Testimony before the Committee on Energy and Commerce
Subcommittee on Health
United States House of Representatives
May 22, 2013

The Pew Charitable Trusts

Dear Chairman Pitts, Ranking Member Pallone and members of the Subcommittee,

Thank you for the opportunity to testify on the need for federal legislation to improve the safety of compounded medicines.

My name is Gabrielle Cosel. I work on pharmaceutical quality and safety at the Pew Charitable Trusts, an independent, nonpartisan research and public policy organization.

Pharmacists have always compounded medicines – it is the origin of the profession – but many of the activities we refer to as compounding today are far removed from the traditional practice of preparing individualized medicines for one patient at a time. Some compounders today produce large volumes of drugs and ship them to clinics and hospitals across the country.

In recent months, this committee has repeatedly stressed the responsibility of FDA to ensure the safety of activities that depart from traditional compounding and are more akin to manufacturing. I will focus today on a regulatory framework that clarifies the Agency's role, ensures that limited resources are used wisely, and sets clear expectations of the industry. First, though, it is important to understand the risks we face.

Examining the risks

The epidemic caused by the New England Compounding Center highlights the dangers to patients from compounded drugs. As of May 6, that outbreak has been associated with 55 deaths and 741 serious infections in 20 states.

But what happened at NECC is not an isolated incident. I have included with my testimony a Pew summary that describes 19 additional pharmacy compounding errors since 2001.[1]

These errors caused serious injuries and deaths in at least 29 different states. The list includes 22 additional deaths, as well as serious infections – meningitis, bloodstream, and at least 38 patients who suffered partial or complete loss of vision. It also includes patients harmed by sub-potent or super-potent doses. For example, three people in Oregon and Washington who died after receiving drugs from Texas – intravenous injections for back pain that were *eight times* the labeled strength.[2]

Recent inspections of compounders raise further concern: For example, two months ago, the FDA announced a recall of all of the products manufactured by a New Jersey compounder because of potential mold contamination. The FDA press release referred to "visible particulate contaminants" in what was supposed to be a sterile product.[3] Also this year, a Georgia compounder conducted a nationwide recall of sterile products after reports of serious eye infections.[4]

Compounding errors can cause exponentially greater harms if the product has been produced in mass quantities. There are companies today that compound thousands of packages or vials of medicine and ship them to buyers all over the country, going well beyond the traditional practice of a pharmacist making a single drug in response to a specific prescription for a specific patient. These activities have outgrown the state regulatory structures established to oversee them.

Congress, through section 503(A) of the Food, Drug and Cosmetic Act, already recognizes FDA's responsibility to oversee some compounding activities. Today, we urge you to amend certain elements of this provision to ensure its effectiveness and provide greater clarity on state and federal roles. We urge the following elements:

1. **When appropriate, large-scale compounding should be subject to higher quality standards – specifically applicable Good Manufacturing Practices (GMPs),**
2. **FDA is the appropriate agency to oversee GMPs, and states should not exercise redundant oversight,**
3. **Patients must be protected by ensuring that compounders do not undermine "gold standard" FDA-approved drugs.**

Today, compounding quality standards are set by states. Some states incorporate United States Pharmacopeia standards for sterile and non-sterile compounding (USP chapters 797 and 795, respectively), but experts at a recent pharmacy compounding summit co-hosted by Pew, the American Hospital Association (AHA), and the American Society of Health-System Pharmacists (ASHP) stressed that USP compounding standards were developed for use in pharmacies and are not suitable for larger-scale production.

Compounding large volumes of repeated batches of medicines implies standardized processes that should be subject to appropriate quality standards such as those outlined in current Good Manufacturing Practices (cGMPs) for drug manufacturers.

For example, cGMP requires manufacturers to validate systems and processes to ensure that medicines meet consistent quality and safety standards. Process validation becomes increasingly important as the same drug is compounded in repeat batches. In addition, USP 797 does not require the testing of a drug's starting ingredients, while cGMP does. And expiration dates are set for a manufactured drug based on extensive stability testing. But a beyond-use date for a compounded medicine may in some cases be set by referencing published studies of drugs that may not conform exactly to the compounded product.[5,6] GMPs are developed by the FDA, and the agency is best placed to enforce them.

Facilities that produce large volumes of sterile products, or carry out particularly high-risk compounding, such as manufacturing from a non-sterile bulk ingredient, should be required to register with the FDA. FDA should issue a regulation clarifying the criteria for registration. As with pharmaceutical manufacturing, FDA should inspect compounding facilities on an ongoing basis, with a frequency based on risk.

To avoid an unfunded mandate, the FDA will need adequate resources to conduct ongoing inspections of registered facilities. These resources should be provided through facility fees.

It is important to state that large-scale compounding cannot be addressed simply by asserting these facilities are making unapproved new drugs and requiring them to submit to the New Drug Approval or Abbreviated New Drug Approval process. For example, some large compounders have become a source of intravenous and epidural therapies for hospitals and health systems that do not have the capacity to compound them in-house. Entities that play a role in our health care system should not be left to default or ad-hoc application of full requirements of the FDCA. The regulatory oversight system for these entities should be clearly defined. However, as addressed below, it is important to ensure that compounding does not encourage the sector to produce new drugs that undermine the FDA-approval paradigm.

Under this framework, states may continue to require FDA-registered compounding facilities to hold state pharmacy licenses, but state enforcement of quality standards should be preempted for these facilities. The section 704 provision that exempts pharmacies from the requirement to provide records access to FDA should be removed for registered facilities. Without this authority the FDA will be challenged when it attempts to investigate a facility that should be under its jurisdiction. Such challenges have been well documented. In the wake of deadly meningitis outbreak a Congressional investigation clearly showed that even when the FDA had access to a facility its ability to access records was challenged.[7] Additionally, in March of 2013 the FDA reported that compounders denied FDA investigators access to records in a number of recent cases.[8]

Key safety requirements should also be set at the federal level, such as a "do not compound" list. Congress has already recognized that certain products are not suitable for compounding (frequently cited examples include transdermal delivery systems, biologic products and sustained release formulations) and has given FDA the authority to establish a "do not compound" list. This authority should be maintained and should apply to both FDA-registered and non-registered facilities, as it does now. The section 704 records exemption should also be removed for purposes of enforcing the do not compound list.

It is important to emphasize that compounded drugs do not go through the pre-market approval process that brand and generic drug companies go through to demonstrate safety, efficacy and bioequivalence, along with pre-approval of manufacturing methods and facilities. These are critical systems to protect patients. Because they do not apply to compounders, compounded medicines can never be an adequate substitute for FDA-approved drugs.

Any new federal regulatory scheme must not encourage compounding at the expense of conventional manufacturing. Legislation should be clear that a compounder may not make a copy or a variation of a marketed drug, except when that drug is in shortage or to address specific medical needs of a specific patient. Congress should also prohibit the wholesale of compounded drugs.

Another important safeguard against circumvention of the approvals process is limiting compounding from bulk to only well-characterized and already in-use active ingredients, such as those described by a USP monograph, or those in an existing drug application. These concepts are not new, but are part of current 503A language.

Conclusion

We thank you for your leadership on this important issue. Congress has long recognized the role of FDA in providing oversight of compounding. It is time to update the Food, Drug and Cosmetic Act to remove ambiguities and create a clear, workable framework to address patient safety.

Thank you for the opportunity to testify, and I welcome your questions.

References

[1] The Pew Charitable Trusts. U.S. Illnesses and Deaths Associated With Compounded Medications (2001-Present). April 15, 2013. http://www.pewhealth.org/other-resource/us-illnesses-and-deaths-associated-with-compounded-medications-85899468587

[2] U.S. Centers for Disease Control and Prevention. "Deaths from Intravenous Colchicine Resulting from a compounding Pharmacy Error—Oregon and Washington, 2007," Morbidity and Mortality Weekly Report. October 12, 2007. 56(40): 1050-1052. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5640a3.htm. Accessed January 8, 2013.

[3] Medprep Consulting Inc. "Medprep Consulting Inc. Announces Voluntary Nationwide Recall Of All Lots Of All Compounded Products Due To Potential Mold Contamination." Press Release. March 20, 2013. http://www.fda.gov/Safety/Recalls/ucm344787.htm.

[4] U.S. Food and Drug Administration. "FDA alerts health care providers and patients of the nationwide recall of all lots of sterile products distributed by Clinical Specialties Compounding Pharmacy". Press Release. March 21, 2013. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm345019.htm

[5] United States Pharmacopoeial Convention. USP–NF General Chapter <797> Pharmaceutical Compounding—Sterile Preparations.

[6] 21 CFR 211. Current good manufacturing practice for finished pharmaceuticals.

[7] Committee on Energy & Commerce, Majority Memo. "The Fungal Meningitis Outbreak: could it have been prevented?" Nov 12, 2012. http://energycommerce.house.gov/sites/republicans.energycommerce.house.gov/files/Hearings/OI/20121114/HMTG-112-HHRG-IF02-20121114-SD001.pdf

[8] Hamburg, Margaret A. "FDA Must Have New Authorities to Regulate Pharmacy Compounding." FDA Voice. March 22, 2013. http://blogs.fda.gov/fdavoice/index.php/2013/03/fda-must-have-new-authorities-to-regulate-pharmacy-compounding/

THE PEW CHARITABLE TRUSTS

U.S. Illnesses and Deaths Associated With Compounded Medications (2001-Present)

APPENDIX B

The Pew Charitable Trusts has identified 20 pharmacy compounding errors associated with 1022 adverse events, including 75 deaths, since 2001. Contamination of sterile products was the most common compounding error, though some incidents were the result of pharmacists' and technicians' miscalculations and mistakes in filling prescriptions.

Year	States	Reported cases	Reported deaths	Adverse events	Compounding error	Product
2012	FL, GA, ID, IL, IN, MD, MI, MN, NC, NH, NJ, NY, OH, PA, RI, SC, TN, TX, VA	733	53	Fungal meningitis and other infections	Contamination[1]	Spinal injections: preservative-free sterile methylprednisolone acetate
2012	CA and six other states	33		Fungal eye infection; 23 cases of partial to severe vision loss	Contamination[2]	Eye injections: Brilliant Blue-G (BBG) retinal dye and triamcinalone
2011	FL, TN	21		Bacterial eye infection; one case of meningitis and encephalitis; four cases of loss of eyesight; three patients had eye removals	Contamination[3]	Eye injections: intravitreal bevacizumab (Avastin) injections
2011	CA	5		Blindness	Unintended presence of another medication[4]	Eye injections: intravitreal bevacizumab (Avastin) injections
2011	AL	19	9	Bacterial bloodstream infection	Contamination[5]	Parenteral nutrition solution
2010	IL	1	1	Fatal overdose	Dose of sodium 60 times stronger than ordered[6]	IV solution: sodium chloride
2007	WA, OR	3	3	Fatal overdose	Dose of colchicine eight times stronger than labeled concentration[7]	IV solution: colchicine
2007	MD, CA	8		Bacterial bloodstream infection	Contamination[8]	IV solution: fentanyl

Year	States	Reported cases	Reported deaths	Adverse events	Compounding error	Product
2004-2006	MI, MO, NY, SD, TX, WY	80		Bacterial bloodstream infection	Contamination[9]	IV flush syringes: heparinized saline
2006	OH	1	1	Fatal overdose	Dose of sodium chloride stronger than ordered[10]	Chemotherapy infusion
2006	NV	1	1	Fatal overdose	Dose of zinc 1,000 times stronger than ordered[11]	Neonatal parenteral nutrition solution
2005		2		Bacterial bloodstream infection	Contamination[12]	IV flush vials: preservative-free heparinized saline
2005	MN and one other state	6		Bacterial eye infection; all cases had partial or complete loss of vision; two patients had eye removals	Contamination[13]	Eye solution: trypan blue
2005	VA	5	3	Systemic inflammatory response syndrome	Contamination[14]	Heart infusion: cardioplegia
2005	CA, NJ, NC, NY, MA	18		Bacterial bloodstream infection	Contamination[15]	IV solution: magnesium sulfate
2004	CT	2		Bacterial bloodstream infection	Contamination[16]	IV flush syringes: heparin-vancomycin
2004	MO, NY, TX, MI, SD	64		Bacterial bloodstream infection	Contamination[17]	IV flush syringes: heparinized saline
2002	NC	5	1	Fungal meningitis and sacroiliitis	Contamination[18]	Spinal injections: methylprednisolone acetate
2001	CA	11	3	Five cases of bacterial meningitis; five cases of epidural abscess; one patient had an infected hip joint	Contamination[19]	Spinal or joint injections: betamethasone
2001		4		Bacterial bloodstream infection	Contamination[20]	IV infusion: ranitidine
TOTAL		**1022**	**75**			

Pew's drug safety project works to ensure a safe, reliable pharmaceutical manufacturing and distribution system. For more information, visit www.pewhealth.org/drugsafety.

References

[1] U.S. Centers for Disease Control and Prevention. Multistate Meningitis Outbreak Investigation. http://www.cdc.gov/HAI/outbreaks/meningitis.html. Accessed January 29, 2013.

[2] U.S. Centers for Disease Control and Prevention. "Notes from the field: Multistate outbreak of postprocedural fungal endophthalmitis associated with a single compounding pharmacy—United States, March-April 2012," *Morbidity and Mortality Weekly Report*. May 2012. 61(17): 310-1. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6117a5.htm. Accessed December 21, 2012.

[3] **Based on two separate outbreaks: 12 in Florida, nine in Tennessee. Respective cites below.**

Goldberg RA, Flynn HW Jr, Isom RF, Miller D, Gonzalez S. "An outbreak of streptococcus endophthalmitis after intravitreal injection of bevacizumab," *American Jounral of Ophthalmology*. February 2012. 153(2): 204-208.e1.

Frost BA, Kainer MA. "Safe preparation and administration of intravitreal bevacizumab injections," *New England Journal of Medicine*. December 2011. 365(23): 2238.

[4] Department of Veterans Affairs Office of Inspector General. "Healthcare Inspection Oversight Review of Ophthalmology Adverse Drug Events VA Greater Los Angeles Healthcare System Los Angeles, California." Report No. 12-01515-151 April 12, 2012. http://www.va.gov/oig/pubs/VAOIG-12-01515-151.pdf. Accessed January 8, 2013.

[5] Thompson, Cheryl A. "Bacteremia outbreak tied to improper filtration by compounding pharmacy," *American Journal of Health System Pharmacy*. November 2011. 68(22): 2110-11. http://www.ashp.org/menu/News/PharmacyNews/NewsArticle.aspx?id=3628. Accessed January 8, 2011.

[6] Vitello, Barbara. "Lutheran General to pay $8.25 million in baby's death," *Daily Herald*. April 5, 2012. http://www.dailyherald.com/article/20120405/news/704059806/. Accessed January 8, 2012.

[7] U.S. Centers for Disease Control and Prevention. "Deaths from Intravenous Colchicine Resulting from a Compounding Pharmacy Error—Oregon and Washington, 2007," *Morbidity and Mortality Weekly Report*. October 12, 2007. 56(40): 1050-1052. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5640a3.htm. Accessed January 8, 2013.

[8] Maragakis LL, Romanee C, Srinivasan A, et al. "Sphingomonas paucimobilis bloodstream infections associated with contaminated intravenous fentanyl," *Emerging Infectious Diseases*. January 2009. 15:12–8. http://wwwnc.cdc.gov/eid/article/15/1/08-1054_intro.htm. Accessed January 9, 2013.

[9] Gershman MD, Kennedy DJ, Noble-Wang J, et al. "Multistate outbreak of Pseudomonas fluorescens bloodstream infection after exposure to contaminated heparinized saline flush prepared by a compounding pharmacy," *Clinical Infectious Diseases*. December 2008. 47(11): 1372-9. http://cid.oxfordjournals.org/content/47/11/1372.full.pdf+html. Accessed January 9, 2013.

[10] Institute for Safe Medication Practices. Medication Safety Alert. "Failed check system for chemotherapy leads to pharmacist's no contest plea for involuntary manslaughter," April 23, 2009. http://www.ismp.org/newsletters/acutecare/articles/20090423.asp. Accessed January 9, 2013.

[11] Grissinger, Matthew RPh, FASCP. "A Fatal Zinc Overdose in a Neonate. Confusion of Micrograms With Milligrams," *Pharmacy and Therapeutics*. July 2011; 36(7): 393-394, 409. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3171817/. Accessed January 9, 2013.

[12] Perz, Joseph F. et al. "Pseudomonas putida Septicemia in a Special Care Nursery Due to Contaminated Flush Solutions Prepared in a Hospital Pharmacy," *Journal of Clinical Microbiology*. October 2005. 43(10): 5316-5318. http://jcm.asm.org/content/43/10/5316.long. Accessed January 9, 2013.

[13] Sunenshine, Rebecca. et al. "An Outbreak of Postoperative Gram-Negative Bacterial Endophthalmitis Associated with Contaminated Trypan Blue Ophthalmic Solution," *Clinical Infectious Diseases*. April 2009. 48(11): 1580-1583. http://cid.oxfordjournals.org/content/48/11/1580.full.pdf+html. Accessed January 9, 2013.

[14] Maryland State Board of Pharmacy. "Order for Summary Suspension." In the matter of Central Admixture Pharmacy Services, Inc. http://www.dhmh.maryland.gov/pharmacy/docs/FormalOrders/C/C.A.P.S%2011-15-05.pdf. Accessed January 9, 2013.

[15] Sunenshine, Rebecca H. et al. "A Multistate Outbreak of Serratia marcescens: Bloodstream Infection Associated with Contaminated Intravenous Magnesium Sulfate from a Compounding Pharmacy," *Clinical Infectious Diseases*. July 2007. 45: 527–33. http://cid.oxfordjournals.org/content/45/5/527.full.pdf. Accessed January 9, 2013.

[16] Held MR, Begier EM, 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*. July 2006. 118:e212–5. http://pediatrics.aappublications.org/content/118/1/e212.long. Accessed January 9, 2013.

[17] **Based on two sets of infections, one immediate and one delayed. Immediate infection cases included nine in Missouri, 12 in New York, 14 in Texas, and one in Michigan. Delayed infection cases included 15 in Michigan and 13 in South Dakota. Respective cites below.**

U.S. Centers for Disease Control and Prevention. "Pseudomonas Bloodstream Infections Associated with a Heparin/Saline Flush—Missouri, New York, Texas, and Michigan, 2004–2005," *Morbidity and Mortality Weekly Report*. March 2005. 54(11): 269-272. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5411a1.htm. Accessed January 9, 2013.

U.S. Centers for Disease Control and Prevention. "Update: Delayed Onset Pseudomonas fluorescens Bloodstream Infections After Exposure to Contaminated Heparin Flush—Michigan and South Dakota, 2005–2006," *Morbidity and Mortality Weekly Report*. September 2006. 55(35): 961-963. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5535a2.htm. Accessed January 9, 2013.

[18] U.S. Centers for Disease Control and Prevention. "Exophiala Infection from Contaminated Injectable Steroids Prepared by a Compounding Pharmacy—United States, July–November 2002," *Morbidity and Mortality Weekly Report*. December 2002. 51(49): 1109-1112. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5149a1.htm. Accessed January 9, 2013.

[19] Civen R, Vugia DJ, Alexander R, et al. "Outbreak of Serratia marcescens infections following injection of betamethasone compounded at a community pharmacy," *Clinical Infectious Diseases*. August 2006. 43: 831–7. http://cid.oxfordjournals.org/content/43/7/831.full.pdf+html. Accessed January 9, 2013.

[20] Selenic, D. et al. "Enterobacter cloacae bloodstream infections in pediatric patients traced to a hospital pharmacy," *American Journal of Health System Pharmacy*. July 2003. 60(14):1440-6.