

Summary Report

Norepinephrine bitartrate

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Food and Drug Administration

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

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Prepared by:

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

University of Maryland School of Pharmacy

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Frequently Used Abbreviations

API	Active Pharmaceutical Ingredient
ASHP	American Society of Health-System Pharmacists
D5W	Dextrose 5% in water
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
IRB	Institutional Review Board
ICU	Intensive care unit
IV	Intravenous
NS	Normal saline
OTC	Over-the-counter
ROA	Route of administration
SME	Subject matter expert
UK	United Kingdom
US	United States

INTRODUCTION

This report was created to assist the Food and Drug Administration (FDA) in their evaluation of the use of norepinephrine bitartrate (UNII code: IFY5PE3ZRW), 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 norepinephrine bitartrate 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 norepinephrine bitartrate 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 norepinephrine bitartrate and thereby assist the FDA to determine whether there is a need for the inclusion of this substance on the 503B Bulks List.

REVIEW OF NOMINATIONS

Norepinephrine bitartrate was nominated for inclusion on the 503B Bulks List by Specialty Sterile Pharmaceutical Society (SSPS), US Compounding Pharmacy, the Outsourcing Facilities Association (OFA), Pentec Health, and Athenex Pharma Solutions, LLC.

Norepinephrine bitartrate was nominated for treatment of cardiogenic shock, hypotension, septic shock, and upper gastrointestinal bleeding via intravenous (IV) bags in strengths ranging from 16-128 mcg/mL in 250 mL dextrose 5% in water (D5W) or normal saline (NS) and prefilled syringes in strengths from 4-16 mcg/mL in 10-20 mL (D5W or NS). The OFA and Pentec Health nominations specified the anticipated dosage form and ROA to be IV injectable vials and syringes. The strengths they intend to compound are norepinephrine bitartrate equivalent to 2 mg/mL and norepinephrine in 4 mg/2 mL, 8 mg/4 mL, and 16 mg/8 mL.

Norepinephrine bitartrate will also be used to treat acute hypotension and cardiac arrest via a 0.004-1 mg/mL IV injection solution diluted into potential diluents such as sterile water for injection, sodium chloride, and dextrose. A preservative-free 32 mcg/mL IV solution added to injection diluents such as sterile water for injection, sodium chloride, dextrose, lactated ringers, and dextrose/lactated ringers will also be compounded.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of norepinephrine bitartrate.^{6,7}

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

- Compounded product may be the only product to effectively treat the indication for which it is intended.
- Patient need for dosage form or strength, including greater concentration, that is not available commercially.
- Patient sensitivities to dyes, fillers, preservatives (i.e., sodium metabisulfite) or other excipients in manufactured products.
- With norepinephrine available as a bulk API, companies can “compound doses diluted to final concentration in a ready to administer form.”

- A ready-to-administer bag reduces contamination risk and the potential for medication error. Compounding norepinephrine will also allow a “hospital to order a ‘standard concentration’ with longer expiration.” American Society of Health System Pharmacists (ASHP) promotes using standard concentrations.
- Manufacturer backorder.
- There is a need for “concentration stable ready-to-use products” due to diluent bag evaporation issues. The medication premixed in plastic IV containers often have their overwraps removed before they are needed (sometimes more than 30 days prior to use). The fluid contents of the IV bags will evaporate over time when the protective overwrap is removed. This may put patients at risk of receiving more drug than prescribed due to decrease in the fluid volume causing the drug concentration to increase. Using commercial FDA approved products may limit the 503B’s ability to assign extended expiration dates since most commercial manufacturers recommend that the product-diluent bag compound must be done within 15-30 days after overwrap removal. This issue along with the time it takes to do sterility and stability testing, makes “formulating/compounding from commercial FDA-approved product impracticable to meet hospital and patients’ needs.” There has also been a shortage of the FDA-approved diluent bags, which could be exacerbated by 503B’s needs for the bags as well.
- There is a need for a concentrated ready-to-use product to improve dose accuracy and keep risk of sterility breaches to a minimum.
- 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 API is safer and more efficient than unmanageable amounts of small vials.
- As required by Current Good Manufacturing Practices, bulk API powders can be formulated to 100 percent 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 norepinephrine bitartrate 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 norepinephrine bitartrate; name variations of norepinephrine bitartrate 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; 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 norepinephrine bitartrate. 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

Norepinephrine bitartrate is a component of an FDA-approved product. The nominated products did not differ substantially from the commercially available product. Therefore, a systematic literature review was not conducted.

Interviews

Semi-structured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances norepinephrine bitartrate was used in a clinical setting. The systematic literature review and indications from the nominations were reviewed to identify medical specialties that would potentially use norepinephrine bitartrate. 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 norepinephrine bitartrate in clinical practice. The online survey was created using Qualtrics® software (refer to Appendix 2 for complete survey). A Google™ search was conducted to identify the professional associations in the US for the relevant medical specialties. An association's website was searched to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used. An email describing the project and requesting distribution of the survey to the association's members was sent to the

identified person(s). Associations that declined, did not respond, or did not provide significant data in project Years 1 and 2 were not contacted to distribute the project Year 3 surveys.

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

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

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

CURRENT AND HISTORIC USE

Results of background information

- Norepinephrine bitartrate is available as an FDA-approved product in the nominated dosage form and ROA.
- Norepinephrine bitartrate is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for norepinephrine bitartrate.
- Norepinephrine bitartrate is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, Latvia, New Zealand, Saudi Arabia, and UK.

Table 1. Currently approved products – US^a

Active Ingredient	Concentration	Dosage Form	Route of Administration	Status	Approval Date^b
Norepinephrine bitartrate	EQ 1 mg base/mL	Injectable	Injection	Prescription	Approved prior to Jan 1, 1982

^aSource: US FDA *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).

^bIf multiple approval dates and/or multiple strengths, then earliest date provided.

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

Active Ingredient ^b	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date ^c
Norepinephrine bitartrate	0.016 mg/mL – 2 mg/mL	Liquid, solution	Infusion, intravenous	Abu Dhabi	Active	–
				Australia	Prescription	11/29/2012
				Belgium	Prescription	12/31/1961
				Canada	Ethical	12/31/1991
				Hong Kong	Prescription	9/11/1998
				Ireland	Prescription-only non-renewable	4/10/1995
				Latvia	Prescription	2/4/2019
				New Zealand	Prescription	9/18/2014
				Saudi Arabia	Prescription	–
				UK	Prescription-only medication	3/2/2010

Abbreviation: “–”, not mentioned.

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

^bNorepinephrine bitartrate used as the standard for name variations, including norepinephrine, norepinephrinum, noradrenaline acid tartrate, and noradrenaline tartrate.

^cIf multiple approval dates and/or multiple strengths, then earliest date provided.

Results of literature review

No literature review was conducted.

Characteristics of included studies

No literature review was conducted.

Use of norepinephrine bitartrate

No literature review was conducted.

Pharmacology and historical use

There were 7 studies identified that provided valuable information about the pharmacology and historical use of norepinephrine bitartrate. Two additional references were found that provided information about the current availability of norepinephrine bitartrate.

Levophed® (norepinephrine bitartrate) injection for IV use is supplied as a 4 mg/4 mL (1 mg/mL) norepinephrine base per vial or ampule.⁸ Per the Levophed® package insert, norepinephrine needs to be diluted prior to use.⁸ One vial or ampule should be added to “1,000 mL of 5% dextrose injection, USP or sodium chloride injection solutions that contain 5% dextrose to produce a 4 mcg per mL dilution.”⁸ For patients needing fluid restriction, higher concentrations can be used.⁸ The Levophed® package insert also states that norepinephrine should be stored at 20°C to 25°C (68°F to 77°F) with excursions permitted to 15°C to 30°C (59°F to 86°F); it should also be in the original carton until administration to protect it from light.⁸

Norepinephrine is frequently used in the intensive care units (ICUs) and in the operating room.^{9,10} Medication errors are frequently associated with the dilution step.⁹ “Compounding hospital pharmacies provides qualitative injectable solutions and avoids the dilution step in the ward.”⁹ Norepinephrine stability is “highly sensitive to storage conditions.”⁹ Norepinephrine easily undergoes oxidation processes because of its catechol substructure, and these degradation processes can be catalyzed by light, air, elevated temperature, heavy metals, basic conditions or other excipients.¹¹ A French study by Gilliot et al investigated the 365 day stability of norepinephrine 0.2 mg/mL and 0.5 mg/mL solutions diluted in NS and stored in polypropylene syringes or cyclic olefin copolymer vials.⁹ Gilliot et al concluded that the ready-to-use norepinephrine solutions “must be stored at refrigerated or frozen temperatures to obtain acceptable 1 year shelf-stability.”⁹ In another Canadian study by Tremblay et al, they evaluated the stability of norepinephrine in D5W and NS solutions (final concentrations of 4 mcg/mL and 16 mcg/mL) for 7 days.¹⁰ Tremblay et al concluded that the diluted norepinephrine solutions were chemically stable for 7 days at room temperature and under ambient light.¹⁰ There was also a Belgium study by Closset et al that explored the physical stability of highly concentrated injectable drugs used in the ICU for 48 hours.¹² Norepinephrine with a final concentration of 0.12 mg/mL and 0.24 mg/mL was among one of the drugs studied in 0.9% sodium chloride polypropylene syringes and Closset et al concluded that norepinephrine was “physically stable at room temperature for 48 hours.”¹²

The ASHP has the Standardize 4 Safety initiative to develop national standardized concentrations for IV medications in both pediatrics and adults.^{13,14} For norepinephrine, the concentration standards are 16 mcg/mL, 32 mcg/mL, and 64 mcg/mL which are not commercially available.^{13,14} ASHP states there is the possibility of concentration and unit mismatch depending on the pharmacy or outsourcing facility label.^{13,14}

The FDA Drug Shortages list does not include norepinephrine products while the ASHP Current Drug Shortage list includes norepinephrine products.^{15,16} The ASHP list includes 1 mg/mL ampules and vials (first posted on February 22, 2017).¹⁶ The 1 mg/mL Levophed® injection by Pfizer 4 mL ampule (10 count) is discontinued while the Levophed® 4 mL vials are on shortage because of increased demand.¹⁶ Pfizer has the vials on back order with an estimated release date in April 2021.¹⁶ The 1 mg/mL norepinephrine injection 4 mL vial (10 count) by the manufacturers Hikma and Mylan Institutional is also on shortage.¹⁶ Hikma has norepinephrine vials available with short expiration dates of before October 2021 while Mylan has vials on back order with an estimated release date in mid-February 2021.¹⁶ Both manufacturers did provide a reason for the shortage.¹⁶ ASHP reports that the manufacturers Baxter and Teva have norepinephrine ampule or vial products available.¹⁶

Table 3. Types of studies

No literature review was conducted.

Table 4. Number of studies by country

No literature review was conducted.

Table 5. Summary of included studies

No literature review was conducted.

Table 6. Dosage by indication – US

No literature review was conducted.

Table 7. Dosage by indication – non-US countries

No literature review was conducted.

Table 8. Number of studies by combination

No literature review was conducted.

Table 9. Compounded products – US

No literature review was conducted.

Table 10. Compounded products – non-US countries

No literature review was conducted.

Results of interviews

One hundred eighty-four SMEs were contacted for interviews; 64 agreed to be interviewed, and 120 declined or failed to respond to the interview request. Zero SMEs discussed norepinephrine bitartrate. Additional information was collected as part of the Expanded Information Initiative, referred to as Phase 3, project in which outreach was conducted to the nominators of the bulk drug substances to remedy information gaps in the initial nomination.

As part of Phase 3, 2 nominators provided additional information regarding the products that will be compounded using norepinephrine bitartrate.

Norepinephrine bitartrate will be compounded as a 2 mg/mL IV solution for the treatment of hypotension. This product is used by practitioners as a non-patient specific compounded product in emergency rooms, operating rooms, inpatient wards, intensive care units, surgical centers, and ambulances. This product is needed because there is no FDA approved ready-to-use norepinephrine IV infusion product available; the commercially available product requires dilution prior to administration.

Norepinephrine bitartrate will be compounded as a 2 mg/mL IV solution packaged in vials and syringes for continuous infusion to treat cardiogenic shock, hypotension, and septic shock. This product is used by practitioners as a non-patient specific compounded product in emergency rooms and operating rooms. This product is needed because the FDA approved product contains sodium metabisulfite, of which 3-10% of asthmatic patients are allergic.

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

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

Participants were asked to discuss the decision-making process used at their facility to determine what products to obtain from an outsourcing facility. One major theme that emerged from this discussion was that many of the products purchased from outsourcing facilities are used in critical care areas, like emergency departments and operating rooms. Participants commented that outsourcing facilities are able to provide ready-to-use products that have longer beyond-use-dates compared to products compounded in-house allowing these products to be stocked in automated dispensing cabinets in these units. One participant commented that "we're always going to outsource a PCA [patient controlled analgesia] syringe because we can store it in a Pyxis machine versus us making it and storing it in a fridge." Another participant commented on the benefits of storing medications in an automated dispensing cabinet, stating that "operationally, if you have a STAT medication or something that needs to be delivered within 10 to 15 minutes, if you're looking at us doing it, you're looking at a 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 are already having to perform a lot of manipulations to products due to a lack of concentrations or sizes available. One participant commented that “at baseline, already, we manipulate about 80% of what we dispense to patients” and another stated that “there's a number of drugs that require additional manipulation, to get them to a concentration that's appropriate for kids.” One participant stated that “we’re trying to minimize compounding, expedite actual therapies to patients in that setting [operating room], minimize manipulations as much as possible.” Similarly in the emergency department, one participant stated they prefer ready-to-use products for some floor-stock items, like vasopressor infusions, to prevent compounding from occurring on the floor and another commented that “we absolutely buy as many presser drips as we can.” One participant remarked that they have received requests from anesthesiologists for products that are commercially available in vials that require manipulation prior to administration to be purchased as syringes from outsourcing facilities stating that “they would prefer to have a syringe form.”

Another theme regarding deciding what products to purchase from an outsourcing facility was focused on the utilization and volume of a product that is needed and the overall impact this would have on the pharmacy workload. Critical care areas, like the emergency department and operating room, typically have a high product utilization and overall turnover leading to several participants obtaining products intended for use in these areas from outsourcing facilities. Participants stated that they evaluate the volume of product needed and the frequency 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 503B's, typically it would be if we just don't have the capacity to keep up with what the demand is.” One participant also commented that they will obtain labor intensive and more complicated products, like epidurals and cardioplegia solutions, from outsourcing facilities to reduce the workload on pharmacy staff. The COVID-19 pandemic has also impacted the operations of hospitals with 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 clean room and therefore perform sterile compounding in a segregated compounding area. United States Pharmacopeia (USP) <797> standards limit the beyond-use-date that can be assigned to these products and, as the participant stated, “we obviously need to provide product with much extensive

beyond use dating than we can provide.” Several participants also commented that they do not perform high-risk compounding in-house and therefore, all of these products are outsourced. There are challenges with mid-size hospitals being able “to operationalize testing compounds we make for extended stability.” One participant stated, “we might make our own syringes if we could get extended dating, but I believe my operations colleagues don’t always know how to do this and adhere to the letter of the law.”

One participant also commented on the impact that The Joint Commission has had on 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 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 with one-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 utilized. However, the products utilized 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 nine 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 continued that “similar with the ADCs [automated dispensing cabinets], we've run into situations where dextrose 50% goes on shortage and the 503Bs would be selling it in a syringe. For safety reasons and for crash cart reasons, without having to retrain thousands of nurses of where things are placed, they said, ‘no, we can't have it, and that's too big it won't fit,’ we want it in this format and then we're stuck again because there's no 503B offering a format during that shortage that fits where it needs to go. Then we're stuck in sourcing.” Additionally, while a commercially available product may be available, the volume may not be appropriate. One participant stated that “3% saline for instance, is sold in a 500 mL bag, but the clinical guideline is a 150 mL bolus. We're either going to draw that out or we're sending it to the ER with stickers all over it saying only give 150 [mL].” The participant continued that “it would be great if the FDA could look at the size of the container that they're approving and whether that's a realistic dose, is it a unit dose or isn't it.”

Participants had differing opinions on the use of outsourcing facilities to obtain drugs during a shortage. Several participants stated that they will typically first restrict use of a drug on shortage, in order to conserve supply, before turning to an outsourcing facility. One participant commented that “most of the time, I will probably pursue restricting, conserving, and looking at all available options prior to going to an outsourcer on my end” and another stated, “I can only think of one time in recent history where we went to an outsourcer.” One participant commented that “503Bs can't accept the additional volume if it's a true shortage. If you're not with them pre-shortage, you're not going to get products when you need it during the shortage” continuing that “typically in a shortage, you learn to live without them. You have

to.” Additionally, in the event of the shortage being the result of lack of an API, outsourcing facilities are likely to be equally affected and unable to provide assistance. However, one participant stated that they first began working with outsourcing facilities because of shortages. This participant commented that “what the 503Bs are starting to do, some of the large ones, is that they are also conducting validation studies on API. If sterile becomes short, they quickly switch to producing through API, which ASHP [American Society of Hospital Pharmacists] and the FDA allows.” This “adds a lot of flexibility so they can bounce back and forth and really try to insulate us from shortages.”

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

A few participants commented on the need for preservative free products, particularly in pediatric patients. The example of methadone was provided as it is used for patients with neonatal abstinence syndrome but is only available as a preservative containing product. So, there is a need for this product to be compounded from API as a preservative free product. One participant stated that “if there's not a preservative-free containing option, it really should be something that should be able to be compounded 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, 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 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. LET (lidocaine-epinephrine-tetracaine) gel, for use as a topical anesthetic, was the most commonly obtained product along with buffered lidocaine to put in J-tips. Another participant stated that they obtain diclofenac suppositories from an outsourcing facility due to the high cost of indomethacin suppositories. One participant commented that most of the products they outsource are nonsterile products, generally for oral or topical administration due to a lack of commercially available products being available. 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 one stating “I think that there is a large opportunity for more nonsterile products to be produced by 503Bs.” Another stated that as their facility grows and acquires more outpatient clinics, they receive a lot of questions regarding obtaining products for office use. The participant noted that they often have to refer these clinics to outsourcing facilities but stated “there's not many 503Bs are doing the non-sterile for clinic use.” As a result, the inpatient pharmacy is often asked to take on this role but “you don't have the space or the staff to do that.”

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

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

Four participants stated that they obtain sodium citrate as ready-to-use syringes for use as a locking solution in patients undergoing dialysis with one commenting that “our nephrologists, like it in place of heparin for some patients to keep the ports patent or so they don't have to go to alteplase or some of the other drugs.” There is a commercially available product; however, it is only available as a 500 mL bag and the dose needed is typically less than 30 mL. If the syringes are prepared in-house, then the beyond-use-date is limited to 12-24 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 2,400, 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 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 “the amount of work for vetting and continually validating quality of these 503B outsourcing facilities.” The participant stated that they have a robust validation process that takes several months and includes a site visit prior to purchasing from an outsourcing facility, followed by continuous reviewing of quality reports and warning letters. Another challenge has been the reliability of the outsourcing facility. One participant commented that “Traditionally, we've found 503B's 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 503B's where we've had agreements for certain products to take it off our plate, and then low and behold they're shut down, or closed, or whatever it may be.” Minimum purchase amounts were also reported as a concern with one participant stating that “what we see consistently is the 503Bs, they want us to commit to giving them a certain volume, but then will not give us a reciprocal commitment or at least will not fulfill that reciprocal commitment. That's a huge problem for us making that type of commitment, when we do ultimately have to split our volume in order to make sure that we consistently are able to take care of our patients.” Another challenge was related to outsourcing facilities utilizing API to compound narcotics. One participant commented that this often worsens drug shortages due to the quotas that the Drug Enforcement Administration (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

A separate survey was not constructed for norepinephrine bitartrate and therefore, no survey was distributed via professional medical associations or available on the project website.

A prequestionnaire was distributed to participants of the roundtable discussion (refer to Appendix 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) utilized outsourcing facilities to obtain drug products, 4 (9%) did not utilize outsourcing facilities, and 4 (9%) did not respond to this question.

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

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

Fifteen respondents (14% of 108 responses, where respondents were allowed to select multiple drug products) obtained norepinephrine bitartrate from a 503B outsourcing facility (refer to Table 18).

Table 11. Characteristics of survey respondents

No separate survey constructed

Table 12. Conditions for which norepinephrine bitartrate prescribed or administered

No separate survey constructed

Table 13. Reasons for using compounded norepinephrine bitartrate

No separate survey constructed

Table 14. Use of non-patient-specific compounded norepinephrine bitartrate

No separate survey constructed

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=38)
< 50	4
50-99	3
100-199	1
200-299	3
300-399	5
400-599	3
> 600	18

^aRespondents allowed to select more than one type of facility.

^bSpecialties provided include cardiology, pulmonary, vascular, home infusion, neurology, psychiatry, 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	6

^aRespondents allowed to select multiple categories.

^bRespondents reported staffing shortages, need for extended dating, volume of product used, standardization projects as additional reasons for utilizing outsourcing facilities.

Table 17. Categories of products obtained from outsourcing facilities

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

^aRespondents allowed to select multiple categories.

^bRespondents 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
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^aRespondents were allowed to select multiple products.

CONCLUSION

Norepinephrine bitartrate was nominated for inclusion on the 503B Bulks List as IV bags in concentrations ranging from 16-128 mcg/mL, 4-16 mg/mL prefilled syringes, 0.004-1 mg/mL IV injection solutions for dilution, and a preservative free 32 mcg/mL IV solution for dilution to treat cardiogenic shock, hypotension, septic shock, acute hypotension, cardiac arrest, and upper gastrointestinal bleeding. Norepinephrine bitartrate is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, Latvia, New Zealand, Saudi Arabia, the UK, and the US.

No literature review was conducted. Zero SMEs interviewed discussed norepinephrine bitartrate. As part of Phase 3, 2 nominators provided additional information regarding the products that will be compounded using norepinephrine bitartrate. Norepinephrine bitartrate will be compounded as a 2 mg/mL IV solution for the treatment of hypotension and as a 2 mg/mL IV solution packaged in vials and syringes for continuous infusion to treat cardiogenic shock, hypotension, and septic shock. These products are needed to provide a ready-to-use infusion product and to prepare vials and syringes that do not contain sodium metabisulfite.

No survey was distributed via professional medical associations. From the prequestionnaire, 15 of the respondents obtained norepinephrine bitartrate from a 503B outsourcing facility.

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APPENDICES

Appendix 1. Search strategies for bibliographic databases

No literature review was conducted.

Appendix 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 specialtiy(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-facilites>.
 - 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

^aAssociations that declined in Year 1 and/or Year 2 were not contacted in Year 3.