Opioid analgesics are essential to the management of pain in many patients, but they are also associated with potential risks for abuse, overdose and diversion, concerns which must be considered in the planning and execution of clinical trials studying these controlled substances. Sponsors who undertake development of controlled substances or novel agents that may eventually be subject to control are often unaware of the amount of effort and planning involved in conducting these types of clinical trials. Faced with a variety of logistical challenges ranging from appropriate protocol design and site selection to careful management of the drug supply chain and clinical supplies, sponsors must take great care in navigating the regulatory requirements and clinical considerations that govern studies involving controlled substances. In this paper, we discuss the challenges of conducting clinical trials of controlled substances, specifically Schedule II and III opioid analgesics, and provide recommendations on addressing regulatory and clinical hurdles on the opioid analgesic development pathway.
Regulations

Internationally, the International Narcotics Control Board (INCB), a United Nations (UN) entity, monitors enforcement of restrictions on controlled substances. The INCB’s authority is defined by 3 international UN treaties – the Single Convention on Narcotic Drugs of 1961, the Psychotropic Convention of 1971 and the Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988, which contains provisions relating to the control of controlled substance precursors. European Union (EU) Member States that have agreed to abide by the provisions of these treaties each create responsible agencies and enact laws or regulations to implement the requirements of these conventions.

In the U.S., clinical trials involving opioid analgesics, whether as a study drug or a comparator, must adhere to the Controlled Substances Act of 1970 (CSA) and its implementing regulations, which are enforced by the Drug Enforcement Agency (DEA), as well as the requirements of the Federal Food, Drug and Cosmetic Act of 1938. The provisions of the Uniform Controlled Substances Act, which have been passed by most of the 50 states, are similar to the CSA. However, each state has its own legislative, regulatory and enforcement structure and process, and state regulations of controlled substances frequently change, so it is important to be aware of the regulatory nuances of each state in which a trial is conducted.

Classification of Controlled Substances

The INCB distinguishes between narcotic and psychotropic controlled substances and classifies these substances according to four Schedules.

Table 1. INCB Classification of Narcotic Drugs

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Description</th>
<th>Degree of Control</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Substances with addictive properties, presenting a serious risk of abuse</td>
<td>Very strict</td>
<td>Cannabis and its derivatives, Cocaine, Heroin, Methadone, Morphine, Opium</td>
</tr>
<tr>
<td>II</td>
<td>Substances normally used for medical purposes and given the lowest risk of abuse</td>
<td>Less strict</td>
<td>Preparations of codeine, Preparations of dicycodeine, Preparations of propiram</td>
</tr>
<tr>
<td>III</td>
<td>Preparations of substances listed in Schedule II, as well as preparations of cocaine</td>
<td>Lenient; according to the World Health Organization, these preparations present no risk of abuse</td>
<td>Cannabis and cannabis resin, Heroin</td>
</tr>
<tr>
<td>IV</td>
<td>The most dangerous substances, already listed in Schedule I, which are particularly harmful and of extremely limited medical or therapeutic value</td>
<td>Very strict, leading to a complete ban on the production, manufacture, export and import of, trade in, possession or use of any such drug except for amounts which may be necessary for medical and scientific research</td>
<td></td>
</tr>
</tbody>
</table>
THE USE OF CONTROLLED SUBSTANCES IN CLINICAL TRIALS:
Studying Opioid Analgesics in the U.S. and European Union

As classification of controlled substances varies among different EU Member States, sponsors must be aware of the prevailing legislation in each country where a clinical trial may be conducted.

Specific EU legislation establishing different classes of controlled substances is limited to EU regulations that define classes of precursors, or substances used in the illicit manufacture of controlled substances, including Regulation (EC) No. 273/2004 of the European Parliament and the Council of 11 February 2004 and the Council Regulation (EC) No. 111/2005 of 22 December 2004. While EU legislation does not establish different classes of narcotic drugs or psychotropic substances, the Council Decision 2005/387/JHA of 10 May 2005 can provoke a Council Decision requiring EU Member States to put a drug under national controls equivalent to those of the INCB. As classification of controlled substances varies among different EU Member States, sponsors must be aware of the prevailing legislation in each country where a clinical trial may be conducted.

In the U.S., there are 3 agencies – the U.S. Food and Drug Administration (FDA), the National Institute on Drug Abuse (NIDA) and the DEA – involved in the scheduling of controlled substances, including both narcotic drugs and psychotropic substances. The U.S. Assistant Secretary of Health (ASH)'s recommendation on control is binding on the DEA, such that if the ASH advises against control, the DEA may not control the substance. However, if the ASH recommends control, it is the DEA that makes the final scheduling decision. Controlled substances are categorized by the DEA according to 5 schedules, based upon 8 factors, including: 1) actual or relative potential for abuse, 2) scientific evidence of pharmacological effect, if known, 3) state of current scientific knowledge about the drug, 4) history and current pattern of abuse, 5) scope/duration/significance of abuse, 6) what, if any, risk to public health, 7) psychic or physiological dependence liability and 8) whether the substance is an immediate precursor of an already controlled substance. Opioid analgesics are classified as Schedule II or III controlled substances.

Table 2. INCB Classification of Psychotropic Substances

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Description</th>
<th>Degree of Control</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Substances presenting a high risk of abuse, posing a particularly serious threat to public health, which are of very little or no therapeutic value</td>
<td>Very strict; use is prohibited except for scientific or limited medical purposes</td>
<td>Lysergic acid diethylamide (LSD) Methyleneoxyamphetamine (MDMA) Mescaline Psilocybine Tetrahydrocannabinol</td>
</tr>
<tr>
<td>II</td>
<td>Substances presenting a risk of abuse, posing a serious threat to public health, which are of low or moderate therapeutic value</td>
<td>Less strict</td>
<td>Amphetamines Amphetamine-type stimulants</td>
</tr>
<tr>
<td>III</td>
<td>Substances presenting a risk of abuse, posing a serious threat to public health, which are of moderate or high therapeutic value</td>
<td>These substances are available for medical purposes</td>
<td>Barbiturates, including amobarbital Buprenorphine</td>
</tr>
<tr>
<td>IV</td>
<td>Substances presenting a risk of abuse, posing a minor threat to public health with a high therapeutic value</td>
<td>These substances are available for medical purposes</td>
<td>Diazepam Phenoobarbital Temazepam</td>
</tr>
</tbody>
</table>
### Table 3. DEA Schedule of Controlled Substances

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I</strong></td>
<td>– High potential for abuse and no accepted medical use in treatment in the U.S.</td>
<td>Dronabinol, Marijuana, Heroin, Crystal methamphetamine</td>
</tr>
<tr>
<td></td>
<td>– Lacks accepted safety for use under medical supervision</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Investigational drugs for actives not currently approved for use in the U.S.</td>
<td></td>
</tr>
<tr>
<td><strong>II</strong></td>
<td>– High potential for abuse</td>
<td>Fentanyl, Hydromorphone, Methamphetamines, Morphine, Tapentadol</td>
</tr>
<tr>
<td></td>
<td>– Currently accepted medical use in treatment in the U.S., or accepted with severe restrictions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Abuse may lead to severe psychological or physical dependence</td>
<td></td>
</tr>
<tr>
<td><strong>III</strong></td>
<td>– Abuse potential less than Schedules I and II</td>
<td>Buprenorphine, Ketamine, Testosterone</td>
</tr>
<tr>
<td></td>
<td>– Currently accepted medical use in treatment in the U.S.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Abuse may lead to moderate or low physical dependence or high psychological dependence</td>
<td></td>
</tr>
<tr>
<td><strong>IV</strong></td>
<td>– Low potential for abuse relative to Schedule III</td>
<td>Diazepam, Clonazepam, Midazolam, Carisoprodol</td>
</tr>
<tr>
<td></td>
<td>– Accepted medical use in treatment in the U.S.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Abuse may lead to limited physical or psychological dependence relative to Schedule III</td>
<td></td>
</tr>
<tr>
<td><strong>V</strong></td>
<td>– Low potential for abuse</td>
<td>Codeine-containing cough medications, Diphenoxylate</td>
</tr>
<tr>
<td></td>
<td>– Accepted medical use in treatment in the U.S.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Abuse may lead to limited physical or physiological dependence</td>
<td></td>
</tr>
</tbody>
</table>

There is no formal definition of ‘abuse’ in the CSA, but historically, abuse includes the following: 1) evidence that individuals are taking the drug in amounts sufficient to create a hazard to their health or to the safety of other individuals and/or the community; 2) evidence of significant diversion of the drug from legitimate channels; 3) evidence that individuals are taking the drug on their own initiative, rather than on the basis of medical advice; or 4) the drug is new and is related to a controlled substance and is likely to have the same potential for abuse as the already controlled substance.\(^\text{10}\)
It is important for sponsors to recognize the abuse potential of a study drug as a risk early in the development process, as abuse potential comprises a dimension of the safety profile and needs to be assessed in pre-clinical testing and Phase 1 first-in-human studies. For drugs with a potential for abuse, sponsors must submit a description and analysis of information related to abuse of the drug, including a proposal for scheduling. The FDA has issued guidance for sponsors who are developing drug products with the potential for abuse that may need to be scheduled, including recommendations on the design and conduct of appropriate studies and investigations to assess abuse potential. Sponsors should interact regularly with the FDA and the Controlled Substances staff and should also provide periodic updates to the DEA, particularly after the sponsor has provided an abuse potential assessment to the FDA. The schedule of the drug and the type of handler determine the degree of strictness of DEA and state control measures. For example, a Schedule II drug with high abuse potential produced by a bulk manufacturer would be subject to the strictest control measures.

### Licensing

In the U.S., all principal investigators or sub-investigators involved in an opioid analgesic clinical trial must obtain both federal and state authorizations to handle controlled substances. DEA registration and state licensure are required at the general physical location where the controlled substances for the clinical trial will be dispensed and/or stored overnight. In some cases, it may be possible to dispense the study drug at a satellite location with a separate license and registration if there is no overnight storage at that satellite location.

Federal registration is granted by the DEA. DEA “Practitioner” registration is valid for 3 years. Sponsors and investigators must remember that PhDs and PharmDs are not considered practitioners and must rely on an MD/DO principal investigator or sub-investigator to dispense controlled substances. Schedule I substances require a DEA “Researcher” registration, valid for one year only, and in this situation, the research protocol must be formally approved by the FDA prior to registration with the DEA.

All practitioners who participate in a clinical trial as a principal investigator or sub-investigator must also be authorized by the state in which they practice to prescribe, dispense, administer and conduct research with controlled substances. In most cases, these activities are authorized when a license is granted to the practitioner by the respective Board. However, some states require a separate, state-issued controlled substance license and other states have a separate state controlled substances authority that requires practitioners to obtain a separate registration, in addition to their Board license.

In the EU, licenses are also required for individuals who wish to produce, dispense, import or export controlled substances, but requirements vary from country to country.

### Import and Export Controls

Importing and exporting of opioid analgesics for global clinical studies requires careful planning which allows adequate time for each step involved in the movement of study drugs. By initiating planning with the DEA and corresponding competent authorities in the EU as early as possible, sponsors can more effectively navigate the import/export process.

Import/export requirements vary from country to country, so sponsors should be aware of how these different requirements impact the timely distribution of study drug to investigative sites in order to avoid delays. For example, U.S. law limits re-exportation of controlled substances exported from the U.S. to other countries, which can restrict international movement of clinical trial supplies. In the EU, several Member States will not initiate the import/export process for controlled substances until the proper regulatory and ethical approvals in place.

In general, exporting nations must obtain advance permission for each transnational shipment, typically in the form of an import permit or authorization from the competent government authority, from each country to which they wish to ship the drug. This import authorization must be received by the exporting nation’s authorities prior to obtaining export authorization or shipping the drug. For some substances, exporting nations are required to verify that the export will be used by the importing nation for legitimate purposes and that the amount of drug being exported does not exceed the importing nation’s estimated requirements for that substance.
Internationally, the INCB serves as a central collection point and clearinghouse for verifying the authenticity of government import/export authorization documents, as well as the names of individuals or agencies authorized to grant such authorizations. A government may specifically prohibit the importation of any substance into its country by notifying the Secretary General of the United Nations.

In the U.S., the responsible entity and competent authority for importation/exportation of controlled substances is the DEA. The DEA requires the importer to be a licensed and registered entity. Importers or exporters of opioid analgesics are required to complete detailed permit applications, DEA-357 for import and DEA-161 for export, prior to movement of opioid analgesics and other controlled substances.

EU regulations require that, prior to releasing any batch of medicinal product for study supply, each production batch of medicinal products coming from third countries must undergo a rigorous analysis by a qualified person (QP) to ensure that the quality of the medicinal product is in accordance with relevant requirements.

Sponsors intending to import opioid analgesics and other controlled substances into the EU are advised to:

1. Ensure that all necessary Chemistry, Manufacturing and Controls (CMC) documentation is prepared in a format that is acceptable to relevant competent authorities
2. Identify and contract with distribution depots that already have the appropriate licenses in place to hold and distribute drugs on their behalf
3. Engage the services of a QP to perform batch release on the study drug
4. Check that depots and investigative site pharmacies can accommodate the study drug, as most import licenses are on a named substance basis

Protocol Design

Open-label titration, randomized withdrawal studies have become the standard for evaluating the efficacy and safety of opioid analgesics. When designing a clinical trial protocol involving opioid analgesics, sponsors must consider many factors related to the transfer, dosing, administration and handling of the study drug. Study design should take into account the advantages of having the investigator order controlled substances through a central manufacturer and maintain a supply at the site for subsequent dispensing to patients, rather than having investigators write prescriptions that need to be filled by a central pharmacy.

The clinical trial protocol should include detailed information on dosing and administration of the investigative medication, including instructions for dose modification and discontinuation and directions for preparing, administering and/or dispensing the study drug. In addition, the protocol should clearly outline the procedure for handling unused study drug. Returns of the controlled substance (by the patient to the investigator or from the clinical site to the supplier) are considered by the DEA to be distributions. Since distributions of controlled substances may only be made between authorized DEA registrants, and patients are not DEA registrants, sponsors should seek waivers in writing from the DEA early in the site startup stage to permit investigators to receive study drug returns from patients.

During protocol design, sponsors also should also determine a policy on what constitutes a ‘significant loss’ of study drug in order to ensure consistency throughout the participating sites, as well as to assist in evaluating any such occurrences as possible adverse events.
Drug Supply Chain Management

In addition to abundant federal and state regulations, increased globalization has made supply chain management for controlled substances even more challenging. Careful, early planning can avoid costly delays and regulatory audits.

Drug Supply Packaging

Sponsors should clearly identify drug strengths, package sizes and batch size and number in order to ensure an efficient supply chain. Drug supply packaging is complex in open-label titration, randomized withdrawal studies of opioid analgesics because study participants each have their own effective dose of opioids and need to be up-titrated to an optimum dose that provides adequate efficacy with good tolerability prior to randomization. Patients that are randomized to placebo will then need to be down-titrated again. As a result, the study drug must be packaged to accommodate all doses that might be required for both the up-titration and down-titration periods. In addition, because pharmacy space is always at a premium, sponsors should review packaging requirements in order to minimize the volume of supplies.

Drug Distribution & Drug Supply Management

The DEA requires that all distributions of Schedule I and II controlled substances be made pursuant to a DEA Form 222, a triplicate form with preprinted information that is unique to each registrant. Sponsors should keep in mind that these forms need to be controlled as tightly as the medications themselves.

An interactive voice response system (IVRS) is an automated, telephone-based system that provides study patients with direct access to pre-recorded questionnaires, educational materials, custom messages and even therapeutic assistance. IVRS has the ability to track symptoms and disease progression; to investigate the relationships between symptom patterns and clinical outcomes; to assess adherence to, and efficacy of, ongoing treatments and to serve as an adjunct to therapeutic treatment for chronic pain. In opioid analgesic clinical trials with multiple packaging configurations and a full range of titration algorithms, IVRS or an interactive web response system (IXRS), collectively referred to as IXRS, is invaluable for documenting titration steps and for assigning blinded drug during the double-blind portion of the study. IXRS also helps to ensure that there are adequate supplies on hand at the site to up- and down-titrate patients correctly.

Drug Accountability

Drug accountability is a crucial component of study data integrity, particularly in clinical trials involving opioid analgesics due to the inherent risk for dependence, abuse or diversion.

Drug accountability is a broad term that includes study drug storage, handling, dispensing and documentation of administration, return and/or destruction of the drug. An accurate investigational drug accounting process begins with the sponsor’s shipping manifest and must include mechanisms to ensure that the study drug has not been dispensed to non-study patients, and that patients have not been exposed to doses in excess of protocol-defined regimens. All investigational medication documented as shipped to a site should reconcile with the documentation of used and unused supplies, along with a chain of custody. When an investigative site receives shipment of the study drug, the investigator or a designated individual should check the shipment by confirming that the contents are intact and comparing the shipping invoice to the lot number, expiration date, quantity and dosage. If there are any discrepancies, the sponsor should be informed immediately.

When destroying opioid analgesics, whether at the investigative site or the distribution depot, sponsors must keep in mind that the appropriate process for destruction is followed. In some countries, this may require the attendance of an authorized witness such as a government official or the local police. Experienced study monitors should periodically review and reconcile drug accountability documentation throughout the study in order to identify inappropriate practices as they occur and to retrain site staff, if needed.
Investigative Site Selection & Responsibilities

Site Selection

Due to strict security, recordkeeping and reporting requirements, investigative site selection is an important clinical consideration in the conduct of an opioid analgesic or other controlled substance clinical trial. Choosing experienced investigative sites and contract research organizations (CROs) helps to ensure that adequate storage and recordkeeping systems for controlled substances are already in place, saving both time and money.

Site Responsibilities

Security

In the U.S., both physical and non-physical security controls are required for the storage of opioid analgesics and other controlled substances during the course of a clinical trial. In general, investigators are required to store controlled substances in a securely locked, substantially constructed cabinet. Double lock security in the form of a locked cabinet inside a locked room has become industry best practice. Controlled substances should be segregated by clinical study and by DEA registration number. While it is recommended that investigators maintain stocks of controlled substances related to clinical studies separate from stocks of controlled substances related to their medical practice, this segregation is not required. Sponsors should keep in mind that local DEA field offices also have the power to require security beyond the minimum provisions outlined in the CSA regulations.

In terms of non-physical controls, investigators must establish a system to safeguard the controlled substances handled during the course of the study, and this system should take into account the type and quantity of controlled substances handled, the number of authorized employees with access to the general area or room where the controlled substances are stored and the specific employees authorized with direct access to keys, locks or combinations to the secure storage container. During study planning, sponsors should consider a prospective process for investigating unexplained drug loss or diversion. The DEA recommends, but does not require, a background check of all employees with general or direct access.

Investigative site security controls requirements in the EU vary from country to country, but are broadly in line with the controls required by the DEA.

Recordkeeping & Reporting

In the U.S., the DEA requires a separate physical count of all controlled substances on hand at a clinical site at the time the site first begins handling controlled substances (initial inventory) and at least once within every following 2-year period (biennial inventory). If stock related to the investigator’s regular medical practice is accidentally used instead of study-supplied drug during the course of a clinical trial, the investigator must document a deviation from the protocol. The DEA also requires a detailed record of every movement or transaction involving a controlled substance, including name of the drug dispensed, the finished form, the number of units or volume, the name and address of the person to whom the drug was dispensed, the date of dispensing and the name or initials of the person who dispensed or administered the drug. The DEA's Office of Diversion Control is available to provide guidance on keeping the required DEA order form records to prevent inadvertent study unblinding. It is important for sponsors and investigators to remember that all DEA-related records must be retained for a minimum of two years. For Schedule I and II controlled substances, these records must be kept separately from all other business records of the site.

The DEA's reporting requirements primarily pertain to manufacturers, distributors, exporters and importers in the drug supply chain. The only mandatory reporting requirement for clinical sites and investigators is for theft or significant loss of a controlled substance using DEA Form 106, which can be completed either on paper or electronically via the DEA website.

In the EU, the competent national authorities of most Member States have developed their own requirements for recordkeeping and reporting related to controlled substances. In addition, pharmacists also need to adhere to guidance issued by their governing professional bodies and institutions. As a result, sponsors, investigators and study monitors need to be attentive to meeting country-specific requirements.
Conclusion

Pain is a significant health problem that impacts quality of life and imparts high costs to society. Opioid analgesics are considered to be essential medicines by the World Health Organization, and there is broad consensus that these drugs are indispensable for the treatment of moderate to severe pain. Opioid analgesics and novel analgesic agents continue to be a cornerstone of active research and progress in our understanding of the mechanisms and molecular basis of pain. However, the magnitude of controls needed to successfully conduct clinical trials involving opioid analgesics can be overwhelming for sponsors, particularly if they do not have prior experience. Careful attention early on in the development program to protocol design, drug supply management and site and investigator selection is critical for meeting the regulatory and clinical requirements of any study involving controlled substances. Partnering with a CRO that has the right mix of people and experience can facilitate the clinical trial process, setting the stage for successful opioid analgesic development.

References