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Drug Supply Chain Security: Wholesalers Exchange Most Tracing Information

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Daniel R. Levinson
Inspector General

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Report in Brief
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Why OIG Did This Review

Drug diversion, counterfeiting, and the importation of unapproved drugs may result in potentially dangerous drugs entering the drug supply chain, posing a threat to public health and safety. To enhance drug supply chain security, the Drug Supply Chain Security Act (DSCSA) requires trading partners in the drug supply chain to create a record of each drug product transaction. The Food and Drug Administration (FDA) can then use such tracing records to investigate suspect and illegitimate drug products and potential diversion.

This study is the first in a series of Office of Inspector General (OIG) examinations of drug supply chain security that will follow the implementation of various DSCSA provisions.

Future OIG work will examine dispensers' exchange of drug product tracing information as well as test whether drug product tracing information can be used to trace drug products through the entire drug supply chain.

How OIG Did This Review

In December 2015 and January 2016, we interviewed 31 of 353 wholesalers identified in FDA's database. These wholesalers from across the country were of varying sizes and included the three largest wholesalers. We also reviewed examples of drug product tracing information provided by each of the 31 wholesalers.

What OIG Found

We found that all 31 selected wholesalers exchange drug product tracing information. Of these, 17 wholesalers – including the 3 largest wholesalers that account for more than 80 percent of drug distribution revenue – exchange all required drug product tracing information. The remaining 14 exchange most elements of drug product tracing information but are missing a few of the required elements. Missing information among these wholesalers raises concerns that complete drug product tracing information may not always be available to support investigations into suspect and illegitimate drug products and potential diversion.

Key Takeaway

We found that selected wholesalers were exchanging drug product tracing information and about half – including the three largest wholesalers that account for more than 80 percent of drug distribution revenues – exchange all required information. Complete drug product tracing information can improve drug supply chain security by supporting FDA and other State and Federal agencies' investigations of suspect and illegitimate drug products and potential diversion.

The 31 wholesalers in this study exchange drug product tracing information using a wide variety of transmission modes and formats, taking advantage of the latitude provided by DSCSA and FDA guidance. Wholesalers may eventually coalesce around one means of exchange as DSCSA requirements are implemented. However, at this time, a standardized way to exchange this information has not emerged.

What OIG Recommends and How the Agency Responded

To ensure that all wholesalers comply with the DSCSA, we recommend that FDA offer technical assistance where appropriate. Specifically, we recommend that FDA provide technical assistance to wholesalers regarding direct purchase statements, exempt drugs, and exchanging drug product tracing information for transactions involving 340B-covered entities and 340B contract pharmacies. FDA concurred with all of our recommendations.

Full report can be found at http://oig.hhs.gov/oei/reports/oei-05-14-00640.asp

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BACKGROUND

Objectives

To describe selected wholesalers' exchange of drug product tracing information in the drug supply chain as required by the Drug Supply Chain Security Act (DSCSA).

Potentially dangerous drugs entering the drug supply chain pose a threat to public health and safety. In one notable example from 2012, several medical practices purchased counterfeit versions of Avastin, an injectable cancer drug, from a foreign supplier. The counterfeit versions contained no active ingredients to treat cancer.[1] In addition, a 2012 congressional report raised concerns about the safety of drugs that pass through complex distribution networks that often involve many secondary wholesale distributors that do not always purchase drugs directly from drug manufacturers.[2]

To strengthen drug supply chain security, Congress passed the DSCSA in November 2013, which established, among other things, drug product tracing requirements for certain prescription drugs.[3] The DSCSA generally requires that trading partners in the drug supply chain (i.e. manufacturers, repackagers, wholesale distributors, and dispensers (primarily pharmacies)) exchange information about each drug every time a transfer of ownership occurs, creating a record of each trading partner's ownership of the drug. This information should help the Food and Drug Administration (FDA), other State and Federal agencies, and other stakeholders investigate and identify harmful drugs in the drug supply chain to prevent further distribution and facilitate efficient drug recalls.

This study is the first in a series of examinations by the Office of Inspector General (OIG) of drug supply chain security and the DSCSA. This series will evolve as new DSCSA provisions become effective. Future OIG work will examine dispensers' exchange of drug product tracing information as well as test whether drug product tracing information can be used to trace drugs through the entire drug supply chain.

The Drug Supply Chain Security Act

The DSCSA, enacted as part of the Drug Quality and Security Act in November 2013, created a Federal framework to address vulnerabilities in the drug supply chain.[4] The DSCSA provides FDA and appropriate State and Federal officials with new tools to trace drugs through the drug supply chain. For example, in the event of a recall or discovery of counterfeit drugs, this system could provide FDA with information to determine at what point in the drug supply chain the problem originated.

The Drug Supply Chain

The distribution of drugs from the drug manufacturer to the patient may involve a variety of trading partners, including drug manufacturers, repackagers, wholesale distributors (hereinafter referred to as wholesalers), and dispensers.[5, 6, 7, 8] Generally, drugs pass between trading partners until they ultimately reach the dispensing pharmacy and the patient. See Exhibit 1 for one way drugs might flow through a wholesaler in the drug supply chain.

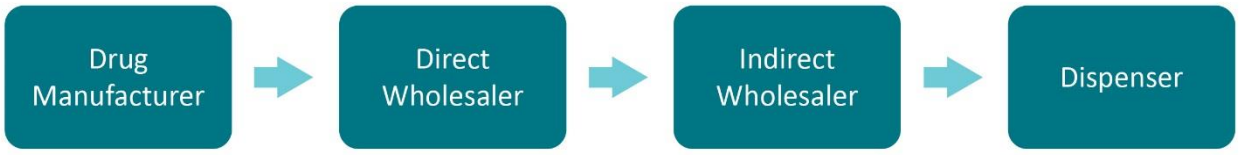
Exhibit 1: Drug Supply Chain Process Example

Source: OIG analysis of the drug supply chain, 2016.

In Exhibit 1, the wholesaler purchases a drug directly from the drug manufacturer. A wholesaler purchases directly when it purchases from the drug manufacturer, from the exclusive distributor of the drug manufacturer, or from a repackager that purchased directly from a drug manufacturer (hereinafter, referred to as the direct wholesaler for relevant transactions).[9]

Alternatively, drugs may pass through additional wholesalers in the drug supply chain. For example, some transactions may involve an additional wholesaler that did not purchase directly from the drug manufacturer, the exclusive distributor of the drug manufacturer, or a repackager that purchased directly from a drug manufacturer (hereinafter, wholesalers engaged in these transactions are referred to as indirect wholesalers for relevant transactions).[10] See Exhibit 2 for how drugs might flow through the drug supply chain when multiple wholesalers are involved.

Exhibit 2: Drug Supply Chain Process Example with Multiple Wholesalers



Source: OIG analysis of the drug supply chain, 2016.

DSCSA Requirements on Exchanging Drug Product Tracing Information

Starting January 1, 2015, the DSCSA required wholesalers and other trading partners to exchange drug product tracing information for transactions involving a product.[11] DSCSA defines a 'product' as "a prescription drug in a finished dosage form for administration to a patient without substantial

further manufacturing" (hereinafter we refer to 'product' as a 'drug product').[12, 13] DSCSA defines a 'transaction' generally as "the transfer of [drug] product between persons in which a change of ownership occurs."[14]

Drug product tracing information includes three components: transaction information, transaction history, and a transaction statement. Transaction information is composed of 10 elements that describe the transaction, including drug product information, such as the National Drug Code (NDC) and dosage form.[15, 16] Transaction history is a statement that shows the transaction information for each prior transaction.[17] The transaction statement is a statement that the trading partner transferring ownership provides to the subsequent purchaser.[18] See Appendix A for complete definitions.

Direct wholesalers do not have to send three of the 10 elements of transaction information (lot number of the product, initial transaction date, and initial shipment date from the drug manufacturer) to the subsequent purchaser (hereinafter referred to as customer). However, direct wholesalers must provide the customer with a statement indicating that they purchased the drug product directly from the drug manufacturer, exclusive distributor of the manufacturer, or repackager that purchased the product directly from the drug manufacturer (hereinafter referred to as a direct purchase statement).[19] Indirect wholesalers that receive a direct purchase statement must inform their customers that they received such a statement.[20] See Exhibit 3 for a summary of the DSCSA requirements for direct and indirect wholesalers.

Exhibit 3: Drug Product Tracing Information Provided by Direct and Indirect Wholesalers

	Drug Product Tracing Information			
	Transaction Information	Transaction History	Transaction Statement	Direct Purchase Information
Direct Wholesaler	✓ *	✓ *	✓	✓ Provides a direct purchase statement to customer
Indirect Wholesaler	✓	✓	✓	✓ Informs customer that it received a direct purchase statement from a direct wholesaler

Source: OIG analysis of DSCSA, 2016.

* Wholesalers purchasing directly do not have to provide the lot number, initial transaction date, or initial shipment date from the drug manufacturer.

In practice, the direct purchase statement helps explain to the customer why the lot number, initial transaction date, and initial shipment date are not in the transaction information for the first trading partner in the transaction history. Without the direct purchase statement, the customer might think that information was erroneously omitted.

Drug product tracing information does not need to be exchanged for drugs that are excluded from the definition of 'product' in the DSCSA or for certain activities that are exempt from the definition of 'transaction' (hereinafter we refer to these as drug product exemptions). Drug product exemptions include, blood or blood components intended for transfusion, any medical gas, and imaging drugs.[21] For a list of excluded drug products and activities, see Appendix A.

FDA Guidance on Exchanging Drug Product Tracing Information

FDA guidance outlines general parameters for the interoperable exchange of drug product tracing information but does not require that trading partners exchange drug product tracing information in the same way. Instead, the guidance provides trading partners with latitude to choose how they exchange information. For example, trading partners may exchange drug product tracing information using any transmission mode, including, electronic data interchange advanced ship notices (EDI/ASN), web portals, and paper. In addition, trading partners may exchange information in any format, including, but not limited to, invoices and packing slips. FDA has indicated that it may revisit the concept of interoperability as "processes and capabilities that promote more standardization become available and as electronic systems evolve and are more widely accessible."[22]

FDA also issued a compliance policy in December 2014 stating that it would delay enforcement of drug product tracing requirements to May 1, 2015.[23] The delay was in response to industry need for additional time to implement drug product tracing requirements.

Methodology

This study reviewed a nonrepresentative selection of 31 wholesalers of varying size. The 31 were comprised of the 3 largest wholesalers that generate more than 80 percent of all revenues from drug distribution, as well as 15 medium wholesalers, and 13 small wholesalers.[24] We designated wholesalers as 'medium' and 'small' on the basis of the number of licenses in the FDA wholesale distributor database. For more detail about the sample selection, see Appendix B.

To address our objective, we first reviewed examples of wholesalers' drug product tracing information and then conducted phone interviews with wholesalers. We interviewed wholesalers about their implementation of drug product tracing requirements. To support our understanding of their implementation, we asked about the drug product tracing information that they provided. Staff who we interviewed were primarily compliance or regulatory managers and, for smaller wholesalers, often included the president or owner.

We collected this information between December 2015 and January 2016. We conducted our data collection in this timeframe – 7 months after the enforcement delay from FDA and a year after the DSCSA required

wholesalers to exchange information – to increase the likelihood that wholesalers had implemented processes to address drug product tracing requirements.

Limitations

We based our findings on wholesalers' self-reported information from interviews and on examples of drug product tracing information. We did not independently verify the responses. Our findings represent only the 31 selected wholesalers and cannot be projected to the whole population of wholesalers.

Standards

This study was conducted in accordance with the Quality Standards for Inspection and Evaluation issued by the Council of the Inspectors General on Integrity and Efficiency.

FINDINGS

All selected wholesalers exchange drug product tracing information and about half, including wholesalers representing the vast majority of transactions, exchange everything required

All 31 wholesalers reported that they had implemented processes to address DSCSA product tracing requirements and were able to exchange drug product tracing information. Of these, 17 wholesalers – including the 3 largest that account for more than 80 percent of revenue from drug distribution – exchange all required drug product tracing information (i.e., transaction information, transaction history, transaction statements – including a direct purchase statement, where applicable).

Of 31 wholesalers, 14 did not exchange all required drug product tracing information

Fourteen wholesalers did not exchange one or more required elements of drug product tracing information. FDA guidance notes that missing drug product tracing information may be an indication that the drug product is suspect and warrants heightened scrutiny.[25] Wholesalers with missing drug product tracing information may not be in compliance with DSCSA requirements. All but one of these wholesalers purchased all or at least a portion of drug products indirectly. See Exhibit 4 for which information each wholesaler was missing.

Exhibit 4: Wholesalers Missing Drug Product Tracing Information

Wholesaler	Size	Transaction Information				Provide Direct Purchase Statement	Inform Receipt of Direct Purchase Statement	Transaction Statement
		NDC	Strength	Dosage form	Container size			
1	Small						X	
2	Small			X				
3	Small							X
4	Small			X				
5	Small	X				X	X	
6	Small					X		
7	Medium	X					X	
8	Medium		X			X		
9	Medium			X			X	
10	Medium							X
11	Medium		X	X	X			
12	Medium						X	
13	Medium						X	
14	Medium						X	
Total wholesalers missing information		7				3	7	2

Source: OIG analysis of wholesaler interview notes and product tracing examples, 2016.

Seven wholesalers were missing one or more elements of transaction information. Dosage form was the most common element of the transaction information that was missing. One wholesaler explained that

the dosage form was not necessary, stating that it was sufficiently conveyed by the NDC. Looking up the NDC is one way to determine product type, including dosage form. Although the NDC can be used to determine the dosage form, the DSCSA lists the NDC and dosage form as distinct required elements of the transaction information.

Three wholesalers reported that they did not provide their customers with a direct purchase statement for relevant transactions. Two of these wholesalers reported that they did not understand the direct purchase statement requirement. The other wholesaler understood the requirement but decided not to include the direct purchase statement because it was constrained by the field size on the packing slip that it uses to convey drug product tracing information. Without the direct purchase statement, the wholesalers' customers may conclude that the lot number of the drug product, initial transaction date, and initial shipment date were erroneously omitted from transaction information.

Seven wholesalers reported that they did not inform customers that they themselves received direct purchase statements for relevant transactions from the suppliers of certain drug products. One wholesaler noted that, without explicitly providing this information, customers could infer whether a drug product was purchased directly by looking at the trading partner names in the transaction history. The wholesaler explained that if the prior transaction involved a large wholesaler, the direct purchase was implied because large wholesalers purchase everything directly. Although this may be true in certain cases, even large wholesalers do not purchase everything directly, so the transaction history will not always be an adequate stand-in for the required direct purchase statement. Further, two wholesalers reported that they did not know that they had to inform customers that they had received a direct purchase statement in instances in which they purchase indirectly.

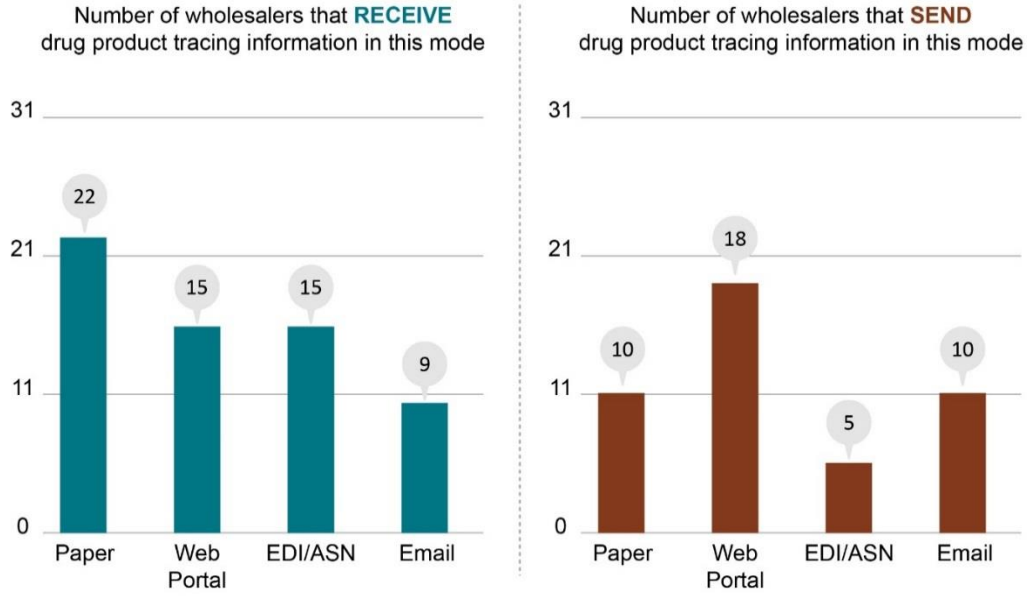
Wholesalers exchange drug product tracing information in a variety of ways

Not all 31 wholesalers in this study exchange drug product tracing information in the same way. Rather, wholesalers exchange this information using a wide variety of transmission modes and formats, taking advantage of the latitude provided by the DSCSA and FDA guidance. Wholesalers may eventually coalesce around one way to exchange drug product tracing information as DSCSA requirements are implemented. However, at this time, they have not adopted a standardized way to exchange this information.

Wholesalers exchange drug product tracing information using four different transmission modes: paper, web portals, EDI/ASN, and email

Wholesalers reported using four different transmission modes to exchange drug product tracing information – most using more than one. The mode in which they receive drug product tracing information is not necessarily the same mode they use to provide information to their customers. Wholesalers receive drug product tracing information from suppliers and then generate new drug product tracing information for their customers specific to each sale. The modes they use to transmit information for each sale depend on the systems they use as well as the systems their suppliers and customers use. See Exhibit 5 for which modes the 31 wholesalers in this study use to receive and send drug product tracing information in their business operations.

Exhibit 5: Wholesalers Use a Variety of Transmission Modes to Exchange Drug Product Tracing Information



Source: OIG wholesaler interviews and drug product tracing examples, 2016.

* Numbers do not add to 31 because wholesalers use multiple modes to receive and send information.

Paper is the most common transmission mode through which wholesalers receive drug product tracing information. Wholesalers reported that paper is prevalent because many drug manufacturers provide drug product tracing information on packing slips or invoices.

Web portals are the most common transmission mode that wholesalers use to provide drug product tracing information to customers. Wholesalers reported using web portals because they do not require the use of a common software program; customers need only an internet connection to access drug product tracing information on the web portal.

Several wholesalers, including all three large wholesalers and several medium wholesalers, use EDI/ASN to electronically receive or send drug product tracing information. EDI/ASN is a set of standards used to electronically communicate the contents of a shipment to a customer.[26] Wholesalers use EDI/ASN to exchange drug product tracing information electronically, in discrete, or "structured," fields. The use of structured data can be advantageous because that data can be easily stored and searched.[27] Searchable data facilitates quick retrieval when, for example, a drug product should be quarantined or recalled.

All wholesalers using EDI/ASN also use other transmission modes because some suppliers and customers cannot send or receive EDI/ASN transmissions. One of the three large wholesalers reported that only about a quarter of its customers, primarily larger hospitals and national retail pharmacies, have implemented the technology required to receive EDI/ASN transmissions.

Email is the least commonly used transmission mode that wholesalers use to receive drug product tracing information. The wholesalers that do use email reported receiving drug product tracing information generally as an email attachment after placing an order.

Wholesalers exchange drug product tracing information using three different formats: product tracing forms, invoices, and packing slips

Wholesalers reported exchanging drug product tracing information using three different formats, with most wholesalers using more than one format. The format refers to the way in which drug product tracing information is organized and presented. See Exhibit 6 for the prevalence of each format that wholesalers receive and use to send drug product tracing information.

Exhibit 6: Wholesalers Use a Variety of Formats to Exchange Drug Product Tracing Information

Source: OIG wholesaler interviews and product tracing examples, 2016.

* Numbers do not add to 31 because wholesalers use multiple formats to receive and send information.

Wholesalers in this study most commonly used product tracing forms to exchange drug product tracing information. Product tracing forms are designed specifically to capture and clearly represent drug product tracing information. See Appendix C for an example of a product tracing form.

Wholesalers also reported that they use invoices and packing slips to exchange drug product tracing information. Invoices include information about the drug products being exchanged and the prices charged for those drug products. Packing slips detail the contents of shipments. See Appendix D and E for examples of a packing slip and invoice used to exchange drug product tracing information.

Wholesalers said two separate issues, exemptions and 340B contract pharmacies, created complications in exchanging drug product tracing information

Wholesalers reported that two separate issues – drug product exemptions and 340B contract pharmacies – have created complications during their implementation of the DSCSA. Several wholesalers expressed an interest in guidance from FDA on these two topics.

Wholesalers reported disagreements with suppliers and customers about drug product exemptions

Ten wholesalers, including two of the large wholesalers, reported that they had disagreements with suppliers or customers about which drugs are exempt from the DSCSA's definition of product and thus do not require drug product tracing information. Although the DSCSA identifies broad drug groups that are exempt from the definition of "product" (e.g., blood products, medical gas, or certain intravenous products – see complete list in Appendix A), it does not provide detailed lists of all drug NDCs that are exempt.[28] In practice, wholesalers identify which drug products are exempt at the NDC level. One of the large wholesalers estimated that approximately 10 percent of the prescription drugs it supplied were exempt from the DSCSA.

Wholesalers reported that these disagreements occur over the interpretation of which NDCs are associated with the general categories used to describe exempt drugs in the DSCSA (e.g., which NDC numbers are associated with "blood products"). These disagreements occur, in part, because wholesalers and others in the drug supply chain determine which NDCs fall under the exemption in different ways. Although some wholesalers reported relying on drug manufactures' determinations, several reported that they rely on other wholesalers or make their own determinations. Other wholesalers reported making no distinction at all, instead choosing to exchange drug product tracing information for all drugs. The following examples illustrate how different trading partners might arrive at different conclusions about whether a specific drug falls under the general category exempted in the DSCSA:

- One of the large wholesalers noted that manufacturers sometimes make different decisions about the same drug being exempt. The wholesaler reported that discrepancies like this have occurred with sodium chloride – where one manufacturer of the drug told the wholesaler it was exempt and another manufacturer said it was not. This wholesaler relies on manufacturers' determinations about which drugs are exempt. In a case like this, the wholesaler sends drug product tracing information only when the drug it sells is made by one of the manufacturers that determined the drug is not exempt. The wholesaler reported that this has led to confusion and complaints from customers.

- A wholesaler also reported that Sevoflurane liquid was the subject of disagreements. Sevoflurane liquid is delivered to the patient in a gas form, but otherwise it is a liquid. The wholesaler explained that some would not consider this drug to be subject to the DSCSA because they believe it is a medical gas, which is one of the exemptions to the definition of "product." The wholesaler also explained that other trading partners would consider the drug to be subject to the DSCSA because it is a liquid, not a gas, when it is transferred to customers.

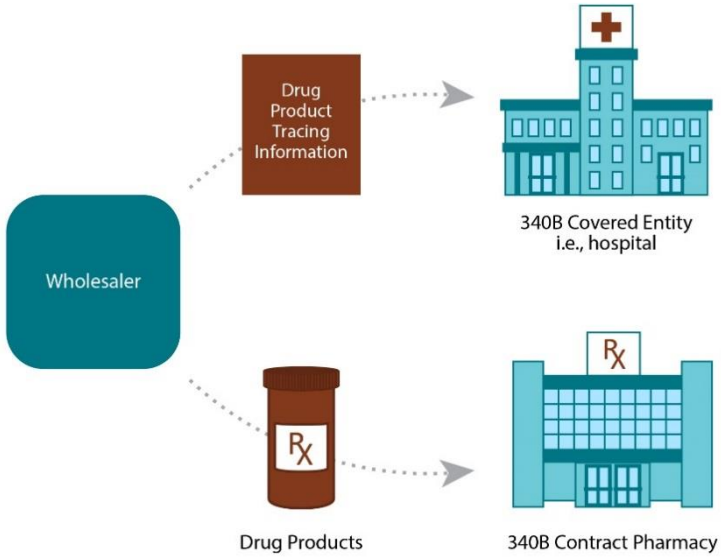
See Appendix F for a list of additional drugs that wholesalers reported as the source of these types of disagreements.

Wholesalers reported that these disagreements lead to inconsistent exchange of drug product tracing information for certain drug products because trading partners do not send information for NDC that they believe to be exempt. These inconsistencies may create an incomplete "record" of the owners of the drug product. Incomplete drug product tracing information may impede the usefulness of this information for FDA and others to investigate suspect and illegitimate drug products.

The three large wholesalers reported complications with sending drug product tracing information to 340B contract pharmacies

The three large wholesalers reported complications with sending drug product tracing information to 340Bcontract pharmacies. They explained that there are two entities to consider when sending drug product tracing information for sales to 340B-covered entities that use 340B contract pharmacies. Wholesalers sell drug products to 340B-covered entities but ship the drug products to the 340B contract pharmacies that dispense on behalf of the 340B-covered entities.[29] To comply with the DCSCA, wholesalers send drug product tracing information to the 340B-covered entities because the 340B-covered entities maintain ownership of the drug product. See Exhibit 7 for an illustration of drug products and the associated drug product tracing information following different paths.

Exhibit 7: Pathway of Drug Product Tracing Information and Drug Products in 340B Contract Pharmacy Arrangements



Source: OIG analysis of wholesaler interviews, 2016.

The three large wholesale distributors reported that 340B contract pharmacies often request drug product tracing information even though they do not take ownership of the product. Two of the large wholesale distributors provide drug product tracing information directly to 340B contract pharmacies if the 340B contract pharmacy has a third-party agreement with the 340B-covered entity to confidentially maintain the information.[30] The third large wholesale distributor sends the information to the 340B-covered entity only.

Wholesalers requested clarification about sharing drug product tracing information with 340B contract pharmacies because they are concerned about sharing information with an entity that does not take ownership of the drug products. Such clarification could help ensure compliance. Specifically, the wholesaler needs to know whether its knowledge of a third-party agreement between the 340B entity and the contract pharmacy is sufficient for the wholesaler to share drug product tracing information with the pharmacy. Similarly, the wholesaler needs to know whether a third-party agreement between the wholesaler and the 340B entity to maintain drug product tracing information is sufficient for the wholesaler to share that product tracing information with the pharmacy.

CONCLUSION AND RECOMMENDATIONS

We found that all selected wholesalers were exchanging drug product tracing information, and about half—including the three largest wholesalers that account for more than 80 percent of drug distribution revenues—exchange all required information. Wholesalers that do not have complete drug product tracing information account for a smaller portion of drug distribution revenues, and of those, most purchase all or at least a portion of drug products indirectly. Although they account for a smaller portion of drug distribution, small or indirect wholesalers have been involved in cases in which illegitimate drugs have played a part. As such, missing information among these wholesalers raises concerns that complete drug product tracing information may not always be available to support investigations into suspect and illegitimate drug products and potential diversion.

We also found that not all 31 wholesalers in this study exchange drug product tracing information in the same way. Rather, wholesalers exchange drug product tracing information using a wide variety of transmission modes and formats, taking advantage of the latitude provided by the DSCSA and FDA guidance. Wholesalers may eventually coalesce around one means of exchange as DSCSA requirements are implemented but, at this time, they have not adopted a standardized way to exchange this information.

We recommend that FDA provide technical assistance to facilitate wholesalers' compliance with the DSCSA. Specifically, we recommend that FDA should:

Provide technical assistance on requirements regarding direct purchase statements

FDA should provide technical assistance to help ensure that wholesalers understand their responsibilities related to exchanging drug product tracing information when conducting direct purchases or engaging in transactions with products that were obtained by direct purchases. We found instances in which wholesalers were not aware of or did not understand DSCSA requirements to provide customers with a direct purchase statement or to inform a customer that they received a direct purchase statement. FDA could also clarify whether wholesalers are responsible for providing direct purchase information when they make purchases from another wholesaler that purchased indirectly.

Provide technical assistance regarding exempt products

FDA should provide technical assistance regarding exempt products. FDA could, for example, hold a webinar or create a frequently-asked-questions document about product exemptions and ideas to resolve or prevent disagreements, including those noted in this report.

Provide technical assistance regarding the exchange of drug product tracing information for sales to 340B-covered entities that use 340B contract pharmacies

FDA should provide technical assistance to ensure that wholesalers understand the circumstances under which they can provide drug product tracing information to 340B contract pharmacies. For example, FDA could clarify whether the presence of a third-party agreement between the 340B contract pharmacy and the 340B-covered entity is sufficient to ensure that the wholesaler is not violating the confidentiality of the drug product tracing information.

AGENCY COMMENTS AND OIG RESPONSE

FDA concurred with all three of our recommendations.

FDA plans to issue additional guidance to facilitate the interoperable exchange of product tracing information. FDA also stated that it is actively working on recommendations for standardization of data and documentation practices.

In response to our first recommendation, FDA intends to provide additional information related to direct purchase statements in a guidance document for industry.

In response to our second recommendation, FDA will explore options for clarifying the types of products that are exempt from the DSCSA. FDA will also consider providing suggestions for how trading partners might resolve or prevent disagreements about whether a particular product has exempt status.

In response to our third recommendation, FDA intends to provide additional information on third-party agreements in a guidance document for industry. In developing this guidance, we encourage FDA to consider clarifying the specific issues raised in our report about confidentiality requirements. In particular, we encourage FDA to consider addressing whether wholesalers may send tracing information directly to contract pharmacies without violating confidentiality requirements.

For the full text of FDA's response, see Appendix G.

APPENDIX A: DSCA Definitions

Transaction (§ 581(24) (A) of the FD&C Act)

Transaction-

In General. – The term "transaction" means the transfer of product between persons in which a change of ownership occurs.

Exemptions (§ 581(24) (B) of the FD&C Act): The term "transaction" does not include—

''(i) intracompany distribution of any product between members of an affiliate or within a manufacturer;

''(ii) the distribution of a product among hospitals or other health care entities that are under common control;

''(iii) the distribution of a product for emergency medical reasons including a public health emergency declaration pursuant to section 319 of the Public Health Service Act, except that a drug shortage not caused by a public health emergency shall not constitute an emergency medical reason;

''(iv) the dispensing of a product pursuant to a prescription executed in accordance with section 503(b)(1);

''(v) the distribution of product samples by a manufacturer or a licensed wholesale distributor in accordance with section 503(d);

''(vi) the distribution of blood or blood components intended for transfusion;

''(vii) the distribution of minimal quantities of product by a licensed retail pharmacy to a licensed practitioner for office use;

''(viii) the sale, purchase, or trade of a drug or an offer to sell, purchase, or trade a drug by a charitable organization described in section 501(c)(3) of the Internal Revenue Code of 1986 to a nonprofit affiliate of the organization to the extent otherwise permitted by law;

''(ix) the distribution of a product pursuant to the sale or merger of a pharmacy or pharmacies or a wholesale distributor or wholesale distributors, except that any records required to be maintained for the product shall be transferred to the new owner of the pharmacy or pharmacies or wholesale distributor or wholesale distributors;

''(x) the dispensing of a product approved under section 512(c);

''(xi) products transferred to or from any facility that is licensed by the Nuclear Regulatory Commission or by a State pursuant to an agreement with such

Commission under section 274 of the Atomic Energy Act of 1954 (42 U.S.C. 2021);

''(xii) a combination product that is not subject to approval under section 505 or licensure under section 351 of the Public Health Service Act, and that is—

''(I) a product comprised of a device and 1 or more other regulated components (such as a drug/device, biologic/device, or drug/device/biologic) that are physically, chemically, or otherwise combined or mixed and produced as a single entity;

''(II) 2 or more separate products packaged together in a single package or as a unit and comprised of a drug and device or device and biological product; or

''(III) 2 or more finished medical devices plus one or more drug or biological products that are packaged together in what is referred to as a 'medical convenience kit' as described in clause (xiii);

''(xiii) the distribution of a collection of finished medical devices, which may include a product or biological product, assembled in kit form strictly for the convenience of the purchaser or user (referred to in this clause as a 'medical convenience kit') if—
''(I) the medical convenience kit is assembled in an establishment that is registered with the Food and Drug Administration as a device manufacturer in accordance with section 510(b)(2);

''(II) the medical convenience kit does not contain a controlled substance that appears in a schedule contained in the Comprehensive Drug Abuse Prevention and Control Act of 1970;

''(III) in the case of a medical convenience kit that includes a product, the person that manufacturers the kit—

''(aa) purchased such product directly from the pharmaceutical manufacturer or from a wholesale distributor that purchased the product directly from the pharmaceutical manufacturer; and

''(bb) does not alter the primary container or label of the product as purchased from the manufacturer or wholesale distributor; and

''(IV) in the case of a medical convenience kit that includes a product, the product is—

''(aa) an intravenous solution intended for the replenishment of fluids and electrolytes;

''(bb) a product intended to maintain the equilibrium of water and minerals in the body;

''(cc) a product intended for irrigation or reconstitution;

''(dd) an anesthetic;

''(ee) an anticoagulant;

''(ff) a vasopressor; or

''(gg) a sympathomimetic;

''(xiv) the distribution of an intravenous product that, by its formulation, is intended for the replenishment of fluids and electrolytes (such as sodium, chloride, and potassium) or calories (such as dextrose and amino acids);

''(xv) the distribution of an intravenous product used to maintain the equilibrium of water and minerals in the body, such as dialysis solutions;

''(xvi) the distribution of a product that is intended for irrigation, or sterile water, whether intended for such purposes or for injection;

''(xvii) the distribution of a medical gas (as defined in section 575); or

''(xviii) the distribution or sale of any licensed product under section 351 of the Public Health Service Act that meets the definition of a device under section 201(h).

Transaction information (§ 581(26) of the FD&C Act)

The term "transaction information" means–

"(A) the proprietary or established name or names of the product;

"(B) the strength and dosage form of the product;

"(C) the National Drug Code of the product;

"(D) the container size;

"(E) the number of containers;

"(F) the lot number of the product;

"(G) the date of the transaction;

"(H) the date of the shipment, if more than 24 hours after the date of the transaction;

"(I) the business name and address of the person from whom ownership is being transferred; and

"(J) the business name and address of the person to whom ownership is being transferred.

Transaction statement (§ 581(27) of the FD&C Act)

The "transaction statement" is a statement, in paper or electronic form, that the entity transferring ownership in a transaction–

"(A) Is authorized as required under DSCSA;

"(B) Received the product from a person that is authorized as required under the DSCSA;

"(C) Received transaction information and a transaction statement from the prior owner of the product, as required under section 582;

"(D) Did not knowingly ship a suspect or illegitimate product;

"(E) Had systems and processes in place to comply with verification requirements under section 582;

"(F) Did not knowingly provide false transaction information; and

"(G) Did not knowingly alter the transaction history.

Product (§ 581(13) of the FD&C Act)

The term "product" means a prescription drug in a finished dosage form for administration to a patient without substantial further manufacturing (such as capsules, tablets, and lyophilized products before reconstitution), but for purposes of section 582, does not include blood or blood components intended for transfusion, radioactive drugs or radioactive biological products (as defined in section 600.3(ee) of title 21, Code of Federal Regulations) that are regulated by the Nuclear Regulatory Commission or by a State pursuant to an agreement with such Commission under section 274 of the Atomic Energy Act of 1954 (42 U.S.C. 2021), imaging drugs, an intravenous product described in clause (xiv), (xv), or (xvi) of paragraph (24)(B), any medical gas (as defined in section 575), homeopathic drugs marketed in accordance with applicable guidance under this Act, or a drug compounded in compliance with section 503A or 503B.

APPENDIX B: Detailed Methodology

Sample Selection

We selected our sample from the FDA wholesale distributor database in October 2015. Although this database is composed of self-reported data that is not verified by FDA, it is the only centralized listing of wholesalers nationwide. At the time we took our sample, the database contained licenses for 353 wholesalers.[31]

To select our sample, we first categorized wholesalers as large, medium, and small to address variations in practices dependent on size of their business. We put the three wholesalers widely acknowledged to generate the vast majority of all revenues from drug distribution -- over 80 percent according to one source -- in the large category.[32] We put the remainder of wholesalers in the small or medium categories on the basis of the number of State licenses they had listed in FDA's wholesaler database. The median number of licenses was seven, so we defined the small group as those with seven or fewer licenses and the medium group as those with more than seven licenses that are not among the three wholesalers in the large group.

To finalize our sample, we included the 3 large wholesalers and selected a simple random sample of 15 medium wholesalers and 15 small wholesalers. We subsequently removed 2 of the small wholesalers from our sample because they dealt only with products not covered by the DSCSA's drug product tracing requirements, leaving 13 small wholesalers in the final sample. See Exhibit 8 for the number and type of wholesalers in the final sample.

Exhibit 8: Wholesaler Sample

Wholesaler size	Data source	Sample size
Large	N/A	3
Medium	FDA Wholesaler Database	15
Small		13
	Total	31

Source: OIG analysis and sampling of the FDA wholesaler database, 2016.

APPENDIX C: Product Tracing Form

Wholsaler's Name

Transaction Statement

[redacted] ("Supplier"), a licensed wholesale pharmaceutical distributor, is providing the following statement pursuant to the requirements of the Federal Food, Drug and Cosmetic Act, and Prescription Drug Marketing Act.

Transaction Information (TI)

NDC :	Product :	Qty :	Lot :	Exp :
63323-0492-57	XYLOCAINE MPF 1% 25X5ML	1	[redacted]	7/31/2019
63323-0492-57	XYLOCAINE MPF 1% 25X5ML	1		9/30/2019

Mfr : FRESENIUS KABI

Transaction Information

Transaction History (TH)

OWNER #1
Name :
Address :
City, State : [redacted]

Ref : N/A
Date : N/A

Contact :
Phone : [redacted]

SOLD TO:
Name :
Address :
City, State : [redacted]

Ref : [redacted]
Date : 10/23/2015

Contact :
Phone :
Email : [redacted]

SOLD TO:
Name :
Address :
City, State : [redacted]

Ref : [redacted]
Date : 10/26/2015

Contact :
Phone : [redacted]

Transaction Information

Transaction History

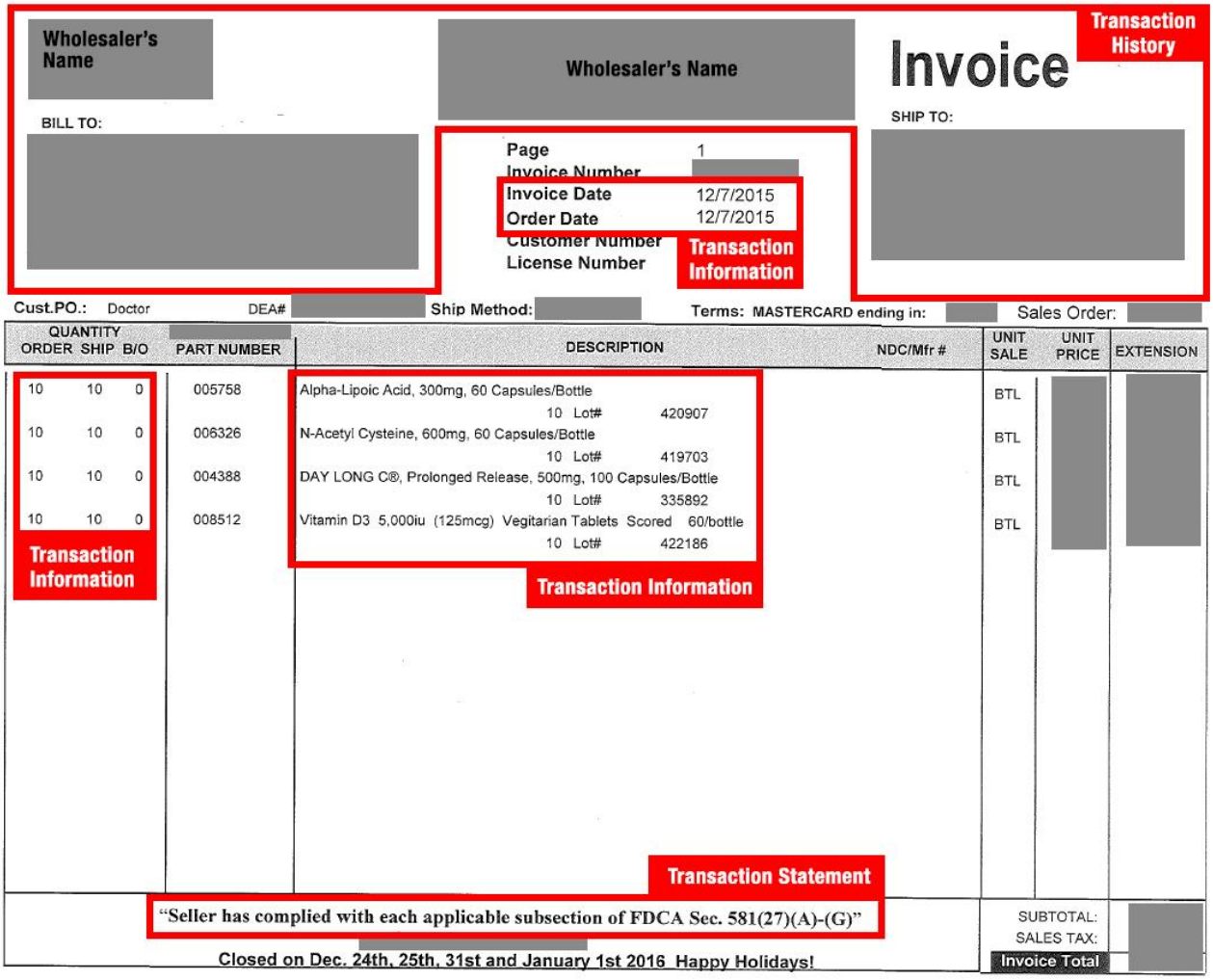
Transaction Statement (TS)

Transaction Statement

- ☑ Is authorized to do the transfer.
- ☑ Has received the product from a person that is authroized.
- ☑ Received the transaction information and statement from the prior owner of the product.
- ☑ Did not knowingly ship a suspect or illegitimate product.
- ☑ Had systems and processes in place to comply with verification requirements.
- ☑ Did not knowingly provide false transaction information.
- ☑ Did not knowingly alter the transaction information.

Authorized Signature : [redacted] Date : 10/26/2015

APPENDIX D: Invoice



APPENDIX E: Packing Slip

PACKING SLIP AND FEDERAL PEDIGREE

TRANSACTION INFORMATION (TI): (DSCSA Sec. 581 (26))

(A) Name of Product: PURIXAN® (mercaptopurine)
(B) Strength and dosage form: 2000 mg/100 mL Oral Suspension
(C) National Drug Code 62480-0020-01
(D) Container Size: 100 mL bottle

Transaction Information

RDT PO#	QTY Shipped	Manufactured Final Product Lot and Exp. Date	Date Shipped	API Lot
[redacted]	1824	[redacted]	10/19/15	[redacted]

TRANSACTION HISTORY (TH):

Manufactured at [redacted]

Shipped from [redacted]

Transaction History

MANDATORY TRANSACTION STATEMENT (TS): (DSCSA Sec. 581 (27))

Rare Disease Therapeutics, Inc. (RDT):
(A) is authorized as required under the Drug Supply Chain Security Act (DSCSA);
(B) received the product from a person that is authorized as required under the DSCSA;
(C) received transaction information and transaction statement from the prior owner, as required under section 582;
(D) did not knowingly ship a suspect or illegitimate product;
(E) had systems and processes in place to comply with verification requirements under section 582;
(F) did not knowingly provide false transaction information;
(G) did not knowingly alter the transaction history.

Transaction Statement

I swear or affirm that the information contained on this pedigree is accurate and complete.

[redacted]

Signature (authorized to bind the company) Print Name and Title

10/15/15

Date

APPENDIX F: Drugs That Wholesalers Reported as a Source of Disagreements About Product Exemptions

Wholesalers reported disagreements with customers or suppliers about whether the following drugs were exempt from DSCSA drug product tracing requirements.

- All presentations of Albumin
- Drugs not in their final finished form/active product ingredients
- Esmolol
- Heparin Loc
- Nutritional fluids and nutritional electrolytes
- Potassium Chloride
- Prescription vitamins
- Sevoflurane liquid
- Sodium Bicarb syringes
- Veterinary drugs manufactured for use in humans (e.g., Claritin)

APPENDIX G: Agency Comments

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993

DATE: July 6, 2017

TO: Daniel R. Levinson, Inspector General

FROM: Associate Commissioner for Public Health Strategy and Analysis

SUBJECT: Food and Drug Administration's General Comments to OIG Draft Report: *Drug Supply Chain Security: Wholesalers Exchanging Most Tracing Information,* OEI-05-14-00640

Enclosed are the Food and Drug Administration's general comments to the Office of Inspector General's draft report: *Drug Supply Chain Security: Wholesalers Exchanging Most Tracing Information,* OEI-05-14-00640.

We appreciate the opportunity to review and comment on this draft report prior to publication.

Peter Lurie, M.D., M.P.H.
Associate Commissioner for Public Health Strategy and Analysis

Attachment

FDA's General Comments to OIG's Draft Report:
Drug Supply Chain Security: Wholesalers Exchanging Most Tracing Information,
OEI-05-14-00640

FDA appreciates the opportunity to review and comment on OIG's draft report. We are committed to protecting public health and the quality and authenticity of prescription drug products through rigorous oversight of the drug distribution system. FDA continues to work with stakeholders to ensure effective implementation of the product tracing requirements of the Drug Supply Chain Security Act (Title II of Public Law 113-54). The Agency's responses to OIG's recommendations are below.

Provide technical assistance on requirements regarding direct purchase statements

FDA concurs with this recommendation. FDA has received comments from trading partners in the supply chain seeking clarification of certain product tracing requirements, including those related to direct purchases and direct purchase statements. FDA intends to provide additional information related to direct purchase statements in a guidance document for industry.

In 2014, FDA issued a draft guidance for industry, *DSCSA Standards for the Interoperable Exchange of Information for Tracing of Certain Human, Finished, Prescription Drugs: How to Exchange Product Tracing Information*, which provided recommendations for how to exchange the product tracing information in paper and electronic formats. We noted in this guidance that FDA intends to issue additional guidance to facilitate the interoperable exchange of product tracing information. The Agency is actively working on recommendations for standardization of data and documentation practices.

Provide technical assistance regarding exempt products

FDA concurs with this recommendation. The requirements of section 582 of the FD&C Act (i.e., product tracing, verification, and product identification) apply to "products," which are defined in section 581(13) as prescription drugs in a finished dosage form for administration to a patient without substantial further manufacturing. Certain types of drugs are excluded from the definition of "product," however, and thus are exempt from the requirements of section 582.

It would be extremely resource intensive for FDA to provide individualized responses to trading partners' requests about exempt status or to identify the exempt status for every prescription drug product. However, FDA will explore its options for clarifying the types of products that are exempt from the requirements of section 582. We will also look into providing suggestions for how trading partners might resolve or prevent disagreements about whether a particular product has exempt status.

1

Provide technical assistance regarding the exchange of drug product tracing information for sales to 340B covered entities that use 340B contract pharmacies

FDA concurs with this recommendation. Stakeholders raised this issue with FDA beginning in 2015 and FDA has had several meetings and communications about this issue since then. In a letter dated March 1, 2016, FDA addressed stakeholder questions related to certain contract pharmacy arrangements with covered entities of the 340B drug pricing program administered by Health Resources and Services Administration (HRSA). FDA's response confirmed that the use of agreements with third parties, as described in section 582(d)(1)(B) of the FD&C Act, is an appropriate mechanism for dispensers to address their responsibilities to maintain product tracing information.

FDA intends to provide additional information related to third-party agreements in a guidance document for industry. In 2014, FDA issued a draft guidance for industry, *DSCSA Standards for the Interoperable Exchange of Information for Tracing of Certain Human, Finished, Prescription Drugs: How to Exchange Product Tracing Information*, which provided recommendations for how to exchange the product tracing information in paper and electronic formats. We noted in this guidance that FDA intends to issue additional guidance to facilitate the interoperable exchange of product tracing information. The Agency is actively working on recommendations for standardization of data and documentation practices, including recommendations for scenarios involving third-party agreements.

ACKNOWLEDGEMENTS

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This report was prepared under the direction of Tom Komaniecki, Regional Inspector General for Evaluation and Inspections in the Chicago regional office, and Laura Kordish, Deputy Regional Inspector General.

To obtain additional information concerning this report or to obtain copies, contact the Office of Public Affairs at Public.Affairs@oig.hhs.gov.

ABOUT THE OFFICE OF INSPECTOR GENERAL

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ENDNOTES

[1] Food and Drug Administration (FDA). *FDA sends letters to 19 medical practices about counterfeit product and other unapproved cancer medicines*. February 14, 2012. Available online at http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/CounterfeitMedicine/ucm338283.htm.

[2] Senate Staff Report. June 25, 2012. *Shining Light on the Gray Market*. Available online at https://democrats-oversight.house.gov/sites/democrats.oversight.house.gov/files/migrated/uploads/7.25.12%20Staff%20Report%20Shining%20Light%20on%20the%20Gray%20Market.pdf.

[3] § 582 of the Federal Food, Drug, & Cosmetic Act (FD&C Act), as amended by DSCSA § 202.

[4] DSCSA, P.L. 113-54, Title II.

[5] A manufacturer is defined as the holder of a product's FDA-approved application or license or, if a product is unapproved, the product's manufacturer. This term also includes a co-licensed partner or an affiliate of the application holder. § 581(10) of the FD&C Act.

[6] A wholesale distributor is defined as a person engaged in wholesale distribution. § 581(29) of the FD&C Act.

[7] A dispenser is defined to include a retail pharmacy, hospital pharmacy, a group of chain pharmacies under common ownership and control, or any person legally authorized to dispense or administer prescription drugs. § 581(3) of the FD&C Act.

[8] The term repackager means a person who owns or operates an establishment that repacks and relabels a product or package for--(A) further sale; or (B) distribution without a further transaction. § 581(16) of the FD&C Act.

[9] § 582(c)(1)(A) of the FD&C Act.

[10] For purposes of this report, an indirect wholesaler does not purchase directly from the manufacturer, the exclusive distributor of the manufacturer, or a repackager that purchased directly from the manufacturer. See § 582 (c)(1)(A)(iii) of the FD&C Act.

[11] § 582(b)(1), (c)(1), (d)(1) and (e)(1) of the FD&C Act.

[12] The definition of product is limited by exemptions listed in Appendix A. See § 581(13) of the FD&C Act.

[13] The DSCSA defines 'product' at § 581(13) of the FD&C Act.

[14] § 581(24)(A) of the FD&C Act.

[15] § 581(26) of the FD&C Act.

[16] Drugs are identified using a unique, three-segment number, called NDC, which serves as a universal product identifier for drugs. Definition available online at http://www.fda.gov/Drugs/InformationOnDrugs/ucm142438.htm.

[17] § 581(25) of the FD&C Act.

[18] § 581(27) of the FD&C Act.

[19] § 582(c)(1)(A)(ii) of the FD&C Act.

[20] § 582(c)(1)(A)(iii)-(iv) of the FD&C Act.

[21] § 581(24) of the FD&C Act and § 581(13) of the FD&C Act.

[22] FDA. *DSCSA Standards for the Interoperable Exchange of Information for Tracing of Certain Human, Finished, Prescription Drugs: How to Exchange Product Tracing Information; Draft Guidance.* November 2014.

[23] FDA. *DSCSA Implementation: Product Tracing Requirements – Compliance Policy. Guidance for Industry.* December 2014.

[24] Modern Distribution Management. *2014 Market Leaders: Top Pharmaceutical Distributors*. Available online at http://www.mdm.com/2014_pharmaceuticals_mdm-market-leaders.

[25] FDA. *Drug Supply Chain Security Act Implementation: Identification of Suspect Product and Notification Guidance for Industry*. December 2016. Available online at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM400470.pdf.

[26] 1EDISource. *EDI 856 Overview*. Available online at http://www.1edisource.com/transaction-sets?tset=856.

[27] Bright Planet. *Structured vs. Unstructured data*. June 28, 2012. Available online at https://brightplanet.com/2012/06/structured-vs-unstructured-data/.
[28] § 581(13) of the FD&C Act.
[29] In the 340B Drug Discount Program the owner of the product is the covered entity (i.e. a federally qualified health center) and the 340B contract pharmacy possesses the physical products and dispenses the products to patients of the covered entity. HRSA. *340B Drug Pricing Program*. Available online at http://www.hrsa.gov/opa/ and HRSA. *Contract Pharmacy Services*. Available online at http://www.hrsa.gov/opa/implementation/contract/.
[30] § 582(d)(1)(B) of the FD&C Act.
[31] Approximate count of unique wholesalers in the FDA database as of October 28, 2015. The count is based on the number of unique reporter contact names in the database for wholesalers with active licenses.
[32] Modern Distribution Management. *2014 Market Leaders: Top Pharmaceutical Distributors*. Available online at http://www.mdm.com/2014_pharmaceuticals_mdm-market-leaders.