

# Deaths From Contaminated Methylprednisolone Highlight Failures of Compounding Pharmacies

## Less Hospital Access to Outside Vendors and More Visits From State Pharmacy Boards

Stephen Barlas

**O**n April 11, 2011, Lisa Cornett, an inspector for the Colorado Board of Pharmacy, wrote a special memo to the board detailing her inspection of the Sky Ridge Medical Center pharmacy in Lone Tree, Colorado, 7 days earlier. She had found 15 vials of methacholine (y) phenol solution (e.g., Provocholine Kit) 5 x 5 mL (used to diagnose bronchial conditions), all of them shipped from the New England Compounding Center (NECC) in Framingham, Mass. That “bulk” shipment of compounded drugs led Ms. Cornett to check with the FDA to see whether the center was registered as a “manufacturer.” (Compounding pharmacies that sell drugs in bulk to hospitals must be licensed as manufacturers by the FDA.) This month’s Prescription: Washington column on page 7 also discusses compounded products.



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Regina Barrell, an FDA official, e-mailed back to say no, the NECC was not licensed. As a result, Colorado issued a cease-and-desist order to the NECC on April 15, 2011.

This notification triggered the Colorado Pharmacy Board to force Sky Ridge pay a \$5,500 fine based on its purchase of multiple doses without providing individual prescriptions, as state law requires.

One would think that other Colorado hospital pharmacies would have gotten the message. A year later, a second Colorado investigator, Susan Martin, found 46 vials of hyaluronidase (e.g., Hydase, PrimaPharm) containing 150 units/mL in a 1-mL injection at Delta County Memorial Hospital in Delta, Colorado. The vials had been shipped by the NECC. This discovery sparked an alert from the Colorado Board to the Massachusetts Board of Pharmacy that NECC, a non-manufacturer, was selling bulk, compounded drugs to hospital pharmacies.

The Massachusetts Board ignored the alert. Had it conducted an immediate inspection of the NECC’s facilities in Framingham, it might have discovered the nonsterile conditions that led to the bacterial contamination of injectable doses of the steroid methylprednisolone acetate doses that to date has resulted in 32 deaths and more than 400 illnesses. The Massachusetts board and the FDA eventually shut down the NECC as well as Ameridose, another compounding licensed by the FDA but linked to the NECC via management.

So far, the Colorado board has not taken final action against Delta Hospital’s pharmacy or against a third pharmacy, Exempla Good Samaritan Medical Center in Lafayette, Colorado, which received repeated bulk shipments from the NECC prior to the Sky Ridge purchases in 2011.

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Cory Everett-Lozano, spokesman for the Colorado board and the larger state department in which it is housed, said, “The board has not yet decided what to do with the hospital in Delta. It’s complicated for a couple reasons, which are not public at this time. The board will decide what to do in the near future.”

Two primary problems, each with thorny complexities, involve hospital pharmacies’ use of compounded drugs arising from the NECC contamination disaster. None of these questions has been answered or elevated to headline level. The obvious problem has to do with hospital purchases of compounded drugs from outside vendors. New federal and state laws may diminish access to those drugs and may increase their costs as outside vendors spend capital (or go out of business) to comply with new regulations. Yet hospitals themselves are significant compounders, and their adherence to U.S. Pharmacopeia Convention (USP) standards, as well as enforcement of those standards and other state laws, is likely to emerge into the spotlight too.

Until now, criticism from the press and Congress has focused narrowly on the NECC and on enforcement failures by the state of Massachusetts and the FDA. More recently, members of Congress asked state boards of pharmacy to explain their policies and enforcement actions regarding compounding. These inquiries could well lead to the requirement for boards in states such as Colorado to explain how they police hospital pharmacies and enforce (or do not enforce) compounding laws—which, of course, vary from state to state.

Hospitals depend heavily on compounding. In hearings by the Senate Health, Education, Labor and Pensions (HELP) Committee on November 15, 2012, David Miller, RPh, Executive Vice-President and Chief Executive Officer of the International Academy of Compounding Pharmacists (IACP), said:

Many, if not most, of the lifesaving intravenous drugs given in hospitals and clinics are compounded. Because hospital patients are often on multiple medications, compounding them into one treatment saves the hospital personnel time and the patient multiple injections or administrations.

William W. Churchill, MS, RPh, Chief of Service in the Department of Pharmacy at Brigham and Women’s Hospital in Boston, said that his hospital provides approximately 8 million doses of medications to its patients annually. Of this total, about 1.5 million doses are compounded sterile products and about 300,000 of those are provided by outside vendors. Those externally compounded drugs typically fall into several categories, including total parenteral nutrition, syringes for patient-controlled analgesia, epidural solutions, and intrathecal

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pain relievers.

"We have a group of chronic pain patients who can be treated only with compounded medications because we cannot get them in the concentrations the patients need from commercial suppliers," Mr. Churchill explains.

Daniel Ashby, Director of the Johns Hopkins Hospital pharmacy in Baltimore, told the Associated Press that he buys 26 drugs, out of a total of 3,000, from three compounding companies, including Ameridose. The other two companies are AnazaoHealth in Tampa, Florida, and PharMEDium of Lake Forest, Illinois.

As with many hospital pharmacies, Johns Hopkins buys compounded drugs when there is a shortage of the commercial alternative from an FDA-regulated manufacturer. Ameridose, which ceased operations on October 12, 2012, in the wake of an FDA and state inspection, sold six injectables that are on the FDA's list of drug shortages: sodium bicarbonate, succinylcholine, atropine sulfate, bupivacaine HCl, lidocaine HCl, and furosemide.

Despite this dependence, hospital pharmacists are often unaware of state and federal laws regarding compounding, the U.S. Pharmacopeia "chapters" that govern on-site compounding, and the conditions at compounding vendors such as NECC. Mr. Churchill says that Brigham and Women's Hospital was using the NECC mostly for intrathecal pain medications and compounded solutions for topical use only. Many of these solutions were compounded and sterilized from raw chemicals in order to meet patient medication needs. Brigham was using Ameridose for "sterile-to-sterile" compounded products and had been doing so for many years. It had conducted its own scheduled on-site audits of both of these facilities (NECC and Ameridose) and had been satisfied with their services until the recent problems came to light. However, the audits were not as extensive as those of the FDA or state regulatory agencies because the hospital lacks legal authority.

Theoretically, Mr. Churchill could have checked to see whether the Pharmacy Compounding Accreditation Board (PCAB), in existence since 2004 in Washington, D.C., had granted accreditation to NECC and Ameridose. The PCAB, a not-for-profit corporation, was founded by a group of pharmacy organizations, including the American Pharmacists Association, the National Community Pharmacists Association, and the IACP.

He said, "I was previously unaware that the PCAB existed. Furthermore, the value of their accreditation would have been unclear, given our lack of familiarity with the agency, its past performance, or how rigorous their accreditation process is."

Joe Cabaleiro, RPh, Executive Director of the PCAB, said that neither the NECC nor Ameridose is accredited. A list of accredited pharmacies is available at [www.pcab.org/accredited-pharmacies](http://www.pcab.org/accredited-pharmacies).

A 50-page manual, published by the PCAB, lists the conditions and procedures that pharmacies must maintain ([www.pcab.org/cms/wp-content/themes/pcab/img/pcab-accreditation-manual.pdf](http://www.pcab.org/cms/wp-content/themes/pcab/img/pcab-accreditation-manual.pdf)).

In the section on Compliance Indicators, one of the two elements is that the pharmacy demonstrates that it has access to all current and applicable standards of the USP Convention. The section on sterile compounding takes up about half a

page. It contains the only mention of USP 797 in the manual, requiring that:

sterile portions of the compounding process such as weighing must, at a minimum, be performed in equipment meeting the requirements above for nonsterile compounding. The equipment must be situated in an environment meeting USP 797 standards.

There are no references in the manual to USP Chapter 71 or 795.

*USP General Chapter 797* describes conditions and practices to prevent harm to patients that could result from microbial contamination, excessive bacterial endotoxins, variability in intended strength, unintended chemical and physical contaminants, and ingredients of inappropriate quality in compounded sterile preparations.

*USP General Chapter 795* provides guidance on applying good compounding practices in preparing nonsterile compounded formulations for dispensing or administration to humans or animals. The latest revision, which became official May 1, 2011, includes these categories:

- compounding (simple, moderate, and complex)
- definitions (e.g., beyond-use date, hazardous drug, and stability)
- criteria for compounding all drug preparations (e.g., a suitable compounding environment and the use of appropriate equipment)

*USP General Chapter 71* specifies how to conduct sterility testing of compounded drugs.

The three USP chapters are good as far as they go, but many hospital pharmacists are still unfamiliar with them. Moreover, neither state nor federal regulatory bodies inspect hospital or retail compounding pharmacies for compliance with those standards. The IACP's David Miller told the Senate Health, Education, Labor and Pensions Committee, "The IACP believes that all states must adopt mandatory compliance with USP 795 and 797 standards."

Only 17 states have done so. Some accreditation bodies appear to use the USP standards, but there is no assurance that those bodies go back to pharmacies after they are accredited to make sure that the facilities could still pass white-glove inspection.

With regard to in-house compounding, which averages about 1 million doses a year, Mr. Churchill says Brigham's pharmacy adheres to USP Chapters 797, 795, and 71. He is fortunate, because hospital leadership has supported his use of an outside expert consultant to assist his leadership team in ensuring that the hospital is complying with those USP regulations.

"The USP chapters 797, 795, and 71 have many intricate details and nuances, and that is why our consultant is so valuable to us," he observed. "But there is a lack of process and lack of resources to ensure compliance," he explained.

One might expect that the Joint Commission or the federal government—because of Medicare's conditions of participation, for example—would survey hospital pharmacies for adherence to USP standards.

"The federal government doesn't walk into a lot of hospital

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pharmacies,” Mr. Churchill noted.

“The Joint Commission doesn’t look at that issue when it visits hospital pharmacies, according to one hospital pharmacist. “They don’t have the resources,” he explained.

One former USP official said that the Joint Commission’s last official statement on USP Chapter 797 was in 2004.

“I am not sure they will even know what USP 795 and 17 are,” he added.

Amy Panagopoulos, RN, MBA, the Joint Commission’s Senior Director of Quality, Evaluation, and Strategy in the Division of Healthcare Quality Evaluation, did not provide any information on Commission’s inspections of hospital pharmacies with regard to USP standards.

Further complicating the issue of USP compliance is confusion over whether the FDA has the authority to enforce the three USP standards, even if it had the inspection staff to do so, at places like the NECC or in hospitals. What *is* clear is that the FDA has the authority to regulate manufacturers of compounded drugs, whether nonsterile-to-sterile or sterile-to-sterile. Ameridose was licensed as a manufacturer. Compounders such as the NECC that consider themselves non-manufacturers are not licensed by the FDA and are not allowed, theoretically, to supply compounded drugs to physicians or hospital pharmacies without receiving an individual prescription for that dose in advance. It is the responsibility of the state board of pharmacy to blow the whistle when violations of the individual prescription law occur. FDA-licensed manufacturers can supply compounded drugs in bulk.

In the middle of those two scenarios is “anticipatory” compounding. According to David Miller, this situation applies when a hospital or an outside vendor can make or supply multiple doses in “reasonable” quantities without a prescription based on the “historical need” of a hospital or other health care facility (such as a pain clinic).

Testimony at House and Senate hearings in November, however, produced numerous allusions to the gray areas in federal law. FDA Commissioner Margaret Hamburg explained that the agency first published a compliance guide on compounding in 1992. The compounding industry had objections to it and asked Congress to make some changes. The FDA Modernization Act of 1997 added a new section to the Federal Food, Drug, and Cosmetic Act that exempted compounded drugs from three critical provisions of the existing law. The new sections also limited advertising of compounded drugs and solicitation by compounders of prescriptions.

“These provisions were the subject of subsequent court challenges, which have produced conflicting case law and amplified the perceived gaps and ambiguity associated with the FDA’s authority over compounding pharmacies,” Margaret Hamburg explained.

Lauren Smith, MD, MP, Interim Commissioner of the Massachusetts Department of Public Health, referred to a “black hole” between state and federal regulation of compounding pharmacies.

Nonetheless, the FDA did inspect the NECC in conjunction with Massachusetts in 2002 and 2006. The FDA’s 2002 inspection was based on *MedWatch* reports of meningitis symptoms in people taking methylprednisolone and on complaints related to betamethasone. In the aftermath of the 2006 inspection, which

examined different problems, the FDA wrote a warning letter threatening to shut the facility down; that never happened.

The Massachusetts Board of Pharmacy inspected the NECC facility in Framingham in 2011, looking at sterile conditions, among other things, and rated the facility satisfactory based on that inspection. The FDA never inspected NECC after 2006.

At hearings in the House Energy and Commerce Subcommittee on Oversight and Investigations on November 14, 2012, Representative Cliff Stearns (R-Fla.), subcommittee chair, complained that the FDA repeatedly documented problems at NECC, some identical to the same problem that had caused the fungal meningitis outbreak in the fall. He asked Commissioner Hamburg whether the FDA had the authority to shut down the NECC.

“That is a very, very complex question,” she answered.

She asked both the House and Senate to clarify that ambiguity by adopting legislation that would modify the Federal Food, Drug, and Cosmetic Act to recognize two categories of compounding pharmacies: traditional and nontraditional. Pharmacies in the latter category would have to comply with federal current good manufacturing practices (cGMPs), for example, from which they had been exempted by the 1997 law. That would give the FDA more authority to deal with the kind of potential contamination that brought low Ameridose and the NECC. Besides mandating cGMP compliance for nontraditional pharmacies, the reforms suggested by the FDA would bar the compounding of most products, with certain exceptions—copies of FDA-approved drugs without a shortage designation and complex dosage forms such as extended-release products.

On November 1, Representative Ed Markey (D-Mass.) introduced a congressional reform bill, the Verifying Authority and Legality in Drug (VALID) Compounding Act (H.R. 6584). The bill would:

- ensure that compounding pharmacies operating as drug “manufacturers” are regulated as such by the FDA.
- allow compounding pharmacies with a legitimate reason to compound drugs before they receive a valid prescription to request a waiver to enable them to do so.
- permit the FDA to waive the requirement to compound drugs solely for individual patients with valid prescriptions in the event of a drug shortage or to protect public health.
- increase transparency to the public by:
  - mandating that compounded drugs be labeled to ensure that recipients know that the drugs have not been tested for safety or effectiveness.
  - publishing a “Do Not Compound” list of unsafe or ineffective drugs.
  - reporting adverse reactions to compounded drugs or to any drug that poses a safety risk.

The American Society of Health System Pharmacists (ASHP) suggests that the gray areas between state and federal regulation be eliminated. Kasey Thompson, ASHP Vice President of Policy, Planning, and Communications, said:

Previous attempts to define compounding in federal law contained certain elements that should be examined in light of practice changes since 1997. Recent legislative proposals merit further discussion

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