Matters To Be Considered: The agenda will include discussions on use of Monkeypox vaccines. A recommendation vote(s) is not scheduled. Agenda items are subject to change as priorities dictate. For more information on the meeting agenda visit *https://www.cdc.gov/vaccines/acip/meetings/meetings-info.html.* A notice of this ACIP meeting has also been posted on CDC's ACIP website at: *http://www.cdc.gov/vaccines/acip/index.html.* In addition, CDC has sent notice of this ACIP meeting by email to those who subscribe to receive email updates about ACIP.

Public Participation

Interested persons or organizations are invited to participate by submitting written views, recommendations, and data. Please note that comments received, including attachments and other supporting materials, are part of the public record and are subject to public disclosure. Comments will be posted on *https://www.regulations.gov.* Therefore, do not include any information in your comment or supporting materials that you consider confidential or inappropriate for public disclosure. If you include your name, contact information, or other information that identifies you in the body of your comments, that information will be on public display. CDC will review all submissions and may choose to redact, or withhold, submissions containing private or proprietary information such as Social Security numbers, medical information, inappropriate language, or duplicate or near duplicate examples of a mass-mail campaign. CDC will carefully consider all comments submitted into the docket.

Written Public Comment: Written comments must be received on or before December 7, 2022.

Oral Public Comment: This meeting will include time for members of the public to make an oral comment. Oral public comment will occur before any scheduled votes, including all votes relevant to the ACIP's Affordable Care Act and Vaccines for Children Program roles. Priority will be given to individuals who submit a request to make an oral public comment before the meeting according to the procedures below.

Procedure for Oral Public Comment: All persons interested in making an oral public comment during the December 9, 2022 ACIP meeting must submit a request at *https://www.cdc.gov/vaccines/acip/meetings/* no later than 11:59 p.m. EST, December 7, 2022, according to the instructions provided.

If the number of persons requesting to speak is greater than can be reasonably accommodated during the scheduled time, CDC will conduct a lottery to determine the speakers for the scheduled public comment session. CDC staff will notify individuals by email on December 8, 2022 regarding their request to speak. To accommodate the significant interest in participation in the oral public comment session of ACIP meetings, each speaker will be limited to three minutes, and each speaker may only speak once per meeting.

The Director, Strategic Business Initiatives Unit, Office of the Chief Operating Officer, Centers for Disease Control and Prevention, has been delegated the authority to sign **Federal Register** notices pertaining to announcements of meetings and other committee management activities for both the Centers for Disease Control and Prevention and the Agency for Toxic Substances and Disease Registry.

Kalwant Smagh,

Director, Strategic Business Initiatives Unit, Office of the Chief Operating Officer, Centers for Disease Control and Prevention.

[FR Doc. 2022–25538 Filed 11–22–22; 8:45 am]

BILLING CODE 4163–18–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2018–N–3240]

List of Bulk Drug Substances for Which There is a Clinical Need Under Section 503B of the Federal Food, Drug, and Cosmetic Act

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA or Agency) is developing a list of bulk drug substances (active pharmaceutical ingredients) for which there is a clinical need (the 503B Bulks List). Drug products that outsourcing facilities compound using bulk drug substances on the 503B Bulks List can qualify for certain exemptions from the Federal Food, Drug, and Cosmetic Act (FD&C Act) provided certain conditions are met. This notice identifies two bulk drug substances that FDA has considered and proposes to include on the 503B Bulks List to compound three categories of compounded drug products: arginine hydrochloride (HCl) for oral use, lysine HCl for oral use, and lysine HCl for intravenous use in combination with FDA-approved, single-ingredient arginine HCl for intravenous use. This notice identifies three bulk drug substances that FDA has considered and proposes not to include on the 503B Bulks List: etomidate, furosemide, and rocuronium bromide. Additional bulk drug substances nominated for inclusion on this list are under consideration and may be the subject of future notices.

DATES: Either electronic or written comments on the notice must be submitted by January 23, 2023.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. The *https://www.regulations.gov* electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of January 23, 2023. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: https://www.regulations.gov.* Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to *https://www.regulations.gov* will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on *https://www.regulations.gov.*
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see ''Written/Paper Submissions'' and ''Instructions'').

Written/Paper Submissions

Submit written/paper submissions as follows:

- *Mail/Hand Delivery/Courier (for written/paper submissions):* Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

• For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in ''Instructions.''

Instructions: All submissions received must include the Docket No. FDA–2018–N–3240 for ''List of Bulk Drug Substances for Which There is a Clinical Need Under Section 503B of the Federal Food, Drug, and Cosmetic Act.'' Received comments, those filed in a timely manner (see **ADDRESSES**), will be placed in the docket and, except for those submitted as ''Confidential Submissions,'' publicly viewable at *https://www.regulations.gov* or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240–402–7500.

• Confidential Submissions—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states ''THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.'' The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on *https://www.regulations.gov.* Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as ''confidential.'' Any information marked as ''confidential'' will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: *https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.*

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to *https://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240–402–7500.

FOR FURTHER INFORMATION CONTACT: Tracy Rupp, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Silver Spring, MD 20993, 301–796–3100.

SUPPLEMENTARY INFORMATION:

I. Background

Section 503B of the FD&C Act (21 U.S.C. 353b) describes the conditions that must be satisfied for drug products compounded by an outsourcing facility to be exempt from section 505 of the FD&C Act (21 U.S.C. 355) (concerning the approval of drugs under new drug applications (NDAs) or abbreviated new drug applications (ANDAs)), section 502(f)(1) (21 U.S.C. 352(f)(1)) (concerning the labeling of drugs with adequate directions for use), and section 582 of the FD&C Act (21 U.S.C. 360eee–1) (concerning drug supply chain security requirements).[1]

Compounded drug products that meet the conditions in section 503B are not exempt from current good manufacturing practice (CGMP) requirements in section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)).[2] Outsourcing facilities are also subject to FDA inspections according to a risk-based schedule, specific adverse event reporting requirements, and other conditions that help to mitigate the risks of the drug products they compound.[3] Outsourcing facilities may or may not obtain prescriptions for identified individual patients and can, therefore, distribute compounded drugs to healthcare practitioners for ''office stock,'' to hold in their offices in advance of patient need.[4]

One of the conditions that must be met for a drug product compounded by an outsourcing facility to qualify for the exemptions under section 503B of the FD&C Act is that the outsourcing facility may not compound a drug using a bulk drug substance unless: (1) the bulk drug substance appears on a list established by the Secretary of Health and Human Services identifying bulk drug substances for which there is a clinical need (the 503B Bulks List) or (2) the drug compounded from the bulk drug substance appears on the drug shortage list in effect under section 506E of the FD&C Act (21 U.S.C. 356e) at the time of compounding, distribution, and dispensing.[5]

Section 503B of the FD&C Act directs FDA to establish the 503B Bulks List by: (1) publishing a notice in the **Federal Register** proposing bulk drug substances to be included on the list, including the rationale for such proposal; (2) providing a period of not less than 60 calendar days for comment on the notice; and (3) publishing a notice in the **Federal Register** designating bulk drug substances for inclusion on the list.[6]

FDA has published a series of **Federal Register** notices addressing bulk drug substances nominated for inclusion on the 503B Bulks List.[7] This notice identifies two bulk drug substances that FDA has considered and proposes to include on the 503B Bulks List and three bulk drug substances that FDA has considered and proposes not to include on the 503B Bulks List.

For purposes of section 503B of the FD&C Act, *bulk drug substance* means an active pharmaceutical ingredient as defined in § 207.1 (21 CFR 207.1).[8] *Active pharmaceutical ingredient* means any substance that is intended for incorporation into a finished drug product and is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body, but the term does not include intermediates used in the synthesis of the substance.[9] [10]

[1] Section 503B(a) of the FD&C Act.

[2] Compare section 503A(a) of the FD&C Act (21 U.S.C. 353a(a)) (exempting drugs compounded in accordance with that section from CGMP requirements) with section 503B(a) of the FD&C Act (not providing an exemption from CGMP requirements).

[3] Section 503B(b)(4) and (5) of the FD&C Act.

[4] Section 503B(d)(4)(C) of the FD&C Act.

[5] Section 503B(a)(2)(A) of the FD&C Act.

[6] Section 503B(a)(2)(A)(i)(I) to (III) of the FD&C Act.

[7] See **Federal Register** of August 28, 2018 (83 FR 43877), March 4, 2019 (84 FR 7383), September 3, 2019 (84 FR 46014), July 31, 2020 (85 FR 46126), and March 24, 2021 (86 FR 15673). The comment period for the July 2020 notice was reopened for 30 days on January 8, 2021 (86 FR 1515), to allow interested parties an additional opportunity to comment. FDA has not yet reached a final determination on whether the substances evaluated in the September 2019, July 2020, or March 2021 notices will be added to the 503B Bulks List. In addition, bumetanide, which was considered in the August 2018 notice, remains under consideration by the Agency.

[8] See section 503B(a)(2) of the FD&C Act, which defines bulk drug substances used in compounding under section 503B according to 21 CFR 207.3(a)(4) ''or any successor regulation.'' Section 207.1 is the successor regulation.

[9] Section 503B(a)(2) of the FD&C Act and § 207.1.

[10] Inactive ingredients are not subject to section 503B(a)(2) of the FD&C Act and will not be included in the 503B Bulks List because they are not included within the definition of a bulk drug substance. Pursuant to section 503B(a)(3) of the FD&C Act, inactive ingredients used in compounding must comply with the standards of an applicable U.S. Pharmacopeia or National Formulary monograph, if a monograph exists.

II. Methodology for Developing the 503B Bulks List

A. Process for Developing the List

In the **Federal Register** of December 4, 2013 (78 FR 72838), FDA requested nominations for specific bulk drug substances for the Agency to consider for inclusion on the 503B Bulks List. FDA reopened the nomination process in the **Federal Register** of July 2, 2014 (79 FR 37747) and provided more detailed information on what FDA needs to evaluate nominations for the list. In the **Federal Register** of October 27, 2015 (80 FR 65770), the Agency opened a new docket, FDA–2015–N–3469, to provide an opportunity for interested persons to submit new nominations of bulk drug substances or to renominate substances with sufficient information or submit comments on nominated substances.

As FDA evaluates bulk drug substances, it intends to publish notices for public comment in the **Federal Register** that describe the FDA's proposed position on each substance along with the rationale for that position.[11] After considering any comments on FDA's proposals regarding whether to include nominated substances on the 503B Bulks List, FDA intends to consider whether input from the Pharmacy Compounding Advisory Committee (PCAC) on the nominations would be helpful to the Agency in making its determination, and if so, it will seek PCAC input.[12] Depending on its review of the docket comments and other relevant information before the Agency, FDA may finalize its proposed determination without change, or it may finalize a modification to its proposal to reflect new evidence or analysis regarding clinical need. FDA will then publish in the **Federal Register** a list identifying the bulk drug substances for which it has determined there is a clinical need and FDA's rationale in making that final determination. FDA will also publish in the **Federal Register** a list of those substances it considered but found that there is no clinical need to use in compounding and FDA's rationale in making this decision.

FDA intends to maintain a list of all bulk drug substances it has evaluated on its website, and separately identify bulk drug substances it has placed on the 503B Bulks List and those it has decided not to place on the 503B Bulks List. This list is available at *https://www.fda.gov/media/120692/download.* FDA will only place a bulk drug substance on the 503B Bulks List when it has determined there is a clinical need for outsourcing facilities to compound drug products using the bulk drug substance. If a clinical need to compound drug products using the bulk drug substance has not been demonstrated, based on the information submitted by the nominator and any other information considered by the Agency, FDA will not place a bulk drug substance on the 503B Bulks List.

FDA is evaluating bulk drug substances nominated for the 503B Bulks List on a rolling basis. FDA intends to evaluate and publish in the **Federal Register** its proposed and final determinations in groups of bulk drug substances until all nominated substances that were sufficiently supported have been evaluated and either placed on the 503B Bulks List or identified as bulk drug substances that were considered, but determined not to be appropriate for inclusion on the 503B Bulks List (Ref. 1).

B. Analysis of Substances Nominated for the List

As noted above, the 503B Bulks List includes bulk drug substances for which the Agency has determined there is a clinical need. The Agency is evaluating bulk drug substances that were nominated for inclusion on the 503B Bulks List, proceeding case by case, under the clinical need standard provided by the statute (Ref. 2).[13] In applying this standard to develop the proposals in this notice, FDA interprets the phrase ''bulk drug substances for which there is a clinical need'' to mean that the 503B Bulks List may include a bulk drug substance if: (1) there is a clinical need for an outsourcing facility to compound the drug product and (2) the drug product must be compounded using the bulk drug substance. FDA does not interpret supply issues, such as backorders, to be within the meaning of ''clinical need'' for compounding with a bulk drug substance. Section 503B of the FD&C Act separately provides for compounding from a bulk drug substance under the exemptions discussed above if the drug product compounded from the bulk drug substance is on the FDA drug shortage list at the time of compounding, distribution, and dispensing. Additionally, FDA does not consider convenience in administering a particular drug product (*e.g.,* a ready-to-use form) or the cost of the compounded drug product as compared with an FDA-approved drug product when assessing ''clinical need.''

All of the bulk drug substances that we are addressing in this notice are components of FDA-approved drug products,[14] and we therefore began our evaluation of the bulk drug substances by asking one or both, as applicable, of the following questions:

(1) Is there a basis to conclude, for each FDA-approved product that includes the nominated bulk drug substance, that: (a) an attribute of the FDA-approved drug product makes it medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation and (b) the drug product proposed to be compounded is intended to address that attribute?

(2) Is there a basis to conclude that the drug product proposed to be compounded must be produced from a bulk drug substance rather than from an FDA-approved drug product?

The reason for question 1 is that unless an attribute of the FDA-approved drug is medically unsuitable for certain patients, and a drug product compounded using a bulk drug substance that is a component of the approved drug is intended to address that attribute, there is no clinical need to compound a drug product using that bulk drug substance. Rather, such compounding would unnecessarily expose patients to the risks associated with drug products that do not meet the standards applicable to FDA-approved drug products for safety, effectiveness, quality, and labeling and would undermine the drug approval process. The reason for question 2 is that to place a bulk drug substance on the 503B Bulks List, FDA must determine that there is a clinical need for outsourcing facilities to compound a drug product *using the bulk drug substance* rather than starting with an FDA-approved drug product. When it is feasible to compound a drug

[11] This is consistent with procedure set forth in section 503B(a)(2)(A)(i) of the FD&C Act. Although the statute only directs FDA to issue a **Federal Register** notice and seek public comment when it proposes to include bulk drug substances on the 503B Bulks List, we intend to seek comment when the Agency has evaluated a nominated substance and proposes either to include or not to include the substance on the list.

[12] Section 503B of the FD&C Act does not require FDA to consult the PCAC before developing a 503B Bulks List.

[13] On March 4, 2019, FDA announced the availability of a final guidance entitled ''Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act'' (84 FR 7390); available at *https://www.fda.gov/media/121315/download.* This guidance describes FDA policies for developing the 503B Bulks List and the Agency's interpretation of the phrase ''bulk drug substances for which there is a clinical need'' as it is used in section 503B of the FD&C Act. The analysis under the statutory ''clinical need'' standard described in this notice is consistent with the approach described in FDA's guidance.

[14] Specifically, arginine HCl, etomidate, furosemide, lysine HCl, and rocuronium bromide.

product by starting with an approved drug product, there are certain benefits of doing so over starting with a bulk drug substance, including that approved drugs have undergone premarket review for safety, effectiveness, and quality, and are manufactured by a facility that is subject to premarket assessment, including site inspection, as well as routine post-approval risk-based inspections. In contrast, FDA does not conduct a premarket review of the quality standards, specifications, and controls for bulk drug substances used in compounding and does not conduct a premarket assessment of the manufacturer of the bulk drug substance.

If the answer to both of these questions is ''yes,'' there may be a clinical need for outsourcing facilities to compound using the bulk drug substance, and we would evaluate the substance further, applying the factors described below. If the answer to either of these questions is ''no,'' we generally would not include the bulk drug substance on the 503B Bulks List, because there would not be a basis to conclude that there may be a clinical need to compound drug products using the bulk drug substance instead of administering an approved drug or compounding starting with an approved drug product. FDA answered ''yes'' to both of the threshold questions for two of the bulk drug substances that are components of approved drug products that we are addressing in this notice. Accordingly, as explained further below, we proceeded further in our evaluation of these substances by conducting a balancing test and are proposing to include those substances on the 503B Bulks List.

We are conducting a balancing test using four factors. Specifically, on a substance-by-substance basis, we consider available data relevant to each factor in the context of the other factors and balance all four factors to determine whether the statutory ''clinical need'' standard has been met. The balancing test includes the following factors:

- The physical and chemical characterization of the substance;
- Any safety issues raised by the use of the substance in compounding;
- The available evidence of effectiveness or lack of effectiveness of a drug product compounded with the substance, if any such evidence exists; and
- Current and historical use of the substance in compounded drug products, including information about the medical condition(s) that the substance has been used to treat and any references in peer-reviewed medical literature.

The discussion below reflects FDA's consideration of these four factors where they are applicable and describes how they were applied to develop FDA's proposal to include three entries addressing two bulk drug substances on the 503B Bulks List.

In this notice, FDA evaluated certain nominated bulk drug substances for potential inclusion on the 503B Bulks List either alone or in combination with other bulk drug substances. FDA will not consider comments raising different combinations of bulk drug substances than those evaluated by FDA in this notice to be within the scope of this notice. New nominations may be submitted to docket FDA–2015–N–3469 for combinations of bulk drug substances that were not previously nominated and included for evaluation in this notice. The docket is available on *https://www.regulations.gov.*

To assess whether there is a clinical need for outsourcing facilities to use a bulk drug substance in compounding, FDA must evaluate the drug products that have been proposed to be made from the nominated bulk drug substances. Therefore, FDA's evaluation of a bulk drug substance includes detailed consideration of the drug products that are proposed to be compounded, including the conditions justifying clinical need under the applicable statutory standard. Comments on FDA's preliminary evaluation of a bulk drug substance should include adequate support for the commenter's position. For example, a commenter writing to support inclusion of a nominated bulk drug substance on the 503B Bulks List should include sufficient information to permit a meaningful clinical need evaluation by FDA of the proposed product. Commenters writing in favor of or in opposition to a proposal to include or not to include an entry on the 503B Bulks List should address, for each proposed compounded drug product, the factors FDA evaluated in making its proposal.[15] After FDA publishes a **Federal Register** notice making a final determination regarding whether a bulk drug substance will be placed on the 503B Bulks List, FDA will no longer consider comments submitted to the docket regarding that bulk drug substance, but interested parties may submit a citizen petition to FDA requesting specific action or relief (see 21 CFR 10.30).

C. Inclusion of Bulk Drug Substances on the 503B Bulks List

In preparing its proposal to include two bulk drug substances on the 503B Bulks List, FDA considered whether the clinical need for the bulk drug substance in the proposed compounded drug product is limited by, for example, route of administration or dosage form. As appropriate, and as explained further below, the Agency has tailored its proposed entries on the 503B Bulks List to reflect its findings related to clinical need for the bulk substances proposed for inclusion on the list. FDA requested comments on the proposal to limit listings in this manner in our **Federal Register** notice of July 31, 2020 (85 FR 46126). The comment period for the July 2020 notice was reopened for 30 days on January 8, 2021 (86 FR 1515), to provide interested parties an additional opportunity to comment before FDA began to develop its final determinations. After considering the comments submitted regarding the proposal, in the **Federal Register** notice of January 27, 2022 (87 FR 4240), FDA listed three bulk drug substances to compound drug products for topical use only.

Consistent with the approach described in the 2020 notice, and as reflected in the entries that appear on the 503B Bulks List to date, the entries proposed in this notice would authorize use of two bulk drug substances. Arginine HCl would be authorized for use to compound single-ingredient drug products for oral use only; lysine HCl would be authorized for use to compound single-ingredient drug products for oral use; and lysine HCl would also be authorized for use in combination with FDA-approved, single-ingredient arginine HCl injection, U.S. Pharmacoepia (USP) to compound drug products for intravenous (IV) use only.[16] As discussed further in this notice, FDA's proposals with respect to inclusion of lysine HCl and arginine HCl on the 503B Bulks List pertain to the L- forms of lysine HCl and arginine HCl exclusively.[17]

III. Substances Considered and Proposed for Inclusion on the 503B Bulks List

Because the substances in this section are components of FDA-approved drug products, we considered whether: (1)

[15] See also FDA's guidance for industry, ''Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act'' (March 2019), and our **Federal Register** notice of October 27, 2015.

[16] In this notice, ''single-ingredient'' refers to a drug product containing one active ingredient. The drug product may also contain excipients.

[17] See footnote 18 below.

there is a basis to conclude that an attribute of each FDA-approved drug product that includes the nominated bulk drug substance makes each one medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation, and the drug products proposed to be compounded are intended to address that attribute in each FDA-approved drug product and (2) whether the drug products proposed to be compounded must be compounded using a bulk drug substance. In addition, because we answered these two questions in the affirmative for certain drug products proposed to be compounded from the nominated bulk drug substances, we applied the four-factor balancing test described above. The bulk drug substances that were evaluated and that FDA is proposing to place on the 503B Bulks List are arginine HCl for oral use only, lysine HCl for oral use only, and lysine HCl for use in combination with FDA-approved, arginine HCl injection for intravenous use only. The reasons for FDA's proposals are included below.

A. Arginine HCl

Arginine HCl was nominated as a bulk drug substance for the 503B Bulks List to compound drug products that are used for acute hyperammonemia in urea cycle disorders (UCDs) and refractory metabolic alkalosis, among other conditions.[18] [19] The proposed routes of administration are oral and intravenous, among others,[20] and the proposed dosage forms are an oral solution or suspension, capsule, powder for dispersion, and injectable, among others.[21] The nominators proposed a range of concentrations (12.5 to 40 percent) and 200 and 500 milligrams/milliliters (mg/mL). They also proposed strengths of 250 mg-500 mg unspecified oral dosage forms and 700 mg-750 mg oral capsules. This nominated bulk drug substance is a component of an FDA-approved drug product (NDA 016931). FDA has approved arginine HCl (R-Gene 10) as a 10 gram (GM)/100 mL (100 mg/mL; 10 percent) injection for intravenous administration [22] (Ref. 3).

Because arginine HCl is a component of an FDA-approved drug product, we considered whether: (1) there is a basis to conclude that an attribute of the FDA-approved drug product that contains arginine HCl makes it medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation, and the arginine HCl drug product proposed to be compounded is intended to address that attribute in the FDA-approved drug product and (2) whether the drug product proposed to be compounded must be compounded using a bulk drug substance. In addition, because we answered these two questions in the affirmative for an oral arginine HCl compounded drug product, we also conducted a balancing test to further evaluate this bulk drug substance by considering and applying the four factors described above.

1. Suitability of FDA-Approved Drug Products

A nominator proposes that there is a clinical need for an oral, single-ingredient arginine HCl compounded drug product to treat patients with certain UCDs. The references submitted with the nomination describe the use of arginine HCl orally for long-term maintenance therapy in patients with UCDs. There is a basis to conclude that the FDA-approved drug product that contains only arginine HCl (R-Gene 10) is medically unsuitable to treat patients who require long-term oral maintenance therapy because the approved drug product is only available for intravenous administration and would not be suitable for the use proposed in the nomination, which would involve daily oral administration.[23] The drug product proposed to be compounded is intended to address the attribute of the approved drug product that makes it medically unsuitable for some patients because the nominator proposes to compound oral formulations (capsules, powder for dispersion, and oral solution/suspension) of arginine HCl. Accordingly, FDA finds that the drug product proposed to be compounded is intended to address the attribute of the approved drug product that makes it medically unsuitable for some patients.

A nominator also proposes that there is a clinical need for an intravenous single-ingredient arginine HCl

[18] See Docket No. FDA–2015–N–3469, document nos. FDA–2015–N–3469–0244, FDA–2015–N–3469–0169, FDA–2015–N–3469–0156-attachment 10, FDA–2015–N–3469–0202, and FDA–2015–N–3469–0320. The nomination in Docket No. FDA–2015–N–3469–0156-attachment 10 was for ''Arginine HCL'' and stated that the common name of the substance is ''L-arginine hydrochloride; D-arginine hydrochloride.'' However, the nominator also stated that the chemical grade of the bulk drug substance is USP. The USP monograph for arginine HCl does not include D-arginine HCl. Therefore, this review focuses on L-arginine HCl, not the mixture of D- and L-arginine HCl. Arginine HCl USP grade consists of L-arginine monohydrochloride. The nomination discussed in this **Federal Register** notice nominated L-arginine HCl USP grade. ''Arginine HCl'' and ''L-arginine HCl'' are used interchangeably throughout this **Federal Register** notice. L-arginine HCl and L-lysine HCl were also nominated (Docket No. FDA–2015–N–3469–0073-attachment 10) to be used in combination for intravenous administration with LUTATHERA (lutetium Lu 177 dotatate injection) treatment. That nomination is the subject of another evaluation.

[19] The following uses will not be considered in this evaluation because the nominations did not provide sufficient information, including citations to relevant literature, supporting a clinical need for the proposed uses: thyroid cysts; arginine deficiency/supplementation; orgasmic dysfunction in women; prevention or treatment of heart and circulatory disease; combat fatigue; stimulation of wound healing; boosting production of nitric oxide, relaxing blood vessels, and treating circulatory and other cardiovascular problems; and reducing waist circumference, visceral fat, weight, and body mass index. In addition, the following labeled uses will not be considered in this evaluation because the nominations did not provide sufficient information, including citations to relevant literature, supporting a clinical need for a more concentrated IV product or for a product to be administered via the oral or topical route of administration: diagnostic aid in conditions such as panhypopituitarism, pituitary dwarfism, chromophobe adenoma, postsurgical craniopharyngioma, hypophysectomy, pituitary trauma, acromegaly, gigantism, and problems of growth and stature.

[20] The topical and IV routes of administration for use of arginine HCl to treat hyperammonemia associated with urea cycle disorder will not be considered further because the nominations did not provide sufficient evidence to support a clinical need for drug products with these routes of administration. Although some of the nominations included articles that describe the use of intravenous arginine HCl for treating patients with hyperammonemia in urea cycle disorder, the articles do not provide support for the nominator's proposal to make a more concentrated product than the approved IV drug product containing the same active ingredient. Therefore, the IV route of administration will not be considered further for treating hyperammonemia in urea cycle disorder because the nominations did not provide information supporting a clinical need for a more concentrated product. Similarly, the oral route of administration will not be considered further for the use of arginine HCl to treat refractory metabolic alkalosis because the nomination did not provide any evidence to support a clinical need for drug products with this route of administration. As explained in section II.B of this notice, if a member of the public would like FDA to evaluate arginine HCl based on a clinical need for a drug product to be compounded containing arginine HCl for administration by a route that was not evaluated in this notice, then that person should submit a nomination to Docket No. FDA–2015–N–3469, which is available on *https://www.regulations.gov.*

[21] The proposed dosage forms (cream, ointment, and gel) are associated with uses or routes of administration that will not be considered in this evaluation.

[22] See, *e.g.,* NDA 016931 labeling available as of the date of this notice at *https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/016931s031lbl.pdf.* Arginine (not HCl salt) is available as a component of several approved drug products that contain multiple amino acids (*e.g.,* for parenteral nutrition) (*e.g.,* AMINOSYN II; NDA 020015). NDA 020015 labeling is available as of the date of this notice at *https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=5b426208-f090-4650-86c3-89040ba45c2d&type=display.* The arginine in these approved drug products is not the same bulk drug substance as arginine HCl, which is the subject of this evaluation.

[23] Empower Pharmacy proposed to make several different dosage forms, including ''oral capsules, powder for dispersion, oral solutions/suspensions.'' We are not commenting on the potential suitability of these various proposed dosage forms due to the lack of data available on the various dosage forms. Furthermore, none of the scientific literature reviewed by FDA referred to off-label use of the approved intravenous arginine HCL drug product in patients with urea cycle disorder.

compounded drug product to treat patients with refractory metabolic alkalosis. The nomination does not identify an attribute of the FDA-approved arginine HCl (R-Gene 10) 10 GM/100 mL (100 mg/mL; 10 percent) injection for intravenous administration that makes it medically unsuitable for certain patients or indicate that the compounded drug product is intended to address any such attribute. FDA finds no basis to conclude that an attribute of the FDA-approved product makes it medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation and that a proposed compounded product is intended to address.

2. Whether the Drug Product Must Be Compounded From a Bulk Drug Substance

FDA finds that there is a basis to conclude that the oral drug products proposed to be compounded must be made from a bulk drug substance rather than from FDA-approved R-Gene 10 because of the difficulties and complexities associated with starting with the approved solution for intravenous administration and converting it either to capsules or to a powder for dispersion that would be administered orally. The nominator also proposed to compound an oral solution of arginine HCl that is at a higher concentration than the approved intravenous product (100 mg/mL). There is a basis to conclude that the proposed oral liquid drug product must also be compounded starting from the bulk drug substance because of the difficulties and complexities associated with compounding a more concentrated solution beginning with the approved product.

With regard to an intravenous, single-ingredient arginine HCl compounded drug product proposed to treat patients with refractory metabolic alkalosis, the nominator has not identified patients for whom the approved products are medically unsuitable or identified an attribute of the approved drug product that the proposed compounded drug product is intended to address. Because the nominations do not identify specific differences between drug products that would be compounded using arginine HCl and the approved drug product containing arginine HCl, there is nothing for FDA to evaluate under question 2 for intravenous single-ingredient arginine HCl.

3. Balancing Test

Because FDA answered ''yes'' to both of the threshold questions for arginine HCl for oral administration, we next conducted the following balancing testing to determine whether the statutory ''clinical need'' standard has been met. We considered data and information regarding the physical and chemical characterization of arginine HCl, safety issues raised by use of this substance in compounding, available evidence of effectiveness or lack of effectiveness, and historical and current use in compounding.

Arginine HCl is a well-characterized amino acid and is stable under ordinary storage conditions. Provided the quality of arginine HCl meets the standards in its USP drug substance monograph, arginine HCl is well characterized physically and chemically.[24]

Oral administration of arginine HCl does not raise serious safety issues. The available literature and general clinical practice guidelines for the treatment of UCDs indicate that the oral formulation of arginine HCl may be effective in treating UCDs. There is evidence of the historical and current use of arginine HCl in compounding as an oral formulation for the treatment of UCDs (except those with arginase deficiency) in the United States, Belgium, and the United Kingdom. There are no FDA-approved oral arginine HCl drug products in the United States.

Arginine HCl is a well-characterized amino acid, does not raise serious safety concerns, may be effective in treating UCDs, and there is evidence of historical and current use of arginine HCl in compounding. Therefore, on balance, the physical and chemical characterization, safety, effectiveness, and historical and current use of arginine HCl for oral use weigh in favor of including this substance on the 503B Bulks List. Accordingly, we propose adding arginine HCl to the 503B Bulks List for oral use only.

B. Lysine HCl

Lysine HCl was nominated as a bulk drug substance for the 503B Bulks List to compound drug products that are used to correct lysine deficiency with lysinuric protein intolerance (LPI) and for prophylaxis and acute treatment of herpes simplex outbreak, among other conditions.[25] [26] The proposed route of administration is oral, among others; the proposed dosage forms are capsules and solutions, among others.[27] The nominations proposed a strength range of 100 to 500 mg. This nominated bulk drug substance is a component of many approved drug products as part of a combination with multiple other amino acids for intravenous administration (*e.g.,* NDA 018931).[28] Lysine HCl is not approved as a single-ingredient drug product in any dosage form (Ref. 4).

Because lysine HCl is a component of FDA-approved drug products, we considered whether: (1) there is a basis to conclude that an attribute of each FDA-approved drug product that contains lysine HCl makes each one medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation, and the lysine HCl drug product proposed to be

[24] See section 503B(a)(2)(B) of the FD&C Act.

[25] See Docket No. FDA–2015–N–3469, document nos. FDA–2015–N–3469–0200 and FDA–2015–N–3469–0245. All of the nominations included in this evaluation nominated lysine HCl USP grade. Lysine HCl USP grade consists of L-lysine hydrochloride. A nominator submitted duplicate nominations for L-lysine HCl to the docket: FDA–2015–N–3469–0199 (submitted on August 31, 2018) and FDA–2015–N–3469–0200 (submitted on September 4, 2018). For the purposes of this evaluation, FDA referred to the information in the most recent nomination submitted to the docket (FDA–2015–N–3469–0200). On February 26, 2021, this nominator provided additional information regarding their nomination for lysine HCl to the University of Maryland Center of Excellence in Regulatory Science and Innovation (M–CERSI). The updated information is also considered in this evaluation. Another nominator nominated ''L-lysine;'' M–CERSI clarified with this nominator that they intended to nominate L-lysine HCl. L-arginine HCl and L-lysine HCl were also nominated by a different nominator (FDA–2015–N–3469–0074) to be used in combination for intravenous administration with LUTATHERA (lutetium Lu 177 dotatate injection) treatment, which is the subject of another evaluation.

[26] The following uses will not be considered in this evaluation because the nominations did not provide any information, including citations to relevant literature, supporting a clinical need for the proposed use: correcting lysine deficiency without LPI, rehydration and immune support, osteoporosis, muscle recovery, prevention of mucositis. The use of lysine HCl during peptide receptor radionuclide therapy to reduce the radiation dose to the kidneys is discussed in a separate evaluation. In the updated nomination information provided to M–CERSI, a nominator proposed an additional use of ''rehydration and immune support'' as an intramuscular injection.

[27] The proposed topical, intravenous, and intramuscular routes of administration will not be considered in this evaluation because the nominations do not provide any evidence to support a clinical need for drug products with these routes of administration for use of lysine HCL to correct lysine deficiency with LPI or for the use of lysine HCL for prophylaxis and acute treatment of herpes simplex outbreak. Accordingly, the proposed dosage forms associated with these routes of administration (cream, ointment, and solutions for injection) will not be considered in this evaluation. A nominator cited one article that studied the use of the topical product ''SuperLysinePlus+'' every 2 hours during waking hours in patients with symptoms of a cold sore consistent with a herpes simplex virus infection of ≤24 hours duration (Ref. 5). ''[L]ysine'' is included in ''SuperLysinePlus+'' as an inactive ingredient. Thus, this study does not provide evidence that there is a need for topical lysine HCl in patients with herpes simplex virus.

[28] See, *e.g.,* NDA 018931 labeling is available as of the date of this notice at *https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=8543b5be-0f43-4891-9e56-d7c39fe839b5&type=display*.

compounded is intended to address that attribute in each FDA-approved drug product and (2) whether the drug product proposed to be compounded must be compounded using a bulk drug substance. In addition, because we answered these two questions in the affirmative for an oral lysine HCl compounded drug product, we also conducted a balancing test to further evaluate this bulk drug substance by considering and applying the four factors described above.

1. Suitability of FDA-Approved Drug Products

A nominator proposes that there is a clinical need for an oral, single-ingredient lysine HCl compounded drug product to treat patients with lysine deficiency with LPI and for prophylaxis and treatment of acute herpes simplex outbreak. We find there is a basis to conclude that the FDA-approved drug products that contain lysine HCl are medically unsuitable for the proposed uses. The approved drug products all contain lysine HCl in combination with multiple other amino acids and are for intravenous administration. The nominators did not provide, and FDA did not otherwise identify, evidence that these additional active ingredients are needed to treat the conditions proposed by the nominators. In addition, the approved products are only available for intravenous administration and would not be suitable for the uses proposed in the nominations, which would involve daily oral administration. Accordingly, FDA finds that the drug products proposed to be compounded, oral formulations of single-ingredient lysine HCl, are intended to address the attribute of the approved drugs that makes them medically unsuitable for some patients.

2. Whether the Drug Product Must Be Compounded From a Bulk Drug Substance

FDA finds that there is a basis to conclude that the oral drug products containing lysine as the single ingredient proposed to treat patients with lysine deficiency with LPI and for prophylaxis and treatment of acute herpes simplex outbreak must be produced from a bulk drug substance because of the difficulties and complexities associated with removing lysine HCl from the approved products, which are all multiple amino acid solutions.

3. Balancing Test

Because FDA answered ''yes'' to both of the threshold questions for lysine HCl, we next conducted the following balancing testing to determine whether the statutory ''clinical need'' standard has been met. We considered data and information regarding the physical and chemical characterization of lysine HCl, safety issues raised by use of this substance in compounding, available evidence of effectiveness or lack of effectiveness, and historical and current use in compounding.

Lysine HCl is well-characterized chemically and physically and is expected to be stable under ordinary storage conditions. Provided the quality of lysine HCl meets the standards in its USP drug substance monograph, lysine HCl is well characterized physically and chemically.[29]

The available data do not provide evidence to support the effectiveness of oral lysine in the prophylaxis or treatment of herpes simplex, and a number of FDA-approved therapies are available for acute treatment and prophylaxis of herpes simplex. Oral lysine is also nominated for use in LPI, an extremely rare disease, the exact prevalence of which in the United States is unknown. Oral lysine is used in the treatment of LPI patients in small doses established and prescribed on a per patient basis to avoid gastrointestinal intolerance. Published data show that oral lysine normalizes plasma concentration of lysine in patients with LPI. While the long-term results are inconclusive as to whether chronic supplementation or intermittent supplementation is consistently helpful (or needed), they do suggest a positive impact on growth in some patients. In addition, there are no FDA-approved products indicated for the treatment of LPI and no FDA-approved, single-ingredient lysine drug products for lysine supplementation. Oral use of lysine HCl does not raise serious safety issues. The most commonly reported adverse events of abdominal pain and diarrhea are associated with high doses of lysine HCl and are usually prevented by titrating the dose to a lower acceptable level. There is evidence regarding the current and historical use of lysine HCl in pharmacy compounding, commonly in an injectable dosage form, within the United States. We found no evidence of current or historical use of a compounded lysine HCl product for oral administration.

Lysine HCl is well-characterized chemically; does not raise serious safety issues; and although the data do not support the effectiveness of lysine HCl in the prophylaxis or treatment of herpes simplex, published data show that oral lysine normalizes plasma concentration of lysine in patients with LPI. There is evidence of historical and current use of lysine HCl in compounding. Therefore, on balance, the physical and chemical characterization, safety, effectiveness, and historical and current use of lysine HCl weigh in favor of including this substance for oral use on the 503B Bulks List. Accordingly, we propose adding lysine HCl to the 503B Bulks List for oral use only.

C. Lysine HCl as a Single Ingredient and in Combination With Single-Ingredient Arginine HCl

Lysine HCl was also nominated for the 503B Bulks List both as a single-ingredient and in combination with arginine HCl.[30] [31] Lysine HCl was nominated to compound single-ingredient drug products that are used for reduction of radiolabeled peptides during peptide receptor radionuclide therapy (PRRT).[32] Lysine HCl in combination with arginine HCl was nominated for post-LUTATHERA [33] treatment. LUTATHERA is indicated to treat somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors, including foregut, midgut, and hindgut neuroendocrine tumors in adults. The proposed route of administration for lysine HCl used in a compounded drug product in combination with arginine HCl, is intravenous and the proposed dosage form is injection. For lysine HCl as a

[29] See section 503B(a)(2)(B) of the FD&C Act.

[30] See Docket No. FDA–2015–N–3469, document nos. FDA–2015–N–3469–0073 attachment 10, FDA–2015–N–3469–0074 attachment 4, and FDA–2015–N–3469–0245. A nominator nominated ''L-lysine.'' M–CERSI clarified with the nominator that they intended to nominate L-lysine HCl. L-arginine HCl as a single ingredient product was nominated by other parties for different uses and in different formulations. Those nominations are the subject of another evaluation. In addition, L-lysine HCl was nominated as a single ingredient product for the following uses: to correct lysine deficiency with or without lysinuric protein intolerance, prophylaxis and treatment of herpes simplex outbreak, osteoporosis, muscle recovery, and prevention of mucositis. These nominated uses are the subject of another evaluation.

[31] Lysine HCl USP grade consists of L-lysine hydrochloride. All the nominations discussed in this **Federal Register** notice nominated lysine HCl USP grade. ''lysine HCl'' and ''L-lysine HCl'' are used interchangeably throughout this **Federal Register** notice. Arginine HCl USP grade consists of L-arginine monohydrochloride. The nomination discussed in this **Federal Register** notice nominated L-arginine HCl USP grade. ''Arginine HCl'' and ''L-arginine HCl'' are used interchangeably throughout this **Federal Register** notice.

[32] FDA interprets the nominator's proposed use to be to reduce the radiation dose to the kidneys during PRRT.

[33] Lutetium Lu-177 dotatate (LUTATHERA) was approved by FDA on January 26, 2018. It is a PRRT used to treat patients with neuroendocrine tumors.

single-ingredient drug product, the proposed route of administration is intravenous, among others, and the proposed dosage form is injection.[34] The nominations proposed a strength range of 25 to 100 mg/mL. The nominated bulk drug substances arginine HCl [35] and lysine HCl [36] are components of FDA-approved drug products labeled for intravenous administration. Lysine HCl is not a component of any single-ingredient, approved drug product in any dosage form, but arginine HCl is a component of one single-ingredient, approved drug product for intravenous administration (Ref. 6).

Because lysine HCl and arginine HCl are components of FDA-approved drug products, we considered whether: (1) there is a basis to conclude that an attribute of each FDA-approved drug product that contains lysine HCl or arginine HCl makes each one medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation, and the lysine HCl and arginine HCl drug products proposed to be compounded are intended to address that attribute in each FDA-approved drug product and (2) whether the drug product proposed to be compounded must be compounded using a bulk drug substance. In addition, because we answered these two questions in the affirmative for lysine HCl for the intravenous route of administration, we also conducted a balancing test to further evaluate both the proposed lysine HCl single-ingredient product and the use of lysine HCl to compound a drug product containing both lysine HCl and FDA-approved arginine HCl by considering and applying the four factors described above.

1. Suitability of FDA-Approved Drug Products

A nominator proposes that there is a clinical need for an intravenous product containing a unique combination of lysine HCl and arginine HCl to be used in patients receiving LUTATHERA treatment.[37] According to the LUTATHERA labeling, a dual combination of arginine HCl and lysine HCl is recommended for renal protection during LUTATHERA treatment.[38] FDA-approved drug products that contain lysine HCl are medically unsuitable for the proposed use for patients. Although approved drug products that contain lysine HCl in combination with multiple other amino acids are used off-label for this indication, the nominators did not provide, and FDA did not otherwise identify, evidence that these additional active ingredients are needed for radiation protection. Furthermore, there is evidence that suggests that combination L-lysine HCl/L-arginine HCl compounded intravenous infusions produce less nausea in patients receiving them for this indication than the FDA-approved amino acid solutions, and therefore would lead to fewer episodes of vomiting. The FDA-approved product containing arginine HCl, R-Gene 10 10 GM/100 mL injection for intravenous administration, is medically unsuitable for patients receiving LUTATHERA treatment because LUTATHERA's labeling recommends administering an amino acid solution containing L-lysine and L-arginine before administering LUTATHERA, rather than administering arginine HCl as a single-ingredient.

The drug product proposed to be compounded is intended to address the attributes of the approved drugs that make them medically unsuitable for some patients because the nominator proposes to compound an intravenous formulation containing both lysine HCl and arginine HCl without additional active ingredients.

A nominator also proposes that there is a clinical need for an intravenous product containing lysine HCl as a single ingredient (*i.e.,* not in combination with arginine-HCl) to reduce radiolabeled peptides during PRRT. The FDA-approved drug products that contain lysine HCl all contain lysine HCl in combination with multiple other amino acids. The FDA-approved drug products that contain lysine HCl are medically unsuitable for the proposed use for some patients. Although FDA-approved drug products that contain lysine HCl in combination with multiple other amino acids are used off-label for this indication, the nominators did not provide, and FDA did not otherwise identify, evidence that these additional active ingredients are needed for radiation protection.

The drug product proposed to be compounded is intended to address the attribute of the approved drug that makes it medically unsuitable for some patients because the nominator proposes to compound an intravenous product containing lysine HCl as the single ingredient, without the other amino acids that are present in the approved drug product.

2. Whether the Drug Product Must Be Compounded From a Bulk Drug Substance

In order to compound the proposed drug product containing a combination of lysine HCl and arginine HCl, FDA has a basis to conclude that lysine HCl must be compounded from bulk drug substance rather than from the FDA-approved drug products. The bulk drug substance lysine HCl must be used because of the difficulties and complexities associated with removing lysine HCl from the approved drug products that contain multiple other amino acids (*e.g.,* TRAVASOL).[39]

FDA does not have a basis to conclude that, in order to compound the proposed drug product, arginine HCl must be compounded from a bulk drug substance rather than from the FDA-approved drug product. There is one FDA-approved drug product containing arginine HCl as the single ingredient (R-Gene 10). R-Gene 10 is a solution of 10 g/100 mL of arginine HCl, USP in water for injection, USP. We do not anticipate compatibility or stability issues if this approved drug product is used as the starting material to be combined with the bulk drug substance lysine HCl to produce a combined solution of lysine HCl and arginine HCl at the concentration proposed in the nomination. The pH of the compounded drug product must be adjusted to the target pH irrespective of the source of arginine HCl (R-Gene 10 or bulk drug substance). In addition, the desired osmolarity of <1050 mOsmol is attainable irrespective of the source of arginine (R-Gene 10 or bulk drug substance) used for compounding the

[34] The oral and topical routes of administration will not be considered in this evaluation because the nomination does not provide any evidence to support FDA's evaluation of these routes of administration for use of lysine HCl to reduce the radiation dose to the kidneys during PRRT.

[35] See NDA 016931 labeling is available as of the date of this notice at *https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/016931s031lbl.pdf.*

[36] See, *e.g.,* NDA 018931 labeling is available as of the date of this notice at *https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/018931s055,020849s025lbl.pdf.* TRAVASOL contains essential (including lysine as the HCl salt) and nonessential amino acids (including arginine base, not HCl salt).

[37] In addition, a letter from the Society of Nuclear Medicine and Molecular Imaging (SNMMI) provided support for the proposed compounded drug product, stating that ''patients receiving lysine and arginine solution suffered from much less vomiting incidents in comparison with patients infused with commercial solutions'' and ''lysine and arginine solution is also more effective in inhibiting renal uptake of radioactivity during peptide receptor radionuclide therapy.'' (Ref. 7).

[38] See NDA 208700 labeling is available as of the date of this notice at *https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208700s000lbl.pdf.*

[39] See, *e.g.,* NDA 018931 labeling available as of the date of this notice at *https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/018931s055,020849s025lbl.pdf.*

lysine HCl and arginine HCl drug product for injection. The nomination does not provide any support for the proposition that the proposed product must be compounded from a bulk drug substance rather than by starting with the FDA-approved drug product R-Gene 10. Because the nomination does not provide support for the proposition that the arginine HCl component of the drug product must be compounded from a bulk drug substance rather than by starting with the FDA-approved drug product R-Gene 10, as explained further below, FDA is proposing not to add arginine HCl to the 503B Bulks List for use in combination with lysine HCl (bulk drug substance).

For the same reason that there is a basis to conclude that lysine HCl for combination with arginine HCl must be compounded from a bulk drug substance, there is also a basis to conclude that lysine HCl as a single-ingredient compounded drug product for the intravenous route of administration must be produced from a bulk drug substance. As with the preceding analysis, this is because of the difficulties and complexities associated with removing lysine HCl from the approved multiple amino acid solutions.

3. Balancing Test

Because FDA answered ''yes'' to both of the threshold questions for lysine HCl as a single ingredient for reducing the radiation dose to the kidneys during PRRT and for use in combination with FDA-approved arginine HCl, we next conducted the following balancing test to determine whether the statutory ''clinical need'' standard has been met. We considered data and information regarding the physical and chemical characterization of lysine HCl as a single ingredient and in combination with arginine HCl, safety issues raised by use of these substances in compounding, available evidence of effectiveness or lack of effectiveness, and historical and current use in compounding.

Arginine HCl and lysine HCl are well characterized physically and chemically. Each of these amino acids has a USP drug substance monograph. In addition, lysine HCl and arginine HCl are stable under ordinary storage conditions. The FDA-approved arginine HCl drug product, R-Gene 10, is stable at room temperature. Therefore, provided the quality of lysine HCl meets the standards in its USP drug substance monograph and L-arginine HCl is used starting from the FDA-approved drug product, R-Gene 10, both these components are physically and chemically well characterized.

Safety risks associated with the combination of lysine HCl and arginine HCl for intravenous infusion are not such that they outweigh the benefits, and can be managed. The most common adverse events associated with its use are nausea and vomiting. Although there are hyperkalemia concerns associated with lysine HCl/arginine HCl infusion, this risk could be monitored and managed, if necessary. There is evidence of effectiveness of lysine HCl as a single ingredient during PRRT; however, lysine HCl as a single ingredient for intravenous administration is associated with a higher risk of and more severe hyperkalemia and a higher incidence of vomiting than the lysine HCl/arginine HCl combination for intravenous administration. There is evidence of effectiveness of combination lysine HCl and arginine HCl infusions for reducing the radiation dose to the kidneys during PRRT in the published literature and as described in the approved labeling of LUTATHERA. There is also evidence in the published literature that suggests that combination lysine HCl/arginine HCl compounded intravenous infusions produce less nausea than FDA-approved amino acid solutions when used to reduce the radiation dose to the kidneys during PRRT, and therefore would lead to fewer episodes of vomiting. There is current and historical evidence that lysine HCl and arginine HCl are used in combination to compound injectable drug products within the United States for nephroprotection during PRRT. There also appears to be current and historical evidence that lysine HCl and arginine HCl are used in combination to compound injectable drug products outside the United States.

On balance, consideration of the physical and chemical characterization, safety, effectiveness, and historical and current use weighs against lysine HCl as a single ingredient (bulk drug substance) for intravenous use, but weighs in favor of placement on the 503B Bulks List of lysine HCl (bulk drug substance) in combination with FDA-approved, single ingredient arginine HCl injection for intravenous use only. Accordingly, we propose adding lysine HCl for use in combination with FDA-approved, single-ingredient arginine HCl injection to the 503B Bulks List for intravenous use only. FDA encourages public comment on any particular considerations related to compounding a drug product using FDA-approved, single-ingredient arginine HCl injection in combination with lysine HCl (bulk drug substance).

4. Additional Comments

Due to the safety risks referred to above, if the lysine HCl in combination with FDA-approved, single-ingredient arginine HCl injection is placed on the 503B Bulks List, FDA intends to make safety information about the use of lysine HCl/arginine HCl available to prescribers, pharmacists, outsourcing facilities, and the public through information on FDA's website, in a safety guide, or through other mechanisms, as appropriate.

IV. Substances Evaluated and Not Proposed for Inclusion on the 503B Bulks List

The three bulk drug substances that have been evaluated and that FDA is proposing not to place on the list are as follows: etomidate, furosemide, and rocuronium bromide. The reasons for FDA's proposals are included below.[40]

Because the substances in this section are components of FDA-approved drug products, we considered, as applicable, one or both of the following questions: (1) is there a basis to conclude that an attribute of each FDA-approved drug product containing the bulk drug substance makes each one medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation, and the drug product proposed to be compounded is intended to address that attribute and (2) is there a basis to conclude that the drug product proposed to be compounded must be compounded using a bulk drug substance.

A. Etomidate

Etomidate has been nominated for inclusion on the 503B Bulks List to compound drug products for the

[40] We note that furosemide injection currently appears on FDA's drug shortage list. Under section 503B(a)(2)(A)(ii of the FD&C Act), outsourcing facilities may compound using a bulk drug substance if the drug compounded from such bulk drug substance appears on FDA's drug shortage list at the time of compounding, distribution, and dispensing, provided all of the conditions in section 503B are met. See also FDA's Guidance for Industry, ''Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act,'' which describes an enforcement policy for compounding a drug product that appeared on FDA's drug shortage list using a bulk drug substance that is not on the 503B Bulks List provided certain conditions are met. We further note that both furosemide and rocuronium bromide appear on the list maintained by FDA of drugs used for hospitalized patients with COVID–19. FDA's Guidance for Industry, ''Temporary Policy for Compounding of Certain Drugs for Hospitalized Patients by Outsourcing Facilities During the COVID–19 Public Health Emergency'' describes an enforcement policy, subject to certain conditions, for compounding a drug product using a bulk drug substance that is not on the 503B Bulks List during the COVID public health emergency.

induction of general anesthesia and as an adjunct in maintenance of general anesthesia.[41] The proposed route of administration is intravenous, the proposed dosage form is a preservative-free solution, and the proposed concentration is 2 mg/mL. The nominations propose to compound a preservative-free solution. However, they fail to acknowledge that there is a preservative-free formulation of etomidate that is FDA-approved or explain why that formulation would be medically unsuitable for certain patients. The nominations state that etomidate might also be used to compound other drug products, but do not identify those products. The nominated bulk drug substance is a component of FDA-approved drug products (*e.g.,* NDA 018227). FDA-approved etomidate is available as a single dose, preservative-free 20 mg/10 mL (2 mg/mL) solution to be administered by intravenous injection.[42] [43]

1. Suitability of FDA-Approved Drug Product(s)

The nominations do not explain why an attribute of each of the FDA-approved single dose, preservative-free 2 mg/mL solution products for intravenous injection is medically unsuitable for certain patients or identify an attribute of the approved drug products that the proposed compounded drug product is intended to address. FDA finds no basis to conclude that an attribute of the FDA-approved products makes them medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation and that a proposed compounded product is intended to address.

2. Whether the Drug Product Must Be Compounded From a Bulk Drug Substance

Because the nominations do not identify specific differences between drug products that would be compounded using etomidate and approved drug products containing etomidate, there is nothing for FDA to evaluate under question 2.

B. Furosemide

Furosemide has been nominated for inclusion on the 503B Bulks List to compound drug products that treat congestive heart failure, edema, renal failure, and hypertension, among other conditions.[44] The proposed routes of administration are intravenous and intramuscular, the proposed dosage forms are both a preservative-free and a preserved solution, and the proposed concentration is 10 mg/mL. The nominations propose to compound both preservative-free and preserved solutions. However, they fail to acknowledge that there is a preservative-free formulation of furosemide that is FDA-approved or explain why that formulation would be medically unsuitable for certain patients. The nominations state that furosemide might also be used to compound other drug products, but do not identify those products. The nominated bulk drug substance is a component of FDA-approved drug products (*e.g.,* ANDA 212174). FDA-approved furosemide is available as a preservative-free 40 mg per 4 mL (10 mg/mL) solution for intravenous or intramuscular administration.[45] [46] [47]

1. Suitability of FDA-Approved Drug Product(s)

The nominations do not explain why an attribute of each of the FDA-approved preservative-free 40 mg per 4 mL (10 mg/mL) solution products for intravenous or intramuscular administration is medically unsuitable for certain patients or identify an attribute of the approved drug products that the proposed compounded drug products are intended to address. For example, the nominations propose to compound a preserved solution because the available FDA-approved products are preservative-free, but the nominations do not identify specific data or information supporting the need for a preserved product. FDA finds no basis to conclude that an attribute of the FDA-approved products makes them medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation and that a proposed compounded product is intended to address.

2. Whether the Drug Product Must Be Compounded From a Bulk Drug Substance

Because the nominations have not identified a population for whom the approved products would be medically unsuitable, FDA has not evaluated whether the proposed preserved drug products containing furosemide must be compounded from bulk drug substances rather than using the approved drug product.

C. Rocuronium Bromide

Rocuronium bromide has been nominated for inclusion on the 503B Bulks List to compound drug products that serve as an adjunct to general anesthesia to facilitate both rapid sequence and routine tracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.[48] The proposed route of administration is intravenous, the proposed dosage form is a preservative-free solution for injection, and the proposed concentration is 10 mg/mL. The nominations propose to compound a preservative-free solution. However, they fail to acknowledge that there is a preservative-free formulation of rocuronium bromide that is FDA-approved or explain why that formulation would be medically unsuitable for certain patients. The nominations state that rocuronium bromide might also be used to compound other drug products, but do not identify those products. The nominated bulk drug substance is a component of FDA-approved drug products (*e.g.,* ANDA 079195). FDA-approved rocuronium bromide is available as a preservative-free 10 mg/mL solution for intravenous administration.[49] [50]

1. Suitability of FDA-Approved Drug Product(s)

The nominations do not explain why an attribute of each of the FDA-approved 10 mg/mL preservative-free solution products is medically unsuitable for certain patients or

[41] See Docket No. FDA–2013–N–1524, document nos. FDA–2013–N–1524–2292 and FDA–2013–N–1524–2298.

[42] See, *e.g.,* NDA 018227 labeling available as of the date of this notice at *https://www.accessdata.fda.gov/spl/data/41253af6-deac-43de-9af3-3b727ea351d8/41253af6-deac-43de-9af3-3b727ea351d8.xml.*

[43] According to the label for NDA 018227, each mL contains etomidate, 2 mg, propylene glycol 35% v/v.

[44] See Docket No. FDA–2013–N–1524, document nos. FDA–2013–N–1524–2292 and FDA–2013–N–1524–2298.

[45] See, *e.g.,* ANDA 212174 labeling available as of the date of this notice at *https://www.accessdata.fda.gov/spl/data/421aa6d5-623b-4dc2-abd5-bb9e7765bf37/421aa6d5-623b-4dc2-abd5-bb9e7765bf37.xml.*

[46] Per the label for ANDA 212174, the solution is preservative-free and is intended for intravenous or intramuscular administration.

[47] Furosemide is also approved as an oral solution and as a tablet.

[48] See Docket No. FDA–2013–N–1524, document nos. FDA–2013–N–1524–2292 and FDA–2013–N–1524–2298.

[49] See, *e.g.,* ANDA 079195 labeling available as of the date of this notice at *https://www.accessdata.fda.gov/spl/data/e21db7bf-3cab-4000-94dd-15c6d2a213de/e21db7bf-3cab-4000-94dd-15c6d2a213de.xml.*

[50] Per the label for ANDA 079195 each mL contains 10 mg rocuronium bromide and 2 mg sodium acetate. The aqueous solution is adjusted to isotonicity with sodium chloride and to a pH of 4 with acetic acid and/or sodium hydroxide.

identify an attribute of the approved drug products that the proposed compounded drug product is intended to address. FDA finds no basis to conclude that an attribute of the FDA-approved products makes them medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation and that a proposed compounded product is intended to address.

2. Whether the Drug Product Must Be Compounded from a Bulk Drug Substance

Because the nominations do not identify specific differences between drug products that would be compounded using rocuronium bromide and approved drug products containing rocuronium bromide, there is nothing for FDA to evaluate under question 2.

VI. Conclusion

For the reasons stated above, we tentatively conclude that there is a clinical need for outsourcing facilities to compound drug products using the bulk drug substances arginine HCl for oral use only, lysine HCl for oral use only, and lysine HCl in combination with FDA-approved single-ingredient arginine HCl for injection for intravenous use only. We therefore propose to include those bulk drug substances on the 503B Bulks List as described in this notice.

At this time, we find no basis to conclude that there is a clinical need for outsourcing facilities to compound drug products using the bulk drug substances etomidate, furosemide, and rocuronium bromide. Therefore, we propose not to include these bulk drug substances on the 503B Bulks List.

VII. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff (see **ADDRESSES**) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at *https://www.regulations.gov.* References without asterisks are not on public display at *https://www.regulations.gov* because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. FDA has verified the website addresses, as of the date this document publishes in the **Federal Register**, but websites are subject to change over time.

*1. FDA, Guidance for Industry, ''Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act,'' January 2017 (available at *https://www.fda.gov/media/94402/download*).

*2. FDA, Guidance for Industry, ''Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act,'' March 2019 (available at *https://www.fda.gov/media/121315/download*).

*3. FDA Memorandum to File, ''Clinical Need for Arginine Hydrochloride in Compounding Under Section 503B of the FD&C Act,'' October 2022.

*4. FDA Memorandum to File, ''Clinical Need for Lysine Hydrochloride in Compounding Under Section 503B of the FD&C Act,'' October 2022.

5. Singh, B.B., J. Udani, S.P, Vinjamury, C, Der-Martirosian, et al, 2005, ''Safety and Effectiveness of an L-lysine, Zinc, and Herbal-Based Product on the Treatment of Facial and Circumoral Herpes,'' *Alternative Medicine Review,* 10: 123–7

*6. FDA Memorandum to File, ''Clinical Need for Lysine Hydrochloride (HCl) Alone and in Combination With Arginine HCl in Compounding Under Section 503B of the FD&C Act,'' October 2022.

*7. Letter from SNMMI to FDA dated May 25, 2018, requesting FDA place arginine and lysine on the 503B Bulks List.

Dated: November 17, 2022.

Lauren K. Roth,

Associate Commissioner for Policy.

[FR Doc. 2022–25549 Filed 11–22–22; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2022–N–2796]

Bristol Myers Products Inc.; Proposal To Withdraw Approval of a New Drug Application for Bufferin (Aspirin) Tablets; Opportunity for a Hearing

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration's (FDA or Agency) Center for Drug Evaluation and Research (CDER) is proposing to withdraw approval of a new drug application (NDA) for Bufferin (aspirin) tablets, for which Bristol Myers Products Inc., 1350 Liberty Ave., Hillside, NJ 07205 is the last holder of record, and is announcing an opportunity for the holder of the NDA to request a hearing on this proposal. The basis for the proposal is that the holder of the NDA has repeatedly failed to file required annual reports for this NDA.

DATES: The holder of the NDA may submit a request for a hearing by December 23, 2022. Submit all data, information, and analyses upon which the request for a hearing relies by January 23, 2023. Submit electronic or written comments by January 23, 2023.

ADDRESSES: The request for a hearing may be submitted by the holder of the NDA by either of the following methods:

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: https://www.regulations.gov.* Follow the instructions for submitting comments to submit your request for a hearing. Comments submitted electronically to *https://www.regulations.gov,* including any attachments to the request for a hearing, will be posted to the docket unchanged.

Written/Paper Submissions

Submit written/paper submissions as follows:

- *Mail/Hand Delivery/Courier (for written/paper submissions):* Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- Because your request for a hearing will be made public, you are solely responsible for ensuring that your request does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. The request for a hearing must include the Docket No. FDA–2022–N–2796 for ''Bristol Myers Products Inc.; Proposal To Withdraw Approval of a New Drug Application for Bufferin (Aspirin) Tablets; Opportunity for a Hearing.'' The request for a hearing will be placed in the docket and publicly viewable at *https://www.regulations.gov* or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday. The holder of the NDA may submit all data and analyses upon which the request for a hearing relies in the same manner as the request for a hearing except as follows:
- Confidential Submissions—To submit any data analyses with confidential information that you do not wish to be made publicly available, submit your data and analyses only as a written/paper submission. You should submit two copies total of all data and analyses. One copy will include the information you claim to be confidential with a heading or cover note that states ''THIS DOCUMENT CONTAINS