



The clinical supply chain: Strategies for scheduled drugs

Regulatory requirements in the clinical trial scheduled-drug supply chain.

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At a time when clinical trials demand increasingly complex supply chain support, managing the special challenges associated with scheduled drugs requires meticulous planning, a thorough understanding of government regulations, and the skill to navigate them successfully.

By definition, a scheduled or controlled drug is one whose use and distribution are highly regulated due to the potential for abuse. Although such drugs are involved in a small minority—just 5% to 10% of the trials for which Fisher Clinical Services manages the clinical supply chain—a disproportionate amount of upfront effort is necessary to meet the regulatory requirements that govern their handling and use.

Failure to do so inevitably leads to costly delays for a sponsor—in shipping and receiving trial materials, getting a clinical trial off the ground, bringing key clinical sites online, and even audits or investigations by regulatory authorities—that can postpone or prevent the completion of a trial or the licensure of an investigational drug.

The Controlled Substance Act

The regulations governing scheduled drugs are detailed in The Controlled Substance Act (CSA), a 1970 law enacted during the Nixon administration at a time

of growing national concern over narcotics abuse and trafficking. The foundation of the CSA, which falls under the jurisdiction of the U.S. Department of Justice's Drug Enforcement Administration (DEA), is a five-tier "schedule" or classification system for drugs based upon their abuse potential.

At the top of the pyramid, occupying Schedule 1, are drugs with the highest abuse potential and no safe, accepted medical use in the U.S.—so-called "street drugs" such as heroin, LSD, PCP, and crack cocaine, as well as marijuana.

In Schedule 2 are drugs with a high risk of abuse, but which nonetheless possess some safe and accepted medical uses—drugs such as morphine, cocaine, oxycodone (Percodan®), methylphenidate (Ritalin®), and dextroamphetamine (Dexadrine®).

Commonly prescribed drugs with less potential for abuse—including tranquilizers, sedatives, stimulants, anti-anxiety drugs such as diazepam (Valium®) and alprazolam (Xanax®), and nonnarcotic analgesics such as acetaminophen with codeine (Tylenol® No. 3)—reside in Schedule III, IV, or V.

The schedules are also commonly known as C-I, C-II, C-III, C-IV, and C-V. As a rule, the schedule to which a drug is assigned dictates the degree of precaution associated with it in the clinical supply chain.¹

Registration and recordkeeping

In addition to classifying scheduled drugs based on abuse potential, the CSA established a closed system of distribution—essentially a sealed supply chain—around those authorized to handle controlled substances. Every person, organization, and activity connected to controlled drugs in any way requires prior authorization from the DEA, significantly increasing the complexities of supply chain management.

- **Individuals.** All individuals and firms responsible for manufacturing, importing, exporting, distributing, or dispensing a scheduled drug must apply for and obtain a DEA registration in advance.

- **Activities.** Each discrete activity involving a controlled drug requires a separate registration from the DEA. If an individual or firm is conducting multiple activities—such as importing and dispensing a scheduled drug, as a clinical investigator might in the conduct of a clinical trial—a separate registration is required for each independent activity. In the context of a clinical supply chain, the requirement for multiple registrations is commonplace.

- **Locations.** If any activities involving a controlled drug take place at multiple locations—as in the case of several distribution sites within the same region, for example—

a separate registration is required for each location.

- **Drugs.** A registration applies only to the specific drug or drugs for which it was expressly issued. For instance, if the same clinical investigator is registered to use one Schedule II drug in a clinical trial, and the trial protocol is revised to substitute another drug from the same schedule, the investigator must obtain an entirely new registration for the drug specified in the protocol.

- **Research protocols.** The protocol itself must also be submitted to the DEA for prior approval before materials can be shipped and the trial can get underway.

Importantly, the DEA also requires all registrants to maintain complete and accurate inventories of scheduled drugs, security for the storage of controlled substances that will be described in further detail, and records of each and every transaction. These records are subject to DEA audits and reconciliation.²

Key importing and exporting challenges

Given rigorous registration requirements, it stands to reason that importing and exporting scheduled drugs demands considerable and careful planning. Planning should allow sufficient time to complete multiple steps, many of which must take place sequentially.

Importing

- First, only individuals who are registered with and authorized by the DEA to import controlled substances may use and submit relevant paperwork, including declarations and applications for permits.

- An importer must have any scheduled drug slated for import added to the DEA

Import Registration. While timelines can vary, allowing four weeks for turnaround is recommended.

- DEA Form 357 must be submitted in order to import controlled substances for domestic and/or scientific purposes.

- The DEA will respond to receipt of Form 357 by issuing DEA Form 35, the permit to import controlled substances. From start to finish, this part of the approval cycle can take up to six weeks.

- A quota application is also required by both the receiving country and site for importing C-II controlled substances. This process can take from four to six weeks.²

Exporting

As one can imagine, the regulations and number of countries to which a scheduled drug is being exported increase the complexity of the export process.

- The only individuals who may use and submit relevant paperwork, including declarations and applications for permits, are those registered with and authorized by the DEA to export controlled substances.

- An exporter must first add a scheduled drug for export to the DEA Export Registration, which generally requires a four-week turnaround.

- Obtaining a permit to export a drug requires submission of either DEA Form 161 or DEA Form 161R. Form 161 should be used for exporting a scheduled drug to a single country. However, if a scheduled drug is bound for one or more countries by way of another—in the case of a regional facility responsible for shipping clinical supplies to sites in multiple countries—then DEA Form 161R, the application for a permit to export a controlled substance for subsequent re-export, is used instead.

- Receipt of Form 161 prompts the DEA

to issue DEA Form 36, the permit to export controlled substances. This approval process often takes up to six weeks.

- Schedule III non-narcotics and Schedules IV and V require the submission of DEA Form 236, a controlled substance import/export declaration. Once Form 236 is submitted, a company must wait 15 days for any DEA objections. Then, it's safe to export the drug.

- Export Forms 236 and 161 must be accompanied by the country import permit.

International standards differ on classifications of scheduled drugs, which are not necessarily global in nature. Fisher Clinical Services relies upon its regional facilities in North America, Europe, Latin America, and Asia for accurate information.

The receiving country and site also require a quota application for exporting C-II drugs. Turnaround time is another four to six weeks.²

References: 1. Drug Enforcement Administration (DEA) website; *The Controlled Substance Act*; <http://www.usdoj.gov/dea/pubs/abuse>

2. The Government Printing Office (GPO) Access website; *Title 21- Food and Drugs, Chapter II – Drug Enforcement Administration – Department of Justice*; <http://ecfr.gpoaccess.gov>

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