asked about their process for verifying the sterility, as you would with a sterile product, we do USP [United States Pharmacopeia] <71> Sterility Testing. They couldn’t really give me an answer. They just say they tested for sterility.” The participants commented that alum is only needed a few times a year. However, as one participant observed, “When you need it, it’s an emergency” and another noting that it “is a challenge for anybody who has the cyclophosphamide-induced hemorrhagic cystitis.” As a result, 1 participant maintains a small inventory of alum product that is purchased from an outsourcing facility but “more times than not, they go unused and expire.” Another stated that they do not keep it in stock because there is a minimum purchase and there are only a few cases a year for whom they need to use alum. The participant had it STAT shipped when needed. Another participant stated that “we had a meeting with the head of urology who was baffled, why they’re even ordering it. He was like, ‘this is an old, really old [treatment]. I don’t even know why we’re using it’ and basically approved for us to not even make it anymore for now.”

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

Four participants stated that they obtain sodium citrate as ready-to-use syringes for use as a locking solution in patients undergoing dialysis with one commenting that “our nephrologists, like it in place of heparin for some patients to keep the ports patent or so they don’t have to go to alteplase or some of the other drugs.” There is a commercially available product; however, it is only available as a 500-mL bag

and the dose needed is typically less than 30 mL. If the syringes are prepared in-house, then the beyond-use date is limited to 12 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 for pH and potassium testing. Obviously, then we're confined to 797 beyond-use dates versus longer beyond-use dates that we get from the 503B." Another participant commented that cardioplegic solutions are managed by the perfusion department, not pharmacy, and they use del Nido solution as well as 3 other formulations.

The participants also discussed challenges with using outsourcing facilities. One participant stated that their facility does not use outsourcing facilities because "it just hasn't been financially, not just the money worth it, but just the lead time for how much time you have to give them and how much you have to... It just isn't worth the dating that they gave us or can give us." Another commented that they obtain very little product from outsourcing facilities due to the "the amount of work for vetting and continually validating quality of these 503B outsourcing facilities." The participant stated that they have a robust validation process that takes several months and includes a site visit prior to purchasing from an outsourcing facility, followed by continuous reviewing of quality reports and warning letters. Another challenge has been the reliability of the outsourcing facility. One participant commented "Traditionally, we've found 503Bs to be fairly unreliable, when we have partnered with certain ones, to be able to keep up with the volume. Everybody knows PharMEDium just closed. But we've had some other smaller 503Bs where we've had agreements for certain products to take it off our plate, and then lo and behold they're shut down, or closed, or whatever it may be." Minimum purchase amounts were also reported as a concern with 1 participant stating that "what we see consistently is the 503Bs, they want us to commit to giving them a certain volume, but then will not give us a reciprocal commitment or at least will not fulfill that reciprocal commitment. That's a huge problem for us making that type of commitment, when we do ultimately have to split our volume in order to make sure that we consistently are able to take care of our patients." Another challenge was related to outsourcing facilities utilizing API to compound narcotics. One participant commented that this often worsens drug shortages due to the quotas that the Drug Enforcement Administration (DEA) places on the quantity that can be produced. The participant stated that "they [outsourcing facilities] want to buy the product that we're trying to buy to take care of our patients today, to sell us tomorrow. We really need the FDA to say that, especially for controlled substances, that 503Bs can consistently prepare those products so that we don't end up with a shortage year after year after year, and then chasing our tail. Also, we may actually want to tell 503Bs, they can't buy those products or that they're limited in the amount of their ability to buy those products to make what are essentially copies of commercially available products, because it actually induces the shortage in many ways."

*Results of survey*

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

The respondent used phytonadione but not as an intravenous solution, subcutaneous solution, or topical cream.

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

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

Twenty-seven respondents (19% of 143 responses, where respondents were allowed to select multiple responses) 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 phytonadione from a 503B outsourcing facility (refer to Table 18).

Table 11. Characteristics of survey respondents

| **Terminal Clinical Degree** | **Responses, n (N = 1)** |
|---|---|
| Doctor of Medicine (MD) | 0 |
| Doctor of Osteopathic Medicine (DO) | 0 |
| Doctor of Medicine in Dentistry (DMD/DDS) | 0 |
| Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm) | 0 |
| Naturopathic Doctor (ND) | 1 |
| Nurse Practitioner (NP) | 0 |
| Physician Assistant (PA) | 0 |
| **Practice Setting** | **Responses, n (N = 1)** |
| Physician office or private practice | 1 |
| Outpatient clinic | 0 |

| | |
|---|---|
| Hospital or health system | 0 |
| Academic medical center | 0 |
| Emergency room | 0 |
| Operating room | 0 |

Table 12. Conditions for which phytonadione prescribed or administered

*No survey respondents provided this information*

Table 13. Reasons for using compounded phytonadione

*No survey respondents provided this information*

Table 14. Use of non-patient-specific compounded phytonadione

*No survey respondents provided this information*

Table 15. Demographics of prequestionnaire respondents' facilities

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

| | |
|---|---|
| Skilled nursing facility | 0 |
| Specialty hospital[b] | 4 |
| Trauma center | 5 |
| Urban hospital | 5 |
| **Number of Beds** | **Responses, n (N = 39)** |
| < 50 | 4 |
| 50-99 | 3 |
| 100-199 | 1 |
| 200-299 | 4 |
| 300-399 | 5 |
| 400-599 | 3 |
| > 600 | 19 |

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

Table 16. Reasons for obtaining products from outsourcing facilities

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

| | |
|---|---|
| Other[b] | 8 |

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

Table 17. Categories of products obtained from outsourcing facilities

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

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

Table 18. Products obtained from an outsourcing facility

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

| | |
|---|---|
| Atropine | 9 |
| Baclofen | 4 |
| Betamethasone | 0 |
| Biotin | 0 |
| Bupivacaine | 8 |
| Calcium chloride | 1 |
| Caffeine sodium benzoate | 0 |
| Cholecalciferol | 1 |
| Chromium chloride | 0 |
| Clonidine | 0 |
| Dexamethasone sodium phosphate | 0 |
| Diclofenac | 0 |
| Gentamicin | 0 |
| Glycerin | 1 |
| Hydroxyzine | 0 |
| Ketamine | 14 |
| Levocarnitine | 0 |
| Lidocaine | 8 |
| Lorazepam | 2 |
| Magnesium sulfate | 4 |
| Manganese chloride | 0 |
| Methylprednisolone | 0 |
| Midazolam | 15 |
| Mupirocin | 1 |
| Norepinephrine | 15 |
| Ondansetron | 0 |

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

[a]Respondents were allowed to select multiple products.

## CONCLUSION

Phytonadione was nominated for inclusion on the 503B Bulks List as an IV or subcutaneous solution for treatment and prevention of coumarin toxicity, hemorrhage, hemorrhagic disease of the newborn, hypoprothrombinemia, nutritional supplementation, osteoporosis, and vitamin K deficiency. In addition, phytonadione was nominated as a topical cream in combination with retinol, vitamin C, and vitamin E for reduction of infraorbital dark circles and wrinkles of the lower eyelids. Phytonadione is available as an injectable product in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, Namibia, New Zealand, Saudi Arabia, the UK, and the US. Phytonadione is not available as a topical product in any of the national medicine registers that were searched.

From the literature review, 6 studies were included. Vitamin K was used as a topical product to treat bruising/purpura and as prophylaxis and/or treatment for cetuximab or panitumumab-induced skin toxicity. In 2 studies, the authors concluded that the use of phytonadione was not recommended for the prophylaxis and/or treatment for cetuximab or panitumumab-induced skin toxicity and bruising/purpura. In 2 studies, the authors concluded that further studies were necessary for the prophylaxis for cetuximab or panitumumab-induced skin toxicity and bruising/purpura. In 1 study, the authors concluded that phytonadione did not prevent bruising after laser treatment but applying phytonadione post-laser treatment reduced the severity of bruising. In 1 study, authors did not provide a definitive conclusion for the use of phytonadione.

From the interviews, vitamin K is a component of commercially available adult and pediatric multivitamin products for addition to TPNs solutions. Additionally, vitamin K is administered as an intramuscular injection to all newborns to prevent hemorrhagic disease of the newborn. Supplemental vitamin K is often done in pediatric patients but rarely in adult patients with several SMEs commenting that outside of a multivitamin shortage there is not a need for supplemental vitamin K to be added to adult TPN solutions. In the event of a shortage, the commercially available vitamin K products are not convenient to use due to the concentration and because they are available as ampules. Vitamin K deficiency is often the result of an underlying condition, commonly liver disease. Patients with elevated PT typically also receive vitamin K even in the absence of deficiency to minimize the risk of bleeding. One SME who discussed the use of topical vitamin K was unable to comment on the effectiveness but mentioned that it was likely “super safe.”

From the survey responses, 1 out of 1 respondent used phytonadione but not via any of the nominated ROA/dosage forms. From the prequestionnaire, 0 respondents obtained phytonadione from a 503B outsourcing facility.

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## APPENDICES

*Appendix 1. Search strategies for bibliographic databases*

MEDLINE search strategy

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process, and other non-indexed citations and daily 1946 to September 4, 2020
- Date last searched: September 8, 2020
- Limits: Humans (search hedge); English language
- Number of results: 77

| | | |
|---|---|---|
| 1 | vitamin k 1/ | 1574 |
| 2 | (antih?emorrahgic adj vitamin$).tw. | 0 |
| 3 | f#tomenadion$.tw. | 1 |
| 4 | f#tonadion$.tw. | 0 |
| 5 | phyllochinon$.tw. | 1 |
| 6 | phylloquinon$.tw. | 804 |
| 7 | phthyl menadion$.tw. | 0 |
| 8 | phthylmenadion$.tw. | 0 |
| 9 | phytomenadion$.tw. | 53 |
| 10 | phytonadion$.tw. | 131 |
| 11 | (vitamin$ adj k 1).tw. | 287 |
| 12 | (vitamin$ adj k1).tw. | 1312 |
| 13 | or/1-12 | 2605 |
| 14 | administration, topical/ | 38,468 |
| 15 | administration, cutaneous/ | 22,105 |
| 16 | skin absorption/ | 11,700 |
| 17 | topical$.tw. | 105,809 |
| 18 | epicutaneous$.tw. | 2014 |
| 19 | transdermal$.tw. | 14,651 |
| 20 | ((cutaneous$ or dermal$ or skin) adj3 (absorb$ or absorpt$ or appl$)).tw. | 12,316 |

| | | |
|---|---|---|
| 21 | emulsions/ | 17,992 |
| 22 | exp gels/ | 52,139 |
| 23 | liniments/ | 123 |
| 24 | ointments/ | 12,796 |
| 25 | skin cream/ | 1037 |
| 26 | emulsion?.tw. | 33,269 |
| 27 | gel?.tw. | 308,738 |
| 28 | liniment?.tw. | 145 |
| 29 | ointment?.tw. | 11,878 |
| 30 | salve?.tw. | 341 |
| 31 | paste?.tw. | 12,526 |
| 32 | unguent$.tw. | 113 |
| 33 | lotion?.tw. | 2315 |
| 34 | cream?.tw. | 19,012 |
| 35 | or/14-34 | 548,012 |
| 36 | and/13,35 | 104 |
| 37 | exp animals/ not humans/ | 4,731,219 |
| 38 | 36 not 37 | 82 |
| 39 | limit 38 to english language | 77 |

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: September 8, 2020
- Limits: Humans (search hedge); English language
- Number of results: 148

| | | |
|---|---|---|
| 1 | ‘phytomenadione’/de | 4697 |
| 2 | (antih$emorrhagic NEAR/1 vitamin*):ti,ab,tn | 7 |
| 3 | ‘fitomenadion*’:ti,ab,tn | 1 |
| 4 | ‘fytomenadion*’:ti,ab,tn | 1 |
| 5 | ‘fitonadion*’:ti,ab,tn | 0 |
| 6 | ‘fytonadion*’:ti,ab,tn | 0 |
| 7 | ‘phyllochinon*’:ti,ab,tn | 3 |
| 8 | ‘phylloquinon*’:ti,ab,tn | 991 |
| 9 | ‘phthyl menadion*’:ti,ab,tn | 0 |
| 10 | ‘phthylmenadion*’:ti,ab,tn | 0 |
| 11 | ‘phytomenadion*’:ti,ab,tn | 121 |
| 12 | ‘phytonadion*’:ti,ab,tn | 223 |
| 13 | (vitamin* NEAR/1 ‘k 1’):ti,ab,tn | 1285 |
| 14 | (vitamin* NEAR/1 k1):ti,ab,tn | 968 |
| 15 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 | 5682 |
| 16 | ‘topical drug administration’/de | 82,867 |
| 17 | ‘cutaneous drug administration’/de | 668 |
| 18 | ‘transdermal drug administration’/de | 9079 |
| 19 | ‘skin absorption’/de | 8061 |
| 20 | ‘topical treatment’/de | 13,105 |
| 21 | ‘topical*’:ti,ab | 150,037 |
| 22 | ‘epicutaneous*’:ti,ab | 3418 |

| | | |
|---|---|---|
| 23 | ‘transdermal*’:ti,ab | 21,448 |
| 24 | ((cutaneous* OR dermal* OR skin) NEAR/3 (absorb* OR absorp* OR appl*)):ti,ab | 17,991 |
| 25 | ‘cream’/de | 9475 |
| 26 | ‘gel’/exp | 77,483 |
| 27 | ‘liniment’/de | 251 |
| 28 | ‘lotion’/de | 2871 |
| 29 | ‘ointment’/de | 17,942 |
| 30 | ‘paste’/de | 2524 |
| 31 | ‘salve’/de | 165 |
| 32 | ‘cream$’:ti,ab | 29,756 |
| 33 | ‘emulsion$’:ti,ab | 45,260 |
| 34 | ‘liniment$’:ti,ab | 234 |
| 35 | ‘lotion$’:ti,ab | 4014 |
| 36 | ‘ointment$’:ti,ab | 21,626 |
| 37 | ‘paste$’:ti,ab | 15,024 |
| 38 | ‘salve$’:ti,ab | 476 |
| 39 | ‘unguent*’:ti,ab | 240 |
| 40 | ‘gel$’:ti,ab | 363,022 |
| 41 | #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 | 722,104 |
| 42 | #15 AND #41 | 216 |
| 43 | [animals]/lim NOT [humans]/lim | 6,085,199 |
| 44 | #42 NOT #43 | 171 |
| 45 | #42 NOT #43 AND [english]/lim | 148 |

*Appendix 2.1. Survey instrument for professional medical associations*

1. How familiar are you with the following terms?

| | Very familiar | Somewhat familiar | Not familiar |
|---|---|---|---|
| Compounded drugs (medications prepared to meet a patient-specific need) | ○ | ○ | ○ |
| 503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need) | ○ | ○ | ○ |
| 503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription) | ○ | ○ | ○ |

2. Do you prescribe or administer phytonadione (vitamin K1) to your patients?
    - Yes
    - No
3. Do you prescribe or administer phytonadione (vitamin K1) by any of the following dosage forms and/or routes of administration? (check all that apply)
    - Intravenous solution
    - Subcutaneous solution
    - Topical cream
    - None of the above
4. I prescribe or administer phytonadione (vitamin K1) for the following conditions or diseases: (check all that apply)
    - Bleeding prophylaxis
    - Coumarin toxicity
    - Hemorrhage
    - Hemorrhagic disease of the newborn (HDN)
    - Hypoprothrombinemia
    - Nutritional supplementation
    - Osteoporosis prophylaxis
    - Reduce infraorbital dark circles and wrinkles of lower eyelids
    - Vitamin K deficiency
    - Other (please explain) _____
5. I prescribe or administer compounded phytonadione (vitamin K1) in combination with other active pharmaceutical ingredients as a multi-ingredient product.
    - Yes
    - No
6. I prescribe or administer phytonadione (vitamin K1) with my patients as the following: (check all that apply)
    - FDA-approved drug product
    - Compounded drug product
    - Over-the-counter drug product
    - Other (please explain) _____

7. I use compounded phytonadione (vitamin K1) 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 phytonadione (vitamin K1)
    - Other (please explain) _____
8. Do you stock non-patient-specific compounded phytonadione (vitamin K1) at your practice?
    - Yes
    - No
    - I'm not sure
9. I obtain compounded phytonadione (vitamin K1) 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) | ○ | ○ | ○ |
| 503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need) | ○ | ○ | ○ |
| 503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription) | ○ | ○ | ○ |

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

- None of the above

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

*Appendix 2.3. Survey instrument for pharmacy roundtable prequestionnaire*

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

| Specialty | Association[a] | Agreed/Declined, Reason for Declining |
|---|---|---|
| Anesthesiology | Society of Cardiovascular Anesthesiologists | Declined – failed to respond |
| Cardiology | American Academy of Cardiovascular Perfusion | Declined |
| | American Board of Cardiovascular Perfusion | Declined – failed to respond |
| | American Society of Extracorporeal Technology | Declined – failed to respond |
| Dermatology | American Academy of Dermatology | Declined – failed to respond |
| Naturopathy | American Association of Naturopathic Physicians | Agreed |
| Nephrology | American Society of Diagnostic and Interventional Nephrology | Declined |
| Ophthalmology | American Academy of Ophthalmology | Declined – failed to respond |
| | American Society of Cataract and Refractive Surgery | Agreed |
| | American Society of Retina Specialists | Declined |
| Podiatry | American Podiatric Medical Association | Agreed |
| Psychiatry | The International Society for Electroconvulsive Therapy and Neurostimulation | Agreed |
| Rheumatology | American College of Rheumatology | Agreed |
| Surgery | American Association of Neurological Surgeons | Declined – failed to respond |
| | American Association for Thoracic Surgery | Declined – failed to respond |
| | American College of Surgeons | Declined – failed to respond |
| | American Society for Reconstructive Microsurgery | Declined – failed to respond |
| Urology | Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction | Declined |
| Wound Care | Association for the Advancement of Wound Care | Declined – failed to respond |

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