

## How Will DEA Affect Your Clinical Study?

By Terrance W. Woodworth

Clinical trials involving controlled substances in the United States (U.S.), whether as the study drug or a comparator, must adhere to the Controlled Substances Act of 1970 (CSA)<sup>1</sup> and its implementing regulations, which are enforced by the Drug Enforcement Administration (DEA). The controlled substance requirements of the CSA and its implementing regulations are in addition to the requirements for all drugs specified in the Federal Food, Drug and Cosmetic Act of 1938.<sup>2</sup> It is essential for sponsors, contract research organizations (CROs), and clinical investigators to comply with these requirements. The provisions of the Uniform Controlled Substances Acts,<sup>3</sup> which have been passed by most of the 50 states, are similar to the federal law; however, each state has its own legislative, regulatory and enforcement structure and process. Nevertheless, federal and state governments enforce eight key control measures, which directly impact all clinical trials with controlled substances:

1. Federal registration and state licensing of clinical investigators
2. Scheduling of the drug or substance
3. Importation and exportation controls
4. Quotas for Schedule 1 and 2 substances
5. Recordkeeping requirements
6. Reporting requirements
7. Site security measures
8. DEA investigations of clinical sites

The fundamental parts of these control measures pertaining to clinical trials are explained below.

### 1. State Licensing and Federal Registration of Clinical Investigators

Practitioners (MD, DO, DDS, DVM, MLP) who will participate in a clinical trial as a principal investigator or sub-investigator must be authorized by the state in which they practice to prescribe, dispense, administer and conduct research with controlled substances.<sup>4</sup> In most cases, these activities are authorized when a license is granted to the practitioner by the respective Board (e.g., State Board of Medical Examiners, Dental Board). These licenses cover the practitioner's entire practice and are not specific to clinical trials. Some states also have a separate state-issued, controlled-substance licensing requirement for prescribing, dispensing or administering (e.g., Alabama Controlled Substance Certificate granted by the Alabama Medical Board). Other states have a separate state controlled-substances authority that requires practitioners to obtain a separate *registration* (e.g., Missouri Bureau of Narcotics and Dangerous Drugs), in addition to the license granted by their respective Board. Consequently, investigators should ensure they are properly licensed and registered with all appropriate state authorities prior to commencing a study. (PhD's and PharmD's are not practitioners and must, therefore, rely on the principal investigator or a sub-investigator to dispense, etc. controlled substances.)

Federal registration is also required for an investigator to handle controlled substances in any manner. Authority for granting federal registrations is vested in DEA. DEA registration for practitioners is predicated on licensure or authorization by the competent state authority but is not automatic. Once approved, a certificate of DEA registration is issued by DEA in the category of "Practitioner." A DEA "Practitioner" registration is valid for three years.

In most cases, DEA registration and state licensure are required at the general physical location where controlled substances for the clinical trial will be dispensed and/or stored overnight.<sup>5</sup> For investigators participating in a clinical study at their primary practice location, registration and licensure would be at this location. For clinical trials conducted at a hospital or other institution, there can be several options for registration and licensing, depending on the circumstances and relevant regulations. In most cases, DEA registration and state licensure at the general location (address) of the hospital is the appropriate course of action, regardless of whether the controlled substances will be dispensed and stored in secure facilities in the investigator's clinic, ward or office at the hospital, or at the pharmacy, if the controlled substances will be dispensed and stored there. This approach can be possible even when, as part of the general ("campus") location of the hospital, the investigator or the pharmacy are located in different buildings. Dispensing of the study drug at off-campus satellite locations also may be feasible without requiring a separate license and registration, depending on the circumstances and only if there is no overnight storage at the satellite locations. DEA permits certain "coincident" activities to be conducted by a registrant without need for a separate DEA registration for that activity. Practitioners who are properly licensed by their respective state authorities and registered with DEA as a Practitioner to handle controlled substances in Schedules 2, 2N (non-narcotic), 3, 3N (non-narcotic), 4 and 5, may conduct research (clinical trials) under their DEA Practitioner registration without a separate DEA registration as a "Researcher."<sup>6</sup>

When research becomes an independent activity not directly associated with a practitioner's regular medical practice, a separate DEA "Researcher" registration is required in the appropriate schedule(s). However, the rules are stricter for controlled substances in Schedule 1 (e.g., heroin, cannabidiol, ibogaine, tetrahydrocannabinol, psilocybin). Clinical trials using Schedule 1 controlled substances require a separate DEA "Researcher" registration for a specific drug code (substance). Schedule 1 research protocols must be formally approved by the Food & Drug Administration (FDA) prior to registration with DEA.<sup>7</sup> For clinical trials, a DEA registration in Schedule 1 is protocol-specific; however, non-clinical trial research registrations (i.e., laboratory research, animal studies) with DEA in Schedule 1 may be associated with multiple DEA- and FDA-approved protocols involving one or more Schedule 1 substances. Additionally, for clinical trials with Schedule 1 controlled substances, most states require a separate Schedule 1 research license. DEA "Researcher" registrations are valid for one year.

## **2. Scheduling of the Drug or Substance**

The threshold factor for control under the CSA is whether a drug or substance has a potential for abuse. While there is no definition of "abuse" in the CSA, there is guidance in the legislative history that indicates abuse includes:

- Evidence that individuals are taking the drug or other substance in amounts sufficient to create a hazard to their health, to the safety of other individuals, or to the community
- Evidence of significant diversion of the drug or substance from legitimate channels
- Evidence that individuals are taking the drug or other substance on their own initiative, rather than on the basis of medical advice from a practitioner licensed by law to dispense or administer such drugs
- The drug or substance is new and is related to a drug or substance already under control and is likely to have the same potential for abuse as the already controlled substance<sup>8</sup>

The law categorizes controlled substances in five schedules: Schedule 1 contains drugs or substances that have a high potential for abuse and no accepted medical use in treatment in the United States, and there is a lack of accepted safety of these drugs or substances under medical supervision. Schedule 1 includes illegal substances such as heroin, marijuana and LSD (lysergic acid diethylamide). Schedules 2, 3, 4 and 5 contain drugs and substances that have a currently accepted medical use in treatment in the United States and varying degrees of abuse potential and physical or psychological dependence liabilities. Schedule 2 drugs or substances, for example, have a high potential for abuse and severe psychological or physical dependence liabilities (e.g., morphine, oxycodone). Schedule 3, 4 and 5 drugs or substances have progressively lesser abuse potential and dependence liabilities.<sup>9</sup> Drugs that are determined to have no abuse potential are not scheduled. Examples of federally non-controlled substances include tramadol, orlistat and rivastigmine.

The scheduling of a drug or substance under the CSA is an involved and detailed process and requires participation by the Department of Health and Human Services (HHS), including FDA and the National Institute on Drug Abuse (NIDA), in conjunction with DEA.<sup>10</sup> The two departments, HHS and Justice (the Attorney General (AG) has delegated this responsibility to DEA) approach scheduling actions independently, but the agency roles are complementary. HHS has a distinct perspective in light of its authority under the Federal Food, Drug and Cosmetic Act of 1938, and DEA, operating under the CSA, is generally required to control an entire substance or basic class (e.g., alprazolam).

HHS, under the direction of the Assistant Secretary of Health (ASH), and the Department of Justice, under the auspices of DEA's Deputy Administrator, independently evaluate eight specific factors enumerated in the CSA with respect to each drug or substance proposed for control:

- Its actual or relative potential for abuse
- Scientific evidence of its pharmacological effect, if known
- The state of current scientific knowledge regarding the drug or other substance
- Its history and current pattern of abuse
- The scope, duration and significance of abuse
- What, if any, risk there is to public health
- Its psychic or physiological dependence liability
- Whether the substance is an immediate precursor of a substance already controlled under the CSA<sup>11</sup>

The ASH provides DEA with a scientific and medical evaluation of the drug or substance and a scheduling recommendation. The ASH scheduling recommendation as to scientific and medical matters is binding on DEA and, if ASH recommends that a drug or substance not be controlled, DEA cannot control it.<sup>12</sup> If ASH recommends control, DEA makes the final scheduling decision, proposes this action for notice and comment with the opportunity for an administrative hearing, and is responsible for defending the action in court.

If a New Drug Application (NDA) is submitted to HHS (FDA) for a drug that has a stimulant, depressant or hallucinogenic effect on the central nervous system and the drug has an abuse potential, HHS is required by law to notify the AG.<sup>13</sup> Therefore, it is important for pharmaceutical companies to recognize abuse potential as a risk early in a drug's development. The abuse potential of a drug comprises a dimension of its safety profile and should be assessed in-depth in pre-clinical testing and particularly in Phase I first-in-human studies. Additionally, data from clinical studies, data from human abuse studies, and epidemiological data likely will carry greater weight than predictive data in evaluating a drug's abuse liability. During the NDA process, it is recommended that Sponsors regularly interact with the respective Review Division at FDA and the Controlled Substances Staff. Sponsors should also provide periodic updates to DEA, particularly after a Sponsor has provided its abuse liability package to FDA.

Once a drug or substance has been scheduled (i.e., 1, 2, 3, 4 or 5), the schedule of the drug or substance, including whether it is a narcotic or non-narcotic, and the type of handler (e.g., bulk manufacturer, pharmacy or practitioner) determine the level or degree of strictness of DEA and state control measures. Therefore, a Schedule 2 drug with high abuse potential produced by a bulk manufacturer would be subject to the strictest control measures. A researcher or practitioner handling a Schedule 4 controlled substance would be required to adhere to fewer control measures and a lower level of applicable controls.

### **3. Importation and Exportation Controls**

Clinical studies are frequently conducted simultaneously in multiple countries and consequently involve the importation and exportation of the study drug in one form or another. For controlled substances, there are three principal international treaties that establish a framework governing importation and exportation of certain substances:

- The Single Convention on Narcotic Drugs of 1961<sup>14</sup> governs narcotics, including the opium poppy, coca bush, and cannabis plant.
- The Psychotropic Convention of 1971<sup>15</sup> governs other abusable substances, including stimulants, such as amphetamines; depressants, such as barbiturates; and hallucinogens, such as mescaline and LSD (lysergic acid diethylamide).
- The Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988<sup>16</sup>, among other issues, governs certain precursor chemicals like ephedrine and pseudoephedrine, and solvents like ether and acetone.

These treaties have led to an international network of member nations that, operating under the auspices of the United Nations, have agreed to abide by the provisions of the treaties and ensure that the substances controlled are used exclusively for legitimate medical, scientific and research purposes. These drug conventions do not impose obligations directly on firms or individuals. The governments of countries that are parties to each convention obligate themselves to create responsible agencies, enact laws and regulations to implement the minimum requirements of the conventions, and establish cooperative initiatives with each other.

In general, exporting nations must seek and obtain permission in advance for each separate transnational shipment, usually in the form of an import permit or authorization, from the country to which the exporting nation desires to ship a drug. The import authorization must be in writing from the competent government authority in the importing nation, and this authorization must be received by the exporting nation's authorities prior to obtaining an export authorization or exporting the drug.<sup>17</sup> For certain substances, exporting nations are also responsible for verifying that an export will be used by the importing nation for legitimate purposes and that the amount of the substance being exported does not exceed the importing nation's estimated legitimate requirements for that substance. Additionally, a United Nations entity, the International Narcotics Control Board (INCB), serves as a central collection point and clearinghouse for verifying the authenticity of government import and export authorization documents and the names of individuals and agencies authorized to grant such permits or authorizations. A government may prohibit the importation of any substance into its country by notifying the Secretary General of the United Nations. The INCB maintains a current listing of such import prohibitions. For example, the U.S. prohibits the importation of flunitrazepam (Rohypnol) and methaqualone (Quaalude).

The responsible entity and competent authority in the U.S. for importation and exportation of controlled substances is DEA. U.S. laws and regulations for importation and exportation derive from the three international drug control treaties and, consequently, the requirements are different for narcotics, for psychotropic substances, and for chemicals.

Generally, the importation and exportation requirements are stricter for all Schedule 1 and 2 controlled substances and any narcotic drugs and substances. DEA issues permits for importation or exportation of Schedule 1 and 2 controlled substances and most narcotic substances in the other schedules only after processing a detailed application completed by the importer or exporter.<sup>18</sup> However, non-narcotic substances in Schedules 3, 4 and 5 may be imported and exported pursuant to a notification to DEA at least 15 days in advance of the importation or exportation.<sup>19</sup>

Global clinical studies involving controlled drugs or substances are directly affected by the international network of import and export requirements, and these requirements vary from country to country. For example, in some countries (e.g., Mexico and India), the government authority requires the CRO to be the official and licensed importer, while in other countries the designated distributor or depot is required to be the official importer for the clinical trial. In the United States, under the CSA, there are some differences in the requirements for controlled substances for commercial purposes versus clinical trial purposes; however, most importation and exportation requirements for controlled substances are the same for commercial and clinical trial products. In the U.S., DEA requires the importer to be the licensed and registered entity.<sup>20</sup>

For controlled substances exported from the United States for commercial purposes or for clinical trials, U.S. law and regulation strictly limit re-exportation to a subsequent country, which can block the international movement of clinical trial supplies.<sup>21</sup> In addition, if a substance is controlled under the CSA in the U.S., all importation and exportation requirements apply, even if the substance is not controlled in the country proposing to import or export it from or to the U.S.

#### **4. Quotas for Schedule 1 and 2 Substances**

The CSA requires DEA to limit the quantities of controlled substances in Schedule 1 and Schedule 2 that may be produced each calendar year in the U.S.<sup>22</sup> Working with the pharmaceutical and related industries, DEA gathers available data on sales and inventories of substances in Schedules 1 and 2. These data are combined with information provided by the FDA regarding estimates of the legitimate medical and scientific needs for these substances. DEA uses these data to formulate aggregate production quotas, which set the maximum amounts that may be produced annually in the U.S. The aggregate production quotas are subdivided into manufacturing quotas for bulk manufacturers and procurement quotas for dosage-form manufacturers.<sup>23</sup> Companies manufacturing controlled substances in Schedule 1 or 2 for commercial or clinical trial purposes must be properly registered with the DEA and obtain the appropriate quota on an annual basis. Supplies of study drug imported into the U.S. in properly labeled finished dosage form do not count against the manufacturing quotas. However, if the study drug is repacked or relabeled in any manner, this activity is defined by DEA as manufacturing, and the entity conducting this repackaging or relabeling must register with DEA as a manufacturer and obtain procurement quota from DEA to acquire the drug or substance. The manufacturer (repacker/relabeler) applies to DEA on an annual basis for a procurement quota. Adjustments can be made during the course of the year depending on the circumstances and legitimate needs.<sup>24</sup>

#### **5. Site Security Measures**

The CSA requires both physical security and non-physical security controls for practitioners participating in clinical trials involving controlled substances. Local DEA field offices have discretion to require greater security than the minimum provisions in the regulations, depending on a number of security-related factors. As a general rule, investigators conducting clinical trials are required to store controlled substances in a securely locked,

substantially constructed cabinet.<sup>25</sup> Controlled substances should be segregated by clinical study and by DEA registration number. Segregation can be accomplished by storing the controlled drugs in a separate box or other container, or on a separate shelf, if overall access to the secure storage facility is not significantly increased. Clinical trial controlled substances in Schedule 1 must be stored separately from controlled substances in Schedules 2, 3, 4 and 5, and also separated from non-controlled substances. It is recommended that an investigator maintain stocks of controlled substances related to his or her regular medical practice separate from stocks of controlled substances related to clinical studies, as well as maintain separate records for both activities. However, such segregation is not required by DEA when the investigator is conducting the clinical trial as a coincident activity of his or her regular DEA Practitioner registration.<sup>26</sup>

DEA requires that an investigator establish a system to safeguard the controlled substances handled during the course of the study. This system should, at minimum, consider the type of controlled substance(s) handled, the quantities handled, the number of authorized employees with access to the general area or room where controlled substances are stored, and the specific employees authorized with direct access to keys, locks or combinations to the secure storage container. "Double lock" security, such as a locked cabinet inside a locked room, has become an industry best practice. DEA recommends a background investigation and evaluation of all employees with general or direct access to controlled substances at the research site.

Practitioners are also required to comply with state security regulations related to substances handled.

## **6. Recordkeeping Requirements**

DEA essentially requires a record of every movement or transaction involving a controlled substance, along with precise details of that movement. Experienced clinical sites and CROs are very familiar with FDA and state recordkeeping requirements for study drug supplies and have implemented adequate record keeping systems. However, they may not be familiar with a few peculiarities in DEA recordkeeping requirements. For example, DEA requires a separate, physical count of all controlled substances on hand at a clinical site at the time the site first begins to handle controlled substances and at least once within every two-year period afterward.<sup>27</sup> DEA calls the first study inventory the "initial inventory" and subsequent inventories "biennial inventories." The biennial inventory is different than a site's accountability log for each study drug, and there are specific details that apply. Additionally, DEA requires that all records (including biennial inventory records) for Schedule 1 and 2 controlled substances be kept separately from all other business records of the site<sup>28</sup>; and all records (including biennial inventory records) of Schedule 3, 4 and 5 controlled substances must be "readily retrievable" from all other business records of the site.<sup>29</sup> "Readily retrievable" can be accomplished by putting an asterisk next to each entry for a Schedule 3, 4 or 5 controlled substance, or by using a different color or some other feature to distinguish controlled substance entries from non-controlled substance entries in the site's records.

DEA requires dispensers to the patient and study personnel to keep a record of the name of the drug dispensed, the finished form (e.g., tablet, capsule, liquid), the number of units or volume, the name and address of the person to whom dispensed, the date of dispensing, and the name or initials of the person who dispensed or administered the drug on behalf of the dispenser.<sup>30</sup>

DEA requires that all distributions of Schedule 1 and 2 controlled substances be made pursuant to a DEA-issued form known as a DEA order form or DEA Form 222. There are very specific requirements for the use of a DEA order form. Clinical sites that obtain

Schedule 1 or 2 substances from a manufacturer or distributor must be familiar with the execution, completion and maintenance of these forms. Some clinical trials using Schedule 2 controlled substances have required investigators to write prescriptions for these substances and have the prescriptions filled by a central pharmacy participating in the study. While this is a feasible study design, an alternative approach would have the investigator order the Schedule 2 substances through a central manufacturer or distributor using the investigator's DEA order forms and maintain a supply of these substances at the site for subsequent dispensing to patients. Since Schedule 2 prescriptions cannot be refilled and the return of unused study medication to a central pharmacy can be complicated or not possible, the alternate design may reduce paperwork and increase efficiency. For double-blind studies with Schedule 1 or 2 substances, the Sponsor or CRO should contact DEA's Office of Diversion Control for guidance on keeping the required DEA order form records to prevent any unblinding of the study.

Returns of study drug (controlled substances) by the patient to the investigator, as well as returns from the clinical site to its supplier, are considered by DEA to be distributions. Distributions of controlled substances may only be made between authorized DEA registrants, and patients are not DEA registrants. However, DEA may permit investigators conducting clinical trials to receive study drug returns from patients to ensure drug accountability and patient safety and compliance with the study protocol, since FDA normally requires this information. It is recommended that Sponsors seek this permission ("waiver") in writing from DEA early in the site startup stage.

## **7. Reporting Requirements**

DEA has several mandatory reporting requirements for almost every controlled substance transaction. These requirements pertain to manufacturers, distributors, exporters, importers and a few other types of registrants.<sup>31</sup> However, for clinical sites (investigators), the only mandatory reporting requirement is when there is any theft or significant loss of a controlled substance. DEA requires use of their DEA Form 106 (Report of Theft or Loss of Controlled Substances) for this purpose.<sup>32</sup> The form is available on DEA's website at [www.deadiversion.usdoj.gov](http://www.deadiversion.usdoj.gov). The site can also report a theft or loss electronically at this website. While it is clear that *any* theft of a controlled substance must be reported to DEA, the determination of a "significant" loss involves consideration of many factors. During the design stage or when drafting the study protocol, the Sponsor should make a policy determination of what constitutes a "significant" loss in the study. Such a policy will aid in ensuring consistency throughout the participating sites, as well as in evaluating any occurrences as possible adverse events.

CROs and investigators should also contact the appropriate state authorities to ensure compliance with any state reporting requirements for theft or loss.

## **8. DEA Investigations of Clinical Sites**

As a federal agency charged with enforcing the CSA, DEA has considerable authority and responsibility for all controlled-substance activity related to the U.S., with particular interest in the upper tiers of the supply chain, including importers, exporters, manufacturers, distributors and various types of narcotic treatment programs. The CSA also delegates significant authority and responsibility to the states, particularly for licensing and regulating practitioners. In carrying out its responsibilities, DEA conducts various types of investigations of registered handlers of controlled substances.

For clinical trials conducted with a Schedule 1 controlled substance, DEA performs an investigation of a site prior to granting a DEA registration. DEA may also conduct a routine

regulatory investigation of a site at a later date, depending on the length of the study. For clinical trials conducted with Schedules 2, 2N, 3, 3N, 4 or 5 controlled substances, DEA does not routinely conduct investigations of the trial sites. Required reporting to DEA of controlled substance transactions by manufacturers, wholesalers and other registrants allows DEA to monitor the supply chain (including clinical sites), observe trends, and detect abnormalities. The routine selection or regular investigation of practitioners conducting clinical trials is not a primary DEA function and is unlikely, barring any suspicious indicators or evidence of wrongdoing. Investigators normally conduct clinical research with Schedule 2, 2N, 3, 3N, 4 and 5 controlled substances as a coincident activity under their regular DEA Practitioner registration, and the protocols for these studies are required to be sent only to FDA. However, as noted above, practitioners should only conduct this "coincident" research as part of their regular practice of medicine.<sup>33</sup>

Regardless, investigators should be prepared for any type of scheduled or unannounced investigation of their site, whether it is by a state agency, FDA, DEA or other authority. Making certain that the site is properly licensed and registered to handle controlled substances, safeguarding all controlled substances at the site, and keeping complete and accurate records of every movement of each controlled substance will help ensure proper conduct of the clinical study, as well as the successful outcome of any investigation of the site.

## **Conclusion**

Federal and state laws and regulations governing controlled substances are designed to prevent, detect and stop abuse and diversion of these substances, while also ensuring that adequate and uninterrupted supplies exist to meet all legitimate medical, scientific and research needs in the U.S. These are competing objectives. While the control system is not meant to be disruptive to clinical trials or the dispensing and marketing of controlled drugs, any system of controls reduces the permissible conditions for use and consumption. DEA recently published its general regulatory investigations work plan for the next several years. In the past, these work plans did not include researchers, but the new work plan indicates that DEA will investigate a minimum of two Schedule 1 researchers and two Schedule 2 through 5 researchers per DEA Diversion Investigator Group per year.<sup>34</sup> With approximately one hundred DEA Diversion Investigator Groups throughout the U.S., the intended regulatory effort would result in DEA investigations of approximately 200 Schedule 1 researchers and 200 Schedule 2 through 5 researchers in the U.S. every year. Sponsors, CROs and investigators conducting clinical trials with controlled substances, including new molecular entities with abuse potential, should examine their study designs, clinical protocols, and study documentation to ensure correct procedures are being employed and federal and state requirements for handling such substances are being met.

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5. Title 21, Code of Federal Regulations, Section 1301.12 (a)
6. Title 21, Code of Federal Regulations, Section 1301.13 (e) (1) (iv)
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21. Title 21, United States Code, Section 953 (f)
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24. Title 21, Code of Federal Regulations, Section 1303.12 (d)
25. Title 21, Code of Federal Regulations, Section 1301.75
26. Title 21, Code of Federal Regulations, Section 1304.03 (a)
27. Title 21, Code of Federal Regulations, Section 1304.11
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31. Title 21, Code of Federal Regulations, Section 1304.31-33
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