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December 22, 2015

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Acting Commissioner
Food and Drug Administration
Department of Health and Human Services
WO 2200
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Silver Spring, MD 20993-0002

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health and Human Services
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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act; Draft Guidance (Docket No. FDA-2015-D-3517)

Dear Drs. Ostroff and Woodcock:

Public Citizen, a consumer advocacy organization with more than 400,000 members and supporters nationwide, submits these comments on the Food and Drug Administration's (FDA's) draft guidance document titled "Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act: Guidance for Industry" (the draft interim policy).[1]

[1] Food and Drug Administration. Interim policy on compounding using bulk drug substances under section 503A of the federal Food, Drug, and Cosmetic Act: Guidance for industry (draft guidance). October 2015. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm469120.pdf. Accessed December 18, 2015.

Overarching Comment

We object to the FDA's decision to rescind its prior stated position that "[u]ntil a bulk drug substances list is published in the Federal Register as a final rule, human drug products should be compounded using only bulk drug substances that are components of drugs approved under section 505 of the FD&C Act, or are the subject of USP [United States Pharmacopeia] or NF [National Formulary] monographs."[2]

This prior policy was based on the FDA's correct interpretation of the intent of Section 503A, which prohibits the compounding of human drug products using bulk drug substances that are not components of FDA-approved drugs or the subject of a USP or NF monograph,[3] except when the FDA has placed such substances on a list of bulk drug substances that may be used in compounding human drugs based on specific criteria developed by the agency (the 503A bulk list).

As stated in the draft interim policy, the FDA now intends to indefinitely disregard this key requirement of section 503A and allow pharmacies to compound drugs using bulk drug substances that are neither components of drugs approved under section 505 of the FDCA nor the subject of USP or NF monographs, provided that:

> (1) Those bulk drug substances were nominated with sufficient supporting information to permit the FDA to evaluate them for inclusion on the 503A bulk list, which is to be developed by the agency through notice-and-comment rulemaking; and
>
> (2) The bulk drug substances do not appear to present safety concerns.[4]

Drugs that meet both of these two criteria will be placed on a list created by the FDA under the draft interim policy (List 1), whereas those that lack sufficient supporting information to permit the FDA to evaluate them are placed on a separate list (List 3). Compounding of human drug products using bulk drug substances on List 1 may continue until the FDA completes sufficient evaluation of the drug substance to place the drug either on a list of bulk drug substances that raise safety concerns (List 2, which currently contains one drug, domperidone) or on a list of bulk drug substances identified by the FDA after notice-and-comment rulemaking as a substance that may not be used in compounding under section 503A (List 4, to be developed).[5,6] Bulk drug

[2] This position was previously stated in the agency's July 2014 guidance titled "Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act [FDCA]." *Ibid*. See page 3, lines 72-78.

[3] 21 U.S.C. 353a(b)(1)(A).

[4] Food and Drug Administration. Interim policy on compounding using bulk drug substances under section 503A of the federal Food, Drug, and Cosmetic Act: Guidance for industry (draft guidance). October 2015. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm469120.pdf. Accessed December 18, 2015. See page 3, lines 84-103.

[5] *Ibid*. See page 3, lines 84-103; and page 7, lines 221-227 and 235-238.

[6] Food and Drug Administration. Bulk drug substances nominated for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act.

substances that eventually are placed on the 503A bulk list legally may be used to compound human drug products under section 503A.

The FDA's justification for this policy change is "to avoid unnecessary disruption to patient treatment while the Agency considers the bulk drug substances that were nominated with sufficient support to permit FDA to evaluate them and promulgates the regulations required under section 503A."[7] But this justification is substantially outweighed by the public health threat posed by allowing widespread production of unapproved new drugs from these bulk drug substances for many years to come, given the following:

(1) For most of the bulk drug substances nominated for inclusion on the 503A bulk list, there is likely to be a lack of evidence that they are safe or effective for any indication. Of note, for 10 out of the 19 drugs reviewed by the Pharmacy Compounding Advisory Committee (PCAC) to date,[8,9,10] both FDA reviewers and a majority of the PCAC have agreed that the drug should not be included on the 503A bulk list because of concerns about safety or a lack of effectiveness for the uses proposed by the nominators (see "Additional Comments," item (1) below for details).

(2) The policy would allow a large number of human drug products to be compounded and used in patients for years, if not decades, without FDA review. There are currently 60 bulk drug substances appearing on List 1.[11] Moreover, the number of drugs on List 1 is likely to expand significantly as nominators resubmit new nominations for many of the several hundred bulk drug substance nominations that currently appear on List 3. Given the pace at which the agency is evaluating nominations to the 503A bulk list and

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http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467373.pdf. Accessed December 18, 2015. See page 2.

[7] Food and Drug Administration. Interim policy on compounding using bulk drug substances under section 503A of the federal Food, Drug, and Cosmetic Act: Guidance for industry (draft guidance). October 2015. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm469120.pdf. Accessed December 18, 2015. See page 3, lines 95-97.

[8] Food and Drug Administration. Pharmacy Compounding Advisory Committee (PCAC) meeting, February 23-24, 2015, questions. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM445387.pdf. Accessed December 17, 2015. See page 3.

[9] Food and Drug Administration. Pharmacy Compounding Advisory Committee (PCAC) meeting, June 17-18, 2015, questions. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM455272.pdf. Accessed December 17, 2015. See page 1.

[10] Food and Drug Administration. Pharmacy Compounding Advisory Committee (PCAC) meeting, October 27-28, 2015, questions. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM473830.pdf. Accessed December 17, 2015.

[11] Food and Drug Administration. Bulk drug substances nominated for use in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467374.pdf. Accessed December 17, 2015. See page 1.

obtaining advice from the PCAC — as noted, there have been only 19 such substances voted on by the PCAC to date[12,13,14] — it likely will take the agency several years, if not decades, to complete the evaluation and rulemaking process for the drugs currently nominated for the 503A bulk list.

(3) In light of the delays in the FDA's evaluation process, important safety concerns about many nominated bulk drug substances likely will not be identified for many years. In addition, the FDA's threshold for placing a drug on List 2 based on known safety concerns appears to be shockingly high, as numerous drugs have failed to appear on List 2 even after FDA reviewers identified significant safety concerns and both FDA reviewers and a majority of the PCAC have agreed the drugs should not be compounded (see "Additional Comments," item (1) below for details).

We therefore urge the FDA to announce that, within a specified time period (for example, six months), it will begin enforcing all requirements of 503A and not allow pharmacies to compound drugs from bulk drug substances that are not components of drugs approved under section 505 of the FDCA, the subject of USP or NF monographs, or drug substances appearing on the 503A bulk list. The specified time interval will allow health care providers sufficient time to transition patients using such unproven compounded drug products to another therapeutic option.

Additional Comments

In the event the FDA decides to proceed with this ill-conceived draft interim policy — with the provision allowing pharmacies to compound drugs under section 503A from bulk drug substances that are not components of drugs approved under section 505 of the FDCA, the subject of USP or NF monographs, or drug substances appearing on the 503A bulk list — we offer the following additional comments:

(1) We strongly urge the FDA to modify the proposed 503A List 2 to be titled "Bulk Drug Substances that Raise Concerns About Safety or Lack of Effectiveness" and to include on this list any bulk drug substance for which the FDA's evaluation resulted in a recommendation against the drug substance being included on the 503A bulk list because of concerns about safety or a lack of effectiveness for the uses proposed by the

[12] Food and Drug Administration. Pharmacy Compounding Advisory Committee (PCAC) meeting, February 23-24, 2015, questions. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM445387.pdf. Accessed December 17, 2015. See page 3.

[13] Food and Drug Administration. Pharmacy Compounding Advisory Committee (PCAC) meeting, June 17-18, 2015, questions. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM455272.pdf. Accessed December 17, 2015. See page 1.

[14] Food and Drug Administration. Pharmacy Compounding Advisory Committee (PCAC) meeting, October 27-28, 2015, questions. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM473830.pdf. Accessed December 17, 2015.

nominators and for which a majority of the PCAC members voted in favor of that recommendation.

Consistent with our comment, the following 10 bulk drug substances should be added to a revised List 2 that may not be compounded from bulk drug substances under section 503a:

(a) Silver protein mild: On February 4, 2015, FDA reviewers recommended that silver protein mild not be included on the 503A bulk list because the drug is not well characterized, it was not effective in clinical trials for its proposed use (primarily for prophylaxis of potential ocular infections, including preoperatively), and chronic use may result in permanent discoloration of the conjunctiva, cornea, or lens.[15] On February 23, 2015, PCAC members voted 12 to 0 against placing silver protein mild on the 503A bulk list.[16]

(b) Piracetam: On January 30, 2015, FDA reviewers recommended that piracetam not be included on the 503A bulk list because of the absence of a clear benefit associated with the drug for any proposed uses, the seriousness of the conditions for which piracetam is used, and the availability of safe and effective medications for many of these uses that have undergone greater scientific scrutiny.[17] On February 24, 2015, PCAC members voted 9 to 1 against placing piracetam on the 503A bulk list.[18]

(c) Oxitriptan: On May 18, FDA reviewers recommended that oxitriptan not be placed on the 503A bulk list because of safety concerns associated with the drug, including gastrointestinal adverse effects (anorexia, diarrhea, vomiting, and epigastric pain) and dizziness; the lack of evidence that the drug is effective for treating depression, a serious condition for which the potential consequences of

[15] Food and Drug Administration. Briefing document: Pharmacy Compounding Advisory Committee (PCAC) meeting. February 23-24, 2015. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM433804.pdf. Accessed December 17, 2015. See PDF pages 543-544 and 551.

[16] Food and Drug Administration. Transcript of the February 23, 2015, afternoon session of the Pharmacy Compounding Advisory Committee meeting. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM444500.pdf. Accessed December 17, 2015. See pages 125, lines 20-22 and page 126, lines 10-11.

[17] Food and Drug Administration. Briefing document: Pharmacy Compounding Advisory Committee (PCAC) meeting. February 23-24, 2015. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM433804.pdf. Accessed December 17, 2015. See PDF page 806.

[18] Food and Drug Administration. Transcript of the February 24, 2015, session of the Pharmacy Compounding Advisory Committee meeting. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM444501.pdf. Accessed December 17, 2015. See page 125, lines 20-22, and page 126, lines 10-11. See page 178, lines 4-15.

failure to treat adequately include death; and the availability of multiple alternative and proven FDA-approved therapies for depression.[19] On June 17, 2015, PCAC members voted 10 to 2 against placing oxitriptan on the 503A bulk list.[20]

(d) Methylsulfonylmethane (MSM): On September 25, 2015, FDA reviewers recommended that MSM not be placed on the 503A bulk list because there is limited evidence that the drug may be minimally effective for treating joint pain associated with osteoarthritis, the optimal dose of MSM is unknown, there is a possibility of serious interaction with anticoagulants and risk of bleeding, and there are FDA-approved alternatives available.[21] On October 27, 2015, the PCAC voted 10 to 1 against placing MSM on the 503A bulk list.[22]

(e) Curcumin: On September 30, 2015, FDA reviewers recommended that curcumin not be placed on the 503A bulk list because it is not well characterized physically or chemically, there is a lack of sufficient data about the drug's safety and effectiveness, and use of the drug may delay effective treatment for the serious conditions for which the drug was nominated.[23] On October 27, 2015, the PCAC voted 6 to 4, with 1 abstention, against placing curcumin on the 503A bulk list.

(f) Germanium sesquioxide: On September 28, 2015, FDA reviewers recommended that germanium sesquioxide not be placed on the 503A bulk list because the drug can contain impurities with significant toxicities, clinical evidence for using the drug in oncology is lacking, and use of the drug could delay the administration of FDA-approved products that have well-established safety and efficacy profiles for

[19] Food and Drug Administration. Briefing document: Pharmacy Compounding Advisory Committee (PCAC) meeting. June 17-18, 2015. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM449535.pdf. Accessed December 17, 2015. See PDF pages 311-312.

[20] Food and Drug Administration. Transcript of the June 17, 2015, afternoon session of the Pharmacy Compounding Advisory Committee meeting. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM458513.pdf. Accessed December 17, 2015. See page 181, lines 6-7, and page 182, lines 4-7.

[21] Food and Drug Administration. Briefing document: Pharmacy Compounding Advisory Committee (PCAC) meeting. October 27-28, 2015. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM466380.pdf. Accessed December 17, 2015. See PDF page 57.

[22] The transcript of the October 27 meeting has not been published. However, Public Citizen staff observed the meeting, and the vote tallies reported here and in subsequent paragraphs are based on data on file with the authors of this letter.

[23] Food and Drug Administration. Briefing document: Pharmacy Compounding Advisory Committee (PCAC) meeting. October 27-28, 2015. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM466380.pdf. See PDF page 108.

oncology indications.[24] On October 27, 2015, the PCAC voted 11 to 0 against placing germanium sesquioxide on the 503A bulk list.

(g) Rubidium chloride: On September 28, FDA reviewers recommended that rubidium chloride not be placed on the 503A bulk list because nonclinical studies demonstrated evidence that the drug has significant toxicity in animals, data are insufficient to attest to the safety or effectiveness of the drug in treating cancer, and use of the drug could delay the administration of FDA-approved products that have well-established safety and efficacy profiles in treating serious and life-threatening cancers.[25] On October 27, 2015, the PCAC voted 11 to 0 against placing rubidium chloride on the 503A bulk list.

(h) Deoxy-D-glucose: On September 29, 2015, FDA reviewers from the Office of Hematology and Oncology Products in the Center for Drug Evaluation and Research (CDER) recommended that deoxy-D-glucose not be placed on the 503A bulk list because there is insufficient data to attest to the safety or efficacy of the drug in treating cancer, controlled clinical trials showed that toxicity was reached before clinical efficacy, and there are available FDA-approved products for oncology indications that have been demonstrated to be safe and effective in well-controlled clinical trials.[26] On September 29, 2015, FDA reviewers from the Division of Antiviral Products in CDER also recommended that deoxy-D-glucose not be placed on the 503A bulk list because there are insufficient data to fully evaluate the safety or efficacy of the drug in the treatment of herpes simplex, and because multiple safe and effective FDA-approved agents (oral and topical) are available for the treatment of herpes infections, including one product sold over the counter.[27] On October 27, 2015, the PCAC voted 9 to 3 against placing deoxy-D-glucose on the 503A bulk list.

(i) Alanyl-L-glutamine: On October 1, 2015, FDA reviewers recommended that alanyl-L-glutamine not be placed on the 503A bulk list because there are concerns about the potential toxicities of possible impurities of this bulk drug substance, data suggesting that the drug may be effective has significant limitations, and some analyses of clinical trial data indicate unfavorable outcomes with glutamine supplementation.[28] On October 28, 2015, the PCAC voted 10 to 1 against placing alanyl-L-glutamine on the 503A bulk list.

(j) Glycyrrhizin: On September 30, 2015, FDA reviewers recommended that glycyrrhizin not be placed on the 503A bulk list because bulk drug substances containing the drug are complex mixtures that are not sufficiently well

[24] *Ibid*. See PDF page 153.
[25] *Ibid*. See PDF page 191.
[26] *Ibid*. See PDF pages 222-223.
[27] *Ibid*. See PDF page 232.
[28] *Ibid*. See PDF pages 281-282.

characterized to be suitable for compounding; the drug is not an antiviral compound and is not effective in treating hepatitis C, hepatitis B, or HIV infection; and the drug is associated with serious pseudo-hyperaldosteronism-related adverse reactions.[29] On October 28, 2015, the PCAC voted 11 to 0 against placing glycyrrhizin on the 503A bulk list.

As we have already stated, compounding human drug products using any of the bulk drug substances appearing on List 1 (as well as Lists 2 through 4) is already prohibited under Section 503A, meaning that the FDA is under no legal obligation to engage in any further process prior to prohibiting the compounding of such drugs under 503A. (In fact, as we argue above, proper enforcement of Section 503A would require that the FDA ban the compounding of human drug products using the bulk drug substances on Lists 1 through 4 within a specified time period). We can think of no conceivable public health rationale for allowing the compounding of these illegal drugs after both the FDA review team and a majority of the PCAC have recommended against such compounding.

Allowing pharmacies to continue compounding drugs under section 503A using any of the above bulk drug substances while FDA completes notice-and-comment rulemaking to exclude them from the 503A bulk list threatens patient health and represents unacceptably bad public health policy.

(2) We strongly support the FDA's proposal that bulk drug substances not nominated or nominated without sufficient supporting information to permit the FDA to evaluate them for inclusion on the 503A bulk list may not be used to compound drugs under section 503A.

Thank you for the opportunity to comment on this important public health matter.

Sincerely,

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[29] *Ibid*. See PDF pages 368-369.