Summary Report

Vitamin D3

Prepared for:

US Food and Drug Administration
Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
Grant number: 5U01FD005946-06

Prepared by:

University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI)
University of Maryland School of Pharmacy

December 2021

This report was supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award (U01FD005946) totaling $2,342,364, with 100 percent funded by the FDA/HHS. The contents are those of the authors and do not necessarily represent the official views of, nor an endorsement by, the FDA/HHS or the U.S. Government.

Table of Contents

Table of Tables

Frequently Used Abbreviations

API	Active pharmaceutical ingredient
EMA	European Medicines Agency
EU	European Union
FDA	US Food and Drug Administration
IM	Intramuscular
IV	Intravenous
IRB	Institutional Review Board
OTC	Over-the-counter
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 vitamin D3 (UNII code: 9VU1KI44GP), 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 vitamin D3 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 vitamin D3 has been used historically and currently.[1-3] Assessments of study quality and risk of bias were not performed because the aim of this report was not to make specific recommendations on the use of this substance in clinical practice.[1,4,5] Rather, the aim was to summarize the available evidence on the use of vitamin D3 and thereby assist the FDA to determine whether there is a need for the inclusion of this substance on the 503B Bulks List.

REVIEW OF NOMINATION

Vitamin D3 was nominated for inclusion on the 503B Bulks List by the Specialty Sterile Pharmaceutical Society (SSPS). Vitamin D3 was nominated for treatment of vitamin D3 deficiency via a 100,000 units/mL solution for intramuscular injection.

Nominators did not provide references from published peer-reviewed literature to describe the pharmacology and support the clinical use of vitamin D3.

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

- Prescriber or hospital preference for various strengths, combinations with other drugs, volumes, and/or final product containers for administration.
- Unsafe to expose the direct compounding area to hundreds of vials or ampoules and hundreds of aseptic manipulations during the compounding of a typical size batch for outsourcing facilities; a single vessel compounded from bulk active pharmaceutical ingredients (APIs) 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.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of vitamin D3 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 vitamin D3; name variations of vitamin D3 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 ROAs similar to those requested in the nominations.

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.5) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing vitamin D3. The availability of OTC products (yes/no) in the US and the ROAs of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

Search strategy

A medical librarian constructed comprehensive search strategies for Ovid MEDLINE and Embase. The search strategies used a combination of controlled vocabulary terms and keywords to describe 3 concepts: vitamin D3; intramuscular or intravenous administration; and therapeutic or preventative use in patients with vitamin D deficiency, chronic kidney disease, and hypoparathyroidism (refer to Appendix 1 for full search strategies). Results were limited to human studies in the English language. Searches were conducted on November 12, 2020. In addition, the ECRI Guidelines Trust® repository was searched on November 12, 2020, for clinical practice guidelines that recommended the use of vitamin D3 and provided sufficient information on dosing and administration.

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

Study selection

Studies in which vitamin D3 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 vitamin D3 was used in an unspecified dosage form or ROA; in a dosage form, ROA, or combination that was not nominated; mentioned briefly as a rescue treatment or as a previously failed treatment; used as the wrong drug or in an unspecified form of vitamin D; or vitamin D3 not used clinically. Studies in which vitamin D3 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 vitamin D3; setting; total number of patients; number of patients who received vitamin D3; patient population; indication for the use of vitamin D3; dosage form and strength; dose; ROA; frequency and duration of therapy; use of vitamin D3 in a combination product; use and formulation of vitamin D3 in a compounded product; use of vitamin D3 compared to FDA-approved drugs or other treatments; outcome measures; and authors' conclusions. One reviewer extracted data from the included studies; a second reviewer checked the data extraction.

Interviews

Semistructured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances vitamin D3 was used in a clinical setting. The systematic literature review and indication from the nomination were reviewed to identify medical specialties that would potentially use vitamin D3. Potential SMEs were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. Select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided verbal informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were synthesized for qualitative data analysis.

In addition to interviews with individual SMEs, a roundtable discussion with pharmacists was held. Participants were identified through outreach to professional associations that would potentially purchase compounded products from outsourcing facilities. A prequestionnaire was distributed to those who agreed to participate to collect information about the types of facilities at which participants worked and the products they purchased from outsourcing facilities (refer to Appendix 3 for complete survey and *Results of survey* section for results of prequestionnaire). The roundtable lasted 60 minutes and was conducted via Zoom, audio recorded, and professionally transcribed. The transcriptions and notes were synthesized for qualitative data analysis.

Survey

A survey was distributed to the members of professional medical associations to determine the use of vitamin D3 in clinical practice. The online survey was created using Qualtrics® software (refer to Appendix 3 for complete survey). A Google™ search was conducted to identify the professional associations in the US for the relevant medical specialties. An association's website was searched to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used. An email describing the project and requesting distribution of the survey to the association's members was sent to the identified person(s). Associations that declined, did not respond, or did not provide significant data in project Years 1 and 2 were not contacted for project Year 3 surveys.

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

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

The University of Maryland, Baltimore Institutional Review Board (IRB) and the US 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

- Vitamin D3 is not available as an FDA-approved product in the nominated dosage form and ROA. Vitamin D3 is available as FDA-approved combination oral products and combination intravenous products.
- Vitamin D3 is not available as an OTC product in the nominated dosage form and ROA. Vitamin D3 is available as various oral OTC products.
- There is a current United States Pharmacopeia (USP) monograph for vitamin D3.
- Vitamin D3 is not available in the nominated dosage form and ROA in any of the foreign registries searched.

Table 1. Currently approved products – US

No approved products in the US

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

No approved products in the selected non-US countries and regions

Results of literature review

Study selection

Database searches yielded 1776 references; 2 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 1394 titles and abstracts were screened. After screening, the full text of 350 articles was reviewed. Sixty-seven studies were included; after multiple reports of the same study were merged, there were 47 included studies. Two hundred eighty-three studies were excluded for the following reasons: wrong study design (186 studies); unspecified dosage form or ROA (50); non-nominated dosage form, ROA, or combination (26); wrong substance (10); no clinical use (5); unable to obtain full text (4); language other than English (2).

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

Characteristics of included studies

The 47 included studies were published between 1984 and 2020. There were 46 experimental studies and 1 observational study. The 46 studies were conducted in the following countries: Argentina, Australia, Austria, Belgium, Brazil, Canada, China, Colombia, Czech Republic, Denmark, Finland, France, Germany, Greece, Guatemala, Hong Kong, India, Iran, Ireland, Italy, Norway, Pakistan, Peru, Poland, Russia, Slovakia, Spain, South Korea, Sri Lanka, Sweden, Switzerland, Turkey, the UK, and the US.

A total of 7486 patients participated in the 47 included studies. The number of patients in each study ranged from 6 to 400.

Outcome measures differed among the included studies and included 25-hydroxyvitamin D3 [25(OH)D] concentrations, adverse events, asymmetric dimethylarginine levels, Beck Depression Inventory scores, blood pressure, bone mineral density and content, cytokine levels, duration of intubation, erythema, Female Sexual Functioning Index, fracture occurrence, hemoglobin A_{1c} levels, high-density lipoproteins, homeostasis model assessment insulin resistance index, itching, liver enzymes, low-density lipoproteins, migraine occurrence and severity, parathyroid hormone, renal function, Scandinavian Stroke Scale, serum adiponectin, total cholesterol, triglycerides, tuberculosis score, and urine albumin.

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

Use of vitamin D3

There were 1369 patients who received intramuscular vitamin D3 as a treatment for vitamin D deficiency or as supplementation, administered in doses ranging from 20,000 to 600,000 IU. Duration of treatment ranged from once to 450 days. Ninety-nine patients received intramuscular vitamin D3 as a treatment for insulin resistance, hyperglycemia, and/or diabetes mellitus, administered once or twice in doses ranging from 150,000 to 600,000 IU. Fifty-seven patients received intramuscular vitamin D3 for mechanical ventilation, administered in a dose of 300,000 IU either once or up to 3 times per week. Fifty-six patients received intramuscular vitamin D3 for chronic urticaria in a dose of 10 mg per week for 4 weeks. Fifty-one patients received intramuscular vitamin D3 for decompensated liver cirrhosis in a single dose of 300,000 IU. Forty-two patients received intramuscular vitamin D3 for diabetic nephropathy in a monthly dose of 50,000 IU for 6 months. Twenty-six patients received

intramuscular vitamin D3 for multiple sclerosis in a monthly dose of 300,000 IU for 6 months. Thirty-seven patients received intramuscular vitamin D3 for nonalcoholic fatty liver disease in a single dose of 600,000 IU. One hundred thirty-two patients received intramuscular vitamin D3 for tuberculosis in a monthly dose of 600,000 IU for 2 months. Forty-six patients received intramuscular vitamin D3 for ulcerative colitis in a single dose of 300,000 IU. Twenty patients received intramuscular vitamin D3 for venous thromboembolism in a single dose of 300,000 IU.

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

Vitamin D3 was not used as a compounded product, nor was it used in a combination product (refer to Tables 8-10).

In 20 studies, the authors' concluding statement recommended the use of intramuscular vitamin D3 for the treatment of vitamin D deficiency or supplementation, diabetes mellitus, pulmonary tuberculosis, decompensated liver cirrhosis, and multiple sclerosis.[6-24] In 21 studies, the authors concluded that further studies were necessary for the use of intramuscular vitamin D3 in the treatment of vitamin D deficiency or supplementation, stress-induced hyperglycemia, insulin resistance, and diabetes mellitus, mechanical ventilation, diabetic nephropathy, nonalcoholic fatty liver disease, ulcerative colitis, and venous thromboembolism.[25-44] There were 2 studies where the authors' concluding statement did not provide a recommendation regarding the use of intramuscular vitamin D3 for the treatment of vitamin D deficiency or supplementation and tuberculosis.[45,46] In 5 studies, the authors' concluding statements did not address the use of intramuscular vitamin D3 for the treatment of vitamin D deficiency or supplementation or chronic urticara.[47-51] One study was just the protocol; no conclusion was provided regarding the use of intramuscular vitamin D3 for lumbar disk herniation.[52] Refer to Table 5 for the 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 vitamin D3.

Vitamin D is a fat-soluble vitamin and an important nutrient for the absorption of intestinal calcium and phosphorous, cellular proliferation and differentiation, muscle function, and immunity.[53,54] There are 2 major forms of vitamin D: vitamin D2, or ergocalciferol, and vitamin D3, or cholecalciferol, which only differ in their side chain structure.[54] Both forms undergo metabolism in the liver, and while there is debate that vitamin D3 is more effective than vitamin D2, the 2011 report from the committee to review dietary reference intakes for vitamin D and calcium states that "firm conclusions about different effects of the 2 forms of vitamin D cannot be drawn," and goes on to say that "at low doses D2 and D3 are equivalent, but at high doses, D2 is less effective than D3."[54] However, "there is evidence from experimental animal data to suggest that D2 is less toxic than D3."[54]

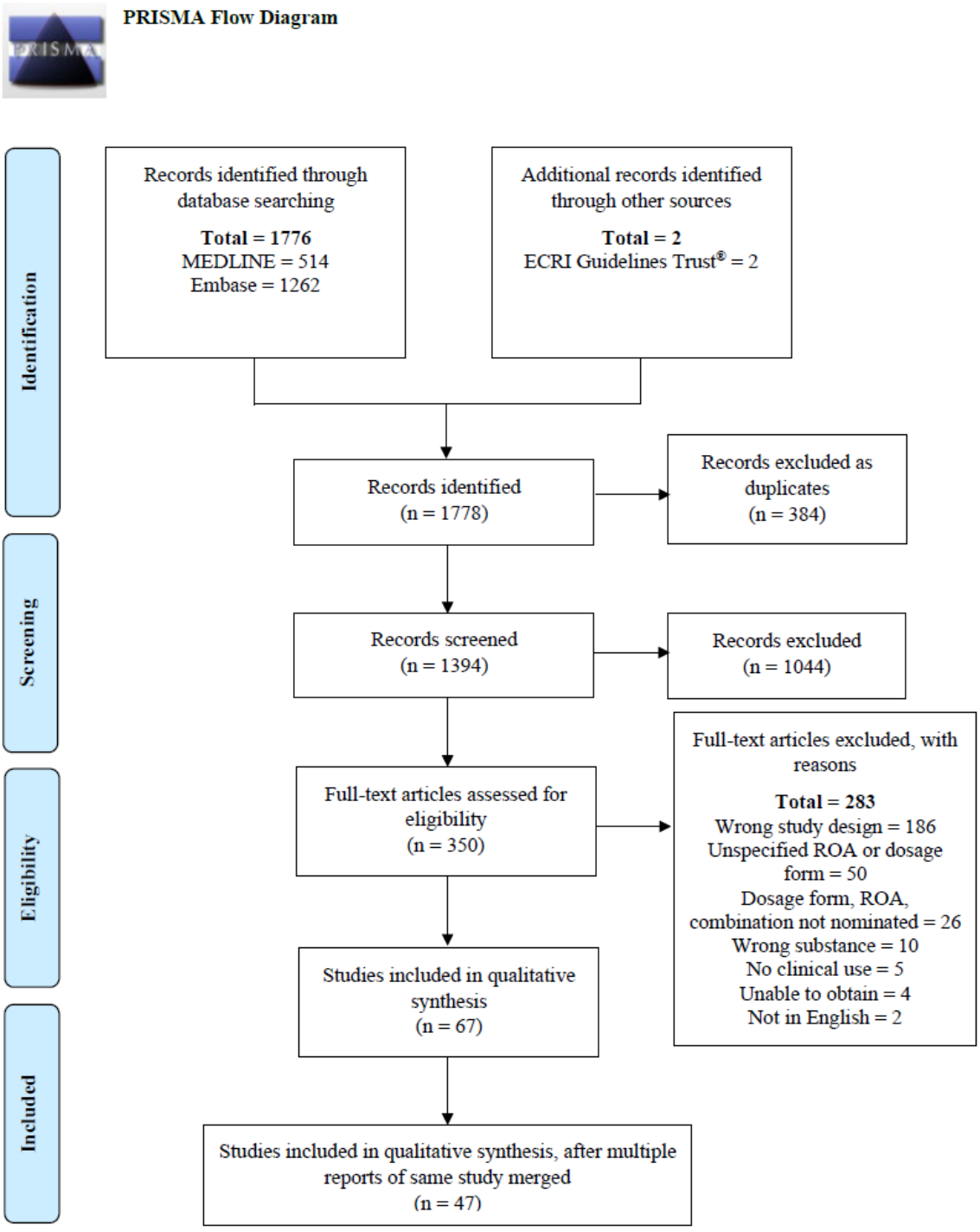
There are few natural sources of vitamin D, including salmon, mackerel, herring, cod liver oil, sardines, tuna, mushrooms, egg yolk, and ultraviolet B radiation.[55] However, several foods are fortified with vitamin D, including milk, orange juice, infant formulas, yogurt, butter, margarine, cheese, and breakfast cereals.[55] Recommended dietary allowances for vitamin D vary depending on age with those 0 to 12 months requiring 10 mcg (400 IU), 15 mcg (600 IU) for those 1 to 70 years, and 20 mcg (800 IU) for individuals over the age of 70.[54,56] To detect deficiency, a serum 25-hydroxyvitamin D (25(OH)D) level is typically measured.[54] Serum 25(OH)D levels less than 30 nmol/L are associated with vitamin D deficiency, levels from 30 to 50 nmol/L are generally considered inadequate, and levels greater than 50 nmol/L are considered adequate.[54] However, "despite multiple meta-analyses including large randomized clinical trials, the definition of

hypovitaminosis D and 'optimal' vitamin D status remains elusive" largely due to the use of unstandardized assays.[57] In 2017, the First International Conference on Controversies in Vitamin D was held to address and potentially resolve controversies that exist in vitamin D research.[57] The panel recommended that 25(OH)D levels less than 30 nmol/L "should be considered to be associated with an increased risk of rickets/osteomalacia" and that levels between 50 nmol/L and 125 nmol/L "appear to be safe and sufficient."[57]

The US Preventative Services Task Force published the results of a systematic review and meta-analysis in 2021 to update their evidence report regarding routine screening for deficiency in adults, but no studies were found that evaluated the benefits or harms of screening.[58] The report found that treatment of asymptomatic patients with low vitamin D levels "has no effect on mortality or the incidence of fractures, falls, depression, diabetes, cardiovascular disease, cancer, or adverse events."[58] The clinical practice guidelines from the Endocrine Society recommends that screening for deficiency only be done in those at risk of deficiency.[56] When treating deficiency, the Endocrine Society recommends that those 0 to 1 year old receive 2000 IU/day of vitamin D2 or D3 or 50,000 IU/week of vitamin D2 or D3 for 6 weeks followed by 400 to 1000 IU/day as maintenance.[56] For those 1 to 18 years old, the recommendation is for 2000 IU/day of vitamin D2 or D3 or 50,000 IU/week of vitamin D2 or D3 for at least 6 weeks followed by 600 to 1000 IU/day as maintenance.[56] Adults should receive 8000 IU/day of vitamin D2 or D3 or 50,000 IU/week of vitamin D2 or D3 for 8 weeks followed by 1500 to 2000 IU/day as maintenance.[56] Patients with malabsorption syndromes, obese patients, or if a patient is on a medication that can affect vitamin D metabolism, doses of at least 6000 to 10,000 IU/day of vitamin D2 or D3 are required, followed by maintenance doses of 3000 to 6000 IU/day.[56]

Vitamin D is currently available as ergocalciferol in 50,000 IU oral capsules and various oral OTC cholecalciferol products. Cholecalciferol is a component of intravenous adult and pediatric multivitamin products but there have been drug shortage issues with these preparations, with a shortage reported as recently as November 30, 2021; there are no single-agent injectable vitamin D products available.[59] The American Society of Parenteral and Enteral Nutrition released considerations for managing the multivitamin shortages with suggestions to switch to the oral or enteral route and to supplement the individual components as needed.[60]

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[6]	1
Experimental[7-52]	46

Table 4. Number of studies by country

Country	**Number of Studies**
Australia[32]	1
Belgium[16]	1
China[51]	1
Finland[48]	1
Germany[20]	1
India[11-14,24,27]	6
Iran[15,23,28,33-39,41-43,45,50,52]	16
Ireland[31]	1
Italy[8,25]	2
Pakistan[22,30,44]	3
South Korea[7,17,29,46]	4
Sri Lanka[40]	1
Sweden[10,18]	2
Switzerland[21,49]	2
Turkey[19,47]	2
UK[9]	1
US[6]	1

Multiple Countries • Argentina, Austria, Belgium, Brazil, Canada, Colombia, Czech Republic, Denmark, Finland, France, Greece, Guatemala, Hong Kong, Norway, Peru, Poland, Russia, Slovakia, Spain, Switzerland, Sweden, Turkey, UK, US[26]	1
	Total US[a]: 2 Total Non-US Countries[a]: 46

[a]Study 26 counted in both US and non-US total.

Table 5. Summary of included studies

Refer to Appendix 2

Table 6. Dosage by indication – US

Indication	Dosage	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Vitamin D deficiency or supplementation[6,26]	50,000-125,000 IU	—	—	Intramuscular	Once
	20,000-40,000 IU every 1-2 months				28-450 days

Abbreviations: —, not provided.

Table 7. Dosage by indication – non-US countries

Indication	Dosage	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Vitamin D deficiency or supplementation[7-20,25-34,44-50]	"6 lac IU"	—	—	Intramuscular	Once – 12 months
	50,000-600,000 IU	200,000-300,000 IU/mL	—		
	200,000-300,000 IU every 4-24 weeks				
	200,000 IU	—	Solution		
Insulin resistance, hyperglycemia, diabetes mellitus[21,35-37]	150,000-600,000 IU	300,000 IU/mL	—	Intramuscular	Once or twice
Mechanical ventilation[38,39]	300,000 IU	—	—	Intramuscular	Once
	300,000 IU up to 3 times per week				—
Chronic urticaria[51]	10 mg per week	—	—	Intramuscular	4 weeks
Decompensated liver cirrhosis[24]	300,000 IU	—	—	Intramuscular	Once
Diabetic nephropathy[40]	50,000 IU per month	200,000 IU/mL	—	Intramuscular	6 months
Lumbar disk herniation[52]	300,000 IU	300,000 IU/mL	—	Intramuscular	Once
Multiple sclerosis[23]	300,000 IU per month	—	—	Intramuscular	6 months
Nonalcoholic fatty liver disease[41]	600,000 IU	300,000 IU/mL	—	Intramuscular	Once
Tuberculosis[22]	600,000 IU per month	—	—	Intramuscular	2 months
Ulcerative colitis[42]	300,000 IU	300,000 IU/mL	—	Intramuscular	Once
Venous thromboembolism[43]	300,000 IU	—	—	Intramuscular	Once

Abbreviations: —, provided.

Table 8. Number of studies by combination

No combination products were nominated

Table 9. Compounded products – US

No compounded products from included studies

Table 10. Compounded products – non-US countries

No compounded products from included studies

Results of interviews

One hundred ninety-nine SMEs were contacted for interviews; 63 agreed to be interviewed, and 136 declined or failed to respond to the interview request. Nine SMEs discussed vitamin D3. Among these 9 SMEs, there were 8 pharmacists and 1 naturopathic doctor. The SMEs specialized and/or were board-certified in naturopathic medicine and nutrition, working in academic medical institutions, inpatient practice, outsourcing facilities, and consulting. The SMEs had been in practice for 8 to 43 years.

There are 7 different structural vitamin Ds, but vitamin D3, or cholecalciferol, is preferred because the binding proteins and receptors in the body have the highest affinity for it compared to other vitamin D molecules, resulting in better absorption. Cholecalciferol is a component of the adult multivitamin product that is added to total parenteral nutrition (TPN) solutions, and there were conflicting opinions on the need for a single-agent product in the high concentration nominated for availability. Two SMEs did not see a need for the product to be available with one stating that this is probably "a low-need product." The SME stated that there have been several papers published about vitamin D but commented that "nobody knows what to do with it. If your vitamin D level's low, what does it mean? It probably just means you have a poor diet, but it doesn't imply that your health is just going to completely deteriorate in days or weeks." The SME also said that studies have found that supplementation has "made no difference" and that they have only seen it cause hypercalcemia. One SME stated that if there is a need to supplement vitamin D in a deficient patient, they will administer large doses of the oral formulation and follow serial 25-hydroxyvitamin D levels to see if the patient improves. However, the SME stated that the only patients for whom they would supplement are ones for whom the SME was worried about the impact the deficiency could have on bone health, like a patient on long-term TPN.

However, several SMEs commented that there is a need for a single-agent product to be available. One SME stated that there are more conditions or diseases that "may be alleviated with vitamin D supplementation" and said that "of all of the supplements, that one has probably more evidence than any others." Another SME commented that the commercially available multivitamin products for use in TPN solutions have a low concentration and that patients on home parenteral nutrition or in the hospital for long periods of time can develop significant deficiencies. The SME referenced a study that found that close to 40% of home TPN patients were deficient. Another SME mentioned that they have several patients on home TPN with short bowel syndrome and the amount of vitamin D provided in the multivitamin products is "a fairly low amount and we find our patients routinely have even severe deficiency." When supplementation is needed for these patients, large doses of the oral formulations of either cholecalciferol or ergocalciferol are administered. This is not ideal because these patients often have malabsorption conditions that prevent absorption and as a result, the supplementation does not provide any increase in a patient's levels.

Two SMEs discussed the need for a single-agent product to be available for use in pediatric patients, stating that a single-agent product is needed. Similar to the adult multivitamin formulation, the pediatric multivitamin product for addition to TPN solutions also contains vitamin D3. However, children with short gut syndrome are unable to absorb enough fluids and nutrients and will require larger doses of vitamins. In some instances, the dose of multivitamins added to the TPN could be doubled, but with the current shortages of multivitamins this is not feasible. Since there is no single-agent product available, large doses of enteral vitamin D are administered and, as one SME stated, "hope they [patients] eat soon." However, not all of these patients will be able to transition off TPN, and malabsorption will likely always be a problem for these patients. One SME stated that these patients often have cholestasis and by eliminating, cholestasis absorption might be improved. One SME mentioned that they may also use multivitamins intended for use by patients with cystic fibrosis because patients with long-term short

bowel syndrome or patients with hyperbilirubinemia are often deficient in the fat-soluble vitamins due to cholestasis and these products have higher amounts of vitamins A, D, E, and K.

If a single-agent vitamin D3 product were available, most SMEs would prefer an intravenous (IV) formulation over an intramuscular (IM) formulation for both adult and pediatric patients. To administer an IM product, a patient must have a sufficient amount of lean body mass, but patients that are deficient in vitamin D have little to no fat or muscle, making an IM formulation not ideal. One SME stated that they try to avoid IM injections in pediatric patients, especially in the home setting, and another commented that "a lot of patients probably wouldn't do an intramuscular injection; they're usually okay doing a subcutaneous injection, and they do that with a vitamin B12 already." Additionally, depending on compatibility and stability, an IV formulation could be added to the TPN as well as used as an individual agent. One SME said that an injectable formulation would also be beneficial "because a lot of our babies are vitamin D deficient and there's nothing we can do for them," and these patients also have "horrible metabolic bone disease." Another SME mentioned that due to shortage issues surrounding both pediatric and adult multivitamins, having single-agent vitamin products available would be extremely useful to help lessen the impact while on shortage.

One SME discussed the use of IM vitamin D3, stating that typically, if a patient is deficient in vitamin D, the patient will be started on an oral trial, but this does not always raise the vitamin D level. As a result, the patient will be started on an IM repletion schedule approximately "100,000 IU IM once a week" for 9 weeks and then "take 3 weeks off as a washout, and then retest the levels." At that point, the patient can typically return to oral supplementation. Patients that require supplementation are typically those in whom there is an absorption problem, like a patient with Crohn's disease; however, some patients with competent gastrointestinal tracts will also require supplementation. Vitamin D3 is preferred because "there's very few metabolic steps [in] getting it active." The SME also stated that vitamin D3 injections are not uncommon "especially in the modern age where vitamin D levels are now important."

One SME mentioned that there was an IM product available but that the manufacturer stopped producing the product about 15 years ago, and another SME commented that there is a product available in Europe. Several SMEs said that vitamin D3 is difficult to formulate and "that may be in part why nobody's jumped into the market." Another SME stated that these products have typically been available from 503A pharmacies.

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 2 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, "We're always going to outsource a PCA [patient-controlled analgesia] syringe because we can store it in a Pyxis machine versus us making it and storing it in a fridge." Another participant commented on the benefits of storing medications in an automated dispensing cabinet, stating that "operationally, if you have a stat medication or something that needs to be delivered within 10 to 15 minutes, if you're looking at us doing it, you're looking at a 5-minute gown and glove. If we don't have somebody in the IV room, if you're doing <797> right, it's 5 minutes. It's 4 minutes to tube it. It's 3 minutes to make it, and then you have a dosage system or a camera system, a few minutes more. We are not able to meet that need or they're just contaminating the IV room if they are trying to do it."

Having ready-to-use products available also minimizes the need for compounding and product manipulations to occur on the floor. This can be especially beneficial in children's hospitals 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, "There's a number of drugs that require additional manipulation to get them to a concentration that's appropriate for kids." One participant said, "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, saying that "they would prefer to have a syringe form."

Another theme regarding deciding what products to purchase from an outsourcing facility 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 in which that volume is needed compared to the time it would take pharmacy staff to prepare this volume. One participant commented, "We look at the impact that it'll have on staff. If our staff are needing to batch, or if we need to mass produce these in particular to meet the patient demand, then those are the items that we're going to look to potentially move out." Another participant said 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 mentioned 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 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. 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 on 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 commercial product may be available, the volume may not be appropriate. One participant stated that "3% saline for instance, is sold in a 500-mL bag, but the clinical guideline is a 150-mL bolus. We're either going to draw that out or we're sending it to the ER with stickers all over it saying

only give 150 [mL].” The participant also said, “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 said, “503Bs can’t accept the additional volume if it’s a true shortage. If you’re not with them preshortage, you’re not going to get products when you need it during the shortage,” adding that “typically in a shortage, you learn to live without them. You have to.” Additionally, if the shortage is due to a scarce API, outsourcing facilities are likely to be equally affected and unable to provide assistance. However, one participant stated that they first began working with outsourcing facilities because of shortages. This participant commented that “what the 503Bs are starting to do, some of the large ones, is that they are also conducting validation studies on APIs. If sterile becomes short, they quickly switch to producing through APIs, which [the] ASHP [American Society of Health-System Pharmacists] and the FDA allow.” This “adds a lot of flexibility so they can bounce back and forth and really try to insulate us from shortages.”

A few participants commented on the use of 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 APIs. Another participant stated that as more outsourcing facilities began using APIs, they became more comfortable with them doing so. However, one participant observed that most outsourcing facilities are switching to sterile-to-sterile and only using APIs if there is a shortage, stating, “I think the FDA has really looked closely at APIs, 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 APIs 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 is 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 said 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 also said 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 said 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 said, "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 the 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 whom they need to use alum. The participant had it stat shipped when needed. Another participant stated, "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 [*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 pharmacy, and they use del Nido solution 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 [the] 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 FDA quality reports and warning letters. Another challenge has been the reliability of the outsourcing facility. One participant explained, "Traditionally, we've found 503Bs to be fairly unreliable, when we have partnered with certain ones, to be able to keep up with the volume. Everybody knows PharMEDium just closed, but we've had some other smaller 503Bs where we've had agreements for certain products to take it off our plate, and then lo and behold they're shut down, or closed, or whatever it may be." Minimum purchase amounts were also reported as a concern, with one participant stating that "what we see consistently is the 503Bs, they want us to commit to giving them a certain volume but then will not give us a reciprocal commitment or at least will not fulfill that reciprocal commitment. That's a huge problem for us making that type of commitment, when we do ultimately have to split our volume in order to make sure that we consistently are able to take care of our patients." Another challenge was related to outsourcing facilities utilizing APIs 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 the 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

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

Among respondents, 4 (100%) used vitamin D3. Respondents used vitamin D3 as an intramuscular solution (1, 25% of respondents) and as an unspecified ROA and/or dosage form (3, 75% of respondents). The one respondent used intramuscular vitamin D3 for vitamin D deficiency or insufficiency.

The one respondent used compounded vitamin D3 due to lack of commercial products in an appropriate dosage form, strength, or combination, patient allergies, and other patient conditions preventing use of commercial products. Refer to Table 13 for reasons for using compounded vitamin D3.

The one respondent who used compounded vitamin D3 did not stock non–patient-specific compounded vitamin D3 at their practice. The respondent obtained compounded vitamin D3 by purchasing, or having the patient purchase, the product from a compounding pharmacy or outsourcing facility. Refer to Table 14 for how respondents obtained compounded vitamin D3.

A prequestionnaire was distributed to participants of the roundtable discussion (refer to Appendix 3.2 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 use outsourcing facilities, and 4 (9%) did not respond to this question.

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

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

One respondent (0.9% of 108 responses, where respondents were allowed to select multiple drug products) obtained vitamin D3 from a 503B outsourcing facility (refer to Table 18).

Table 11. Characteristics of survey respondents

Terminal Clinical Degree	Responses, n (N = 4)
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)	4
Doctor of Nursing (DNP) or Master of Nursing (MSN)	0
Physician Assistant (PA)	0
Practice Setting	**Responses, n (N = 4)**
Physician office or private practice	4
Outpatient clinic	0
Hospital or health system	0
Academic medical center	0
Emergency room	0
Operating room	0

Table 12. Conditions for which vitamin D3 prescribed or administered

Condition	Responses, n (N = 1)
Vitamin D deficiency or insufficiency	1

Table 13. Reasons for using compounded vitamin D3

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

[a]Survey respondents were allowed to select multiple reasons.

Table 14. Use of non–patient-specific compounded vitamin D3

Do you stock non–patient-specific compounded vitamin D3 at your practice?	**Responses, n (N = 1)**
Yes	0
No	1
Not sure	0
How do you obtain your stock of non–patient-specific compounded vitamin D3?	**Responses, n (N = 2)[a]**
Compound yourself at practice	0
Product compounded by in-house pharmacy	0
Purchase from compounding pharmacy	1
Purchase from outsourcing facility	1

[a]Survey respondents were allowed to select multiple avenues.

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 were allowed to select more than one type of facility.
[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]
Back orders	20
Convenience	19
Cost	10
Need for concentrations not commercially available	19
Need for multi-ingredient products not commercially available	10
Need for preservative-free products	3
Need for ready-to-use products	27
No FDA-approved product available	7
No on-site compounding facility	1
On-site compounding facility not equipped to compound all necessary products	19
Other[b]	8

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

Table 17. Categories of products obtained from outsourcing facilities

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

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

[a]Respondents were 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

Vitamin D3 was nominated for inclusion on the 503B Bulks List as 100,000 units/mL solution for intramuscular injection to treat vitamin D3 deficiency. Vitamin D3 is not available in the nominated dosage form and ROA in any of the national medical registries searched.

From the literature review, 47 studies were included. Vitamin D3 was used as an IM injection as a vitamin D supplement or to treat vitamin D deficiency, insulin resistance, hyperglycemia, diabetes mellitus, mechanical ventilation, chronic urticaria, decompensated liver cirrhosis, diabetic nephropathy, lumbar disk herniation, multiple sclerosis, nonalcoholic fatty liver disease, tuberculosis, ulcerative colitis, and venous thromboembolism. While 20 studies recommended the use of IM vitamin D3, 21 studies stated that additional studies were needed. Vitamin D3 was not used as a compounded product in any of the included studies.

From the interviews, there were conflicting opinions on the need for a single-agent injectable vitamin D3 product. Some SMEs stated that while there is a lot of literature focused on supplementing vitamin D3, the results have not shown any benefit to supplementation. However, several SMEs stated that there is a need for a single-agent product to be available, especially for patients on home TPN and pediatric patients with malabsorption issues. Additionally, commercially available multivitamin products contain vitamin D3 but have been on shortage periodically and having a product available while the multivitamin is on shortage would be beneficial. While several SMEs would appreciate a single-agent vitamin D3 product to be available, most would prefer an IV formulation over an IM product. The SMEs stated that there are challenges with IM products in patients with poor nutritional status and that an IV formulation would not have the same issues and could be added to a TPN. However, one SME stated that IM supplementation with vitamin D3 is not a rare occurrence and discussed a protocol for IM supplementation.

From the survey responses, 1 out of 4 respondents used intramuscular vitamin D3. The most common indication respondents used compounded vitamin D3 for was vitamin D deficiency or insufficiency. Commercial products not available in the dosage form, strength, or combination needed, and patient allergies and patient conditions preventing the use of commercially available products were the reasons for using a compounded vitamin D3 product over an FDA-approved product. No respondents reported stocking compounded vitamin D3 in their practice. From the prequestionnaire, 1 respondent obtained vitamin D3 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. Bertino JS, Jr., Reed MD, Halpin TC, Jr. Prophylaxis and treatment of childhood rickets with parenteral cholecalciferol. *JPEN J Parenter Enteral Nutr.* 1984;8(5):556-559.
7. Choi HS, Chung YS, Choi YJ, Seo DH, Lim SK. Efficacy and safety of vitamin D3 B.O.N intramuscular injection in Korean adults with vitamin D deficiency. *Osteoporos Sarcopenia.* 2016;2(4):228-237.
8. Falasca K, Ucciferri C, Di Nicola M, Vignale F, Di Biase J, Vecchiet J. Different strategies of 25OH vitamin D supplementation in HIV-positive subjects. *Int J STD AIDS.* 2014;25(11):785-792.
9. Hamdy RC, Coles JA, Downey LJ. A comparative study of cholecalciferol, dihydrotachysterol and alfacalcidol in the treatment of elderly patients with hypocalcaemia. *Age Ageing.* 1987;16(3):178-180.
10. Hultin H, Stevens K, Sundbom M. Cholecalciferol injections are effective in hypovitaminosis D after duodenal switch: a randomized controlled study. *Obes Surg.* 2018;28(10):3007-3011.
11. Mondal K, Seth A, Marwaha RK, et al. A randomized controlled trial on safety and efficacy of single intramuscular versus staggered oral dose of 600 000IU Vitamin D in treatment of nutritional rickets. *J Trop Pediatr.* 2014;60(3):203-210.
12. Narasimhan S, Balasubramanian P. Role of vitamin D in the outcome of ischemic stroke—a randomized controlled trial. *J Clin Diagn Res.* 2017;11(2):CC06-CC10.
13. Rao YK, Midha T, Singh S, Bajpai A, Tilak A. Increment in vitamin D level and bone mineral accrual in children with vitamin D deficiency. *Korean J Pediatr.* 2016;59(7):292-297.
14. Reddy SV, Ramesh V, Bhatia E. Double blind randomized control study of intramuscular vitamin D3 supplementation in tropical calcific pancreatitis. *Calcif Tissue Int.* 2013;93(1):48-54.
15. Rostami M, Tehrani FR, Simbar M, et al. Effectiveness of prenatal vitamin D deficiency screening and treatment program: a stratified randomized field trial. *J Clin Endocrinol Metab.* 2018;103(8):2936-2948.
16. Rousseau AF, Foidart-Desalle M, Ledoux D, et al. Effects of cholecalciferol supplementation and optimized calcium intakes on vitamin D status, muscle strength and bone health: a one-year pilot randomized controlled trial in adults with severe burns. *Burns.* 2015;41(2):317-325.
17. Shin C. Effect of Vitamin D supplementation on symptoms in patients with migraine. *Eur J Neurol.* 2020;27:1089.

18. Sundbom M, Berne B, Hultin H. Short-term UVB treatment or intramuscular cholecalciferol to prevent hypovitaminosis D after gastric bypass—a randomized clinical trial. *Obes Surg.* 2016;26(9):2198-2203.

19. Tellioglu A, Basaran S, Guzel R, Seydaoglu G. Efficacy and safety of high dose intramuscular or oral cholecalciferol in vitamin D deficient/insufficient elderly. *Maturitas.* 2012;72(4):332-338.

20. Wylon K, Drozdenko G, Krannich A, Heine G, Dolle S, Worm M. Pharmacokinetic evaluation of a single intramuscular high dose versus an oral long-term supplementation of cholecalciferol. *PLoS One.* 2017;12(1):e0169620.

21. Jehle S, Lardi A, Felix B, Hulter HN, Stettler C, Krapf R. Effect of large doses of parenteral vitamin D on glycaemic control and calcium/phosphate metabolism in patients with stable type 2 diabetes mellitus: a randomised, placebo-controlled, prospective pilot study. *Swiss Med Wkly.* 2014;144:w13942.

22. Salahuddin N, Ali F, Hasan Z, Rao N, Aqeel M, Mahmood F. Vitamin D accelerates clinical recovery from tuberculosis: results of the SUCCINCT Study Supplementary Cholecalciferol in recovery from tuberculosis: a randomized, placebo-controlled, clinical trial of vitamin D supplementation in patients with pulmonary tuberculosis. *BMC Infect Dis.* 2013;13:22.

23. Mosayebi G, Ghazavi A, Ghasami K, Jand Y, Kokhaei P. Therapeutic effect of vitamin D3 in multiple sclerosis patients. *Immunol Invest.* 2011;40(6):627-639.

24. Jha AK, Jha Sharad K, Kumar A, Dayal VM, Jha Sanjeev K. Effect of replenishment of vitamin D on survival in patients with decompensated liver cirrhosis: a prospective study. *World J Gastrointest Pathophysiol.* 2017;8(3):133-141.

25. Cipriani C, Romagnoli E, Pepe J, et al. Long-term bioavailability after a single oral or intramuscular administration of 600,000 IU of ergocalciferol or cholecalciferol: implications for treatment and prophylaxis. *J Clin Endocrinol Metab.* 2013;98(7):2709-2715.

26. Colón-Emeric CS, Caminis J, Suh TT, et al. The HORIZON recurrent fracture trial: design of a clinical trial in the prevention of subsequent fractures after low trauma hip fracture repair. *Curr Med Res Opin.* 2004;20(6):903-910.

27. Gupta N, Farooqui KJ, Batra CM, Marwaha RK, Mithal A. Effect of oral versus intramuscular vitamin D replacement in apparently healthy adults with vitamin D deficiency. *Indian J Endocrinol Metab.* 2017;21(1):131-136.

28. Jalali-Chimeh F, Gholamrezaei A, Vafa M, et al. Effect of vitamin D therapy on sexual function in women with sexual dysfunction and vitamin D deficiency: a randomized, double-blind, placebo controlled clinical trial. *J Urology.* 2019;201(5):987-993.

29. Kim J, Nam JS, Kim H, Lee HS, Lee JE. No effect of vitamin D supplementation on metabolic parameters but on lipids in patients with type 2 diabetes and chronic kidney disease. *Int J Vitam Nutr Res.* 2021;91(5-6):649-658.

30. Masood MQ, Khan A, Awan S, et al. Comparison of vitamin D replacement strategies with high-dose intramuscular or oral cholecalciferol: a prospective intervention study. *Endocr Pract.* 2015;21(10):1125-1133.

31. McGreevy C, Barry M, Davenport C, et al. The effect of vitamin D supplementation on arterial stiffness in an elderly community-based population. *J Am Soc Hypertens.* 2015;9(3):176-183.

32. Nair P, Venkatesh B, Lee P, et al. A randomized study of a single dose of intramuscular cholecalciferol in critically ill adults. *Crit Care Med.* 2015;43(11):2313-2320.

33. Pourrashid MH, Dastan F, Salamzadeh J, Eslaminejad A, Edalatifard M. Role of vitamin D replacement on health related quality of life in hospitalized patients with “acute exacerbation of chronic obstructive pulmonary disease.” *Iran J Pharm Res.* 2018;17(2):801-810.

34. Zabihiyeganeh M, Jahed A, Nojomi M. Treatment of hypovitaminosis D with pharmacologic doses of cholecalciferol, oral vs intramuscular: an open labeled RCT. *Clinical Endocrinol.* 2013;78(2):210-216.

35. Alizadeh N, Khalili H, Mohammadi M, Abdollahi A, Ala S. Effect of vitamin D on stress-induced hyperglycaemia and insulin resistance in critically ill patients. *Int J Clin Pract.* 2016;70(5):396-405.

36. Heshmat R, Tabatabaei-Malazy O, Abbaszadeh-Ahranjani S, et al. Effect of vitamin D on insulin resistance and anthropometric parameters in Type 2 diabetes; a randomized double-blind clinical trial. *Daru.* 2012;20(1):10.

37. Mozaffari-Khosravi H, Hosseinzadeh-Shamsi-Anar M, Salami MA, Hadinedoushan H, Mozayan MR. Effects of a single post-partum injection of a high dose of vitamin D on glucose tolerance and insulin resistance in mothers with first-time gestational diabetes mellitus. *Diabet Med.* 2012;29(1):36-42.

38. Hasanloei MAV, Rahimlou M, Eivazloo A, Sane S, Ayremlou P, Hashemi R. Effect of oral versus intramuscular vitamin D replacement on oxidative stress and outcomes in traumatic mechanical ventilated patients admitted to intensive care unit. *Nutr Clin Pract.* 2020;35(3):548-558.

39. Yousefian M, Sadegi SRGP, Sakaki M. Vitamin D supplements’ effect on expediting the weaning process in patients with the stroke. *Electron J Gen Med.* 2019;16(2).

40. Liyanage P, Lekamwasam S, Weerarathna T, Liyanage C. Effect of vitamin D therapy on urinary albumin excretion, renal functions, and plasma renin among patients with diabetic nephropathy: a randomized, double-blind clinical trial. *J Postgrad Med.* 2018;64(1):10-15.

41. Hosseini SM, Aliashrafi S, Ebrahimi-Mameghani M. The effect of a single intramuscular injection of cholecalciferol on the serum levels of vitamin D, adiponectin, insulin resistance, and liver function in women with non-alcoholic fatty liver disease (NAFLD): a randomized, controlled clinical trial. *Iran Red Crescent Med J.* 2018;20(10).

42. Sharifi A, Vahedi H, Honarvar MR, et al. Vitamin D decreases CD40L gene expression in ulcerative colitis patients: a randomized, double-blinded, placebo-controlled trial. *Turk J Gastroenterol.* 2020;31(2):99-104.

43. Gholami K, Talasaz AH, Entezari-Maleki T, et al. The effect of high-dose vitamin D3 on soluble P-selectin and hs-CRP level in patients with venous thromboembolism: a randomized clinical trial. *Clin Appl Thromb Hemost.* 2016;22(5):483-489.

44. Fahan Rashid HM, Syed U, Ahmad Z, Chauhdary KK, Musharraf U, Kumar S. Comparison of different formulations of vitamin D. *J Ayub Med Coll Abbottabad.* 2017;29(4):650-653.

45. Jelveh-Moghaddam H, Fani K, Hekmat M, Azari AA. The effects of Vitamin D3 in pediatric patients undergoing congenital heart surgery. *J Cellular Molecular Anesthesia.* 2020;5(2):66-73.

46. Zhang D, Seo DH, Choi HS, Park HS, Chung YS, Lim SK. Effects of single vitamin D3 injection (200,000 units) on serum fibroblast growth factor 23 and sclerostin levels in subjects with vitamin D deficiency. *Endocrinol Metab.* 2017;32(4):451-459.

47. Imga NN, Berker D, Can B, Guler S. Effect of three regimens of cholecalciferol supplementation in vitamin D deficiency among obese and non-obese women. *Endocr Rev.* 2017;38(3).

48. Kilpinen-Loisa P, Arvio M, Ilvesmäki V, Mäkitie O. Vitamin D status and optimal supplementation in institutionalized adults with intellectual disability. *J Intellect Disabil Res.* 2009;53(12):1014-1023.

49. Mohammad J, Scanni R, Bestmann L, Hulter HN, Krapf R. A controlled increase in dietary phosphate elevates BP in healthy human subjects. *J Am Soc Nephrol.* 2018;29(8):2089-2098.

50. Moslemi L, Esmaeili Dooki M, Moghadamnia AA, et al. Stoss therapy using fortified biscuit for vitamin D-deficient children: a novel treatment. *Pediatr Res.* 2018;84(5):662-667.

51. Xiong X, Song L, Chen F, Ma X. Effects of combination of mizolastine and proteoglycan on chronic urticaria: a randomized controlled trial. *Arch Dermatol Res.* 2019;311(10):801-805.

52. Sedighi M, Haghnegahdar A. Role of vitamin D3 in treatment of lumbar disc herniation—pain and sensory aspects: study protocol for a randomized controlled trial. *Trials.* 2014;15:373.

53. Yu SB, Lee Y, Oh A, Yoo H-W, Choi J-H. Efficacy and safety of parenteral vitamin D therapy in infants and children with vitamin D deficiency caused by intestinal malabsorption. *Ann Pediatr Endocrinol Metab.* 2020;25(2):112-117.

54. IOM (Institute of Medicine). 2011. *Dietary Reference Intakes for Calcium and Vitamin D.* Washington, DC: The National Academies Press.

55. Holick MF. The D-lightful vitamin D for child health. *JPEN J Parenter Enteral Nutr*. 2012;36(suppl 1):9S-19S.

56. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2011;96:1911-1930.

57. Sempos CT, Heijboer AC, Bikle DD, et al. Vitamin D assays and the definition of hypovitaminosis D: results from the First International Conference on Controversies in Vitamin D. *Br J Clin Pharmacol.* 2018;84:2194-2207.

58. Kahwati LC, LeBlanc E, Weber RP, et al. Screening for vitamin D deficiency in adults: updated evidence report and systematic review for the US Preventative Services Task Force. *JAMA.* 2021;325(14):1443-1463.

59. US Food and Drug Administration. Drug shortages. Updated January 29, 2021. Accessed March 26, 2021. https://www.fda.gov/drugs/drug-safety-and-availability/drug-shortages.

60. Holcombe B. 2021 Parenteral nutrition multivitamin product shortage considerations. The American Society of Parenteral and Enteral Nutrition. Published 2021. Updated March 10, 2021. Accessed December 3, 2021. https://www.nutritioncare.org/Guidelines_and_Clinical_Resources/Product_Shortages/2021_Parenteral_Nutrition_Multivitamin_Product_Shortage_Considerations/.

61. Adachi JD, Lyles K, Boonen S, et al. Subtrochanteric fractures in bisphosphonate-naive patients: results from the HORIZON-recurrent fracture trial. *Calcif Tissue Int.* 2011;89(6):427-433.

62. Boonen S, Orwoll E, Magaziner J, et al. Once-yearly zoledronic acid in older men compared with women with recent hip fracture. *J Am Geriatr Soc.* 2011;59(11):2084-2090.

63. Lyles KW, Colón-Emeric CS, Magaziner JS, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med.* 2007;357(18):1799-1809.

64. Colón-Emeric C, Nordsletten L, Olson S, et al. Association between timing of zoledronic acid infusion and hip fracture healing. *Osteoporos Int.* 2011;22(8):2329-2336.

65. Gupta N, Mithal A, Mishra S, Batia CM, Singh S, Mapwaha RK. Effect of oral versus intramuscular vitamin D replacement in healthy Indians adults. *Osteoporos Int.* 2011;22:S588.

66. Kilpinen-Loisa P, Arvio M, Ilvesmäki V, Mäkitie O. Vitamin D status and optimal supplementation in institutionalized adults with intellectual disability. *Bone.* 2009;45:S88-S89.

67. Masood Q, Naureen G, Dar FJ, Khan AH. Assessing and monitoring serum vitamin D levels in patients with vitamin D deficiency at tertiary care hospital in Karachi, Pakistan. *Osteoporos Int.* 2013;24:S603.

68. Nair P, Venkatesh B, Hoechter DJ, et al. Vitamin D status and supplementation in adult patients receiving extracorporeal membrane oxygenation. *Anaesth Intensive Care.* 2018;46(6):589-595.

69. Bhatia E, Reddy SVB. Double-blind randomized study to determine the efficacy of intramuscular vitamin D3 supplementation in tropical chronic pancreatitis. *Endocr Rev.* 2011;32(3).

70. Tellioɨlu A, Başaran S, Güzel R. Effects of high dose intramuscular cholecalciferol and oral cholecalciferol on vitamin D levels and physical performance in elderly. *Turk Fiz Tip Rehab D.* 2011;57:260.

71. Zabihiyeganeh M, Ahmadi F, Jahed SA. Treatment of hypovitaminosis D with pharmacologic doses of cholecalciferol, oral versus intramuscular: an open labeled RCT. *Int J Rheum Dis.* 2012;15:102.

72. Zabihiyeganeh M, Jahed S, Nekooghadam S, Ahmadi F. Treatment of vitamin D deficeincy with cholecalciferol, which route is the best? *Int Med J.* 2012;42:27-28.

73. Liyanage PLGC, Lekamwasam S, Weerarathna TP, Liyanage C. Effect of vitamin D therapy on bone mineral density among patients with diabetic nephropathy: a randomized, double-blind placebo controlled clinical trial. *Osteoporos Int.* 2015;26(1):S230.

74. Liyanage GC, Lekamwasam S, Weerarathna TP, Liyanage CE. Effects of high-dose parenteral vitamin D therapy on lipid profile and blood pressure in patients with diabetic nephropathy: a randomized double-blind clinical trial. *Diabetes Metab Syndr.* 2017;11(suppl 2):S767-S770.

75. Rao N, Hasan Z, Ali F, Mahmood F. Supplementary cholecalciferol in recovery from pulmonary tuberculosis. *Eur Respir J.* 2012;40.

76. Sharifi A, Hosseinzadeh-Attar MJ, Vahedi H, Nedjat S. A randomized controlled trial on the effect of vitamin D3 on inflammation and cathelicidin gene expression in ulcerative colitis patients. *Saudi J Gastroenterol.* 2016;22(4):316-323.

77. Sharifi A, Vahedi H, Nedjat S, Mohamadkhani A, Hosseinzadeh Attar MJ. Vitamin D decreases beck depression inventory score in patients with mild to moderate ulcerative colitis: a double-blind randomized placebo-controlled trial. *J Diet Suppl.* 2019;16(5):541-549.

78. Sharifi A, Vahedi H, Nedjat S, Rafiei H, Hosseinzadeh-Attar MJ. Effect of single-dose injection of vitamin D on immune cytokines in ulcerative colitis patients: a randomized placebo-controlled trial. *APMIS.* 2019;127(10):681-687.

79. Javad Hosseinzadeh-Attar M, Sharifi A, Nedjat S, Mohamadkhani A, Vahedi H. The effect of vitamin D on serum asymmetric dimethylarginine in patients with mild to moderate ulcerative colitis. *Int J Vitam Nutr Res.* 2020;90(1-2):17-22.

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 November 11, 2020
- Date last searched: November 12, 2020
- Limits: Humans (search hedge); English language
- Number of results: 514

1	cholecalciferol/	7394
2	c?olecalciferol$.tw.	2581
3	hydroxyc?olecalciferol$.tw.	1392
4	hydroxyvitamin$ d3.tw.	2625
5	hydroxyvitamin$ d 3.tw.	464
6	oleovitamin$ d3.tw.	0
7	oleovitamin$ d 3.tw.	0
8	vitamin$ d3.tw.	10,372
9	vitamin$ d 3.tw.	1872
10	or/1-9	18,677
11	exp administration, intravenous/	143,823
12	infusions, parenteral/	26,288
13	injections/	42,827
14	injections, intramuscular/	31,129
15	(parenteral$ adj3 (administ$ or deliver$ or infus$ or therap$ or treat$)).tw.	15,223
16	intravenous$.tw.	343,940
17	intra venous$.tw.	582
18	intravascular$.tw.	48,275
19	intra vascular$.tw.	306
20	intramuscular$.tw.	52,965

21	intra muscular$.tw.	723
22	inject$.tw.	749,397
23	infus$.tw.	273,217
24	or/11-23	1,344,924
25	drug therapy/	30,651
26	de.fs.	3,012,732
27	dt.fs.	2,250,664
28	ad.fs.	1,427,616
29	tu.fs.	2,245,202
30	pc.fs.	1,303,632
31	exp vitamin d deficiency/	28,211
32	exp renal insufficiency, chronic/	116,763
33	exp hypoparathyroidism/	6864
34	((c?olecalciferol$ or oleovitamin$ d3 or vitamin$ d3 or vitamin$ d 3) adj3 (deficien$ or deplet$ or insufficien$ or supplement$)).tw.	1873
35	avitamin$.tw.	691
36	hypovitamin$.tw.	2615
37	ricket$.tw.	18,336
38	rachit$.tw.	1258
39	osteodystroph$.tw.	3853
40	osteomalac$.tw.	5193
41	((chronic$ or end stage$ or endstage$) adj3 (kidney$ or renal$) adj3 (deficien$ or disease$ or disorder$ or fail$ or insufficien$)).tw.	116,749
42	((chronic$ or end stage$ or endstage$) adj3 (glomerulopath$ or nephropath$)).tw.	3836
43	ckd mbd.tw.	718
44	esrd.tw.	16,180
45	hypoparathyr$.tw.	5747
46	(parathyroid$ adj3 (deficien$ or hypofunction$ or insufficien$)).tw.	431

47	therap$.tw.	2,839,278
48	treat$.tw.	5,602,403
49	prevent$.tw.	1,445,753
50	prophyla$.tw.	167,536
51	or/25-50	11,227,232
52	and/10,24,51	1201
53	exp animals/ not humans/	4,755,456
54	52 not 53	562
55	limit 54 to english language	514

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: November 12, 2020
- Limits: Humans (search hedge); English language
- Number of results: 1262

1	‘colecalciferol'/de	22,247
2	‘c$olecalciferol*':ti,ab,tn	4203
3	‘hydroxyc$olecalciferol*':ti,ab,tn	1795
4	‘hydroxyvitamin* d3':ti,ab,tn	1281
5	‘hydroxyvitamin* d 3':ti,ab,tn	2551
6	‘oleovitamin* d3':ti,ab,tn	0
7	‘oleovitamin* d 3':ti,ab,tn	0
8	‘vitamin* d3':ti,ab,tn	8332
9	‘vitamin* d 3':ti,ab,tn	8893
10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	34,956
11	‘intramuscular drug administration'/de	71,806
12	‘intravascular drug administration'/de	342
13	‘intravenous drug administration'/exp	394,020
14	‘injection'/exp	248,200
15	‘infusion'/exp	143,546
16	(parenteral* NEAR/3 (administ* OR deliver* OR infus* OR therap* OR treat*)):ti,ab	22,810
17	‘intravenous*':ti,ab	496,563
18	‘intra venous*':ti,ab	1474
19	‘intravascular*':ti,ab	69,475
20	‘intra vascular*':ti,ab	704
21	‘intramuscular*':ti,ab	76,392
22	‘intra muscular*':ti,ab	1292

23	‘inject*':ti,ab	1,113,191
24	‘infus*':ti,ab	399,827
25	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24	2,162,983
26	‘drug therapy'/de	763,127
27	‘drug dose':lnk	627,641
28	‘drug administration':lnk	1,774,693
29	‘drug therapy':lnk	3,969,308
30	‘prevention':lnk	1,187,731
31	‘vitamin d deficiency'/de	31,082
32	‘chronic kidney failure'/exp	155,291
33	‘hypoparathyroidism'/exp	15,509
34	‘avitamin*':ti,ab	1692
35	‘hypovitamin*':ti,ab	4448
36	((c$olecalciferol* OR 'oleovitamin* d3' OR 'vitamin* d3' OR 'vitamin* d 3') NEAR/3 (deficien* OR deplet* OR insufficien* OR supplement*)):ti,ab	3007
37	‘ricket*':ti,ab	24,261
38	‘rachit*':ti,ab	2230
39	‘osteodystroph*':ti,ab	5306
40	‘osteomalac*':ti,ab	7714
41	((chronic* OR 'end stage*' OR endstage*) NEAR/3 (kidney* OR renal*) NEAR/3 (deficien* OR disease* OR disorder* OR fail* OR insufficien*)):ti,ab	175,311
42	((chronic* OR 'end stage*' OR endstage*) NEAR/3 (glomerulopath* OR nephropath*)):ti,ab	5465
43	‘ckd mbd':ti,ab	1083
44	‘esrd':ti,ab	26,721
45	‘hypoparathyr*':ti,ab	8539
46	(parathyroid* NEAR/3 (deficien* OR hypofunction* OR insufficien*)):ti,ab	824
47	‘treat*':ti,ab	8,117,423

48	‘therap*':ti,ab	4,272,993
49	‘prevent*':ti,ab	1,965,741
50	‘prophyla*':ti,ab	266,813
51	#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	13,699,711
52	#10 AND #25 AND #51	2269
53	[animals]/lim NOT [humans]/lim	6,119,435
54	#52 NOT #53	1404
55	#52 NOT #53 AND [english]/lim	1262

Appendix 2. Table 5. Summary of included studies

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 1: Vitamin D deficiency or supplementation					
Bertino et al, 1984, US[6]	—	16 Patients who were either diagnosed with rickets or were at high risk for development of rickets (52.3%, range 2-18 y)	Patients with rickets: • Intramuscular (IM) cholecalciferol (6) • Intravenous cholecalciferol (1) Patients receiving prophylaxis: • IM cholecalciferol (5) • Intravenous cholecalciferol (4)	Radiographic evidence of healing, development of bone disease, side effects	"A parenteral formulation of cholecalciferol was found to be safe and effective in the treatment and prophylaxis of rickets. The advantage of this preparation is its lack of other vitamin components and its documented stability."
Choi et al, 2016, South Korea[7]	Prospective, multicenter, randomized, double-blind, placebo-controlled clinical trial	84 Patients with vitamin D deficiency • Vitamin D3 (16.1%, mean 37.4 y ± 10.4) • Placebo (10.7%, mean 36.2 y ± 10.6)	IM injection of either: • Vitamin D3 (56) • Placebo (28)	Serum 25-hydroxyvitamin D [25(OH)D] concentration	"Intramuscular injection of vitamin D3 200,000 IU was superior to placebo in terms of its impact on serum 25(OH)D concentrations, and is considered to be safe and effective in Korean adults with vitamin D deficiency."
Cipriani et al, 2013, Italy[25] Cipriani et al, 2012,	Prospective intervention study	24 Patients with vitamin D deficiency (25%, mean 63.9 y ± 7.1)	Vitamin D3 via either: • Oral administration (6) • IM administration (6) Vitamin D2 via either: • Oral administration (6) • IM administration (6)	Serum 25(OH)D and 1,25-dihydroxyvitamin D [1,25(OH)2D] levels	"We believe that these results offer the basis for 2 possible alternative treatment regimens in different clinical conditions. Further studies investigating the bioavailability and the metabolism of vitamin D are also needed, in relation to the reported variation in vitamin D receptor gene."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Adachi et al, 2011, Multiple countries[b,61] Boonen et al, 2011, Multiple countries[b,62] Lyles et al, 2007, Multiple countries[b,63] Colon-Emeric et al, 2004, Multiple countries[b,26] Colon-Emeric et al, 2011, Multiple countries[b,64]	Randomized, placebo-controlled, triple-blind study	2127 Patients after surgical repair of a low-trauma hip fracture • Placebo (24.5%, mean 74.6 y ± 9.86) • Zoledronic acid (23.3%, mean 74.4 y ± 9.48)	• Placebo (1062) • Zoledronic acid (1065) All patients received a loading dose of either vitamin D3 or D2, given either orally or IM (number of patients receiving each option not reported). Afterwards, all patients received oral supplementation of calcium and vitamin D	Occurrence of vertebral and nonvertebral fractures, adverse events	"An annual infusion of zoledronic acid within 90 days after repair of a low-trauma hip fracture was associated with a reduction in the rate of new clinical fractures and with improved survival."
Fahan Rashid et al, 2017, Pakistan[44]	Cross-sectional study	320 Patients receiving vitamin D supplementation • Group A (53.75%, mean 40.12 y ± 2.165) • Group B (48.75%, mean 41.61 y ± 3.936) • Group C (43.75%, mean 45.12 y ± 2.037) • Group D (41.25%, mean 41.32 y ± 5.367)	• Group A: Oral vitamin D3 600,000 IU once (80) • Group B: Oral vitamin D3 200,000 IU monthly (80) • Group C: Intramuscular vitamin D3 200,000 IU monthly (80) • Group D: Oral vitamin D3 50,000 weekly (80)	Vitamin D levels	"Different preparations of vitamin D are equally effective in raising vitamin D levels at 12 weeks. However, there is a need to conduct large-scale studies to further validate these results."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Falasca et al, 2014, Italy[8]	Prospective cohort study	153 Patients with human immunodeficiency virus (HIV) infection (75.8%, mean 45.0 y ± 10.6)	• Patients who refused vitamin supplementation (39) • Oral cholecalciferol (67) • IM cholecalciferol (47) Patients who received vitamin supplementation were randomized to either oral or IM administration	Serum 25(OH)D levels	"Our findings showed that the supplementation with cholecalciferol in patients with HIV infection improved 25OH vitamin D serum levels, and suggest that the 2 types of administration are equivalent, but are insufficient for severe forms of hypovitaminosis."
Gupta et al, 2011, India[65] Gupta et al, 2017, India[27]	Prospective, randomized, open-label single institution study	40 Patients with vitamin D deficiency • Oral (35%, mean 28.45 y ± 5.29) • IM (35%, mean 29.75 y ± 6.31)	• Oral cholecalciferol (20) • IM cholecalciferol (20)	Serum 25(OH)D levels	"Both oral and IM routes are effective for the treatment of Vitamin D deficiency. In the IM cholecalciferol group, serum 25OHD levels showed a sustained increase from baseline. A larger randomized control trial utilizing a larger dose and longer duration of follow-up is needed to further characterize the pros and cons of the oral and IM route."
Hamdy et al, 1987, UK[9]	—	50 Patients with hypocalcemia (gender not specified, mean 83 y)	• Dihydrotachysterol (20) • Alfacalcidol (14) • IM cholecalciferol (16)	Serum calcium, phosphate and alkaline phosphatase levels	"The single intramuscular injection of 400,000 units of cholecalciferol offers additional advantages over oral therapy in terms of compliance, and also overcomes any possible impairment of absorption"

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Hultin et al, 2018, Sweden[10]	Randomized controlled study	20 Patients who had undergone biliopancreatic diversion with duodenal switch (BPD/DS) 4 years previously • Cholecalciferol (38.5%, mean 42.0 y ± 7.0) • Control (27.3%, mean 38.0 y ± 8.0)	• IM cholecalciferol (11) • Control (9)	Serum 25(OH)D levels, parathyroid hormone (PTH) levels, serum calcium	"In BPD/DS patients having hypovitaminosis D despite full oral supplementation, a single injection of 600,000 IU of cholecalciferol was effective in normalizing intact PTH and vitamin D levels. The treatment is simple and highly effective and thus recommended, especially in populations subjected to reduced UV-B radiation."
Imga et al, 2017, Turkey[47]	—	231 Patients, both obese and nonobese (0%, age not specified)	• Daily oral vitamin D3 drop (not reported) • Weekly oral vitamin D3 (not reported) • Monthly IM vitamin D3 (not reported)	25(OH)D levels	"It is estimated that most people worldwide are vitamin D deficient. In non-obese orally daily therapy and in obese patients orally weekly cholecalciferol therapy is effective for the raise vitamin D status. Daily administration of orally cholecalciferol is adequate regimen to maintain blood levels of 25(OH) D above to 30 ng/ml in all patients."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Jalali-Chimeh et al, 2019, Iran[28]	Randomized, double-blind, placebo-controlled clinical trial	76 Patients with sexual dysfunction • Placebo (0%, mean 35.9 y ± 6.7) • Vitamin D3 (0%, mean 34.9 y ± 6.2)	• Placebo (38) • IM cholecalciferol (38)	Female Sexual Functioning Index score	"Vitamin D therapy in women with sexual dysfunction and vitamin D deficiency may improve sexual function. Treatment with vitamin D may also improve symptoms of depression in these women. However, the influence of vitamin D treatment on sexual function does not seem to be mediated by the improvement in depression symptoms. Further studies with longer follow-ups, and larger and more heterogeneous samples are required to better evaluate the potential benefits of vitamin D therapy and/or supplementation in women with sexual dysfunction and investigate possible underlying mechanisms."
Jelveh-Moghaddam et al, 2020, Iran[45]	—	90 Patients undergoing cardiac surgery (50%, mean 3.69 y ± 1.97)	• Normal vitamin D levels and no supplementation (30) Abnormal vitamin D levels with: • IM vitamin D (30) • No supplementation (30)	Cytokine levels, hemodynamic and metabolic measurements, patient morbidity and mortality	"No significant difference in the rates of postoperative parameters in patients with normal and those with deficient levels of vitamin D3 was observed."
Kilpinen-Loisa et al, 2009, Finland[66] Kilpinen-Loisa et al, 2009, Finland[48]	—	138 Patients with intellectual disability • Oral (68.1%, mean 44.5 y ± 11.3) • IM (69.7%, mean 50.0 y ± 15.3)	Vitamin D3 via either: • Oral (72) • IM (66)	Vitamin D level	"Based on this study, vitamin D supplementation with peroral 800 IU/day is recommended to all adults with [intellectual disability] living in nursing homes."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Kim et al, 2020, South Korea[29]	Open label randomized clinical trial	92 Patients with vitamin D deficiency, type 2 diabetes, and chronic kidney disease • Placebo (69.7%, mean 59.7 y ± 10.7) • Oral cholecalciferol (52.9%, mean 58.2 y ± 10.5) • IM cholecalciferol (52.0%, mean 59.7 y ± 9.3)	• Placebo (33) • Oral cholecalciferol (34) • IM cholecalciferol (25)	Serum 25(OH)D concentration, metabolic parameters	"In conclusion, this study revealed that 2 different doses and routes of vitamin D administration significantly and safely increased serum 25(OH)D concentrations in vitamin D-deficient T2D [type 2 diabetes] patients with comorbid CKD [chronic kidney disease]. In the group that received the higher vitamin D dose, the lipid profiles showed significant improvement, but there were no beneficial effects on other metabolic parameters. Longer-term and larger prospective studies are needed to clarify residual controversies regarding vitamin D supplementation in T2D patients with CKD."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Masood et al, 2015, Pakistan[30] Masood et al, 2013, Pakistan[67]	Prospective intervention study	95 Healthy volunteers and patients with vitamin D deficiency and diabetes • IM 600,000 IU (17.4%, mean 41.2 y ± 13) • Oral 600,000 IU (12.5%, mean 44.3 y ± 14.3) • IM 200,000 (20.8%, mean 41 y ± 16.4) • Oral 200,000 IU (16.7%, mean 44.3 y ± 13.3)	Cholecalciferol as: • IM 600,000 IU (23) • Oral 600,000 IU (24) • IM 200,000 IU (24) • Oral 200,000 IU (23)	Serum 25(OH)D levels, calcium and creatinine	"The findings of this study will have important implications in the way VDD [vitamin D deficiency] and VDI [vitamin D insufficiency] are treated with megadose preparations. First, a dose of VD3 [vitamin D3] ranging from 200,000 to 600,000 IU given PO [orally] or IM will correct the deficiency in more than 70% of individual at 2 months. Second, a dose of vitamin D 600,000 IU given IM will correct the deficiency in more than 90% of individuals at 2 months and maintain levels >20 ng/mL in 83% of individuals at 6 months. Third, as frequent mega doses are not required, the risk of toxicity is minimized. Daily maintenance doses may be necessary to maintain levels, particularly after the oral loading dose; however, this will require further studies."
McGreevy et al, 2015, Ireland[31]	Double-blind randomized controlled clinical trial	102 Patients with vitamin D deficiency • Cholecalciferol 50,000 IU (51%, mean 80.5 y ± 6.6) • Cholecalciferol 100,000 IU (54.9%, mean 79.3 y ± 7)	IM administration of cholecalciferol: • 50,000 IU (51) • 100,000 IU (51)	Serum 25(OH)D	"Vitamin D deficiency remains an issue in the older Irish population, and poor responses to IM therapy suggest that higher IM doses or oral therapy may be more beneficial. High-dose vitamin D3 resulted in an improvement in Aix [augmentation index] with nonsignificant improvements noted in PWV [pulse wave velocity] readings. Further randomized controlled trials are needed to expand our knowledge of the pathogenesis of arterial stiffness and its association with vitamin D deficiency in the older population."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Mohammad et al, 2018, Switzerland[49]	Prospective, exploratory, single-blind, outpatient study design	20 Healthy human subjects • High phosphate (60%, mean 23.1 y ± 3.2) • Low phosphate (60%, mean 23.4 y ± 3.4)	• High phosphate diet (10) • Low phosphate diet (10) All patients received IM vitamin D3 after 6 weeks	Systolic and diastolic blood pressure (SBP and DBP), pulse rate (PR), biomarkers, measures of endothelial and arterial function	"Increased phosphate intake (controlled for sodium) significantly increases SBP, DBP, and PR in humans with normal renal function, in part, by increasing sympathoadrenergic activity."
Mondal et al, 2014, India[11]	Randomized controlled trial	71 Patients with nutritional rickets • Oral vitamin D3 (gender not specified, mean 12.81 months ± 7.14) • IM vitamin D3 (gender not specified, mean 13.33 months ± 7.92)	• Oral vitamin D3 (34) • IM vitamin D3 (37)	Serum calcium, phosphate, alkaline phosphatase, urinary calcium/creatinine ratio, serum 25(OH)D, radiological score	"To conclude, results of our study indicate that a dose of 600,000 IU vitamin D administered through the oral or the intramuscular route is effective and safe in treatment of nutritional rickets. Occurrence of mild elevation in serum 25(OH)D and total serum calcium levels warrants looking at efficacy of lower doses of vitamin D in treating rickets."
Moslemi et al, 2018, Iran[50]	Randomized single-blind clinical trial	108 Patients with vitamin D deficiency • Fortified biscuit (39.4%, mean 49.55 months ± 11.8) • Cholecalciferol capsule (33.3%, mean 49.88 months ± 11.9) • IM cholecalciferol (46.7%, mean 50.1 months ± 11.35)	• Fortified biscuit (35) • Oral cholecalciferol capsule (36) • IM cholecalciferol (33) 2 Patients allocated to fortified biscuit group and 1 patient allocated to intramuscular cholecalciferol did not receive their intervention.	Serum 25(OH)D concentration	"Stoss therapy using fortified biscuit may be an effective way to improve compliance in children who cannot take capsules without adverse effects and may also be recommended for prevention purposes."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Nair et al, 2015, Australia[32] Nair et al, 2018, Australia[68]	Prospective randomized interventional study	50 Patients with systemic inflammatory response syndrome (72%, mean 54 y ± 17.7)	IM cholecalciferol at either: • 150,000 IU (25) • 300,000 IU (25)	Serum 25(OH)D levels	"Vitamin D deficiency is highly prevalent in critically ill patients. Correction of vitamin D deficiency in critical illness is challenging but can be reasonably predictably and safely achieved by a single dose of intramuscular cholecalciferol. Vitamin D repletion is associated with a fall in proinflammatory biomarkers and greater vitamin D increments were associated with augmented antimicrobial cytokine responses. It is now imperative to investigate the biological and clinical impact of vitamin D repletion in critically ill patients in adequately powered intervention trials."
Narasimhan and Balasubramanian, 2017, India[12]	Non blinded, randomized controlled trial	60 Patients with ischemic stroke and vitamin D deficiency or insufficiency • IM cholecalciferol (63.3%, median 62 y) • Control (70%, median 65 y)	• IM cholecalciferol (30) • Control (30)	Scandinavian Stroke Scale	"Vitamin D is a potential risk factor for stroke and vitamin D supplementation has better outcome in ischemic stroke patients with vitamin D deficiency. Single dose replacement of vitamin D has significantly improved the outcome of ischemic stroke. Screening for vitamin D status is essential in ischemic stroke patients and supplementation to be done to maintain vitamin D at normal level."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Pourrashid et al, 2018, Iran[33]	Placebo-controlled randomized clinical trial	62 Patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) and vitamin D deficiency • Placebo (84.38%, mean 64.06 y ± 8.77) • Vitamin D (83.33%, mean 62.73 y ± 8.26)	• Placebo (32) • IM cholecalciferol (30)	Health Related Quality of Life (HRQOL) and symptom recovery	"HRQOL in hospitalized AECOPD patients with concomitant deficient levels of vitamin D was significantly impaired. Vitamin D replacement with a single parenteral injection could be an effective intervention to improve patients' HRQOL; however, improvement in other clinical outcomes such as LOS [length of stay], rehospitalization and mortality rates were not achieved. Further studies with a longer follow-up period are recommended."
Rao et al, 2016, India[13]	Prospective randomized clinical trial	45 Patients with vitamin D deficiency • Oral 4,000 IU/day (gender not specified, mean 3.0 y ± 0.9) • Oral 30,000 IU/week (gender not specified, mean 3.2 y ± 0.7) • IM (gender not specified, mean 3.4 y ± 1.4)	Vitamin D3 as: • Oral 4,000 IU/day (15) • Oral 30,000 IU/week (15) • IM (15)	Serum vitamin D levels, bone mineral concentration (BMC), bone mineral density (BMD)	"The injectable form of vitamin D was more efficacious than the oral forms in increasing the serum level to the normal range. All 3 regimens were equally effective in increasing the BMC and BMD. The 400 IU/day maintenance dose was sufficient to keep the serum level within the normal range."
Bhatia et al, 2011, India[69] Reddy et al, 2013, India[14]	Double blind randomized control study	40 Patients with tropical pancreatitis and vitamin D deficiency (65%, mean 33 y ± 9)	IM injection of: • Cholecalciferol 600,000 IU (13) • Cholecalciferol 300,000 IU (14) • Placebo (13)	Serum 25(OH)D	"In conclusion, in patients with CP [chronic pancreatitis], a single IM injection of 600,000 IU was more effective at achieving vitamin D sufficiency over 6 months compared with 300,000 IU vitamin D3."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Rostami et al, 2018, Iran[15]	Stratified randomized field trial, with screening and nonscreening arms A randomized controlled trial was conducted within the screening arm	1800 Pregnant patients (0%, range 25-32 y) Of the 1400 patients found to have vitamin D deficiency, 800 were enrolled in the randomized controlled trial, with 400 diagnosed with moderate deficiency and 400 with severe deficiency	Vitamin D3 as: • Oral 50,000 IU weekly (200) • Oral 50,000 IU weekly plus monthly maintenance dose of 50,000 IU until delivery (200) • IM 300,000 IU (200) • IM 300,000 IU plus monthly maintenance dose of oral 50,000 IU until delivery (200)	Maternal concentration of 25(OH)D at delivery, rate of pregnancy complications	"To conclude, the screening and supplementation policy could effectively detect and treat women who were deficient in vitamin D and improve adverse outcomes compared with the nonscreening site. Moreover, in the absence of any untoward supplement-related outcome, we cautiously conclude that doses of 300,000 IU in moderately deficient women and 600,000 IU (divided in 2 doses) in severely deficient women, followed by a monthly maintenance therapy, could be well tolerated with a high rate of patient compliance to treatment."
Rousseau et al, 2015, Belgium[16]	Monocentric randomized controlled trial	15 Patients with severe thermal burns dating from 2-5 years (73.3%, range 25-64 y)	• Placebo (7) • IM cholecalciferol and optimized calcium regimen (8)	Vitamin D status, bone remodeling markets, knee muscle strength, bone mineral density	"This VD3 supplementation was safe and efficient to correct hypovitaminosis D in burn adults. When combined with optimized Ca [calcium] intakes, it demonstrated positive effects on muscle health but not on bone health. A high prevalence of hypovitaminosis D and osteopenia in these patients, as well as their wide range of muscle performances, seem to be worrying when considering rehabilitation and quality of life."
Shin, 2020, South Korea[17]	Randomized, double-blinded, placebo-controlled trial	60 Patients with migraine disorder and low vitamin D levels (33.3%, range 20-65 y)	• IM cholecalciferol (30) • Control (30)	Change in migraine frequency, severity, and duration	"Vitamin D supplementation was significantly beneficial in decreasing duration, frequency, and severity of headache attacks."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Sundbom et al, 2016, Sweden[18]	Randomized clinical trial	73 Roux-en-Y-gastric bypass patients • UVB treatment (23.1%, mean 40.5 y ± 5.7) • IM cholecalciferol (20%, mean 38.2 ± 5.3) • Control (25.9%, mean 40.6 y ± 6.3)	• UVB treatment (26) • IM cholecalciferol (20) • Control (27)	Serum 25(OH)D, intact PTH, calcium, and albumin	"In this randomized trial, both interventions, UVB and cholecalciferol, given as an adjunct to oral supplementation in gastric bypass patients, increased the levels of 25[OH]D. Simplicity makes injection therapy suitable for maintaining vitamin D levels during the Nordic winter."
Tellioglu et al, 2012, Turkey[19] Tellio›lu et al, 2011, Turkey[70]	Randomized prospective study	66 Patients with either vitamin D deficiency or insufficiency • IM (35.3%, mean 75.5 y ± 6.1) • Oral (34.4%, mean 75.3 y ± 7.5)	• IM cholecalciferol (34) • Oral cholecalciferol (32)	25(OH)D levels	"In vitamin D deficient/insufficient elderly, a single megadose of cholecalciferol increased vitamin D levels significantly and the majority of the patients reached optimal levels. Although both administration routes are effective and appear to be safe, IM application is more effective in increasing 25(OH)D levels and balance performance."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Wylon et al, 2017, Germany[20]	Open-label study / Placebo-controlled pilot study	43 Patients with vitamin D deficiency in an open-label study • Oral vitamin D (64%, mean 33.4 y ± 6.6) • Oral placebo (61.1%, mean 31.7 y ± 5.2) • 18 Patients with vitamin D deficiency in a randomized pilot study • IM vitamin D (33.3%, mean 34.9 y ± 9.1) • IM placebo (33.3%, mean 36 y ± 13)	• Oral cholecalciferol (25) • Oral placebo (18) • IM cholecalciferol (12) • IM placebo (6)	25(OH)D concentrations	"Oral and intramuscular cholecalciferol supplementation effectively increased serum 25(OH)D concentrations."
Zabihiyeganeh et al, 2012, Iran[71] Zabihiyeganeh et al, 2012, Iran[72] Zabihiyeganeh et al, 2013, Iran[34]	Open label randomized controlled trial	79 Patients with hypovitaminosis D • IM (23.1%, mean 49.6 y ± 1.5) • Oral (17.5%, mean 48.1 y ± 1.2)	• IM cholecalciferol (39) • Oral cholecalciferol (40) 61 Patients completed the study, but 79 patients were included in the final per-protocol analysis	Serum 25(OH)D level	"Although we revealed superiority of oral route, at least in the early short time of our study, facing the widespread worldwide pandemic of hypovitaminosis D, physicians should firstly be aware of its presence and secondly may choose the way of treatment based on patient's wish, compliance and availability of various forms of the drug in their regions. Further investigations with longer follow-up in future will help to definitely recommend such a therapeutic approach."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Zhang et al, 2017, South Korea[46]	Randomized, double-blinded, and placebo-controlled clinical trial	34 Patients with vitamin D deficiency (14.7%, mean 33.2 y ± 7.7)	• IM vitamin D3 (24) • Placebo (10)	Serum fibroblast growth factor 23 concentrations, sclerostin levels, dickkopf-1 levels, parathyroid hormone levels	"Serum fibroblast factor 23, sclerostin, parathyroid hormone, and dickkopf-1 levels were not affected significantly by single intramuscular injection of vitamin D3."
Indication 2: Insulin resistance, hyperglycemia, diabetes mellitus					
Alizadeh et al, 2016, Iran[35]	Prospective, double-blinded, placebo-controlled, randomized clinical trial	50 Patients with stress-induced hyperglycemia and insulin resistance in the intensive care unit (ICU; 52%, mean 53.21 y ± 17.51)	IM administration of either: • Vitamin D3 (25) • Placebo (25)	Plasma levels for vitamin D, glucose, insulin, and adiponectin	"Various aspects of vitamin D in critically ill patients are not fully described. Daily requirement, route of administration, time of intervention, appropriate analogue, optimum serum level, hormonal and nonhormonal effects, association between serum level and severity of acute illnesses, change on its metabolism, effects on morbidity and mortality should be considered in future studies regarding vitamin D in critically ill patients."
Heshmat et al, 2012, Iran[36]	Randomized double-blind clinical trial	42 Patients with type 2 diabetes mellitus (64%, range 37-79 y)	• IM vitamin D3 (21) • Placebo (21)	Insulin resistance, anthropometric parameters	"The present data is not convincing and further studies with large sample sizes are needed to show the definite effect of injection of vitamin D on control of diabetes and its risk."
Jehle et al, 2014, Switzerland[21]	Prospective, randomized, double-blind, placebo-controlled pilot study	55 Patients with type 2 diabetes mellitus • Vitamin D3 (34.5%, mean 66.9 y ± 3.1) • Placebo (38.5%, mean 63.7 y ± 3.5)	• IM cholecalciferol (29) • Placebo (26)	Change in HbA_{1c} levels	"D3 improved insulin sensitivity (based on HOMA-IR) and affected the course of HbA_{1c} positively compared with placebo in patients with T2DM [type 2 diabetes mellitus]."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Mozaffari-Khosravi et al, 2012, Iran[37]	Randomized controlled trial	45 Patients with gestational diabetes • IM vitamin D3 (0%, mean 30.7 y ± 6.2) • Control (0%, mean 29.5 y ± 4)	• IM vitamin D3 (24) • Control (21)	HbA_{1c}, serum 25(OH)D, fasting insulin and blood glucose, C-peptide, homeostasis model assessment insulin resistance index (HOMA-IR), β-cell function, insulin sensitivity, Quantitative Insulin Sensitivity Check Index (QUICKI)	"A single postpartum injection of 300,000 IU of vitamin D3 in women with gestational diabetes provides a satisfactory serum 25-hydroxyvitamin D of 50-80 nmol/ L after 3 months and is an efficient, effective, and safe procedure for improving vitamin D status and reducing insulin resistance in mothers with gestational diabetes after delivery. Further investigation is needed, however, to determine whether long-term maintenance of adequate vitamin D status may reduce the risk of later type 2 diabetes in such women."
Indication 3: Mechanical ventilation					
Hasanloei et al, 2020, Iran[38]	Randomized controlled clinical trial	72 Patients in need of mechanical ventilation in the ICU • Placebo (50%, mean 48.71 y ± 7.90) • Oral (70.8%, mean 50 y ± 16.45) • Injection (45.8%, mean 44.37 y ± 15.40)	• Placebo (24) • Oral cholecalciferol (24) • IM cholecalciferol (24)	Oxidative stress biomarkers, weaning from the ventilator	"Vitamin D administration improved clinical signs and biochemical biomarkers in a small group of patients with traumatic injury. Well-designed multicenter clinical studies with longer intervention duration are necessary for this field."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Yousefian et al, 2019, Iran[39]	—	99 Patients mechanically ventilated in the ICU due to stroke (54.54%, mean 60.64 y)	• Patients with vitamin D level > 20 ng/mL, no intervention (33) Patients with vitamin D level < 20 ng/mL and either: • IM vitamin D3 plus calcium tablet (33) • Placebo (33)	Duration of intubation	"Given the importance of patients' faster weaning from mechanical ventilation in ICU and the relationship between lower levels of vitamin D and the prolongation of weaning process which itself leads to an increase in the duration of ventilator dependency and prolongs hospitalization in ICU, it seems that by conducting more studies on this issue with larger sample sizes, more effective ways can be identified so as to increase the level of vitamin D in such patients."
Indication 4: Chronic urticaria					
Xiong et al, 2019, China[51]	Double-blind, randomized, single-center study	100 Patients with chronic urticaria • Treatment (44.6%, mean 35.45 y ± 12.11) • Control (43.2%, mean 34.97 y ± 13.76)	• Calcium gluconate, proteoglycan, mizolastine, and IM vitamin D3 (56) • Control (44)	Itching, erythema number and size	"The combination of mizolastine plus proteoglycan is effective in treating chronic urticaria with better therapeutic effect and lower relapse rate through promoting IFN-γ [interferon-gamma] production."
Indication 5: Decompensated liver cirrhosis					
Jha et al, 2017, India	Single-center prospective study	101 Patients with decompensated liver cirrhosis and vitamin D deficiency • Control (74%, mean 43.28 y ± 12.53) • IM cholecalciferol (80%, mean 46.21 y ± 14.93)	• Control (50) • IM cholecalciferol followed by maintenance with oral cholecalciferol and calcium supplementation (51)	Vitamin D level, survival	"VD [Vitamin D] deficiency is very common in patients of decompensated CLD [chronic liver disease]. Replenishment of VD may improve survival in patients with decompensated liver cirrhosis."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 6: Diabetic nephropathy					
Liyanage et al, 2015, Sri Lanka[73] Liyanage et al, 2017, Sri Lanka[74] Liyanage et al, 2018, Sri Lanka[40]	Randomized, double-blind clinical trial	85 Patients with diabetic nephropathy • Control (42.9%, mean 59 y ± 8) • IM vitamin D3 (48.8%, mean 56 y ± 10)	• Placebo (43) • IM vitamin D3 (42)	Changes in urine albumin, renal functions, vitamin D, renin, and PTH, blood pressure, total cholesterol, low-density lipoproteins, triglycerides, high density lipoproteins, bone mineral density, bone mineral content	"This randomized double-blind placebo-controlled clinical trial conducted among patients with earl DN [diabetic nephropathy] showed a significant reduction of UA [urinary albumin] excretion with Vitamin D treatment. We also observed an improvement in the GFR [glomerular filtration rate] which requires to be confirmed in further studies with longer duration of follow-up and using directly measured GFR in addition to estimated GFR."
Indication 7: Lumbar disk herniation					
Sedighi and Haghnegahdar, 2014, Iran[52]	Randomized, placebo-controlled, double-blind clinical trial protocol	Patients with one-level and unilateral lumbar disk herniation with a duration of discogenic pain less than 8 weeks	• IM vitamin D3 (not reported) • Placebo (not reported)	Pain scores, sensory deficits	*At time of writing protocol, recruitment had not been initiated*
Indication 8: Multiple sclerosis					
Mosayebi et al, 2011, Iran[23]	Prospective randomized controlled trial study	59 Patients with multiple sclerosis • IM vitamin D3 (34.6%, mean 37 y ± 9) • Control (24.2%, mean 35 y ± 9)	• IM vitamin D3 (26) • Control (33)	Expanded disability status scale scores, number of gadolinium-enhancing lesions	"This result suggests that vitamin D therapy may help prevent the development of MS [multiple sclerosis] and could be a useful addition to the therapy."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 9: Nonalcoholic fatty liver disease (NAFLD)					
Hosseini et al, 2018, Iran[41]	Randomized controlled clinical trial	75 Patients with NAFLD and vitamin D insufficiency • Vitamin D (0%, mean 34.4 y ± 6.7) • Control (0%, mean 34.05 y ± 7.2)	Vitamin E plus either: • IM cholecalciferol (37) • Control (37)	Changes in serum 25(OH)D, serum adiponectin, HOMAR-IR, liver enzymes, and grade of NAFLD	"Based on the results of the present study, a single intramuscular injection of Vitamin D (600,000 IU) in women with NAFLD could significantly increase serum 25(OH)D after one month and no change in serum calcium, phosphorus, and PTH were observed. In addition, it resulted in a relative improvement in hepatic steatosis based on grade of fatty liver. Furthermore, changes in serum levels of liver enzymes, adiponectin, and IR were not significant. However, more clinical trials with larger sample size, longer follow-up duration, and measuring other biochemical factors are needed to determine the effects of Vitamin D supplementation on NAFLD progression."
Indication 10: Tuberculosis					
Rao et al, 2012, Pakistan[75] Salahuddin et al, 2013, Pakistan[22]	Randomized double-blinded, multi-center, placebo-controlled clinical trial	259 Patients with pulmonary tuberculosis • IM vitamin D3 (53.8%, mean 27.8 y ± 13.2) • Placebo (55.1%, mean 28.3 y ± 14.1)	• IM cholecalciferol (132) • Placebo (127)	Weight gain, resolution of chest radiograph abnormalities	"Supplementation with high doses of vitamin D accelerated clinical, radiographic improvement in all [patients with TB (tuberculosis)] and increased host immune activation in patients with baseline 'Deficient' serum vitamin D levels. These results suggest a therapeutic role for vitamin D in the treatment of TB."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 11: Ulcerative colitis					
Sharifi et al, 2016, Iran[76] Sharifi et al, 2019, Iran[77] Sharifi et al, 2019, Iran[78] Javad Hosseinzadeh-Attar et al, 2020, Iran[79] Sharifi et al, 2020, Iran[42]	Double-blinded, randomized, placebo-controlled trial	86 Patients with mild to moderate ulcerative colitis • Vitamin D3 (56.5%, mean 37.5 y ± 9.0) • Placebo (56.8%, mean 35.0 y ± 9.2)	• IM cholecalciferol (46) • Placebo (40) 4 Patients from the placebo group were lost to follow-up	Fold changes in CD40 ligand (CD40L) mRNA, serum levels of vitamin D and calcium, ESR, Hs-CRP, mean change of LL37 gene expression, asymmetric dimethylarginine levels, Beck Depression Inventory score, Serum levels of IL-4, IL-10, IL-12p70, IFN-γ, and TNF-α	"In conclusion, for the first time, we showed that vitamin D supplementation not only can diminish the CD40L/CD40 inflammatory downstream but it can also directly decrease the CD40L gene expression, which seems to be a therapeutic target in patients with IBD [inflammatory bowel disease]."
Indication 12: Venous thromboembolism					
Gholami et al, 2016, Iran[43]	Prospective, randomized, controlled trial	60 Patients with confirmed acute deep vein thrombosis and/or pulmonary embolism (60%, mean 53.2 y ± 17.3)	• IM vitamin D3 (20) • No intervention (40)	Plasma level of 25(OH)D, P-selectin, and high-sensitive C-reactive protein (hs-CRP)	"In conclusion, this study could not support the potential benefit of the high-dose vitamin D on plasma level of P-selectin and hs-CRP in patients with VTE [venous thromboembolism]. Therefore, our study showed that vitamin D plus anticoagulants did not have a greater effect than anticoagulants alone in the case of VTE."

Abbreviations: —, not provided; 1,25(OH)2D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; BPD/DS, biliopancreatic diversion with duodenal switch; ESR, erythrocyte sedimentation rate; HbA_{1c}, hemoglobin A_{1c}; HIV, human immunodeficiency virus; HOMAR-IR, homeostasis model reassessment insulin resistance index; Hs-CRP, high-sensitivity C-reactive protein; ICU, intensive care unit; IL, interleukin; IM, intramuscular; INF-γ, interferon-gamma; mRNA, messenger RNA; NAFLD, nonalcoholic fatty liver disease; PTH, parathyroid hormone; TNF-α, tumor necrosis factor alpha.

[a]As defined by authors.
[b]Multiple countries defined as: Argentina, Austria, Belgium, Brazil, Canada, Colombia, Czech Republic, Denmark, Finland, France, Greece, Guatemala, Hong Kong, Norway, Peru, Poland, Russia, Slovakia, Spain, Switzerland, Sweden, Turkey, UK, US.

Appendix 3.1. Survey instrument for professional medical associations

1. How familiar are you with the following terms?

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

2. Do you prescribe or administer vitamin D3 to your patients?
    - Yes
    - No
3. Do you prescribe or administer vitamin D3 by any of the following dosage forms and/or routes of administration? (check all that apply)
    - Intramuscular solution
    - None of the above
4. I prescribe or administer vitamin D3 for the following conditions or diseases: (check all that apply)
    - Vitamin D deficiency or insufficiency
    - Other (please explain) _____
5. I use compounded vitamin D3 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 vitamin D3
    - Other (please explain) _____
6. Do you stock non–patient-specific compounded vitamin D3 at your practice?
    - Yes
    - No
    - I'm not sure
7. I obtain compounded vitamin D3 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) _____
8. 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) _____

9. What degree do you hold? (check all that apply)
    - Doctor of Medicine (MD)
    - Doctor of Osteopathic Medicine (DO)
    - Doctor of Medicine in Dentistry (DMD/DDS)
    - Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
    - Naturopathic Doctor (ND)
    - Nurse Practitioner (NP)
    - Physician Assistant (PA)
    - Other (please describe) _____

Appendix 3.2. Survey instrument for 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
    - Back orders
    - Convenience
    - Cost
    - Need for concentrations not commercially available
    - Need for preservative-free products
    - Need for ready-to-use products
    - No FDA-approved products available
    - No on-site compounding facility
    - On-site compounding facility not equipped to compound all necessary products
    - Other, please explain _____
5. Please select the type(s) of products obtained from an outsourcing facility.
    - Nonsterile products
    - Sterile products
6. Please select the category(ies) of products obtained from an outsourcing facility.
    - Cardioplegic solutions
    - Dermatologic preparations
    - Dialysate solutions

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

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

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

Appendix 4. Survey distribution to professional associations

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

[a]Associations that declined, did not respond, or did not provide significant data in project Years 1 and 2 were not contacted for project Year 3 surveys.