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December 17, 2013

Margaret A. Hamburg, M.D.
Commissioner
Food and Drug Administration
Department of Health and Human Services
WO 2200
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: Message to hospitals and health care providers regarding pharmacy compounding

Dear Commissioner Hamburg:

Public Citizen, a research-based advocacy group representing more than 300,000 members and supporters nationwide, writes to express our concern over the Food and Drug Administration's (FDA's) recent public announcements encouraging hospitals and other health care providers to purchase medical products from outsourcing facilities. We are concerned that these messages give the false impression that drugs manufactured by outsourcing facilities will now be subject to the same federal oversight as FDA-approved drugs, which will in turn lead health care providers to purchase and prescribe the products as substitutes for FDA-approved products.

Whether produced by an outsourcing facility or a traditional compounder, compounded products are fundamentally riskier than FDA-approved products. They are not assessed by the agency for safety and efficacy prior to marketing, and their labels need not contain adequate directions for use. Following enactment of the Drug Quality and Security Act of 2013, drugs produced in an outsourcing facility are subject to current good manufacturing practice (cGMP) requirements, which is the same standard the FDA applies to FDA-approved manufactured drugs. However, outsourcers will not be subject to *pre-market* inspections or assessment for compliance with cGMP, and they will only have to undergo *post-market* inspections on a "risk-based" schedule as opposed to once every two years, which is the standard for FDA-approved drugs. This will make it more difficult for the FDA to ensure outsourcers' compliance with cGMP.

Because compounded products are fundamentally higher-risk than FDA-approved products, health care providers should only rely on compounded products after first carefully assessing whether an FDA-approved product is available to meet the clinical needs of their patients. Unfortunately, not all health care providers are aware that they should be making this assessment, believing that compounded products and FDA-approved products are similar in terms of safety, efficacy, and quality.

By prescribing compounded products when FDA-approved products are readily available, health care providers expose their patients to needless risk, which is particularly high when the drug products are intended to be sterile and injected. One horrifying example of the risk is the 2012 outbreak associated with compounded steroids produced by the New England Compounding Center (NECC). To date, 751 patients have become ill and 64 have died after receiving injections from three lots of contaminated steroids produced by NECC even though an FDA-approved version of the same steroid was available at the time of the outbreak.[1,2] Although more effective and aggressive enforcement action by the FDA could have prevented the NECC-linked disease outbreak, the scope of the outbreak would have been much more limited if health care providers had been properly educated to carefully assess FDA-approved alternatives before relying on a compounded product.

Recent messaging by the FDA is likely to contribute to further misinformation about the relative safety, efficacy, and quality of compounded products when compared to FDA-approved drugs. For example, in a blog post you authored on December 2, 2013, you made the following statement to health care providers:

> The [Drug Quality and Security Act] will enable [certain] compounders to register with the FDA to become "outsourcing facilities," making them subject to certain other requirements including Federal quality standards, known as current good manufacturing practice. These facilities will also be subject to inspection by FDA on a risk-based schedule. If compounders register with FDA as outsourcers, hospitals and other health care providers will be able to provide their patients with drugs that were compounded in facilities that are subject to FDA oversight and federal requirements for current good manufacturing practice, among others. **To that end, we will be encouraging healthcare providers and health networks to consider purchasing compounded products from facilities that are registered with FDA and subject to risk based inspections**.[3] [Emphasis added]

Perhaps it was your intention to encourage hospitals, clinics, and other health care providers to consider buying from registered "outsourcing facilities" rather than purchasing unapproved drugs from unregistered traditional compounders, including facilities that have engaged in illegal drug manufacturing under the guise of pharmacy compounding. It is true that outsourcing facilities will receive relatively greater federal oversight than traditional compounders. However, your statement fails to mention that although outsourcing facilities will be subject to *some* federal requirements, **they are not subject to new drug approval regulations** or other important federal provisions that have made FDA-approved products the gold standard for safety, efficacy,

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[1] Centers for Disease Control and Prevention. Multi-state meningitis outbreak – current case count. October 23, 2013. http://www.cdc.gov/hai/outbreaks/meningitis-map-large.html. Accessed December 13, 2013.

[2] Pfizer. Material safety data sheet: methylprednisolone acetate. September 6, 2012. http://www.pfizer.com/files/products/material_safety_data/PZ01044.pdf. Accessed December 13, 2013.

[3] Hamburg MA. New law enhances safety of compounded drugs and protection of the drug supply chain. December 2, 2013. http://blogs.fda.gov/fdavoice/index.php/2013/12/new-law-enhances-safety-of-compounded-drugs-and-protection-of-the-drug-supply-chain/?source=govdelivery&utm_medium=email&utm_source=govdelivery#sthash.T19NeOuU.dpuf. Accessed December 13, 2013.

and quality for more than half a century. As a result, your statement appears to be a broad endorsement of pharmaceutical products produced by outsourcing facilities, even in cases in which FDA-approved products are also available to treat patients.

The failure to discuss important details regarding the lower regulatory standards for drugs made by outsourcing facilities in comparison to FDA-approved drugs is extremely disturbing. Such messaging is likely to contribute to the dangerous impression among health care providers and patients that compounded products made by outsourcing facilities are equivalent in safety, efficacy, and quality to FDA-approved drugs. Some may even assume, incorrectly, that federal regulation over drugs made by outsourcers means that these products will be approved as safe and effective prior to marketing.

Making a similar statement, Jane Axelrad, Associate Director for Policy, Center for Drug Evaluation and Research, encouraged health care providers to purchase from outsourcing facilities during the Office of Health and Consumer Affairs stakeholder call of 10:00 a.m. EST on Tuesday, December 3, 2013.

We urge you to correct your blog post and other similar misleading statements you and other FDA officials have made since the enactment of the Drug Quality and Security Act of 2013. You should explain the difference between products produced by an outsourcing facility and FDA-approved drugs. You also should encourage health care providers to carefully consider whether there is a legitimate clinical need for a non-FDA-approved product that outweighs the risks associated with using such a product to treat patients.

We additionally urge the FDA to coordinate with the medical community on a broader campaign to educate physicians on the relative risks associated with treating patients with drugs obtained from traditional compounders or outsourcing facilities versus treating patients with FDA-approved products. The FDA should encourage physicians to become familiar with these risks, determine whether FDA-approved alternatives are available, and assess whether the compounded product offers a clear clinical benefit that outweighs its inherent risks prior to making a decision to purchase or prescribe the compounded drug. (For example, a compounded product may be appropriate if a patient is allergic to an ingredient in the FDA-approved product and the compounded product removes the problematic ingredient.) Such a campaign might include public safety announcements, communications to physicians and patients published on the FDA's website, blog posts, and articles in major medical journals written by agency officials familiar with the issue.

We know that the FDA is committed to preventing another public health disaster due to compounded drugs, and we hope that the FDA will step up enforcement under the Drug Quality and Security Act to enhance the safety and quality of compounded products. Nevertheless, as the agency engages in this effort, it also must take care to publicly recognize that FDA pre-market approval remains the gold standard for ensuring the safety, efficacy, and quality of pharmaceutical products. An unapproved compounded product should only be used when it offers a clear clinical benefit that outweighs the inherent risks of relying on an unapproved product. By carefully and repeatedly emphasizing this point moving forward, we hope that the

agency can guide health care providers to make appropriate decisions that will avoid exposing patients to unnecessary risk.

Sincerely,

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