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IN THIS ISSUE

What's in a Name? Quantifying the Economic Value of Label Information
by Anthony J. Anscombe

Skinny Labeling after *Hospira v. Burwell:* An End-Run around Pharmaceutical Method of Use Patents?
by Herman H. Yue & John D. Garretson

Solving or Compounding the Problem?—Issues in the Compounding & "Transaction Trinity" under the Drug Quality and Security Act

By Sung Park, John Johnson III, and Benjamin L. England

In 2013, Congress amended the federal Food, Drug, and Cosmetic Act (FDCA) through the Drug Quality and Security Act (DQSA). DQSA is composed of two titles: Title I of DQSA (Compounding Quality Act – CQA) created a new section 503B whereby mass-compounding pharmacies can be designated "outsourcing facilities," while Title II (Drug Supply Chain Security Act – DSCSA) created a new system to identify and trace prescription drugs as they are distributed in the United States.

Through DQSA, Congress intended to address several issues at once. In CQA, Congress sought to address the jurisdictional confusion highlighted in the infamous New

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England Compounding Center (NECC) incident[1] by creating new entities called "outsourcing facilities" and giving FDA full jurisdiction to regulate those entities. In addition, through DSCSA, Congress sought to address the seemingly growing counterfeit drug problem by strengthening the pedigree requirement and establishing a mechanism to remove illegitimate products.

It seems, however, that Congress did not closely examine DQSA to determine its safety or efficacy prior to passing the law. DQSA is not effective because its provisions actually preclude outsourcing facilities from achieving their intended functions, and it is not safe because it does not provide sufficient protections for confidential information that trading partners must provide to dispensers under the law.

Outsourcing Facilities' (in)Ability to Address Prescription Drug Shortages

Despite what Congress intended, CQA inadvertently prevents outsourcing facilities from compounding *any* drugs, because as currently written, CQA does not allow any drugs containing the same Active Pharmaceutical Ingredient (API) as an approved drug to be compounded.

Through CQA, Congress sought to achieve two goals: first, CQA increased safety of mass-compounded drugs by creating new entities called "outsourcing facilities" and subjecting them to FDA's oversight, including inspections. With this new status, Congress created a definitive regulatory category for mass-compounding pharmacies, as compared to the unclear line between a pharmacy and a manufacturing facility. Second, Congress also hoped to solve some of the prescription drug shortage problems by having outsourcing facilities only compound drugs on FDA's drug shortage list.

Under CQA, outsourcing facilities are defined as entities (1) engaged in compounding of sterile drugs, (2) registered as outsourcing facilities with FDA, and (3) complying with all requirements of DQSA.[2] Once registered, an outsourcing facility can mass-compound drugs without having to rely on individual patient-specific prescriptions.

Importantly, entities that register as outsourcing facilities receive significant benefits under CQA. The drugs compounded by an outsourcing facility are exempt from key provisions of FDCA, including section 505 (Approval of drugs under new drug applications (NDAs) or abbreviated new drug applications (ANDAs)); section 502(f)(1) (requirement to label products with adequate directions for use) and; section 582 (DQSA Title II's transaction record requirements). These are significant benefits, as they remove the threat that FDA may suddenly allege the facility is making and distributing unapproved new drugs and/or misbranded drugs.

In return for providing exemption from these requirements, DQSA subjects outsourcing facilities to certain requirements that traditional compounding pharmacies are not subject to. Some of these requirements as listed in section 503B(a) are:

1. Registration, reporting, and fees;
2. Prohibition on using Active Pharmaceutical Ingredients (API) to compound, unless:
   a. The API is on FDA's clinical need list, or the finished drug is on FDA's drug shortage list,
   b. The API complies with established monographs and,
   c. The API is manufactured by an FDA-registered facility;
3. A drug compounded by an outsourcing facility is not "essentially a copy of an approved drug";
4. An outsourcing facility may not sell its compounded drugs to entities other than individual patients or healthcare facilities; and
5. The label of a drug compounded by an outsourcing facility must bear certain statements, such as the statement "This is a compounded drug."

Of these, perhaps two of the most significant restrictions are that (1) an outsourcing facility can only compound drugs on FDA's drug shortage list established under section 506E[3] and, (2) an outsourcing facility may not compound a drug that is "essentially a copy of an approved drug."[4]

The first restriction reflects the congressional intent of reducing prescription drug shortages by enticing outsourcing facilities to compound drugs in FDA's drug shortage list. The second restriction against mass-compounding of an approved drug prevents outsourcing facilities from circumventing the new drug approval process by mass-compounding drugs with approvals. This restriction seems appropriate, especially as one of CQA's purposes was to properly regulate mass-compounding pharmacies that are acting as drug manufacturers (e.g., NECC).

It seems, however, that Congress over-exerted itself in attempting to prevent outsourcing facilities from manufacturing drugs, because this provision essentially guts the outsourcing facilities' ability to mass-compound *any* drugs, whether the drugs are on the drug shortage list or not.

Under section 503B(d)(4), "essentially a copy of an approved drug" is defined as:

> (A) a drug that is identical or nearly identical to an approved drug, or a marketed drug not subject to section 503(b) and not subject to approval in an application submitted under section 505, unless, in the case of an approved drug, the drug appears on the drug shortage list in effect under section 506E at the time of compounding, distribution, and dispensing; or
>
> (B) a drug, a component of which is a bulk drug substance that is a component of an approved drug or a marketed drug that is not subject to section 503(b) and not subject to approval in an application submitted under section 505, unless there is a change that produces for an individual patient a clinical difference, as determined by the prescribing practitioner, between the compounded drug and the comparable approved drug.

Section 503B(d)(4) defines the term "essentially a copy of an approved drug" in two ways. First, a compounded drug is essentially a copy of an approved drug if it is identical or nearly identical to a drug with an approved New Drug Application (NDA) or an Abbreviated New Drug Application (ANDA)—unless it is on FDA's drug shortage list—or if it is identical or nearly identical to an over-the-counter drug.

Second, a compounded drug is essentially a copy of an approved drug if the drug contains the same Active Pharmaceutical Ingredient (API) as an ANDA drug, or an OTC drug, unless the drug is compounded pursuant to a patient-specific prescription.

However, Congress must not have carefully considered the effect of the disjunctive "or" that connects parts (A) and (B). Because the two sections are connected by an "or," a compounded drug must avoid both definitions in order to avoid section 503B(a)(5)'s prohibition on compounding essentially a copy of an approved drug. But here, no drug compounded by an outsourcing facility can avoid both definitions of parts (A) and (B). While a drug could avoid part (A)'s definition by being on FDA's drug shortage list, that drug can never avoid part (B)'s definition, because it would necessarily contain the same API as that of an approved drug if it wants to be effective for the same indications.

To make this easier to understand, let us hypothesize that an FDA-registered outsourcing facility is planning to compound epinephrine injection drugs, which are currently listed in FDA's drug shortage list. Several manufacturers, such as Hospira and Par Pharmaceutical, currently hold ANDA approvals for manufacturing and marketing of the drug.

The outsourcing facility can avoid compounding "essentially a copy of an approved drug" as defined in part (A) because epinephrine injection drugs are on FDA's drug shortage list. Therefore, the compounded drug would not be a copy of an approved drug as defined under CQA.

There is no way, however, for the outsourcing facility to avoid the definition of part (B). In order for the compounded drug to be effective for the same indications as the drug in shortage, the drug would need to include, at a minimum, the API epinephrine. Yet, doing so would cause the drug to run against part (B)'s definition, because the compounded drug contains the same API as that of Hospira's and Par's approved versions of the drug.

Therefore, an outsourcing facility could not compound any drugs on the drug shortage list without violating the prohibition regarding "essentially a copy of an approved drug." Of course, an outsourcing facility could avoid part (B)'s definition by only compounding drugs based on a patient-specific individual prescription, but this would nullify Congress's intent of allowing mass-compounding of drugs on the drug shortage list. In fact, the only drugs outsourcing facilities can compound under the current law are drugs with undetermined approval status, such as DESI-pending drugs.

Despite this structural problem of the statute, FDA has been issuing guidance documents that presume an outsourcing facility's ability to compound drugs without patient-specific prescriptions.[5] Likewise, the industry also has been following suit by registering as outsourcing facilities with FDA, and informing eligible compounding facilities about the new opportunity. While this unlawful dance may continue in the near future because no party seemingly has an interest in challenging the legality of both parties' conduct, industry would be well-advised to remain vigilant about this deficiency in the

statute, which in fact does not allow compounding of any drugs on FDA's drug shortage list.

Where's the Confidentiality and Protection of Trade Secrets for Transactional Information?

The Drug Supply Chain Security Act (DSCSA) is Congress's second attempt to establish a regulatory regime to ensure that the drug supply-chain only consists of legitimate products. Through the trinity of transactional items (transactional statement, information, and history), each participant in the drug supply chain must collect and transmit information to verify a product's legitimacy. However, although the transactional trinity requires disclosing several pieces of confidential commercial information, DSCSA fails to adequately protect against illegitimate use of this information.

The concern with counterfeit drugs is not a new problem, and Congress first addressed the issue in 1965 in the Drug Abuse Control Amendments.[6] The first systematic approach occurred in 1988 with the passage of the Prescription Drug Marketing Act (PDMA).[7] This act included a prohibition on prescription drug re-importation, requirements regarding wholesale distributor state licenses, and pedigree requirements for unauthorized wholesale distributors.

Despite passage in 1988, PDMA's pedigree requirement was slow to be implemented by FDA. In 1999, FDA promulgated the pedigree regulations and required the pedigree to include additional information beyond what was stated in PDMA, such as container size and number of containers.[8] A group of drug wholesalers successfully obtained a court injunction against FDA's implementation of these requirements. The court justified this action by asserting that the agency's regulation did not comport with the statutory text in PDMA.[9]

In DSCSA, Congress picked up where FDA left off by including in the statute aspects of the transactional information that a court previously enjoined FDA from requiring under the PDMA regulation. Thus, a firm must provide for each transaction the container size, number of containers, lot number of the product, the date of transaction, and date of shipment (if more than 24 hours after date of transaction), among other requirements.[10]

This transactional information is rational when examining the system from a regulatory standpoint of traceability. For example, knowing the quantity a trading partner received is a valuable piece of information to ensure that you are receiving legitimate goods. It would be suspicious if you received a total of 600 cartons of a product with the same transaction history over a time period where the distributor only received 500 cartons.

However, this information also provides important insight into the commercial practices of a supplier.

Recognizing the sensitive nature of this information, Congress mandated that drug wholesalers must maintain the confidentiality of transactional items that they receive.[11] Despite rightfully imposing this obligation on wholesalers, a similar requirement of confidentiality for dispensers is worrisomely absent.[12] It is unclear why Congress did not impose a similar obligation on dispensers as well. While one hopes this was an oversight, from a legal standpoint, the courts would assume that Congress meant to do it.[13] The only mention of confidentiality with dispensers is when they engage a third party to maintain the transaction trinity. Here, the confidentiality requirement is on the third party and not the dispenser.[14]

In other sections, Congress required that FDA issue guidance establishing systems for secure and "confidential" information transfer. This only addresses the secureness of the information transfer and does not obligate a dispenser to maintain the confidentiality of the information once it is received.[15] In this way, Congress took an approach that companies must disclose first, and figure out protecting confidentiality later.

Congress largely has left wholesale distributors to fend for themselves to protect their confidential information. If a wholesaler fails to maintain confidentiality, it is technically a prohibited act.[16] However, it is unlikely that this prohibition will scare wholesalers intending to leak information, as the likelihood of enforcement is low due to enforcement priorities and the ambiguity of the term "confidentiality."

FDA has limited resources, which it generally focuses on health and safety issues. It is unlikely that the agency would go after a violator unless it is flagrantly abusing the system. Compounding this is the issue of what would constitute breaching confidentiality. While disclosing the information to a third party is clearly prohibited, would using the information to one's own commercial advantage constitute a breach of confidentiality?

This leaves a wholesaler to look to a remedy in state trade secret laws or unfair competition laws, but these offer little comfort. First, this system is reactive and can only be invoked after the damage is done. Second, wholesalers would have to deal with non-uniformity in the protections offered under the state law. This is both ironic and unsatisfactory given that DSCSA sought to create a national uniform tracing system that preempted state law.[17]

Recognizing these gaps, we recommend that Congress fill these holes by amending the law. First, it should impose a confidentiality requirement on dispensers similar to the requirement placed on drug wholesalers. Second, it should create a national private right of action, whereby drug wholesalers can defend against firms that wrongly use the transactional trinity for commercial advantage. Beyond establishing the right of action, this revision needs to detail what would constitute an abuse of confidentiality.

1. NECC was a compounding pharmacy that sold compounded drugs to other pharmacies and practitioners. NECC compounded many of its drugs without first obtaining prescriptions for individual patients. NECC's contaminated drugs were shipped across the nation, and ended up causing a meningitis outbreak, resulting in 64 deaths. *See* Jess Bidgood and Sabrina Tavernise, *Pharmacy Executives Face Murder Charges in Meningitis Deaths*, New York Times, Dec. 17, 2014.
2. FDCA, section 503B(d)(4)(A).
3. FDCA, Section 503B(a)(2)(ii).
4. FDCA, Section 503B(a)(5).
5. See, *e.g.*, FDA, Guidance for Industry, Registration of Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act (2014).
6. Public Law, 89-74 (July 15, 1965).
7. Public Law, 100-293 (April 22, 1988).
8. 21 C.F.R. 203.50(a).
9. *See* RxUSA Wholesale, Inc., v. Dept. of Health and Human Servs., 285 Fed. Appx. 809 (2d Cir. 2008).
10. FDCA, Section 5
11. FDCA, Section 582(c)(1)(A)(v).
12. *See* FDCA, Section 582(d).
13. *See* Russello v. United States, 464 U.S. 16, 23 (1983) ("'Where Congress includes particular language in one section of a statute but omits it in another section of the same Act, it is generally presumed that Congress acts intentionally and purposely in the disparate inclusion or exclusion.'" *quoting* United States v. Wong Kim Bo, 472 F.2d 720, 722 (5th Cir. 1972)).
14. FDCA, Section 582(d)(1)(B).
15. *See* FDCA section 582 (i)(1)(B); *see also* section 582 (g)(1)(E)(ii) and (h)(3)(iii).
16. FDCA, Section 301(t).
17. FDCA, Section 585.