Summary Report

Biotin

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

ADC	Automated dispensing cabinets
API	Active Pharmaceutical Ingredient
ED	Emergency department
EMA	European Medicines Agency
EU	European Union
FDA	US Food and Drug Administration
IRB	Institutional Review Board
IM	Intramuscular
IV	Intravenous
OR	Operating room
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 Food and Drug Administration (FDA) in its evaluation of the use of biotin (UNII code: 6SO6U210H04), 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 biotin 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 biotin has been used historically and currently.[1-3] Assessment of study quality and risk of bias were not performed because the aim of this report was not to make specific recommendations on the use of this substance in clinical practice.[1,4,5] Rather, the aim was to summarize the available evidence on the use of biotin 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

Biotin was nominated for inclusion on the 503B Bulks List by Fagron for biotin deficiency via a 60-mcg intravenous (IV) injection.

The nominator provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of biotin.[6-11]

The reasons provided for nomination to the 503B Bulks List included that there are no FDA-approved injectable biotin products and that patients receiving parenteral nutrition are at risk for biotin deficiency; IV administration may be the only option for replacement.

METHODOLOGY

Background information

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

Each medicine register was searched for biotin; name variations of biotin were entered if the initial search retrieved no results. The following information from the search results of each register was recorded in a spreadsheet: product trade name; active ingredient; strength; form; ROA; status and/or schedule; and approval date. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations.

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.5) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing

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

Systematic literature review

Search strategy

A medical librarian constructed comprehensive search strategies for Ovid MEDLINE and Embase. The search strategies used a combination of controlled vocabulary terms and keywords to describe three concepts: biotin; IV or intramuscular (IM) administration; and therapeutic or preventative use (refer to Appendix 1 for full search strategies). Results were limited to human studies in 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 biotin, and provided sufficient information on dosing and administration.

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

Study selection

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

Interviews

Semistructured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances biotin 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 biotin. Potential SMEs were identified through recommendations and referrals from professional associations,

colleagues' professional networks, and authors of relevant literature. Select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided oral informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were synthesized for qualitative data analysis.

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

Survey

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

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

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

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

CURRENT AND HISTORIC USE

Results of background information

- Biotin is not available as an FDA-approved product in the nominated dosage form and ROA. Biotin is available as an FDA-approved multi-ingredient product in combination with other vitamins and minerals for parenteral administration.
- Biotin is available as oral and topical OTC products in the US.
- There is a current United States Pharmacopeia (USP) monograph for biotin.
- Biotin is not available in the nominated dosage form and ROA in any of the foreign medical registries searched. However, biotin is available as a multi-ingredient product in combination with other vitamins and minerals for parenteral administration in Australia, Canada, Belgium, Hong Kong, Ireland, New Zealand, and UK.

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 1229 references; 0 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 906 titles and abstracts were screened. After screening, the full text of 92 articles was reviewed. Seven studies were included; after multiple reports of the same study were merged, there were 5 included studies. Eighty-five studies were excluded for the following reasons: wrong study design (66 studies), wrong dosage form or ROA (11), dosage form or ROA not specified (5), wrong substance (2), and unable to obtain full text (1).

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

Characteristics of included studies

The 5 included studies were published between 1969 and 1988. There were 0 experimental studies, 0 observational studies, 5 descriptive studies, and 0 clinical practice guidelines. All the studies took place in the US.

A total of 11 patients participated in the 5 included studies. The number of patients in each study ranged from 1 to 4.

Outcome measures differed among the included studies and included: signs and symptoms of biotin deficiency and/or depression; and improvement and/or resolution of organic aciduria, hair, fingernail, and skin lesions.

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

Use of biotin

Ten patients received biotin as a treatment for biotin deficiency and/or dependency, administered via IV or parenterally in doses ranging from 0.06 mg/day to 10 mg/day. Duration of treatment ranged from a single dose to long-term use up to 3 months.

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

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

In 2 studies, the authors' concluding statement recommended the use of biotin for biotin deficiency.[10,12] For 1 study, the authors concluded that the recommended biotin supplementation of 20 mcg/day for pediatric patients receiving parenteral alimentation may not be adequate to maintain normal biotin status.[13] In 2 studies, the authors did not provide a definitive conclusion for the recommendation of biotin.[14,15] Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

In addition to the 5 included studies, 16 additional studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of biotin.

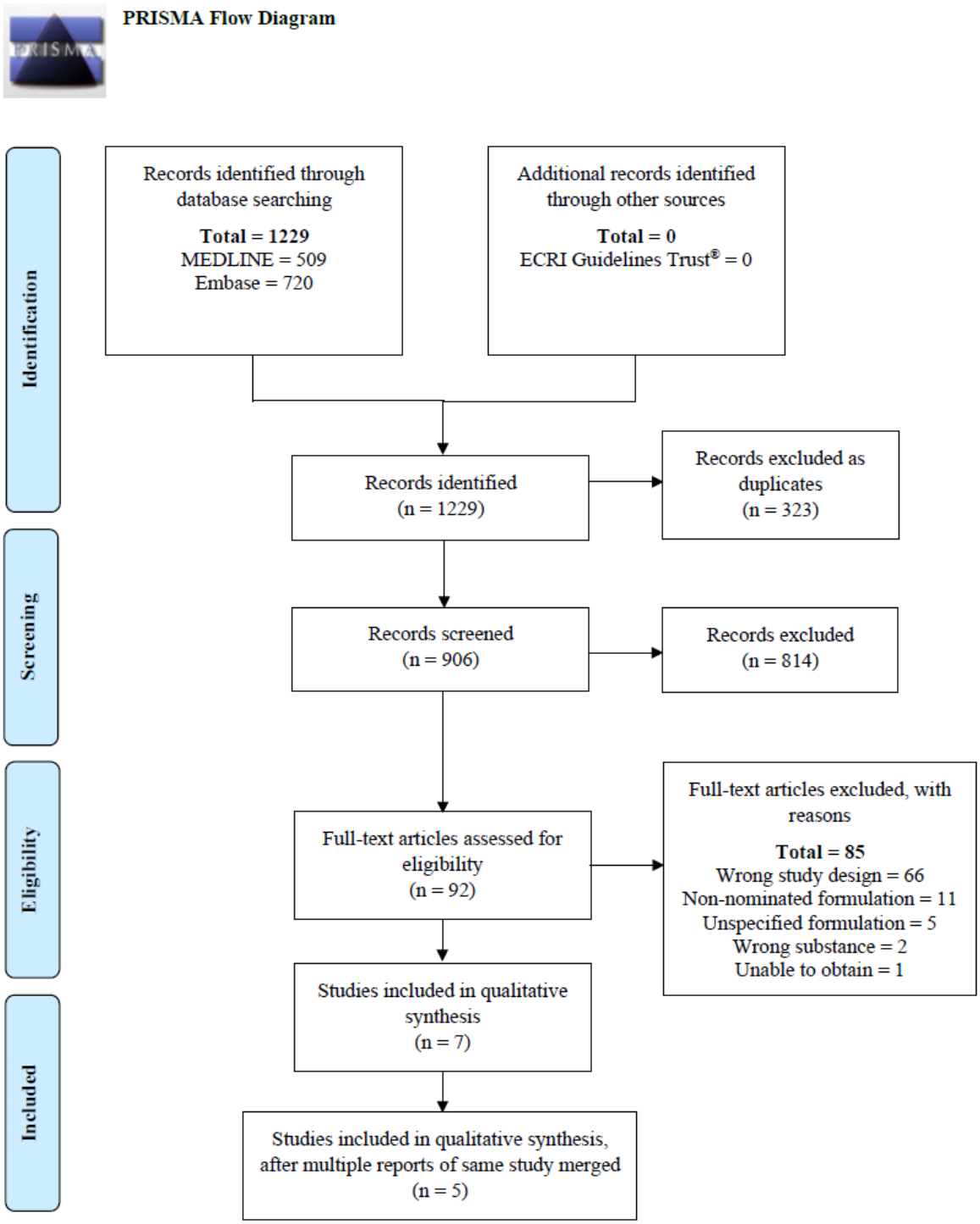
Biotin, also known as vitamin H or coenzyme R, is a water-soluble vitamin that acts a cofactor to several enzymes including pyruvate carboxylase, acetyl-coenzyme A (CoA) carboxylase, propionyl-CoA carboxylase, and 3-methylcrotonyl-CoA carboxylase.[13,16] Biotin can be obtained from diet and "bacterial synthesis in the intestine."[17] There are many biotin-containing foods, "although the absolute amount of biotin present in even the richest dietary sources is very low."[16] Biotin deficiency is rare unless the patient has been deprived of biotin in the diet, has consumed large amounts of raw egg white (due to the glycoprotein avidin binding to biotin preventing absorption), or has inborn error of metabolism disorder, such as biotinidase deficiency.[14,16-18] Other patients who may be at risk for biotin deficiency include alcoholics, pregnant and lactating patients, and patients with partial or total gastrectomy or burns.[18] Symptoms of biotin deficiency include skin lesions, alopecia, anorexia, pallor, nausea and vomiting, hyperesthesia, glossitis, muscle pain, elevated serum cholesterol and bile pigments, depression, angular cheilosis, dry eyes, developmental delays in infants, and central nervous system (CNS) abnormalities.[14,16-19] In the 1980s, biotin deficiency was reported in patients on long-term, biotin-free total parenteral nutrition (TPN). TPN-related biotin deficiency has not been reported since biotin became a routine addition to parenteral nutrition formulations but "marginal biotin status may be more prevalent than thought."[17,19] There have been no reports of biotin toxicity.[18-20] A couple of studies found that adding biotin to parenteral nutrition solutions could possibly promote the growth of *Candida albicans* in catheters, and increase the risk of bacterial and fungal catheter-related bloodstream infections.[21,22] One study suggested the growth of *C. albicans* is promoted when multivitamins or water-soluble vitamins are added to parenteral nutrition solutions without lipid, "and that this effect is mostly attributable to biotin."[21]

Several guidelines and/or clinical reviews touching upon use of parenteral biotin were found. In the 2019 American Society for Parenteral and Enteral Nutrition (ASPEN) recommendations for appropriate parenteral nutrition dosing, biotin 60 mcg/day is the daily parenteral requirement for adults with a note that the full daily dose should be prescribed unless the patient is "able to ingest

and/or absorb orally/enterally. [The] full dose of most multivitamin products available in the US provides the above requirements."[23] The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)/European Society for Parenteral and Enteral Nutrition (ESPEN)/European Society of Paediatric Radiology (ESPR)/Chinese Society for Parenteral and Enteral Nutrition (CSPEN) 2018 guidelines on pediatric parenteral nutrition for vitamins conditionally recommended (strong consensus) biotin 5-8 mcg/kg/day for preterm and term infants (up to 12 months old) and biotin 20 mcg/day for older children on parenteral nutrition.[20] However, they note that "the adequacy of current recommendations needs to be confirmed."[20] The Australasian Society for Parenteral and Enteral Nutrition (*Au*SPEN) 2016 guidelines for vitamin supplementation during parenteral and enteral nutrition recommended biotin 60 mcg/day for both short-term and long-term parenteral nutrition.[19] In a 2018 review about inborn errors of metabolism in the emergency department (ED) (undiagnosed and management of the known) by MacNeill and Walker, biotin 10-mg IV or oral was listed for treatment of organic acidemia.[24] For pyruvate disorders, biotin should be "administered at a dose of 5-20 mg/day."[24] In a 2014 proposed guidelines for diagnosis and management of methylmalonic and propionic acidemia by Baumgartner et al, biotin was noted as the treatment of choice for holocarboxylase synthetase and biotinidase deficiency.[25] The proposed guideline also indicated use of a biotin dose 10 to 40 mg/day IV or oral for patients with symptomatic hyperammonemia (ammonia level 100 to 250 μmol/l) in undiagnosed patients and known patients with methylmalonic and propionic acidemia.[25] From a 2020 review on biotinidase deficiency, oral biotin is used for treatment and "patients with profound biotinidase deficiency are treated with 5-20 mg/day biotin."[26]

There were additional studies that mentioned use of parenteral biotin that did not meet the literature review inclusion criteria. Three of the studies were case reports on biotin deficiency due to long-term TPN.[27-29] The 3 case reports were from Canada in 1982,[28] Japan in 1985,[29] and UK in 1995.[27] In all 3 cases, the symptoms resolved after biotin was given.[27-29] One case gave biotin as a dose of 10 mg/day IV,[28] the other case added a 120 mcg/day biotin supplementation,[27] and the last case was given 1 mg/day biotin IM.[29] Another 2016 case report from UK was related to biotinidase deficiency in which an 18-month-old female was started on IV biotin and thiamine, and showed rapid neurological improvement.[30] In a 1975 study from Greece that included infants with generalized seborrheic dermatitis, patients were given 1 of 4 treatments.[31] The treatments included biotin 5 mg plus vitamin B complex IV over 24 hours, biotin 5 mg IV alone over 2-3 hours, biotin 5 mg alone within 1-2 minutes, and biotin IV plus antibiotics.[31] There were excellent results across all groups, and Messaritakis et al concluded that "IV administration of biotin is recommended as less painful and less dangerous than multiple intramuscular injections."[31]

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[10,12-15]	5
Observational	0
Experimental	0
Clinical practice guideline	0

Table 4. Number of studies by country

Country	**Number of Studies**
US[10,12-15]	5
	Total US: 5 Total Non-US Countries: 0

Table 5. Summary of included studies

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 1: Biotin deficiency/dependency					
Khalidi et al, 1984, US[14]	Case report	1 Patient with short bowel syndrome on home parenteral nutrition who developed biotin deficiency (0%, 54 y)	• Oral biotin and intravenous (IV) biotin	Signs and symptoms of biotin deficiency	The patient remains free from signs and symptoms of biotin deficiency and is maintained on an IV multivitamin product with 60 mcg biotin/day.
Kien et al, 1981, US[12]	Case report	2 Patients with congenital syndrome of secretory diarrhea and seizures on a biotin-free total parenteral nutrition developed skin rash, alopecia, and mucocutaneous candidiasis (50%, range 5.42-6.75 y) *Note: Patients were siblings, the younger sister died before biotin determinations were available.	• IV biotin	Improvement and/or resolution of organic aciduria, hair, fingernail, and skin lesions	"We speculate that biotin-responsive in vivo carboxylase deficiency may develop in children receiving biotin-free [total parenteral nutrition] TPN particularly if they have malabsorption syndromes or diarrhea. We suggest, based on our experience and the recommendations of others, that biotin be routinely administered to patients receiving TPN."
Levenson, 1983, US[15]	Case report	1 Patient with multiple enteric fistuale who developed severe depression after months of parenteral hyperalimentation (100%, 34 y)	• Parenteral biotin	Improvement of signs of symptoms of depression	"Biotin-deficiency should be suspected in patients on hyperalimentation (without biotin supplementation) who develop similar symptoms."
Mock et al, 1985, US[13]	Case reports	3 Patients who developed biotin deficiency during parenteral alimentation (66.67%, range 11-13 months)	• IV biotin	Improvement and resolution of rash and alopecia; acceleration of mental and neuromotor development	"We conclude that plasma biotin concentration does not reflect biotin status in all cases and speculate that the biotin supplement currently recommended for pediatric patients (20 ug/day) may not be adequate therapy for biotin deficiency and might not even be adequate to maintain normal biotin status during TPN."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Nisenson, 1969, US[10]	Case reports	4 Patients with extensive seborrheic dermatitis or Leiner disease (33.33%*, range 1-3 weeks) *The gender for 1 patient was not specified so it was not included in the male % count. The other patients include 2 females and 1 male.	• Parenteral biotin* *Note: Biotin injections were given to the mother so the infant could receive it via breast milk.	Improvement of skin lesions and rash clearing	"On the basis of this limited experience, injections of biotin to the nursing mother appear to be a useful treatment."

Abbreviations: IV, intravenous; TPN, total parenteral nutrition.
[a]As defined by study authors.

Table 6. Dosage by indication – US

Indication	Dosage	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Biotin deficiency[10,12-15]	0.06-10 mg/day	5 mg/mL	–	Intravenous, parenteral	Single dose – 3 months Long-term

Abbreviation: –, not provided.

Table 7. Dosage by indication – non-US countries

No non-US studies were included

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 biotin. Among the 9 SMEs, there were 8 pharmacists and 1 naturopathic doctor. The SMEs specialized and/or were board-certified in nutrition and naturopathic medicine, and were working in academic medical institutions, inpatient practice, outsourcing facilities, and consulting. The SMEs had been in practice for 8 to 43 years.

Several SMEs commented that biotin deficiency is extremely rare with 1 SME stating, "We have quite a number of patients on long-term parenteral nutrition [at] home for 20 or more years, and have not seen anybody with that deficiency." One SME explained that this is partly because there is no readily available test and even if a blood test was performed, it does not "necessarily tell you definitively that they truly have a deficiency. You'd have to do it based upon clinical suspicion." Patients who are malnourished usually have multiple vitamin and micronutrient deficiencies; it's rarely 1 deficiency. Additionally, biotin deficiency is difficult to identify because many symptoms could be the result of other deficiencies that would need to be ruled out before considering checking a biotin level. There have been case reports published from the 1970s and 1980s, but the SME added, "Nowadays I think it's a pretty rare occurrence to actually see it in clinical practice."

While biotin deficiency is rare, 2 SMEs discussed providing supplementation to patients. One SME stated that they provide biotin supplementation to "kids with inborn errors in metabolism, but it's enteral, it's not parenteral, and they get it in the B complex and their MVI [multi-vitamin injection] if it's a PN [parenteral nutrition] patient. Never had a request in my 40 years for biotin supplementation in PN, or for anybody. Just the enteral." Another SME mentioned that "in the adults, over my 40 years in practice, we probably had one or two dieticians, maybe, pick up a suspected biotin deficiency. But most of those patients, we can manage with oral products." One SME had a patient diagnosed with biotinidase deficiency, a rare genetic condition that requires supplementation with "massive amounts of biotin," at newborn screening. The SME stated that the normal requirement for a neonate is 5 mcg/day, and this patient required 5 to 20 mg/day. The patient was able to eat and take oral medications, so an oral suspension was used for treatment. Due to the increased requirements for these patients, there is a need for higher concentrations than what is commercially available, as well as alternative dosage forms since this condition is diagnosed at birth. But, as the SME stated, "It was a once in a lifetime opportunity."

In contrast, 1 SME who specializes in naturopathy commented they use biotin a lot, but typically "as an addition to a multi-nutrient IV formula." This addition is typically done in patients with neurological autoimmune conditions, especially in patients with multiple sclerosis. Another indication with anecdotal benefit is general neuroinflammatory or chronic pain conditions, such as polymyalgia, fibromyalgia, and peripheral neuropathy. The goal is "generally palliative or symptom management" and is "a very small part of a much larger treatment strategy." They "have seen [biotin] used alongside standard autoimmune therapies to first treat symptoms, but…sometimes it actually can slow a progression of degeneration in those sorts of conditions." The SME stated that biotin is involved in the biochemical neurological repair

process and neurological support pathways because it is a co-factor along with a few other vitamin Bs. Biotin is a big co-factor involved in carboxylase reactions, and this SME has found that "other B vitamins [also] do that, but if you [do not] have biotin and apparently people are not as replete with biotin, with neurological problems, the carboxylase reactions slow down," backing up a lot of neuro-inflammatory activity. The SME expressed that in about 90% of patients will be given infusion with the remaining 10% receiving biotin added to a B-complex IM injection; infusion or injection administration would occur in office. The frequency would depend on the severity of inflammation and/or aggravation. For a more severe case, "[patients] might do two infusions a week for a month, and then one infusion, and then taper off. If [it is] more of a chronic case, [it is] usually one infusion weekly or biweekly." This SME stated there is no commercially available biotin product.

Biotin is a component of the commercially available injectable multivitamin products, which currently are on shortage. The current recommendation is to reduce administration to 3 times a week, and if possible, supplement with oral vitamins with the understanding that "they may not absorb 100% of it." In the event of a shortage there may be a need to provide the individual components; however, 1 SME stated "if we were to compound our own multivitamins… let's say there's usually quite a number of other components that are a little bit more critical than biotin. So, if I was ranking them, it would be a little further down the list."

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

Participants were asked to discuss the decision-making process used at their facility to determine what products to obtain from an outsourcing facility. One major theme that emerged from this discussion was that many of the products purchased from outsourcing facilities are used in critical care areas, such as EDs and operating rooms (ORs). Participants commented that outsourcing facilities are able to provide ready-to-use products that have longer beyond-use dates compared to products compounded in-house, allowing these products to be stocked in automated dispensing cabinets (ADCs) in these units. One participant commented that "we're always going to outsource a PCA [patient-controlled analgesia] syringe because we can store it in a Pyxis machine versus us making it and storing it in a fridge." Another participant commented on the benefits of storing medications in an ADC, stating that "operationally, if you have a stat medication or something that needs to be delivered within 10 to 15 minutes, if you're looking at us doing it, you're looking at a five-minute gown and glove. If we don't have somebody in the IV room, if you're doing 797 right, it's five minutes. It's four minutes to tube it. It's three minutes to

make it, and then you have a dosage system or a camera system, a few minutes more. We are not able to meet that need or they're just contaminating the IV room if they are trying to do it."

Having ready-to-use products available also minimizes the need for compounding and product manipulations to occur on the floor. This can be especially beneficial in children's hospitals as they face a unique need in that they already perform a lot of manipulations to products due to a lack of concentrations or sizes available. One participant commented that "at baseline, already, we manipulate about 80% of what we dispense to patients" and another stated that "there's a number of drugs that require additional manipulation, to get them to a concentration that's appropriate for kids." One participant stated that "we're trying to minimize compounding, expedite actual therapies to patients in that setting [OR], minimize manipulations as much as possible." Similarly in the ED, 1 participant stated they prefer ready-to-use products for some floor-stock items, like vasopressor infusions, to prevent compounding from occurring on the floor. Another commented that "we absolutely buy as many pressor drips as we can." One participant remarked that they have received requests from anesthesiologists for products that are commercially available in vials that require manipulation prior to administration to be purchased as syringes from outsourcing facilities stating that "they would prefer to have a syringe form."

Another theme regarding the decision of which products to purchase from an outsourcing facility was focused on the use and volume of a product that is needed and the overall impact this would have on the pharmacy workload. Critical care areas, such as the ED and OR, typically have a high-product utilization and overall turnover leading to several participants obtaining products intended for use in these areas from outsourcing facilities. Participants stated that they evaluate the volume of product needed and the frequency in which that volume is needed compared to the time it would take pharmacy staff to prepare this volume. One participant commented that "we look at the impact that it'll have on staff. If our staff are needing to batch, or if we need to mass produce these in particular to meet the patient demand, then those are the items that we're going to look to potentially move out." Another participant, while they do not obtain a lot of products from outsourcing facilities, stated that "when we do purchase from 503Bs, typically, it would be if we just don't have the capacity to keep up with what the demand is." One participant also commented that they will obtain labor-intensive and more complicated products, such as epidurals and cardioplegia solutions, from outsourcing facilities, to reduce the workload on pharmacy staff. The COVID-19 pandemic also impacted the operations of hospitals with 1 participant who stated, "It's just really high volume, and the bigger the hospital, the higher the volume, especially when you have one disease state in half of your hospital," and another who expressed that "without 503B, we would've been in significant trouble." One participant commented that "even though the number might be small [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 1 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; therefore, they perform sterile compounding in a segregated compounding area. United States Pharmacopeia (USP) <797> standards limit the beyond-use-date that can be assigned to these products and, as the participant stated, "we obviously need to provide product with much extensive beyond-use-dating than we can provide." Several participants also commented that they do not perform high-risk compounding in-house, and, therefore, all of these products are outsourced. There are

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

Standardization of products, including concentration, volume, and labeling, was also a driver for obtaining products from an outsourcing facility. However, such standardization may not always be possible. One participant stated that when evaluating similar facilities, it would be expected that they would 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, 1 participant observed, "These practices had evolved somewhat disparately. Even if we had clinical practice guidelines, nobody was putting concentrations into those guidelines and volumes into those guidelines." This has led to challenges with obtaining certain products from outsourcing facilities. As another participant said, "I think we made nine different epidural concentrations, all driven by anesthesia, and they want what they want and 503Bs may not offer that. [If] no one else in the country is buying that same concentration, a 503B isn't going to go through the expense of adding that to their product list." The participant continued that "similar with the ADCs, we've run into situations where dextrose 50% goes on shortage, and the 503Bs would be selling it in a syringe. For safety reasons and for crash cart reasons, without having to retrain thousands of nurses of where things are placed, they said, 'No, we can't have it, and that's too big it won't fit.' We want it in this format and then we're stuck again because there's no 503B offering a format during that shortage that fits where it needs to go. Then we're stuck in sourcing." Additionally, while a commercially available product may be available, the volume may not be appropriate. One participant stated that "3% saline for instance, is sold in a 500 mL bag, but the clinical guideline is a 150 mL bolus. We're either going to draw that out or we're sending it to the ER [emergency room] with stickers all over it saying only give 150 [mL]." The participant continued that "it would be great if the FDA could look at the size of the container that they're approving and whether that's a realistic dose. Is it a unit dose, or isn't it?"

Participants had differing opinions on the use of outsourcing facilities to obtain drugs during a shortage. Several participants stated that they will typically first restrict use of a drug on shortage to conserve supply before turning to an outsourcing facility. One participant commented that "most of the time, I will probably pursue restricting, conserving, and looking at all available options prior to going to an outsourcer on my end," and another stated, "I can only think of one time in recent history where we went to an outsourcer." One participant commented that "503Bs can't accept the additional volume if it's a true shortage. If you're not with them pre-shortage, you're not going to get products when you need it during the shortage… typically in a shortage, you learn to live without them. You have to." Additionally, in the event of the shortage being the result of lack of an API, outsourcing facilities are likely to be affected equally and unable to provide assistance. However, 1 participant stated that they first began working with

outsourcing facilities because of shortages. This participant commented that "what the 503Bs are starting to do, some of the large ones, is that they are also conducting validation studies on API. If sterile becomes short, they quickly switch to producing through API, which ASHP [American Society of Hospital Pharmacists] and the FDA allows." This "adds a lot of flexibility so they can bounce back and forth, and really try to insulate us from shortages."

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

A few participants commented on the need for preservative-free products, particularly in pediatric patients. The example of methadone was provided as it is used for patients with neonatal abstinence syndrome but is only available as a preservative-containing product. There is a need for this product to be compounded from API as a preservative-free product. One participant stated that "if there's not a preservative-free containing option, it really should be something that should be able to be compounded for bulk... especially for the pediatric patient population." However, another participant from a children's hospital stated that the need for a preservative-free option has never been a reason why they have obtained a product from an outsourcing facility. Preservative free is also an issue for ophthalmic products; however, 1 participant observed this is more on the 503A side. One participant stated that obtaining ophthalmic products from outsourcing facilities has been a challenge and that there are products they would like to obtain from outsourcing facilities but cannot, forcing them to compound them in-house. This participant also commented that there are 2 outsourcing facilities that compound ophthalmic products but when they reviewed the facilities, they did not pass their internal quality standards; 1 facility had been banned from distributing products in California by the Board of Pharmacy. There is an additional challenge with obtaining cephalosporins and beta-lactams due to the potential cross reactivity in patients with allergies. One participant stated that there are some cephalosporins they would like to obtain from an outsourcing facility but cannot because "they would have to build a separate clean room with a dedicated HVAC [heating, ventilation, and air conditioning], so you're talking millions of dollars in investment for actually very low volume. Right now, the ROI [return on investment] isn't there." Another participant stated that the concentrations required for ophthalmic antibiotics are not available but the labor and risk of compounding these products in-house is not worth it.

A few participants commented on purchasing nonsterile products from outsourcing facilities. Lidocaine-epinephrine-tetracaine (LET) gel used as a topical anesthetic was the most-commonly obtained product along with buffered lidocaine to put in J-Tips. Another participant stated that they obtain diclofenac suppositories from an outsourcing facility due to the high cost of indomethacin suppositories. One participant commented that most of the products they outsource are nonsterile products, generally for oral or topical administration, due to a lack of availability of commercial products. The participant stated that they purchase low-dose naltrexone for oral use in patients with refractory fibromyalgia and ketamine troches for patients with chronic pain. The participant continued that while the evidence does not support many of the ingredients used in topical pain products; "however, there are select patients. It's very rare that taking that cream away from them actually causes more harm than good." A few participants

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

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

other drugs." There is a commercially available product; however, it is only available as a 500-mL bag and the dose needed is typically less than 30 mL. If the syringes are prepared in-house, then the beyond-use-date is limited to 12 to -24 hours depending on storage, which results in waste.

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

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

The participants also discussed challenges with using outsourcing facilities. One participant stated that their facility does not use outsourcing facilities because "it just hasn't been financially, not just the money worth it, but just the lead time for how much time you have to give them and how much you have to... It just isn't worth the dating that they gave us or can give us." Another commented that they obtain very little product from outsourcing facilities due to the "amount of work for vetting and continually validating quality of these 503B outsourcing facilities." The participant stated that they have a robust validation process that takes several months, and includes a site visit prior to purchasing from an outsourcing facility, followed by continuous reviewing of quality reports and warning letters. Another challenge has been the reliability of the outsourcing facility. One participant commented, "Traditionally, we've found 503Bs to be fairly unreliable, when we have partnered with certain ones, to be able to keep up with the volume. Everybody knows PharMEDium just closed. But we've had some other smaller 503Bs where we've had agreements for certain products to take it off our plate, and then, lo and behold, they're shut down, or closed, or whatever it may be."

Minimum purchase amounts were also reported as a concern with 1 participant stating that "what we see consistently is the 503Bs, they want us to commit to giving them a certain volume, but then will not give us a reciprocal commitment or at least will not fulfill that reciprocal commitment. That's a huge problem for us making that type of commitment, when we do ultimately have to split our volume in order to make sure that we consistently are able to take care of our patients." Another challenge was related to outsourcing facilities using API to compound narcotics. One participant commented that this often worsens drug shortages due to the quotas that the Drug Enforcement Administration (DEA) places on the quantity that can be produced. The participant stated that "they [outsourcing facilities] want to buy the product that we're trying to buy to take care of our patients today, to sell us tomorrow. We really need the FDA to say that, especially for controlled substances, that 503Bs can consistently prepare those products so that we don't end up with a shortage year after year after year, and then chasing our tail. Also, we may actually want to tell 503Bs, they can't buy those products or that they're limited in the amount of their ability to buy those products to make what are essentially copies of commercially available products because it actually induces the shortage in many ways."

Results of survey

Two 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, 2 (100%) used biotin. Respondents used biotin as an IV injection (1, 50% of respondents) and in an unspecified ROA (1, 50%).

A prequestionnaire was distributed to participants of the roundtable discussion (refer to Appendix 2.2 for survey instrument).

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

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

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

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

Table 11. Characteristics of survey respondents

Terminal Clinical Degree	**Responses, n (N = 2)**
Doctor of Medicine (MD)	0
Doctor of Osteopathic Medicine (DO)	0
Doctor of Medicine in Dentistry (DMD/DDS)	0
Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)	0
Naturopathic Doctor (ND)	1
Doctor of Nursing (DNP) or Master of Nursing (MSN)	0
Physician Assistant (PA)	0
No Response	1
Practice Setting	**Responses, n (N = 2)**

Physician office or private practice	1
Outpatient clinic	0
Hospital or health system	0
Academic medical center	0
Emergency room	0
Operating room	0
No response	1

Table 12. Conditions for which biotin was prescribed or administered

Condition	Responses, n (N = 2)
Biotin deficiency	1
No Response	1

Table 13. Reasons for using compounded biotin

No survey respondents provided this information

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

No survey respondents provided this information

Table 15. Demographics of prequestionnaire respondents' facilities

Type of Facility	Responses, n (N = 102)[a]
Academic medical center	15
Acute care hospital	16
Children's hospital	8
Community hospital	11
Critical access hospital	2
Dialysis center	2
Federal government hospital	4

Health system	15
Inpatient rehabilitation center	4
Long-term acute care hospital	3
Outpatient surgery center	6
Rural hospital	2
Skilled nursing facility	0
Specialty hospital[b]	4
Trauma center	5
Urban hospital	5
Number of Beds	**Responses, n (N=39)**
< 50	4
50-99	3
100-199	1
200-299	4
300-399	5
400-599	3
> 600	19

[a]Respondents allowed to select 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]
Backorders	20
Convenience	19
Cost	10
Need for concentrations not commercially available	19
Need for multi-ingredient products not commercially available	10

Need for preservative-free products	3
Need for ready-to-use products	27
No FDA-approved product available	7
No onsite compounding facility	1
Onsite compounding facility not equipped to compound all necessary products	19
Other[b]	8

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

Table 17. Categories of products obtained from outsourcing facilities

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

[a]Respondents allowed to select multiple categories.
[b]Respondents reported obtaining alum for bladder irrigation, oxytocin, anticoagulant sodium citrate solution, narcotic drips, high-cost antiseizure 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

Biotin was nominated for inclusion on the 503B Bulks List as a 60-mcg IV injection to treat biotin deficiency. Biotin is not available in the nominated dosage form and ROA in any of the national medical registries searched.

From the literature review, 5 studies were included. All the studies were case reports in which biotin was used as an injection to treat biotin deficiency.

From the interviews, biotin is a component of the commercially available multivitamin injection products, and while most SMEs stated that biotin deficiency is rare, 1 had an experience with a patient diagnosed with biotinidase deficiency at birth that required supplementation with large doses of biotin. When biotin supplementation is needed, the commercially available oral products are typically sufficient; however, since true deficiencies are often diagnosed at birth there is a need for higher concentrations and different dosage forms to be available to treat these patients. One SME stated that they have used biotin as part of a multi-nutrient IV formulation in patients with neurological autoimmune conditions.

From the survey responses, 2 out of 2 respondents used biotin. Only 1 respondent reported using biotin as an IV product to treat biotin deficiency. No responses were received for the reasons for using the compounded biotin product instead of an FDA-approved product. From the prequestionnaire, 0 respondents obtained biotin from a 503B outsourcing facility.

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APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process, and other non-indexed citations and daily 1946 to November 10, 2020
- Date last searched: November 12, 2020
- Limits: Humans (search hedge); English language
- Number of results: 509

1	biotin/	14,003
2	biotin$.tw.	40,955
3	vitamin$ b7.tw.	30
4	vitamin$ b 7.tw.	2
5	vitamin$ bw.tw.	0
6	vitamin$ b w.tw.	0
7	vitamin$ h.tw.	75
8	w factor.tw.	9
9	or/1-8	44,536
10	exp administration, intravenous/	143,813
11	infusions, parenteral/	26,287
12	injections/	42,824
13	injections, intramuscular/	31,129
14	exp parenteral nutrition/	24,105
15	parenteral nutrition solutions/	457
16	(parenteral$ adj2 (administ$ or deliver$ or nutrit$ or therap$ or treat$)).tw.	31,766
17	intravenous$.tw.	343,695
18	intra venous$.tw.	582
19	intravascular$.tw.	48,281
20	intra vascular$.tw.	306

21	intramuscular$.tw.	52,934
22	intra muscular$.tw.	722
23	inject$.tw.	748,927
24	or/10-23	1,208,716
25	biotin deficiency.rs.	104
26	exp amino acid metabolism, inborn errors/	26,241
27	lactic acidosis congenital infantile.rs.	9
28	lactic acidosis, congenital infantile, due to lad deficiency.rs.	7
29	acidosis, lactic/	3251
30	methylmalonyl-coa decarboxylase/	342
31	drug therapy/	30,650
32	de.fs.	3,012,397
33	dt.fs.	2,250,307
34	ad.fs.	1,427,464
35	tu.fs.	2,244,917
36	pc.fs.	1,303,432
37	abiotin$.tw.	7
38	((biotin$ or vitamin$ b or vitamin$ b7 or vitamin$ h) adj3 (deficien$ or deplet$ or insufficien$ or supplement$)).tw.	3193
39	avitamin$.tw.	638
40	hypovitamin$.tw.	2590
41	((inborn error or inherited error) adj3 metabol$).tw.	1902
42	((biotinidase or carboxylase or holocarboxylase) adj3 (deficien$ or deplet$ or insufficien$)).tw.	920
43	(propionic adj3 (acid?em$ or acidur$)).tw.	779
44	propionicacid?em$.tw.	25
45	propionicacidur$.tw.	0
46	(ketotic adj3 (glycin?em$ or hyperglycin?em$)).tw.	195

47	(lact$ adj3 acidosis).tw.	7061
48	lactacidosis.tw.	188
49	therap$.tw.	2,837,130
50	treat$.tw.	5,595,425
51	prevent$.tw.	1,445,744
52	prophyla$.tw.	167,177
53	or/25-52	11,134,226
54	and/9,24,53	1445
55	exp animals/ not humans/	4,754,888
56	54 not 55	540
57	limit 56 to english language	509

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: 720

1	'biotin'/de	23,436
2	'biotin*':ti,ab,tn	49,257
3	'vitamin* b7':ti,ab,tn	53
4	'vitamin* b 7':ti,ab,tn	10
5	'vitamin* bw':ti,ab,tn	1
6	'vitamin* b w':ti,ab,tn	0
7	'vitamin* h':ti,ab,tn	135
8	'w factor':ti,ab,tn	28
9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	54,336
10	'intravascular drug administration'/de	342
11	'intravenous drug administration'/exp	394,020
12	'intramuscular drug administration'/de	71,806
13	'injection'/exp	248,200
14	'parenteral nutrition'/exp	51,494
15	'nutrition supplement'/exp	18,614
16	(parenteral* NEAR/2 (administ* OR deliver* OR nutrit* OR therap* OR treat*)):ti,ab	46,951
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	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23	1,947,356
25	‘biotin deficiency’/de	185
26	‘disorders of amino acid and protein metabolism’/exp	111,695
27	‘disorders of carbohydrate metabolism’/de	3402
28	‘carboxylase deficiency’/de	13
29	‘lactic acidosis’/de	14,024
30	‘drug therapy’/de	763,127
31	‘drug dose’:lnk	627,641
32	‘drug administration’:lnk	1,774,693
33	‘drug therapy’:lnk	3,969,308
34	‘prevention’:lnk	1,187,731
35	‘abiotin*’:ti,ab	18
36	((biotin* OR ‘vitamin* b’ OR ‘vitamin* b7’ OR ‘vitamin* h’) NEAR/3 (deficien* OR deplet* OR insufficien* OR supplement*)):ti,ab	7024
37	‘avitamin*’:ti,ab	1692
38	‘hypovitamin*’:ti,ab	4448
39	((‘inborn error’ OR ‘inherited error’) NEAR/3 metabol*):ti,ab	3271
40	((biotinidase OR carboxylase OR holocarboxylase) NEAR/3 (deficien* OR deplet* OR insufficien*)):ti,ab	1254
41	(propionic NEAR/3 (acid$em* OR acidur*)):ti,ab	1169
42	‘propionicacid$em*:ti,ab	28
43	‘propionicacidur*:ti,ab	0
44	(ketotic NEAR/3 (glycin$em* OR hyperglycin$em*)):ti,ab	309
45	(lact* NEAR/3 acidosis):ti,ab	10,393
46	‘lactacidosis’:ti,ab	238
47	‘therap*’:ti,ab	4,272,993

48	‘treat*’:ti,ab	8,117,423
49	‘prevent*’:ti,ab	1,965,741
50	‘prophyla*’:ti,ab	266,813
51	#25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50	13,637,144
52	#9 AND #24 AND #51	1901
53	[animals]/lim NOT [humans]/lim	6,119,435
54	#52 NOT #53	775
55	#52 NOT #53 AND [english]/lim	720

Appendix 2.1. Survey instrument for professional medical associations

1. How familiar are you with the following terms?

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

2. Do you prescribe or administer biotin to your patients?
    - Yes
    - No
3. Do you prescribe or administer biotin by any of the following dosage forms and/or routes of administration? (check all that apply)
    - Intravenous injection
    - None of the above
4. I prescribe or administer biotin for the following conditions or diseases: (check all that apply)
    - Biotin deficiency
    - Other (please explain) _____
5. I use compounded biotin 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 biotin
    - Other (please explain) _____
6. Do you stock non-patient-specific compounded biotin at your practice?
    - Yes
    - No
    - I'm not sure
7. I obtain compounded biotin 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 2.2. 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
    - Backorders
    - Convenience
    - Cost
    - Need for concentrations not commercially available
    - Need for preservative-free products
    - Need for ready-to-use products
    - No FDA-approved products available
    - No onsite compounding facility
    - Onsite compounding facility not equipped to compound all necessary products
    - Other, please explain _____
5. Please select the type(s) of products obtained from an outsourcing facility.
    - Nonsterile products
    - Sterile products
6. Please select the category(ies) of products obtained from an outsourcing facility.
    - Cardioplegic solutions
    - Dermatologic preparations
    - Dialysate solutions

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

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

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

Appendix 3. Survey distribution to professional associations

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

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