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A Decade's Quest for Safer Drugs: Congressional Committee Green Lights Regulation of Drug Supply Chains and Compounding Manufacturers

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By Mary Ann Chirba and Alice A. Noble

On May 22. 2013, the Senate Health, Education, Labor and Pensions (HELP) Committee unanimously approved S.959, "The Pharmaceutical Compounding Quality and

Accountability Act," and S.957, "The Drug Supply and Security Act," (now incorporated into S. 959 as an amendment). Congressional efforts to enact comprehensive legislation to improve drug safety and secure the nation's drug supply chain have lingered for over a decade. The lack of federal uniformity has allowed a patchwork of state legislation to emerge, attracting the less scrupulous to those states with the lowest security. The issue finally gained traction among HELP Committee members when 55 people died and 741 more became ill after contracting fungal meningitis from contaminated steroid injections made by the New England Compounding Center (NECC). Committee member Sen. Pat Roberts (R-KS) stated that given prior reports of problems with NECC, this tragedy could have been averted but for a "shocking failure to act" by NECC, state and federal regulators, and Congress.

As NECC's role in the meningitis outbreak came to light,gaps in regulatory oversight did, too. The federal Food Drug and Cosmetic Act (FDCA)[1] currently recognizes only two categories of pharmaceutical manufacturers: commercial pharmaceutical companies and compounding pharmacies. To qualify as the latter under federal law, the entity must make individual or small batch, patient-specific drugs and do so only with a physician's prescription for that patient. Compounded drugs must be either be unavailable in the commercial market or needed in commercially unavailable doses or combinations. The FDCA exempts such compounders from its pre-marketing requirements applicable to commercially manufactured drugs. Thus, federal law clearly covers commercial pharmaceutical manufacturers, state law just as clearly oversees and licenses pharmacies but as the NECC case demonstrates, there is nothing clear about the responsibility for inspecting, licensing or otherwise overseeing compounders that do not fill prescriptions on a per patient basis.

Instead of compounding in response to an individual prescription, the New England Compounding Center made large batches of drugs for institutional buyers such as hospitals. Many of its drugs were commercially unavailable but some

were knock-offs of marketed FDA-approved drugs – a practice which is clearly unauthorized. NECC's business model was certainly not unique; neither was the limited and erratic response of state and federal regulators to complaints about the facility's unsafe manufacturing practices. Congress knew that large-scale compounders existed along with concerns about their safety. Several members of the Senate HELP Committee had worked on curative legislation for over ten years, but made few inroads until the NECC crisis prompted the HELP Committee to shift from park into drive.

In its current form, S. 959's Pharmaceutical Compounding Quality and Accountability Act pursues two overriding objectives: clarifying lines of regulatory authority and accountability, and ensuring that a compounded drug is what it says. As they have been, traditional compounders would continue to be regulated by state law and commercial manufacturers would remain subject to federal law. To these two categories of drug manufacturers, however, S.959 would amend the FDCA to add a third type of drug manufacturer to fit the NECC-type mode. "Compounding manufacturers" that compound sterile drugs before receiving a prescription, and ship in interstate commerce (excluding shipments within a hospital system) would now be regulated exclusively by federal law. The bill permits States to impose heavier requirements, but preempts state laws that do less.

While federally regulated, the compounding manufacturer would need to have a state-licensed pharmacist directly oversee its products. In addition, the compounding manufacturer would be subject to FDA inspection and pay a registration fee to offset the cost of the inspection program. Compounding manufacturers with gross sales of $1m or more will pay an annual $15,000 registration fee while those with lower sales will pay $5000. Reporting requirements include submitting semi-annual reports of drugs sold, and informing the FDA of serious adverse events within 15 days. The compounding manufacturer cannot wholesale its products and

must label them as “not for resale.” Failing to pay the annual registration fee, selling drugs that are not for resale, and selling drugs that are already marketed as FDA-approved will all be treated as unlawful drug misbranding. Through notice and comment rulemaking, the agency will develop a list of drugs that may not be compounded due, for example, to their complex dosage forms or their use of biologics. This list would be updated at least every 5 years.

State-regulated, traditional compounders would remain exempt from the FDCA Good Manufacturing Practices[2] that apply to commercial manufacturers. Although compounding manufacturers will also be exempt from the FDCA’s CGMPs, the FDA will develop GMPs that are suitable to this category of manufacturer.

Dealing with drug compounding was not the HELP Committee’s only concern. The national attention on drug safety spurred the Committee to act on another decade-long effort to improve the drug supply chain. S.957’s “Drug Supply Chain Security Act,” (now incorporated into S. 959), updates a system that has remained unchanged for 25 years despite quantum improvements in technology and steady increases in security threats. As Senator Michael Bennet (D-CO) observed, “we know more from a bar code on a gallon of milk than we do on a bottle of pills that could mean the difference between life and death for patients and families.”

To make the drug supply chain safer, the so-called “Track and Trace” bill would phase-in an electronic, inter-operable, unit level system designed to, again in Senator Benett’s words, provide “certainty and most importantly, get bad actors out of the drug supply chain. It will give peace of mind to the everyday family picking up their prescription at the drug store.” Senator Barbara Mikulski (D-MD) explained that the FDCA’s current drug pre-marketing requirements focus on a drug’s safety and efficacy at the point of manufacture. However, once a drug is released to the supply chain, the statute and the agency do little to prevent it from being contaminated, tampered with, or replaced by counterfeit drugs after leaving the manufacturer. As

a result, the safety of clinical practice is threatened and patients cannot be confident that the medication in their home is the safe and effective one that their doctor prescribed.

To fill this gap, the Track and Trace law would impose a blend of licensing, reporting, labeling and coding requirements on each “trading partner” at each link in the supply chain, from the manufacturer to the patient. Its major components can be summarized as follows:

1. Drugs: The Drug Supply Chain Act covers prescription drugs in their finished dosage form that are ready to be dispensed or administered to the patient without substantial further remanufacturing. It does not cover blood, blood products, compressed medical gases or other specified products.

2. Licensing: Only authorized “trading partners” can handle drugs in the supply chain from initial manufacture to the patient. Manufacturers and re-packagers must register with the FDA. Federal licensing is required of wholesale distributors and third party logistics providers (such as warehousing or transporting without assuming ownership). State licensing will continue to cover pharmacies and other persons authorized to dispense or administer drugs to the patient.

3. Individual Product Identifiers: Each unit of each drug must carry a product identifier that can be read by both person and machine and include a standardized medical identifier for the product; lot number; expiration date; and an individualized, standardized numerical identifier for each unit or package of a uniquely coded, specific product.

4. Transaction History: Each transfer of the product during the process of moving from the manufacturer to the patient or return from the patient to the manufacture, must be documented with a paper or electronic form tracking each transaction and prior transactions (or links in the

supply chain), starting with the manufacturer. It must denote the business names and addresses of each party to each transaction, and the date and shipment date of each transaction. In addition, it must state the product's name, strength, dosage, numerical drug code, container size, and lot number.

5. Suspect Products include those that are potentially counterfeit, diverted, stolen, adulterated, fraudulent, or otherwise unfit for distribution and must be reported to the FDA.

6. Secure Electronic Databases must be established or used by each trading partner to track and trace drugs, through each step of the supply chain.

All of these features will be used to develop a secure, interoperable electronic data exchange system to facilitate the exchange of information among all trading partners in order to track and trace each package through each link in the drug supply chain. This will also enable the FDA to respond quickly and appropriately to products that are known or suspected to be unsafe, and do so even at the individual package level.

In drafting both the compounding manufacturer and the drug supply bills, the HELP Committee worked closely with numerous stakeholders including patients and consumers, doctors and hospitals, pharmacies and manufacturers, and state and federal regulators. Although it approved the bills unanimously, the Committee acknowledged that S.959 (which again, incorporates S. 957) may face significant obstacles as it progresses to the Senate floor for debate and voting and, if successful, to the full Congress for more of the same. If ultimately enacted, a sizeable hurdle will remain: obtaining full funding. Each initiative will be costly, particularly developing and implementing a nation-wide secure, interoperable electronic system for tracking and tracing drugs at the package level. Hopefully, however, those costs will be offset by reductions in the many costs generated by unsafe drugs, the largest of which are obviously human lives. In the words of

Senator Burr, the bill was a “key milestone” for patients and drug supply stakeholders.

The HELP Committee seems confident that S.959 as amended to include S.957 will ultimately be signed into law given the gathering momentum for its passage. The bill’s supporters will hope Senator Mikulski was right when she stated that passage is “achievable [and] doable” because it makes sense, has bipartisan support, and “solves a problem of compelling human need.” Therefore, if it does not pass, the legislators may need to answer to their constituents because, as recognized by Senator Bennet, “though what we’re doing in some ways is historic, I think most people that we represent have an expectation that this has already been done.”

[Cross-posted from HealthLawProf Blog]

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