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May 22, 2014

Dr. Ilisa Bernstein
Deputy Director, Office of Compliance
Food and Drug Administration
10903 New Hampshire Avenue
Bldg. 51, Rm 5271
Silver Spring, MD 20993-0002

Re: Pharmaceutical Distribution Security Alliance Questions and Answers Regarding the Drug Supply Chain Security Act

Dear Dr. Bernstein:

As you know, the Pharmaceutical Distribution Security Alliance (PDSA) is a multi-stakeholder coalition with membership that spans the entire spectrum of the U.S. pharmaceutical distribution system, including manufacturers, wholesale distributors, third-party logistics providers, and pharmacies. More than 30 companies are formal members of PDSA (a membership list is enclosed), while many other external stakeholders provide additional policy and technical support. Our primary goal is ensuring patients have uninterrupted access to safe, authentic, FDA-approved medicine.

Since enactment of the Drug Supply Chain Security Act (DSCSA) members of PDSA have identified a number of questions that are not clearly answered by the plain language of the DSCSA and create operational issues. Working together, members from all sectors of the supply chain have developed answers to these questions that PDSA believes constitute reasonable and appropriate interpretations of the statutory text and account for the operational realities faced by supply chain participants. A copy of these questions and proposed answers is enclosed for use by the Agency.

PDSA respectfully asks that the FDA provide direction and clarity with regard to, and consistent with, the issues identified in the enclosed questions and answers document through Agency

FAQs, in guidance documents or preambles to Agency rules mandated by DSCSA, and through other means the Agency considers appropriate. Where appropriate, PDSA also encourages the Agency to use the authority granted to it under 21 U.S.C. § 360eee–1(a)(3) to provide greater clarity on the issues PDSA has raised. In light of operational planning that is currently underway, the investments being made in infrastructure for compliance with the DSCSA, and the need to avoid industry confusion, we respectfully request that FDA issue such clarifying documents promptly.

PDSA appreciates the FDA's consideration of the enclosed document, and we welcome the opportunity for further discussion about these important topics.

Sincerely,

Vince Ventimiglia

Pharmaceutical Distribution Security Alliance
Questions & Answers on DSCSA

These questions and answers have been prepared by the Pharmaceutical Distribution Security Alliance (PDSA), a multi-stakeholder coalition with membership that spans the entire spectrum of the U.S. pharmaceutical distribution system, including manufacturers, wholesale distributors, third-party logistics providers, and pharmacies. This document includes a number of operational questions that have been identified by PDSA with regard to the Drug Supply Chain Security Act (DSCSA). The answers provided in this document reflect PDSA's understanding of the DSCSA and are being provided to the FDA for its consideration. Where appropriate, we ask that FDA clarify its position on these issues through guidance documents, regulations or their preambles, or other proper means.

This document, in its current form, is being presented for discussion purposes only and is not intended for use by any individual or entity other than the FDA.

1. How should the grandfathering provisions for information sharing in Section 582(a)(5)(B) be interpreted and applied?

Trading partners must comply with any applicable requirements of the Prescription Drug Marketing Act (PDMA) for transactions that occur before January 1, 2015. For transactions that occur on and after January 1, 2015, trading partners must comply with any applicable requirements under Section 582(b) through (e); provided however, a trading partner is not required to capture, maintain, pass, or otherwise provide or make available any information it was not required to receive with respect to the product involved in the transaction.

The grandfathering provisions in Section 582(a)(5)(B) do not clearly describe how industry should transition from pedigree requirements under PDMA to the new transaction information-based system under DSCSA. Trading partners should be required to comply with any applicable requirements of PDMA for transactions that occur before January 1, 2015. Section 582(a)(5)(B) should be read as requiring trading partners to comply with any applicable[1] requirements under Section 582(b) through (e) for transactions that occur on and after January 1, 2015; provided however, a trading partner is not required to capture, maintain, pass, or otherwise provide or make available any information it was not required to receive with respect to the product involved in the transaction. The trading partner that is receiving the product may take ownership of the product with the transaction information, transaction history, and transaction statement provided by the seller.

We respectfully ask that the FDA clarify through rule, guidance or other reasonable means the implications of the grandfathering provisions in Section 582(a)(5)(B) consistent with this understanding.

[1] Some requirements under Section 582(d) are not applicable until July 1, 2015.

2. What is a contract manufacturer (CMO)?

For purposes of the DSCSA, a CMO is an entity that performs manufacturing operations for the NDA/ANDA/BLA holder or a co-licensed partner of the NDA/ANDA/BLA holder, to fulfill a contractual obligation with such manufacturer, but is not responsible for the introduction of the product into interstate commerce.

This definition is consistent with definitions established by the FDA in its May 2013 *Draft Guidance for Industry on Contract Manufacturing Arrangements for Drugs: Quality Agreements*, and we respectfully ask that the FDA adopt this definition through rule, guidance or other reasonable means.

3. Is a CMO responsible for the obligations of a manufacturer under the DSCSA?

No, a CMO is not responsible for the obligations of a manufacturer under the DSCSA.

A CMO is "an extension of" the manufacturer, as defined in Section 581(10), and any transfer of product between such manufacturer and a CMO is part of the manufacturing process (regulated by FDA under the manufacturer's quality system, such as through the application of cGMPs), and not part of the distribution process regulated by the DSCSA. *See* 21 C.F.R. 200.10. As explained in FDA's May 2013 *Draft Guidance for Industry on Contract Manufacturing Arrangements for Drugs: Quality Agreements*, the entity that introduces, or causes introduction of, the product into interstate commerce bears the responsibility for the quality, safety, and efficacy of those products, whether or not manufactured through use of a CMO. Because the CMO's activities are part of the manufacturer's manufacturing process, and because the CMO engages in those activities at the direction of the manufacturer, a CMO is not responsible for the manufacturer obligations in Section 582(b), and the transfer of product between a manufacturer and CMO, regardless of whether there is a legal change of title, is not a "transaction" under the DSCSA.

We respectfully ask that the FDA clarify through rule, guidance or other reasonable means that a CMO is not responsible for the obligations of a manufacturer under the DSCSA.

4. Is a CMO considered a "co-licensed partner" or "affiliate" under the DSCSA?

No, a CMO is not a co-licensed partner or affiliate under the DSCSA definition of "manufacturer."

A CMO is distinct from a co-licensed partner. As defined in Section 581(10), a co-licensed partner satisfies the definition of a "manufacturer" for purposes of the DSCSA. However, a CMO arrangement does not typically involve a license or other grant of legal right from the NDA/ANDA/BLA holder and, therefore, does not satisfy the definition of a "manufacturer" for purposes of the DSCSA.

A CMO also is not an affiliate of the relevant manufacturer. The definition of an "affiliate" under the DSCSA is intended to mirror the definition of an affiliate under Section 735(11) of the

FDCA, and in that context, the FDA has made clear that an "affiliate" is a company that is legally controlled, directly or indirectly, by another company or can be controlled by another company. 66 Fed. Reg. 59,138, at 59,146. Mere contractual obligations or business arrangements with a company are not sufficient to make that company an affiliate. Therefore, a CMO that is not legally controlled by, or under common control with, a manufacturer is not an affiliate for purposes of the DSCSA.

We respectfully ask that the FDA clarify through rule, guidance or other reasonable means that a CMO is not a co-licensed partner or affiliate for purposes of the DSCSA.

5. How are the manufacturer obligations satisfied when a product is produced by the co-licensed partner of an NDA/ANDA/BLA holder?

When a co-licensed partner of an NDA/ANDA/BLA holder is engaged in the production, marketing or distribution of a product, the NDA/ANDA/BLA holder and the co-licensed partner should contractually assign responsibility for each of the obligations under Section 582(b) between or among themselves.

An NDA/ANDA/BLA holder and a co-licensed partner of the NDA/ANDA/BLA holder both meet the definition of a "manufacturer" under Section 581(10). Although more than one entity therefore meets the definition of "manufacturer," the structure of the obligations under the DSCSA clearly contemplates that there is only one set of manufacturer obligations (*i.e.*, the obligations under Section 582(b)) with respect to the distribution of a given package or case of product. For example, Section 582(b) requires a manufacturer to provide transaction information and transaction history to the subsequent owner, but unlike other sectors, there is no obligation for a manufacturer to receive that information. This suggests that a manufacturer-to-manufacturer transaction is not contemplated by the Act. Similarly, Section 581(25) defines "transaction history" as a statement that includes "the transaction information for each prior transaction going back to the manufacturer of the product," which contemplates a single manufacturer with respect to the distribution of a given package or case. Therefore, when a co-licensed partner of an NDA/ANDA/BLA holder is engaged in the production, marketing or distribution of a product, the NDA/ANDA/BLA holder and the co-licensed partner should contractually assign responsibility for each of the obligations under Section 582(b) between or among themselves.

Practical realities of pharmaceutical distribution also require that an NDA/ANDA/BLA holder and its co-licensed partners be able to contractually assign responsibility for the obligations under Section 582(b). The inclusion of more than one manufacturer in a transaction history would create confusion downstream and unnecessarily complicate and slow the process of validating or verifying suspect product.

We respectfully ask that the FDA clarify through rule, guidance or other reasonable means that an NDA/ANDA/BLA holder and its co-licensed partner should contractually assign responsibility for each obligation under Section 582(b) between or among themselves.

6. Is an entity that has a sales and marketing partnership with a manufacturer considered a "co-licensed partner" under the definition of "manufacturer" in Section 581(10)(B)?

Yes. The term "co-licensed partner" is not defined in the DSCSA or in the FDCA or PHSA. The term appears in the definition of "manufacturer" under Section 581(10). Pursuant to that definition, a person that receives product directly from the NDA/ANDA/BLA holder (or an affiliate of the NDA/ANDA/BLA holder) may itself be considered a "manufacturer" if it is a "co-licensed partner" of the NDA/ANDA/BLA holder. The term "co-licensed partner" by its very terms requires some type of a licensing or other similar agreement conferring a right on the person. The person would not qualify as a co-licensed partner if the person merely purchases product from the NDA/ANDA/BLA holder for resale; there must also be a contractual or other similar business relationship conferring a right on the person.

"Co-licensed partner," while undefined in federal law, is a commonly used industry term and has been defined in various state laws. Those state-law definitions include either "business activities" between the parties, or "marketing and manufacturing a prescription drug." *See, e.g.*, Md. Health Occ. Code § 12-6C-01 (defining a co-licensed partner as "person in a relationship in which two or more persons have the right to engage in the manufacturing or marketing of a prescription drug, consistent with the U.S. Food and Drug Administration's implementation of the federal Prescription Drug Marketing Act"); Neb. Rev. Stat. § 71-7439 (defining co-licensed products as "prescription drugs that have been approved by the federal Food and Drug Administration and are the subject of an arrangement by which two or more parties have the right to engage in a business activity or occupation concerning such drugs"). In either case, state-law definitions of "co-licensed partner" include sales, marketing and other business activities under a contractual license. Therefore, an entity, including a private label distributor, that receives product from the NDA/ANDA/BLA holder pursuant to a license or similar contractual agreement that confers a right on the entity to sell the product through its distribution channels is a co-licensed partner of the NDA/ANDA/BLA holder and therefore meets the DSCSA definition of "manufacturer." Accordingly, such entity's obligations with respect to that product are determined as set forth in Q&A #6.

We respectfully ask that the FDA clarify this understanding through rule, guidance or other reasonable means.

7. How should a company determine the relevant dates to be included in transaction information?

It is critical that industry have flexibility to determine and include dates in transaction information in a manner that is reasonable for a company's given business arrangements but ensures the ability to establish the relevant chain of control for a product as part of an investigation consistent with the intent of the DSCSA.

As defined in Section 581(26), transaction information includes "the date of the transaction" and "the date of the shipment, if more than 24 hours after the date of the transaction." Industry relies on countless arrangements with complex and varying contractual terms related to sale, shipment, ownership, and billing and invoicing. A single approach applicable to every arrangement is not

feasible. For example, supply agreements may specify different points for the actual transfer of title of products. In one arrangement title may pass when goods leave the shipper's dock, but in another arrangement title might pass when the goods are delivered to the buyer's dock. In yet other arrangements, title may pass when the buyer opens the truck, inspects the delivery, and accepts it. Thus, the point in time at which the trading partners will know with certainty the date on which title will transfer will vary from transaction to transaction. Therefore it is critical that industry have flexibility to determine and include dates in transaction information in a manner that is reasonable for a company's given business arrangements but ensures the ability to establish the relevant chain of control for a product as part of an investigation consistent with the intent of the DSCSA. The trading partner receiving the transaction information may take ownership of the product with the transaction date and the shipment date if included as provided by the seller.

We respectfully ask that the FDA provide, through rule, guidance or other reasonable means, the necessary operational flexibility with regard to relevant dates to be included in transaction information.

8. **Section 582(d)(1)(D) provides, until 4 years after enactment, with regard to requests for information, the Secretary shall "limit the request time period to the 6 months preceding the request or other relevant date." How does this look-back period apply to products received prior to July 1, 2015?**

During this time period, the Secretary's request for information, including requests from another federal or state official, to a dispenser does not require the dispenser to respond with any transaction information, transaction history, or transaction statement that may have been received by the dispenser prior to July 1, 2015. With respect to transaction information, transaction history, and transaction statements received on and after July 1, 2015, but prior to November 27, 2017, a request for information may not require a dispenser to provide such information further back than July 1, 2015 or require a dispenser in any request to respond for more than the immediate six-month period that commences upon the dispenser's receipt of the product. For example, a request for information on October 1, 2015 would not require the dispenser to look further back than July 1, 2015.

We respectfully ask that the FDA clarify this position through rule, guidance or other reasonable means.

9. **Section 582(d)(4)(A)(i)(III) requires a dispenser, beginning January 1, 2015, as part of an investigation of suspect product, to validate "any applicable transaction history and transaction information in the possession of the dispenser." However, dispensers are not required to receive transaction history and transaction information until July 1, 2015. When must dispensers begin validation of transaction history and transaction information?**

A dispenser will not have "applicable" transaction history or transaction information in its possession for products received prior to July 1, 2015. Therefore, a dispenser is only required to

validate the transaction history and transaction information of product received on and after July 1, 2015.

We respectfully ask that the FDA clarify this position through rule, guidance or other reasonable means.

10. Is the transfer of product to or through a patient assistance program intended to be subject to Section 582 requirements?

No, the transfer of product to or through a patient assistance program is not intended to be subject to Section 582 requirements.

The transfer of product to or through a patient assistance program is not intended to constitute a transaction under the DSCSA. Patient assistance programs are structured in a variety of ways. Transfers to or through many patient assistance programs are exempt from DSCSA requirements because they are intracompany transfers, involve products not intended for sale or further distribution, or are transfers to or by a 501(c)(3) organization. Together, the exemptions applicable to many transfers of product to or through a patient assistance program demonstrate an intent to exempt *all* transfers of product to or through a patient assistance program, whether it is to a 501(c)(3) organization or to a licensed health care practitioner. Indeed, prior to the Senate vote on the DSCSA, Senator Burr made the following statement: "The charitable distribution of prescription drugs from the manufacturer to patients through patient assistance programs, PAPs, is a valuable and unique approach to providing American patients access to critical lifesaving medicines. As this legislation is implemented, the varied and unique approaches of PAPs should be taken into consideration to ensure patients who access needed treatments through these effective programs are able to continue accessing the prescription drug medications provided through PAPs." 159 CONG. REC. S8075 (daily ed. Nov. 18, 2013) (statement of Sen. Burr).

Because we believe this was the intent, we respectfully ask that the FDA clarify in rule or guidance, or if necessary, clarify through an exemption under 582(a)(3)(A)(iii), that trading partners are not required to provide TI/TH/TS when transferring product as part of participating in a patient assistance program.

11. Are all products used in clinical trials exempt from DSCSA requirements?

All clinical trial products should be exempt from DSCSA requirements because they are already subject to strict regulatory controls.

"Clinical trial products" exist in a variety of situations. First, traditional, investigational new products not yet licensed and used in authorized clinical trials are a "clinical trial product." Second, "clinical trial product" may include marketed product studied post-approval (*e.g.*, phase IV studies). Third, some manufacturers supply "clinical trial product" in commercial packaging (*i.e.*, the product has been FDA-approved) to investigators who have purchased the product to use in their own "investigator initiated" clinical studies. Fourth, a manufacturer may purchase another manufacturer's existing commercial product, either directly from that manufacturer or

from a wholesale distributor, and such product may be used as a comparator or a combination product in an authorized clinical trial.

While the statutory language does not expressly exclude "clinical trial product,"[2] we think that it is likely that Congress did not intend for transfers of "clinical trial products" to be subject to DSCSA requirements. This is because applying DQSA requirements to drugs for investigational use is neither necessary nor practical given that they are not introduced into the supply chain in the same unrestrained manner as commercial products but rather are already subject to comprehensive regulations and/or study-based controls that govern their distribution and dispensing, as well as drug accountability requirements that require controlling and accounting for their use and disposition.[3] Additionally, clinical trial products may be required to be packaged and labeled in such a manner as to blind the identity of the drug. Imposing pedigree requirements may break the blind, thereby compromising the integrity of the study.

We respectfully ask that the FDA clarify in rule or guidance, or if necessary, clarify through an exemption under 582(a)(3)(A)(iii), that clinical trial products, as described above, are exempt from the requirements of the DSCSA.

12. Does checking the wholesale distributor database established pursuant to Section 503(e)(2)(B) on a recurrent basis protect a trading partner from liability or enforcement action if wholesale distributor was not, in fact, authorized?

Yes, checking the wholesale distributor database established pursuant to Section 503(e)(2)(B) on a recurrent basis protects a trading partner from liability under the DSCSA or enforcement action if a wholesale distributor listed in the database as authorized is not, in fact, authorized.

The DSCSA provisions regarding the establishment, maintenance of, and public access to the wholesale distributor database suggest that it is intended to be used by trading partners, the States, and FDA to determine whether a wholesale distributor is authorized. For this reason, we believe that no enforcement action should be taken against a trading partner for engaging in a transaction with an unauthorized wholesale distributor if the wholesale distributor was listed as authorized in the wholesale distributor database established pursuant to 503(e)(2)(B), the trading partner was not negligent in checking the database (*e.g.*, checked the database against its customer list periodically), and the trading partner had no other information to suggest that the wholesale distributor was not authorized.

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[2] These types of transfers are not listed under the exemptions from the definition of "transaction." In many instances, clinical trial product, especially those subject to an IND, will never be involved in a "transaction" which means the DSCSA would not apply. Additionally, even though the DSCSA applies only to transactions of "prescription drugs," it is not clear from the definition in FDCA § 503(b) that a clinical trial product could not be a prescription drug.

[3] *See* 21 C.F.R. §§ 312.6 (labeling of an investigational new drug), 312.50 (general responsibilities of sponsors), 312.52 (transfer of obligations to a contract research organization), 312.57 (recordkeeping and record retention), 312.59 (disposition of unused supply of investigational drug), 312.60 (general responsibilities of investigators), 312.61 (control of the investigational drug), 312.62 (investigator recordkeeping and record retention), and 312.69 (handling of controlled substances). For studies that would not be subject to Part 312, there are appropriate non-FDA guidelines. *See e.g.*, World Health Organization, Guidelines for good clinical practice (GCP) for trials on pharmaceutical products, WHO Technical Report Series, No. 850, 1995, Annex 3, *available at* http://apps.who.int/medicinedocs/pdf/whozip13e/whozip13e.pdf.

We respectfully ask that the FDA clarify in rule or guidance, or through other reasonable means, that trading partners will be afforded such protections.

13. Are manufacturers, repackagers, and wholesale distributors that deliver product to a dispenser by drop shipment required to send transaction information, transaction history, and transactions statements to the wholesale distributor that does not physically handle or store the product?

No, a manufacturer, repackager, or wholesale distributor is not required to send transaction information, transaction history, and a transaction statement to the wholesale distributor that does not physically handle or store the product.

The DSCSA requires the entity performing a drop shipment to provide information "directly" to the dispenser, and states that the wholesale distributor that does not physically handle or store the product "shall be exempt" from the requirement to maintain transaction information, transaction history, and transaction statements. The DSCSA's exemption for drop shipments would be essentially meaningless if the manufacturer, repackager, or other wholesale distributor that distributes the product by means of a drop shipment were nevertheless required to provide the transaction information, transaction history, and transaction statement to wholesaler distributors, who could then throw it away.

We respectfully ask that the FDA clarify in rule or guidance, or through other reasonable means, that the entity performing a drop shipment is not required to provide transaction information, transaction history, and transaction statements to the wholesale distributors that do not physically handle or store the product.