PUBLICCITIZEN
1600 20th Street, NW • Washington, D.C. 20009 • 202/588-1000 • www.citizen.org

March 4, 2014

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

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health and Human Services
WO51/Room 6133
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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

Re: Drug Products That Present Demonstrable Difficulties for Compounding Under Sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act; Request for Nominations; Docket Number FDA-2013-N-1523

Dear Commissioner Hamburg and Dr. Woodcock:

Public Citizen, a consumer advocacy organization with more than 300,000 members and supporters nationwide, submits these comments in response to the Food and Drug Administration (FDA) request for nominations for Drug Products That Present Demonstrable Difficulties for Compounding Under Sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act (FDCA; Docket Number FDA-2013-N-1523).

We wish to express our concern that the FDA intends to develop and publish a single list of drug products and categories of drug products that cannot be compounded because they present demonstrable difficulties for compounding. Sections 503A and 503B of the FDCA, which create exemptions from new drug approval and other requirements for compounding pharmacies and outsourcing facilities, respectively, each separately authorize the FDA to publish a distinct list identifying drug products that present demonstrable difficulties for compounding and therefore

cannot be produced under the exemptions. We believe two separate lists are necessary, because drugs compounded at compounding pharmacies under a Section 503A exemption will be subject to reduced regulatory standards and fewer enforcement mechanisms relative to drugs compounded at outsourcing facilities under a Section 503B exemption. (Although it is important to note that drugs qualifying for either type of exemption will be subject to reduced requirements relative to drugs that undergo new drug approval, and therefore in general pose greater risk to patients than FDA-approved drugs).

We urge the FDA to classify products involving nonsterile-to-sterile compounding as a category of products presenting demonstrable difficulties for compounding under 503A, but not under 503B. Production of drugs using this inherently high-risk process should be carried out only by a facility that is regularly inspected to verify compliance with current federal Good Manufacturing Practices (cGMP) requirements. Compounding pharmacies regulated under 503A are not required to follow cGMP, will rarely—if ever—be inspected by the FDA, and may or may not be regularly inspected by state officials, depending on the pharmacy regulations in each state, and any such state inspections are likely to be far less rigorous than those conducted by the FDA. By contrast, 503B outsourcing facilities, while not required to obtain new drug approval for their drug products, are nevertheless required to comply with cGMP and will be inspected by FDA officials on a risk-based schedule.

Alternatively, if the FDA chooses to proceed with its proposed plan of establishing only one list, we urge the agency to identify compliance with cGMP and the requirements of 503B as conditions necessary to prevent certain drugs or categories of drugs from presenting demonstrable difficulties for compounding, and to require such conditions for high-risk nonsterile-to-sterile compounding. Outsourcing facilities that register under Section 503B and comply fully with the FDCA will be permitted to compound such products, whereas compounding pharmacies regulated under 503A would not be allowed to compound such products.

We also recommend designation of several additional product categories as presenting demonstrable difficulties for compounding, and which therefore cannot be produced under 503B and/or 503A exemptions. A full list of product categories we urge the FDA to identify as demonstrably difficult to compound, along with our recommendations for their appropriate regulatory classification, is summarized as follows:

1. Nonsterile-to-sterile compounding (non-exempt under 503A only)
2. Metered dose inhaler (MDI) products (non-exempt under 503A and 503B)
3. Dry powder inhaler (DPI) products (non-exempt under 503A and 503B)
4. Transdermal Delivery Systems (TDSs) (non-exempt under 503A and 503B)
5. Sustained or time-release dosage forms (non-exempt under 503A and 503B)
6. Enteric-coated preparations (non-exempt under 503A and 503B)

I. Regulatory Background and Relevant Statutory Authority

Section 503A of the FDCA, created under the Food and Drug Administration Modernization Act of 1997 (FDAMA),[1] describes the conditions under which a human drug product, compounded for an identified individual based on a prescription, is entitled to an exemption from the federal requirements for new drug approval, compliance with cGMP, and specific federal labeling requirements.[2] Rather than follow cGMP requirements, pharmacies qualifying for a 503A exemption must produce drug products under conditions that comply with the United States Pharmacopoeia (USP) chapter on pharmacy compounding, including USP Chapter 797, addressing sterile compounding. [3,4]

Pharmacies may qualify for a Section 503A exemption only when producing a drug product "not . . . identified by the Secretary by regulation as a drug product that presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product."[5] Section 503A requires that the FDA consult an advisory committee on pharmacy compounding prior to identifying such products, absent urgent public health need.[6]

Following passage of FDAMA, the FDA initiated an administrative process aimed at creating a list of drugs presenting demonstrable difficulties for compounding. In 2000, the FDA requested comments on a concept paper describing the agency's preliminary thoughts on the matter (FDA Concept Paper).[7] However, these preliminary efforts were suspended following a 2002 Supreme Court decision holding portions of Section 503A unconstitutional.[8]

Regulation under Section 503A has been revived by the Drug Quality and Security Act of 2013, which verified the constitutionality of the portions Section 503A that had not been addressed in the Supreme Court's 2002 decision, including the relevant sections addressing the difficult-to-compound list, by removing the provisions deemed unconstitutional by the Court.[9] The 2013 Act also added Section 503B to the FDCA, creating a new category of drug producers, known as

---

[1] Pub. Law No. 105-115.
[2] FDCA Section 503A, *codified as* 21 U.S.C. § 353a.
[3] 21 U.S.C. § 353a (b)(1)(A)(i).
[4] Food and Drug Administration Draft Guidance: Pharmacy compounding of human drug products under Section 503A of the Federal Food, Drug and Cosmetics Act. December 2013. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM377052.pdf. Accessed February 18, 2014.
[5] 21 U.S.C. § 353a (b)(3)(A).
[6] 21 U.S.C. § 353a (c)(1).
[7] FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness. http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDAMA/ucm100205.htm. Accessed February 18, 2014.
[8] 78 Fed. Reg. 72,840, 72,840 (Dec 4, 2013).
[9] *Ibid.*

"outsourcing facilities."[10] Like compounding pharmacies regulated under 503A, outsourcing facilities that qualify for Section 503B are exempt from new drug approval and specific federal labeling requirements, and are therefore subject to lighter federal regulation than manufacturers of FDA-approved drugs. However, unlike Section 503A compounding pharmacies, Section 503B outsourcing facilities will be required to comply with cGMP. Outsourcing facilities must also comply with additional requirements, including federal registration and periodic reporting requirements, as well as federal inspections of facilities and records, conducted on a risk-based schedule.

Like Section 503A, Section 503B excludes drugs that present demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug or category of drugs.[11] However, rather than cross-reference the same list of products identified under Section 503A, Section 503B outlines distinct procedural steps for the FDA to follow in identifying drugs that are difficult to compound, including a specific timeline and process for creating a list of such products.[12] Section 503B also requires the FDA to "tak[e] into account the risks and benefits to patients" when identifying products for the list and authorizes the agency to identify "conditions that are necessary to prevent the drug or category of drugs from presenting demonstrable difficulties [for compounding]."[13]

Neither Section 503A nor Section 503B require that the FDA develop and publish a single list of drug products that present demonstrable difficulties for compounding. If anything, Congress, having identified two distinct processes and two slightly different sets of requirements and authorities for each section, appears to have contemplated that the FDA would create two separate lists. Moreover, even if two separate lists are not statutorily required, the FDA can certainly exercise its discretion to promulgate two separate lists. Separate lists would represent sound public health policy because the conditions for compounding in each type of facility are markedly different, with 503A compounding pharmacies subject to significantly lower regulatory standards than 503B outsourcing facilities.

Alternatively, if the FDA proceeds with its proposed plan to promulgate only one list, the agency has the authority to identify compliance with 503B and cGMP requirements as conditions necessary to prevent certain drugs or categories of drugs from presenting demonstrable difficulties for compounding. Outsourcing facilities that register under Section 503B and comply fully with cGMP would then be permitted to compound such products, whereas compounding pharmacies that qualify for exemption under 503A that have not verified compliance with cGMP would not be allowed to compound such products.

[10] Section 503B, *not yet codified.* Pub. Law 113-54.
[11] Pub. Law 113-54. Sec. 503B (a)(6).
[12] Pub. Law 113-54. Sec. 503B (c)(2).
[13] Pub. Law 113-54. Sec. 503B (a)(6).

II. Specific Drug Product Categories

We propose six categories of drug products for placement on the list or lists of products presenting demonstrable difficulties for compounding under Sections 503B and/or 503A.

1. Nonsterile-to-sterile compounding

Certain drugs must be sterile (in other words, free from all living microorganisms) in order to be administered safely. These include dosage forms administered parenterally (injections, infusions, or implants), aqueous-based inhalation solutions, and ophthalmic products.[14] As stated in the 2000 FDA Concept Paper, "[s]terility is absolute and should never be considered in a relative manner -- a product cannot be partially or almost sterile."[15]

Problems that develop in compounding sterile products can have serious and far-reaching consequences for patient safety. In September 2012, the Centers for Disease Control and Prevention (CDC) and the FDA announced the beginning of what would become the largest outbreak of infection linked to a medical product in more than four decades: healthcare facilities in 23 states received three lots of contaminated preservative-free injectable methlyprednisolone acetate produced by the New England Compounding Center (NECC), a compounding pharmacy in Framingham, Massachusetts.[16] Over the next year, the CDC tracked 751 cases of infection, including meningitis, paraspinal/spinal infection, stroke, and joint infection. Sixty-four of those cases resulted in death.[17]

While the NECC-linked outbreak was by far the largest ever associated with a compounding pharmacy, it was by no means an isolated event. Table 1 contains a list of infection outbreaks linked to compounding pharmacies since 2004. Many more small-scale outbreaks or isolated infections caused by compounded products likely went undetected because the source of such infections is often not suspected or challenging to identify.

Table 1: Infection Outbreaks Associated with Compounded Products, 2004-2013

Date of Outbreak	Type of Injury	Pharmacy	Source

[14] Food and Drug Administration. FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness. http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDAMA/ucm100205.htm. Accessed February 18, 2014.
[15] *Ibid.*
[16] Centers for Disease Control. Multistate outbreak of fungal meningitis and other infections – healthcare facilities. October 23, 2013. http://www.cdc.gov/hai/outbreaks/meningitis-facilities-map.html. Accessed February 21, 2014.
[17] Centers for Disease Control. Multistate outbreak of fungal meningitis and other infections – case count. October 23, 2013. http://www.cdc.gov/hai/outbreaks/meningitis-map-large.html#casecount_table. Accessed February 21, 2014.

Dec 2004 – Feb 2005	Bloodstream infections; 36 cases, including at least 13 children	Anonymous	CDC2005[18]
Jun – Jul 2004	Bloodstream infections; 2 children	Anonymous	Held2006[19]
Jan – Mar 2005	11 cases of bacteremia, including 5 cases of sepsis	PharMEDium	CDC2005[20]
Mar 2005	6 cases of sepsis; 1 resulting in death	PharMEDium	FDA2007(1)[21]
Dec 2004 – Aug 2005	Eye infection resulting in permanent loss of vision; 6 cases	Anonymous	Sunenshine2009[22]
Dec 2006	70 complaints indicating signs of infection	Med-South Pharmacy	FDA2007(2)[23]
Oct – Nov 2007	7 bloodstream infections	Anonymous	Maragakis2009[24]
Mar 2011	19 bloodstream infections	Meds IV	FDA2011[25]
Jul 2011	12 eye infections; 11 resulting in vision loss	Infupharma	Goldberg2013[26]
Aug 2011 – Mar 2012	47 eye infections; 39 resulting in vision loss	Franck's Compounding Lab	Mikosz2014[27]

[18] Centers for Disease Control. Pseudomonas bloodstream infections associated with a heparin/saline flush --- missouri, new york, texas, and michigan, 2004—2005. MMWR 2005;54(11):269-272. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5411a1.htm. Accessed February 26, 2014.

[19] Held MR, BegierEM, Beardsley DS, et al. Life-threatening sepsis caused by *Burkholderia cepacia* from contaminated intravenous flush solutions prepared by a compounding pharmacy in another state. Pediatrics 2006;118(1):e212-5.

[20] Centers for Disease Control. Health Advisory: Serratia marcescens blood stream infections associated with contaminated magnesium sulfate solutions. March 18, 2005. http://www.randolphcountyhealth.org/docs/educ/pr/031805_CDC.html. Accessed February 21, 2014.

[21] Food and Drug Administration. Warning Letter to PharMEDium. April 13, 2007. http://www.fda.gov/iceci/enforcementactions/warningletters/2007/ucm076357.htm. Accessed February 21, 2014.

[22] Sunenshine R, Schultz M, Lawrence MG, et al. An outbreak of postoperative gram-negative bacterial endophthalmitis associated with contaminated trypan blue ophthalmic solution. *Clin Infect Dis* 2009;48:1580-3.

[23] Food and Drug Administration. Warning Letter to Med-South Pharmacy. September 28, 2007. http://www.fda.gov/iceci/enforcementactions/warningletters/2007/ucm076516.htm. Accessed February 21, 2014.

[24] Maragakis LL, Chaiwarith R, Srinivasan A, et al. *Sphingomonas paucimobilis* bloodstream infections associated with contaminated intravenous fentanyl. *Emerg Infect Dis* 2009;15(1):12-18.

[25] Food and Drug Administration. CDC and ADPH investigate outbreak at Alabama hospitals; products recalled. March 29, 2011 (republished from Alabama Department of Public Health). http://www.fda.gov/safety/recalls/archiverecalls/2011/ucm249068.htm. Accessed February 21, 2014.

[26] Goldberg RA, Flynn HW, Miller D, et al. *Streptococcus* endophthalmitis outbreak after intravitreal injection of Bevacizumab: One-year outcomes and investigative results. *Opthalmology* 2013; 120(7):1448-53.

[27] Mikosz CA, Smith RM, Kim M, et al. Fungal endophthalmitis associated with compounded products. *Emerg Infect Dis* 2014;20(2):248-256.

Mar 2013	5 eye infections	Clinical Specialties	FDA2013(1)[28]
May 2013	7 skin abscesses	Main Street Family Pharmacy	FDA2013(2)[29]

In addition to being free of microorganisms, injectable compounded pharmaceuticals must also be free from pyrogens (the byproducts of microorganisms that can cause reactions when introduced into humans) and particulate matter, which can cause harmful blood clots, particularly when a product is administered in large quantities.[30]

Sterile-to-sterile compounding, described as "low" or "medium" risk compounding by the U.S. Pharmacopeial Convention, involves manipulating sterile ingredients entirely within an ISO Class 5 or better environment (a "clean room" carefully controlled to exclude microbial growth) using only sterile ingredients, products, components, and devices.[31] Depending on the number of sterile products and aseptic manipulations involved, sterile-to-sterile compounding may involve low or medium risk of microbial contamination.[32]

Nonsterile-to-sterile compounding, described as "high" risk compounding by the U.S. Pharmacopeial Convention, involves compounding using nonsterile ingredients or materials, including nonsterile active pharmaceutical ingredients (API), finished FDA-approved products not intended for sterile routes of administration (e.g., oral), or nonsterile devices or packaging.[33] It also includes sterile contents of commercially manufactured products that have been exposed to conditions that would render them nonsterile (e.g., exposure to air quality worse than ISO Class 5 for more than one hour). To engage in this process safely, an appropriate sterilization method must be used to ensure that such products are sterile and free of pyrogens and particulate matter prior to distribution.[34]

The high-risk process of nonsterile-to-sterile compounding is not appropriate for compounding pharmacies exempt under Section 503A, as these entities are not held to cGMP standards and

[28] Food and Drug Administration. Clinical Specialties Compounding Pharmacy announces voluntary nationwide recall of all lots of sterile products repackaged and distributed by Clinical Specialties Compounding due to lack of sterility assurance. March 20, 2013. http://www.fda.gov/safety/recalls/ucm344786.htm. Accessed February 21, 2014.

[29] Food and Drug Administration. Main Street Pharmacy, LLC issues voluntary nationwide recall of all sterile compounded products. May 28, 2013. http://www.fda.gov/safety/recalls/ucm354182.htm. Accessed February 21, 2014.

[30] Food and Drug Administration. FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness. http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDAMA/ucm100205.htm. Accessed February 18, 2014.

[31] <797> Pharmaceutical Compounding—Sterile Preparations. The United States Pharmacopeial Convention. 2008.

[32] *Ibid.*

[33] *Ibid.*

[34] *Ibid.*

instead must comply with USP standards only. USP standards for sterile compounding, laid out in Chapter 797 of the USP, are set by the U.S. Pharmacopeial Convention, a private organization that sets standards for drugs, food ingredients, and dietary supplements.[35] While USP standards have advanced over time, they remain relatively lax compared to the cGMP standards developed and enforced by the FDA. One key difference is that cGMP requires a drug manufacturer to validate and periodically re-validate each step in the production process through direct testing, whereas USP Chapter 797 routinely allows pharmacists to base production design on review of available literature and the pharmacist's prior experience.

For example, in determining sterilization methods, cGMP requires that any sterilization process used to prevent microbial contamination be validated through appropriate direct studies,[36] and offers detailed guidance on the design and conduct of such validation studies.[37] Once production begins, a single contaminated product in any batch smaller than 5,000 should trigger an investigation and revalidation of the entire manufacturing process.[38] USP, by contrast, does not generally require product-specific validation, instead allowing the pharmacist to select a method based on "experience and appropriate information sources," stating that the sterilization method should "preferably" be verified "whenever possible."[39]

Similarly, federal cGMP regulations require a detailed written stability testing program to determine appropriate storage conditions and expiration dates.[40] By contrast, USP describes the practice of establishing "beyond use dating (BUD)," and the especially high-risk practice of "theoretical beyond use dating," both of which can be based on a review of general literature and do not require direct product testing. [41] The USP acknowledges that "[t]heoretically predicted beyond-use dating introduces varying degrees of assumptions and, hence, a likelihood of error or at least inaccuracy," yet USP Chapter 797 does not require direct stability testing to avoid such problems. Indeed, actual testing is only "strongly urged" to support dating periods exceeding 30 days.[42]

---

[35] U.S. Pharmacopeial Convention. http://www.usp.org/about-usp. Accessed February 28, 2014.
[36] 21 CFR 211.113(b).
[37] Food and Drug Administration. Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice. September 2004.
[38] Food and Drug Administration. Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice. September 2004.
[39] <797> Pharmaceutical Compounding—Sterile Preparations. The United States Pharmacopeial Convention. 2008.
[40] 21 CFR § 211.166. ("There shall be a written testing program designed to assess the stability characteristics of drug products. The results of such stability testing shall be used in determining appropriate storage conditions and expiration dates. The written program shall be followed and shall include: (1) Sample size and test intervals based on statistical criteria for each attribute examined to assure valid estimates of stability; (2) Storage conditions for samples retained for testing; (3) Reliable, meaningful, and specific test methods; (4) Testing of the drug product in the same container-closure system as that in which the drug product is marketed; (5) Testing of drug products for reconstitution at the time of dispensing (as directed in the labeling) as well as after they are reconstituted.").
[41] <797> Pharmaceutical Compounding—Sterile Preparations. The United States Pharmacopeial Convention. 2008.
[42] *Ibid.*

We are aware that the FDA previously issued a preliminary conclusion in its Concept Paper published in 2000, which indicated that sterile compounding could be carried out by compounding pharmacies compliant with USP requirements for sterile compounding.[43] We urge the FDA to reconsider this preliminary conclusion, which addressed all sterile compounding, rather than focusing separately on, and requiring more stringent standards for, especially high-risk nonsterile-to-sterile compounding.

The FDA's earlier preliminary conclusion was also based in part on a perceived "substantial need for compounded sterile products, especially in the area of extemporaneous compounding."[44] While a general need for extemporaneously compounded sterile products may have existed under the conditions that the FDA considered in 2000, no substantial need exists for high-risk nonsterile-to-sterile compounding to be performed in compounding pharmacies exempt under Section 503A. First, most needs for sterile compounded products can be met through modifying federally regulated commercially available sterile products, a low- to medium-risk form of sterile compounding, rather than through high-risk compounding from nonsterile-to-sterile ingredients. Second, following the passage of the Drug Quality and Security Act, any residual needs requiring nonsterile-to-sterile compounding (in other words, making products from bulk API rather than modifying FDA-approved sterile products) are more appropriately met by carrying out such high-risk compounding in outsourcing facilities compliant with Section 503B and federal cGMP requirements (as opposed to relying on 503A compounding pharmacies exempt from cGMP requirements).

Furthermore, more information is now available on the actual conditions of practice in compounding pharmacies, historically subject to minimal federal oversight. Recent FDA inspections of compounding pharmacies have revealed widespread sterility concerns, some of which may violate USP standards in addition to cGMP standards, suggesting that the safety of high-risk nonsterile-to-sterile compounding cannot be assured without increased federal oversight.[45] Some of these violations are discussed in greater detail below.

Companies that have registered as outsourcing facilities under Section 503B will now be held to higher federal standards, and we hope that conditions in these facilities will improve. However, the FDA cannot reasonably expect these conditions to improve substantially in compounding pharmacies exempt from federal oversight under Section 503A, as the current regulatory environment does not provide for appropriate oversight of compounding pharmacies that qualify for this exemption. While the FDA does have authority to inspect and take enforcement action against compounding pharmacies for violations of federal law, the agency has no plans to carry

[43] Food and Drug Administration. FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness. http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDAMA/ucm100205.htm. Accessed February 18, 2014.

[44] *Ibid.*

[45] Food and Drug Administration. Compounding: Inspections, recalls, and other actions. February 6, 2014. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339771.htm. Accessed February 24, 2014.

out regular inspections, leaving day-to-day oversight up to state boards of pharmacy.[46] Many compounding pharmacies are not routinely monitored by state boards to verify compliance with USP Chapter 797 requirements for sterile compounding. A 2012-2013 survey of state boards of pharmacy published by the office of U.S. Rep. Edward J. Markey (now Senator Markey), indicated that 37 state boards of pharmacy do not routinely track which pharmacies are providing sterile compounding services, and only 19 state boards of pharmacy provide inspectors with special training to identify problems with sterile compounding.[47]

For these reasons, as well as our comments on more specific factors below, we urge the FDA to identify nonsterile-to-sterile compounding as a category presenting demonstrable difficulties for compounding under Section 503A, but not necessarily Section 503B.

The FDA has requested comment on specific relevant factors, including the complexity of compounding, facilities and equipment, personnel training, and testing and quality assurance. We now address each of these factors in turn with regard to nonsterile-to-sterile compounding:

Complexity of Compounding

Nonsterile-to-sterile compounding involves extremely complex production processes. As stated in the FDA's Concept Paper:

> The preparation of sterile products is often unavoidably complex, involving many steps and manipulations. Each step poses an opportunity for microbial contamination. The manipulation of a sterile drug product may contaminate it, especially when nonsterile components are used (e.g., if the product is packaged into a nonsterile syringe or vial purported to be sterile), nonsterile equipment is used, or novel, complex, or prolonged aseptic processes are employed.[48]

Even a relatively small change in the production process, such as a switch to new packaging material, may result in unanticipated and far-reaching consequences. The largest infection outbreak associated with a pharmaceutical product in United States history occurred as the result of one such seemingly minor change: Between April and September 1970, Abbott Laboratories began phasing in a new type of cap liner that relied on synthetic plastic, rather than natural

[46] Food and Drug Administration. Compounding and the FDA: Questions and Answers. December 2, 2013. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339764.htm#regulates. Accessed February 24, 2014.

[47] Report of the US House of Representatives. State of Disarray. How states' inability to oversee compounding pharmacies puts public health at risk. April 15, 2013.

[48] FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness. http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDAMA/ucm100205.htm. Accessed February 18, 2014.

rubber.[49] The rubber previously used in the caps had antibacterial properties that synthetic liners lacked. Inadequate environmental control and sampling protocols contributed to microbial contamination of the liners, which thrived on the new synthetic medium. The result was catastrophic: Abbott Laboratories distributed approximately 45 percent of all intravenous fluids sold in the United States at the time, and the outbreak is estimated to have led to between 2,000 and 8,000 cases of infection, and between 200 and 800 deaths.[50]

Both USP and cGMP standards have been updated dramatically over the ensuing decades, yet complex production processes remain challenging to monitor.[51] Any change in the production process should be validated through direct testing to ensure that it does not result in unforeseen consequences. This type of direct validation can only be ensured in facilities verified as fully compliant with cGMP. Nonsterile-to-sterile compounding, therefore, presents demonstrable difficulties for compounding under any other conditions.

Facilities and Equipment

Nonsterile-to-sterile compounding requires sophisticated facilities and equipment that must be maintained to rigorous standards. As stated in the FDA's concept paper:

> To maintain the essential characteristics of sterile products (i.e., sterility and freedom from particulate matter and pyrogens), the products and their components must be manipulated in a suitable environment using aseptic techniques. ... It is important to minimize bioburden during the production process even when terminal sterilization is used. Therefore, the production facilities and associated procedures must meet exacting standards.[52]

While USP and cGMP have developed harmonized standards regarding appropriate levels of bioburden (the accumulation of potential biological contaminants during the production process) in the environment, recent FDA inspections of compounding pharmacies have revealed repeated failures in maintaining the environmental monitoring necessary to meet these standards. In 2013, FDA inspectors cited dozens of compounding pharmacies for failing to assess airflow patterns with adequate smoke studies performed under dynamic conditions and/or failing to conduct appropriate environmental monitoring.[53] While FDA inspectors focused on violations of cGMP

[49] Centers for Disease Control. Epidemiologic notes and reports nosocomial bacteremias associated with intravenous fluid therapy – USA. MMWR Weekly. December 26, 1997/46(51);1227-1233. http://www.cdc.gov/mmwr/preview/mmwrhtml/00050554.htm. Accessed February 18, 2014.
[50] *Ibid.*
[51] *Ibid.*
[52] FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness. http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDAMA/ucm100205.htm. Accessed February 18, 2014.
[53] Food and Drug Administration. Compounding: Inspections, recalls, and other actions. February 6, 2014. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339771.htm. Accessed February 24, 2014.

standards, many of the conditions identified would be unacceptable under either cGMP or USP standards. For example, FDA inspectors also noted visible dust, stains, splatters, residue, rust, live or dead insects, and other sources of potential contamination in a disturbing number of facilities.[54,55,56,57,58,59,60,61,62]

Some of the pharmacies cited by FDA inspectors in 2013 have subsequently registered as outsourcing facilities.[63] While we remained concerned that outsourcing facilities will not be required to undergo new drug approval or verify compliance with cGMP prior to producing sterile products, we assume that the FDA will make every effort to ensure that these facilities comply with cGMP standards moving forward. (If this assumption proves to be incorrect, then nonsterile-to-sterile compounding by outsourcing facilities will also pose unacceptable risks to patients.)

By contrast, many pharmacies that have not registered as outsourcing facilities continue to claim that their compounding facilities adequately comply with applicable state and USP standards

[54] Food and Drug Administration. Axium Healthcare Pharmacy dba Balanced Solutions Compounding. March 15, 2013. http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM345694.pdf. Accessed February 24, 2014.

[55] Food and Drug Administration. 483 Inspection Report. Custom Compounding Centers, LLC. December 13, 2012. http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM348232.pdf. Accessed February 24, 2014.

[56] Food and Drug Administration. 483 Inspection Report: Anazaohealth Corporation. February 22, 2013. http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM341368.pdf. Accessed February 24, 2014.

[57] Food and Drug Administration. 483 Inspection Report: University Pharmacy, Inc. February 26, 2013. http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM342275.pdf. Accessed February 24, 2014.

[58] Food and Drug Administration. 483 Inspection Report: College Pharmacy Incorporated. March 15, 2013. http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM345701.pdf. Accessed February 24, 2014.

[59] Food and Drug Administration. 483 Inspection Report: The Compounding Shop, Inc. March 22, 2013. http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM345933.pdf. Accessed February 24, 2014.

[60] Food and Drug Administration. 483 Inspection Report: Pentec Health, Inc. April 1, 2013. http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM346817.pdf. Accessed February 24, 2014.

[61] Food and Drug Administration. 483 Inspection Report: Pallimed Solutions, Inc. April 9, 2013. http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM348236.pdf. Accessed February 24, 2014.

[62] Food and Drug Administration. 483 Inspection Report: Central Admixture Pharmacy Services, Inc. February 19, 2013. http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM348237.pdf. Accessed February 24, 2014.

[63] Food and Drug Administration. Registered Outsourcing Facilities. Updated as of February 21, 2014. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm. Accessed February 28, 2014.

even when they have been informed by the FDA of sterility concerns, making them unlikely to adjust their practices or upgrade their current facilities. In fact, one pharmacy, NuVision, recently refused a request by the FDA to recall all sterile products after the agency identified safety concerns related to sterility during a facility inspection.[64,65] The pharmacy still claims on its website to adhere to USP standards for sterile compounding.[66] In addition, three other compounding pharmacies have responded following FDA inspections with their opinion (without citing verification by independent inspectors) that the current facilities satisfy USP requirements, in spite of the fact that federal inspectors had identified serious sterility concerns.[67,68,69] Regardless of whether these pharmacies do, in fact, comply with USP requirements (a claim that has not been confirmed through independent inspections), it is clear that they are unlikely to dramatically upgrade their facilities in the near future. Appropriately, at least one of these compounding pharmacies has reported that it does not engage in nonsterile-to-sterile compounding.[70] We urge the FDA to ensure that all compounding pharmacies exempt under 503A avoid this type of high-risk compounding, which cannot be performed safely except in a facility that has been regularly inspected for compliance with cGMP standards.

Personnel Training

Specialized, highly technical training is essential to ensure proper compounding of nonsterile-to-sterile drug products. As stated in the FDA's Concept Paper:

> The processes used in pharmacies to prepare sterile products are highly personnel-intense. The contamination of pharmacy-prepared products (e.g., intravenous admixtures and prefilled syringes) by aseptic processing most likely will be caused by personnel-associated factors. These factors may include the shedding of contaminants from people into the controlled environment, improper procedures under laminar air flow, and the use of poor aseptic technique. Therefore, pharmacy personnel involved in compounding

[64] FDA reminds health care providers not to use sterile products from NuVision Pharmacy. August 16, 2013. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm365402.htm. Accessed February 26, 2014.
[65] Food and Drug Administration. Warning Letter. NuVision Pharmacy. Jul 26, 2013. http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM363761.pdf. Accessed February 28, 2014.
[66] Nuvision. Sterility Testing. http://nuvisionpharmacy.com/sterility-testing/. Accessed February 26, 2014.
[67] Foundation Care. Reponse Letter to the Food and Drug Administration. April 9, 2013. http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM349684.pdf. Accessed February 24, 2014.
[68] IV Solutions of Lubbock. Response Letter to the Food and Drug Administration. April 25, 2013. http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM349813.pdf. Accessed February 24, 2014.
[69] Pharmacy Creations. Response Letter to the Food and Drug Administration. September 3, 2013. http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM371359.pdf. Accessed February 24, 2014.
[70] Foundation Care. Reponse Letter to the Food and Drug Administration. April 9, 2013. http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM349684.pdf. Accessed February 24, 2014.

> sterile products must have sufficient knowledge, training, and experience to perform the task correctly and safely. Furthermore, a pharmacy's quality assurance program for sterile products must include requirements that personnel consistently adhere to performance standards; that performance problems be monitored, detected, and corrected; and that personnel undergo initial and periodic certification.[71]

Appropriate training is essential to ensure that sterile solutions do not become contaminated during preparation. A study of pharmacy students by Isanhart et al, published in 2008, assessed procedures performed at the beginning and end of a 16-week parenterals laboratory course offering instruction in aseptic technique.[72] Prior to undergoing training, 21 of 504 syringes (4 percent) prepared by the students were contaminated during media fill tests, a number that was reduced to 0 of 498 by the end of the course.

While zero contamination is clearly possible with appropriate technique, reports from the FDA and published literature suggest that use of inadequate technique is widespread. Rates of contamination during medium and low risk compounding operations remain highly variable and unacceptably high in practice, ranging from 0 percent to over 6 percent among experienced, practicing pharmacists and technicians.[73,74,75,76,77] FDA inspection reports from 2013 also document numerous examples of inappropriate aseptic technique and inadequate monitoring of pharmacy personnel. Observations included inadequate gowning that leaves skin exposed, failure to adequately monitor employees for microbial contamination during aseptic operations, uncontrolled movement of employees in and out of the ISO Class 5 clean room where sterile drugs are prepared, inappropriate use of nonsterile objects in aseptic operations, and failure to adequately clean and sanitize equipment and surfaces in the clean room. [78,79,80,81] Such high-risk

---

[71] FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness. http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDAMA/ucm100205.htm. Accessed February 18, 2014.

[72] Isanhart CM, McCall KL, Kretschmer D, Grimes BA, Parenterals laboratory course to reduce microbial contamination rates in media fill tests performed by pharmacy students. Am J Pharm Educ. 2008;72(2):27.

[73] Reiter PD. Sterility of intravenous fat emulsion in plastic syringes. Am J Health Syst Pharm 2002;59:1857-9.

[74] van Grafhorst JP, Foudraine NA, Nooteboom F, Crombach WH, Oldenhof NJ, van Doorne H. Unexpected high risk of contamination with staphylococci species attributable to standard preparation of syringes for continuous intravenous drug administration in a simulation model in intensive care units. Crit Care Med. 2002;30:833-6.

[75] Trissel LA, Ogundele AB, Ingram DS et al. Using medium-fill simulation to establish a benchmark microbiological contamination rate for low-risk-level compounding. *Am J Health-Syst Pharm.* 2003; 60:1853-5.

[76] Thomas M, Sanborn M, Couldry R. IV admixture contamination rates: traditional practice site versus a class 1000 cleanroom. Am J Health-Syst Pharm. 2005;62:2386-92.

[77] Trissel LA, Gentempo JA, Anderson RW, Lajeunesse JD. Using a medium-fill simulation to evaluate the microbial contamination rate for USP medium-risk-level compounding. *Am J Health-Syst Pharm.* 2005;62:285-8.

[78] Food and Drug Administration. 483 Inspection Report: Avella of Deer Valley, Inc. February 25, 2013. http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM342276.pdf. Accessed February 26, 2014.

[79] Food and Drug Administration. 483 Inspection Report: FVS Holdings, Inc. dba Green Valley Drugs. March 15, 2013.

nonsterile-to-sterile compounding by improperly trained personnel poses unacceptable risk to patients. To avoid this risk, nonsterile-to-sterile compounding must be carried out only in facilities that are regularly inspected for compliance with cGMP.

Testing and Quality Assurance

Testing and quality assurance are especially important in nonsterile-to-sterile compounding as a means of verifying that sterility has been successfully achieved. As the FDA stated in its Concept Paper:

> All compounded sterile products should be inspected prior to use in patients. Low-risk compounded sterile products (e.g., sterile products prepared from sterile components using proper techniques and equipment) should, at a minimum, be inspected physically and visually for cloudiness and particulate matter. High-risk compounded sterile products (e.g., sterile products prepared from nonsterile components using proper techniques and equipment) should undergo end-product sterility and pyrogen testing before they are dispensed from the pharmacy.[82]

Sterility testing is required under cGMP, with samples taken at the beginning, middle, and end of the aseptic processing operation.[83] Any positive test result is considered a serious cGMP issue requiring thorough investigation.[84] Under USP standards, only high-risk sterile products prepared in groups of 25 or more or that are exposed to certain temperatures for varying lengths of time must be tested for sterility prior to release, and the pharmacy need not await test results before dispensing the products to patients.[85] Moreover, products intended for inhalation or ophthalmic administration need not be tested for bacterial endotoxins (pyrogens) prior to release.[86]

---

http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM348241.pdf. Accessed February 26, 2014.

[80] Food and Drug Administration. University Pharmacy, Inc. February 26, 2013. http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM342275.pdf. Accessed February 26, 2014.

[81] Food and Drug Administration. 483 Inspection Report: Lowlyn Pharmacies, Inc. March 8, 2013. http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM345695.pdf. Accessed February 26, 2014.

[82] FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness. http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDAMA/ucm100205.htm. Accessed February 18, 2014.

[83] Food and Drug Administration. Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice. September 2004.

[84] *Ibid.*

[85] <797> Pharmaceutical Compounding—Sterile Preparations. The United States Pharmacopeial Convention. 2008.

[86] *Ibid.*

As might be expected, a disturbing number of compounding pharmacies forgo testing and quality assurance measures that would be required under cGMP. FDA inspection reports of compounding pharmacies in 2013 identified widespread failure to conduct sterility, endotoxin, and potency testing on all end products. Many pharmacies also failed to document adequate investigation after identifying particulates, discoloration, microbial contamination, leaking product, or other issues with finished samples. In two cases, particulate matter was discovered in products from lots that had already been shipped to customers.[87,88] Half a dozen pharmacies were also cited for failing to adequately follow up on complaints, including reports indicating mislabeling, particulate matter, and other serious concerns with drug products, including fever, injection-site redness, abscess, and other disturbing adverse events in patients.[89,90,91,92,93,94]

Based on the factors identified above, high-risk nonsterile-to-sterile compounding cannot be conducted safely in compounding pharmacies that are not regularly inspected for full compliance with cGMP standards. We therefore urge the FDA to identify nonsterile-to-sterile compounding as a category of products presenting demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety and effectiveness of such drug products under Section 503A, but not necessarily Section 503B.

---

[87] Food and Drug Administration. 483 Inspection Report: Village Fertility Pharmacy, Inc. March 13, 2013. http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM348242.pdf. Accessed February 24, 2014.

[88] Food and Drug Administration. 483 Inspection Report: Axium Healthcare Pharmacy dba Balanced Solutions Compounding. http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM345694.pdf. Accessed February 24, 2014.

[89] Food and Drug Administration. 483 Inspection Report: MedPREP Consulting, Inc. April 3, 2013. http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM348230.pdf. Accessed February 24, 2014.

[90] Food and Drug Administration. 483 Inspection Report: Wedgewood Village Pharmacy, Inc. February 11, 2013. http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM342543.pdf. Accessed February 24, 2014.

[91] Food and Drug Administration. 483 Inspection Report: PharMEDium Services LLC (Parsippany, NJ). February 28, 2013. http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM342271.pdf. Accessed February 24, 2014.

[92] Food and Drug Administration. 483 Inspection Report: Village Fertility Pharmacy, Inc. March 13, 2013. http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM348242.pdf. Accessed February 24, 2014.

[93] Food and Drug Administration. 483 Inspection Report: NuVision Pharmacy, Inc. April 17, 2013. http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM348772.pdf. Accessed February 24, 2014.

[94] Food and Drug Administration. 483 Inspection Report: Central Admixture Pharmacy Services (Chicago, IL). February 22, 2013. http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM341365.pdf. Accessed February 24, 2014.

Alternatively, if the FDA creates a single unified list, we urge the FDA to identify nonsterile-to-sterile compounding as a category of products presenting demonstrable difficulties for compounding except under conditions present in outsourcing facilities compliant with Section 503B and cGMP requirements.

2. Metered dose inhaler (MDI) products

The FDA's Concept Paper published in 2000 recommended that MDI products be identified as presenting demonstrable difficulties in compounding. Specifically, the FDA stated:

> The MDI is one of the most complicated drug delivery systems currently marketed by the pharmaceutical industry ….MDI products are primarily used by patients suffering from chronic lung diseases such as asthma and chronic obstructive pulmonary disease (COPD). Individuals suffering from asthma and COPD tend to have airways that are hyper-reactive to inhalants. It is therefore critical that the contents and the delivery characteristics of MDI products be carefully controlled to ensure that the product will be safe and effective. Even slight changes in the formulation, drug substance particle size, valve, or actuator can have a major effect on the aerosol delivery and potency characteristics. This effect can significantly alter the safety and effectiveness of the device. For example, a change in particle size distribution may lead to greater systemic absorption of a beta agonist drug, which can increase the amount of systemic side effects and may also decrease the local effectiveness of the drug in the lungs.[95]

The FDA concluded that MDI products present demonstrable difficulties in compounding because:

> • Metered dose inhalers are sophisticated drug delivery systems that require extensive development to ensure dosing accuracy and reproducibility.
> • A sophisticated formulation of the drug product is required to ensure dosing accuracy and reproducibility, and product-to-product uniformity is critical for dosing accuracy and is usually difficult to achieve.
> • Reproducible bioavailability of the compounded drug product is difficult to achieve.
> • The compounding of MDI products is complex.
> • Sophisticated facilities and equipment are required to ensure proper compounding of the drug product.
> • Specialized, technical training is essential to ensure proper compounding of the drug product.
> • Sophisticated, difficult to perform testing of the compounded drug product is required to ensure potency and purity.[96]

[95] FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness. http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDAMA/ucm100205.htm. Accessed February 18, 2014.
[96] *Ibid.*

We agree with the FDA's prior analysis and conclusions with respect to MDI products and urge the agency to identify MDI products as presenting demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety and effectiveness of such drug products under Sections 503A and 503B.

3. Dry powder inhaler (DPI) products

The FDA's Concept Paper published in 2000 also recommended that DPI products be identified as presenting demonstrable difficulties in compounding. Specifically, the FDA stated:

> DPIs are complex drug products that differ in many aspects from more conventional drug products. … There is a wide array of potential DPI designs, all complex in their design and function and many with characteristics unique to the particular design.
>
> Regardless of design, the most crucial attributes of DPIs are the reproducibility of the dose and particle size distribution. It is difficult to maintain these qualities through the expiration date and to ensure the functionality of the device during the period of patient use. The unique characteristics of DPIs must be considered in their preparation, particularly with respect to the product's formulation, container closure system, and testing.[97]

The FDA concluded that DPI products present demonstrable difficulties in compounding because:

> • Dry powder inhalers are sophisticated drug delivery systems that require extensive development to ensure dosing accuracy and reproducibility.
> • A sophisticated formulation of the drug product is required to ensure dosing accuracy and reproducibility, and the product-to-product uniformity that is critical for dosing accuracy is usually difficult to achieve.
> • Reproducible bioavailability of the compounded drug product is difficult to achieve.
> • The compounding of DPI products is complex.
> • Sophisticated facilities and equipment are required to ensure proper compounding of the drug product.
> • Specialized, technical training is essential to ensure proper compounding of the drug product.
> • Sophisticated, difficult to perform testing of the compounded drug product is required to ensure potency and purity.[98]

[97] FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness. http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDAMA/ucm100205.htm. Accessed February 18, 2014.
[98] *Ibid.*

We agree with the FDA's prior analysis and conclusions with respect to DPI products, and urge the agency to identify DPI products as presenting demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety and effectiveness of such drug products under Sections 503A and 503B.

4. Transdermal Delivery Systems (TDSs)

Finally, the FDA's Concept Paper published in 2000 recommended that TDS products be identified as presenting demonstrable difficulties in compounding. Specifically, the FDA stated:

> TDS products are complex to develop and may require the use of new technologies. Each system is formulated to meet specific biopharmaceutical and functional criteria. The materials of construction, configurations, and combination of the drug with the proper cosolvents, excipients, penetration enhancers, and membranes must be carefully selected and matched to optimize adhesive properties and drug delivery requirements. The equipment and the technology required for the manufacture of TDS products limit their preparation to properly equipped manufacturers.[99]

The FDA concluded that TDS products present demonstrable difficulties in compounding because:

> • TDSs are sophisticated drug delivery systems that require extensive development to ensure dosing accuracy and reproducibility.
> • A sophisticated formulation of the drug product is required to ensure dosing accuracy and reproducibility.
> • Reproducible bioavailability of the compounded drug product is difficult to achieve.
> • The compounding of TDS products is complex.
> • Sophisticated facilities and equipment are needed to ensure proper compounding of TDS products.
> • Specialized technical training is essential to ensure proper compounding of TDS products
> • Sophisticated, difficult to perform testing of the compounded product is required to ensure potency, purity, and quality of the drug product prior to dispensing.[100]

We agree with the FDA's prior analysis and conclusions with respect to TDS products and urge the agency to identify TDS products as presenting demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety and effectiveness of such drug products under Sections 503A and 503B.

---

[99] FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness. http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDAMA/ucm100205.htm. Accessed February 18, 2014.

[100] *Ibid.*

5. Sustained or time-release dosage forms

Public Citizen previously submitted comments on the FDA's Concept Paper published in 2000.[101] In those comments, we recommended that the FDA evaluate sustained or time-release dosage forms for categorization as products presenting demonstrable difficulties for compounding. As we stated previously:

> Because there is no requirement to test [compounded sustained or time-release] products, it is no known if 90 percent of the active ingredient is released within the first 30 minutes after the dose is taken, or if 90 percent of the active ingredient remains in the dosage form after the dose is taken.[102]

Variation in rates of release of the active ingredient could impact bioavailability, potentially reducing the drug's efficacy or increasing safety risks. Clinical testing is necessary to ensure appropriate bioavailability for sustained or time-release dosage forms. Such clinical testing is not required under either Section 503A or Section 503B and can only be required for drug products that undergo premarket approval by the FDA. We therefore urge the FDA to categorize sustained or time-released dosage forms as presenting demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety and effectiveness of such drug products under Sections 503A and 503B.

6. Enteric-coated preparations

Public Citizen also previously recommended that the FDA evaluate enteric-coated preparations for categorization as products presenting demonstrable difficulties for compounding.[103] Enteric-coated preparations are preparations intended for drugs that are either destroyed by gastric acidity or that cause gastric irritation. As we previously stated, "enteric-coated preparations may, if not properly formulated, resist dissolution in the intestine, and very little if any of the active drug may be absorbed into the blood stream."[104]

As with sustained-release dosage forms, improperly formulated enteric-coated preparations could impact bioavailability, potentially reducing the drug's efficacy or increasing safety risks. Clinical testing is necessary to prevent these problems. Because such testing is not required under either Section 503A or Section 503B, we urge the FDA to categorize enteric-coated preparations as presenting demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety and effectiveness of such drug products under Sections 503A and 503B.

---

[101] Public Citizen. Comments on Drugs that Present Difficulties for Compounding. August 2, 2000. http://www.citizen.org/Page.aspx?pid=3626. Accessed March 3, 2014.
[102] *Ibid.*
[103] *Ibid.*
[104] *Ibid.*

III. Conclusion

We are concerned that the FDA intends to develop and publish a single list of drug products and categories of drug products that cannot be compounded because they present demonstrable difficulties for compounding, and urge the agency to withdraw its proposal and instead develop two separate lists. Drugs compounded at compounding pharmacies under a Section 503A exemption should be treated differently than those subject to Section 503B, as the regulations governing each category of facility are different.

Alternatively, if the FDA chooses to proceed with its proposed plan of establishing only one list, we urge the agency to identify compliance with cGMP and the requirements of 503B as conditions necessary to prevent certain drugs or categories of drugs from presenting demonstrable difficulties for compounding.

Regardless of whether one or two lists is used, we urge the FDA to classify high-risk nonsterile-to-sterile compounding as a category of products presenting demonstrable difficulties for compounding under compounding pharmacies exempt under Section 503A, but not necessarily outsourcing facilities exempt under 503B. This high-risk process may be safely carried out only by a facility that is regularly inspected to verify compliance with federal cGMP requirements.

We have also recommended designation of several additional product categories as presenting demonstrable difficulties for compounding.

A full list of product categories that we urge the FDA to identify as demonstrably difficult to compound, along with our recommendations for their appropriate regulatory classification, is summarized as follows:

1. Nonsterile-to-sterile compounding (non-exempt under 503A only)
2. Metered dose inhaler (MDI) products (non-exempt under 503A and 503B)
3. Dry powder inhaler (DPI) products (non-exempt under 503A and 503B)
4. Transdermal Delivery Systems (TDSs) (non-exempt under 503A and 503B)
5. Sustained or time-release dosage forms (non-exempt under 503A and 503B)
6. Enteric-coated preparations (non-exempt under 503A and 503B)

Thank you for your consideration of these comments.

Sincerely,

Sarah Sorscher, J.D., M.P.H.
Attorney
Public Citizen's Health Research Group

Michael Carome, M.D.
Director
Public Citizen's Health Research Group