EDITORIALS

Compounding Errors

Jeffrey M. Drazen, M.D., Gregory D. Curfman, M.D., Lindsey R. Baden, M.D., and Stephen Morrissey, Ph.D.

Small pharmacies that produce and package (or repackage) specific drugs for individual patients are an important part of the medical landscape. These so-called compounding pharmacies formulate therapeutic and diagnostic products for physicians in practice and those engaged in research. They make individualized chemotherapeutic agents, noncommercial formulations (e.g., a liquid rather than a tablet) and doses, preservative-free and dye-free products, flavored products, combination products, products without specific allergens, diagnostic agents, and other customized products. These pharmacies are essential if our health care system is to serve populations with particular needs.

Recently, the valuable role that such pharmacies fill has been eclipsed by the havoc that can be wreaked when the materials they produce are contaminated by infectious microbes. We are in the midst of an epidemic of meningitis and deadly strokes attributable to the mold *Exserohilum rostratum.* This mold was allegedly introduced into patients during epidural injections with contaminated methylprednisolone acetate to treat back pain, a practice for which there are no compelling data.[1-4] This sort of outbreak is not new: fungal meningitis associated with *Exophiala dermatitidis* was associated a decade ago with epidural injections of methylprednisolone acetate.[5]

We believe that the best way to balance the need for "designer therapeutics" from these pharmacies with the need for product safety is to give the Food and Drug Administration (FDA) broader powers to monitor and control the agents produced by such pharmacies and any adverse events that are associated with them. The current system, in which regulation is almost entirely state-based, is clearly inadequate to protect the public health. Although Massachusetts, the home of the implicated New England Compounding Center (NECC), has instituted stronger penalties in the wake of the current fungal meningitis outbreak, and other states have increased their oversight, states lack the resources to supervise what has become a national industry with interstate activity.

FDA regulation of compounding pharmacies is not a new idea.[6] A compounding law was enacted in 1997 but was then in part overturned by the U.S. Supreme Court in 2002 in *Thompson v. Western States Medical Center.* The Court decision, which was based on arguments protecting commercial free speech, left the unchallenged provisions of the law in limbo. This led the FDA to issue new, and weaker, guidance that was apparently largely ignored by the NECC, the pharmacy most closely linked to the current cases of meningitis.

These events make it clear that we need new legislation that gives the FDA stronger and better control of compounding pharmacies. Representative Ed Markey (D-MA) has introduced such legislation: the Verifying Authority and Legality in Drug (VALID) Compounding Act.[7] The bill, if passed, would give the FDA broader powers to regulate compounding pharmacies while at the same time giving the agency the latitude to ensure that such pharmacies can continue to produce needed medical products. It would preserve state regulatory authority over traditional compounding pharmacies that make customized drugs for individual patients but would place pharmacies that operate as drug manufacturers under FDA regulation. This bill is a generally ap-

propriate step forward, and we believe it should receive strong bipartisan support.

Compounding pharmacies are businesses that produce important products for patients. These patients, however, do not have the means to check the clinical indications for the use of the products, to ensure the accuracy of the compounding, and to verify the sterility of the delivered products. The FDA has the technical expertise and drug-evaluation experience to do so and should have this authority, and there needs to be a mechanism to ensure that the funding is in place to exercise it effectively.

Regulators need a strong mandate to protect the public health. Too many patients have suffered and died as a result of compounding errors, which should be made a thing of the past.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Compelling Evidence for Coronary-Bypass Surgery in Patients with Diabetes

Mark A. Hlatky, M.D.

Seventeen years ago, the National Heart, Lung, and Blood Institute issued a clinical alert[1] that coronary-artery bypass grafting (CABG) had better rates of survival than percutaneous coronary intervention (PCI) in patients with diabetes. The alert was based on the results of the Bypass Angioplasty Revascularization Investigation (BARI) trial,[2] in which patients with multivessel coronary artery disease were randomly assigned to undergo either CABG or PCI.

This recommendation has been controversial ever since, largely because subsequent trials comparing CABG and PCI have enrolled only small numbers of patients with diabetes. A pooled analysis of 10 randomized trials involving 1233 patients with diabetes confirmed that such patients had a particular survival advantage after CABG, as compared with PCI.[3] But this evidence was discounted because drug-eluting stents were not used in PCI procedures in the earlier trials, and more recent trials in which drug-eluting stents were used[4,5] enrolled relatively few patients with diabetes. Settling this controversy would require a trial with a large number of patients with both diabetes and multivessel coronary artery disease in whom CABG or PCI would be performed with the use of contemporary methods.

Farkouh et al.[6] now report in the *Journal* the results of the definitive Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial, in which 1900 patients with diabetes (about as many patients with diabetes as in all previous trials combined) were randomly assigned to undergo either CABG or PCI with drug-eluting stents.

As a cardiologist who does not perform either procedure, I find that the FREEDOM trial provides compelling evidence of the comparative effectiveness of CABG versus PCI in patients with diabetes and multivessel coronary artery disease. After 5 years of follow-up, the 947 patients assigned to undergo CABG had significantly lower mortality (10.9% vs. 16.3%) and fewer myocardial infarctions (6.0% vs. 13.9%) than the 953 patients assigned to undergo PCI. However, patients in the CABG group had significantly more strokes (5.2% vs. 2.4%), mostly because of strokes that occurred within 30 days after revascularization. In the CABG group, the primary