Partnerships and Technology Innovation, Center for Devices and Radiological Health, *cdrh-pro@fda.hhs.gov,* 800–638–2041 or 301–796–7100.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a draft guidance for industry entitled ''Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints for Regulatory Decision-Making.'' This draft guidance (Guidance 4) is the fourth of a series of four methodological patient-focused drug development guidance documents that describe how stakeholders (patients, researchers, medical product developers, and others) can collect and submit patient experience data and other relevant information from patients and caregivers to be used for medical product development and regulatory decision-making. This series of guidance documents is intended to facilitate the advancement and use of systematic approaches to collect and use robust and meaningful input that can more consistently inform medical product development and regulatory decision-making.

The purpose of Guidance 4 is to: (1) address methods to better incorporate clinical outcome assessment into endpoints that are considered significantly robust for regulatory decision-making; (2) address methodologies, standards, and technologies that may be used for the collection, capture, storage, and analysis of patient perspective data; and (3) identify resources that offer considerations regarding submissions of patient experience data.

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the current thinking of FDA on ''Incorporating Clinical Outcome Assessments Into Endpoints for Regulatory Decision-Making.'' It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations.

II. Paperwork Reduction Act of 1995

This guidance refers to collections of information from ''individuals under treatment or clinical examination in connection with research,'' which are not subject to review by the Office of Management and Budget (OMB) under 5 CFR 1320.3(h)(5). This guidance also refers to previously approved FDA collections of information. These collections of information are subject to review by OMB under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3521). The collections of information in 21 CFR parts 312 and 812 for investigational new drug applications and investigational device exemptions have been approved under OMB control numbers 0910–0014 and 0910–0078, respectively. The collections of information in 21 CFR parts 314 and 601 for new drug applications and biologic license applications have been approved under OMB control numbers 0910–0001 and 0910–0338, respectively, and the collections of information in 21 CFR part 814, subparts A through E, 21 CFR part 860, subpart D, and 21 CFR part 807, subpart E, for premarket approval applications, De Novo classification requests, and premarket notifications have been approved under OMB control numbers 0910–0231, 0910–0844, and 0910–0120, respectively.

III. Additional Information

Section 3002 of Title III, Subtitle A of the 21st Century Cures Act (Pub. L. 114–255) directs FDA to develop patient-focused drug development guidance to address a number of areas, including under section 3002(c)(4): methodologies, standards, and technologies to collect and analyze clinical outcome assessments for purposes of regulatory decision-making.

In addition, FDA committed to meet certain performance goals under the sixth authorization of the Prescription Drug User Fee Act. These goal commitments were developed in consultation with patient and consumer advocates, healthcare professionals, and other public stakeholders, as part of negotiations with regulated industry. Section I.J.1 of the commitment letter ''Enhancing the Incorporation of the Patient's Voice in Drug Development and Decision-Making'' (*https://www.fda.gov/media/99140/download*) outlines work, including the development of a series of guidance documents and associated public workshops to facilitate the advancement and use of systematic approaches to collect and utilize robust and meaningful patient and caregiver input that can more consistently inform drug development, and, as appropriate, regulatory decision-making.

IV. Electronic Access

Persons with access to the internet may obtain the draft guidance at *https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs, https://www.fda.gov/regulatory-information/search-fda-guidance-documents,* or *https://www.regulations.gov.*

Dated: April 3, 2023.

Lauren K. Roth,

Associate Commissioner for Policy.

[FR Doc. 2023–07243 Filed 4–5–23; 8:45 am]

BILLING CODE 4164–01–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, the Agency, or we) is evaluating substances that have been nominated for inclusion on a list of bulk drug substances (active pharmaceutical ingredients (APIs)) 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 one bulk drug substance that FDA has considered and is including on the list at this time: quinacrine hydrochloride (HCl) to compound drug products for oral use only. This notice also identifies 10 bulk drug substances that FDA has considered and is not including on the list at this time: hydroxyzine HCl, mannitol, methacholine chloride, metoclopramide HCl, nalbuphine HCl, potassium acetate, procainamide HCl, sodium bicarbonate, sodium nitroprusside, and verapamil HCl. Additional bulk drug substances nominated by the public for inclusion on this list are currently under consideration and will be the subject of future notices.

DATES: The announcement of the notice is published in the **Federal Register** on April 6, 2023.

ADDRESSES: 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 in an outsourcing facility to be exempt from section 505 (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, 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 (the Secretary) 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 one bulk drug substance that FDA has considered and is including on the 503B Bulks List and 10 bulk drug substances that FDA has considered and is not including 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 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]

II. Methodology for Developing the 503B Bulks List

A. Process for Developing the List

FDA requested nominations for specific bulk drug substances for the Agency to consider for inclusion on the 503B Bulks List in the **Federal Register** of December 4, 2013 (78 FR 72838). 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. On 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, 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 its 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 final determination 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 final determination regarding those substances it considered but found that there is no clinical need to use in compounding and FDA's rationale in making this decision.

[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)) with section 503B(a) of the FD&C Act (not providing the 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), March 24, 2021 (86 FR 15673), and November 23, 2022 (87 FR 71642). 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 21 CFR 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), inactive ingredients used in compounding must comply with the standards of an applicable United States Pharmacopeia (USP) or National Formulary (NF) monograph, if a monograph exists.

[11] This is consistent with procedures 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 the 503B Bulks List.

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).[13]

B. Analysis of Substances Nominated for the List

As noted above, the 503B Bulks List will include bulk drug substances for which 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 standard provided by the statute (Ref. 2).[14] In applying this standard to make its determinations regarding the substances set forth 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 from the FD&C Act 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 compounded 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 addressed in this notice, with the exception of quinacrine HCl, are components of FDA-approved drug products.[15] FDA began its evaluation of the bulk drug substances that are components of FDA-approved drug products 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 to be compounded using a bulk drug substance that is a component of the FDA-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 product by starting with an FDA-approved drug product, there are certain benefits of doing so over starting with a bulk drug substance, including that FDA-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 the above 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 FDA-approved drug or compounding starting with an FDA-approved drug product. FDA did not answer ''yes'' to both of the threshold questions for the 10 bulk drug substances that are components of FDA-approved drug products that we are addressing in this notice. Accordingly, as explained below, we did not proceed further in our evaluation of these substances and have decided not to include them on the 503B Bulks List.

With respect to the bulk drug substance addressed in this notice that is not a component of an FDA-approved drug, quinacrine HCl, we conducted a balancing test using four factors. Specifically, we considered available data relevant to each factor in the context of the other factors and balanced all four factors to determine whether the

[13] In January 2017, FDA announced the availability of a revised final guidance for industry that provides additional information regarding FDA's policies for bulk drug substances nominated for the 503B Bulks List pending our review of nominated substances under the ''clinical need'' standard entitled ''Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act'' (the ''Interim Policy''), available at *https://www.fda.gov/media/94402/download.*

[14] In March 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'' (the ''Clinical Need Guidance''), 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. The analysis under the statutory ''clinical need'' standard described in this notice is consistent with the approach described in FDA's guidance.

[15] Specifically, hydroxyzine HCl, mannitol, methacholine chloride, metoclopramide HCl, nalbuphine HCl, potassium acetate, procainamide HCl, sodium bicarbonate, sodium nitroprusside, and verapamil HCl.

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 and describes how they were applied to develop FDA's decision to include quinacrine HCl for oral use on the 503B Bulks List.

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

In evaluating a bulk drug substance for the 503B Bulks List, FDA has 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. In the **Federal Register** notice of July 31, 2020 (85 FR 46126), FDA requested comments on the proposal to limit listings in this manner. On January 8, 2021 (86 FR 1515), the comment period for the July 2020 notice was reopened for 30 days to allow 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 its findings related to clinical need for those bulk drug substances.

FDA has also determined that to be eligible for the statutory exemptions under section 503B, drug products compounded using a bulk drug substance that appears on the 503B Bulks List cannot contain other APIs unless those APIs have been listed in combination on the 503B Bulks List (87 FR 4240). FDA's assessment of the clinical need for compounding with a particular bulk drug substance or combination of bulk drug substances could be affected if a bulk drug substance is commonly used in compounded drug products that contain multiple bulk drug substances (APIs). The use of certain APIs in combination with other APIs in a compounded drug product could also pose a safety risk or affect the compounded drug product's effectiveness. These considerations of the composition of a nominated compounded combination, the history of its use in compounding, and evidence of safety or effectiveness would be included in FDA's clinical need evaluation.

In accordance with these considerations and the clinical need analysis set forth below, FDA is adding one bulk drug substance—quinacrine HCl—to the 503B Bulks List to compound single-ingredient drug products for oral use only.[16]

III. FDA's Determinations Regarding Substances Proposed for the 503B Bulks List

In September 2019, the Agency issued a **Federal Register** notice in which it evaluated nine nominated bulk drug substances under the section 503B statutory standard—dipyridamole, ephedrine sulfate, famotidine, hydralazine HCl, methacholine chloride, sodium bicarbonate, sodium tetradecyl sulfate, trypan blue, and vecuronium bromide—and proposed not to include them on the 503B Bulks List (the September 2019 notice).[17] In this notice, after review of the comments submitted to the docket for the September 2019 notice, FDA is making its final determination not to include methacholine chloride and sodium bicarbonate on the 503B Bulks List. At this time, FDA is not making a final determination regarding ephedrine sulfate, famotidine, hydralazine HCl, sodium tetradecyl sulfate, trypan blue, and vecuronium bromide.[18] These substances remain under consideration by FDA.

In July 2020, the Agency issued a **Federal Register** notice in which it evaluated 23 nominated bulk drug substances under the section 503B statutory standard (the July 2020 notice).[19] FDA proposed to include diphenylcyclopropenone (DPCP), glycolic acid, squaric acid dibutyl ester (SADBE), and trichloroacetic acid (TCA) on the 503B Bulks List. FDA proposed not to include diazepam, dobutamine HCl, dopamine HCl, edetate calcium disodium, folic acid, glycopyrrolate, hydroxyzine HCl, ketorolac tromethamine, labetalol HCl, mannitol, metoclopramide HCl, moxifloxacin HCl, nalbuphine HCl, polidocanol, potassium acetate, procainamide HCl, sodium nitroprusside, sodium thiosulfate, and verapamil HCl on the 503B Bulks List. In this notice, after review of the comments submitted to the docket for the July 2020 notice, FDA is making its final determination not to include hydroxyzine HCl, mannitol, metoclopramide HCl, nalbuphine HCl, potassium acetate, procainamide HCl, sodium nitroprusside, and verapamil HCl on the 503B Bulks List. FDA has previously made final determinations for DPCP, glycolic acid, SADBE, TCA, diazepam, dobutamine HCl, dopamine HCl, edetate calcium disodium, folic acid, glycopyrrolate, and sodium thiosulfate (except the topical route of administration) (87 FR 4240). At this time, FDA is not making a final determination regarding ketorolac tromethamine, labetalol HCl, moxifloxacin HCl, and polidocanol. These substances remain under consideration by FDA.

In March 2021, the Agency issued a **Federal Register** notice in which it evaluated five bulk drug substances under the section 503B statutory standard (the March 2021 notice).[20] FDA proposed to include quinacrine HCl on the 503B Bulks List to compound drug products for oral use only. FDA proposed not to include bromfenac sodium, mitomycin-C, nepafenac, and hydroxychloroquine sulfate on the 503B Bulks List. In this notice, after review of the comments submitted to the docket for the March 2021 notice, FDA is making its final determination to include quinacrine HCl on the 503B Bulks List to compound drug products for oral use only. At this time, FDA is not making a final determination regarding bromfenac sodium, mitomycin-C, nepafenac, and hydroxychloroquine sulfate. These substances remain under consideration by FDA. Additional bulk drug substances nominated by the public for inclusion on the 503B Bulks List are currently under consideration and may be the subject of future notices.

A. Substance Evaluated and Included on the 503B Bulks List

FDA is placing quinacrine HCl on the 503B Bulks List. FDA evaluated quinacrine HCl and proposed to include it on the 503B Bulks List in the March 2021 notice. The reasons for FDA's proposal to place quinacrine HCl for oral use on the 503B Bulks List are

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

[17] See 84 FR 46014.

[18] FDA made a final determination not to include dipyridamole on the 503B Bulks List (see 87 FR 4240).

[19] 85 FR 46126.

[20] 86 FR 15673.

included below (Ref. 3).[21] For the reasons set forth in the proposal, FDA is now placing quinacrine HCl on the 503B Bulks List for oral use only.

Quinacrine HCl

FDA considered the bulk drug substance quinacrine HCl for inclusion on the 503B Bulks List to compound drug products in oral dosage forms at strengths of 25–100 milligrams (mg) for the treatment of cutaneous lupus erythematosus (CLE), as described in the Agency's nomination and evaluation.[22]

Quinacrine HCl is not a component of an FDA-approved drug product. The Agency therefore evaluated quinacrine HCl for potential inclusion on the 503B Bulks List under the clinical need standard in section 503B of the FD&C Act using the balancing test described above. FDA considered data and information regarding the physical and chemical characterization of quinacrine 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 (Ref. 3).

Quinacrine HCl is well-characterized physically and chemically. Although there are concerns about its safety profile in certain patient populations, FDA believes these risks are well known within the rheumatology and dermatology specialties that most often treat CLE, and the known risks could be controlled with appropriate dosing and monitoring. Quinacrine HCl has been used for several decades to treat systemic lupus erythematosus and CLE, and there is a significant body of experience, documented in the scientific literature, that quinacrine HCl may be effective in the treatment of patients with cutaneous lupus, and patients who are not fully clinically responsive to, or are intolerant of, treatment with FDA-approved products alone. These patients may respond to the addition of quinacrine HCl to their existing therapy, or to the use of quinacrine HCl alone. On balance, the physical and chemical characterization, safety, effectiveness, and historical and current use of quinacrine HCl weigh in favor of including this substance on the 503B Bulks List. Two commenters supported FDA's proposal to include quinacrine HCl on the 503B Bulks List, although one of them disagreed with FDA's proposal to limit the entry to oral use only. No commenters opposed adding quinacrine HCl to the 503B Bulks List. Several commenters objected generally to FDA's proposals, and these overarching concerns are addressed in section IV of this notice. Accordingly, FDA is adding quinacrine HCl to the 503B Bulks List for oral use only. The entry on the 503B Bulks List is limited in this way because, as discussed above, FDA's evaluation only revealed a clinical need for outsourcing facilities to compound drug products containing the bulk drug substance quinacrine HCl for the oral route of administration.

Due to the safety risks referred to above, FDA is making safety information about the use of quinacrine HCl available to prescribers, pharmacists, outsourcing facilities, and the public through a safety guide on FDA's website, available at *https://www.fda.gov/drugs/human-drug-compounding/consumer-and-health-care-professional-information.*

B. Substances Evaluated and Not Included on the 503B Bulks List

The 10 bulk drug substances that FDA has evaluated, proposed not to include on the 503B Bulks List in a **Federal Register** notice, and has now decided not to place on the 503B Bulks List are: hydroxyzine HCl, mannitol, methacholine chloride, metoclopramide HCl, nalbuphine HCl, potassium acetate, procainamide HCl, sodium bicarbonate, sodium nitroprusside, and verapamil HCl.

Because the substances discussed in this section are components of FDA-approved drug products, FDA considered 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(s) proposed to be compounded is intended to address that attribute in each FDA-approved drug product, and (2) is there a basis to conclude that the drug product(s) proposed to be compounded must be compounded using a bulk drug substance. FDA considered comments to the docket submitted within the public comment period, but as explained below, none of the comments received on these bulk drug substances provided information that led FDA to change its determination.

1. Hydroxyzine HCl

Hydroxyzine HCl has been nominated for inclusion on the 503B Bulks List to compound drug products that treat alcohol withdrawal syndrome, analgesia in labor, pre- and postpartum reduction of narcotic use, and relief of anxiety, among other conditions.[23] The proposed route of administration is intramuscular, the proposed dosage form is a solution, and the proposed concentration is 50 milligrams/milliliters (mg/mL). The nominators proposed to compound a preserved solution. However, they failed to acknowledge that there is a preserved formulation of hydroxyzine HCl that is FDA-approved or identify an attribute of that formulation that makes it medically unsuitable for certain patients. The nominations state that hydroxyzine HCl 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 087408). FDA-approved hydroxyzine HCl is marketed as a preserved 50 mg/mL solution for intramuscular administration.[24] [25] [26]

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

The nominations do not identify an attribute of the FDA-approved preserved 50 mg/mL hydroxyzine HCl solution for intramuscular administration that makes it medically unsuitable for certain patients or identify an attribute of the FDA-approved drug products that the proposed compounded drug product is intended to address. Two commenters supported FDA's proposal not to include hydroxyzine HCl on the 503B Bulks List. No new information supporting the clinical need for compounding from the bulk drug substance hydroxyzine HCl was provided by the commenters.

Accordingly, FDA finds no basis to conclude that there is an attribute of the

[21] In addition to FDA's evaluation of the quinacrine HCl nomination for the 503B Bulks List, the Agency considered data and information from its earlier evaluation regarding the use of this bulk drug substance for the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act (the 503A Evaluation) (see appendices A–D in ''FDA Memo to File, Clinical Need for Quinacrine Hydrochloride in Compounding Under Section 503B of the FD&C Act'' (Ref. 3)). FDA also considered a report provided by the University of Maryland Center of Excellence in Regulatory Science and Innovation and conducted a search for relevant scientific literature and safety information, focusing on materials published or submitted to FDA since the 503A Evaluations (see appendix H in Ref. 3).

[22] See appendix G in Ref. 3.

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

[24] See, *e.g.,* ANDA 087408 labeling available as of the date of this notice at *https://www.accessdata.fda.gov/spl/data/e711ee73-c054-4f3f-a189-bb3c01c7aecc/e711ee73-c054-4f3f-a189-bb3c01c7aecc.xml.*

[25] Per the label for ANDA 087408, each mL contains hydroxyzine HCl 25 mg or 50 mg, benzyl alcohol 0.9 percent, and water for injection q.s. pH is adjusted with sodium hydroxide and/or hydrochloric acid.

[26] Hydroxyzine HCl is also FDA-approved as an oral tablet and as an oral syrup.

FDA-approved products that 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.

b. 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 hydroxyzine HCl and the FDA-approved drug product containing hydroxyzine HCl, there is nothing for FDA to evaluate under question 2. No further information was supplied on this point during the comment period. Therefore, FDA finds no basis to conclude that the drug product proposed to be compounded must be prepared using a bulk drug substance rather than an FDA-approved drug product.

2. Mannitol

Mannitol has been nominated for inclusion on the 503B Bulks List to compound drug products for treatment of acute renal failure, inhalation bronchial challenge testing, and irrigation of the urinary bladder, among other conditions.[27] The proposed route of administration is intravenous, the proposed dosage form is a solution, and the proposed concentration is 25 percent. The nominators proposed to compound a preservative-free solution. However, they failed to acknowledge that there is a preservative-free formulation of mannitol that is FDA-approved or identify an attribute of that formulation that makes it medically unsuitable for certain patients. The nominations state that mannitol 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 016269). FDA-approved mannitol is marketed as a preservative-free solution in water for injection in various concentrations, including a 25 percent concentration in a flip-top vial for administration by intravenous infusion only.[28] [29] [30]

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

The nominations do not identify an attribute of each of the FDA-approved 25 percent preservative-free solution products that makes them medically unsuitable for certain patients or identify an attribute of the FDA-approved drug products that the proposed compounded drug product is intended to address. Two commenters supported FDA's proposal not to include mannitol on the 503B Bulks List. The commenters provided no new information supporting the clinical need for compounding from the bulk drug substance mannitol.

Accordingly, FDA finds no basis to conclude that there is an attribute of the FDA-approved products that 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.

b. 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 mannitol and FDA-approved drug products containing mannitol, there is nothing for FDA to evaluate under question 2. No further information was supplied on this point during the comment period. Therefore, FDA finds no basis to conclude that drug products must be compounded using a bulk drug substance rather than an FDA-approved drug product.

3. Methacholine Chloride

Methacholine chloride has been nominated for inclusion on the 503B Bulks List to compound drug products that aid in the diagnosis of bronchial airway hyperactivity.[31] The proposed route of administration is inhalation tapering dose kits, the proposed dosage form is an inhalant, and the proposed strengths are as follows: 8 dilutions (0.125 mg/mL, 0.25 mg/mL, 0.5 mg/mL, 1 mg/mL, 2 mg/mL, 4 mg/mL, 8 mg/mL, 16 mg/mL) and 10 dilutions (0.031 mg/mL, 0.0625 mg/mL, 0.125 mg/mL, 0.25 mg/mL, 0.5 mg/mL, 1 mg/mL, 2 mg/mL, 4 mg/mL, 8 mg/mL, 16 mg/mL). The nominated bulk drug substance is a component of an FDA-approved drug product (NDA 019193). FDA-approved methacholine chloride is marketed as a 100 mg/vial powder for solution to be administered only by inhalation.[32] Per its labeling, methacholine chloride is reconstituted and diluted to the following concentrations with 0.9 percent sodium chloride injection or 0.9 percent sodium chloride injection containing 0.4 percent phenol (pH 7.0): 0.025 mg/mL, 0.25 mg/mL, 2.5 mg/mL, 10 mg/mL, and 25 mg/mL.

a. Suitability of FDA-Approved Drug Product

The nomination does not identify an attribute of the FDA-approved drug product that makes it medically unsuitable to treat certain patients and that the proposed compounded drug products are intended to address. Specifically, the nomination does not identify an attribute of the FDA-approved 100 mg/vial powder for solution (for reconstitution) that makes it medically unsuitable for certain patients. The commenters propose to compound a ready-to-use product from a bulk drug substance to seek improved efficiency for prescribers or healthcare providers, or to address the possibility that the FDA-approved drug might be mishandled by a medical professional, neither of which falls within the meaning of clinical need to compound a drug product using a bulk drug substance.[33] Several commenters supported FDA's proposal not to include methacholine chloride on the 503B Bulks List. The commenters provided no additional information supporting the clinical need for compounding from the bulk drug substance methacholine chloride.

Accordingly, FDA finds no basis to conclude that there is an attribute of the FDA-approved product that 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.

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

The nomination does not provide support for the position that drug products containing methacholine chloride must be compounded from a bulk drug substance rather than by diluting the FDA-approved drug

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

[28] See, *e.g.,* NDA 016269 labeling available as of the date of this notice at *https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/016269s056lbl.pdf*.

[29] Per the label for NDA 016269, the solutions contain no bacteriostat, antimicrobial agent, or added buffer (except for pH adjustment) and each is intended only as a single-dose injection.

[30] Mannitol is also FDA-approved as a single ingredient as a solution for irrigation and as a powder for inhalation.

[31] See Docket No. FDA–2013–N–1524, document no. FDA–2013–N–1524–2292.

[32] See, *e.g.,* NDA 208943 labeling available as of the date of this notice at *https://www.accessdata.fda.gov/spl/data/7f538d73-80e2-4c00-911a-df2637e5a4d1/7f538d73-80e2-4c00-911a-df2637e5a4d1.xml*.

[33] See, *e.g.,* ''List of Bulk Drug Substances for Which There Is a Clinical Need Under Section 503B of the Federal Food, Drug, and Cosmetic Act,'' 87 FR 4240 at 4248.

product. None of the commenters provided support for such a position during the comment period. Some commenters stated that there could be a benefit from using a bulk drug substance to compound drug products to avoid the manipulations that the FDA-approved drug products that contain methacholine chloride require before they can be administered (*e.g.,* dilution). Commenters also contended that outsourcing facilities, as opposed to hospitals, are better able to prepare methacholine in the sterile environment that is necessary for the sterility of an injectable drug product. This is essentially an argument that the approved drug might be mishandled by a medical professional, which, as discussed above, does not fall within the meaning of clinical need to compound a drug product using a bulk drug substance. The commenters also did not establish that drug products in the relevant concentrations, including ready-to-use products, cannot be prepared from the FDA-approved drug products, which are labeled for dilution.

Having considered these arguments, and because no further information was supplied regarding the clinical need for compounding from the bulk drug substance, FDA finds no basis to conclude that the methacholine chloride drug products proposed to be compounded must be prepared using a bulk drug substance rather than the FDA-approved drug product.

4. Metoclopramide HCl

Metoclopramide HCl has been nominated for inclusion on the 503B Bulks List to compound drug products that treat chemotherapy-induced nausea and vomiting, diabetic gastroparesis, gastroesophageal reflux disease, and postoperative nausea and vomiting, among other conditions.[34] The proposed routes of administration are intravenous and intramuscular, the proposed dosage form is a suspension, and the proposed concentration is 5 mg/mL. The nominators proposed to compound both preservative-free and preserved suspensions. However, they failed to acknowledge that there is a preservative-free formulation of metoclopramide HCl that is FDA-approved or identify an attribute of that formulation that would be medically unsuitable for certain patients. The nominations state that metoclopramide HCl 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 073118). FDA-approved metoclopramide HCl is marketed as a preservative-free 10 mg/2 mL (5 mg/mL) solution for intravenous or intramuscular administration.[35] [36] [37]

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

The nominations do not identify an attribute of each of the FDA-approved preservative-free 10 mg/2 mL (5 mg/mL) solution products for intravenous or intramuscular administration that makes them medically unsuitable for certain patients or identify an attribute of the FDA-approved drug products that the proposed compounded drug product is intended to address. In particular, the nominations do not identify any data or information indicating that there are some patients who need a preserved product rather than the FDA-approved preservative-free products. In addition, the nominations do not identify any data or information indicating that there are some patients who need a suspension rather than a solution for intravenous and intramuscular administration. Two commenters supported FDA's proposal not to include metoclopramide HCl on the 503B Bulks List. Commenters provided no new information supporting the clinical need for compounding from the bulk substance metoclopramide HCl.

Accordingly, FDA finds no basis to conclude that there is an attribute of the FDA-approved products that 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.

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

Because the nominations have not identified an attribute of the FDA-approved drug product that makes it medically unsuitable for certain patients, FDA has not evaluated whether the proposed drug products containing metoclopramide HCl must be compounded from bulk drug substances rather than using the FDA-approved drug product. No further information was supplied on this point during the comment period. Therefore, FDA finds no basis to conclude that the drug products proposed to be compounded must be prepared using a bulk drug substance rather than an FDA-approved drug product.

5. Nalbuphine HCl

Nalbuphine HCl has been nominated for inclusion on the 503B Bulks List to compound drug products that are used for general anesthesia and to treat moderate to severe pain as a preoperative, postoperative, and obstetrical analgesia.[38] The proposed routes of administration are intravenous, intramuscular, and subcutaneous, the proposed dosage form is a solution, and the proposed concentrations are 10 mg/mL and 20 mg/mL. The nominators proposed to compound a preservative-free solution and a preserved solution. However, they failed to acknowledge that there are both a preservative-free solution formulation and a preserved solution formulation of nalbuphine HCl that are FDA-approved or identify an attribute of those formulations that makes them medically unsuitable for certain patients. The nominations state that nalbuphine HCl 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.,* ANDAs 070914 and 070918). FDA-approved nalbuphine HCl is marketed as both preservative-free and as preserved 10 mg/mL and 20 mg/mL solutions for intravenous, intramuscular, and subcutaneous administration.[39] [40]

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

The nominations do not identify an attribute of each of the FDA-approved 10 mg/mL and 20 mg/mL nalbuphine HCl solutions for intravenous, intramuscular, and subcutaneous administration that makes them medically unsuitable for certain patients or identify an attribute of the approved drug products that the proposed compounded drug products are

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

[35] See, *e.g.,* ANDA 073118 labeling available as of the date of this notice at *https://www.accessdata.fda.gov/spl/data/d693380f-94fa-46df-ad37-4ecf3c59b8b8/d693380f-94fa-46df-ad37-4ecf3c59b8b8.xml.*

[36] Per the label for ANDA 073118, the solution is preservative-free and is intended for intravenous or intramuscular administration.

[37] Metoclopramide is also FDA-approved as an oral solution, metered nasal spray, and tablet.

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

[39] See, *e.g.,* ANDA 070914 and 070918 labeling available as of the date of this notice at *https://www.accessdata.fda.gov/spl/data/f118d0a9-270f-4ced-ba4c-c62e32e0d635/f118d0a9-270f-4ced-ba4c-c62e32e0d635.xml* and *https://www.accessdata.fda.gov/spl/data/0e1346b6-7c47-4957-b0be-849a84b18a89/0e1346b6-7c47-4957-b0be-849a84b18a89.xml,* respectively.

[40] Per the labels for ANDA 070914 and 070918, single-dose products contain no bacteriostat or antimicrobial agent and unused portions must be discarded.

intended to address. Two commenters supported FDA's proposal not to include nalbuphine HCl on the 503B Bulks List. The commenters provided no new information supporting the clinical need for compounding from the bulk substance nalbuphine HCl.

Accordingly, FDA finds no basis to conclude that there is an attribute of the FDA-approved products that 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.

b. 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 nalbuphine HCl and approved drug products containing nalbuphine HCl, there is nothing for FDA to evaluate under question 2. No further information was supplied on this point during the comment period. Therefore, FDA finds no basis to conclude that the drug products proposed to be compounded must be prepared using a bulk drug substance rather than an FDA-approved drug product.

6. Potassium Acetate

Potassium acetate has been nominated for inclusion on the 503B Bulks List to compound drug products that facilitate electrolyte management.[41] The proposed route of administration is intravenous, the proposed dosage form is a solution, and the proposed concentration is 2 milliequivalents per milliliter (mEq/mL). The nominators proposed to compound a preservative-free solution. However, they failed to acknowledge that there is a preservative-free formulation of potassium acetate that is FDA-approved or identify an attribute of that formulation that makes it medically unsuitable for certain patients. The nominations state that potassium acetate 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 018896). FDA-approved potassium acetate is marketed as a 40 mEq/20 mL (2 mEq/mL) preservative-free solution for intravenous administration.[42] [43]

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

The nominations do not identify an attribute of each of the FDA-approved 2 mEq/mL preservative-free solution products that makes them medically unsuitable for certain patients or identify an attribute of the approved drug products that the proposed compounded drug product is intended to address. Two commenters supported FDA's proposal not to include potassium acetate on the 503B Bulks List. The commenters provided no new information supporting the clinical need for compounding from the bulk substance potassium acetate. Accordingly, FDA finds no basis to conclude that there is an attribute of the FDA-approved products that 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.

b. 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 potassium acetate and approved drug products containing potassium acetate, there is nothing for FDA to evaluate under question 2. No further information was supplied on this point during the comment period. Therefore, FDA finds no basis to conclude that the drug products proposed to be compounded must be prepared using a bulk drug substance rather than an FDA-approved drug product.

7. Procainamide HCl

Procainamide HCl has been nominated for inclusion on the 503B Bulks List to compound drug products that treat ventricular arrhythmia.[44] The proposed routes of administration are intramuscular and intravenous, the proposed dosage form is a solution, and the proposed concentrations are 100 mg/mL and 500 mg/mL. The nominators proposed to compound a preserved solution. However, they failed to acknowledge that there is a preserved formulation of procainamide HCl that is FDA-approved or identify an attribute of that formulation that makes it medically unsuitable for certain patients. The nominations state that procainamide HCl 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 089069). FDA-approved procainamide HCl is marketed as 100 mg/mL and 500 mg/mL preserved solutions for intramuscular and intravenous administration.[45] [46]

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

The nominations do not identify an attribute of each of the FDA-approved 100 mg/mL and 500 mg/mL preserved solutions that makes them medically unsuitable for certain patients or identify an attribute of the approved drug products that the proposed compounded drug products are intended to address. Two commenters supported FDA's proposal not to include procainamide HCl on the 503B Bulks List. Commenters provided no new information supporting the clinical need for compounding from the bulk drug substance procainamide HCl. Accordingly, FDA finds no basis to conclude that there is an attribute of the FDA-approved products that 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.

b. 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 procainamide HCl and approved drug products containing procainamide HCl, there is nothing for FDA to evaluate under question 2. No further information was supplied on this point during the comment period. Therefore, FDA finds no basis to conclude that the drug products proposed to be compounded must be prepared using a bulk drug substance rather than an FDA-approved drug product.

[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 018896 labeling available as of the date of this notice at *https://www.accessdata.fda.gov/spl/data/28f98aef-8865-4faf-b491-a77b56513d5d/28f98aef-8865-4faf-b491-a77b56513d5d.xml.*

[43] Per the label for NDA 018896, the potassium acetate solution contains no bacteriostat, antimicrobial agent, or added buffer but may contain acetic acid for pH adjustment.

[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 089069 labeling available as of the date of this notice at *https://www.accessdata.fda.gov/spl/data/6918f728-6c39-4be9-b0f6-6eb5f12bbcaf/6918f728-6c39-4be9-b0f6-6eb5f12bbcaf.xml.*

[46] Per the label for ANDA 089069, each milliliter of the 2 mL vial contains procainamide hydrochloride 500 mg, methylparaben 1 mg, and sodium metabisulfite 1.8 mg added in water for injection, and may contain hydrochloric acid and/or sodium hydroxide for pH adjustment.

8. Sodium Bicarbonate

Sodium bicarbonate has been nominated for inclusion on the 503B Bulks List to compound drug products that treat various conditions, including metabolic acidosis, certain drug intoxications, severe diarrhea, and indigestion.[47] The proposed route of administration is intravenous, the proposed dosage forms are an injectable solution and injection solutions, and the proposed strengths range from 4.2 percent to 8.4 percent. The nominators proposed to compound a preservative-free solution. However, they failed to acknowledge that there is an FDA-approved preservative-free formulation of sodium bicarbonate or identify an attribute of that formulation that makes it medically unsuitable for certain patients. The nominations state that sodium bicarbonate 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.,* ANDAs 203449 and 202494). FDA-approved sodium bicarbonate is a single-dose, preservative-free 1 mEq/mL (8.4 percent) solution for intravenous administration. [48] [49] [50]

a. Suitability of FDA-Approved Drug Product

The nominations do not identify an attribute of the FDA-approved drug products, including the single-dose, preservative-free 1 mEq/mL (8.4 percent) solution, that makes them medically unsuitable to treat certain patients and that the proposed compounded drug products are intended to address. Two commenters supported FDA's proposal not to include sodium bicarbonate on the 503B Bulks List. Commenters provided no new information supporting the clinical need for compounding from the bulk drug substance sodium bicarbonate. Accordingly, FDA finds no basis to conclude that there is an attribute of the FDA-approved product that makes it medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation and that the proposed compounded product is intended to address.

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

The nominations do not provide support for the position that the proposed sodium bicarbonate products with concentrations at or below 8.4 percent (1 mEq/mL) must be compounded from bulk drug substances rather than by diluting the FDA-approved drug product. Because no data or information was submitted supporting the need for a higher concentration, we have not considered whether a bulk drug substance must be used to compound a sodium bicarbonate drug product at concentrations higher than 8.4 percent. No comments provided support for the position that the proposed sodium bicarbonate products with concentrations at or below 8.4 percent (1 mEq/mL) must be compounded from bulk drug substances rather than by diluting the FDA-approved drug product. Several commenters stated that the ability to compound sodium bicarbonate using a bulk drug substance was crucial to address persistent drug shortages. However, as explained above, section 503B of the FD&C Act already provides for compounding from a bulk drug substance if the drug product compounded from such bulk drug substance is on the FDA drug shortage list at the time of compounding, distribution, and dispensing. The Agency does not interpret supply issues, such as shortages and backorders, to be within the meaning of ''clinical need'' for compounding with a bulk drug substance.[51] Other commenters asserted that there could be a benefit from using the bulk drug substance sodium bicarbonate to compound drug products to avoid the manipulations that the FDA-approved drug products that contain sodium bicarbonate require before they can be administered (*e.g.,* dilution or drawing the drug into a syringe before administration). One commenter proposes to compound ready-to-use products from bulk drug substances to seek improved efficiency for prescribers or healthcare providers and to address the possibility that the approved drug might be mishandled by a medical professional, neither of which falls within the meaning of clinical need to compound a drug product using a bulk drug substance.

Having considered these arguments, and because no further information was supplied regarding the clinical need for compounding from the bulk drug substance, FDA finds no basis to conclude that the drug products proposed to be compounded must be prepared using a bulk drug substance rather than an FDA-approved drug product.

9. Sodium Nitroprusside

Sodium nitroprusside has been nominated for inclusion on the 503B Bulks List to compound drug products to treat acute decompensated heart failure and acute hypertension.[52] The proposed route of administration is an injection, the proposed dosage form is a solution, and the proposed concentration is 12.5 mg/mL. The nomination states that sodium nitroprusside might also be used to compound other drug products but does not identify those products. The nominated bulk drug substance is a component of FDA-approved drug products (*e.g.,* ANDA 209493). FDA-approved sodium nitroprusside is marketed as a 50 mg/2 mL (25 mg/mL) solution that must be diluted prior to injection. [53] [54]

a. Suitability of FDA-Approved Drug Products

Although the nominator proposes to make a drug product that has a lower concentration than the approved drug product with the same API, the nomination does not identify an attribute of each of the FDA-approved 50 mg/2 mL solution for dilution products that makes them medically unsuitable for certain patients or identify an attribute of the FDA-approved drug products that the proposed compounded drug product is intended to address. Two commenters supported FDA's proposal not to include sodium nitroprusside on the 503B Bulks List. Commenters provided no new information supporting the clinical need for compounding from the bulk drug substance sodium nitroprusside. Accordingly, FDA finds no basis to conclude that there is an attribute of the FDA-approved products

[47] See Docket No. FDA–2013–N–1524, document nos. FDA–2013–N–1524–2292 and FDA–2013–N–1524–2298; see also Docket No. FDA–2015–N–3469, document no. FDA–2015–N–3469–0095.

[48] See, *e.g.,* ANDA 203449 labeling available as of the date of this notice at *https://www.accessdata.fda.gov/spl/data/0e955d36-928c-4f09-9b34-0cc954e5b1f4/0e955d36-928c-4f09-9b34-0cc954e5b1f4.xml.*

[49] Per the label for ANDA 203449, the solutions contain no bacteriostat, antimicrobial agent, or added buffer and are intended only for use as a single-dose injection.

[50] Sodium bicarbonate is also FDA-approved in combination with other ingredients as an injectable, solution for irrigation, and various oral formulations.

[51] See, *e.g.,* ''List of Bulk Drug Substances for Which There Is a Clinical Need Under Section 503B of the Federal Food, Drug, and Cosmetic Act,'' 87 FR 4240 at 4248.

[52] See Docket No. FDA–2015–N–3469, document no. FDA–2015–N–3469–0238.

[53] See, *e.g.,* ANDA 209493 labeling available as of the date of this notice at *https://www.accessdata.fda.gov/spl/data/37060217-1ad1-462b-a1d0-7271c68ed881/37060217-1ad1-462b-a1d0-7271c68ed881.xml.*

[54] Sodium nitroprusside is also FDA-approved as a solution for intravenous administration.

that 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.

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

The nomination does not provide support for the position that drug products containing sodium nitroprusside must be compounded from bulk drug substances rather than using the FDA-approved drug products. No further information was supplied on this point during the comment period. Therefore, FDA finds no basis to conclude that the drug products proposed to be compounded must be prepared using a bulk drug substance rather than an FDA-approved drug product.

10. Verapamil HCl

Verapamil HCl has been nominated for inclusion on the 503B Bulks List to compound drug products that treat atrial fibrillation and flutter, hypertension, and paroxysmal supraventricular tachycardia, among other conditions.[55] The proposed route of administration is intravenous, the proposed dosage form is a solution, and the proposed concentration is 2.5 mg/mL. The nominators proposed to compound a preservative-free solution. However, they failed to acknowledge that there is a preservative-free formulation of verapamil HCl that is FDA-approved or identify an attribute of that formulation that makes it medically unsuitable for certain patients. The nominations state that verapamil HCl 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 070737). FDA-approved verapamil HCl is marketed as a preservative-free 5 mg/2 mL (2.5 mg/mL) solution for intravenous administration. [56] [57] [58]

a. Suitability of FDA-Approved Drug Products

The nominations do not identify an attribute of each of the FDA-approved preservative-free 5 mg/2 mL (2.5 mg/mL) solution products for intravenous administration that makes them medically unsuitable for certain patients or identify an attribute of the FDA-approved drug products that the proposed compounded drug products are intended to address. Two commenters supported FDA's proposal not to include verapamil HCl on the 503B Bulks List. Commenters provided no new information supporting the clinical need for compounding from the bulk drug substance verapamil HCl. Accordingly, FDA finds no basis to conclude that there is an attribute of the FDA-approved products that 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.

b. 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 verapamil HCl and FDA-approved drug products containing verapamil HCl, there is nothing for FDA to evaluate under question 2. No further information was supplied on this point during the comment period. Therefore, FDA finds no basis to conclude that drug products proposed to be compounded must be prepared using a bulk drug substance rather than an FDA-approved drug product.

IV. Other Issues Raised in Nominations and Comments

Two commenters expressed concern that nominations submitted before FDA issued the Clinical Need Guidance in March 2019 are disadvantaged in demonstrating clinical need because the nominators might not have fully understood FDA's thinking on clinical need when they submitted their nominations.[59] In addition, one commenter expressed concern that FDA is evaluating bulk drug substances for clinical need pursuant to a non-binding guidance document.

FDA disagrees with these comments. First, as explained in section II.B of this notice, FDA is evaluating bulk drug substances nominated for inclusion on the 503B Bulks List under the ''clinical need'' standard provided by the FD&C Act, as amended by the Drug Quality and Security Act in 2013.[60] The analysis under the statutory ''clinical need'' standard described in this notice is consistent with the approach described in FDA's Clinical Need Guidance. Second, the commenters fail to note the many opportunities that nominators and interested members of the public had to provide information supporting a clinical need to compound drug products containing the bulk drug substances that are the subject of this notice. As explained in section II.A, a public docket, FDA–2015–N–3469, is available for interested persons to submit nominations, including updated or revised nominations, or comments on nominated substances. Furthermore, during the comment periods for the September 2019 and July 2020 **Federal Register** notices, commenters had an additional opportunity to submit comments to the docket associated with those notices to provide additional supporting information for the bulk drug substances that are the subject of this notice, and many did so. Moreover, in response to a request from a commenter, FDA reopened the comment period on the July 2020 **Federal Register** notice for an additional 30 days to allow interested persons yet another opportunity to submit additional comments.

Three commenters on the bulk drug substances addressed in this notice asserted that FDA is regulating and interfering with the practice of medicine by not placing bulk drug substances on the 503B Bulks List despite some physicians wanting to prescribe drug products compounded from those bulk drug substances. FDA disagrees with these comments. The Agency's evaluation under the clinical need standard only regulates the ability of certain compounded drug products to reach the market and is well within the Agency's authorities.[61] The Agency is fulfilling its statutory mandate of regulating outsourcing facilities'

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

[56] See, *e.g.,* ANDA 070737 labeling available as of the date of this notice at *https://www.accessdata.fda.gov/spl/data/072b89b5-6d71-4f63-9686-d715d9256241/072b89b5-6d71-4f63-9686-d715d9256241.xml.*

[57] Per the label for ANDA 070737, the solution contains no bacteriostat or antimicrobial agent, is intended for single-dose intravenous administration, and may contain hydrochloric acid for pH adjustment.

[58] Verapamil HCl is also FDA-approved in various oral capsule and tablet formulations.

[59] See 84 FR 7383, which is available at *https://www.federalregister.gov/documents/2019/03/04/2019-03807/evaluation-of-bulk-drug-substances-nominated-for-use-in-compounding-under-section-503b-of-the.*

[60] See Public Law 113–54, section 102(a) (2013), which is available at *https://www.govinfo.gov/content/pkg/PLAW-113publ54/pdf/PLAW-113publ54.pdf.*

[61] See *United States* v. *Evers,* 643 F.2d 1043, 1048 (5th Cir. 1981) (''[W]hile the [FDCA] was not intended to regulate the practice of medicine, it was obviously intended to control the availability of drugs for prescribing by physicians.''); *United States* v. *Regenerative Scis., LLC,* 741 F.3d 1314, 1319–20 (D.C. Cir. 2014); (citing Evers and noting that the FDCA ''regulate[s] the distribution of drugs by licensed physicians''); *Gonzales* v. *Raich,* 545 U.S. 1, 28 (2005) (''the dispensing of new drugs, even when doctors approve their use must await federal approval.'').

production and distribution of compounded drug products, not interfering with physicians' clinical decisions regarding which drug products to prescribe. Indeed, a Federal court considered the very claim raised in these comments and determined that FDA's evaluation under the clinical need standard ''regulates the type of drug that reaches the marketplace,'' a decision that ''rests well within FDA's regulatory authority under the FDCA . . . and . . . does not intrude on the practice of medicine.'' [62]

Several commenters expressed concern that FDA is promoting the off-label use of FDA-approved drug products. FDA disagrees with this comment. In performing the clinical need evaluation, FDA asks a limited, threshold question to determine whether there might be a clinical need for a compounded drug product, by asking what attributes of the approved drug product the proposed compounded drug product would change and why. Asking this question helps ensure that if a bulk drug substance is included on the 503B Bulks List, it is to compound drug products that include a needed change to an approved drug product rather than to compound drug products without such a change. We do not suggest that the approved drug product or products prepared from it are approved for the use proposed by the nomination being evaluated.

One commenter expressed concern with FDA's decision to evaluate clinical need in the context of the specific drug products proposed to be compounded in the nomination. This commenter stated that requiring nominators to provide information on specific drug products is unnecessary to determine whether there is a clinical need for the bulk drug substance. This commenter also asserted that FDA should not evaluate bulk drug substances in the context of finished dosage forms for drug products. FDA disagrees with these comments. As explained in section I of this notice, section 503B of the FD&C Act limits the bulk drug substances that outsourcing facilities can use in compounding to those that are used to compound drugs in shortage or that appear on a list developed by FDA of bulk drug substances for which there is a clinical need.[63] Section 503B of the FD&C Act includes this limitation, among others, to help ensure that outsourcing facilities do not grow into conventional manufacturing operations making unapproved new drug products without complying with critical requirements, such as new drug approval. Outsourcing facilities, as opposed to other compounders, may compound and distribute drug products for ''office stock'' without first receiving a prescription for an individually identified patient [64] and without conditions on interstate distribution that are applicable to other compounded drugs (Ref. 4).[65] Because of these differences and others, section 503B of the FD&C Act places different conditions on drugs compounded by outsourcing facilities, including limitation on the outsourcing facilities' use of bulk drug substances, which are more stringent than those placed on other compounders' use of bulk drug substances.[66] The clinical need standard in section 503B of the FD&C Act requires FDA to perform a sorting function—to distinguish bulk drug substances for which there is a clinical need from those for which there is not—and this requires FDA to apply its expertise to consider whether there is a need for the finished drug product that would be compounded from the bulk drug substance. Indeed, a Federal court considered the very claim raised in these comments and determined that ''[o]nly when 'clinical need' is assessed against the availability and suitability of an approved drug does the term perform the classifying function that Congress intended.'' In reaching this view, the court found that only when the clinical need evaluation ''considers the actual way in which the active pharmaceutical ingredient supplies a therapeutic benefit—by its administration as a finished drug product—does the inquiry produce the categorization that Congress surely envisioned'' in enacting section 503B of the FD&C Act.[67] FDA's clinical need assessments help limit patient exposure to compounded drug products that have not been demonstrated to be safe and effective to those situations in which the compounded drug product is necessary for patient treatment. In addition, FDA's assessments preserve the incentives for applicants to invest in the research and testing required to obtain FDA approval and continue to manufacture FDA-approved drug products, thereby helping to maintain a supply of high-quality, safe, and effective drugs.

Some of the bulk drug substance nominations and comments discussed above asserted that there could be a benefit from using a bulk drug substance to compound drug products to avoid the manipulations that the FDA-approved drug products that contain these bulk drug substances require before they can be administered (*e.g.,* dilution or drawing the drug into a syringe before administration). As explained above, when a bulk drug substance is a component of an FDA-approved drug, we ask whether there is a basis to conclude that an attribute of each FDA-approved drug product makes each one medically unsuitable to treat certain patients for their condition, an interpretation that protects patients and the integrity of the drug approval process. The nominations proposing to compound drug products in ready-to-use form containing bulk drug substances in one or more FDA-approved drug products do not show

[62] *Athenex Inc.* v. *Azar,* 397 F. Supp. 3d 56, 72 (D.D.C. 2019).

[63] Section 503B(a)(2(A)(i) and (ii) of the FD&C Act.

[64] By contrast, to qualify for the exemptions in section 503A of the FD&C Act, drug products compounded by licensed pharmacists in State-licensed pharmacies or Federal facilities, or by licensed physicians, must be compounded based on the receipt of a valid prescription for an individually identified patient. This means that for drug products compounded under section 503A to meet the conditions of that section and qualify for the exemptions in the statute, the pharmacist or physician compounding under section 503A of the FD&C Act must compound either: (1) after receiving a valid prescription for an identified, individual patient or (2) before receiving a patient-specific prescription, in limited quantities, based on a history of receiving valid orders generated solely within the context of an established relationship with the patient or prescriber. See FDA's final guidance for industry ''Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act'' (December 2016).

[65] For drug products compounded under section 503A of the FD&C Act to meet the conditions of that section and qualify for the exemptions in the statute, drug products must be compounded in a State: (i) that has entered into a memorandum of understanding with the Secretary which addresses the distribution of inordinate amounts of compounded drug products interstate and provides for appropriate investigation by a State agency of complaints relating to compounded drug products distributed outside such State; or (ii) that has not entered into the memorandum of understanding described in clause (i) and the licensed pharmacist, licensed pharmacy, or licensed physician distributes (or causes to be distributed) compounded drug products out of the State in which they are compounded in quantities that do not exceed 5 percent of the total prescription orders dispensed or distributed by such pharmacy or physician (see section 503A(b)(3)(a)(B)(i) and (ii) of the FD&C Act).

[66] Licensed pharmacies and physicians who compound drugs under the conditions of section 503A of the FD&C Act, including the requirement to compound drugs only pursuant to a prescription for an identified individual patient, may use many bulk drug substances by operation of the statute, without action by FDA. See section 503A(b)(1)(A)(i)(I) and (II) of the FD&C Act (providing that a drug product may be compounded consistent with the exemptions in section 503A of the FD&C Act if the licensed pharmacist or licensed physician compounds the drug product using bulk drug substances that comply with the standards of an applicable USP or NF monograph, if a monograph exists, and the USP chapters on pharmacy compounding; or if such a monograph does not exist, are drug substances that are components of drugs approved by the Secretary).

[67] *Athenex Inc.* at 65.

that the FDA-approved drug product, when not manufactured in the ready-to-use form, is medically unsuitable for certain patients. Nor do the nominations and comments establish that drug products in the relevant concentrations, including ready-to-use products, cannot be prepared from the FDA-approved drug products. Rather, they propose to compound a ready-to-use product from bulk drug substances to seek improved efficiency for prescribers or healthcare providers, or to address the possibility that the FDA-approved drug might be mishandled by a medical professional, neither of which falls within the meaning of clinical need to compound a drug product using a bulk drug substance.

Two commenters requested changes to the Interim Policy. These comments are outside the scope of FDA's bulk drug substance evaluations and decisions that are the subject of this notice. FDA welcomes public comments on its guidance documents that address human drug compounding. Comments on the Interim Policy may be submitted to the docket for the guidance, Docket No. FDA–2015–D–3539, at any time at *https://www.regulations.gov.*

V. Conclusion

For the reasons stated above, we find that there is a clinical need for outsourcing facilities to compound drug products using the bulk drug substance quinacrine HCl for oral use only, and therefore we are now including it on the 503B Bulks List. In addition, we find that there is no clinical need for outsourcing facilities to compound using the bulk drug substances hydroxyzine HCl, mannitol, methacholine chloride, metoclopramide HCl, nalbuphine HCl, potassium acetate, procainamide HCl, sodium bicarbonate, sodium nitroprusside, and verapamil HCl, and therefore we are not including these bulk drug substances on the 503B Bulks List.

VI. References

The following references 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.* 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 Quinacrine Hydrochloride in Compounding Under Section 503B of the FD&C Act,'' March 2021.
4. FDA Guidance for Industry, ''Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act,'' December 2016 (available at *https://www.fda.gov/media/97347/download*).

Dated: April 3, 2023.

Lauren K. Roth,

Associate Commissioner for Policy.

[FR Doc. 2023–07237 Filed 4–5–23; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institute of Dental and Craniofacial Research; Notice of Closed Meeting

Pursuant to section 10(d) of the Federal Advisory Committee Act, as amended, notice is hereby given of the following meeting.

The meeting will be closed to the public in accordance with the provisions set forth in sections 552b(c)(4) and 552b(c)(6), Title 5 U.S.C., as amended. The grant applications and the discussions could disclose confidential trade secrets or commercial property such as patentable material, and personal information concerning individuals associated with the grant applications, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

Name of Committee: National Institute of Dental and Craniofacial Research Special Emphasis Panel; Practice-Based Research in Dental Schools.

Date: May 11, 2023.

Time: 9:00 a.m. to 7:00 p.m.

Agenda: To review and evaluate grant applications.

Place: National Institute of Dental and Craniofacial Research, 6701 Democracy Boulevard, Bethesda, MD 20892 (Virtual Meeting).

Contact Person: Yun Mei, MD, Scientific Review Officer, Scientific Review Branch, National Institute of Dental and Craniofacial Research, National Institutes of Health, 6701 Democracy Boulevard, Bethesda, MD 20892, (301) 827–4639, *yun.mei@nih.gov.*

(Catalogue of Federal Domestic Assistance Program No. 93.121, Oral Diseases and Disorders Research, National Institutes of Health, HHS)

Dated: April 3, 2023.

Melanie J. Pantoja,

Program Analyst, Office of Federal Advisory Committee Policy.

[FR Doc. 2023–07217 Filed 4–5–23; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute; Notice of Closed Meetings

Pursuant to section 10(d) of the Federal Advisory Committee Act, as amended, notice is hereby given of the following meetings.

The meetings will be closed to the public in accordance with the provisions set forth in sections 552b(c)(4) and 552b(c)(6), Title 5 U.S.C., as amended. The grant applications and contract proposals and the discussions could disclose confidential trade secrets or commercial property such as patentable material, and personal information concerning individuals associated with the grant applications and contract proposals, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

Name of Committee: National Cancer Institute Special Emphasis Panel; FFRDC Review Meeting.

Date: May 4–5, 2023.

Time: 9:00 a.m. to 6:00 p.m.

Agenda: To review and evaluate contract proposals.

Place: National Cancer Institute Shady Grove, 9609 Medical Center Drive, Room 7W530, Rockville, Maryland 20850 (Telephone Conference Call).

Contact Person: Shamala K. Srinivas, Ph.D., Associate Director, Office of Referral, Review, and Program Coordination, Division of Extramural Activities, National Cancer Institute, NIH, 9609 Medical Center Drive, Room 7W530, Rockville, Maryland 20850, 240–276–6442, *ss537t@nih.gov.*

Name of Committee: National Cancer Institute Special Emphasis Panel; NCI SPORE (P50) Review SEP–I.

Date: May 18, 2023.

Time: 9:00 a.m. to 6:30 p.m.

Agenda: To review and evaluate grant applications.

Place: National Cancer Institute Shady Grove, 9609 Medical Center Drive, Room 7W244, Rockville, Maryland 20850 (Telephone Conference Call).

Contact Person: John Paul Cairns, Ph.D., Scientific Review Officer, Research Programs Review Branch, Division of Extramural Activities, National Cancer Institute, NIH, 9609 Medical Center Drive, Room 7W244, Rockville, Maryland 20850, 240–276–5415, *paul.cairns@nih.gov.*