

Controlled Substances and Pain Management: Regulatory Oversight, Formularies, and Cost Decisions

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Pharmacists, physicians, and other health care personnel practice within an integrated system of laws and regulations that influence many treatment modalities. Capitation, managed care, and other controls strain these relationships by mandating greater oversight of how health care is delivered. From a pharmacist's perspective, any use of medication requires knowledge of three omnipresent factors: regulatory control, formularies (product selection), and economic decision making. My objective is to raise awareness of these issues as they relate to the prescription of pain medication and to pain management generally.

Federal drug law

All practice-oriented drug law and regulation is based on the federal Controlled Substances Act of 1970.¹ The Act, also known as Title II, is part of a much larger piece of legislation, the Comprehensive Drug Abuse Prevention and Control Act of 1970 (CSA).² CSA was enacted to regulate the manufacturing, distribution, dispensing, and delivery of drugs or substances that are subject to, or have the potential for, abuse or physical or psychological dependence. These drugs are designated *controlled substances* because they are "controlled" under CSA.³

CSA falls under the regulatory authority of the Drug Enforcement Administration (DEA), which controls access to regulated substances through the federal registration of all persons in the legitimate chain of manufacturing, distribution, or dispensing of controlled substances, except the ultimate user.⁴ The "ultimate user" is defined as (1) the patient who is competent to use these drugs as prescribed

by a practitioner, or (2) the patient's caregiver who administers them to the incompetent patient, for example, the parent of a sick child.⁵ All health care providers who deal with controlled substances are subject to CSA as well as to those drug control laws of the state in which they are licensed and practicing (unless such practice is exclusively in a federal facility, for example, a Veteran's Administration hospital).⁶

CSA empowers DEA to register all persons, businesses, and institutions conducting any activity that involves controlled substances. DEA does this by issuing registration numbers. Each DEA number must be renewed tri-annually.⁷ In addition, CSA establishes a closed system of record keeping that controls and tracks the flow of controlled substances through the health care system. For example, if a practitioner who has a DEA registration wants to order a controlled substance from a wholesaler or manufacturer, very specific record-keeping provisions exist depending on how the drugs ordered are categorized or scheduled.⁸ All registrants who order, fulfill an order, store, distribute, or dispense a controlled substance must report this activity to DEA and also maintain their own records for a period of two years.

CSA classifies medicinal substances into schedules based on their potential for abuse, psychological or physiological dependence, and medical use. These substances include narcotics, amphetamines, and barbiturates, and they are denoted CI, CII, CIII, CIV, and CV (see Table 1). Scheduling provisions also include prescription dispensing limitations.

Much of what appears in the Controlled Substances Act also appears in state acts and regulations, which also contain more stringent modifications. For example, in Massachusetts, prescriptions issued for medications listed in Schedule II must be filled by a pharmacy within five

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days of the date of issue.⁹ Drugs listed in Schedule II or III are only fillable for a thirty-day supply on any single filling.¹⁰ In addition, Massachusetts considers any prescription drug not included in a federal schedule to be designated as Schedule VI.¹¹ Therefore, in Massachusetts, an antihypertensive medication or prescription eye drops are controlled substances.

Federal versus state laws and regulations

Each state has enacted various laws and regulations and has a counterpart to a federal administrative agency that controls the manufacture, distribution, and sale of drugs within the state and that regulates the practice of health care professionals. Because one state’s drug control laws may vary greatly from the federal, certain basic principles must be followed by health professionals in order to comply. Joseph Fink et al. suggest the following.

- (1) Health professionals are responsible for compliance to the same degree with both federal and state laws and regulations that govern their practice.
- (2) A state drug control law or regulation may be more stringent than its federal counterpart.
- (3) Health professionals must comply with a state drug control law or regulation when it is stricter than federal law or when there is no similar prohibition or requirement under federal law.
- (4) If a federal drug control law or regulation is more stringent than the comparable state law or regulation, the federal regulation must be followed.¹²

Generally, most health care professionals do not make meaningful distinctions between federal and state laws and regulations in their day-to-day practice.

Prescription basics

Federal laws and regulations as well as those of many states require that prescriptions be dispensed with all requisite information (see Figure 1). Prescriptions must be written in ink, indelible pencil, or typewritten. Information can be entered onto a prescription by a designee, called an agent, of the prescriber or by a pharmacist when a clarification is needed. The only information required to be in the prescriber’s own handwriting is a personal signature. Federal law also allows prescriptions from Schedules III–V to be given orally or telephoned into pharmacies from prescribers or their agents; pharmacists are then required to record the name of that person onto that prescription.¹³ These oral prescriptions must then be supplemented with a written hard copy within seven days of issuance. This hard copy back-up is the prescriber’s responsibility. Pharmacists who do not receive the back-up within seven days are required to report this missing information to DEA. If the pharmacist does not report missing information, he is in violation of DEA regulations and therefore subject to penalties.

As mentioned, federal law categorizes prescription medications into schedules based on their abuse potential. As a result, these drugs need to be handled by prescribers and pharmacists in very specific ways. Schedule II controlled substances, which are generally used for moderate to severe pain, have the most restriction. Prescriptions written for medications listed in Schedule II can only be refilled with a written prescription.¹⁴

Prescriptions for Schedule II controlled substances may be partially filled for quantities less than those prescribed if the pharmacy is out-of-stock or a patient requests less, provided that the pharmacy dispenses the remainder to the patient within seventy-two hours. If this is not possible, the prescription becomes void and the prescriber is so informed.

Schedule	CI	CII	CII	CIV	CV
examples	heroin, phencyclidine, high abuse potential and no accepted medical use in the U.S.	morphine, Percodan, amphetamines, glutethimide,	Tylenol, codeine, Fiorinal, anabolic steroids	diazepam, phenobarbital, meprobamate, propoxyphene	cough syrups, codeine, Lomotil
time valid for filling	none	none or state mandate	180 days from date of issue	180 days from date of issue	none
max. days supply per fill	none	none or state mandate	180 days	180 days	none
max. refills	none	no refills allowed	5 refills	5 refills	none
oral prescription allowed	none	emergency only	yes	yes	yes

Table 1. Summary of Federal Prescription Filling Laws and Regulations.

Pharmacists may dispense partial quantities of Schedule II medications to patients in long-term care facilities or to the terminally ill for up to sixty days from the original date of the prescription’s issuance. The dispensing pharmacist is required to record that the patient is in a long-term care facility or is

Name of Practitioner		Date of Issue
Address of Practitioner		
Name: <u>Name of Patient (Unless Veterinary)</u>		
Address: <u>Address of Patient</u>		
Rx		
Name / Strength / Dosage of Medication		
Quantity		
Sig: Directions for use and any cautionary statements required		
Number of Times to Be Refilled.		
		<u>Signature of Prescriber</u>
Controlled substance registration number		

Figure 1. Information Required on Prescriptions.

terminally ill, along with the date of dispensing, quantity dispensed and remaining, and with the dispensing pharmacist signature on the back of the prescription.¹⁵

Schedule II medications also have restrictions on oral or telephone transmissions. CSA allows prescribers to call pharmacies and orally transmit prescriptions for Schedule II drugs only in an emergency. An "Emergency Situation," as stated under CSA, means that immediate administration of the controlled substance is necessary for the proper treatment of the intended ultimate user; no appropriate alternative treatment is available, including administration of a drug that is not a controlled substance under Schedule II of CSA; and, it is not reasonably possible for the prescribing physician to provide a written prescription to be presented to the person dispensing the substance, prior to dispensing.¹⁶

In an emergency, a pharmacist may dispense a controlled substance in Schedule II on receiving the orally transmitted authorization of a prescribing practitioner, provided that the quantity prescribed and dispensed is limited to the amount adequate to treat the patient during the emergency. The prescribing practitioner must then provide a written prescription for the emergency quantity. The written prescription must be delivered or postmarked to the dispensing pharmacist within seventy-two hours after authorizing an emergency oral prescription. The prescription must also have written on its face "Authorization for Emergency Dispensing." On receipt of the written prescription, the dispensing pharmacist must attach the prescription to the oral one. If the prescribing practitioner fails to deliver a written prescription within seven days, the pharmacist must notify DEA.

The regulations for emergencies can be cumbersome for home infusion pharmacies, hospice, and long-term care

pharmacies. Frequent dosage modifications of parenteral or controlled-release narcotic substances for patients who require these services can place pharmacies and prescribers at a regulatory disadvantage because the pharmacy would have to enforce the existing regulations. However, DEA has provided an easier mechanism for handling prescriptions for Schedule II pain medications. In May 1994, DEA issued a rule that allows controlled substance prescription orders to be transmitted from a prescriber to a dispensing pharmacy by facsimile.¹⁷ The rule covers all controlled substance prescriptions. DEA allows pharmacies to receive facsimile prescriptions for intravenous pain therapy and to retain them as the original prescription, thereby substantially reducing the need for oral emergency prescriptions in these settings. One must

note that these rules do not apply to oral dosage forms.

Prescriptions written for Schedules III and IV are regulated somewhat less stringently. They are refillable up to five times if so authorized, or for six months from their date of issue, whichever terminates first; and, when filled with a partial quantity, they must have the quantity recorded on the back, along with the date of refilling and the dispensing pharmacist's initials.¹⁸ Prescriptions for Schedule V are also refillable. However, the number of refills is not set by law, and the authorized number of refills depends on the professional judgment of both the prescriber and the pharmacist.¹⁹

Pharmacists and prescribers are co-liable for prescriptions written for patients. This is called *corresponding responsibility*.²⁰ A prescription for a controlled substance must be issued in good faith and for a legitimate medical purpose by a practitioner in the usual course of his professional practice; likewise, pharmacists have the corresponding responsibility to ensure that the prescription is issued and dispensed in good faith for a legitimate medical purpose by a practitioner acting in the usual course of his practice.

For instance, a pharmacist receives a prescription written by a radiologist for her child. Radiologists are medical doctors with a specialty. They may prescribe medication outside their specialty provided that the prescription is written in good faith, for a legitimate medical purpose, and in the usual course of medical practice. If the radiologist has conducted all of the medically required tests and generated a patient record, thereby establishing a physician-patient relationship, the pharmacist may fill the prescription under federal law. Pharmacists will question prescriptions such as this in order to protect themselves and their patients.

Product selection

Product selection causes pharmacists and prescribers much anguish. Product selection can be divided into two categories: (1) the substitution of products that are pharmaceutically equivalent and are bioequivalent, that is, a brand name product and a generic copy; and (2) the substitution of chemically dissimilar products that are in the same therapeutic class, that is, two therapeutic moieties that treat the same medical condition.

The substitution of products with the same active ingredients is well defined in the regulations of many states. Generally, substitutable products used by pharmacists and sanctioned by the states are listed in *Approved Drug Products with Therapeutic Equivalence Evaluations* (the *Orange Book*), published since 1979 by the Food and Drug Administration (FDA). This federal publication is a guide to health care professionals for making product selection decisions. It lists marketed drug products that are considered by FDA to be safe and effective and it provides information on therapeutic equivalence evaluations for approved multisource prescription drug products.²¹

The *Orange Book* rates drugs based on their therapeutic equivalence. For a product to be therapeutically equivalent, it must be both *pharmaceutically equivalent* (that is, the same dose, dosage form, strength, and so on) and *bioequivalent* (that is, the rate and extent of its absorption are not significantly different from the rate and extent of absorption of the drug with which it is to be interchanged).

FDA allows pharmaceuticals to be considered bioequivalent in one of two methods. The first method studies the rate and extent of absorption of a test drug, which may or may not be a generic variation, and a reference or brand name drug under similar experimental conditions and in similar dosing schedules, where the test results do not show significant differences. The second approach uses the same method to determine whether a difference exists in the test drug's rate and extent of absorption, but the difference is considered to be medically insignificant for the proper clinical outcome of that drug.

Bioequivalence of different formulations of the same drug substance involves equivalence with respect to the rate and extent of drug absorption. Two formulations whose rate and extent of absorption differ by 20% or less are generally considered bioequivalent. The use of the 20% rule is based on a medical decision that, for most drugs, a 20% difference in the concentration of the active ingredient in blood will not be clinically significant.²²

The *Orange Book* uses a letter coding system to help practitioners determine which drug products are therapeutically equivalent. The first letter, either an A or a B, indicates a drug product's therapeutic equivalence rating. The

second describes dose forms and can be designated by any one of a number of different letters.

For example, in the *Orange Book*, A codes are described as follows:

Drug products that FDA considers to be therapeutically equivalent to other pharmaceutically equivalent products, i.e., drug products for which:

1) there are no known or suspected bioequivalence problems. These are designated AA, AN, AO, AP or AT, depending on the dose form;

or

2) actual or potential bioequivalence problems have been resolved with adequate in vivo and/or in vitro evidence supporting bioequivalence. These are designated AB.²³

A B-code rating is much less desirable than an A rating. Products rated B may be commercially marketed; however, they may not be considered therapeutically equivalent. B codes are defined as follows:

Drug products that FDA at this time does not consider to be therapeutically equivalent to other pharmaceutically equivalent products, i.e., drug products for which actual or potential bioequivalence problems have not been resolved by adequate evidence of bioequivalence. Often the problem is with specific dosage forms rather than with the active ingredients. These are designated BC, BD, BE, BN, BP, BR, BS, BT, or BX.²⁴

FDA has adopted an additional subcategory of B codes. The designation B* is assigned to former A-rated drugs "if FDA receives new information that raises a significant question regarding therapeutic equivalence."²⁵

Not all drugs are listed in the *Orange Book*. Drugs obtainable only from a single manufacturing source, DESI-drugs, or drugs manufactured prior to 1938 are not included. Those that do appear are listed by generic name. Drug products with an A rating that are determined by FDA to be therapeutically equivalent may be substituted. Drug products with B ratings that are not considered by FDA to be therapeutically equivalent may not be substituted. However, because the *Orange Book* is merely a guide to therapeutic equivalence, state agencies, for instance, the Massachusetts Department of Public Health, have the option to allow some B-rated products to be substituted if a determination can be made that bioequivalence is not essential.²⁶ The only practical way for health professionals to determine whether a drug is listed is to consult both the *Orange Book* and other reference material available from the appropriate agency in one's home state.

Currently, at least thirteen states require pharmacists

to substitute one product for another, depending on how a prescription is written. This is called *mandatory substitution*. Thirty-nine states allow *permissive substitution* where patients may be asked if they want to substitute a product based on cost or pharmacist suggestion. Many states also have a *positive formulary* where pharmacists may only dispense substitutable products from an established list of drugs. Others have a *negative formulary* where pharmacists may substitute any product provided it *does not* appear on the established list.²⁷

The substitution of products within a therapeutic category in which two therapeutic moieties can be used alternatively to treat the same medical condition is problematic for pharmacists. Hospital pharmacy and therapeutics committees, managed care organizations (MCOs), and others who control a formulary are constantly searching for the most therapeutic and cost-effective medication to treat patients. At issue is the great breadth of medications available. A pharmacist would have many choices that might be considered optimal were it not for the product cost. Therefore, medication management decision-makers must make choices about which medications will be used for particular medical conditions or patients based on overall clinical effectiveness and cost. These decisions lead into the discussion of pharmacoeconomics.

Pharmacoeconomic decision making

Pharmacoeconomics is a very pervasive term in much of the pharmacy literature. Pharmacoeconomics explains pharmacy and therapeutics in terms of cost and patient outcomes, and helps decision-makers make the best possible decision regarding the use of available resources and pharmacy dollars.²⁸

According to Lyle Bootman et al., pharmacoeconomic research helps health care providers:

- determine which drugs should be included in a hospital formulary;
- evaluate clinical pharmacy services to assess cost and outcomes; and
- determine whether particular drug therapy decisions improve patients' quality of life.²⁹

For example, an MCO administrator is asked to evaluate two competing pharmaceuticals for possible inclusion in its closed formulary. One product will be listed, the other will not. Both are used to treat the same disease. Each has different side-effects. One is dosed daily, the other four times daily. Both cost approximately \$4.00 per day of therapy.

If the administrator selects one product over the other without first evaluating one against the other, the decision may be short sighted. Is it cost effective for the health plan to select a once-daily product that has known side-effects

which cause such severe gastrointestinal irritation that patients become noncompliant, resulting in additional physician visits and new medications prescribed to sicker patients? Or, is it cost effective to prescribe the product dosed four times daily, which requires a significantly longer therapy but has fewer severe side-effects? Both considerations may have ancillary issues that need to be evaluated before a product goes into the formulary.

Pharmacists use various methods to answer such product-selection issues arising in daily practice (see Figure 2). The most often used include the following:

- cost-benefit analysis;
- cost-effectiveness analysis;
- cost-minimization analysis; and
- cost-utility analysis.

Cost-benefit analysis

Cost-benefit analysis is a method by which a pharmacist assigns a dollar value to all of the benefits of the medication, and then subtracts all of the costs to supply those benefits. When done with two or more products, comparison of the data is beneficial.

For example, a pharmacist must evaluate several pain medications. He needs to determine two things: first, how much are the perceived benefits worth monetarily; and second, how much the drug "really" costs. The monetary value of the benefit may include the addition of several months of pain-free life, which may result in extra income to the patient's family. The pharmacist determines the costs by calculating the price of the medication, its administration, hospital time, and so forth, and then subtracts the difference for each medication. The product with the highest present value has the highest cost-benefit. However, not all benefits easily lend themselves to a dollar value, for instance, the value of increased patient satisfaction when the patient can continue to work while undergoing pain management therapy. Some allocations may very well be up to the decision-maker's own values.³⁰

- Document the number of interventions related to change or discontinuation of target drug. Then calculate the cost of medication saved, cost of medication avoided, and total cost saved and avoided.
- Compare actual dollars spent before and after a target intervention.
- Based on the types of intervention, calculate the amount of personnel costs saved.
- Compare the cost per milligram and the approximate cost for equipotent dosage for a typical patient (70 kg) in the target drug class and/or category.
- Review the literature for new or updated information related to the targeted drug class and/or category, particularly economic or patient outcome data.

Figure 2. Suggested Steps in Pharmacoeconomic Evaluation.

Cost-effectiveness analysis

Cost-effectiveness analysis is a method used to assess value among a group of alternatives.³¹ For example, drug A and drug B are equally effective in managing cancer pain. Drug A can be purchased at a lower price than drug B. However, drug B requires less administration time and is better tolerated by the patient. Drug B is more cost-effective.³² This methodology is beneficial when one wants to determine the best overall value from a group of drugs.

Cost-minimization analysis

Cost-minimization analysis is used to determine the least expensive of those drug products that provide equal benefit. An example of this analysis is evaluation of equivalent drug products where the selection of one over the others is primarily based on lowest acquisition cost.

Cost-utility analysis

Cost-utility analysis is a more humanistic methodology. Like cost-effectiveness analysis, it measures the cost of something relative to its effectiveness, from some perspective, many times that of the patient. But in cost-utility analysis, an intervention, for instance, the cost of pain management therapy, is also measured in terms of the quality of health care outcomes, such as how a patient feels about his life after the treatment. In broader terms, cost-utility analysis puts into economic perspective the patient's feelings regarding how much a few more years of productive life is worth relative to how much the therapy costs.

Case study

Below, I apply the four analyses to demonstrate how each operates in practice.

A sixty-eight-year-old male is diagnosed with pancreatic cancer. He initially presents with abdominal discomfort, not yet described as acute pain. The patient refuses all attempts at chemotherapy. The patient requests only to be kept comfortable at all stages of his illness. The physician may have many alternatives available, all of which will manage the patient's pain equally.

The overall treatment goal for this patient is achievement of a pain-free existence at a minimal cost. Can one methodology determine how to treat this patient and yield a similar or more positive therapeutic outcome of pain control at a lower cost? Health care professionals base their therapeutic decisions primarily on therapeutic outcomes. Health care administrators, however, may take an entirely different view, such as determining the least costly way to

achieve the desired outcome. Total treatment costs need to be considered, and they may include nursing and medical staff time, administration supplies, and all other costs related to home or hospice care.

A cost-effectiveness strategy requires the physician to evaluate several treatment modalities and consider the price of the product and the required administration time to achieve the desired pain control outcome. An oral, long-acting opioid can be chosen over an intravenous alternative because it may have greater savings to the health system in that the patient can self-administer an oral dosage without the additional costs of professional homecare. This savings is the value.

A cost-minimization strategy requires the physician to evaluate the price of the available products. The decision to prescribe is based solely on the least expensive therapeutic alternative.

A cost-benefit strategy requires the physician to calculate the net dollar value benefits relative to the cost of each alternative therapy. If the cost of one drug is greater than the others (after the inclusion of product, administration, time, and so on), but the value of the benefits to the patient is greater (less inconvenience or greater compliance), then that product would be a better cost-benefit choice.

A cost-utility strategy includes the calculation, from the patient's perspective, of the net costs of the products used to keep him pain-free. A cost-utility strategy might include presenting the patient with a list of alternatives and an explanation of the benefits and side-effects of each medication. The patient would be allowed to decide which best fits his needs and treatment goals.

Several other issues need to be addressed. Initially, at the community pharmacy level, patients at home receive prescriptions from their prescriber. The pharmacy might be required by federal or state law to dispense a less expensive drug, possibly a generic alternative to the medication written. The patient's medical insurer may also require substitution if legal. Frequently, physicians prescribe certain medications that are then substituted due to insurers' cost-minimization policies. In many states, pharmacies must comply.

Changes in therapy might be needed to accommodate breakthrough pain. For community pharmacies, the issue is one of record keeping and explaining therapeutic duplication to insurers. The physician may feel that the patient's needs are best met by a fentanyl patch³³ applied once every three days. The question then becomes whether the patient's insurer will pay for it. Cost-effectiveness analysis could be conducted in this situation to make the case that the patch is the proper treatment modality.

One cannot help notice that each of these methodologies can be employed, with varying degrees of difficulty, in most medical situations. Pharmacy and therapeutic issues readily lend themselves to economic assessment due to the

high cost of drugs. Pharmacoeconomic research is one way to ensure that patients benefit from the most cost-justified treatment modalities.

Conclusion

Pain management, from the pharmacist's perspective, is dominated by regulations, formularies, and cost controls. Regulatory issues are cumbersome due to the volume of record-keeping provisions imposed by both federal and state agencies. Failure by pharmacists and other health care providers to keep accurate records can result in a \$25,000 fine imposed by DEA. Health care institutions who treat large numbers of pain management patients are certainly at risk for great financial exposure.

Product selection expands the concerns of health care practitioners. FDA allows substitution of products based on therapeutic equivalence. Many states and third-party payers promote product substitution based on their own economic or therapeutic criteria. Prescribers and pharmacists must be aware of these localized dilemmas.

Decision-makers in today's health care market are increasingly influenced by operating costs. Data that can be used to generate information which results in knowledge is a valuable commodity to them. Pharmacy is in a unique position to capture and produce clinical, economic, and risk management data. This data can produce timely information to inform clinical decision-makers about how to provide proper patient management. It is important for health professional pharmacists and administrators not only to focus on clinical information in drug product decision making, but also to include broader health economics considerations under the rubric of clinical decision making for modern selection of drug therapy.

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29. *Id.* at 5.
30. *Id.* at 6.
31. *Id.* at 6-7.
32. *Id.* at 78-79.
33. A fentanyl patch is a transdermal patch containing the Schedule II drug fentanyl, which is applied to the skin and used in pain management.