

Effective Controlled Substances Supply Chain Management: What You Need to Know to Ensure Compliance and Optimize Efficiency

INTRODUCTION

At a time when supply chain management has become increasingly complex, managing the unique challenges of the controlled substance supply chain can seem daunting for companies lacking in-house capabilities and resources.

Controlled substances are highly regulated and must be vigilantly monitored from the laboratory to the marketplace to prevent theft and illicit sale in the black market, a growing trend. In addition to abundant federal and state regulations, increased globalization – with its stringent import and export restrictions, permits and declarations required for controlled substances – has made compliance even more challenging.

Effective management of the controlled substance supply chain and navigation of the regulatory process with minimal costs and delays requires considerable time, effort and expertise. For a drug company and/or its contract development and manufacturing organization (CDMO), management calls for rigorous attention to compliance, thorough planning, robust risk-management capabilities and the skills for effective implementation. Understanding and complying with federal, local and, if applicable, global regulatory requirements of your supply chain destinations is critical to prevent delays and penalties.

With supply chains growing faster than resources today, many companies producing controlled substances are outsourcing to gain the needed expertise, efficiency and flexibility. Partnering with a CDMO experienced in supply chain management of controlled substances can prevent costly delays, steep penalties for noncompliance, and the potential postponement of a clinical trial.

SCHEDULED DRUGS AND LISTED CHEMICALS

Controlled Substances

A controlled substance is a drug or chemical substance that is highly regulated under the Controlled Substance Act (CSA). The foundation of the CSA is a five-tier “schedule,” a classification system for drugs based on their abuse potential, with Schedule I having the highest potential. The

schedule generally dictates the degree of precaution used with the substance in the clinical supply chain. Products or actives can move up or down in the schedules as determined by the Drug Enforcement Administration (DEA), or be added to or deleted from the schedules, and an active can be in a different schedule than the finished product.

Schedule I

- High potential for abuse and no accepted medical use in treatment in the U.S.
- Lacks accepted safety for use under medical supervision
- Investigational drugs for actives not currently approved for use in the U.S.
- Examples: dronabinol, marijuana, heroin, crystal methamphetamine

Schedule II

- High potential for abuse
- Currently accepted medical use in treatment in the U.S., or accepted with severe restrictions
- Abuse may lead to severe psychological or physical dependence
- Examples: fentanyl, hydrocodone, hydromorphone, methamphetamines, methylphenidate, morphine

Schedule III

- Abuse potential less than Schedules I and II
- Currently accepted medical use in treatment in the U.S.
- Abuse may lead to moderate or low physical dependence or high psychological dependence
- Examples: buprenorphine, dronabinol (marinol), ketamine, testosterone

Schedule IV

- Low potential for abuse relative to Schedule III
- Accepted medical use in treatment in the U.S.
- Abuse may lead to limited physical or psychological dependence relative to Schedule III
- Examples: diazepam, clonazepam, midazolam

Schedule V

- Low potential for abuse
- Accepted medical use in treatment in the U.S.
- Abuse may lead to limited physical or physiological dependence
- Examples: codeine-containing cough medications, diphenoxylate (Lomotil)

Listed Chemicals

Listed chemicals (List I and II) are specifically designated chemicals and precursor chemicals that, in addition to their legitimate use, are used in the illicit manufacture of a controlled substance in violation of the CSA. For example, pseudoephedrine HCl is referred to as a scheduled List I

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chemical because it can be converted to methamphetamine. Acetone is a List II chemical.

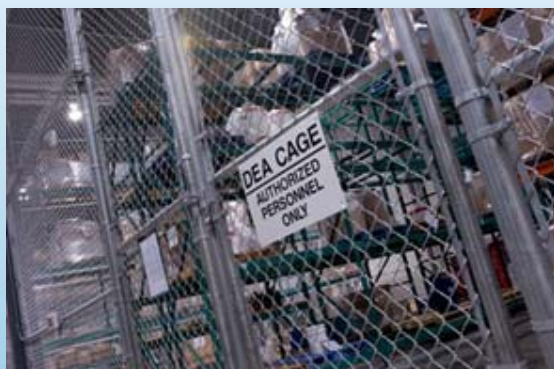
Regulation of Controlled Substances

Three treaties establish the framework for an international drug control system and the statutory basis of the Controlled Substance Act of 1970, as well as most of U.S. drug control policy. Their purpose is to limit the use of narcotic drugs and psychotropic substances and their precursors to legitimate medical and scientific purposes. The role of the DEA is to assure the U.S. meets the treaty commitments by enforcing the provisions of the CSA and regulations of the U.S., including the manufacture, distribution and dispensing of controlled substances.

The DEA has decentralized the enforcement of diversion-control operations. Each local office has significant autonomy, with local interpretation and enforcement of regulations.

There are also separate state regulations of controlled substances, which frequently change. For example, a state may have more stringent requirements for substances with the highest abuse in their state. It is important for the manufacturer or its service provider to know the regulatory nuances of each state and DEA office along its supply chain route.

Navigating the maze of regulations and managing the required paperwork demands considerable skill, time and expertise, as well as meticulous planning.



REGISTRATIONS, RECORDS AND REPORTS A Closed Distribution System

The CSA created closed system of distribution for controlled substances. Every person and company authorized to handle controlled substances along the supply chain must be registered with the DEA and keep records with respect to all transfers.

In addition to substantial registrations, two other requirements contribute to the complexity of the controlled substance supply chain. First, to prevent diversion, it is essential to account for and report the location of all drug supply as it moves from one DEA-registered activity to another -- such as distribution to a wholesaler, any lost in manufacturing or testing, and the remainder from clinical trial.

Second, the manufacturer/distributor must also report suspicious orders to the DEA. The DEA expects the distributor to know its customers, and be able to flag unusual orders -- such as orders of unusual size or frequency, and those deviating substantially from a normal pattern.

Registrations

Manufacturers/distributors must obtain a DEA registration to handle controlled substances. A controlled substance registrant can also be registered to handle listed chemicals.

In some cases, multiple registrations may be required, depending on the type of activity and location. Beyond the basic security and record-keeping requirements for all schedules, Schedule I, II and III (narcotics) have additional documentation requirements. For the clinical supply chain, multiple registrations are typically required. Clinical trial research protocols for Schedules I and II must be submitted to the DEA for prior approval before the materials can be shipped.

Most states require a separate registration for controlled substances. The DEA will ask for proof of registration with the state before approving and upon each renewal application. Registrations may also be required for each state to where the product is being shipped – this can often be a major challenge and cause shipping delays.

Importing or exporting a listed chemical requires a separate registration. In certain circumstances, a registration can be amended to add a new controlled substance in the schedule – and in some cases, it is not required. Registrations can have a narrow or wide scope. For example, an exporter may only export, whereas an importer may distribute what it imports. A manufacturer may test material it manufactured or ship the material to another location within the U.S. However, it

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may not import, export, or receive samples for testing from another registration.

Normally each physical location requires a separate registration, but not always. Often one location will have multiple registrations – such as export, import, listed chemical import, manufacturer, distributor, and analytical.

Records and Reports

All DEA-related records must be retained for a minimum of two years. These include documentation of purchases, shipments, material consumed in testing, batch and waste disposition.

Quarterly reports must be submitted to the DEA regarding the movement of all Schedule I and Schedule II raw materials, standards and finished goods, and raw materials and standards of Schedule III narcotics. Annual reports must be submitted to DEA regarding movement and inventory for Schedules I and II materials and Schedule III narcotics as well as selected psychotropic agents as required by international treaty. Inventory must be conducted at least biennially and records documenting receipt and disposition are required.

EXPORTING AND IMPORTING CHALLENGES

Exporting controlled substances demands careful planning, allowing adequate time for each step. The number of countries to which a controlled substance is being exported, and each country's regulations, determine the complexity of exporting. Applicants who can submit the required paperwork must be registered with and authorized by the DEA to export controlled substances.

Adding a drug to a DEA Export Registration requires a written request to the local DEA office requesting an amendment to the registration. The response time from the DEA can range from one to more than six weeks.

If you are outsourcing this function, be sure to provide all needed information to your CDMO in a timely manner, including ports of entry/export, mode/name of transport/transporter, and dates of departure/entry, as well as the addresses for each destination and re-export recipient, or the letter of no re-export.

ENSURING AN EFFICIENT SUPPLY CHAIN

The starting point for successful, compliant supply chain management of controlled substances is a project management team that includes participants with demonstrated expertise in the regulatory requirements, transportation, logistics and storage of these materials. Whether you are working with a service provider or managing the supply chain internally, here are considerations for maximizing efficiency and accuracy while reducing delays and potential penalties.

Planning

Begin planning with the DEA as early as possible. If you are working with a CDMO, provide detailed information in a timely manner. The sooner the supply chain manager knows what is required and when, the better the chances of effectively navigating shipping, regulatory, and storage requirements. If importing and exporting are considered well in advance, they should not impact time to market.

Start by developing a definitive plan for production and sharing the plan with your CDMO. Determine drug strengths, package sizes, batch sizes, number of batches, and targeted production date. Include:

- What are the intended primary and secondary package sizes?
- Where do you plan to market the product?
- When do you plan to submit the application to the FDA?
- Who will be your distributor and where are they located?
- Are DEA List I chemicals required to manufacture the product?
- What is the plan for handling unused clinical materials?
- What is the controlled substance/ impurity-related substance reference standard? Will it cause a delay in testing raw materials or products before they can be released for distribution?

The supply chain manager will then develop a detailed plan with targeted dates for movement of materials.

Manufacturing and Distribution

When determining the shipping schedule, the sooner the CDMO knows what is to be shipped and to whom, the less likely the chance of a DEA-related issue. The CDMO should coordinate with the recipient to assure receipt of any required documentation well in advance of shipping, and must first obtain confirmation of each recipient's DEA registration. Schedules I and II substances require DEA Form 222, and in some instances a Certification of Available Quota from the recipient.

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All Schedule I and II substances and pseudoephedrine require a quota from the DEA, which can take 8 to 12 weeks to obtain and is one of the most significant barriers to beginning distribution. Your service provider needs a letter of intent from your company stating the number of batches planned to include with the quota application. Depending on the schedule, adding a new active or finished product may require an amendment to the registration. In some cases, a DEA inspection may be required prior to approval, usually involving a storage issue. The schedule can also impact the type of storage space required for raw material, finished goods pending shipment, samples and waste.

Occasionally a reference standard has a different controlled substance schedule than the active ingredient. This may require amending a registration and possibly applying for quota to purchase the standard if purchased under the manufacturing registration.

Clinical Trials

Timing and compliance are critical to ensure materials reach clinical trial sites on time. Failure to follow all regulations can lead to costly delays and regulatory audits or investigations. If the recipient/investigator and a third party responsible for clinical labeling do not have the appropriate DEA registration, the trial can be delayed.

The procedure for unused trial material is particularly important for controlled substance products that require a quota. The best approach is for the site to arrange a transfer to a reverse distributor. In some cases, the manufacturer may not have sufficient quota to buy back unused clinical trial materials.

Storage

DEA regulations have specific storage requirements for controlled substances. Schedule I and II material must be stored in a vault or other structure approved by the local DEA office, depending on the type of registration. Schedule III to V material may be stored in a caged area built to the specifications provided in the regulations. The local DEA office makes the final call as to what is appropriate.

Common Issues: Avoiding Regulatory Purgatory

One of the most common reasons companies receive fines or noncompliance warnings from the DEA is failure to identify and report suspicious orders both for controlled substances and listed chemical sales. It is important to vigilantly monitor sales and flag any unusual orders of commonly abused substances.

Another reason is incomplete or inadequate documentation, resulting in lack of traceability. A qualified service provider will ensure that all required documentation is accurately completed and efficiently submitted.

CONCLUSION

Maintaining the supply chain of controlled substances from development to the final destination is more challenging than ever. As supply chain dynamics grow in complexity, life science companies responsible for controlled substances are recognizing the need for considerable expertise, vigilant oversight of processes and movement of materials, and substantial attention to regulatory requirements. Increasingly, they are realizing the value of strategically partnering with a highly competent CDMO to gain needed efficiencies and a competitive edge.

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2. ClariNet. Commentary: Prescription drugs black market booms. October 6, 2003. http://quickstart.clari.net/qs_se/webnews/wed/al/Uus-blackmarketdrugs.RkZr_DO6.html
3. 3. What's New. Notice of proposed rule change. Drug Enforcement Administration website. July 6, 2011. www.deadiversion.usdoj.gov

About DPT Laboratories:

DPT is a contract development and manufacturing organization (CDMO) providing companies the best solutions to their sterile and non-sterile pharmaceutical development and manufacturing needs through innovation, technology, and service. Specializing in semi-solid and liquid dosage forms, DPT has a reputation for quality, unmatched technical expertise, extensive manufacturing capabilities, and an exemplary regulatory compliance record. With five cGMP facilities in San Antonio, Texas, and Lakewood, New Jersey, DPT offers full-service outsourcing solutions, including stand-alone development, site transfers, state-of-the-art manufacturing, packaging, and worldwide distribution. For more information, call 210-476-8100 or visit www.DPTLabs.com.