Challenges in the Federal Regulation of Pain Management Technologies

Lars Noah

Those who write about pain management have focused almost entirely on delivery issues, paying essentially no attention to the federal regulatory challenges that affect the development of pain relief technologies — namely, pharmaceuticals and medical devices indicated for analgesic uses. The academic literature is strangely devoid of any sophisticated discussion of the difficulties that attend, first, the product approval decisions of the Food and Drug Administration (FDA) and, second, the scheduling decisions made by the Drug Enforcement Administration (DEA). If a "bottleneck" develops upstream, it could have serious repercussions downstream — without pain relief technologies, the issues of access that have preoccupied previous commentators would have little practical consequence.

The modern pharmaceutical industry traces its origins back more than a century, around the time that the German company Bayer first synthesized aspirin (acetylsalicylic acid) and began marketing it as an analgesic.[1] Federal regulation of drug products in the United States began shortly thereafter,[2] and it has evolved alongside the growing sophistication of the pharmaceutical industry. Although not specifically geared toward the control of pain management technologies, these various laws have had important consequences for the availability and use of analgesic products, at least in part because of certain peculiar aspects of these pharmaceuticals. In parallel, Congress has imposed special requirements on narcotics often used for analgesia because of concerns about addiction and abuse.

This article considers, in turn, the roles played by the FDA and the DEA in regulating pain management technologies. Whether a company wishes to market an over-the-counter pain reliever containing a well-known active ingredient, a prescription drug containing a novel analgesic compound, or a medical device intended for the treatment of pain, it must satisfy a number of requirements designed to ensure the safety and effectiveness of the product. In addition, if a drug product contains a narcotic or other controlled substance, its availability will depend on the manner in which the DEA has classified that substance. Although implemented by two quite dissimilar agencies — the former preoccupied with medical and scientific questions, while the latter focuses on law enforcement matters — these two regulatory regimes operate in tandem and overlap in potentially important ways.

Several themes emerge from this discussion. First, both agencies have shown a marked resistance to making narcotics available as analgesic products, though the FDA has better appreciated the value of providing patients with a wide range of options for treating pain. Second, notwithstanding its far more limited understanding of clinical practice, the DEA has demonstrated a greater enthusiasm for efforts to keep physicians in line than has the FDA. These and similar examples of contrasting behavior by the two federal agencies in this field — reflecting their distinctly different missions and cultures — provide important lessons about comparative institutional competence and suggest that Congress might want to reconsider this sometimes unstable division of regulatory authority.

Finally, the tools currently available to both agencies may be too blunt for sensibly addressing the conflict that often arises between the needs of patients and efforts to prevent irresponsible use. Once it decides to approve a new drug, the FDA can restrict access to prescription-only and then hope to influence physician use through recommendations in labeling. For the DEA, most of the important restrictions on access to controlled substances represent an

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But there are issues that need to be resolved with electronic prescription monitoring programs. The lack of accuracy within them is troubling, according to the article, with pharmacists reporting their data to the program using patient identification information that is often incomplete, inconsistent, or wrong. The other issue is one of confidentiality. Legal rules of confidentiality have not evolved for pharmacy records as fast as they have for medical records. Pharmacists now maintain a lot of information about patients, and because the information is computerized, it may be easy to access. As a result, information that could not be obtained from a patient's physician may now be readily available from the patient's pharmacy. While the advent of electronic prescription monitoring programs may help establish a "standard of care" for prescribing and dispensing controlled substances, without a clear idea of how that standard should be applied, physicians and pharmacists could choose to play it safe and avoid prescribing controlled substances altogether.

There already exists a background of tension between drug control authorities and health care practitioners regarding the enforcement of controlled substances laws. The author warns that poorly constructed electronic monitoring programs could exacerbate this existing tension. An effective program will require law enforcement personnel who are aggressive in the prosecution of controlled substance diversion, as well as professional license boards that have zero tolerance for those licensees who abuse the privilege of prescribing or dispensing controlled substances. A successful program will require the availability of high quality continuing education programs on pain management and on the appropriate use of controlled substances for other medical conditions, as well as a trusting atmosphere in which regulatory authorities and health care practitioners can communicate openly to avoid misunderstandings.

The article outlines suggestions for increasing the utility of electronic prescription monitoring programs. An effective program should be flexibly designed to permit program operators to require the reporting and aggregation of data from the dispensing of all drugs that are subject to abuse, not just some of them. In addition, all pharmacies should be included in the system. The state agency receiving the data should have sufficient expertise to evaluate the significance of a pattern of dispensing; this could include a state department of health or a state board of pharmacy. The author also urges that there be timely and meaningful feedback to those who prescribe, dispense, and monitor a patient's therapy. A medication profile provided to a pharmacist or a physician by an electronic prescription monitoring program would be very useful in constructing longitudinal trends in medication use.

The availability of comprehensive information about a patient's controlled substance use would enable pharmacists and physicians who fully utilize the services of an electronic prescription monitoring program to improve the quality of care they provide to their patients. The extent to which this opportunity for learning more information about patients changes the standard of care is presently unknown. Health providers will need to be given clear standards of practice against which their care will be judged by licensing boards or in malpractice proceedings. Uncertainty of standards may lead to risk-averse medical and pharmacy practices. Standards should produce both decreased prescribing for patients who have received too many controlled substances and increased prescribing for patients who have received too few controlled substances. Finally, each state electronic prescription monitoring program should be periodically reviewed and evaluated. Although the criteria for evaluation could vary state to state, program evaluation can show whether specified criteria have been met within a given timeframe in each state.

The author concludes that the goals of improved drug therapy and reduced controlled substance abuse are not mutually exclusive; rather, they are synergistic. Nevertheless, the implementation of uncoordinated programs in these two areas has in the past led to distrust and antagonism between law enforcement personnel and health care providers. Properly designed and implemented electronic prescription monitoring programs have the potential to create a collaborative regulatory environment that reduces substance abuse and actually improves the quality of drug therapy with controlled substances.

But the value of electronic prescription monitoring programs should not be assumed. A high enough level of scrutiny has not been applied to these programs, and it seems reasonable that new drug surveillance systems be subject to the same safety and efficacy expectations of new drugs. The public deserves some level of assurance that electronic prescription monitoring programs will be a benefit to diversion control and will not deter relief to the 75 million people in the United States who suffer from severe pain.

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Both the Food and Drug Administration (FDA) and the Drug Enforcement Administration (DEA) play a role in regulating pain management technologies, including

pharmaceutical products and medical devices indicated for analgesic use. Yet, as things stand, these two key federal entities, with their distinctly different missions and cultures, contribute to the persistent undertreatment of pain through both overregulation and duplicative regulation. The solution lies in refining pain regulation so that a better balance is created between the need to ensure patient access to pain relief and the need to prevent and reduce drug diversion.

Various federal regulatory mechanisms — such as limits on supplies and distribution channels — have created barriers that ultimately affect access to pain management technologies for legitimate users. As the FDA and DEA focus their attention on the misuse of legitimate pain technologies, patients ultimately may be deprived of valuable analgesic agents. In the classic tug of war over the medical needs of individual patients versus the broader societal hazards associated with the availability of pain products, the FDA and the DEA face difficult pain management regulation challenges.

The FDA, which is part of the U.S. Department of Health and Human Services, is responsible for assessing the safety and effectiveness of pain management technologies, which include prescription and over-the-counter pharmaceuticals and medical devices. A long and difficult process generally, obtaining FDA approval for a pain medication is particularly difficult because of the subjective nature of pain and the significant variability in patient response.

As part of the FDA approval process for marketing a product, a manufacturer must work with the FDA to determine whether the drug should be available over the counter or only through a physician's prescription. A prescription mandate is one way to reduce the risk of abuse. But it also impedes patient access to needed medication.

Another restriction involves label and insert content for pharmaceutical products. Product inserts, in particular, contain detailed prescribing information, including indications for use, which are an important consideration for pain management. Historically, Congress has followed a guiding principle that frowns upon federal interference with the practice of medicine. That typically includes what is often referred to as "off-label" prescribing. Once the FDA has approved marketing a drug product for a specific indication or labeled use, a physician can prescribe that product for uses not included in the drug's labeling.

In the case of "controlled substances," however, the DEA can limit a physician's prescribing. Thus, by eliminating the ability to prescribe off-label, the DEA has chipped away at the taboo on federal interference with medical practice.

Controlled substances, which represent most of the significant pain management technologies available today, are primarily opioid analgesics. These powerful drugs must undergo the same FDA-approval process as any other pharmaceutical product. But these drugs are subject to additional control by the DEA, which is part of the U.S. Department of Justice.

In 1970, Congress enacted the Controlled Substances Act, which established different "schedules" of narcotics and other substances prone to abuse or diversion. The most restrictive classification, Schedule I, includes those drugs or substances that are highly subject to abuse, that have no currently accepted medical use in the United States, and for which there is a lack of accepted safety. Drugs in this category include heroin and marijuana.

Schedule II includes drugs or substances that are also highly subject to abuse, but are accepted for medical use in the United States (possibly with severe restrictions). For these drugs, there is recognition that abuse may lead to severe psychological or physical dependence. Schedule II includes drugs containing synthetic forms of morphine. Schedules III, IV, and V all have drugs with a currently accepted medical use in the United States, with progressively lower potentials for abuse and severity of dependence.

Under the Controlled Substances Act, the DEA supervises the manufacture and distribution of legal narcotics. For example, manufacturers of Schedule II drugs must register their operations and the DEA assigns production quotas. Although Congress typically makes the initial decision on how to schedule a controlled substance, the DEA may have to make its own scheduling decisions on newly synthesized chemicals or in response to new information about previously scheduled controlled substances. In these cases, Congress, attempting to strike a balance between law enforcement and clinical considerations, has mandated that the DEA consult first with the Department of Health and Human Services — through the FDA — when weighing these decisions.

This effort underscores the constant struggle in attempting to find a middle ground between law enforcement criteria and medical and scientific determinations. The incongruities between a traditional law enforcement agency and one that focuses on patient health have made down-scheduling of controlled substances — such as marijuana — exceedingly difficult.

Still, a number of intermediate regulatory responses could provide a public health approach for dealing with overuse of narcotic analgesics. These include: (1) limiting access to narcotic analgesics to medical specialists — oncologists, orthopedic surgeons, and pain management specialists — who typically work with patients suffer-

ing from severe or chronic pain; (2) tighter regulation of promotional efforts for controlled substances; (3) enhanced tracking of prescriptions; and (4) better education for health care professionals.

Excessive preoccupation with abuse and diversion issues may result in unnecessary pain and suffering for patients with legitimate medical needs. A more refined approach to pain regulation can ensure that both sets of goals — those of law enforcers and those of patient care providers — are achieved.

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Pain Relief, Prescription Drugs, and Prosecution: A Four-State Survey of Chief Prosecutors

Stephen J. Ziegler and Nicholas P. Lovrich, Jr.

A recurring theme in the debate over adequate pain management is the extent to which physicians' fear of criminal investigation and prosecution has set up barriers to appropriate dispensing of pain relief to patients. While there have been several studies looking at the regulatory environment and its effect on physicians' prescribing practices and the treatment of pain, there has been scant research on the probability of investigation or prosecution of physicians who aggressively prescribe opioids for pain management.

To understand whether physicians' fear of investigation or prosecution is based on a realistic assessment of risk, the authors surveyed chief prosecutors in four states (Maryland, Connecticut, Oregon, and Washington), all of which have varying degrees of focus, prosecutorial culture, and regulatory attitudes toward this issue.

The survey examined local prosecutors' knowledge, opinions, and attitudes toward opioids and the extent to which physicians are prosecuted for aggressive treatment of terminally ill patients or those suffering from chronic noncancer pain. Building on earlier research, they set out to assess whether prosecutions involving physicians were more common than what was being reported, and to document what factors may contribute to and predict the likelihood of an investigation or prosecution in these cases.

Studies have shown that the fear of iatrogenic addiction and increased regulatory scrutiny are two of the most prominent reasons for the underdispensing of opioids. Although the use of narcotics in the management of pain is a legitimate and recognized protocol and the evidence shows that the rate of addiction is very low, health care professionals continue to overestimate the level of regulatory scrutiny to which they are exposed. Although many physicians admit that their pain management practices may be lacking, they nevertheless fear that aggressive opioid therapy for those suffering from pain will harm patients or attract heightened scrutiny from state medical licensing boards, county prosecutors, or even the federal government.

Physicians also are concerned that their prescribing practices will raise suspicions of pharmaceutical diversion, particularly when treating chronic noncancer pain. More than a quarter of Texas physicians responding to a recent survey said they believe that prescribing narcotics for patients with chronic pain will likely trigger a Drug Enforcement Administration (DEA) investigation. The authors point out that while pharmaceutical diversion is a part of the national drug abuse problem, physician perception of regulatory risk far exceeds reality. In fact, they say, only a relatively small percentage of prescription drugs are actually diverted to illicit use by patients; and to an even lesser extent when dealing with physicians.

To examine what factors may contribute to, and predict the likelihood of, criminal investigation and prosecution in these cases, the authors asked prosecutors about a range of topics, including pharmaceutical diversion, pain relief, addiction risk, physician-assisted suicide, and euthanasia. They also asked what factors would contribute to a physician being charged with an offense. Prosecutors responded to different scenarios involving patients and physicians and estimated the likelihood they would take action on a scale of 0 percent to 100 percent. The article reports on the findings from two scenarios entailing the aggressive treatment of pain among terminally ill and chronic noncancer patients.

One scenario involved the legitimate but aggressive treatment of chronic noncancer pain identified as a potential problem by a pharmacist. The authors were curious to see if prosecutors would recommend a police investigation of the physician, refer the matter to the DEA, or refer it to the state medical board. The second scenario involved the treatment of a terminally ill patient experiencing respiratory distress who, after morphine administration, goes into respiratory arrest and dies. This has been described by one doctor as a daily occurrence in the United States; thus, the authors hypothesized that prosecutors would likely not take action against the physician in this case.

When it came to the treatment of chronic nonmalignant pain, there was a broad spectrum of opinion among prosecutors on the prospects for a police investigation. The overall mean likelihood of recommending an investigation was nearly 49 percent. In Oregon (a state with a heightened sensitivity to these issues), however, the likelihood was the lowest, while prosecutors from Maryland said there was 73 percent average likelihood of recommending a police investigation.

outgrowth of initial decisions about appropriate scheduling, which may cause the agency to overschedule substances in order to serve law enforcement purposes. Providing more refined regulatory options may allow for a more sensible resolution of the perennial tension between patient access and drug diversion.

If federal agencies become excessively concerned about misuse, they may deprive patients of valuable new analgesic agents. Indeed, depending on the stringency of the restrictions imposed, companies may be unable or unwilling to develop such products in the first place, or health care professionals may fail to make full use of them.[3] Already hesitant to approve powerful analgesics, the FDA and the DEA may be forced to revisit their original clearance decisions due to the growing problems with the theft and diversion of currently marketed painkillers containing ingredients such as oxycodone and fentanyl. Any such regulatory actions — whether expressed as a refusal to allow an analgesic product to enter the market initially or the withdrawal of such a product in the face of rampant abuse — would have to grapple with the classic difficulty of choosing between the medical needs of individual patients and the broader societal hazards associated with the availability of such products. These questions do not admit of any simple answers, of course, but they cannot be avoided. This article delineates the nature of the various challenges that the federal government has faced in regulating pain management technologies before tentatively recommending a public health approach that attempts to bridge the FDA's predominantly clinical focus and the DEA's preoccupation with the potential adverse consequences for third parties.

FDA Regulation of Analgesic Products

Before pain management technologies can reach patients, the Food and Drug Administration must assess their safety and effectiveness. If a product has not received marketing approval (or an exemption) from the agency, then it cannot be sold. Even if a company has surmounted the often difficult hurdle of proving that a product serves a therapeutic purpose without posing an undue risk, the FDA's decisions about appropriate labeling may affect how readily patients will be able to access it.

Product approval requirements

Over the course of the last century, federal regulation of medical technologies has shifted from an emphasis on policing against economic frauds to a premarket approval system mandating proof to support therapeutic claims.[4] The FDA has, for example, expressed long-standing and largely justified skepticism about "quack" medical devices, including products indicated for pain relief.[5] As a result, legitimate articles used for analgesia may encounter significant regulatory obstacles originally fashioned to protect consumers from wasting their resources on worthless remedies.

In particular, the FDA's insistence on placebo-controlled clinical trials when evaluating the effectiveness of pharmaceuticals and medical devices means that firms seeking to market pain management technologies shoulder a particularly challenging evidentiary burden given the pronounced placebo effect that researchers encounter in this context.[6] Moreover, because of difficulties in measuring a largely subjective condition such as pain,[7] coupled with the significant variability in patient response,[8] the agency may struggle to interpret placebo-controlled clinical trials submitted as part of an application for new drug approval (NDA).[9]

Even if persuaded that a drug works, the agency will have to decide whether or not the inevitable side-effects pose too great a hazard to justify granting product approval. In making these risk-benefit judgments, "the FDA takes into account the significance of a targeted health condition, or the status of that condition as a treatable disease."[10] Interventions such as analgesics that provide *only* symptomatic relief may not fare as well in this process,[11] though some experts maintain that pain should qualify as a serious disease process in its own right.[12] A similar dichotomy, between curative and palliative care,[13] may account for the persistent undertreatment of pain by health care professionals.[14]

Notwithstanding this pair of potential obstacles — namely, the heightened difficulty of establishing efficacy and the presumption that symptomatic relief represents a less compelling clinical endpoint for purposes of making risk-benefit judgments — no one has accused the FDA of overcaution in reviewing new analgesics. On the contrary, some observers have criticized the agency for approving too many new nonsteroidal antiinflammatory drugs (NSAIDs) that offer no particular advantage over existing, and typically less expensive, drugs in the class.[15] The FDA usually does not, however, make judgments about comparative efficacy,[16] preferring to leave that task for physicians and patients based on the information supplied in the labeling dictated by agency reviewers.

In some instances, the management of side-effects associated with analgesics rather than any differential effectiveness accounts for the need to have a range of therapeutic options. In 1999, the FDA approved Vioxx® (rofecoxib) and Celebrex® (celecoxib), the first in a new class of painkillers called COX-2 inhibitors.[17] NSAIDs represent peripherally acting analgesics, which means that they lessen the localized inflammation (and production of prostaglandins) that triggers a sensation of pain.[18] They do this by blocking the enzyme cyclooxygenase. As it turns out, this enzyme has two isoforms, one associated with inflammation (COX-2) and the other one thought to protect the lining of the stomach (COX-1). Older NSAIDs blocked both isoforms, which may explain their association with the development of ulcers.[19] By selectively blocking only the form of the enzyme linked to inflammation, COX-2 inhibitors promised to offer compa-

rable pain relief, especially in arthritis patients, without the associated risk of gastrointestinal side-effects.[20] These drugs appear, however, to pose a heightened risk of cardiovascular side-effects.[21]

As may happen with any new drug product, serious side-effects associated with analgesics may become evident only after approval and widespread use.[22] During the 1980s, the FDA received numerous adverse event reports for three NSAIDs that led to their hasty withdrawal from the market: Zomax® (zomepirac), Oraflex® (benoxaprofen), and Suprol® (suprofen).[23] Zomax was, however, notable for another reason. Even though the FDA conceded that it knew at the time of approval that the drug represented a potential human carcinogen (and that some patients would use it chronically), Zomax received an NDA because agency reviewers thought that it could substitute for narcotics used in the treatment of severe pain.[24] This excessive concern about patient use of any controlled substances — so much so that it would displace the FDA's normal resistance to approving nonessential products that create a risk of cancer — appears repeatedly in other contexts. When patients mysteriously began dying from anaphylactic reactions, even the supposed advantage of Zomax as a substitute for narcotic analgesics could not prevent the drug's commercial demise.[25]

In July 1997, the prescription analgesic Duract® (bromfenac sodium) entered the U.S. market. Less than a year later, the manufacturer withdrew the drug from the market after it had been associated with liver toxicity resulting in at least four deaths and eight liver transplants.[26] During clinical trials, researchers had reported an unexpectedly high incidence of elevated liver enzymes in patients who took Duract for relatively long periods,[27] and one FDA reviewer voiced significant concerns about the drug's potential hepatotoxicity.[28] Nonetheless, as happened with Zomax, the agency viewed the product as a substitute for narcotic analgesics, so it decided to approve Duract, though only for short-term use and with labeling information about the risk of elevated liver enzymes.[29] Many physicians, however, prescribed Duract for longer than the 10 days specified by the FDA, and the agency soon began receiving reports of liver failure.

As the FDA initially became aware of liver problems in patients taking Duract, it tried to notify physicians about the emerging safety problems.[30] The agency required the addition of a prominent boxed warning in the drug's labeling, and the manufacturer mailed out a "Dear Doctor" letter emphasizing the drug's dangers and providing guidelines for proper use.[31] These efforts did not, however, completely prevent the inappropriate prescribing of Duract for long-term use. After the FDA concluded that it could not impose effective restrictions to limit the duration of use,[32] the manufacturer voluntarily withdrew the drug from the market in June 1998.[33] Duract may well have offered a net benefit over other drugs in some class of patients when used as recommended, but the agency could not ignore the pattern of physician misuse causing risks to other patients.

Over-the-counter marketing

One fundamental labeling question is whether to make a product available only upon a prescription from — or through direct administration by — a licensed health care professional. Because analgesics relieve symptoms and do not purport to treat any underlying disease process, they would seem to represent natural candidates for nonprescription or over-the-counter (OTC) marketing.[34] Even if most consumers would not need a physician's diagnostic skills in order to decide whether to select a particular pain reliever, however, the safety profile of a product may justify some restriction on access. At least initially, most new ingredients are available only by prescription while the FDA collects additional adverse event data.[35] In addition, the risk of abuse has, from the outset, represented one of the primary rationales for limiting drugs to prescription-only sale.[36]

The FDA may decide to authorize OTC marketing for drugs that do not require the supervision of a physician, have a history of safe use, and present no abuse potential. This may happen in a couple of different ways. First, a company may sell an OTC drug if it abides by the terms of the applicable "monograph," which specifies for particular categories of products the active ingredients and dosages that the FDA has determined to be safe and effective, along with the precise labeling necessary to facilitate appropriate consumer use.[37] The agency's OTC drug review for internal analgesics began with a call for data in 1972.[38] Five years later, the review panel, which had considered forty-nine active ingredients, issued its recommendations.[39] More than one decade later, the FDA published a tentative final monograph (TFM) for this OTC drug category.[40] In brief, this proposed rule includes aspirin and acetaminophen as permitted active ingredients and allows labeling "for the temporary relief of minor aches and pains" with directions against taking the product for more than 10 days along with an assortment of warnings.[41] After more than 30 years, the OTC monograph for internal analgesics remains at least 1 year from finalization.[42]

The second route to OTC marketing requires that a company secure supplemental NDA for a reformulation (including revised labeling) of a product previously approved for prescription use.[43] Among its most prominent Rx to OTC switches, the FDA authorized nonprescription sale of a lower dose product containing ibuprofen (e.g., Motrin®).[44] It later switched a number of other NSAIDs, including ketoprofen and naproxen, from prescription to OTC status.[45] Of course, it did not take long for consumers to realize that they could self-medicate with a prescription strength simply by exceeding the dose recommended in the OTC labeling.[46]

Nonprescription marketing does not mean that a drug product entails no serious risks,[47] as again revealed by the

FDA's experience with analgesics. For instance, in the early 1980s, the agency became aware of a link between Reye syndrome and the use of aspirin by children suffering from viral infections.[48] The labels of OTC drug products containing aspirin now must include the following statement: "WARNING: Children and teenagers should not use this medicine for chicken pox or flu symptoms before a doctor is consulted about Reye syndrome, a rare but serious illness reported to be associated with aspirin."[49] Notably, the FDA rejected suggestions urging "more drastic measures such as banning use of aspirin in products for individuals under 21 years of age or limiting such products to prescription use."[50] More recently, after it received reports of an association between acetaminophen and liver toxicity, the agency imposed special warning requirements.[51]

DEA Restrictions on Analgesic Products

Although NSAIDs dominate both the prescription and OTC markets in terms of volume,[52] most of the truly significant pain management technologies used by physicians qualify as "controlled substances," primarily opioid analgesics.[53] (Less frequently, health care professionals may try behavioral therapy, surgical interventions such as nerve blocks, or medical devices such as transcutaneous electrical nerve stimulators.[54]) Unlike peripherally acting drugs, opioids relieve pain by acting directly on the central nervous system, binding with the receptors that are involved in the transmission of pain signals to the brain. These drugs must undergo the same FDA premarket review process as any other pharmaceutical product, but special authority over controlled substances resides with a separate agency, the Drug Enforcement Administration of the U.S. Department of Justice.[55]

Classification of controlled substances

In 1970, Congress enacted the Controlled Substances Act (CSA), which establishes different "schedules" of narcotics and other substances prone to abuse or diversion. The most restrictive classification, Schedule I, is defined as follows:

> (A) The drug or other substance has a high potential for abuse.
> (B) The drug or other substance has no currently accepted medical use in treatment in the United States.
> (C) There is a lack of accepted safety for use of the drug or other substance under medical supervision.[56]

The statute then provides the following definition for Schedule II:

> (A) The drug or other substance has a high potential for abuse.
> (B) The drug or other substance has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions.
> (C) Abuse of the drug or other substance may lead to severe psychological or physical dependence.[57]

Schedules III, IV, and V, which all have "a currently accepted medical use in treatment in the United States," contain drugs with progressively lower potentials for abuse and severity of dependence.[58] Most states have adopted parallel legislation modeled on the federal statute.[59]

By way of illustration,[60] Schedule I includes substances such as heroin (diacetylmorphine) and marijuana (cannabis). Schedule II includes, for instance, drugs containing synthetic forms of morphine sold as Dilaudid® (hydromorphone hydrochloride) and Demerol® (meperidine hydrochloride). Schedule III includes products such as Tylenol® (acetaminophen) with codeine. Schedule IV includes products such as Darvon® (propoxyphene hydrochloride). Schedule V includes products such as Robitussin®, a cough syrup which contains a limited amount of codeine.

Congress understood that "[m]any of the drugs included within this subchapter have a useful and legitimate medical purpose and are necessary to maintain the health and general welfare of the American people."[61] This explains the central role, for purposes of distinguishing Schedule I from all other controlled substances, of the criterion that asks whether the drug has "a currently accepted medical use in treatment in the United States."[62] Congress did not provide further guidance on this score,[63] but it insisted that the Attorney General request and abide by recommendations from the Secretary of Health and Human Services (HHS) when revising the schedule.[64] In amending the CSA in 1978 to implement the United Nations Convention on Psychotropic Substances, Congress announced its intent that the legislation not "interfere with ethical medical practice in this country as determined by the Secretary of [HHS] on the basis of a *consensus* of the views of the American medical and scientific community,"[65] which suggests a somewhat more restrictive standard than "a currently accepted medical use."

Under the statute, the DEA supervises the manufacturing and distribution of legal narcotics.[66] For Schedule II drugs, manufacturers must register their operations, and the DEA assigns aggregate and individual production quotas.[67] Schedule II drugs must be produced in a secure facility, transported with care, stored in a vault, tracked using a precise inventory system, supplied in response to an order form completed by a registered practitioner, and dispensed only upon a written prescription and without refills.[68] Progressively weaker restrictions apply to Schedule III, IV, and V drugs. Physicians wishing to prescribe controlled substances first must register with the DEA, which enjoys sweeping authority to suspend or revoke certificates of registration.[69] The agency has, for

instance, threatened to use this authority to discipline physicians who have done nothing more than recommend that their patients consider taking a Schedule I substance as permitted under limited circumstances in a growing number of states.[70]

Legislative scheduling decisions

Congress typically makes the initial decision about how to schedule a controlled substance. In *United States v. Oakland Cannabis Buyers' Co-operative*,[71] the U.S. Supreme Court showed tremendous deference to the legislature's judgment about the appropriate classification of marijuana. The dispute arose after California voters passed Proposition 215 (the Compassionate Use Act of 1996), which created a limited safe harbor from prosecution under the state's controlled substances act for the medical use of marijuana.[72] The state law could not, of course, protect critically ill patients or their health care providers from the risk of federal prosecution for the medical use of marijuana. As part of its multipronged response to the California initiative, the Department of Justice sought to enjoin buyers' clubs from dispensing the drug to patients with severe pain and other debilitating symptoms. The U.S. Supreme Court rejected these groups' argument that a medical necessity defense might be implied under federal law. It held that persons manufacturing or distributing Schedule I controlled substances for medical uses could not avoid federal sanctions,[73] though three members of the Court wrote separately to emphasize that it had not decided whether a seriously ill patient could raise a medical necessity defense if prosecuted for using marijuana.[74]

The Supreme Court's decision turned entirely on the notion that, in placing marijuana within Schedule I, Congress necessarily had concluded that the drug lacked any currently accepted medical use: "It is clear from the text of the Act that Congress has made a determination that marijuana has no medical benefits worthy of an exception."[75] The Court rejected the argument that, although placed within Schedule I because its medical use had not yet achieved "general acceptance," a controlled substance may offer therapeutic benefits for some narrow class of patients. It also rejected the suggestion that Congress may have placed a controlled substance into Schedule I without strictly abiding by the criteria (such as the lack of any currently accepted medical use) that it had established to govern scheduling decisions made by the DEA.[76]

In fact, when it enacted the CSA, Congress had expressed a good deal of ambivalence about whether marijuana belonged in Schedule I.[77] After all, the *United States Pharmacopeia* (*U.S.P.*), which Congress has cross-referenced in other statutes as a source for information about therapeutic products,[78] had listed marijuana as a drug for almost a century (until 1941), and prominent physicians had endorsed its use early in the twentieth century for treating maladies such as migraine headaches.[79] Although neither one of these facts would establish that the drug offers genuine therapeutic benefits, subsequent research has suggested that marijuana may have analgesic and other clinically useful properties.[80] Within the last few years, both the National Institutes of Health and the Institute of Medicine have recommended further scientific work on this question.[81]

Although more than half a dozen states,[82] along with Canadian health officials,[83] have concluded that marijuana may have legitimate medical uses, Congress has decided to abide by its earlier, contrary conclusion: A resolution passed in 1998 "oppose[d] efforts to circumvent this [federal scheduling] process by legalizing marijuana, and other Schedule I drugs, for medicinal use without valid scientific evidence and the approval of the Food and Drug Administration."[84] This leaves an opening, of course, for revisiting the original scheduling judgment administratively if new research emerges to persuade regulatory officials that marijuana has medical utility, an issue taken up more fully below.

A similar controversy arose in the early 1980s in connection with the ultimately unsuccessful efforts by some in Congress to reschedule heroin. Unlike marijuana, which may have multiple therapeutic applications and an arguably exaggerated abuse potential, no one seriously doubts that heroin causes addiction, but, in common with the Schedule II drugs cocaine and morphine, it also offers a powerful analgesic effect. In fact, some have argued that it has unique properties as a pain reliever for terminally ill patients or, at the very least, offers an alternative for those who do not respond well to approved opioids.[85] For this reason, the United Kingdom continues to recognize the medical usefulness of heroin;[86] however, the CSA requires that a controlled substance have a currently accepted use *in the United States* in order to avoid classification in Schedule I.[87] In the end, fears of diversion and confidence in the effectiveness of already available opioid analgesics — coupled with the understandable political imperative against appearing to be soft on drugs — scuttled the effort to reschedule heroin.[88]

In another instance, Congress decided to reclassify a drug as Schedule I even though it clearly enjoyed a currently accepted medical use. The FDA previously had approved methaqualone for treating insomnia, which concededly gave the drug a currently accepted use in treatment, but Congress concluded that methaqualone offered no advantages over other products that posed less of a risk of abuse.[89] For that reason, Congress directed the DEA to reschedule the drug and the FDA to withdraw its NDA.[90] Although this did not alter the statutory criteria generally applicable to scheduling decisions, the legislative rescheduling of methaqualone arguably set a troublesome precedent.[91] In effect, Congress adopted a "one size fits all" approach, which fails to account for the possibility that this drug might provide some unique benefit to a small group of patients who are refractory to the drug of choice, whether because of their physiologic or genetic deviation from the norm, progression of disease, heightened

susceptibility to side-effects, co-morbid factors, or concomitant use of other medications. If aggregate risk-benefit balancing of this sort becomes the standard for future scheduling decisions, then the needs of individual patients will compete against the consequences of the irresponsible behavior of abusers, and the DEA may opt to sacrifice products that offer insufficiently dramatic advantages over existing alternative treatments.

Administrative scheduling decisions

In the case of newly synthesized chemicals, or in response to new information about previously scheduled controlled substances, the DEA may have to make its own scheduling decisions. As mentioned previously, Congress mandated that the agency first consult with HHS,[92] which has subdelegated that task to the FDA, and then abide by any recommendations that the DEA receives from the Department.[93] In this way, Congress hoped to "strike[] a balance between the extent to which control decisions should be based upon law enforcement criteria, and the extent to which such decisions should be based on medical and scientific determinations."[94] Given the long-running "war on drugs" in this country, it is difficult to maintain this sort of balance.[95]

Such cooperative arrangements between agencies or "split enforcement" models have posed challenges in other contexts.[96] In some instances, Congress has decided against consolidating authority in a single administrative agency to counteract the tendency toward tunnel vision in regulatory decisions, or it has established a separate watchdog group for an agency,[97] as it did when assigning the responsibility for accident investigations to the National Transportation Safety Board (NTSB), which often criticizes the Federal Aviation Administration (FAA) for taking inadequate steps to improve safety.[98] In other instances, the division of authority over a field between multiple agencies does not reflect any purposeful design but instead an accident of history that subsequently leads to calls for consolidation.[99] Apart from questions of efficiency, these organizational choices can have significant impacts on substance, especially if two agencies have different sorts of expertise and missions, and respond to different constituencies.[100] Without meaning to exaggerate the cultural explanations for their contrasting approaches to pain management technologies, the FDA probably would have implemented the Controlled Substances Act differently than the DEA has done.

Immediately after passage of the Act, the National Organization for the Reform of Marijuana Laws (NORML), together with a couple of allied organizations, attempted to persuade the DEA and its predecessor agency to reschedule marijuana. Starting in 1972, the agency repeatedly denied these rescheduling petitions, though on four separate occasions the reviewing court remanded the dispute to the DEA for further consideration.[101] In contrast, constitutional challenges to the DEA's refusal to down-schedule marijuana have not fared as well in the courts.[102]

Perhaps the refusal to down-schedule marijuana arises from a concern that, unlike chemicals synthesized by pharmaceutical companies, the FDA could not effectively exercise its regulatory authority to demand proof of safety and efficacy over a raw product with variable composition that individuals can grow in their homes.[103] After the FDA approved an NDA for Marinol® (dronabinol), an antiemetic drug containing synthetic tetrahydrocannabinol (THC), the principal psychoactive component in marijuana, the DEA placed this controlled substance into Schedule II.[104] In 1999, the DEA further down-scheduled that drug as the FDA began to approve additional indications for its use.[105]

In 1992, 20 years after NORML first petitioned the agency, the DEA Administrator opined that "no responsible physician could conclude that marijuana is safe and effective for medical use,"[106] echoing his predecessor's earlier conclusion that it was "not recognized as medicine in generally accepted pharmacopeia, medical references, journals or textbooks."[107] This time around the federal appellate court upheld the agency's decision.[108] Late in 1997, after receiving yet another petition for the rescheduling of marijuana, the DEA once again referred the matter to HHS for a recommendation.[109] In 2001, the DEA appeared to soften its stance somewhat when it authorized use by researchers at the University of California to conduct clinical trials investigating marijuana's analgesic properties in multiple sclerosis and AIDS patients with peripheral neuropathy.[110]

The protracted effort to reschedule marijuana forced the DEA to elaborate on the meaning of the critical statutory phrase "currently accepted medical use."[111] The agency decided to demand that there be adequate safety information coupled with adequate and well-controlled studies establishing efficacy, which are widely available and accepted by qualified experts.[112] These criteria closely track the FDA's test for whether to exempt a product from new drug approval requirements. Indeed, after noting Congress's failure to define "currently accepted medical use," the DEA looked to the FDA's enabling statute for guidance.[113] Under that statute, a manufacturer need not secure an NDA for a drug that is "generally recognized as safe and effective" (GRASE), which the FDA has defined as requiring essentially the same proof of safety and efficacy that it demands for new drugs.[114] In effect, a controlled substance could only avoid inclusion in Schedule I if the FDA already had approved it or exempted it from new drug approval requirements, a standard that seems overly stringent and inconsistent with the statutory design.[115] Congress could have explicitly linked scheduling decisions to a drug's FDA regulatory status, but it did not do so, choosing instead the arguably more flexible standard of "currently accepted medical use."

This distribution of regulatory authority, between a traditional law enforcement agency and one that focuses on

patient health, can generate incongruities. In some instances, the DEA's desire to facilitate prosecution of drug abusers by placing a substance into Schedule I or II conflicts with the FDA's effort to promote the development of a drug potentially valuable in the treatment of a legitimate class of users.[116] In other instances, at least where it has not already approved a drug proposed for inclusion in Schedule I, the FDA has done little more than "rubber stamp" DEA scheduling recommendations.[117] Once placed in Schedule I, of course, it becomes exceedingly difficult to conduct the sort of research necessary to secure FDA approval and subsequent down-scheduling by the DEA.

Off-label prescribing

The DEA has overlaid another "currently accepted medical use" requirement in regulating prescriptions for narcotics. Physicians may prescribe controlled substances only for "a legitimate medical purpose."[118] In turn, pharmacists may dispense controlled substances only pursuant to a valid prescription, which might require a comparison between the indications appearing in the FDA-approved labeling and the patient's condition.[119]

In contrast, the FDA has long recognized the legitimacy of "off-label" drug prescribing, an outgrowth of Congress's admonition against federal interference with the practice of medicine.[120] As the agency has explained, "[o]nce a drug product has been approved for marketing, a physician may, in treating patients, prescribe the drug for uses not included in the drug's approved labeling."[121] Apart from deferring to the congressional decision against undue interference with the practice of medicine, this policy acknowledges the inevitability of incomplete information, the lag time before widely accepted new uses appear in revised labeling (if they ever do), and patient variability. Thus, physicians routinely, and often appropriately, deviate from the directions contained in approved prescription drug labeling.[122]

In the case of controlled substances, however, physicians may not have the freedom to engage in such off-label prescribing.[123] In contrast to the FDA, which focuses its attention on the activities of commercial entities, the DEA enjoys the power to supervise the activity of individual physicians by virtue of its registration requirements. The agency also has shown less deference to medical practitioners and the regulatory prerogative of the states, instead seeming to regard them with some suspicion. For example, when it down-scheduled THC, the DEA formally announced a policy threatening to revoke (as inconsistent with the public interest) the registration of anyone "who engages in the distribution or dispensing of dronabinol for medical indications outside the [FDA] approved [antiemetic] use associated with cancer treatment."[124]

For a variety of reasons, patients respond variably to opioids,[125] which explains the need for a range of alternatives and the interest in using powerful analgesics in different combinations. For instance, a certain genetic polymorphism found in more than 5 percent of patients makes them poor metabolizers of codeine.[126] In addition, patients may develop tolerance from chronic treatment. Would a physician or pharmacist face DEA sanctions for prescribing or dispensing a Schedule II drug approved only for nonanalgesic indications to a patient with severe pain refractory to the other available drugs? In recent testimony before Congress, the DEA Administrator seemed to imply otherwise,[127] but the agency's position remains unclear.

Contemporaneously with the Administrator's congressional appearance, and in an effort to undercut Oregon's Death with Dignity Act, the Attorney General threatened to sanction physicians who assist in the suicide of terminally ill patients using Schedule II drugs approved by the FDA for other purposes (primarily sedatives such as secobarbital).[128] In effect, the DEA decided that, notwithstanding state law to the contrary, physician-assisted suicide does not qualify as legitimately within the scope of medical practice.[129] A federal court subsequently invalidated the Attorney General's order, holding that Congress had never intended to grant the DEA such sweeping power to define the contours of legitimate medical practice.[130] If affirmed on appeal, this decision may have broader consequences for the DEA's authority to limit off-label prescribing and dispensing of other controlled substances for analgesic uses.

Formulation issues and distribution controls

Dosage forms

For the most part, scheduling decisions relate to the intrinsic characteristics of active ingredients, paying little attention to product formulation and dosage,[131] though the DEA's differential treatment of smoked marijuana and THC encapsulated for ingestion may represent an exception. In contrast, the FDA routinely addresses precisely these sorts of issues when it reviews an NDA application,[132] and the choices that it makes may have important repercussions for the threat of abuse and diversion.

Fentanyl citrate is a Schedule II controlled substance. During the last decade, the FDA approved products containing this opioid analgesic in unusual dosage forms. First, it authorized the marketing of a transdermal fentanyl patch (Duragesic®).[133] Within a couple of years, the misuse of these patches — for instance, a few individuals died after sucking on them — led the agency to demand stronger warnings to physicians and patients.[134] More controversially, in 1994, the FDA approved a transmucosal form of fentanyl — a lollipop intended for use by children (Oralet®) — notwithstanding objections that it had received from the DEA and others that this would promote abuse.[135] In 1997, another manufacturer received approval to market a lollipop form of fentanyl (Actiq®), though this time intended only for use by cancer

patients experiencing breakthrough pain and with special packaging designed to minimize the risk of accidental poisoning by children.[136]

Recent years have seen widespread misuse of other opioid analgesics, especially OxyContin® (oxycodone hydrochloride).[137] Introduced in 1996, shortly after securing FDA approval, OxyContin quickly became the most widely prescribed narcotic painkiller, recording more than $1 billion in sales last year. The drug's active ingredient is a synthetic form of morphine regulated as a Schedule II controlled substance. Older painkillers such as Percocet® and Percodan® also contain oxycodone, but OxyContin uses a time-released formulation designed to offer sustained relief over a 12-hour period to patients with chronic moderate-to-severe pain. In contrast, the older drug products in this class (including the related hydrocodone drugs such as Vicodin® and Lortab®) may offer uneven relief over just a 3–4 hour period.

It is difficult trying to quantify the benefits of this drug. Anecdotal reports from physicians testify to the effectiveness of OxyContin in particular patients, but these give no sense for the drug's aggregate utility. One could use the number of prescriptions written each year — now in excess of 6 million — as a rough proxy. Even if some number of physicians prescribed the drug to patients who did not actually suffer from severe pain or to those for whom the older opioids had offered satisfactory relief, the high volume of prescribing suggests that OxyContin has helped to fill a significant unmet need and that many "thousands" of patients have benefited from its availability.[138] If nothing else, the slow-release feature made OxyContin more convenient than older opioids, which patients with severe pain would have to take every 4 hours throughout the day and night.

The time-released formulation also seemed to make OxyContin less prone to abuse because it would not provide a quick euphoric effect upon initial ingestion. As a result, Purdue Pharma and Abbott Labs promoted their drug to a broader group of physicians and as presenting a lower risk of abuse and diversion.[139] The companies apparently failed to appreciate the creativity of drug abusers. To defeat the slow-release feature, these individuals chewed, crushed, dissolved, or scraped the coating off of the tablets, leaving stronger dosages of oxycodone than found in individual Percocet or Percodan tablets. They would then ingest, snort, or inject the substance. Reports indicate that hundreds of people have died after overdosing in this fashion,[140] usually as a result of acute pulmonary edema.

Diversion occurs in several ways. Individuals might feign pain and shop for doctors willing to prescribe the drug, or they might engage in prescription fraud and theft. These individuals then might use the drugs themselves or sell their supplies to others. A few desperate addicts have committed armed robberies at pharmacies, demanding OxyContin rather than cash.[141] Most of the deaths and other injuries linked to the drug have occurred in persons other than legitimate patients.

Although deaths resulting from OxyContin have received significant publicity, they should be put in context: The diversion of other prescription controlled substances over the years has resulted in numerous deaths among drug abusers, and the toll pales in comparison to the injuries associated with the lawful use of nonnarcotic drugs. NSAIDs may represent a far more serious public health menace, contributing to thousands of patient deaths each year.[142] The volume of use is also higher, but these comparative statistics raise an interesting policy question: Should injuries to third parties who misuse prescription drugs attract greater concern from public officials than injuries suffered by legitimate patients?

Purdue recently announced plans to investigate the possibility of including another ingredient (naltrexone) that might counteract efforts to defeat the slow-release mechanism, but it will have to conduct trials to determine the safety and efficacy of this combination and then await FDA approval of a supplemental NDA, which could take several years.[143] What if naltrexone reduces the effectiveness of OxyContin, as happened during clinical trials using a similar ingredient (naloxone),[144] or else causes adverse reactions in some subset of users? From the perspective of the patient with cancer or other type of intractable pain, such a new form of the drug definitely would not represent an improvement.

Moreover, what if naltrexone does not really help prevent misuse — should OxyContin never have been marketed because it poses greater risks to nonusers than some of the older opioids? Is the extended-release feature not a substantial enough utility compared to other narcotic pain relievers to justify continued marketing in light of emerging patterns of diversion (much in the same way that Congress evaluated relative risks and benefits when it decided to reschedule methaqualone)? And, finally, who should make these sorts of choices? Tentative answers to such questions appear below, after first considering some of the other possible regulatory responses.

Marketing and distribution

Just as happens with formulation issues, the abuse potential of a drug may extend beyond the intrinsic characteristics of the active ingredient to include how the manufacturer promotes the drug product to health care professionals. Some critics have alleged that Purdue Pharma overpromoted OxyContin for the treatment of temporary or less serious pain, arguing that this led to excessive prescribing and created a larger supply for potential diversion.[145] Even though the DEA does not regulate the marketing of controlled substances (leaving that task to the FDA), it has castigated the manufacturer for its aggressive promotion of OxyContin to physicians.[146]

Critics also object that Purdue and Abbott made OxyContin generally available for prescribing by any physi-

cian and dispensing by any pharmacy. The companies might have decided to supply the drug only to hospital pharmacies for dispensing, and only in response to a prescription by a pain management (or similar) specialist, but such a restricted distribution network would have been unprecedented and perhaps even unlawful.[147] The FDA generally does not have the authority to restrict the distribution of drugs that it approves.[148] Although the DEA clearly enjoys the power to limit the channels of distribution for controlled substances by virtue of its scheduling decisions, it does not usually impose more precise restrictions tailored to a particular drug.[149] Either agency could attempt to persuade a manufacturer to accept nominally voluntary limitations that they could not mandate directly,[150] but that did not happen at the time of OxyContin's approval.

In whatever manner achieved, distribution restrictions would have important practical consequences for patients. Although more stringent limitations may reduce the threat of diversion and abuse, they also may complicate access for legitimate users of these drugs. For instance, with just over 1,000 pain management specialists practicing in the United States,[151] patients would have difficulty getting prescriptions for needed drugs if only such specialists were permitted to prescribe them. Similarly, patients would find it inconvenient if they regularly had to fill their prescriptions at a hospital pharmacy. Even without distribution restrictions, of course, physicians hesitate before prescribing controlled substances,[152] and local pharmacists may fail to stock them.[153] One should not lose sight of the fact that the FDA's decision to restrict access to some analgesics on prescription-only creates an important barrier,[154] both because physicians have ethical and legal obligations designed to limit inappropriate prescribing and because of the practical (especially financial) hurdles involved in visiting a physician. Schedule II, by further restricting physician flexibility and by insisting on repeat office visits (through the no-refill rule), enhances these barriers to patient access.

In July 2001, the FDA mandated labeling revisions for OxyContin to provide stronger warnings,[155] and, a few months later, it convened one of its advisory committees to provide additional recommendations.[156] States have gotten involved as well: A few have limited Medicaid reimbursement for OxyContin,[157] and members of the National Association of Attorneys General have discussed options for curbing abuse of the drug with representatives from the manufacturer.[158] At the same time, the DEA urged Purdue Pharma to consider restricting distribution to pain management specialists on the theory that these physicians would know to use the drug only as a last resort, if other pharmaceutical options did not help a patient.[159] In testimony before Congress, the acting Administrator of the DEA even threatened to slash the company's annual production quota by approximately 95 percent.[160]

Ultimately, such responses to widespread misuse may undermine recent efforts to provide patients with better pain management. It makes little sense to protect irresponsible physicians and illegitimate users from their own bad judgment if it means sacrificing the welfare of those in genuine need.[161] Abuse and diversion remain unlawful, of course, and persons who violate the CSA may suffer serious legal and other consequences, but agency initiatives that attempt to restrict access by limiting supplies or channels of distribution would reflect an unfortunate pursuit of administrative expediency or a response to the failure of more precisely targeted law enforcement efforts.

It is particularly challenging, of course, to target abusers when large supplies of a drug legally move through channels of commerce. Unlike illicit substances that law enforcement officials can attempt to interdict at the source or while still moving through a distribution network, controlled substances approved for medical use do not become a law enforcement concern until diverted by drug abusers fairly late in the distribution process. Agencies will have a natural inclination to reduce the undoubted difficulty of their task by restricting supplies, but they must not lose sight of the other half of the equation.[162] To its credit, the DEA recently took the unprecedented step of issuing a public statement joined by numerous public health groups to emphasize the importance of not letting concerns about abuse interfere with the legitimate use of OxyContin.[163] Although an important gesture, it remains to be seen whether this conciliatory rhetoric translates into more enlightened regulatory responses by the agency when confronted with calls for swift action to crack down on the next wave of controlled substances abuse.

The experience with antibiotics may offer an instructive contrast. Physicians continue to overprescribe these often powerful prescription drugs with attendant risks to their patients' health.[164] Patients also may abuse antibiotics, whether by disregarding dosage and duration of use instructions or by passing them along to family members and friends.[165] Unlike the abuse and diversion of controlled substances, none of this unwise behavior violates federal law. The same problems may, of course, arise with any pharmaceutical product,[166] but antibiotic misuse carries a societal risk as well — widespread overuse has created drug-resistant strains of infectious agents.[167] As with analgesics, this explains the need to continue developing new and improved antimicrobial agents even though the old stand-bys usually work well enough for most patients with simple bacterial infections.[168] So far, public health agencies have responded by pleading with physicians to exercise restraint in prescribing,[169] but some commentators would go further and restrict access to the latest compounds.[170] Because individual physicians and patients do not directly bear the diffuse societal risks associated with the spread of resistance, and because they do not face any real legal consequences for misusing antibiotics, a paternalistic strategy of limiting access has much to recommend it.[171] Because law enforcement tools already exist to deal with the abuse and diversion of controlled substances, however, fed-

eral access restrictions that may interfere with legitimate use seem far less defensible.

Perhaps the central lesson from this brief discussion of antibiotics is that neither the FDA nor the DEA has approached pain management issues from the proper perspective. Traditionally, the FDA has adopted a clinical (or individualistic) mindset, leaving most of the difficult risk-benefit judgments in the hands of health care professionals and patients. Although such an attitude has much to commend it, the agency may have placed excessive faith in the good sense of physicians and the power of labeling to encourage proper use and to limit the occasions for inappropriate prescribing.[172] Conversely, the DEA's law enforcement mindset goes to the opposite extreme, giving perhaps undue weight to the negative externalities associated with access to narcotics and not trusting health care professionals. A public health perspective, which the Centers for Disease Control and Prevention (CDC) has expressed in connection with antibiotics as well as vaccine programs,[173] might help to mediate between these two potentially incompatible perspectives.

A public health approach to concerns about the overuse of narcotic analgesics might bring with it a variety of intermediate regulatory responses. For one thing, the government might limit access to those medical specialists who usually encounter persons suffering severe or chronic pain — including, for instance, oncologists and orthopedic surgeons along with pain specialists — in the hopes that such specialists would better resist the tendency to prescribe Schedule II analgesics for patients for whom milder agents would work equally well. As mentioned previously, however, this would risk creating serious access problems for legitimate patients, at least if the range of specialists was defined too narrowly.

The federal government also could try to limit promotional efforts. At present, the FDA does not permit manufacturers of Schedule II drugs to advertise directly to consumers, and it might restrict the distribution of free samples to physicians. An outright prohibition on advertising directed to physicians could, however, run afoul of the First Amendment.[174] Enhanced tracking of prescriptions offers still another — though controversial — option worth exploring, and the DEA has encouraged more states to set up prescription monitoring programs.[175] Perhaps enhanced agency efforts to educate health care professionals would offer the best mechanism for achieving the ideal balance between promoting appropriate use in patients and discouraging excessive or otherwise inappropriate prescribing.[176]

Conclusion

Federal agencies represent the first, but hardly the only, line of defense against the misuse of pain management technologies. Their licensing decisions should not reflect an excessive preoccupation with the potential for abuse unless the products genuinely have no value as therapeutic interventions. If an analgesic drug or medical device offers a relatively safe and effective option for the treatment of pain in some group of patients, then any concerns about misuse and diversion need to balance the therapeutic benefit for legitimate users against the risk that individuals who act unlawfully may injure themselves and others. It would be unfortunate if an inability to deal with the latter problem by other means (including educational efforts as well as state and local policing) led to regulatory decisions that denied effective relief to those in pain. Federal officials must resist the temptation to place law enforcement imperatives ahead of genuine medical need.

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17. See S. Hensley, "FDA Approves Pharmacia's Bextra Months Sooner Than Expected," *Wall Street Journal*, Nov. 19, 2001, at B5 (adding that the FDA has begun to approve newer versions).

18. See J.N. Cashman, "The Mechanisms of Action of NSAIDs in Analgesia," *Drugs*, 52, suppl. 5 (1996): 13–23.

19. See M.J. Langman et al., "Risks of Bleeding Peptic Ulcer Associated with Individual Non-Steroidal Anti-Inflammatory Drugs," *Lancet*, 343 (1994): 1075–78; M.M. Wolfe et al., "Gastrointestinal Toxicity of Non-Steroidal Anti-Inflammatory Drugs," *N. Engl. J. Med.*, 340 (1999): 1888–99.

20. See C. Bombardier et al., "Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis," *N. Engl. J. Med.*, 343 (2000): 1520–28; M.J. Langman et al., "Adverse Upper Gastrointestinal Effects of Rofecoxib Compared with NSAIDs," *JAMA*, 282 (1999): 1929–33; L.S. Simon et al., "Anti-Inflammatory and Upper Gastrointestinal Effects of Celecoxib in Rheumatoid Arthritis: A Randomized Controlled Trial," *JAMA*, 282 (1999): 1921–28. But see P. Jüni et al., Editorial, "Are Selective COX 2 Inhibitors Superior to Traditional Non Steroidal Anti-Inflammatory Drugs?," *British Medical Journal*, 324 (2002): 1287–88.

21. See D. Mukherjee et al., "Risk of Cardiovascular Events Associated with Selective COX-2 Inhibitors," *JAMA*, 286 (2001): 954–59, at 958; see also R.A. Bonnel et al., "Aseptic Meningitis Associated with Rofecoxib," *Annals of Internal Medicine*, 162 (2002): 713–15; L. Neergaard, "Painkillers May Delay Bone Healing," *Associated Press Newswire*, May 27, 2002 (reporting on research that suggests narcotic analgesics may avoid an NSAID side-effect in one class of patients).

22. See U.S. General Accounting Office, *FDA Drug Review:*

Postapproval Risks 1976–1985, PEMD-90-15 (1990): at 25, 101–05.

23. See U.S. General Accounting Office, *FDA Premarket Approval: Process of Approving Ansaid as a Drug*, HRD-92-85 (1992): at 3; B.L. Strom & P. Tugwell, "Pharmacoepidemiology: Current Status, Prospects, and Problems," *Annals of Internal Medicine*, 113 (1990): 179–81, at 180; see also *Deficiencies in FDA's Regulation of the New Drug "Oraflex"*, H.R. Rep. No. 98-511 (1983): at 3–4 (noting liver toxicity and other serious reactions); A.C. Rossi et al., "The Importance of Adverse Reaction Reporting by Physicians: Suprofen and the Flank Pain Syndrome," *JAMA*, 259 (1988): 1203–04.

24. See *FDA's Regulation of Zomax*, H.R. Rep. No. 98-584 (1983): at 7–8; see also *Nichols v. McNeilab, Inc.*, 850 F. Supp. 562, 564–65 (E.D. Mich. 1993) (holding that the manufacturer had a duty to inform the public directly of the withdrawal); D. Ross-Degnan et al., "Examining Product Risk in Context: Market Withdrawal of Zomepirac as a Case Study," *JAMA*, 270 (1993): 1937–42; cf. D.A. Kessler et al., "Approval of New Drugs in the United States," *JAMA*, 276 (1996): 1826–31, at 1831 ("[K]etorolac, a parenteral analgesic, has been retained on the market ... despite [serious] adverse effects ... [because they] were not deemed to outweigh ketorolac's benefits, which include an absence of the respiratory depression normally associated with narcotic analgesics, typically the alternative therapeutic choice.").

25. See *id.*

26. See J. Schwartz, "New Painkiller Taken Off Market After Deaths," *Washington Post*, June 23, 1998, at A2.

27. See R. Sharpe, "How a Drug Approved by the FDA Turned into a Lethal Failure," *Wall Street Journal*, Sept. 30, 1998, at A1.

28. See *id.*

29. See *id.*

30. The FDA alerted physicians that the drug was unsafe when used longer than the 10 days tested in the clinical trials. See *id.*; FDA, *Warning Label Changes for Pain Reliever Duract*, *Talk Paper*, No. T98-6 (Feb. 10, 1998), *available at* <http://www.fda.gov/bbs/topics/ANSWERS/ANS00849.html>.

31. See Letter from Wyeth-Ayerst Laboratories to Health Care Professionals (Feb. 1998), *available at* <http://www.fda.gov/medwatch/safety/1998/duract.htm>.

32. See B.A. Noah, "Adverse Drug Reactions: Harnessing Experiential Data to Promote Patient Welfare," *Catholic University Law Review*, 49 (2000): 449–504, at 488–89.

33. See FDA, "Wyeth-Ayerst Laboratories Announces the Withdrawal of Duract from the Market," *Talk Paper*, No. T98-36 (June 22, 1998), *available at* <http://www.fda.gov/bbs/topics/ANSWERS/ANS00879.html>.

34. See *United States v. Article of Drug Labeled "Decholin"*, 264 F. Supp. 473, 482 n.9 (E.D. Mich. 1967) (noting that the FDA would not limit aspirin to prescription use even though "at the root of a headache may lie anything from nervous tension to a malignant brain tumor").

35. See L. Noah, "Informed Consent and the Elusive Dichotomy Between Standard and Experimental Therapy," *American Journal of Law & Medicine*, 28 (2002): 361–408, at 395 & n.178.

36. See Food, Drug & Cosmetic Act, ch. 675, §§ 502, 503, 52 Stat. 1040, 1050 (1938) (codified at 21 U.S.C. §§ 352(d), 353(b)) (requiring prescriptions for all habit-forming drugs), *amended by* Durham-Humphrey Amendments, Pub. L. No. 215, ch. 578, § 1, 65 Stat. 648 (1951), *amended by* Drug Abuse Control Amendments of 1965, Pub. L. No. 89-74, § 4, 79 Stat. 226, *amended by* Controlled Substances Act, Pub. L. No. 91-513, title II(G), 84 Stat. 1242, 1281-82 (1970); see also P.B. Hutt, "A Legal Framework for Future Decisions on Transferring Drugs from Prescription to Nonprescription Status," *Food Drug Cosmetic Law Journal*, 37 (1982): 427–40, at 428, 435, 440; cf. 21 U.S.C. § 829(d) (2000) (allowing the DEA to recommend to the FDA prescription status for OTC drugs with an abuse potential).

37. See 21 C.F.R. pt. 330 (2002); see also *Cutler v. Hayes*, 818 F.2d 879, 883–85 (D.C. Cir. 1987) (describing the OTC drug review process); P.R. Jones, Note, "Protecting the Consumer from Getting Burned: The FDA, the Administrative Process, and the Tentative Final Monograph on Over-the-Counter Sunscreens," *American Journal of Law & Medicine*, 20 (1994): 317–35.

38. See 37 Fed. Reg. 14,633 (1972); see also 37 Fed. Reg. 26,456 (1972) (call for data on topical analgesics).

39. See 42 Fed. Reg. 35,346 (1977) (concluding, for instance, that a few ingredients used in then-marketed analgesics (e.g., phenacetin) were not generally recognized as safe and/or effective); see also 44 Fed. Reg. 69,768 (1979) (panel report for external analgesics).

40. See 53 Fed. Reg. 46,204 (1988); see also 48 Fed. Reg. 5,852 (1983) (TFM for external analgesics), *amended*, 51 Fed. Reg. 27,360 (1986).

41. The TFM includes a number of warnings applicable to aspirin. See 53 Fed. Reg. at 46,256 (to be codified at 21 C.F.R. § 343.50(c)). In addition, with the OTC drug review for internal analgesics still pending, the FDA promulgated a requirement that any nonprescription products containing aspirin include a special warning against use during pregnancy. See 55 Fed. Reg. 27,776, 27,784 (1990) (codified at 21 C.F.R. § 201.63(e)).

42. See 66 Fed. Reg. 61,555, 61,575 (2001) (semiannual unified regulatory agenda forecasting final action on this monograph by Dec. 2002). The most recent unified regulatory agenda does not provide any estimated date of finalization for this rule. See 67 Fed. Reg. 33,058 (2002).

43. See 21 C.F.R. § 330.11 (2002); 65 Fed. Reg. 24,704, 24,704–05 (2000); *Farquhar v. FDA*, 616 F. Supp. 190, 192 (D.D.C. 1985); see also S.P. Mahinka & E. Bierman, "Direct-to-OTC Marketing of Drugs: Possible Approaches," *Food & Drug Law Journal*, 50 (1995): 49–63; L.R. Rook, "Listening to Zantac: The Role of Non-Prescription Drugs in Health Care Reform and the Federal Tax System," *Tennessee Law Review*, 62 (1994): 107–39; P. Temin, "Realized Benefits from Switching Drugs," *Journal of Law & Economics*, 35 (1992): 351–69.

44. See I. Molotsky, "Agency Approves Painkiller for Over-the-Counter Sales," *New York Times*, May 19, 1984, at 1. The FDA recently proposed amending the internal analgesics TFM to include ibuprofen, which would eliminate the need to continue filing applications for supplemental or abbreviated new drug approval for future OTC drug products containing this active ingredient. See 67 Fed. Reg. 54,139 (2002).

45. See G. Mays, "Pain-Killer Wars Can Be a Pain for Ailing Consumers," *Chicago Tribune*, Nov. 24, 1995, at Bus. 1.

46. Cf. *Bober v. Glaxo Wellcome PLC*, 246 F.3d 934, 939–40, 942 (7th Cir. 2001).

47. See S.G. Boodman, "Painful Choices: Consumers Face a Baffling Wall of Choices — and a Surprising Number of Serious Risks — When They Seek Relief from Minor Pains and Illnesses at the Drug Store," *Washington Post*, Feb. 11, 2003, at Z1. Apart from the risks associated with the proper use of OTC products, they also may pose hazards of misuse. For example, responding to numerous instances of childhood poisoning from the accidental ingestion of aspirin and similar products, Congress enacted special child-proof packaging requirements. See Poison Prevention Packaging Act of 1970, Pub. L. No. 91-601, 84 Stat. 1670 (codified as amended at 15 U.S.C. §§ 1471–1476 (2000)); 16 C.F.R. pt. 1700 (2002). In addition, after seven people in the Chicago area suffered cyanide poisoning in 1982 from ingesting

tainted Extra-Strength Tylenol® capsules, the FDA swiftly imposed tamper-resistant packaging requirements for most OTC drugs. See 47 Fed. Reg. 50,442, 50,449–50 (1982) (codified as amended at 21 C.F.R. § 211.132); see also Federal Anti-Tampering Act, Pub. L. No. 98-127, 97 Stat. 831 (1983) (codified at 18 U.S.C. § 1365 (2000)). Although one occasionally hears complaints that such rules have made it difficult for elderly and arthritic consumers to open containers, these controls have reduced instances of dangerous misuse at relatively trivial additional cost to users.

48. See 50 Fed. Reg. 51,400, 51,401 (1985); see also *Public Citizen Health Research Group v. Comm'r, FDA*, 740 F.2d 21, 34–35 (D.C. Cir. 1984) (remanding for lower court to consider claim of unreasonable delay by the FDA in acting on a citizen petition urging it to require a warning of this risk); *American Home Prods. Corp. v. Johnson & Johnson*, 672 F. Supp. 135, 137–41 (S.D.N.Y. 1987) (offering a detailed account of the history behind the early Reye syndrome warning efforts).

49. 21 C.F.R. § 201.314(h)(1) (2002).

50. 53 Fed. Reg. 21,633, 21,635 (1988).

51. See 63 Fed. Reg. 56,789, 56,801–02 (1998) (codified at 21 C.F.R. § 201.322 (2002)) (warning against the use of internal analgesics in combination with heavy alcohol consumption); see also *Benedi v. McNeil-P.P.C., Inc.*, 66 F.3d 1378, 1387, 1389 (4th Cir. 1995) (sustaining a negligence claim and punitive damage award against the seller of Tylenol where it had delayed submitting adverse reaction reports — concerning liver toxicity resulting from interactions between acetaminophen and alcohol — to the FDA during the OTC monograph review process for internal analgesics); C. Adams, "Makers of Rival Pain Relievers Trade Jabs on Safety," *Wall Street Journal*, Sept. 18, 2002, at B1.

52. See S.H. Roth, Editorial, "Nonsteroidal Anti-inflammatory Drugs: Gastropathy, Deaths, and Medical Practice," *Annals of Internal Medicine*, 109 (1988): 353–54; C.M. Wilcox et al., "Striking Prevalence of Over-the-Counter Nonsteroidal Anti-Inflammatory Drug Use in Patients with Upper Gastrointestinal Hemorrhage," *Archives of Internal Medicine*, 154 (1994): 42–46, at 42; J. Foreman, "Painkillers Often Take Toll on Stomach," *Boston Globe*, July 8, 1996, at 25; J. Weber & Z. Schiller, "Painkillers Are About to O.D.," *Business Week*, Apr. 11, 1994, at 54. These two categories do not, however, exhaust the range of options. For example, the prescription drug tramadol (Ultram® and Ultracet®) qualifies as neither an NSAID nor an opioid analgesic. See J.E. Edwards et al., "Combination Analgesic Efficacy: Individual Patient Data Meta-Analysis of Single-Dose Oral Tramadol Plus Acetaminophen in Acute Postoperative Pain," *Journal of Pain & Symptom Management*, 23 (2002): 121–30.

53. See N.I. Cherny, "Opioid Analgesics: Comparative Features and Prescribing Guidelines," *Drugs*, 51 (1996): 713–37; A. Jacox et al., "New Clinical-Practice Guidelines for the Management of Pain in Patients with Cancer," *N. Engl. J. Med.*, 330 (1994): 651–55, at 653 ("Of the many methods available to manage pain in cancer, drug therapy is the cornerstone because it entails relatively little risk, is usually inexpensive, and as a rule works quickly."); M.H. Levy, "Pharmacologic Treatment of Cancer Pain," *N. Engl. J. Med.*, 335 (1997): 1124–32; H. McQuay, "Opioids in Pain Management," *Lancet*, 353 (1999): 2229–32; C. Ripamonti & E.D. Dickerson, "Strategies for the Treatment of Cancer Pain in the New Millennium," *Drugs*, 61 (2001): 955–77; P.C. Crowley, Comment, "No Pain, No Gain? The AHCPR's Attempt to Change Inefficient Health Care Practice of Withholding Medication from Patients in Pain," *Journal of Contemporary Health Law & Policy*, 10 (1994): 383–403, at 391–93. See generally C. Stein, ed., *Opioids in Pain Control: Basic and Clinical Aspects* (Cambridge, England: Cambridge Univ. Press, 1999).

54. See J. Laurance, "Are We Really Born to Suffer?," *Times of London*, Jan. 27, 1997, at 18; see also 21 C.F.R. § 882.5890 (2002) (FDA regulation classifying transcutaneous electrical nerve stimulation devices for pain relief); M.I. Johnson et al., "An In-Depth Study of Long-Term Users of Transcutaneous Electrical Nerve Stimulation," *Pain*, 44 (1991): 221–29; cf. R.A. Deyo et al., "A Controlled Clinical Trial of Transcutaneous Electrical Nerve Stimulation (TENS) and Exercise for Chronic Low Back Pain," *N. Engl. J. Med.*, 332 (1990): 1627–34 (finding the treatment ineffective); E.A. Ghoname et al., "Percutaneous Electrical Nerve Stimulation for Low Back Pain: A Randomized Crossover Study," *JAMA*, 281 (1999): 818–23 (evaluating a method supplying deeper stimulation).

55. See Controlled Substances Act, Pub. L. No. 91-513, title II, 84 Stat. 1242 (1970) (codified as amended at 21 U.S.C. §§ 801–904 (2000)).

56. 21 U.S.C. § 812(b)(1).

57. *Id.* § 812(b)(2).

58. See *id.* § 812(b)(3)–(5).

59. See Uniform Controlled Substances Act of 1994; see also R.L. Brown, "Uniform Controlled Substances Act of 1990," *Campbell Law Review*, 13 (1991): 365–74.

60. These examples come from the lists of substances appearing in each of the schedules. See 21 U.S.C. § 812; 21 C.F.R. pt. 1308 (2002). The brand-name versions of analgesic products come from the *Physicians' Desk Reference*, 56th ed. (Montvale, New Jersey: Medical Economics Co., 2002).

61. 21 U.S.C. § 801(1).

62. See *Alliance for Cannabis Therapeutics (ACT) v. DEA*, 930 F.2d 936, 938 (D.C. Cir. 1991); see also L. Scott, "The Pleasure Principle: A Critical Examination of Federal Scheduling of Controlled Substances," *Southwestern University Law Review*, 29 (2000): 447–500, at 455 ("The purpose of the legislation is to legalize the possession and use of certain drugs for medical purposes, and to criminalize their possession and use for any other purposes.").

63. Congress did set out a number of factors to consider, but these relate primarily to the potential for abuse rather than what qualifies as currently accepted medical use:

> (1) [A substance's] actual or relative potential for abuse.
> (2) Scientific evidence of its pharmacological effect, if known.
> (3) The state of current scientific knowledge regarding the drug or other substance.
> (4) Its history and current pattern of abuse.
> (5) The scope, duration, and significance of abuse.
> (6) What, if any, risk there is to the public health.
> (7) Its psychic or physiological dependence liability.
> (8) Whether the substance is an immediate precursor of a substance already controlled under this subchapter.

21 U.S.C. § 811(c); see also *National Organization for the Reform of Marijuana Laws (NORML) v. DEA*, 559 F.2d 735, 747–48 (D.C. Cir. 1977) (suggesting that the potential for abuse rather than medical use distinguishes the schedules).

64. See 21 U.S.C. § 811(b) (directing HHS to consider the listed factors); 116 Cong. Rec. 33,300 (1970) (statement by Rep. Springer) (emphasizing "that purely enforcement responsibilities are placed with the Department of Justice while medical and scientific judgments necessary to drug control are left where they properly should lie and that is with the Department of Health, Education, and Welfare"); *NORML*, 559 F.2d at 745–47.

65. Pub. L. No. 95-633, § 101, 92 Stat. 3768 (1978) (codified as amended at 21 U.S.C. § 801a(3)(C)) (emphasis added).

66. See 21 U.S.C. §§ 821–829.

67. See *id.* §§ 823(a), 826; 21 C.F.R. pt. 1303; see also *MD*

Pharm., Inc. v. DEA, 133 F.3d 8, 10–11, 16 (D.C. Cir. 1998) (rejecting methylphenidate manufacturer's challenge to the registration of a competitor); *Western Fher Lab. v. Levi*, 529 F.2d 325, 330–32 (1st Cir. 1976) (affirming challenged production quotas for phenmetrazine); L. Noah, "Sham Petitioning as a Threat to the Integrity of the Regulatory Process," *North Carolina Law Review*, 74 (1995): 1–73, at 9 n.24, 69 (discussing the DEA's effort to combat the delays that result when competitors routinely file objections to each other's manufacturer registration and production quota applications).

68. See 21 U.S.C. § 829(a); 21 C.F.R. §§ 1301.72(a), 1301.73, 1301.74(e), 1304.11(e)(3)(i), 1305.03, 1306.11(a), 1306.12; *United States v. Poulin*, 926 F. Supp. 246, 249–55 (D. Mass. 1996) (concluding that a pharmacy had violated numerous requirements applicable to Schedule II drugs); D.J. Pisano, "Controlled Substances and Pain Management: Regulatory Oversight, Formularies, and Cost Decisions," *Journal of Law, Medicine & Ethics*, 24 (1996): 310–16, at 311–12.

69. See 21 U.S.C. §§ 822–824; 21 C.F.R. § 1301.36; see also *Humphreys v. DEA*, 96 F.3d 658 (3d Cir. 1996) (reversing the revocation of a physician's certificate of registration); *Kirk v. Mullen*, 749 F.2d 297, 298 (6th Cir. 1984) (noting that the DEA processed more than half a million CSA registrations annually).

70. See 62 Fed. Reg. 6,164 (1997); see also *Conant v. McCaffrey*, 2000 WL 1281174 (N.D. Cal. 2000) (invalidating one aspect of this policy as inconsistent with the CSA when read to take the First Amendment into account), *aff'd*, 309 F.3d 629 (9th Cir. 2002); G.J. Annas, "Reefer Madness — The Federal Response to California's Medical-Marijuana Law," *N. Engl. J. Med.*, 337 (1997): 435–39.

71. *United States v. Oakland Cannabis Buyers' Co-operative*, 532 U.S. 483 (2001). For some of the relevant academic commentary that predated the Court's decision, see M.N. Cohen, "Breaking the Federal/State Impasse over Medical Marijuana: A Proposal," *Hastings Women's Law Journal*, 11 (2000): 59–74; J.P. Kassirer, Editorial, "Federal Foolishness and Marijuana," *N. Engl. J. Med.*, 336 (1997): 366–67; A.J. LeVay, Note, "Urgent Compassion: Prosecutorial Discretion and the Medical Necessity Defense," *Boston College Law Review*, 41 (2000): 699–753; E.R. Neusch, Comment, "Medical Marijuana's Fate in the Aftermath of the Supreme Court's New Commerce Clause Jurisprudence," *University of Colorado Law Review*, 72 (2001): 201–55.

72. See Cal. Health & Safety Code Ann. § 11362.5 (West Supp. 2002) (decriminalizing only the cultivation and possession for use based on a physician's recommendation); *People v. Mower*, 49 P.3d 1067 (Cal. 2002). See generally A.W. Bock, *Waiting to Inhale: The Politics of Medical Marijuana* (Santa Ana: Seven Locks Press, 2000).

73. See *Oakland Cannabis*, 532 U.S. at 491–94.

74. See *id.* at 500–01 & n.2 (Stevens, J., concurring in judgment) (calling the majority's suggestion to the contrary dicta).

75. *Id.* at 493.

76. See *id.* at 492–93.

77. See H.R. Rep. No. 91-1444 (1970), *reprinted in* 1970 U.S.C.C.A.N. 4566, 4577–79; *NORML v. Ingersoll*, 497 F.2d 654, 657 (D.C. Cir. 1974).

78. See 21 U.S.C. § 321(g)(1)(A) (2000); see also *State v. Wakeen*, 57 N.W.2d 364, 369 (Wis. 1953) (noting that the pharmacy practice statutes in most states cross-reference the *U.S.P.*). But cf. *United States v. Article of Drug . . . Ova II*, 414 F. Supp. 660, 665–66, 667–73 (D.N.J. 1975) (rejecting an FDA effort to assert its drug authority over a product simply by virtue of its inclusion in the *U.S.P.*), *aff'd mem.*, 535 F.2d 1248 (3d Cir. 1976).

79. See E. Russo, "Cannabis for Migraine Treatment: The Once and Future Prescription? An Historical and Scientific Review," *Pain*, 76 (1998): 3–8. See generally L. Grinspoon & J.B. Bakalar, *Marihuana: The Forbidden Medicine*, rev. ed. (New Haven: Yale Univ. Press, 1993); M.L. Mathre, ed., *Cannabis in Medical Practice: A Legal, Historical and Pharmacological Overview of the Therapeutic Use of Marijuana* (Jefferson, North Carolina: McFarland & Co., 1997).

80. See I.D. Meng et al., "An Analgesia Circuit Activated by Cannabinoids," *Nature*, 395 (1998): 381–83; E.M. Williamson & F.J. Evans, "Cannabinoids in Clinical Practice," *Drugs*, 60 (2000): 1303–14; R.L. Hotz, "Chemicals in Pot Cut Severe Pain, Study Says," *Los Angeles Times*, October 27, 1997, at A1; see also L. Grinspoon & J.B. Bakalar, "Marihuana as Medicine: A Plea for Reconsideration," *JAMA*, 273 (1995): 1875–76.

81. See J.E. Joy et al., eds., *Marijuana and Medicine: Assessing the Science Base* (Washington, D.C.: National Academy Press, 1999): at 145 (concluding that cannabinoid drugs may have a therapeutic potential for pain relief); *id.* at 179 ("Until a nonsmoked rapid-onset cannabinoid drug delivery system becomes available, we acknowledge that there is no clear alternative for people suffering from chronic conditions that might be relieved by smoking marijuana, such as pain….").

82. See *Oakland Cannabis*, 532 U.S. at 502 n.4 (Stevens, J., concurring in judgment) (noting, in addition to California's law, the passage of voter initiatives in Alaska, Colorado, Maine, Nevada, Oregon, and Washington, along with legislative action in Hawaii); M. Tiersky, Comment, "Medical Marijuana: Putting the Power Where It Belongs," *Northwestern University Law Review*, 93 (1999): 547–95, at 551, 578–84 (describing and defending these various state initiatives).

83. See E. Goodman, Editorial, "The Uses of Pot," *Washington Post*, Aug. 4, 2001, at A23.

84. Not Legalizing Marijuana for Medicinal Use, Pub. L. No. 105-277, Div. F, 112 Stat. 2681–760, 2681–761 (1998).

85. See A.S. Trebach, *The Heroin Solution* (New Haven: Yale Univ. Press, 1982): at 59–84; A. Mondzac, "In Defense of the Reintroduction of Heroin into American Medical Practice and H.R. 5290 — The Compassionate Pain Relief Act," *N. Engl. J. Med.*, 311 (1984): 532–35, at 533; E.L. Shapiro, "The Right to Privacy and Heroin Use for Painkilling Purposes by the Terminally Ill Cancer Patient," *Arizona Law Review*, 21 (1979): 41–59, at 43–48.

86. See T. Bennett, "The British Experience with Heroin Regulation," *Law & Contemporary Problems*, 51 (Winter 1988): 299–314.

87. In a related vein, the FDA at one time categorically refused to consider prior foreign use of an ingredient in food as providing evidence of the safety of a substance, but a court invalidated the policy because it found "no basis for a purely ethnocentric distinction of this kind, divorced from demographic considerations." *Fmali Herb, Inc. v. Heckler*, 715 F.2d 1385, 1390 (9th Cir. 1983); see also L. Noah & R.A. Merrill, "Starting from Scratch?: Reinventing the Food Additive Approval Process," *Boston University Law Review*, 78 (1998): 329–443, at 354–55; R.G. Pinco, "Implications of FDA's Proposal to Include Foreign Marketing Experience in the Over-the-Counter Drug Review Process," *Food & Drug Law Journal*, 53 (1998): 105–22.

88. See S.M. Stoll, Comment, "Why Not Heroin? The Controversy Surrounding the Legalization of Heroin for Therapeutic Purposes," *Journal of Contemporary Health Law & Policy*, 1 (1985): 173–94, at 190–93; see also *id.* at 179 ("Clearly, the United States maintains a model of drug control more suited to law enforcement than to medical concerns."); P.W. Fitzgerald, Comment, "Members of Congress as Medical Experts: Heroin and the Compassionate Pain Relief Act," *St. Louis University Public Law Review*, 6 (1987): 371–90.

89. See H.R. Rep. No. 98-534, at 5 (1984) (asking "whether the adverse health effects caused by diversion of a drug outweigh its therapeutic usefulness," and concluding that methaqualone "has no unique therapeutic advantages over other available drugs and has a significantly higher incidence of and potential for abuse"), *reprinted in* 1984 U.S.C.C.A.N. 540, 543–44.

90. See Pub. L. No. 98-329, 98 Stat. 280 (1984).

91. Congress may have set a similar precedent when it originally decided to classify cocaine as a Schedule II "narcotic" even though pharmacologically the substance does not qualify as a narcotic. See *United States v. Whitley*, 734 F.2d 1129, 1140–41 (6th Cir. 1984) (upholding the classification as rational in order to promote law enforcement purposes); *United States v. Alexander*, 673 F.2d 287 (9th Cir. 1982).

92. See 21 U.S.C. § 811(b) (2000).

93. See *id.*; *Touby v. United States*, 500 U.S. 160, 162, 167 (1991) (noting that the parties characterized this provision as giving a "'veto power' to the Secretary of HHS"); *American Pharm. Ass'n v. Weinberger*, 377 F. Supp. 824, 831 n.16 (D.D.C. 1974) (explaining that the DEA "must first call upon FDA for its recommendation. The recommendations of FDA, insofar as they concern 'scientific and medical matters' relating to the 'appropriate schedule, if any, under which such drug or substance should be listed' are binding on the Attorney General."), *aff'd*, 530 F.2d 1054 (D.C. Cir. 1976).

94. H.R. Rep. No. 91-1444 (1970), *reprinted in* 1970 U.S.C.C.A.N. 4566, 4589.

95. See D.F. Musto, *The American Disease: Origins of Narcotic Control*, 3d ed. (New York: Oxford Univ. Press, 1999); R.E. Barnett, Book Review, "Bad Trip: Drug Prohibition and the Weakness of Public Policy," *Yale Law Journal*, 103 (1994): 2593–630 (reviewing S.B. Duke & A.C. Gross, *America's Longest War: Rethinking Our Tragic Crusade Against Drugs* (New York: G.P. Putnam's Sons, 1993)); E.G. Luna, "Our Vietnam: The Prohibition Apocalypse," *DePaul Law Review*, 46 (1997): 483–568; E.A. Nadelmann, "Drug Prohibition in the United States: Costs, Consequences, and Alternatives," *Science*, 245 (1989): 939–47; M.D. Newcomb, "Substance Abuse and Control in the United States: Ethical and Legal Issues," *Social Science & Medicine*, 35 (1992): 471–79.

96. See L. Noah, "Divining Regulatory Intent: The Place for a 'Legislative History' of Agency Rules," *Hastings Law Journal*, 51 (2000): 255–323, at 301; S. Shapiro & T. McGarity, "Reorienting OSHA: Regulatory Alternatives and Legislative Reform," *Yale Journal on Regulation*, 6 (1989): 1–63, at 57–62.

97. See Inspector General Act, Pub. L. No. 95-452, 92 Stat. 1101 (1978) (codified as amended at 5 U.S.C. app. II (2000)); M.J. Gates & M.F. Knowles, "The Inspector General Act in the Federal Government: A New Approach to Accountability," *Alabama Law Review*, 36 (1985): 473–513; see also L. Noah, "Scientific 'Republicanism': Expert Peer Review and the Quest for Regulatory Deliberation," *Emory Law Journal*, 49 (2000): 1033–83.

98. See 49 U.S.C. § 1131 (2000); M. Wald, "Two Positions on Safety," *New York Times*, Aug. 30, 1998, at A16; "The FAA Should Inspect Itself," *Washington Post*, May 23, 1996, at A20; see also A.J. Wood et al., "Making Medicines Safer — The Need for an Independent Drug Safety Board," *N. Engl. J. Med.*, 339 (1998): 1851–54, at 1852–53 (advocating the creation of a similar counterweight to the FDA in order to improve postmarket surveillance of drugs approved by the agency).

99. See, e.g., R.A. Merrill & J.K. Francer, "Organizing Federal Food Safety Regulation," *Seton Hall Law Review*, 31 (2000): 61–173; M. Allen & J. Mintz, "Homeland Department May Take a Year to Take Shape," *Washington Post*, Nov. 21, 2002, at A8.

100. See J. Mashaw et al., *Administrative Law: The American Public Law System*, 4th ed. (St. Paul: West Group, 1998): at 21–28, 174–75; E. Meidinger, "Regulatory Culture: A Theoretical Outline," *Law & Policy*, 9 (1987): 355–86, at 360, 372–74.

101. See 37 Fed. Reg. 18,097 (1972), *remanded*, *NORML v. Ingersoll*, 497 F.2d 654, 660–61 (D.C. Cir. 1974), *petition denied*, 40 Fed. Reg. 44,164 (1975), *remanded*, *NORML v. DEA*, 559 F.2d 735, 757 (D.C. Cir. 1977), *petition denied*, 44 Fed. Reg. 36,123 (1979), *remanded*, *NORML v. DEA*, No. 79-1660 (D.C. Cir. Oct. 16, 1980), *hearing announced*, 51 Fed. Reg. 22,946 (1986), *petition denied*, 54 Fed. Reg. 53,767, 53,784 (1989) ("The administrative law judge's conclusion that a 'respectable minority' of physicians is all that is necessary to establish accepted medical use in treatment in the United States is preposterous."), *remanded*, *ACT v. DEA*, 930 F.2d 936, 940–41 (D.C. Cir. 1991).

102. See *United States v. Greene*, 892 F.2d 453, 455–56 (6th Cir. 1989); *Pearson v. McCaffrey*, 139 F. Supp. 2d 113, 120–23 (D.D.C. 2001); *NORML v. Bell*, 488 F. Supp. 123, 132–43 (D.D.C. 1980) (three-judge court); cf. *Washington v. Glucksberg*, 521 U.S. 702, 791 (1997) (Breyer, J., concurring in the judgment) (suggesting that the Court might hold it unconstitutional "were state law to prevent the provision of palliative care, including the administration of drugs as needed to avoid pain at the end of life"); R.A. Burt, "The Supreme Court Speaks: Not Assisted Suicide but a Constitutional Right to Palliative Care," *N. Engl. J. Med.*, 337 (1997): 1234–36. A lower federal court once found a fundamental right to receive acupuncture treatment. See *Andrews v. Ballard*, 498 F. Supp. 1038, 1047–57 (S.D. Tex. 1980) (invalidating a state's licensing restriction).

103. Cf. *United States v. McMahon*, 861 F.2d 8, 11 (1st Cir. 1988) (noting the "organic-synthetic distinction in Schedule I" between marijuana and THC). Of course, similar concerns did not dissuade the agency from its ill-fated effort to assert regulatory jurisdiction over cigarettes containing variable quantities of the drug nicotine from tobacco leaves. See *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120 (2000); L. Noah & B.A. Noah, "Nicotine Withdrawal: Assessing the FDA's Effort to Regulate Tobacco Products," *Alabama Law Review*, 48 (1996): 1–63.

104. See 51 Fed. Reg. 17,476, 17,478 (1986) (synthetic dronabinol in sesame oil encapsulated in soft gelatin capsules); see also 47 Fed. Reg. 10,080 (1982) (announcing the FDA's proposed rescheduling recommendation pending approval of the NDA); R.M. Cooper, "Therapeutic Use of Marihuana and Heroin: The Legal Framework," *Food Drug Cosmetic Law Journal*, 35 (1980): 68–82, at 76–79 (defending the FDA's earlier recommendation against down-scheduling).

105. See 64 Fed. Reg. 35,928, 35,930 (1999).

106. See 57 Fed. Reg. 10,499, 10,507–08 (1992) (adding that, "[b]y any modern scientific standard, marijuana is no medicine"); *id.* at 10,503 ("Beyond doubt, the claims that marijuana is medicine are false, dangerous and cruel."). Although one can understand the DEA Administrator's exasperated tone in once again denying the petition, the published explanation contains a surprising note of glibness and sarcasm.

107. 54 Fed. Reg. 53,767, 53,784 (1989). On the pitfalls of relying on the biomedical literature in this fashion, see L. Noah, "Sanctifying Scientific Peer Review: Publication as a Proxy for Regulatory Decisionmaking," *University of Pittsburgh Law Review*, 59 (1998): 677–717.

108. See *ACT v. DEA*, 15 F.3d 1131, 1135–37 (D.C. Cir. 1994).

109. See *United States v. Cannabis Cultivators Club*, 5 F. Supp. 2d 1086, 1105 (N.D. Cal. 1998). Four years later, HHS again recommended against down-scheduling marijuana. See *Gettman v. DEA*, 290 F.3d 430, 432 (D.C. Cir. 2002) (holding that the petitioners lacked standing to challenge the DEA's subsequent

rejection of their request).

110. See P.J. Hilts, "After Two-Decade Halt, Marijuana Research Is Set," *New York Times*, Dec. 15, 2001, at A16; see also M. Robichaux, "Would Marijuana Be OK by Prescription If You Didn't Get High?," *Wall Street Journal*, Feb. 28, 2001, at A1 ("Recent findings suggest that THC holds more potential as a painkiller than anyone ever guessed.").

111. See 21 U.S.C. § 812(b) (2000).

112. See 57 Fed. Reg. at 10,504–07 (also requiring that the drug's chemistry be known and reproducible); *id.* at 10,505 ("When a drug lacks NDA approval and is not accepted by a consensus of experts outside FDA, it cannot be found ... to have a currently accepted medical use."). The DEA had first described these factors a few years earlier, but in combination with a few others, see 53 Fed. Reg. 5156, 5157–58 (1988) (classifying methylenedioxymethamphetamine (MDMA), commonly known as Ecstasy, as a Schedule I controlled substance), 54 Fed. Reg. at 53,783–84, which the reviewing court rejected as unworkable, see *ACT v. DEA*, 930 F.2d at 940.

113. See 57 Fed. Reg. at 10,503–04.

114. See *United States v. 50 Boxes More or Less*, 909 F.2d 24, 26–28 (1st Cir. 1990) (sustaining an FDA enforcement action against an unapproved prescription drug for the treatment of vascular headaches); *United States v. Seven Cardboard Cases . . . "Esgic with Codeine Capsules"*, 716 F. Supp. 1221, 1224–25 (E.D. Mo. 1989).

115. See *Grinspoon v. DEA*, 828 F.2d 881, 886–91 (1st Cir. 1987) (rejecting the notion that the absence of FDA approval demonstrated the lack of a legitimate medical use); *NORML v. DEA*, 559 F.2d 735, 748–50 & n.65 (D.C. Cir. 1977); see also *Reckitt & Colman, Ltd. v. DEA*, 788 F.2d 22, 24 (D.C. Cir. 1986) (describing the DEA's decision to move buprenorphine, an opiate derivative, from Schedule II to Schedule V on the recommendation of HHS after the FDA approved the drug as an analgesic). After the remand in *Grinspoon*, the DEA adhered to its decision to place MDMA in Schedule I. See *United States v. Carlson*, 87 F.3d 440, 444–45 (11th Cir. 1996); cf. R. Weiss, "On Ecstasy, Consensus Is Elusive," *Washington Post*, Sept. 30, 2002, at A7 (reporting that the FDA now has approved research — pending authorization from the DEA — into MDMA's possible efficacy as a treatment for post-traumatic stress disorder).

116. See D.D. Rohde, "The Orphan Drug Act: An Engine of Innovation? At What Cost?," *Food & Drug Law Journal*, 55 (2000): 125–43, at 138–39 (discussing the disagreement between the agencies over gamma hydroxybutyrate (GHB), which appears to be an effective treatment for narcolepsy but also facilitates date rapes); see also Pub. L. No. 106-172, § 3(a)(1), 114 Stat. 7, 8 (2000); R. Rubin, "Company Wants 'Date Rape' Drug Approved for Sleep Disorder Treatment," *USA Today*, June 6, 2001, at 10D (describing compromise legislation that placed GHB into Schedule I for most purposes but Schedule III when used in FDA-approved studies); A. Zitner, "Date-Rape Drug OK'd to Treat Sleep Disorder," *Los Angeles Times*, July 18, 2002, at A12 (reporting that the FDA approved GHB subject to stringent restrictions on patient access).

117. See *Grinspoon*, 828 F.2d at 897. In connection with the DEA's decision to up-classify methamphetamine to Schedule II, the courts have rejected objections that HHS had done too cursory a medical and scientific review. See *United States v. Lafoon*, 978 F.2d 1183, 1184–85 (10th Cir. 1992).

118. 21 C.F.R. § 1306.04(a) (2002); see also *United States v. Moore*, 423 U.S. 122, 141–42 (1975) ("[P]rovisions throughout the Act reflect the intent of Congress to confine authorized medical practice within acceptable limits."); *id.* at 126–27, 139–45 (allowing felony conviction of physician who prescribed methadone in an unorthodox detoxification program that more closely resembled the activities of a "pusher"); *United States v. Betancourt*, 734 F.2d 750, 757 (11th Cir. 1984) ("[T]he jury needed medical testimony as to what the drug is, how it is properly used, how it can be abused and the medical profession's view of the drug."); *Noell v. Bensinger*, 586 F.2d 554, 557–58 (5th Cir. 1978) (upholding the revocation of a physician's certificate of registration notwithstanding the fact that the only expert who testified had stated that the prescription of amphetamines to counteract fatigue comported with accepted standards of medical practice); *United States v. Green*, 511 F.2d 1062, 1069–70 (7th Cir. 1975) (upholding the DEA's regulation even though the statute did not explicitly require that a controlled substance only be prescribed for a legitimate medical use); D.J. Behr, "Prescription Drug Control Under the Federal Controlled Substances Act: A Web of Administrative, Civil, and Criminal Law Controls," *Washington University Journal of Urban & Contemporary Law*, 45 (1994): 41–119, at 61–65, 109, 112–13; Annotation, "Federal Criminal Liability of Licensed Physician for Unlawfully Prescribing or Dispensing 'Controlled Substance' or Drug in Violation of the Controlled Substances Act," 33 A.L.R. Fed. 220 (1977 & Supp. 2002).

119. See D.B. Brushwood & J.J. Carlson, "The Pharmacist's Responsibility to Evaluate Suspicious Prescriptions," *Food Drug Cosmetic Law Journal*, 46 (1991): 467–85, at 481 (noting that the DEA's *Pharmacist Manual* lists as one indicia of an illegitimate prescription "whether the purported prescription order contains an indication other than one found in the package insert"); *id.* at 475 n.45 ("Pharmacists would have to question the appropriateness of virtually every prescription that is out of the ordinary, in a way that is inconsistent with the federal framework in which physicians are allowed wide latitude in prescribing."); see also *United States v. Leal*, 75 F.3d 219, 223 (6th Cir. 1996) (upholding conviction of pharmacist); *United States v. Hayes*, 595 F.2d 258, 261 n.6 (5th Cir. 1979) ("[A] pharmacist can know that prescriptions are issued for no legitimate medical purpose without his needing to know anything about medical science.").

120. See 21 U.S.C. § 396 (2000) (medical device regulation); 42 U.S.C. § 1395 (2000) ("Nothing in [Medicare] shall be construed to authorize any Federal officer or employee to exercise any supervision or control over the practice of medicine or the manner in which medical services are provided."); 37 Fed. Reg. 16,503, 16,504 (1972) ("[I]t is clear that Congress did not intend the [FDA] to regulate or interfere with the practice of medicine....").

121. 48 Fed. Reg. 26,720, 26,733 (1983); see also 21 C.F.R. § 312.2(d) (explaining that the FDA's investigational new drug requirements "do[] not apply to the use in the practice of medicine for an unlabeled indication of [an approved] new drug"); *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 350–51 & n.5 (2001); *FTC v. Simeon Mgmt. Corp.*, 391 F. Supp. 697, 706–07 (N.D. Cal. 1975), *aff'd*, 532 F.2d 708, 717 (9th Cir. 1976) ("FDA has specifically recognized the legality of using drugs for purposes other than those for which they have been found safe and effective."); J.D. Archer, Editorial, "The FDA Does Not Approve Uses of Drugs," *JAMA*, 252 (1984): 1054–55.

122. See L. Noah, "Constraints on the Off-Label Uses of Prescription Drugs," *Journal of Products & Toxics Liability*, 16 (1994): 139–65, at 139–44.

123. See J.R. Cooper et al., "Prescription Drug Diversion Control and Medical Practice," *JAMA*, 268 (1992): 1306–10, at 1308–09.

124. 51 Fed. Reg. 17,476, 17,477 (1986) (adding, by way of explanation, that the "DEA has encountered practitioners who attempt to justify illegal or improper distribution or dispensing

by claiming unique knowledge of a drug's effectiveness for a broad range of medical indications"). One decade later, the DEA announced a similar threat against any physicians in California who simply recommended the use of marijuana. See 62 Fed. Reg. 6,164 (1997).

125. See B.S. Galer et al., "Individual Variability in the Response to Different Opioids: Report of Five Cases," *Pain*, 49 (1992): 87–91; R.K. Portenoy, "Opioid Therapy for Chronic Nonmalignant Pain: Clinicians' Perspective," *Journal of Law, Medicine & Ethics*, 24 (1996): 296–309, at 298–99; see also C. Ripamonti et al., "An Update on the Clinical Use of Methadone for Cancer Pain," *Pain*, 70 (1997): 109–15.

126. See S.H. Sindrup & K. Brøsen, "The Pharmacogenetics of Codeine Hypoalgesia," *Pharmacogenetics*, 5 (1995): 335–46, at 343; see also S. Olivier, "Tailor-Made Drugs?," *Times of London*, Feb. 12, 2002 (describing the impact of hormonal differences on the effectiveness of analgesics). See generally L. Noah, "The Coming Pharmacogenomics Revolution: Tailoring Drugs to Fit Patients' Genetic Profiles," *Jurimetrics Journal*, 43 (2002): 1–28.

127. See *Departments of Commerce, Justice, and State, the Judiciary, and Related Agencies Appropriations for 2002: Part 10 — OxyContin: Hearings Before a Subcomm. of the House Comm. on Appropriations*, 107th Cong., at 19 (2001) (statement of Asa Hutchinson, Administrator, DEA) ("Federal laws and regulations do not attempt to define or set standards as to what constitutes 'legitimate medical purpose' or 'the usual course of professional practice,' the requisite elements of lawful prescriptions under the CSA and DEA regulations. Instead, DEA relies upon the medical community to make these determinations."); see also D.E. Joranson & A.M. Gilson, "Policy Issues and Imperatives in the Use of Opioids to Treat Pain in Substance Abusers," *Journal of Law, Medicine & Ethics*, 22 (1994): 215–23, at 216 (describing the dronabinol restriction as an aberration).

128. See 66 Fed. Reg. 56,607, 56,608 (2001) (adding, however, that "[p]ain management, rather than assisted suicide, has long been recognized as a legitimate medical purpose justifying physicians' dispensing of controlled substances"); see also R. Steinbrook, "Physician-Assisted Suicide in Oregon: An Uncertain Future," *N. Engl. J. Med.*, 346 (2002): 460–64; J. Cordaro, Note, "Who Defers to Whom? The Attorney General Targets Oregon's Death with Dignity Act," *Fordham Law Review*, 70 (2002): 2477–514; A. Trafford, "Don't Dismiss This as Physician Paranoia," *Washington Post*, Mar. 12, 2002, at Z1.

129. In contrast, when a group of death row inmates petitioned the FDA in the early 1980s to restrict the off-label use of Schedule II drugs for lethal injection, that agency declined to exercise its enforcement discretion in deference to the choices made by state penal officials. See *Heckler v. Chaney*, 470 U.S. 821 (1985) (rejecting a challenge to the agency's decision); see also L. Noah, Letter, "Attorney General's Intrusion into Clinical Practice," *N. Engl. J. Med.*, 346 (2002): 1918.

130. See *Oregon v. Ashcroft*, 192 F. Supp. 2d 1077 (D. Or. 2002), *appeal pending*, No. 02-35587 (9th Cir. 2003).

131. In the less stringent schedules, some of the listed substances refer to particular formulations and dosage strengths. See 21 U.S.C. § 812(c)(III)(d) & (V); see also *id.* § 811(g)(1) (calling for the descheduling of any nonnarcotic substance used in an FDA-approved OTC drug product); *United States v. Martinez*, 950 F.2d 222, 223–24 (5th Cir. 1991) (construing this provision); *United States v. Caperell*, 938 F.2d 975, 978–79 (9th Cir. 1991).

132. For instance, alternative modes of delivery for other pharmaceutical products may reflect attempts to reduce pain associated with their administration. See T. Chea, "MedImmune's Pain-Free Ambitions: If Approved by the FDA, FluMist Would Become First Vaccine Delivered as a Nasal Spray," *Washington Post*, Mar. 18, 2002, at E1.

133. See K.H. Mosser, "Transdermal Fentanyl in Cancer Pain," *American Family Physician*, 45 (1992): 2289–94; see also W. Jeal & P. Benfield, "Transdermal Fentanyl: A Review of Its Pharmacological Properties and Therapeutic Efficacy in Pain Control," *Drugs*, 53 (1997): 109–38; D.M. Neighbors et al., "Economic Evaluation of the Fentanyl Transdermal System for the Treatment of Chronic Moderate to Severe Pain," *Journal of Pain & Symptom Management*, 21 (2001): 129–43.

134. See "Deaths Are Followed by Pain Patch Restrictions," *Chicago Sun-Times*, Feb. 6, 1994, at 54 (reporting that the manufacturer strengthened warnings after several deaths were associated with misuse of the Duragesic patch); see also *Erony v. Alza Corp.*, 913 F. Supp. 195 (S.D.N.Y. 1995) (allowing an inadequate warning claim to proceed on behalf of a teenager who died after sucking on his father's used Duragesic patches).

135. See D. Brown & J. Schwartz, "The Good and Bad Sides of a Narcotic Lollipop," *Washington Post*, Jan. 31, 1994, at A3; P.J. Hilts, "U.S. Urged to Bar Narcotic Lollipop for Children," *New York Times*, Jan. 26, 1994, at A10 (describing the DEA's objections); see also J. Brody, "The Forgotten Child in Treating Pain Is the Child," *New York Times*, Oct. 25, 1995, at C11 (noting "drug companies' reluctance to develop pediatric analgesics," and explaining that doctors have resisted using the fentanyl lollipop with children).

136. See S.G. Boodman, "Narcotic Lollipop Gets Approval by FDA Panel," *Washington Post*, Sept. 23, 1997, at Z5; see also R. Payne et al., "Long-Term Safety of Oral Transmucosal Fentanyl Citrate for Breakthrough Cancer Pain," *Journal of Pain & Symptom Management*, 22 (2001): 575–83.

137. See Hutchinson statement, *supra* note 127, at 15–17; A. Kumar, "Prescription Drug Abuse Soars," *Los Angeles Times*, Jan. 17, 2003, at A30. In 2001, the National Institute of Drug Abuse (NIDA) issued a report documenting startling levels of prescription drug abuse. See K. Fackelmann, "Health Campaign Takes Aim at Prescription Drug Abuse," *USA Today*, Apr. 10, 2001, at D7; see also B. Vastag, "Mixed Message on Prescription Drug Abuse," *JAMA*, 285 (2001): 2183–84, at 2184 ("At the same time that NIDA is raising alarm bells about abuse potential, new studies point to chronic underprescribing of appropriate pain relief and a low risk of addiction to prescription drugs.").

138. See N. Aoki, "Abusing Pain Pills: Is Maker to Blame?," *Boston Globe*, July 4, 2001, at D1; Editorial, "Curbing the OxyContin Scourge," *Pittsburgh Post-Gazette*, May 30, 2001, at A11 ("OxyContin has provided long-lasting pain relief for hundreds of thousands of cancer patients and others suffering from chronic pain."); see also C. Adams, "Painkiller's Sales Far Exceeded Maker's Plans," *Wall Street Journal*, May 16, 2002, at D2.

139. See P. Tough, "The Alchemy of OxyContin," *New York Times Magazine*, July 29, 2001, at 32; cf. *Crocker v. Winthrop Lab.*, 514 S.W.2d 429 (Tex. 1974) (allowing a tort claim to proceed against the seller of the prescription analgesic Talwin® (pentazocine) for misrepresenting it as nonaddictive).

140. See B. Meier, "Overdoses of Painkiller Are Linked to 282 Deaths," *New York Times*, Oct. 28, 2001, at A20; see also D.E. Hoffmann & A.J. Tarzian, "Achieving the Right Balance in Oversight of Physician Opioid Prescribing for Pain: The Role of State Medical Boards," *Journal of Law, Medicine & Ethics*, 31 (2003): 21–40.

141. See E. Mehren, "Hooks of 'Hillbilly Heroin': Abuse of Prescription Painkiller OxyContin Ravages Poor Areas in the East," *Los Angeles Times*, Oct. 4, 2001, at A1.

142. See G. Singh, "Recent Considerations in Nonsteroidal Anti-Inflammatory Drug Gastropathy," *American Journal of Medi-*

cine, 105, suppl. 1B (1998): 31–38, at 33 (estimating 16,500 deaths annually just among arthritis patients); see also G.C. Curhan et al., "Frequency of Analgesic Use and Risk of Hypertension in Younger Women," *Archives of Internal Medicine*, 162 (2002): 2204–08.

143. See R. Rubin, "Abuse-Resistant OxyContin Planned," *USA Today*, Aug. 9, 2001, at 2A.

144. See L. Neergaard, "Abuse-Resistant OxyContin Hits Snag," *Associated Press Newswire*, June 18, 2002.

145. See J. White, "Va. Class-Action Suit Filed Against OxyContin Firm," *Washington Post*, June 19, 2001, at A6; see also *McCaulley v. Purdue Pharma, L.P.*, 172 F. Supp. 2d 803, 804–05 (W.D. Va. 2001) (summarizing the plaintiffs' allegations in the course of resolving preliminary motions); *Salisbury v. Purdue Pharma, L.P.*, 166 F. Supp. 2d 546, 548 (E.D. Ky. 2001); *McCallister v. Purdue Pharma, L.P.*, 164 F. Supp. 2d 783, 787–88, 791–92 (S.D. W. Va. 2001); R.C. Ausness, "Will More Aggressive Marketing Practices Lead to Greater Tort Liability for Prescription Drug Manufacturers?," *Wake Forest Law Review*, 37 (2002): 97–139, at 133–35. Opponents of efforts to down-classify marijuana make a similar argument — namely, that decriminalization for medical use will create a larger supply subject to possible diversion.

146. See J. White, "OxyContin Abuse Is Increasing, DEA Says," *Washington Post*, Dec. 12, 2001, at A10; see also C. Adams, "FDA Asks Maker of OxyContin to Pull 'Misleading' Print Ads," *Wall Street Journal*, Jan. 23, 2003, at D3; J. Carter, "Senate Committee Examines Marketing Practices of OxyContin Manufacturer," *Associated Press Newswire*, Feb. 12, 2002.

147. See D.B. Brushwood & F.H. Fern, "Clozaril and the Threat of Product Liability: Defensive Drug Distribution Invites Regulatory Reform," *Journal of Products & Toxics Liability*, 15 (1993): 145–62, at 145–46, 150, 158–59; J.H. Krause, "Accutane: Has Drug Regulation in the United States Reached Its Limits?," *Journal of Law & Health*, 6 (1991): 1–29, at 18–23; M.A. Hurwitz, Note, "Bundling Patented Drugs and Medical Services: An Antitrust Analysis," *Columbia Law Review*, 91 (1991): 1188–220, at 1192–95.

148. See *American Pharm. Ass'n v. Weinberger*, 377 F. Supp. 824, 831 (D.D.C. 1974) (invalidating the FDA's effort to restrict the distribution of methadone, primarily because Congress had assigned this responsibility to the DEA), *aff'd*, 530 F.2d 1054 (D.C. Cir. 1976); L. Noah, "A Miscarriage in the Drug Approval Process? Mifepristone Embroils the FDA in Abortion Politics," *Wake Forest Law Review*, 36 (2001): 571–603, at 584–86; see also M. Kaufman, "FDA Reapproves Bowel Drug After Pulling It for Safety," *Washington Post*, June 8, 2002, at A4; F.L. Kritz, "FDA to Weigh New Controls on Problematic Drugs," *Washington Post*, Apr. 16, 2002, at Z1.

149. Methadone represents an exception. See S.P. Molinari et al., "Federal Regulation of Clinical Practice in Narcotic Addiction Treatment: Purposes, Status, and Alternatives," *Journal of Law, Medicine & Ethics*, 22 (1994): 231–39, at 238 ("The [Narcotic Addict Treatment Act of 1974] has created a closed distribution system unique to pharmacotherapy and the practice of medicine.").

150. See L. Noah, "Administrative Arm-Twisting in the Shadow of Congressional Delegations of Authority," *Wisconsin Law Review* (1997): 873–941, at 881–82.

151. See T. Pasko & B. Seidman, *Physician Characteristics and Distribution in the US* (Chicago: AMA Press, 2002): at 15, 18; see also "DEA Overreaches in Effort to Stop Abuse of Painkiller," *USA Today*, June 13, 2001, at 16A (citing an estimate that "there are fewer than 4,000 certified pain specialists" in the United States).

152. See C.S. Cleeland, Editorial, "Undertreatment of Cancer Pain in Elderly Patients," *JAMA*, 279 (1998): 1914–15, at 1915 (noting that "the optimal management of pain and adverse effects of analgesics requires aggressive use of controlled substances, potentially raising fears of regulatory scrutiny"); C. Gillespie, "Getting OxyContin Can Be an Ordeal for Those Who Need It," *Los Angeles Times*, Oct. 14, 2001, at A26; P. Recer, "Experts Say Cancer Pain Undertreated," *Associated Press Newswire*, July 17, 2002 (describing the conclusions reached at a National Institutes of Health consensus conference on the subject).

153. See L. Marsa, "OxyContin Abuse May Curb Progress in Pain Field," *Los Angeles Times*, Aug. 13, 2001, at S1; "Supermarket Chain Pulls Oxycontin," *Associated Press Newswire*, Apr. 16, 2002.

154. See J.A. Henderson, Jr., & A.D. Twerski, "Drug Designs Are Different," *Yale Law Journal*, 111 (2001): 151–81, at 168–72; L. Noah, "Advertising Prescription Drugs to Consumers: Assessing the Regulatory and Liability Issues," *Georgia Law Review*, 32 (1997): 141–80, at 172–73. In fact, after the FDA authorized the reintroduction of Lotronex with restrictions on who may prescribe the drug, patients have found it difficult to secure. See F.L. Kritz, "Still Irritable, Still Waiting: After Return to Market, Lotronex Can Be Hard to Get," *Washington Post*, Feb. 11, 2003, at Z1.

155. See J. White, "More Warnings About OxyContin," *Washington Post*, July 26, 2001, at B2.

156. See 66 Fed. Reg. 38,713, 38,714 (2001).

157. See S. Satel, Op-Ed, "Keeping OxyContin out of the Wrong Hands," *Boston Globe*, Aug. 11, 2001, at A15; see also D.H. Kreling et al., "The Effects of an Internal Analgesic Formulary Restriction on Medicaid Drug Expenditures in Wisconsin," *Medical Care*, 27 (1989): 34–44, at 36–37, 42 (concluding that this approach to reducing the use of narcotic analgesics had limited success). In addition, one state has sued for reimbursement of Medicaid expenditures for overprescribing of the drug. See M.T. Reidy & M.H. Brown, "Suit Targets State Firm That Makes OxyContin," *Hartford Courant*, June 13, 2001, at A6.

158. See "OxyContin Maker Calls Plaintiffs' Allegations Baseless, Pledges to Ensure Supply for Patients," *Product Safety & Liability Reporter*, 29 (2001): 666–68, at 667.

159. See B. Meier, "U.S. Asks Painkiller Maker to Help Curb Wide Abuse," *New York Times*, May 1, 2001, at A12. Along similar lines, the DEA regulations include a rule of last resort for the use of opioid analgesics, authorizing the administration of narcotics in hospital settings "to persons with intractable pain in which no relief or cure is possible or none has been found after reasonable efforts." 21 C.F.R. § 1306.07(c).

160. See *Departments of Commerce, Justice, and State, the Judiciary, and Related Agencies Appropriations for 2002: Hearings Before a Subcomm. of the House Comm. on Appropriations*, 107th Cong., at 334 (2001) (testimony of Donnie R. Marshall, Acting Administrator, DEA). Although reportedly not done at the agency's behest, the manufacturer decided to discontinue marketing its highest dosage form (160 mg). See J. White, "Shipment of Potent Pain Pills Suspended: Company Interrupts Sales of Strongest Dosage of OxyContin Because of Abuse," *Washington Post*, May 12, 2001, at A9.

161. See R.L. DuPont & C.M. DuPont, "The Treatment of Anxiety: Realistic Expectations and Risks Posed by Controlled Substances," *Journal of Law, Medicine & Ethics*, 22 (1994): 206–14, at 212–13 ("When physicians and patients abuse the social 'contract' on drugs of abuse, they should be subjected to professional and legal sanctions because such transgressions pose potentially serious clinical and public health dangers."); D.A.

Kessler, "Regulating the Prescribing of Human Drugs for Nonapproved Uses Under the Food, Drug, and Cosmetic Act," *Harvard Journal on Legislation*, 15 (1978): 693–760, at 737 ("Withdrawal of a drug that has value to a certain patient population because the drug may be misused by a larger population in effect imposes an unfair hardship on those patients who could use the drug safely and profitably."); cf. *Swayze v. McNeil Labs., Inc.*, 807 F.2d 464, 468, 471–72 (5th Cir. 1987) (rejecting the plaintiff's claim that, if the manufacturer could not reduce the risk that health care professionals would act negligently and administer excessive doses of fentanyl, it should have withdrawn the drug from the market).

162. See D.R. Wesson & D.E. Smith, "Prescription Drug Abuse: Patient, Physician, and Cultural Responsibilities," *Western Journal of Medicine*, 152 (1990): 613–16, at 613 ("Prescription drug abuse is more difficult to conceptualize than the abuse of cocaine, marijuana, or even alcohol because there is the need for a balance between restricting access and maintaining availability in drug control policy."); B.B. Wilford et al., "An Overview of Prescription Drug Misuse and Abuse: Defining the Problem and Seeking Solutions," *Journal of Law, Medicine & Ethics*, 22 (1994): 197–203, at 198 ("[U]nlike illicit drug abuse, programs to control prescription drug abuse appear to affect medical care as well.... Such a large collateral effect deserves careful thought...."); *id.* at 202 (calling this issue "the 'social algebra' of the system, that is, the extent to which undermedication of some individuals will be tolerated in exchange for reductions in overmedication of others").

163. See J. White, "DEA Backs Medical Use of OxyContin," *Washington Post*, Oct. 24, 2001, at A26.

164. See J.A. Linder & R.S. Stafford, "Antibiotic Treatment of Adults with Sore Throat by Community Primary Care Physicians: A National Survey, 1989–1999," *JAMA*, 286 (2001): 1181–86; L.F. McCaig & J.M. Hughes, "Trends in Antimicrobial Drug Prescribing Among Office-Based Physicians in the United States," *JAMA*, 273 (1995): 214–19. The latest surveys suggest that things have begun to improve. See L.F. McCaig et al., "Trends in Antimicrobial Prescribing Rates for Children and Adolescents," *JAMA*, 287 (2002): 3096–102.

165. See S.B. Levy, *The Antibiotic Paradox: How Miracle Drugs Are Destroying the Miracle* (New York: Plenum Press, 1992): at 209–10; L. Neergaard, "U.S. Acting to Stem Misuse and Prolong Life of Antibiotics," *Philadelphia Inquirer*, June 11, 2002, at A10; A. Zuger, "The 'Other' Drug Problem: Forgetting to Take Them," *New York Times*, June 2, 1998, at F1.

166. For instance, in response to the escalating prices of new drugs, some patients have turned to black markets (supplied by diversion and counterfeiting) as well as cross-border purchases, each of which creates potential quality control problems that have prompted federal intervention. See L. Noah, "NAFTA's Impact on the Trade in Pharmaceuticals," *Houston Law Review*, 33 (1997): 1293–326, at 1307–09, 1311–14.

167. See J. Gillis & C. Connolly, "Emphasis on Cipro Worries Officials," *Washington Post*, Oct. 19, 2001, at A17 (reporting that drug-resistant strains of bacteria may contribute to 70,000 deaths each year in the United States); see also U.S. Office of Technology Assessment, *Impacts of Antibiotic-Resistant Bacteria*, OTA-H-629 (Washington, D.C.: Government Printing Office, 1995); M.L. Cohen, "Epidemiology of Drug Resistance: Implications for a Post-Antimicrobial Era," *Science*, 257 (1992): 1050–55.

168. See S.B. Levy, "The Challenge of Antibiotic Resistance," *Scientific American*, 278 (Mar. 1998): 46–53, at 52; H.C. Neu, "The Crisis in Antibiotic Resistance," *Science*, 257 (1992): 1064–73, at 1064, 1072. Until recently, vancomycin represented the last line of defense, but resistant strains have emerged. In 2000, the FDA approved Zyvox® (linezolid), the first of a new class of antibiotics called oxazolidinones. See T. Hayden, "Infectious Arms Race," *U.S. News & World Report*, Dec. 17, 2001, at 50.

169. See 65 Fed. Reg. 81,082, 81,095 (2000) (proposing revisions in the content of prescription drug labeling to reduce the tendency to overprescribe antibiotics); 65 Fed. Reg. 56,511, 56,518 (2000) (proposing a best practices statement in the labeling of antibiotics to remind physicians against overprescribing).

170. See S.B. Markow, Note, "Penetrating the Walls of Drug-Resistant Bacteria: A Statutory Prescription to Combat Antibiotic Misuse," *Georgetown Law Journal*, 87 (1998): 531–62, at 546–47 (suggesting that only infectious disease specialists in hospitals be permitted to use new antibiotics).

171. See 65 Fed. Reg. 24,704, 24,705 (2000) ("How should the risks and benefits to individuals and risks and benefits to the public health be assessed and weighed in any decision on OTC marketing? For example, how should the agency balance the potential benefits of OTC antimicrobial agents with the potential risks to society at large of the development of resistant organisms associated with increased, and potentially improper, use?").

172. See L. Noah, "Medicine's Epistemology: Mapping the Haphazard Diffusion of Knowledge in the Biomedical Community," *Arizona Law Review*, 44 (2002): 373–466, at 438–42; see also T.J. Moore et al., "Time to Act on Drug Safety," *JAMA*, 279 (1998): 1571–73, at 1572 ("[N]ew warnings about the addictive properties of propoxyphene had no effect on either prescription volume or the number of overdose deaths.").

173. See R. Gonzales et al., "Principles of Appropriate Antibiotic Use for Treatment of Acute Respiratory Tract Infections in Adults: Background, Specific Aims, and Methods," *Annals of Internal Medicine*, 134 (2001): 479–86, at 481–82 (introducing a series of CDC guidelines calling for restraint in prescribing antibiotics for adults); see also T. Brewer and G.A. Colditz, "Postmarketing Surveillance and Adverse Drug Reactions: Current Perspectives and Future Needs," *JAMA*, 281 (1999): 824–29, at 826 (describing the CDC's vaccine adverse event surveillance efforts). See generally E.W. Etheridge, *Sentinel for Health: A History of the Centers for Disease Control* (Berkeley: Univ. of California Press, 1992); L.O. Gostin, *Public Health Law: Power, Duty, Restraint* (Berkeley: Univ. of California Press, 2000); L. Noah, "Triage in the Nation's Medicine Cabinet: The Puzzling Scarcity of Vaccines and Other Drugs," *South Carolina Law Review*, 54 (forthcoming 2003).

174. See *Thompson v. Western States Med. Ctr.*, 535 U.S. 357 (2002) (invalidating a restriction on advertising by pharmacists who compound drug products); L. Noah, "What's Wrong with 'Constitutionalizing Food and Drug Law,'" *Tulane Law Review*, 75 (2000): 137–48 (discussing litigation challenging the FDA's restrictions on indirect industry efforts to promote off-label drug uses).

175. See *OxyContin — It's Use and Abuse: Hearing Before the Subcomm. on Oversight & Investigations of the House Comm. on Energy & Commerce*, 107th Cong., at 9 (2001) (statement by Terrance W. Woodworth, Deputy Director, DEA Office of Diversion Control) ("[T]he five states with the lowest number of per capita OxyContin® prescriptions all have long standing prescription monitoring programs in place."); see also D. Brushwood, "Maximizing the Value of Electronic Prescription Monitoring Programs," *Journal of Law, Medicine & Ethics*, 31 (2003): 41–54. Doctors and drug companies generally oppose such programs. See M. Petersen & B. Meier, "Few States Track Prescriptions as Way to Prevent Overdoses," *New York Times*, Dec. 21, 2001, at A1.

176. See J. Avorn & S.B. Soumerai, "Improving Drug-Therapy Decisions Through Educational Outreach: A Randomized Controlled Trial of Academically Based 'Detailing,'" *N. Engl. J. Med.*,

308 (1983): 1457–63; M.D. Cabana et al., "Why Don't Physicians Follow Clinical Practice Guidelines? A Framework for Improvement," *JAMA*, 282 (1999): 1458–65; R.L. Kane & J. Garrard, Editorial, "Changing Physician Prescribing Practices: Regulation vs. Education," *JAMA*, 271(1994): 393–94; P.R. Manning et al., "Changing Prescribing Practices Through Individual Continuing Education," *JAMA*, 256 (1986): 230–32; S.B. Soumerai et al., "Improving Drug Prescribing in Primary Care: A Critical Analysis of the Experimental Literature," *Milbank Quarterly*, 67 (1989): 268–317; S.B. Soumerai & J. Avorn, "Principles of Educational Outreach ('Academic Detailing') to Improve Clinical Decision Making," *JAMA*, 263 (1990): 549–56.

Washington, D.C. firm specializing in food and drug law. She received her J.D. from Harvard Law School.

Lars Noah, J.D., is the Research Foundation Professor of Law at the University of Florida in Gainesville.

T. Howard Stone, J.D., LL.M., is Associate Professor at the University of Louisville School of Medicine in the Institute for Bioethics, Health Policy, and Law and the Department of Family and Community Medicine. Dr. Stone has worked at the World Health Organization and the New York City Department of Health. He received his B.A. from the University of California at Los Angeles, his J.D. from the New York Law School, and his LL.M. in health law from the University of Houston Law Center.

Anita J. Tarzian, Ph.D., R.N., is Research Associate for the Law and Health Care Program at the University of Maryland School of Law and an independent consultant in research and ethics. She received a Ph.D. in Nursing and Ethics and an M.S. in Intercultural Nursing from the University of Maryland School of Nursing. Her research and professional interests have been concentrated in the areas of health care ethics, end-of-life care/hospice, palliative care, multiculturalism, and underserved populations.

Stephen J. Ziegler, J.D., M.A., is a Ph.D. candidate at Washington State University (degree expected May 2003), and has conducted research and published on a variety of issues at the intersection of law, medicine, politics, and criminal justice. He recently accepted an appointment as an assistant professor at Indiana University, School of Public and Environmental Affairs at the Indiana-Purdue campus in Fort Wayne, Indiana. He received his B.S. *cum laude* from Texas Christian University, his M.A. from Washington State University, and his J.D. *cum laude* from the T. M. Cooley School of Law where he was a 3-year merit scholar.

Letter to the Editor

Dear Madam: In her article alleging the failure of equipoise to resolve the ethical tension in a randomized clinical trial, Professor Deborah Hellman misconceives the nature of equipoise in relation to the design and conduct of such trials ("Evidence, Belief, and Action: The Failure of Equipoise to Resolve the Ethical Tension in the Randomized Clinical Trial," *JLME*, Fall 2003). Conceptually, equipoise relates to evidential uncertainty concerning the relative merits of comparator interventions, and is directly relevant to the scientific validity and value of randomized clinical trials, and the ethical recruitment of patients.

Uncertainty may be considered at three levels: (1) the community of "expert" clinical practitioners and trialists, who propose a trial for its resolution; (2) the individual physician, who must both decide whether to participate in a trial and whether to offer enrollment to particular eligible patients; and (3) the patient, who must decide whether to accept an offer of enrollment.[1] The first level is that of "clinical equipoise" as proposed by Freedman.[2]

With respect to data produced by research, including the results of randomized clinical trials, Professor Hellman makes distinctions between evidence obtained in trials (Q1), one's belief given the evidence (Q2), and action taken in regard to such evidence (Q3): "the question that is of interest to the patient is *what should I do?* It is a question directed at decision-making and action. The concept of equipoise relates to a very different question; it relates to the question *what should I believe?*"

The notion that clinical equipoise is irrelevant to an action decision is puzzling. The action required of a patient is a choice among available medical interventions for her condition. A patient is surely interested in the reasoned beliefs of physicians expert in her condition. The notion of equipoise is well-recognized in utility theory, the basis of the strategy of clinical decision analysis,[3] commonly used by physicians and their patients when making treatment choices in clinical care. Utility theory takes account of a patient's values and preferences in decisions about treatment options. If, after being apprised of community uncertainty concerning the relative efficacy of the comparator interventions, and the nature of the interventions and their harms, a patient is also "maximally uncertain" (in equipoise) about their relative merits, enrollment is a rational option.[4] Indeed, randomization will offer the patient-participant the best odds (50 percent) of getting the best treatment, if one is subsequently shown to be superior. Thus, equipoise enables the best *treatment* choice under conditions of uncertainty: the trial.[5] The notion of leaving the choice of treatment to chance, the flip of a coin, is seemingly at odds with the notion that "care requires that patients get the treatment that is best suited to the action-oriented question—*given the data, what should I do*[?]" However, it is best to remember that the "casting and drawing of lots" is a time-honored method of dealing with uncertainty.[6] Appropriate acknowledgment of uncertainty enables the concurrent achievement of two objectives: the acquisition of valuable scientific knowledge (the trialist's primary goal), and the best