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March 14, 2013

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
Department of Health and Human Services  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

Re: Docket No. FDA-2013-N-0124

The Food and Drug Administration (FDA) recently requested public comment from interested persons in drafting a strategic plan on drug shortages. Public Citizen, an organization representing more than 300,000 members and supporters nationwide, submits these comments in response, urging the FDA to cease its current practice of permitting companies representing themselves as compounding pharmacies to engage in what is clearly large-scale manufacturing of unapproved drugs to meet demand in times when FDA-approved products are in short supply. This policy of lax enforcement puts patients at risk in the short term by exposing them to unsafe, ineffective, mislabeled, and contaminated drugs. Moreover, in the long term, it exacerbates shortages by allowing compounded products to “hollow out” the market by cutting corners on quality and underselling FDA-approved products. The FDA’s current regulations also offer providers, prescribers, and consumers no means to identify low-quality compounded products and make informed purchases. These practices discourage manufacturers from establishing and maintaining high-quality manufacturing practices, making it more likely that shortages will become prolonged or permanent.

## **I. General Comments**

Shortages of drugs and biological products present an urgent public health problem, particularly when the product is necessary to prevent imminent risk of death or serious injury. Public Citizen encourages the FDA’s efforts to work with registered drug manufacturers to minimize shortages of FDA-approved products and ensure a steady supply of these products to consumers. These efforts should include working to bring facilities into compliance with good manufacturing practices (GMP) and increase production of FDA-approved products. Efforts should specifically include requesting manufacturers to ramp up production, offering assistance in addressing quality control problems, and expediting reviews of those new-drug applications (NDAs) or abbreviated-new-drug applications (ANDAs) that can address drug shortages. If no facility is capable of meeting

demand with FDA-approved products, the FDA should coordinate with comparable foreign drug-regulatory authorities to import foreign-approved drugs, meeting demand temporarily until an FDA-approved version can be supplied.

**Under no circumstances should the FDA rely on unregistered facilities, such as companies manufacturing drugs under the guise of pharmacy compounding, to supply the market with unapproved products in times of shortage.** The role of compounding pharmacies should be restricted to dispensing specialized products tailored to an individualized medical need for the compounded product. Such products should be dispensed in response to a valid, patient-specific prescription or order from a licensed practitioner documenting the specialized medical need. The FDA should not permit compounding pharmacies to fill the role of drug manufacturers in times of shortage by mass-producing standardized products.

FDA-registered drug manufacturers that produce FDA-approved products are required to comply with high quality and safety standards and undergo rigorous review during the FDA's NDA or ANDA approval process. To obtain approval, these firms must demonstrate that they have the facilities, procedures, and training in place to make safe, effective, correctly labeled, and contamination-free versions of the product. Compounding pharmacies and other firms making unapproved products have made no such showing and frequently operate in substandard facilities with poorly trained personnel and inadequate procedures in place to avoid contamination, product-mix-ups, mislabeling, and other risks.

Moreover, waiving requirements for companies representing themselves as compounding pharmacies and other nonregistered entities in times of shortage creates perverse incentives that could make safe, high-quality drugs scarcer in the long term. Often, shortages result when the FDA identifies safety or quality issues with an FDA-approved product. The FDA should not employ a double standard, stopping production of the FDA-approved version while turning a blind eye to compounding pharmacies that have not complied with the same safety or quality regulations imposed on the approved product.

Failure to enforce regulations uniformly creates such perverse incentives, discouraging mainstream drug manufacturers from investing in quality and undercutting the regulatory protections designed to ensure a safe drug supply to our nation's health care system. These perverse incentives are exacerbated by the fact that providers, prescribers, and consumers have no way of distinguishing between FDA-approved products that comply with federal quality standards and those produced under the guise of pharmacy compounding that do not comply.

The FDA must address these issues by stepping up enforcement against companies engaged in drug manufacturing under the guise of pharmacy compounding. These companies exacerbate shortages by flooding the market with mass-produced, unapproved products.

The FDA should not waive quality standards except in emergencies where all other options have been exhausted and the drug or biologic is necessary to prevent death or other serious injury. Moreover, the FDA should never waive the requirement that manufacturers register and obtain FDA approval for their products, as this ensures they have the facilities, procedures, and trained staff to make the drug or biologic correctly. The agency also should take clear steps to ensure that providers, prescribers, and consumers are explicitly notified under any circumstances in which specific quality standards are waived in response to a shortage.

## **II. The Risks of Substandard Manufacturing Under the Guise of Pharmacy Compounding in Times of Drug Shortages**

Currently, the FDA does not adequately enforce federal regulations against companies representing themselves as compounding pharmacies, even when they engage in drug manufacturing. As Public Citizen has reported previously,<sup>1</sup> the FDA has not been transparent about initiating and following through with appropriate enforcement actions against these companies for violations of the federal Food, Drug, and Cosmetics Act, even when the pharmacies engage in activities that clearly cross the line from compounding into standardized, mass-produced drug manufacturing. The recent well-reported outbreak of fungal meningitis and other serious infections caused by contaminated steroid injections manufactured by the New England Compounding Center (NECC) clearly demonstrates the grave public health risk these companies pose to the public. That ongoing outbreak has now led to 722 cases of illness as well as the deaths of at least 50 people, and the case count continues to rise.<sup>2</sup>

What may be less well-understood is the role that companies representing themselves as compounding pharmacies have been permitted to play in addressing drug shortages. A number of these companies have taken advantage of the FDA's lax regulatory environment by advertising themselves as suppliers when FDA-approved products are unavailable or in short supply. For example, the compounding pharmacy PharMEDium keeps an updated list on its website of the most recent drug shortages and encourages purchasers to contact PharMEDium customer service for additional information and assistance.<sup>3</sup>

When facing a shortage, it is nearly impossible for health care providers or other consumers to verify whether the product being advertised by a compounding pharmacy is of comparable safety, efficacy, quality, purity, and potency to the FDA-approved version of the product. On its

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<sup>1</sup> Public Citizen. Letter to the FDA Urging Re-Inspection of Compounding Pharmacies with Serious Safety Violations. November 29, 2012. <http://www.citizen.org/hrg2085>. Accessed March 11, 2013.

<sup>2</sup> Centers for Disease Control. Multistate fungal meningitis outbreak investigation. Last updated March 11, 2013. <http://www.cdc.gov/hai/outbreaks/meningitis.html>. Accessed March 11, 2013.

<sup>3</sup> PharMEDium. Drug shortage updates. March 4, 2013. [http://www.pharmedium.com/news/type/2/drug\\_shortage\\_updates/](http://www.pharmedium.com/news/type/2/drug_shortage_updates/). Accessed March 11, 2013.

website, PharMEDium describes itself as a compounding pharmacy, and the company does not currently hold any NDAs or ANDAs for FDA-approved products.<sup>4,5</sup> Yet PharMEDium also represents its services as equivalent to those offered by a more traditional manufacturer:

PharMEDium commits to quality by design, compliance with FDA guidelines, upholding the highest ethical standards in the industry, and ensuring the best clinical care and patient safety in the industry. PharMEDium is registered with the FDA and DEA, holds State Board of Pharmacy in-state and out-of-state licenses, adheres to applicable cGMP [current Good Manufacturing Practices] requirements and meets or exceeds USP Chapter <797> requirements.<sup>6</sup>

PharMEDium is registered as a “Drug Establishment” on FDA’s website, making it indistinguishable from other drug manufacturers that are required to register with FDA.<sup>7</sup>

Health care providers seeking drugs in times of shortage, or at other times, have no way to verify whether PharMEDium or similar companies actually comply with current Good Manufacturing Practices (GMP). It is typically not evident from the company’s promotional materials that the products sold by the firm are not FDA-approved, since compounding pharmacies are not required to label their products with a statement to that effect. Moreover, firms like PharMEDium may actively represent compliance with GMP and other regulations in spite of their failure to seek regulatory approval for their products.

While the FDA has repeatedly insisted, since the NECC-linked fungal meningitis outbreak, that it lacks authority to regulate compounding pharmacies,<sup>8</sup> the FDA does inspect many firms representing themselves as such — in some cases repeatedly. Through these inspections and other reports, the agency does learn of cases in which particular companies violate GMP or market products that are not FDA-approved. These inspections often tell a much darker story than the information the agency has previously made publicly available.

For example, through a Freedom of Information Act (FOIA) request, Public Citizen recently obtained copies of nine FDA 483 report forms filled out by FDA inspectors following inspections of PharMEDium facilities in multiple states conducted over the course of the past decade. The FDA inspected PharMEDium facilities in 2004, 2006, 2007, 2009, 2010, and three

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<sup>4</sup> PharMEDium. About. <http://www.pharmedium.com/about/index.html>. Accessed March 11, 2013.

<sup>5</sup> Statement by Rich Kruzynski, President, PharMEDium Services, LLC. Food and Drug Law Institute Dialogue: Pharmacy Compounding. February 12, 2013.

<sup>6</sup> PharMEDium. About. <http://www.pharmedium.com/about/index.html>. Accessed March 11, 2013.

<sup>7</sup> Drug establishments current registration site. <http://www.accessdata.fda.gov/scripts/cder/drls/getDRLS.cfm>. Accessed March 11, 2013.

<sup>8</sup> Public Citizen. Letter to HHS Secretary Regarding the FDA Commissioner’s Congressional Testimony on Compounded Drugs. <http://www.citizen.org/documents/2087.pdf>. Accessed March 14, 2012.

times in 2013. Only the 2013 inspection report forms are currently available online. During each inspection, FDA inspectors raised concerns that PharMEDium had failed to take steps to ensure the sterility of finished sterile drug products. FDA inspectors also noted a number of other quality issues over the course of these inspections, including failure to conduct adequate tests of active ingredients and finished products to ensure purity, strength, and quality, as well as failure to investigate and document problems and complaints when they occur.

These issues are ongoing. In the FDA's February 2013 inspection of PharMEDium's Texas facility, an inspector noted the following evidence of filth and other conditions that could contribute to microbial contamination of sterile injectable drugs:

- "I observed white and yellow residue (rough or crystalline in appearance) on the HEPA filters and filter manifolds installed on hood . . . I observed residue in areas up to approximately eight inches square on the filter and manifold surfaces facing the operator work area where sterile injectable drug products were being pooled and mixed. These laminar flow hoods are designed to move air through the HEPA filter, through the drug handling space, and out of the hood towards the operator who is handling the drug product and other materials. . . [T]here is no investigation or corrective action documented for these residues."<sup>9</sup>

In the FDA's inspection of PharMEDium's Missouri facility, conducted the same month, FDA investigators noted the following:

- "[T]here is no sterile filtration performed during the aseptic processing of sterile injectable drug products."
- "[W]e observed equipment and various items blocking or partially blocking the return airflow vents for the ISO 7 clean room which contains the firm's ISO 5 hoods. Items blocking these vents included trash cans, sharps containers, and metering pumps."
- "[W]e observed various holes, approximately ¼ inch in diameter, in the wall near laminar airflow hoods 6 and 3 where aseptic processing occurs. We also observed an off white colored residue on this same wall, where an air return flow vent for the firm's clean room HEPA air filtration system was located."

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<sup>9</sup> 483 Inspection Form, PharMEDium Services, LLC, 12620 W Airport Blvd Ste 130, Sugar Land, TX 77478-6200. Issued 2/27/2013.

<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORR/ORA/ORAElectronicReadingRoom/UCM342277.pdf>. Accessed March 11, 2013.

- “[W]e noted an employee dragging a full trash bag across the clean room floor with laminar flow hoods located on each side where aseptic processing activities [were] occurring.”<sup>10</sup>

At the firm's New Jersey facility, inspectors documented that PharMEDium had failed to thoroughly investigate complaints after a patient experienced side effects because PharMEDium does not retain samples of batches that have been sold to test when complaints are reported:

- “[T]he firm's complaint investigation #3712, initiated on 10/05/2012, recorded that two patients experienced fever, chills and flu-like symptoms, after being administered Propofol Injectable Emulsion [an injectable drug used for anesthesia] lot 12271033E. The firm's investigation, which was completed on 11/07/2012, was not thorough because the firm did not have retains available for visual examination and testing. The firm does not collect or store retains for any of their finished sterile drug product lots.”<sup>11</sup>

These reports of continuing violations are more disturbing because the FDA is aware that multiple patients experienced life-threatening harms after being exposed to tainted PharMEDium products. In 2005, PharMEDium products were linked to a multistate outbreak of bacterial infection that sickened at least 18 people in five states and lead to at least one death.<sup>12</sup> Officials at the Centers for Disease Control and Prevention (CDC) reported that a rare bacterial strain was found in bags of magnesium sulfate made by PharMEDium.<sup>13</sup> The CDC confirmed that the contamination had occurred at PharMEDium by identifying patients at another facility in a different state infected with the same rare strain of bacteria after receiving intravenous magnesium sulfate solutions made by PharMEDium.<sup>14</sup> In March 2005, the FDA inspected a PharMEDium facility in Houston, Texas, and found that drugs manufactured by the firm were adulterated because they were “prepared, packed, or held under insanitary conditions whereby

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<sup>10</sup> 483 Inspection Form, PharMEDium Services, LLC, 913 N Davis Ave Cleveland, MS 38732-2106. Issued 2/22/2013. <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAA/ElectronicReadingRoom/UCM341364.pdf>. Accessed March 11, 2013.

<sup>11</sup> 483 Inspection Form, PharMEDium Services, LLC, 43 Distribution Blvd, Edison, NJ 08817-6055. Issued 2/28/2013. <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAA/ElectronicReadingRoom/UCM342271.pdf>. Accessed March 11, 2013.

<sup>12</sup> FDA Warning Letter to PharMEDium. April 13, 2007. <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2007/ucm076357.htm>. Accessed March 11, 2013.

<sup>13</sup> CDC. *Serratia macescens* blood stream infections associated with contaminated magnesium sulfate solutions. CDCHAN-00224-05-03-18-ADV-N. March 2005. <https://www.premierinc.com/safety/public-health/downloads/cdc-advisory-serratia-03-18-05.pdf>. Accessed March 11, 2013.

<sup>14</sup> Kindy, K, Sun LH, Compounding pharmacies have been linked to deaths, illnesses and safety failures for years. *Washington Post*. February 7, 2013. [http://www.washingtonpost.com/national/health-science/compounding-pharmacies-have-been-linked-to-deaths-illnesses-for-years/2013/02/07/5ba90132-6b19-11e2-ada3-d86a4806d5ee\\_story\\_3.html](http://www.washingtonpost.com/national/health-science/compounding-pharmacies-have-been-linked-to-deaths-illnesses-for-years/2013/02/07/5ba90132-6b19-11e2-ada3-d86a4806d5ee_story_3.html). Accessed March 11, 2013.

they may be contaminated with filth, or whereby they may be rendered injurious to health.”<sup>15</sup> Yet the agency took no other enforcement action immediately following this inspection.

Then, in 2006, the FDA received an additional report of a patient injured after taking drugs made by PharMEDium — this time at the company's Cleveland, Mississippi, facility. A hospital patient nearly lost consciousness after being injected with morphine labeled as fentanyl/bupivacaine, a different pain medication. The hospital examined other PharMEDium products in its inventory and found that bags labeled as containing morphine actually contained fentanyl/bupivacaine. The FDA inspected the Cleveland facility after the report and found that PharMEDium did not test every lot of its finished products for identity, potency, and sterility, and it failed to adequately label its finished products to prevent mix-ups.<sup>16</sup>

The FDA's response to these findings? The agency issued a warning letter to PharMEDium on April 13, 2007, *nearly two years after the FDA's initial inspection revealed that the firm was selling an adulterated drug*.<sup>17</sup> Public Citizen is aware of no subsequent enforcement actions against PharMEDium and knows of no criminal or civil prosecution against the company or its employees.

The FDA's failure to respond with appropriately aggressive enforcement action may have contributed to the death of another patient in 2009. In August 2009, PharMEDium received a complaint that a patient had died while being administered hydromorphone manufactured by PharMEDium. FDA inspectors visited the firm's Memphis, Tennessee, facility later that month and reviewed the company's records of the batch, which revealed that:

[D]uring the final container processing the filling technician observed particulate matter (declared as a thick blue ball) in the solution of one of the filled 30 mL PCA vials. Per this batch record this one PCA vial was destroyed and the remaining 181/30 mL PCA vials were distributed by the firm. The firm performed no investigations regarding the particulate matter observed in this batch. Also, the firm performed no microbial/endotoxin testing on this finished drug product lot. No root cause was determined.<sup>18</sup>

As of today, the FDA has not published any other warning letters or initiated other public enforcement actions against PharMEDium.

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<sup>15</sup> FDA Warning Letter to PharMEDium. April 13, 2007.

<http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2007/ucm076357.htm>. Accessed March 11, 2013.

<sup>16</sup> 483 Inspection Form, PharMEDium Services, LLC, 913 N Davis Ave Cleveland, MS 38732-2106. Issued 1/27/2006.

<sup>17</sup> FDA Warning Letter to PharMEDium. April 13, 2007.

<http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2007/ucm076357.htm>. Accessed March 11, 2013.

<sup>18</sup> 483 Inspection Form, PharMEDium Services, LLC, 6100 Global Drive, Memphis, TN 38141-8385. Issued 9/30/2009.

There is no reason to believe that PharMEDium is the only drug manufacturer representing itself as a compounding pharmacy that continues to operate in spite of evidence of serious quality problems. The true scope of this practice remains unknown. Also unclear is the extent to which the FDA declines to enforce the law against PharMEDium and companies like it in order to address or prevent drug shortages.

What is clear is that the FDA can no longer continue to permit companies such as PharMEDium, which represent themselves as compounding pharmacies, to take advantage of drug shortages by flooding the market with unsafe, low-quality products. Instead, the FDA must vigorously enforce the law against so-called compounding pharmacies that engage in drug manufacturing, both in times of shortage and at other times. The FDA's oversight failures not only threaten patients during times of shortage, they encourage shortages of FDA-approved drugs to continue by allowing compounding pharmacies to compete with manufacturers of high-quality, FDA-approved products. Fewer of these mainstream manufacturers will invest in obtaining FDA approval and meeting safety and quality standards when they can be easily undersold in the marketplace by manufacturers that need not comply with the same requirements.

Moreover, there is almost no way for health care providers to verify the quality of unapproved products manufactured under the guise of pharmacy compounding. This problem is exacerbated by the fact that the FDA has made few inspection reports available publicly, generally only doing so after receiving a FOIA request.

The policy of maintaining the secrecy of 483 inspection reports not only makes it impossible for providers, prescribers and consumers to identify low-quality products; it also makes it harder for health care providers to identify the cause of injuries when they occur. For example, the *Washington Post* recently reported that Mary Washington Hospital in Fredericksburg, Maryland, had difficulty identifying the source of an infection that caused the death of two patients who had undergone open-heart surgery and seriously injured nine others in 2005.<sup>19</sup> After conducting several mock surgeries in an attempt to identify the source, the hospital suspected the cardioplegia solution used in the operation was responsible. It had purchased the solution from California-based Central Admixture Pharmacy Services, a company representing itself as a compounding pharmacy with a facility in Lanham, Maryland.

The hospital sought assistance from the FDA, which inspected the Lanham facility. Shockingly, FDA officials refused to inform the hospital of what inspectors had found at the facility. The hospital eventually filed a FOIA request and finally received the inspection report six months

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<sup>19</sup> Kindy, K, Sun LH, Compounding pharmacies have been linked to deaths, illnesses and safety failures for years. *Washington Post*. February 7, 2013. [http://www.washingtonpost.com/national/health-science/compounding-pharmacies-have-been-linked-to-deaths-illnesses-for-years/2013/02/07/5ba90132-6b19-11e2-ada3-d86a4806d5ee\\_story\\_3.html](http://www.washingtonpost.com/national/health-science/compounding-pharmacies-have-been-linked-to-deaths-illnesses-for-years/2013/02/07/5ba90132-6b19-11e2-ada3-d86a4806d5ee_story_3.html). Accessed March 11, 2013.



later. Half a year after the deaths had occurred, Mary Washington Hospital finally had an answer: The cardioplegia solution was tainted with the species of bacteria that matched those found at the hospital.<sup>20,21</sup> The FDA also had identified multiple safety violations at the Lanham facility that could have led to the contamination.<sup>22</sup>

These examples demonstrate the urgent need for the FDA to step up enforcement actions against drug manufacturers representing themselves as compounding pharmacies and promptly make records of violations publicly available. Only through consistent, transparent enforcement against unapproved products can the agency offer manufacturers the incentives and confidence to make the investments needed to prevent shortages of FDA-approved products.

### III. Response to Specific FDA Questions

In its request for comments, the FDA Drug Shortages Task Force has sought public input on a series of specific questions. Public Citizen has specific responses to questions 1a, 1c, 2, 3, and 4.

**FDA Question 1a:** *To assist in the evaluation of product manufacturing quality, FDA is exploring the broader use of manufacturing quality metrics. With that in mind, FDA would like input on the following issues: What metrics do manufacturers currently use to monitor production quality? To what extent do purchasers and prescribers use information about manufacturing quality when deciding how to purchase or utilize products? What kinds of manufacturing quality metrics might be valuable for purchasers and prescribers when determining which manufacturers to purchase from or which manufacturers' products to prescribe? What kinds of manufacturing quality metrics might be valuable for manufacturers when choosing a contract manufacturer? How frequently would such metrics need to be updated to be meaningful?*

**Public Citizen's Response to Question 1a:** Currently, purchasers and prescribers have limited options available to assess manufacturing quality, and this severely restricts the extent to which quality concerns can influence purchasing decisions. Public Citizen supports efforts, clearly available within existing regulatory authority, to develop quality metrics to assist purchasers and prescribers in making treatment decisions.

**However, these quality metrics should not supplant government enforcement against firms that violate regulations designed to ensure that all drugs are safe and of high quality.** The FDA should not allow compounding pharmacies and other companies to mass produce unapproved products and violate new drug approval and GMP requirements. Any metrics

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<sup>20</sup> *Ibid.*

<sup>21</sup> FDA Warning Letter to Central Admixture Pharmacy Services (CAPS). March 15, 2006.

<http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2005/ucm075828.htm>. Accessed March 11, 2013.

<sup>22</sup> *Ibid.*

developed to assess quality should express quality gradations *among products that meet basic federal standards for drug approval and manufacturing*. Products that do not meet these standards should not be merely assessed through “metrics,” they should be removed from the market.

In addition, all 483 FDA inspection reports should be made available online as soon as possible following an inspection. To date, Public Citizen is aware of no centralized location where a consumer or health care provider can view all inspection reports and enforcement actions taken against a particular drug manufacturing facility, regardless of whether that facility is registered with the FDA or is operating as an unregistered pharmacy compounder. Currently, the FDA publishes the date and time of FDA inspections in an online database, but it does not publish any information on the nature of the violations identified, if any are found.<sup>23</sup> Also, the database is not kept comprehensive and up-to-date.

Public Citizen performed a search of the FDA's inspections database on March 11, 2013, using the search term “PharMEDium,” resulting in only four inspection records. Yet Public Citizen is aware of at least eight FDA inspection reports for this company between 2004 and 2013. Moreover, the FDA did not post the actual 483 inspection report forms documenting observations made during the inspection or provide a summary of any violations. To the best of our knowledge, only the PharMEDium inspection reports from 2013 have been posted on the FDA's website.<sup>24</sup> The remaining inspection reports, not available on the FDA website, were obtained by Public Citizen through a FOIA request.

All 483 forms and final inspection reports should, when completed, promptly be made publicly available to allow providers and prescribers to assess whether a facility actually complies with GMP. The FDA should host a searchable database on its website that would permit a health care provider to plug in the name of the facility and immediately view inspection reports from that facility. Such inspection reports are currently made available in other areas of regulation, including regulation of nursing homes, where they are useful in guiding treatment decisions.<sup>25</sup>

Such reports are essential not only to guide purchasing decisions but also to assist providers in identifying the source of potential contamination when injury occurs. Health care providers should not have to submit a FOIA request to discover which tainted products are killing their patients.

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<sup>23</sup> <http://www.accessdata.fda.gov/scripts/inspsearch/>. Accessed March 11, 2013.

<sup>24</sup> Food and Drug Administration. 2013 Pharmacy Inspections. <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAElectronicReadingRoom/ucm340853.htm> Accessed March 11, 2013.

<sup>25</sup> ProPublica has provided a consumer-friendly database that allows patients and their families to search for nursing homes in their area and view actual copies of inspection reports. <http://projects.propublica.org/nursing-homes/>. Accessed March 11, 2013.

**FDA Question 1c:** *Are there incentives that FDA can provide to encourage manufacturers to establish and maintain high-quality manufacturing practices, to develop redundancy in manufacturing operations, to expand capacity, and/or to create other conditions to prevent or mitigate shortages?*

**Public Citizen's Response to Question 1c:** As Public Citizen has stated repeatedly, the FDA should encourage manufacturers to establish and maintain high-quality manufacturing practices by vigorously enforcing the law against competitors who fail to meet existing federal standards. Firms that mass produce standardized drugs without complying with federal requirements are able to undercut companies that invest heavily in meeting these important federal standards. This creates a strong disincentive for manufacturers to seek drug approval or expand existing capacity, increasing the risk of shortages.

**FDA Question 2:** *In our work to prevent shortages of drugs and biological products, FDA regularly engages with other U.S. Government Agencies. Are there incentives these Agencies can provide, separately or in partnership with FDA, to prevent shortages?*

**Public Citizen's Response to Question 2:** As Public Citizen has stated previously, the Centers for Medicare and Medicaid Services (CMS) has established irresponsible reimbursement policies that encourage health care providers to shift to lower-cost compounded products.<sup>26</sup> CMS reimburses for compounded products at the same rate as it reimburses for higher-cost FDA-approved products, allowing health care providers to profit from the price difference.<sup>27</sup> This practice reduces demand for FDA-approved products, encouraging or exacerbating shortages.

CMS has the authority to deny Medicare coverage for compounded drugs that are not FDA-approved, as these drugs are manufactured in violation of the Food, Drug, and Cosmetics Act.<sup>28</sup> CMS has periodically denied coverage in the past for specific categories of compounded products. For example, in 2007, CMS regional carriers across the country issued identical determinations denying Medicare coverage for compounded inhalation drugs administered with nebulizer devices.<sup>29</sup> In doing so, the carriers noted that these compounded inhalational drugs were not tested for safety and effectiveness and therefore had the potential of putting patients at increased risk of injury, illness, or death.<sup>30</sup>

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<sup>26</sup> Public Citizen. Letter to the Secretary of Health and Human Services Calling for Expanded Investigation Into Deadly Meningitis Outbreak. <http://www.citizen.org/documents/2084.pdf>. Accessed March 12, 2013.

<sup>27</sup> *Ibid.*

<sup>28</sup> *Ibid.*

<sup>29</sup> *Ibid.*

<sup>30</sup> *Ibid.*

CMS should extend this rationale, using its authority in a consistent manner and uniformly denying coverage for compounded drugs manufactured unsafely without FDA approval or oversight. This will help prevent shortages of FDA-approved drugs by ensuring a larger market for FDA-approved products.

**FDA Question 3:** *When notified of a potential or actual drug or biological product shortage, FDA may take certain actions to mitigate the impact of the shortage, including expediting review of regulatory submissions, expediting inspections, exercising enforcement discretion, identifying alternative manufacturing sources, extending expiration dates based on stability data, and working with the manufacturer to resolve the underlying cause of the shortage. Are there changes to these existing tools that FDA can make to improve their utility in managing shortages? Are there other actions that FDA can take under its existing authority to address impending shortages?*

**Public Citizen Response to Question 3:** The actions listed by the FDA are all appropriate responses to mitigate the impact of a shortage. However, the FDA should make only limited use of its enforcement discretion to waive regulatory requirements in times of shortage. This is because regulatory requirements, including GMP and new drug approval or biologics licensing, are necessary to ensure that drugs sold in the United States are safe, effective, correctly labeled, and contamination free. These requirements should only be waived through the exercise of enforcement discretion, in which the drug or biological product in short supply is necessary to prevent loss of life or other serious injury, and in which all other options have been explored. Prior to waiving this requirement, the FDA should consider importing drugs or biological products that are compliant with comparable foreign regulatory requirements, including products approved by the European and Canadian regulatory authorities. While these drugs are not approved by the FDA, they are compliant with equivalent or similar foreign regulatory standards and therefore present a lower risk to consumers than unapproved products manufactured in the United States.

Moreover, under no circumstances should the FDA rely on unregistered facilities, such as companies representing themselves as compounding pharmacies, to supply the market with standardized, mass-produced, unapproved products. Instead, the FDA should exercise its enforcement discretion to allow companies that have already received FDA approval of a product to manufacture that product. To obtain approval, a company must demonstrate that appropriate facilities, procedures, and training are in place to make safe, effective, correctly labeled, and contamination-free versions of the product. Compounding pharmacies and other firms making unapproved products need make no such showing and frequently operate in substandard facilities with poorly trained personnel and inadequate procedures in place to avoid contamination, product-mix-ups, mislabeling, and other risks.

**FDA Question 4.** *To manage communications to help alleviate potential or actual shortages, FDA uses a variety of tools, including posting information on our public shortages Web sites and sending targeted notifications to specialty groups. Are there other communication tools that FDA should use or additional information the Agency should share to help health care professionals, manufacturers, distributors, patients, and others manage shortages more effectively? Are there changes to our public shortage Web sites that would help enhance their utility for patients, prescribers, and others in managing shortages?*

**Public Citizen Response to Question 4:** Providers, prescribers, and consumers should be informed of the actions the FDA takes to address a shortage. In particular, the FDA must communicate in instances in which GMP or other regulatory requirements are lifted through the exercise of enforcement discretion. Exercise of enforcement discretion in such circumstances should be predicated on the requirement that manufacturers provide notice to purchasers that federal standards have been waived, offer a summary of the regulations being waived and the reason for the waiver, and offer an approximate timeline for bringing the product into compliance with FDA regulations. This notice also should be posted on the FDA's public shortage website.

Such notice is necessary to allow providers, prescribers, and consumers to make informed treatment decisions. Even if the drug or biologic is deemed essential to prevent death or other serious injury, some patients may be better positioned than others to delay treatment until quality issues are resolved. These patients cannot make informed health care decisions unless they are informed of actions taken during a shortage that could affect the quality of the treatment they receive.

#### **IV. Conclusion**

Public Citizen supports the FDA's efforts to identify, prevent, and solve shortages of FDA-approved drug products. However, in its effort to address shortages, the agency should not allow any company to cut corners to put patients at risk from tainted products or allow unapproved drugs to flood the market and prevent the reintroduction of approved versions. To protect consumers, the FDA must ensure that its policy on drug shortages includes the following elements:

- The FDA must step up enforcement against companies representing themselves as compounding pharmacies to prevent these firms from filling shortages by flooding the market with unsafe, ineffective, and low-quality products and competing with FDA-approved versions.
- Under no circumstances should the FDA rely on un-registered facilities, such as compounding pharmacies, to supply the market with unapproved products in times of shortage.

- The FDA should work with manufacturers of FDA approved products to increase production or bring facilities into compliance with GMP, or expedite review and approval of new products. If no FDA-approved version of a product is available, the FDA should work with comparable foreign agencies to import products approved in other countries under standards similar to FDA's.
- The Centers for Medicare and Medicaid Services should not allow federal programs to reimburse for unapproved drugs, as this practice creates a disincentive for healthcare providers to purchase FDA-approved products, thereby increasing the risk of shortages for approved products.
- The FDA should not waive GMP requirements through the exercise of enforcement discretion unless all other options have been exhausted, and the product is necessary to prevent death or other serious injury.
- The FDA should ensure that purchasers are informed of regulatory actions taken during a shortage, especially any decisions to waive GMP requirements. This can be done by requiring companies to inform the end-purchaser of any requirements that have been temporarily waived, as a pre-requisite to any exercise of enforcement discretion.
- To allow hospitals, doctors, and patients to assess production quality when purchasing drugs and biological products, all 483 forms and final inspection reports conducted by the FDA should, when completed, promptly be made publicly available in an online database, searchable by company name.

Over the past two decades, the FDA has failed in its role as a public-health agency by allowing companies representing themselves as compounding pharmacies to encroach further and further into the realm of drug manufacturing. These firms have been allowed to grow in size to the point where they can drive mainstream manufacturers out of business, at least for certain products. Yet too many of the products they sell are so far removed in quality from FDA-approved products that few consumers would knowingly chose to be treated with them, were the true differences rendered transparent. The FDA must put an end to this untenable situation and ensure a future in

which providers, prescribers, and — most of all — patients can trust that the mass-produced drugs sold in this country are safe, effective, correctly labeled, and contamination-free.

Sincerely,

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