

New Congressional Bill Attempts to Aid Pharmacy Response to Drug Shortages

Compounding and Tracing Provisions Seek to Improve Quality of Drug Supply

Stephen Barlas

The major drug-safety bill that President Barack Obama signed on November 27 attempts to remediate two specific problems concerning pharmaceutical distribution. The Drug Quality and Security Act (H.R. 3204)¹ is intended to prevent the sale of contaminated compounded drugs such as the steroidal injections sold by the New England Compounding Center (NECC)—which caused 64 deaths—and the diversion of legitimate drugs into unsafe gray market channels, from whence they infiltrate legitimate hospital and retail pharmacies.

The compounding half of the bill is more important for pharmacists, and for those in hospitals doubly so, because they do much of the purchasing of outsourced products from companies such as NECC, which is now out of business. Hospitals are also increasingly performing a sizable amount of compounding. To the extent the bill *attempts* to improve the quality of outsourced compounded drugs, it is a potentially significant piece of legislation. Hospital compounding is unaffected by any new regulations, despite a push from the compounding industry. The drug-tracing provisions force hospitals to pay more attention to transaction statements (outlining terms of the agreement) that they receive from wholesalers, which will be either paper documents or electronic e-mails or web-based transmissions. The information in those statements will have to be verified if questions arise about the provenance of a shipment. Hospitals were specifically excluded from the requirement to “tag” repackaged drugs.

The bill started out as two separate pieces of legislation and was eventually combined into H.R. 3204. Its intentions are good, but weaknesses and half-measures threaten the effectiveness of both halves. Large anticipatory compounders² that sell to hospitals can voluntarily choose to be regulated by the FDA. They would be placed in a new regulatory category called an “outsourcing facility.” Earlier versions of the bill made federal registration mandatory for those NECC-sized compounders. The inspection standards that the FDA will have to use for these new outsourcing facilities are vague. Also, there is no additional funding for state boards of pharmacy, which will continue to inspect hospital pharmacies and local compounding pharmacies. There are some new requirements for communication between the state boards and the FDA. Miscommunication was an issue in the NECC disaster. Overall, the compounding provisions are fairly toothless, and they may do little more than complicate the problem.

The bill does not mandate “track and trace” at the item or drug-package level as did the California law, which was scheduled to go into effect in January 2015. The California law is now

pre-empted by this new federal law, however. The new federal standard requires drug manufacturers, with some exceptions, to put two-dimensional (2-D) DataMatrix bar-code product identifiers on salable units of packages after 4 years. Those bar codes must contain a Standardized Numerical Identifier (SNI), the lot number, and the expiration date on every medication package and case. For the next 4 years, however, tracing will be accomplished primarily via “Stone Age” transaction statements and information on paper.



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Skeptics Worry About Bill's Compromise Provisions

The many compromises made to achieve a passable bill dimmed enthusiasm for it in some key quarters.

“Although it is a scaled-back version of earlier legislation, this bill is an important first step in assuring that compounded sterile products are prepared safely,” says Paul Abramowitz, Chief Executive

Officer of the American Society of Health-System Pharmacists (ASHP).³ This year, the Department of Health and Human Services’ Office of Inspector General reported that nearly all of the hospitals it surveyed use compounded sterile drugs and about 75% have purchased some compounded drugs from an external pharmacy.

Edith A. Rosato, RPh, IOM, Chief Executive Office of the Academy of Managed Care Pharmacy, is more specific in her criticism. She is concerned that the bill’s voluntary registration scheme in the compounding section will not achieve the main goal (i.e., protecting the public from the unauthorized compounding of drugs). She adds:⁴

AMCP is also concerned about another regulatory wrinkle in the bill. A licensed pharmacy (which is already regulated by state pharmacy boards) that registers as an ‘outsourcing facility’ will then be subject to FDA regulation. We believe this dual regulatory scheme will lead to administration and regulatory confusion, creating opportunities for gaps in responsibility and accountability.

The FDA moved quickly to implement the compounding provisions. The requirements as to which drugs can be compounded by outsourcing facilities and how these facilities will be regulated are subject to a fast, one-year rule-making process. On December 2, the agency published some guidance documents.

The specter of drug shortages hung over both original bills. Hospital pharmacists in particular opted either to compound their own drugs if a manufacturer’s product suddenly became unavailable or to turn to large compounders, such as NECC, when a shortage developed. Similarly, when confronted with a particular shortage, gray-market wholesalers have come out of the woodwork to offer hospital pharmacists the short-supply

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drug, which might not have been properly stored since leaving the packaging line of its legitimate manufacturer, or it could even be a counterfeit item.

The FDA has been trying to eliminate shortages administratively. Its latest step came at the end of October, when it issued a proposed rule that would require manufacturers of valuable drugs to notify the FDA within 60 days of a permanent discontinuance or an interruption that is likely to be serious. But if a 60-day advance is not possible, the manufacturer must do so within 5 days *after* the supply disruption. The proposed rule doesn't provide the FDA with any additional tools with which to *prevent* or mitigate a drug shortage.

Compounding Provisions Are a Wing and a Prayer

In the case of a drug shortage, the congressional bill does nothing to limit the compounding that hospitals can perform themselves, nor does it place limits on the outsourcing facilities from which the hospitals can purchase products. All outsourcers in business today can stay in business tomorrow. The hope is that a large number of major outsourcing anticipatory compounders will voluntarily register for FDA regulation. If they pass muster during an FDA inspection, they will have an informal seal of approval and theoretically can be the compounders that hospital pharmacies turn to during a shortage.

However, it is not clear how big this new class will be. To begin with, the cost of entry is a minimum \$15,000 annual fee. Each outsourcing pharmacy must then meet standards to be hammered out by the FDA. For a company to even be able to compound a drug, the FDA must first certify that there is a clinical need for a drug to be produced by an outsourcing facility or that it is a drug in short supply. The drug has to be compounded according to the U.S. Pharmacopeia, the National Formulary, or another compendium or pharmacopeia recognized by the FDA. This means that the FDA will be inspecting these outsourcing facilities to determine whether they comply with USP chapters 71, 795, and 797.

There is a long list of disclosures that the outsourcing pharmacy must provide on the drug's label. The bill sets no specific schedule for inspection of these compounding facilities. The agency is supposed to come up with a risk-based schedule for inspection, which takes into account the facility's history, the inherent risk of the drugs it is compounding, and whether the premises have been inspected within the previous 4 years. No minimum time between inspections has been established. In fact, the guideline could even be read to imply that the FDA generally doesn't have to inspect more frequently than once every 4 years.

The final bill is silent on the current Good Manufacturing Practice (cGMP) requirements that this new category of outsourcing pharmacies will have to meet; no quality standards are mentioned. The absence of specific data about inspection was an issue during the Senate's consideration of its bill. The compounding industry complained that when the FDA inspected its facilities, which wasn't very often, the FDA sought compliance with the cGMP standards written for conventional drugs.

In a May 2013 letter to the two Senate committee chairmen who were key authors of that body's compounding legislation, Michael A. Koch, RPh, MBA, Vice President of Marketing and Support Services, Central Admixture Pharmacy Services, Inc.

(CAPS), argued that companies like his are not "manufacturers," such as the PfiZers and Eli Lillys of the world. He wrote:⁵

[The] FDA has recognized that a compounding pharmacy does not perform many of the operations of a manufacturer of finished pharmaceuticals. However, in many cases, the FDA has claimed that particular cGMP obligations apply to particular compounding operations, and these claims have varied widely depending on the particular views of the specific FDA investigator conducting an inspection. The result has been confusion in the regulated industry and an unfair and uneven enforcement environment.

As a result of that complaint, the Senate included a provision in its version of the bill that would require FDA to promulgate a new set of cGMP regulations applicable specifically to "compounding manufacturers." The final bill dropped that provision.

Joseph M. Hill, Director of Federal Legislative Affairs at ASHP, said in an interview, "Our expectation is that the FDA will be inspecting based on cGMPs, and if it has to develop new ones for outsourcing compounders, it will do so."

In an e-mail, David G. Miller, RPh, Executive Vice President and Chief Executive Officer of the International Academy of Compounding Pharmacists (IACP), explains that the final bill falls short in another area:

It's important to note that the new 'outsourcing facility' is not only voluntary in nature; it does not have to be a pharmacy. In fact, one of IACP's primary concerns is that because anyone can establish an outsourcing facility, so long as they have a pharmacist compounding or supervising the compounding of medications, there may be new entities emerging which are not required to be overseen or comply with the laws and regulations of a state board of pharmacy. Because the wording of H.R. 3204 in this section is so broad, there is no way to know which pharmacies may pursue becoming outsourcing facilities or how many physicians, clinics, health systems, pharmaceutical companies, etc., may decide to establish and operate an outsourcing facility.

Richard Kruzynski, RPh, President of PharMEDium, a large-scale anticipatory compounder, says his company will register in the new category.⁶ In the past, PharMEDium, as an independent hospital-supply compounder, had to obtain licenses from both state boards of pharmacy and one as a "manufacturer" from the FDA. The requirements in either case did not quite fit PharMEDium, which is neither a corner pharmacy nor a major drug manufacturer. The "outsourcing facility" category fits PharMEDium's operations more precisely. As a result of becoming an outsourcing facility, PharMEDium will have to submit reports to the FDA regarding production volumes and adverse events; it will also have to meet new labeling requirements.

Mr. Kruzynski says that he has no problems with those requirements but hopes that FDA inspections in the future will differ in nature from previous inspections. He expects the FDA to develop cGMPs that recognize the differences between major drug companies, which can produce 50,000 doses of a standard dose premixed drug using large mix tanks, and an anticipatory compounder like PharMEDium, which produces small batches (e.g., 10–20 units) for each hospital it works with. PharMEDium's model is "sterile-to-sterile"; the drug vials arrive sterile from pharmaceutical manufacturers. This practice

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is consistent with 99% of hospital needs for anticipatory-class compounds, does not include a big mix tank, and does not create sterile water.

Drug-Tracing Provisions Exempt Hospitals as ‘Repackagers’

The drug-tracing portion of the Drug Quality and Security Act has a much less significant impact, both immediate and long term, on pharmacies. Drug manufacturers are its sole, near-term target, and even there, the final bill appears to relax even the already diminished requirements in the bills that Congress passed earlier in the year.

Starting in January 2015, manufacturers must provide the subsequent owner of a “lot” of product with a transaction’s history, information, and statement in a single paper document or in electronic format. Four years after passage of the bill, that information must be transmitted electronically in the form of a product identifier regarding the individual salable units of the drugs, with some exceptions. The electronic identifier will be specific to the individual salable package. It will have to include the National Drug Code (NDC), a unique alphanumeric serial number containing up to 20 characters—together referred to as the Standard Numerical Number (SNI)—and the lot number and expiration date. This identifier will be printed as both a 2D bar code and in “human-readable” form.

There was some concern that hospital pharmacies would be classified as “repackagers” under the law. In some cases, repackagers must put product identifiers on small packages, but the bill calls pharmacies “dispensers” and relieves them of having to pass transaction information when they relabel products or of having to place product identifiers on salable units.

Manufacturers have already moved, albeit in small numbers, to label individual drug packages with electronic SNIs. The FDA has produced guidance on how those SNIs should be displayed, and almost all major companies are following the guidelines published by GS1 Healthcare, the international standards organization.

The key initial responsibility of pharmacists is to obtain transaction data and statements from wholesalers. The pharmacy can sign an agreement with its wholesaler to allow the wholesaler to store this information. These details must be included:

- proprietary or established name or names of the product
- strength and dosage form of the product
- National Drug Code number of the product
- container size
- number of containers
- lot number of the product
- date of the transaction
- date of the shipment if it occurs more than 24 hours after the date of the transaction
- business name and address of the person from whom ownership is being transferred
- business name and address of the person to whom ownership is being transferred

A pharmacy cannot accept any product after January 1, 2015, unless it comes with this transaction information and a transaction statement.

Verifying the Key Responsibility of Pharmacies

In many cases, wholesalers will be handing over transaction information and statements (the latter must contain some specific elements too) in paper form, as they have been doing for some time. However, some wholesalers may begin sending that information in electronic form, and some may already be doing so.

“The electronic data could be provided to the hospital pharmacy as a B2B [business-to-business] data transaction to the pharmacy system or potentially through a web portal,” says Brian Daleiden, Vice President of Marketing at Tracelink.

Some hospitals will have to make hardware, software, and process changes starting on January 1, 2015. Any changes will be dedicated to allowing them to verify and reconcile received product shipments against transaction data received from the supplier during pharmacy receiving operations. Hospitals will also need a repository to store transaction data records, documents, and other information about investigations of “dubious” products for 6 years after the date of the transaction (e.g., purchase of the product) or at the investigation’s conclusion. The hospitals, though, can contract with their wholesalers to establish that repository. Brian Daleiden explains:

For the receipt, storage, and update of paper-based transaction data, the relative changes to current hardware and software systems might be relatively minor outside of modifications to the document-management system. For the receipt, storage, and update of electronic transaction data, I expect that the typical hospital pharmacy system was not designed to manage the product, production, transaction, and attestation statement information [that] they will be required to receive for Drug Quality and Security Act compliance.

Four years after the bill becomes law, manufacturers will have to put an electronic product identifier on each salable package, printing the SNI in human-readable form as well. At that point, pharmacies will be able to verify individual items instead of lots. During the first 4 years, the transaction statement includes only the lot. The promise of electronic verification of the individual salable unit, instead of the multiproduct lot, is great. Recalls will be cheaper and faster, and there will be gains for pharmacy inventory management—but only if pharmacies buy 2D barcode readers. There is no requirement that they do so; they will not have to, because the item-level product identifier will also be printed in human-readable form on the salable package.

Verifying an individual unit, based on ostensibly human-readable product identifiers, could turn out to be an exercise of looking for a needle in a haystack. If a pharmacy receives a recall notice or a similar request from a state or federal official, the pharmacy must quarantine the product and conduct an investigation. There are specific requirements for what this investigation must entail and how quickly it must be done, generally within two business days.

Bob Celeste, Senior Director of Health Care for GS1 Healthcare, explains that not all human-readable SNIs are understandable. The GS1 put out guidance earlier this year on that subject, urging, for example, that manufacturers not mix numbers and letters in any alphanumeric coding.

“Sometimes zeroes can be mistaken for the letter ‘O,’” he said.

There has also been some uncertainty in the industry about

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whether to put the code “(17)” in front of the numeric representation of the expiration date, as recommended in the GS1 guidance, or whether to simply use the letters “exp” before the expiration date. These kinds of matters relating to the understandability of SNIs need to be resolved and ideally will be, through the FDA rule-making process.

The legislation is confusing. When it mentions an “investigation” that a pharmacy must conduct, it specifies additional steps that must take place after 7 years. This includes verifying that the product identifier (including the SNI) of at least three packages, or 10% of such suspected products (whichever is greater), or all packages (if fewer than three), corresponds with the product identifier for the product.

Presumably, by this time, manufacturers will have electronic databases that list all of their SNIs so that they can quickly respond to a request for verification. However, there is no requirement that a manufacturer must develop a database. It is possible that even after 7 years, some pharmacies will be verifying products using the human-readable SNI.

Conclusion

The drug-safety bill may be envisioned as a full-scale, interoperable, electronic item-level track-and-trace system, like California’s, after 10 years, but only if a number of conditions are met. Along the way, the FDA will have to hold numerous public meetings, issue multiple guidance documents, and initiate various rules, including one to allow dispensers, such as hospital pharmacies, to receive exemptions for any final interoperable tracking system. Thus, the package-tracking provisions of the Drug Quality and Security Act shouldn’t keep any pharmacists up at night. For the next 7 years, they simply have to make sure that they and their wholesalers are providing correct transaction information and statements, which they may already be doing.

The bill’s provisions may lead to a shakeup of the anticipatory compounding industry, with the cream rising to the top as the most credible pharmacies seek and gain FDA registration. Hospital pharmacies will vie to skim that cream, but will there be enough of it?

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