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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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10903 New Hampshire Avenue
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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
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Re: Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act; Draft Guidance for Industry (Docket No. FDA-2015-D-3539)

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than 400,000 members and supporters nationwide, submits these comments on the Food and Drug Administration's (FDA's) draft guidance document titled "Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act: Guidance for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using bulk drug substances under section 503B of the federal Food, Drug, and Cosmetic Act: Guidance for industry (draft guidance). October 2015. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm469122.pdf. Accessed December 18, 2015.

Overarching Comment

We object to the FDA's proposal in the draft interim policy to indefinitely disregard a key requirement of section 503B, which prohibits registered outsourcing facilities from mass-producing unapproved drugs using bulk drug substances, unless:

(1) The drugs are currently on a list of drug shortages maintained by the FDA; or

(2) The bulk drug substances appear on a list of such substances for which there is a clinical need (the 503B bulk list), which will be developed by the FDA following notice and comment in the Federal Register.[2]

This limitation was an essential part of the framework of 503B, as without it there is little to prevent outsourcing facilities from effectively circumventing the FDA approval process and manufacturing unapproved new drugs on an unlimited scale. Drugs mass-produced by outsourcing facilities without FDA approval lack adequate testing to establish safety and effectiveness and have not undergone rigorous premarket review to verify compliance with good manufacturing practices.

Public Citizen has grave concerns that the standards and processes that will be established for including bulk drug substances in the 503B bulk list are not sufficiently rigorous, and the 503B statutory framework will therefore permit the widespread marketing of dangerous unapproved new drugs that are unsafe, ineffective, or both. We are particularly concerned because drugs produced by outsourcing facilities under 503B will likely compete with FDA-approved products, putting patients at unnecessary risk from untested and substandard products and undermining the market for FDA-approved drugs, which can lead to shortages of these drugs.

Yet the FDA appears poised to disregard even the minimal level of review required by 503B, as the proposed draft interim policy would allow outsourcing facilities to mass-produce drugs not found on the drug shortage list using bulk drug substances that have not yet even qualified for inclusion on the 503B bulk list. Under the proposed draft interim policy, outsourcing facilities may mass-produce drugs that were nominated with sufficient supporting information to permit the FDA to evaluate them for inclusion on the 503B bulk list, provided the agency has not yet identified the bulk drug substances as presenting safety concerns.[3]

Bulk drug substances that may be used in outsourcing under the draft interim policy will be placed on a list generated by the FDA (List 1), whereas those that lack sufficient supporting information to permit the FDA to evaluate them are placed on a separate list (List 3).

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[2] 21 U.S.C. § 353b(a)(2).

[3] Food and Drug Administration. Interim policy on compounding using bulk drug substances under section 503B of the federal Food, Drug, and Cosmetic Act: Guidance for industry (draft guidance). October 2015. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm469122.pdf. Accessed December 18, 2015. See page 5, lines 152-159 and lines 167-171; page 6, lines 226-232; and page 7, lines 248-260.

Outsourcing facilities may continue to produce drugs using any bulk drug substance on List 1 until the FDA completes its evaluation of the drug substance and places it either on a list of bulk drug substances that raise safety concerns (List 2, which currently contains no drugs) or on a list of bulk drug substances identified by the FDA as a substance that may not be used in compounding under section 503B, following notice in the *Federal Register* and public comment (List 4, to be developed).[4,5] Bulk drug substances that eventually are placed on the 503B bulk list legally may be used by outsourcing facilities to produce drugs under section 503B.

The FDA's justification for this policy change is "to avoid unnecessary disruption to patient treatment while FDA considers the bulk drug substances that were nominated with sufficient support to permit FDA to evaluate them and promulgates the list required under section 503B."[6] But this justification is substantially outweighed by the public health threat posed by allowing widespread production by outsourcing facilities of unapproved new drugs from these bulk drug substances for many years to come, particularly given the following:

(1) For most of the bulk drug substances nominated for inclusion on the 503B bulk list, there is likely to be a lack of evidence that they are safe or effective for any indication. Furthermore, some of the nominated bulk drug substances are active ingredients already available in one or more FDA-approved drugs. There can be no clinical need for outsourcing facilities to manufacture human drug products using such bulk drug substances when safe and effective FDA-approved alternatives are already widely available.[7]

(2) The FDA has proposed including nearly 190 bulk drug substances on List 1.[8] Moreover, the number of such nominations is likely to expand significantly as nominators resubmit new nominations for many of the several hundred bulk drug substances currently proposed for List 3. Since section 503B came into effect in November 2013, the FDA has not yet published a single notice in the Federal Register proposing bulk drug substances to be included in the list. If the pace with which the agency is evaluating nominations to the 503A bulk list is any indication, it is likely that the agency will take several years, if not decades, to complete the evaluation of all of the current nominations for the 503B

[4] *Ibid*. See page 6, lines 212-216, and page 7, lines 255-260.
[5] Food and Drug Administration. Bulk drug substances nominated for use in compounding under section 503B of the Federal Food, Drug, and Cosmetic Act. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467374.pdf. Accessed December 18, 2015. See pages 3 and 10.
[6] Food and Drug Administration. Interim policy on compounding using bulk drug substances under section 503B of the federal Food, Drug, and Cosmetic Act: Guidance for industry (draft guidance). October 2015. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm469122.pdf. Accessed December 18, 2015. See page 6, lines 226-228.
[7] The draft interim policy will affect the status of only widely available drugs, as drugs on the shortages list may be legally manufactured under 503B regardless of whether they have been nominated for the 503B bulk list.
[8] Food and Drug Administration. Bulk drug substances nominated for use in compounding under section 503B of the Federal Food, Drug, and Cosmetic Act. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467374.pdf. Accessed December 18, 2015. See pages 1-3.

bulk drug list and decide whether the nominated drugs go on this list after publication of notices in the Federal Register and public comment.

(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. We are also concerned that the FDA's threshold for placing a drug on List 2 may be unacceptably high, as no bulk drug substances have appeared on this list to date.

The current proposed draft interim policy will have tremendously damaging long-term implications for public health. This proposal is as ludicrous and harmful as if the FDA had declared that unapproved new drugs could henceforth be legally marketed starting at the point the agency agrees to file a New Drug Application. (In fact, this proposal is far worse, because the package of information included in even the highest-quality 503B bulk nomination is undoubtedly so much inferior in quality and scope to that provided in a New Drug Application that the two submissions are hardly comparable.)

We therefore urge the FDA to announce that, within a specified time period (for example, six months), it will begin enforcing all requirements of 503B and not allow outsourcing facilities to produce drugs from bulk drug substances unless those substances appear on either the 503B bulk list or the drug shortage list in effect under section 506E of the FD&C Act at the time of compounding, distribution, and dispensing. The specified time interval will allow healthcare 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 outsourcing facilities to compound drugs under section 503B from bulk drug substances that are not found on either the 503B bulk list or the drug shortage list, we offer the following additional comments:

(1) We strongly urge the FDA to modify the proposed 503B 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 503B bulk list because of concerns about safety or a lack of effectiveness for the uses proposed by the nominators. Allowing outsourcing facilities to continue producing drugs not found on the drug shortage list using bulk drug substances nominated for the 503B bulk list while FDA completes a lengthy review process that includes a Federal Register notice and public comment period (requirements to placement on List 4) threatens patient health and represents unacceptably bad public health policy.

(2) We urge the FDA to remove from List 1 any bulk drug substances that are already components of FDA-approved drugs. Inclusion of such bulk drug substances on List 1 places patients at unnecessary risk by encouraging the substitution of FDA-approved drugs with untested products mass-produced by outsourcing facilities. These substitutions

also will undermine the market for FDA-approved products, exacerbating drug shortages. One way to remove these drugs from List 1 would be to place these bulk drug substances on a new 503B List 5 that includes bulk drug substances for which there is no clinical need because the substances are already components of FDA-approved drugs.

(3) 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 503B bulk list may not be used to compound drugs under section 503B.

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

Sincerely,

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