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REQUEST AND RATIONAL FOR AUTHORIZATION FOR SERUM TOXICOLOGY DRUG SCREENING

There exists a practitioner's manual 2006 edition entitled, An Informational Outline of the Controlled Substances Act. It is issued by the United States Department of Justice Drug Enforcement Administration Office of Diversion Control. It was provided to me by Rachael Aranas, Diversion Investigator in Fresno. She visited my office along with her associate on 10/30/2008. This was part of a routine visitation that she and her associate were doing at that time to all physicians in pain management in the Fresno area. The purpose of the visit was to disseminate information as it relates to the DEA's position of attempting to address the issue of diversion in the Fresno/Clovis area.

The Drug Enforcement Administration (DEA), was established in 1973 to serve as a primary federal agency responsible for the enforcement of the Controlled Substances Act (CSA). The CSA sets forth the federal law regarding both illicit and licit (pharmaceutical) controlled substances. With respect to pharmaceutical controlled substances, DEA' s statutory responsibility is twofold: to prevent diversion and abuse of these drugs while ensuring inadequate and uninterrupted supply available to meet the country's legitimate medical, scientific and research needs. The DEA understands that it can best serve the public interest by working with practitioners to prevent **diversion of legal pharmaceutical controlled substances into the illicit market.** The DEA is authorized under federal law to pursue legal action in order to prevent the diversion of controlled substances and to protect the public safety. A lack of compliance may result the need for corrective action, such as administrative action or in extreme cases, civil or criminal action. The drugs and other substances that are considered controlled substances under the CDA are divided into five schedules: I, II, III, IV, and V.

Under Section 3 Security Requirements, the required controls are mandated by title 21, CFR Section 1301.71 (a), which requires that all (registrants, physicians) provide effective **controls** and **procedures** to guard against death and diversion of controlled substances. The factors affecting practitioners include:

1. The location of the premises and the relationship of such location bear on security needs.
2. The type of building and office construction.
3. And quantity of controlled substances stored on the premises.
4. The type of storage medium (safe, vault or still cabinet).
5. The control of public access to the facility.

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6. The adequacy of registrant's monitoring system (alarms and detection systems).
7. Availability of local police protection.

Practitioners are required to store stocks of schedule II through V controlled substances in a securely locked, substantially constructed cabinet. It is clear by the Controlled Substance Act that we must have in effect a **monitoring system** to include a **detection system**. The detection system of concern relates to diversion.

On 02/10/2009, the US Food and Drug Administration (FDA), held a meeting of Stakeholders and prescription opioid abuse. The intent was to inform Stakeholders about new approaches that the FDA might adopt to control the growing problem of prescription opioid abuse and misuse, and open to dialogue. Why is the US government seeking to intervene now? The restriction of opioid prescribing for pain was an **unintended consequence of the drug laws, but pain advocacy effectively restored opioid treatment for pain, and no radical change in the laws seems necessary**. In recent years, there has been a marked change in prescribing habits relating to chronic pain. Not surprisingly, interest was focused on the use of opioids and patients with chronic pain – a large population with an unmet lead. As opioid use in the Unites States has increased, as opioid prescribing in the United States has increased, so has opioid misuse. In some surveys, rates of prescription opioid abuse in the United States have overtaken those of illicit opioid abuse. Prescription drugs have been increasingly favored because of their purity, relative safety, and easy availability. A report from the Centers for Disease Control and Prevention reported a rise in prescription opioid-related that of 68% between 1999 and 2004. In West Virginia, more than 90% of unintentional deaths due to medication overdoses were attributed to both opioids. Fewer than 50% of the individuals had actually been prescribed opioids, suggesting that **a diversion was a factor in many cases**. A further indication that casual or careless diversion has become a major problem is the finding in the 2007 National Survey that 56.5% of non-medical use of prescription opioids came from a friend or relative, 18.1% came from one doctor, 14.1% was bought from a friend or relative and 4.1% came from a drug dealer or stranger. The regulatory authorities are rightly concerned and they have now decided to intervene.

After a preliminary meeting in February 2009, the FDA rather than the DEA decided to act as the primary agency to address the problem. Risk Evaluation and Mitigation Strategies (REMS) would be the chosen mechanism for controlling misuse. The elements to assure safe use include the following:

1. Healthcare providers who prescribe the drug must have particular training or experience or special certifications.
2. Pharmacies, practitioners or healthcare settings that dispense the drug must be specially certified.
3. The drug may be dispensed only in certain healthcare settings.
4. The drug may only be dispensed the patients with evidence of safe use conditions such as **laboratory test results**.
5. Each patient using the drug would be subject to monitoring.
6. Each patient using drug would be enrolled in a registry.

The FDA will mandate and approve the development and institution of REMS by pharmaceutical companies. The opioid analgesics that will be required to have REMS include:

1. All extended-release oral opioid analgesics.
2. Methadone.
3. Transdermal fentanyl.

On 07/16/2009, the FDA announced approval of a new buccal-soluble fentanyl product (ONSOLIS) that would be subject to the new FDA REMS restricted distribution program named FOCUS (Full Ongoing Commitment to User Safety). The FOCUS program will incorporate enrollment of patients, prescribers, distributors and pharmacies, training and provision of educational materials are prescribers in pharmacies, patient education and counseling, a verification process for each prescription written, and supplied by courier only. According to the FDA, similar restricted distribution will be shortly extended to two other approved transmucosal fentanyl formulations Actiq and Fentora. The FDA concedes that the FOCUS program has not been field tested so it is unknown that the program will work, with the patients, prescribers and pharmacies will be able to overcome the barriers, or whether the program will succeed and reduce misuse and abuse. It is clear that the REMS for transmucosal fentanyl is a harbinger for what is to come – hastily introduced restrictions, with little thought about whether they will achieve the generally agreed goal of preserving opioids for those that need through confident and the methods to control misuse, abuse and death.

I have provided enough information not only from the Controlled Substance Act but also from the more recent information regarding the FDA that there is no doubt that we need to proceed to test (serum) any patient that is prescribed opioids by any route inclusive of an intrathecal delivery system.

Drug testing falls into two categories, forensic and compliance. The ultimate goal of forensic testing is to produce results that can be used, if necessary, in a court of law. In the case of compliance testing, such as a pain practice, the doctor is looking for the presence of prescribed medications as evidence of their use. Positive results are reassuring to both the patient and the doctor, indicating compliance with the agreed-upon treatment plan. In compliance testing, not finding the prescribed drug or finding un-prescribed or illicit drugs, is disconcerting, and certainly merits further discussion. Substance misuse issues which are identified are then managed effectively. Toxicology testing, like all diagnostic tests, improves patient care. It will enhance the relationship between the doctor and the patient by providing documentation of adherence to mutually agreed-upon treatment plans. Drug testing is an objective diagnostic test that is part of the medical record. In the cases where inappropriate, un-prescribed or illicit substances are identified, a dialogue regarding drug misuse or addiction will occur. The results can be used to encourage change to more functional behavior. In the pain management setting, the presence of an illicit or un-prescribed drug must not negate the patient's complaints of pain, but may suggest a concordant disorder such as addiction that may frustrate the effective management of an underlying pain condition. While acute or chronic pain can be treated in the patient with an addictive disorder, it is impossible to successfully treat a complaint of chronic pain in the face of an untreated addiction. To satisfactorily treat either

condition, the patient must be willing to accept assessment and treatment of both. The diagnosis of a concordant addictive disorder, when it exists, is vital to the successful treatment of chronic pain.

It is clear from this discussion that the DEA insists on "detection systems" to prevent diversion. It is also clear that the FDA has now taken over the role of instituting Risk Evaluation and Mitigation Strategies utilizing for ongoing commitment to user safety programs starting with the new buccal-soluble Fentanyl produce (ONSOLIS). The element to ensure "safe use" includes monitoring of each patient using the drug. There is no question that any pain practice and (without a doubt) any physician who prescribes opioids, will have to "monitor" his patient very closely as per the DEA and FDA. Serum testing is preferred since it can be performed immediately, avoiding patient issues regarding the inability to provide a *urine* specimen. Also, serum (blood) allows the evaluation of "steady state," which is a more accurate method of determining if a patient is taking the amount prescribed. The detection windows are much narrower in serum testing and therefore, patients are held to a higher degree of accountability. Urine testing only tells us if the patient has taken medications in the past and may be taking them currently. Urine testing will not tell us how much the patient is taking and therefore lacks pharmacokinetic accountability. Due to the potential for diversion, which is a big issue with the DEA and the State Medical Board, serum testing is the best method to be in compliance with the regulatory agencies.

Following administration of a dose of drug, its effects usually show a characteristic temporal pattern. The onset of the effect is preceded by a lag, after which the magnitude of the effect increases to a maximum and then declines; if a further dose is not administered, the effect eventually disappears. This time-course reflects changes in the drug's concentration, as determined by the pharmacokinetics of its absorption, distribution, and elimination accordingly. The intensity of a drug's effect is related to its concentration above a minimum effective concentration, whereas the duration of this effect is a reflection of the length of time the drug level is above this value. These considerations, in general, apply to both desired and undesired (adverse) drug effects, and as a result, **a therapeutic window exists** reflecting a concentration range that provides efficacy without unacceptable toxicity. Similar considerations apply after multiple dosing associated with long-term therapy; therefore, they determine the amount and frequency of drug administration to achieve an **optimal therapeutic effect.** For many drugs, toxicity and lack of efficacy are both potential dangers and the therapeutic index may be narrow. In these circumstances, doses must be titrated carefully and drug dosage is limited by toxicity, rather than efficacy. **Thus, the therapeutic goal is to maintain steady state drug levels within the therapeutic window. For most drugs, the actual concentrations associated with this desired range are not and need not be known. It is sufficient to understand that efficacy and toxicity are generally concentration-dependent.** Metabolism can be subject to a number of factors such as genetics, disease state and co-administration of other compounds. Other compounds may inhibit or induce metabolic activity. Therefore, a patient's blood concentration relative to the predicted steady state range should be assessed on a patient-by-patient basis. Expected steady state ranges are calculated using pharmacokinetic parameters associated with specific medications and patient-specific information.

In most clinical situations, drugs are administered in a series of repetitive doses to maintain a steady state concentration of drug associated with the therapeutic window. **Thus, calculation of the**

appropriate maintenance dosage is a primary goal. Certain practical details and pitfalls associated with therapeutic drug monitoring should be kept in mind for intermittent dosing; a concentration of drug measured in a sample taken **virtually any time during the dosing interval will provide information that may aid in the assessment of drug toxicity.** When concentrations of drugs are used for purposes of adjusting dosage regimens, the sample should be taken well after the previous dose, as a rule of thumb, just before the next planned dose, when the concentration is at its minimum. In general, this is how we sample in this office, in that patients drive here and are cautioned not to take medication when they are driving, unless they have a driver.

Another important aspect of the timing of sampling is its relationship to the beginning of the maintenance dosage regimen. **When constant dosage is given, steady state is reached only after four half lives have passed.** In almost all of the situations in this clinical practice, the sampling occurs well beyond the first four half lives. **Ultimately, therapeutic success is dependent on the patients actually taking the drug according to the prescribed dosage regimens. Non-compliance with the dosing schedule is a major and often unappreciated reason for therapeutic failure, especially in the long term management of diseases, such as chronic pain. Many times, reduction in the number of required dosing occasions will improve adherence to a prescribed dosing regimen. In this practice, we attempt to reduce the number of required dosing. Equally important, is the need to involve patients in the responsibility for their own health, using a variety of strategies based on improving communication regarding the nature of their chronic pain and the overall therapeutic plan. This is reinforced continually in every office visit. (Goodman and Gilman 12th edition)**

Achieving steady state in this particular patient is directly reflective of appropriate prescribing and appropriate utilization of the medication as prescribed, based on the previous discussion.

Patients will fall into three risk categories: Low, moderate and high. High risk patients are those who take schedule II opioids. Patients on schedule III opioids are considered moderate risk by the DEA guidelines. Patients on schedule IV opioids are considered low risk. Anyone taking schedule I drugs (illicit) is also considered high risk. High risk patients will be tested **at least** four times per year. Moderate risk patients will be tested two to four times per year. Low risk patients will be tested up to two times per year.

Should you have any further questions or wish any documentation that was utilized to prepare this report, I will be delighted to provide such.

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Rev: 8/2015