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Marketed Unapproved Drugs

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This monograph explains why some currently marketed drugs that are dispensed by pharmacists have not been approved by the FDA. The process through which the FDA is currently reviewing unapproved drugs is discussed. Legal case studies are used to illustrate the factors that can lead to the marketing of unapproved drugs and the challenges faced in pharmacy when evaluating the safety and efficacy of unapproved drugs in the care of specific patients.

Learning Objectives

Pharmacist

1. State the factors that will lead to a "drug" being classified as a "new drug" under the federal Food, Drug and Cosmetic Act.
2. Differentiate between a New Drug Application submission and the other pathways available for legal marketing of unapproved new drugs. Recognize effective policies
3. Recognize effective policies for pharmacy review of the safety and efficacy of drugs that have not been approved by the FDA and that have been prescribed or ordered for use in the care of a specific patient.

Nurse

1. State the factors that will lead to a "drug" being classified as a "new drug" under the federal Food, Drug and Cosmetic Act.
2. Differentiate between a New Drug Application submission and the other pathways available for legal marketing of unapproved new drugs.
3. Recognize effective policies for pharmacy review of the safety and efficacy of drugs that have not been approved by the FDA and that have been prescribed or ordered for use in the care of a specific patient.

Pharmacy Technician

1. State the factors that will lead to a "drug" being classified as a "new drug" under the federal Food, Drug and Cosmetic Act.
2. Differentiate between a New Drug Application submission and the other pathways available for legal marketing of unapproved new drugs.
3. Recognize effective policies for pharmacy review of the safety and efficacy of drugs that have not been approved by the FDA and that have been prescribed or ordered for use in the care of a specific patient.

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Pharmacists, Pharmacy Technicians, Nurses

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Introduction

Most drugs on the market require FDA approval, but some drugs do not require FDA approval. Only "new drugs" require FDA approval. Drugs that do not meet the definition of "new drug" may be marketed without FDA approval, although they are subject to all of the requirements of the adulteration and misbranding standards within the Food, Drug and Cosmetic Act (FDCA) and FDA regulations.

The reality that some drugs dispensed by pharmacists are not FDA approved, and that they need not be, may come as a surprise to both pharmacists and their patients. It is important to note that an unapproved drug is not necessarily an unsafe or ineffective drug. The FDA is slowly working through a process that may eventually result in all marketed drugs being approved, although practicalities suggest it is unlikely that the lofty goal of "every marketed drug is an approved drug" will ever be reached. It is impossible to know every drug that is being marketed and to know whether all marketed drugs have been approved.

Many drugs that have been marketed for decades have been approved only within the past several years. These recently approved but long-used drugs include quinine, colchicine, and ergotamine. Chloral hydrate, phenobarbital, and many other drugs still have not been approved by the FDA. The FDA's most recent estimate is that "perhaps as many as several thousand drug products" are currently being marketed without FDA approval. This "rough estimate comprises several hundred different active ingredients, in various strengths, combinations, and dosage forms from multiple distributors." The number of marketed drugs that are unapproved must be placed in the category of "known unknowns" because their existence is recognized but their extent is undetermined.

The challenge for pharmacists is to assure that the medications they provide to patients are safe and effective, regardless of FDA approval. Some approved drugs may be unsafe or ineffective for a particular individual patient. Some unapproved drugs may be perfectly safe and effective for a particular individual patient. Whether or not a drug has been approved by the FDA should not be the sole determining factor in a pharmacist's decision about the safety and efficacy of a drug for a patient, but it is a very significant factor to consider.

Pharmacists who are uncertain of a drug's approval status should consult the FDA's online Orange Book ("Approved Drug Products with Therapeutic Equivalence Evaluations"). As the title of the book suggests, FDA-approved products are listed in the book. Unapproved drug status is different from the off-label use of an approved drug. The difference can be confusing because "off-label use" is sometimes incorrectly referred to as "unapproved use."

The term "off-label use" is preferred because the FDA does not approve uses; the agency approves drugs along with the labeling that accompanies the drugs. The prescribing of a drug for an indication not included in the approved labeling is neither approved nor unapproved, and it is perfectly legal. The distribution of an unapproved drug is viewed as

illegal by the FDA, although this agency interpretation is open to challenge under certain circumstances.

The Statutory Framework

An understanding of how some drugs can be marketed without FDA approval begins with a review of two important definitions in the federal Food, Drug and Cosmetic Act. The first of these is the definition of "drug."

Section 201(g) of the FDCA states: "The term "drug" means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C)."

The importance of this definition is that all products falling within the definition are subject to a high level of regulatory oversight that does not apply to products falling outside the definition. The marketing of a product that meets the definition of "drug" raises complex issues of regulatory compliance that can pose administrative and financial barriers to the viability of the product. An article cannot be considered a "new drug" if it is not a "drug" to begin with. For example, articles that are considered cosmetics or foods are regulated by the FDA, but they could not possibly require premarket approval because they are not drugs.

The second important definition in the FDCA is the definition of "new drug."

Section 201(p) of the FDCA states: "The term 'new drug' means— Any drug the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a 'new drug' if at any time prior to June 25, 1938, it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use."

The definition of "new drug" also includes: "Any drug the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions."

What is immediately apparent from a literal interpretation of these two separate definitions is that the FDCA does not intend for all drugs to be classified as new drugs. There would be no point in creating a category of "new drug" and also a separate definition from "drug" if all drugs were new drugs. An example may help illustrate this point. We all have an idea of what "fruit" means and what "fresh fruit" means. All fruit is not fresh fruit. If all fruit were fresh fruit, then we would not need to use the adjective "fresh" for a subset of fruit that has been recently harvested. Likewise, if all drugs were new drugs, then only a single definition would be necessary. The definitional approach of the United States Congress within the FDCA is to create a large set of marketed products known as "drugs" and a subset of marketed products known as "new drugs." The clear intent of Congress is that not all drugs are new drugs. This literal interpretation of the FDCA definitions is not followed by the FDA, which has adopted a policy that all drugs must be approved because all drugs are new drugs.

There are two major criteria for classification of a drug as a new drug under the FDCA definition. First, a new drug lacks general recognition of safety and effectiveness. This is often referred to as lacking a state of GRASE (pronounced like "grace" and sometimes referred to with the alternative acronym "GRAS/E"). Second, a drug may be GRASE, but if the drug has not been used to a material extent or for a material time then it is still new. Either way, the drug is classified by definition as a "new drug."

Over several decades of discussion and occasional litigation, the FDA has established a position that to escape the definition of "new drug," and therefore to avoid the necessity of new drug approval, a drug must have been adequately studied through clinical investigations that support its safety and efficacy. The studies must be published in the scientific/professional literature, and qualified experts must generally agree that the drug is safe and effective. This is essentially the same evidentiary burden that is required to support a New Drug Application (NDA). Thus, there is no realistic "shortcut" to market through recognition of "not new drug" status, although it is theoretically not impossible.

Manufacturers and distributors will occasionally attempt to gain "not new drug" recognition for their product through the submission to the FDA of a GRASE Affirmation Petition.

Some drugs may be "grandfathered," and therefore not require FDA approval. The definition of "new drug" establishes grandfathered status for drugs that were marketed prior to the creation of new requirements for marketing (there is a 1938 grandfather clause and a 1962 grandfather clause), subject to the condition that the drug continues to be labeled with the same conditions for use as the original labeling. This is also a potential "shortcut" to marketing without approval, but it is a long shot. Manufacturers and distributors will occasionally attempt to acquire grandfathered status for their product through the submission to the FDA of a Grandfathered Drug Petition.

The Historical Context

Why are unapproved drugs on the market? Why hasn't the FDA already removed these drugs from the market? The answers to these questions lie in the background of drug regulation and the enforcement discretion given to the FDA by Congress.

The first federal drug law, passed in 1906, established criteria for misbranding and adulteration of drugs, but there was no requirement for drug approval, thus there was no issue of unapproved drugs. The modern Food, Drug and Cosmetic Act was passed in 1938 with a requirement that drugs be approved for safety prior to their marketing. The active ingredients of many pharmaceutical products currently on the market had been introduced, at least in some form, prior to 1938. In 1962, the FDCA was amended, adding a requirement that drugs be approved for efficacy prior to their being marketed. Between 1938 and 1962, if a drug product obtained approval, the FDA allowed drug products that were identical, related, or similar to be marketed without an additional approval. Many drugs were introduced into the market between 1938 and 1962 based on the manufacturer's opinion that the drug was safe or based on an FDA opinion that the product was not a new drug.

Between 1938 and 1962, the FDA issued many such opinions, all of which were formally revoked in 1968. The revocation of these opinions did not lead to an automatic withdrawal from the marked of the unapproved drugs.

The 1962 drug efficacy amendments resulted in a process known as the Drug Efficacy Study Implementation (DESI), which undertook to evaluate all 3,400 products approved based on safety since 1938, plus an even larger number of products that had entered the market during that time without FDA approval. Unsurprisingly, due to the vastness of the undertaking, the DESI process has not yet been completed. It is agency policy that products subject to an ongoing DESI proceeding may remain on the market during the pendency of the proceeding, even though they have not been approved. Many products remain on the market without the required approval even though the DESI proceedings have been completed for these drugs.

Beginning in 1983, the FDA began what is called the "Prescription Drug Wrap-Up." The goal of this program is to speed up the evaluation of drugs that have not yet been reviewed for safety or effectiveness, and to remove from the market those drugs that did not meet modern standards. The approach taken by the FDA to this program is one of extreme skepticism toward the idea that any currently marketed unapproved drugs are either grandfathered or are GRASE, although the agency recognizes that both are "at least theoretically possible."

It is important to mention that some marketed unapproved drugs are not the result of any loophole in the law or a modernization of previous policies. They are the result of dishonest persons who put profit ahead of patient safety, and who are deliberately marketing unapproved drugs with full knowledge that their activity is illegal. This sort of illegal activity will continue until it is stopped, just as is the case with any illegal activity.

The continued marketing of unapproved drugs is not only a matter of legality. It is also a result of the FDA's pragmatic enforcement policy. The agency is fully aware of the significant resources that would be required to seek out and remove all unapproved drugs from the market. As an agency with extensive, but limited, resources, the FDA has adopted a "worst first" policy that starts with the most egregious offenders and moves deliberately through the queue toward those whose offenses are less threatening to the public health. This cautious approach also reduces the possibility that a much needed and useful drug will be removed from the market without careful consideration of the consequences.

Here is the list of FDA enforcement priorities for unapproved marketed drugs, from highest to lowest priority:

- Drugs with potential safety risks.
- Drugs that lack evidence of effectiveness.
- Health fraud drugs.
- Drugs that present direct challenges to new drug approval.
- Unapproved drugs that violate the Act in other ways.
- Drugs that have been reformulated to evade FDA enforcement.

The deliberate approach taken by the FDA is illustrative of the regulatory principle of "balance," which is also known as the "Goldilocks" principle. Not too hard; not to soft; but just right. The FDA maintains public respect and a high level of independence by "doing it right" rather than "doing it quick." In the meantime, some unapproved drugs continue to be marketed, pending the outcome of the evidence-based process being undertaken by the FDA.

The Levothyroxine Sodium Example

The story of levothyroxine sodium is a fitting example of the process through which unapproved marketed drugs are brought through the approval process. The story begins with the status of thyroid extract in 1938. That natural occurring drug had been marketed for a decade prior to enactment of the FDCA, so it was grandfathered at that time. As is the case with most agencies and people, records of actions taken are more enduring than are records of actions not taken. FDA does not have a record of how synthetic levothyroxine

was allowed on the market without approval. So, it is difficult to know what happened next. The best speculation is that when synthetic levothyroxine sodium was initially marketed in 1955, the agency decided that it was similar enough to thyroid extract to consider this new synthetic drug to be grandfathered as well.

Fast forward to the 1990s, when generic drug use was expanding. Because the branded levothyroxine sodium had not been approved, generic manufacturers were not able to obtain marketing approval based on equivalency studies with the branded product. The Abbreviated New Drug Application (ANDA) that is ordinarily used for generic product approval requires a showing of therapeutic equivalence with an approved "reference listed drug." The absence of an approved reference listed drug slowed down the approval of generic levothyroxine sodium products, thus there were financial as well as regulatory concerns.

In 1997, the agency approved two additional levothyroxine products through the full NDA path, and one additional product was close to its approval. The original manufacturer of the branded product chose to file a GRASE Petition for its product rather than submit an NDA, but this approach was abandoned when a new company took over the product and decided to submit data in support of an NDA. What resulted was the approval of four products, each pursuant to an NDA, meaning that they were all approved but were not rated as therapeutically equivalent with each other. Subsequent studies, done at the urging of the FDA have resulted in therapeutic equivalence ratings. However, instead of the straightforward "AB" rating given to most equivalent products of the same molecular entity, levothyroxine sodium products are given the ratings of "AB1" or "AB2" or "AB3" or any combination of the three, to show which products are rated as therapeutically equivalent to other products. The FDA calls this a "special situation" and it is fully described in a special section of the Orange Book.

The levothyroxine sodium story is important because many other marketed unapproved drugs could be in a similar "special" situation. An unapproved drug may be the recognized therapeutic solution to a particular disease. Or, it could be the "go-to" therapy used by physicians in a specialized practice with a particular group of patients. The costs of conducting studies to support approval of a marketed unapproved drug might be so great that the price of the approved product would be prohibitive for some patients. While there are very good reasons to require approval of currently unapproved drugs, there are perhaps equally good reasons not to rush into a requirement for approval if that will limit access to a currently useful medication.

Fortunately, there are legal cases that shed additional light on the complicated subject of marketed unapproved drugs. What follows in this monograph is an overview of cases in which the status of marketed unapproved drugs is described, and the responsibilities of those who market unapproved drugs are reviewed.

The Case That Shocked the Regulatory Community

Regulatory agencies rely heavily on voluntary compliance. It has often been said that regulations are unnecessary for the vast majority of individuals and businesses who would comply with applicable standards in the absence of legal coercion; on the other hand, regulations are necessary for the small number of individuals and businesses that would choose to violate the law to enhance profitability for themselves. The marketing of the intravenous vitamin E product E-Ferol IV illustrates the reality of this perspective. The facts of this case are hard to believe, but they are true.

A pharmaceutical executive was convicted of misbranding violations and of introducing into interstate commerce an unapproved new drug. The product that led to the conviction was E-Ferol IV, which was first marketed in the fall of 1983. It consisted of vitamin E and two polysorbates that were used as emulsifying agents. Approximately 26,000 vials of E-Ferol IV were distributed until a recall was ordered by the FDA and the product was permanently removed from the market in April 1984. The product had been identified as causing the death of approximately 40 premature infants. The development of E-Ferol IV was prompted by the need for an intravenous form of vitamin E to prevent retrolental fibroplasia (RLF) that causes impaired vision or permanent blindness in premature infants. The two principle forms of vitamin E that were available in the early 1980s were an oral formulation and an intramuscular (IM) formulation. Both of these products were sold as nutritional supplements and not as drugs. The manufacturer already was distributing an intramuscular injection product known as E-Ferol IM, with labeling that made no reference to RLF or to any other medical condition.

In 1982, a neonatologist wrote to the manufacturer suggesting that there must be a market for an IV formulation because the IM formulation was difficult to administer to neonates.

The executive responded that "the amount of polysorbates needed may be detrimental," and he pointed out that "fat emulsions for IV use are very tricky products and fraught with particulate size problems." The executive was aware that another manufacturer was attempting to obtain FDA approval of an IV vitamin E product. He expressed caution to a colleague noting that "if we make some attempt to solubilize the vitamin E and use the wrong proportions and kill a few infants, we'd have some serious problems."

Notwithstanding these concerns, the manufacturer went ahead and developed E-Ferol IV. The manufacturer never did any testing to determine whether E-Ferol IV would be safe and effective for use in premature infants. In the "Clinical Pharmacology" section of the package insert, the manufacturer included this language: "Reports in the literature indicate that substantial doses of vitamin E will reduce the severity of retrolental fibroplasia in neonatals, which are administered oxygen because of their low weight, under 1500 grams." A regulatory consultant sent to the company a memorandum stating, "I do not believe that legally we can make a claim that vitamin E is effective against RLF if given to infants. This will

require an NDA for the use of vitamin E as a drug." The executive claimed that he never saw the memorandum.

The E-Ferol IV product was marketed to approximately one thousand directors of neonatal intensive care units. Nothing in the promotional materials indicated that the product had not been tested for safety and efficacy. Physicians and pharmacists testified at trial that they thought the product had been approved by the FDA based on the manner in which it was being marketed.

Almost immediately concerns about the product were sent to the manufacturer. In December 1983, a neonatologist in Honolulu reported that two neonates had developed "unusual symptoms" following the administration of E-Ferol IV. In early January 1984 a pharmacist "expressed concern about the large amount of polysorbate." At about this same time another pharmacist was critical "of the company representing the product as appropriate for the treatment of RLF without any studies to support this claim."

In late January 1984, a neonatologist in Spokane reported three neonatal deaths resulting from E-Ferol IV use. The company ceased distribution of the product, informing customers that the product was "unavailable because it was on back order," rather than sharing any information about possible toxicities. An attorney for the manufacturer told the company that "the references to RLF in the package insert made the product a drug and that the FDA would probably consider it to be a new drug." The attorney advised the company to stop shipping the drug until experts could evaluate its safety and efficacy.

The manufacturer then revised E-Ferol IV's package insert to omit all references to RLF and to reduce the recommended dosage. However, shipments were resumed before the revised package inserts could be included with the product.

On March 27, 1984, a pharmacist in Tennessee informed the companies that her hospital had stopped administering E-Ferol IV because of neonatal deaths associated with its use.

Shipments of E-Ferol IV continued until April 6, 1984, when the FDA contacted the manufacturer resulting in a recall of the product and the permanent removal of the product from the market.

The pharmaceutical executive appealed his conviction, arguing that (1) FDA policy led him to believe that E-Ferol IV could be marketed lawfully without a new drug approval, and (2) this same policy was so vague and indefinite as to deprive him of fair warning that his conduct was illegal.

The court applied what is known as the "willful blindness theory," under which criminal liability may be imposed on people who recognize the likelihood of wrongdoing but consciously refuse to take basic investigatory steps. The conviction was affirmed.

The awareness this case brings us is that sometimes the profit motive can override safety concerns. Regulatory agencies have been established to prevent this sort of illegal conduct.

But regulators can't be in all places at all times. It is the responsibility of health professionals to be knowledgeable of regulatory requirements for new drugs, and to protect patients under circumstances where manufacturers or distributors may not be fulfilling this role. The E-Ferol IV case was the impetus for the Prescription Drug Wrapup in which the FDA is currently engaged.

No Special Status for Unapproved Cancer Drug

In 1979, the United States Supreme Court was asked to resolve a controversy between the FDA and cancer patients who asked for freedom to have their physicians prescribe for them the unapproved drug laetrile. The FDA would not allow use of laetrile because the drug had not been shown to be safe and effective. A trial court had concluded that laetrile was entitled to an exemption from premarketing approval requirements based on the FDCA's grandfather provisions. The intermediate appellate court affirmed the trial court's decision, but on different grounds. The appellate court reasoned that the terms "safety" and "effectiveness" have no reasonable application to terminally ill cancer patients because they will "die of cancer regardless of what may be done." However, based on some evidence that the oral formulation of laetrile was toxic, the appellate court limited unapproved use to intravenous injection.

The Supreme Court reversed the decisions that allowed access to unapproved laetrile. The court said, "There is a special sense in which the relationship between drug effectiveness and safety has meaning in the context of incurable illnesses. If an individual suffering from a potentially fatal disease rejects conventional therapy in favor of a drug with no demonstrable curative properties, the consequences can be irreversible. The FDA's practice reflects the recognition, amply supported by expert medical testimony in this case, that with diseases such as cancer it is often impossible to identify a patient as terminally ill except in retrospect. Cancers vary considerably in behavior and in responsiveness to different forms of therapy. Even critically ill individuals may have unexpected remissions and may respond to conventional treatment. To accept the proposition that the safety and efficacy standards have no relevance for terminal patients is to deny the FDA's authority over all drugs, however toxic or ineffectual, for such individuals."

The awareness this case brings us is the comprehensiveness of the FDCA's new drug approval provisions. Courts will not allow groups of patients to carve out exceptions to the general rule based on differences they have from the general population of patients.

"Right-to-Try" Litigation and Legislation

In 2006, a patient advocacy group known as the Abigail Alliance sued the FDA on behalf of terminally ill patients, seeking access to drugs that have successfully passed the Phase I stage of new drug approval, yet are still years away from final approval for general use. The plaintiff's requested that they be given a "right of access to unapproved drugs." They claimed that "as their lives hang in the balance, the decision to assume known or unknown risks should be left to the terminally ill patient and not to the FDA." A panel of appellate judges agreed with the plaintiffs based on a "liberty interest" in the use of unapproved drugs. One year later, the full appellate court disagreed, concluding that there is no fundamental right to access experimental therapies for anyone, including the terminally ill.

The ruling in the Abigail Alliance case led many states to pass so-called "Right-to-Try" laws that allow the use of unapproved new drugs in those states. The reality that federal law made it illegal to ship drugs to those states was one factor that resulted in the logistical impossibility that the state laws would make any difference for anyone. In fact, a study from 2016 by researchers at New York University School of Medicine reported that although 32 states had passed Right-to-Try legislation, there was no evidence that even one patient had received unapproved medication under any of those laws. In 2018 a federal Right-to-Try law was passed. Supporters of the legislation claim that it will allow terminally ill patients to use medications that previously were unavailable to them. Opponents of the legislation contend that it creates false hopes among the most vulnerable individuals within the population, because there are many disincentives for manufacturers to distribute drugs that have not yet been approved by the FDA.

The awareness this case brings us is the eagerness of patients to try any drug that might help them, regardless of the FDA approval status of the drug. Since there are already many official mechanisms to qualify patients for investigational new drug use, pharmacists can support patient needs by assisting them in gaining access to these available investigational drugs.

Approved Manufacturing v Unapproved Compounding

This case challenged the FDA's failure to exercise its enforcement discretion against pharmacies that compounded unapproved drugs after a manufacturer had obtained new drug approval of a product containing that drug.

The product in question was hydroxyprogesterone caproate injection, which had been approved under the brand name Makena in 2011 for use by pregnant women with a history of preterm birth to reduce the risk that they would experience another preterm birth.

Because this product was granted "orphan drug" status because there were fewer than 200,000 people with the condition it was intended to treat, the approved product was granted a seven-year marketing exclusivity period beginning on the day it was approved in 2011.

The lawsuit by the manufacturer against the FDA contended that the agency had failed to use its enforcement powers to curtail the activities of pharmacies that were compounding "on a commercial scale" a generic version that was not approved. A formal statement issued by the FDA said: "Approved products, such as Makena, provide a greater assurance of safety and effectiveness than do compounded products. The drugs that pharmacists compound (including hydroxyprogesterone caproate) are not FDA approved, which means that they do not undergo premarket review nor do they have an FDA finding of safety and efficacy."

Despite these statements, the FDA declined to prevent pharmacies from compounding the product, as long as the pharmacies were practicing within the scope of traditional pharmacy compounding. The manufacturer claimed that the FDA "statements and inaction have undermined the exclusivity conferred with the orphan drug designation and devalued their substantial investment in the drug."

The court adhered to a long tradition of not second guessing the discretion of an administrative agency in the enforcement of its own rules. The court said, "an agency's decision not to prosecute or enforce, whether through civil or criminal process, is a decision generally committed to an agency's absolute discretion and is therefore unreviewable" by a court. "This case is fundamentally an effort to get the court to direct and oversee the FDA's enforcement actions, and that it cannot do." The manufacturer's case was dismissed.

The awareness this case brings us is the high level of deference granted to the FDA by the courts. Courts will not order the FDA to exercise enforcement discretion over unapproved drugs any differently from the way the FDA chooses to exercise it. Some unapproved drugs, whether compounded or not, are below the FDA radar and purposefully so. The FDA opts not to enforce the FDCA against these drugs, and there is very little anyone can to do force the agency to change their policy. Health professionals, and not the FDA, are the decision makers about the availability of these drugs for patients.

The Grandfathering Process

Morphine sulfate (MSO4) is one of the decades-old drugs that was not approved by the FDA until very recently. Not surprisingly, there have been several lawsuits resulting from the requirement that MSO4 be approved. One such lawsuit was filed against the FDA by a pharmaceutical manufacturer contending that the product falls under the grandfather clause within the FDCA and therefore does not require FDA approval. The FDA responded that "the grandfather clause is exceedingly narrow and applies only to drugs that have been marketed in essentially identical form since 1938."

Meanwhile, another manufacturer obtained NDA approval for MSO4 under the FDA policy of expedited approval, since no approved product existed at that time. The manufacturer who was fighting for grandfather status then submitted its own NDA which was not

subjected to expedited review since an approved product was already in existence. The manufacturer continued its lawsuit seeing grandfather status because if this were granted, the manufacturer "would face a different and apparently lighter regulatory burden, and would be exempt from the product fee that applies to a NDA approved drug."

The court ruled that the process the manufacturer needed to follow was the filing with the FDA of a Grandfathered Drug Petition, which the manufacturer had not yet done. The court noted the formality of the petition process that would be based on evidence that had not yet been presented to the FDA, "given that grandfathering status hinges on the fact-intensive history of the drug's marketing and use."

The awareness this case brings us is of the several ways to obtain FDA's blessing to market a drug, all of which require adherence to a formal process. Litigation is unlikely to result in a positive outcome for a party who had not followed the requirements of the administrative process. Grandfather status does not just happen; it must be recognized by the FDA through a formal petition. Courts will not step in until a petitioner has exhausted the available administrative remedies.

False Advertising of a Marketed Unapproved Drug

In 2017, a manufacturer obtained FDA approval of a cocaine hydrochloride solution used for "nasal" administration by ear, nose and throat specialists as a local anesthetic during diagnostic and surgical procedures. A competing unapproved product was already on the market when this product was approved. The manufacturer of the competing product listed its route of administration as "topical." Because of the different route of administration, the two products were not considered as interchangeable in reference databases, even though the two products had the same active ingredient, the same strength, and the same dosage form. The new approved product was not able to compete successfully with the traditional unapproved product.

The manufacturer of the approved product sued the manufacturer of the unapproved product, alleging false advertising. The defendant manufacturer insisted that no statements had ever been made in advertising to any health professional indicating that their product was approved. The defendant sought to have the case dismissed on that basis.

The plaintiff manufacturer did not refute the absence of any explicit claim of approval, but it based its case on inferences that accompanied the activities of the defendant, rather than on any explicit statements. The plaintiff pointed to the results of a nationwide survey of pharmacists that showed 91% of pharmacists thought that all drugs they dispensed were FDA approved. The plaintiff contended that the defendant manufacturer had taken advantage of the pharmacists' lack of knowledge regarding drug approval. The plaintiff also claimed that the defendant claimed in advertisements that the product was being legally

marketed under a "preliminary new drug application," which the plaintiff alleged is a "fictitious regulatory category fabricated by the defendant."

The court refused to dismiss the false advertising case. In particular, the court referred to the results of the survey of pharmacists and the characterization of the route of administration as "topical" when in fact it is "nasal." The court said, "It takes no special expertise to determine that the inside of the nose, mouth, and larynx are not on the outside of the body.

This ruling does not mean that the plaintiff has won the case. It just means that the defendant cannot be dismissed from the case.

The awareness we derive from this case is that many pharmacists do not know that some drugs they dispense have not been approved by the FDA, and this lack of knowledge may support a false advertising lawsuit against a manufacturer who creates an inference of drug approval. On the other hand, there is nothing necessarily wrong with dispensing an unapproved drug if the patient's best interests are being served.

Conclusion

Marketed unapproved drugs may expose patients to potential harm, but not necessarily any greater harm than approved drugs. Pharmacists can evaluate available scientific information and determine whether an unapproved drug poses unacceptable risks in patient care. The approval status of the drug need not be a determining factor in this pharmacy evaluation.

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Marketed Unapproved Drugs

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LESSON EVALUATION

Please fill out this section as a means of evaluating this lesson. The information will aid us in improving future efforts. Either circle the appropriate evaluation answer, or rate the item from 1 to 7 (1 is the lowest rating; 7 is the highest).

1a. PHARMACISTS AND TECHNICIANS ONLY: Does this lesson meet the learning objectives? (Circle choice).

State the factors that will lead to a "drug" being classified as a "new drug" under the federal Food, Drug and Cosmetic Act.	YES	NO
Differentiate between a New Drug Application submission and the other pathways available for legal marketing of unapproved new drugs.	YES	NO
Recognize effective policies for pharmacy review of the safety and efficacy of drugs that have not been approved by the FDA and that have been prescribed or ordered for use in the care of a specific patient.	YES	NO

2. Was the program independent & non-commercial? YES NO

3. Relevance of topic Low Relevance Very Relevant
1 2 3 4 5 6 7

4. What did you like MOST about this lesson? _____

_____

5. What did you like LEAST about this lesson? _____

_____

6. How would you improve this lesson? _____

_____

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PLEASE MARK THE CORRECT ANSWER(S)

Marketed Unapproved Drugs

A passing grade of 70 or higher and completion of an activity evaluation are required to earn credit.

1. What is the FDA's most recent estimate of the number of unapproved drug products that are currently being marketed?

a. 10 to 20.
b. As many as 100.
c. As many as 500.
d. As many as several thousand.

2. If a drug is not generally recognized as safe and effective, what will it be called according to the FDCA?

a. Old drug.
b. Dangerous drug.
c. New drug.
d. Unapproved drug.

3. What submission to the FDA is usually used to request "not new drug" status?

a. Malpractice lawsuit.
b. GRASE Affirmation Petition.
c. Package insert.
d. Pharmacy licensure.

4. Some drugs that were originally marketed prior to 1938 may theoretically qualify for a status that relieves the manufacture from the requirement of new drug approval. What is this status called?

a. Grandmother.

b. Grandfather.
c. Grandson.
d. Granddaughter.

5. In what year was the FDCA amendment passed that led to the Drug Efficacy Study Implementation?

a. 1951.
b. 1962.
c. 1984.
d. 1998.

6. The FDA has prioritized its enforcement actions against unapproved drugs. What drugs have the highest priority under this policy?

a. Drugs that lack evidence of effectiveness.
b. Health fraud drugs.
c. Drugs with potential safety risks.
d. Drugs that present direct challenges to new drug approval.

7. In what year was levothyroxine sodium initially marketed?

a. 1938.
b. 1955.
c. 1962.
d. 1997.

8. What unapproved formulation of vitamin E resulted in the death of approximately 40 premature infants, and the conviction of a pharmaceutical executive?

a. Intravenous.
b. Oral liquid.
c. Oral solid.
d. Intramuscular.

9. The Abigail Alliance lawsuit led to the passage of legislation intended to provide patient access to unapproved drugs. What is this legislation called?

a. Expanded Access.
b. Fast Track Approval.
c. Right to Try.
d. Expedited Review.

10. In the cocaine hydrochloride case, a study was cited in which a certain percent of pharmacists thought that all drugs they dispensed were FDA approved. What percent of pharmacists thought that all drugs they dispensed were FDA approved?

a. 51%.
b. 71%.
c. 91%.
d. 100%.