

The Formulary Process from a Risk Management Perspective

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During their evolution over the past 6 decades, hospital formularies have become more than a list of drugs that an institution keeps in stock. Today, an agent under formulary consideration must be examined not only in light of its relative efficacy, safety, and acquisition cost, but consideration must also be given to the potential indirect costs that accompany its use. Federal regulations have, for some drugs, added layers of administrative actions that must be followed to ensure their appropriate use. Examples of this are risk evaluation and mitigation strategies (REMS) and duties that may be implied or expressly addressed in the black-box warnings associated with some classes of agents and, in isolated instances, specific drugs within a given class. Regulatory interpretation of these programs and warnings has often led to the expectation that the institution providing the agent will implement effective protocols and procedures to minimize the risk of adverse events to a patient in addition to or in accordance with required programs such as REMS. The consequences for failing to meet this expectation can lead to regulatory sanctions; the potential also exists for liability exposure. Risk management principles apply to all levels of the decision-making process for evaluating a new agent for formulary inclusion or when reevaluating an agent's formulary status. Pharmacists play an important role in mitigating these risks by carefully evaluating every agent from a broader perspective.

Key Words: formulary, pharmacy and therapeutics committee, P&T, risk evaluation and mitigation strategies, REMS, pharmacy regulation, pharmacy risk management.

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The concept of hospital formularies has evolved from simple drug lists in the 1940s to formulary systems that became a condition of participation for the Medicare program in 1965.¹ In 1982, the Tax Equity and Fiscal Responsibility

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Act (TEFRA) was passed by Congress and signed into law by President Ronald Reagan. Among the various aspects of TEFRA was a prospective payment system in which reimbursement for the care of hospitalized Medicare patients would be fixed based on several factors including discharge diagnoses. The cost of pharmaceuticals would be included in the total reimbursement that the hospital would receive rather than as a stand-alone cost. This subsequently turned the pharmaceutical services component of hospitals from profit centers to cost centers; pharmacy managers had to view their products and services in terms of cost-effectiveness, cost-benefit, and safety, rather than as a commodity whose costs could simply be passed along to the government.

Private insurance carriers soon followed in changing their reimbursement practices that used a fee-for-service or fee-for-product model to a per diem model in which pharmaceutical costs were included in the total reimbursement. Implicit in these new paradigms was effective financial management of the formulary from a cost perspective and effective risk management of the formulary from a clinical and safety perspective. Pharmacists must always be concerned with the latter, although most would agree that when pharmaceuticals are managed in a clinically appropriate and safe manner, the issue of acquisition cost becomes a secondary concern.

Risk management is classically defined as the identification, measurement, control, and minimization of safety, legal, liability, and regulatory issues. Systems must be developed to reduce the occurrence of preventable error and lessen the consequences of nonpreventable error. Risk management issues specifically associated with the formulary process include, but are not limited to, the following: making formulary decisions based solely on the acquisition cost of a particular drug; failure to put systems in place to ensure safe and effective use of potentially problematic formulary drugs (e.g., drugs with black-box warnings) and drugs that require specialized protocols; failure to restrict the use of problematic drugs to certain subspecialties or to certain areas of the hospital; and failure to monitor use of problematic drugs on an ongoing basis once the drug is given formulary status. Unfortunately, little or no case law exists regarding the logistics of hospital formularies; thus, too often, risk management is empiric and occurs only after regulatory issues arise or a therapeutic mishap has occurred.

Financial Decisions and the Formulary Process

One area of potential concern to stakeholders in the formulary process is the issue of cost minimization. Although no case law specifically addresses the financial decisions that underlie the formulary process, the case entitled *Wickliffe versus State of California* provides some guidance to hospital pharmacy directors, risk managers, and pharmacy and therapeutics committee members on how to balance costs and benefits with respect to formulary decisions.² In the *Wickliffe* case, the California Medicaid Program, known as Medi-Cal, made a utilization review decision to extend a patient's hospital stay for 4 days despite the fact that the physician initially

requested an 8-day extension. Nine days after discharge, the patient experienced serious complications and required readmission. The patient subsequently sued Medi-Cal. A trial court jury found in favor of the patient, but the verdict was reversed on appeal. It was the opinion of the court that the physician, and not Medi-Cal, was responsible, that cost concerns should never affect a practitioner's judgment when delivering medically necessary health care, and that the physician should have more vigorously challenged Medi-Cal's utilization review decision on clinical grounds.

One caveat that may be taken from the decision in this case, specifically with regard to hospital formularies, is that it is acceptable to factor cost containment as part of the formulary process, but that cost containment must be balanced against an unbiased review of the literature to determine a drug's clinical effectiveness and safety, or lack thereof. It has been suggested that the formulary inclusion process be bifurcated into economic issues and clinical issues and that any discussion, written reports, or committee minutes reflect this bifurcation.³ It is further recommended that hospitals have reasonable procedures in place that allow physicians to prescribe drugs that are not on the formulary when clinical situations indicate such a need and that these procedures are in writing and are well communicated to the medical staff. The latter is especially important given that there may be some legal basis to the idea that the more rigid the formulary system is, the more likely that corporate negligence could be applied if there were a therapeutic mishap.³

Drugs with Black-Box Warnings

The Federal Food, Drug, and Cosmetic Act of 1938 requires drugs to be safe for their intended uses. The 1962 Kefauver-Harris amendment to this act subsequently required that drug manufacturers show that their products were effective as well as safe and to report adverse events to the United States Food and Drug Administration (FDA). Furthermore, it required that information provided to physicians (e.g., package inserts) disclose both the benefits and risks of their products. Thus, the *Code of Federal Regulations* Title 21 Section 201.57(e) [21 CFR §201.57(e)] requires that drug labeling include information on serious adverse reactions, potential safety hazards, limitations on use, and steps that should be taken if adverse reactions occur. In addition, "...special problems, particularly those that may

lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displayed box. The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data...⁴ These types of warnings, commonly known as black-box warnings because they are enclosed in a black border, deal primarily with avoidance of the drug in high-risk patients, dosing and/or drug interaction caveats, or need for special training or use in a special setting.⁵ It is expected that clinicians perceive black-box warnings as being associated with the highest level of risk and prescribe accordingly.⁶

Usually, the need for black-box warnings emerges during postmarketing surveillance. Presently, 438 drugs or chemical entities used to treat diseases carry FDA-mandated black-box warnings.⁷ Between 1975 and 1999, the FDA approved 548 new drugs: 45 (8%) remain on the market with at least one black-box warning and 11 (2%) were withdrawn after a warning was mandated. The probability of a new drug requiring a black-box warning or being withdrawn from the market is 20% during its first 25 years on the market.⁸

Because serious drug-related adverse events are more often a function of the pharmacologic class of drug rather than specific drugs residing within that class, with few exceptions, black-box warnings are typically applied in a classwise fashion. Examples of drug classes that carry these warnings are fluoroquinolone antibiotics (tendinitis and tendon rupture), nonsteroidal antiinflammatory agents (cardiovascular risk, gastrointestinal risk), long-acting narcotic analgesics (abuse potential, use in opiate-naïve patients), thiazolidinedione antidiabetic agents (congestive heart failure), aminoglycosides (neurotoxicity, nephrotoxicity), antiretrovirals (hepatic toxicity), antineoplastics (bone marrow suppression), atypical neuroleptics (use in dementia), central nervous system stimulants (abuse potential), gadolinium-based contrast agents (nephrogenic systemic fibrosis), low-molecular-weight heparins and heparinoids (spinal and epidural hematomas), inhalable long-acting β -agonists (risk of asthma-related death), anabolic steroids (hepatic toxicity, lipid disorders), antidepressants (suicidal ideation), and loop diuretics (electrolyte disorders).⁷

The *Code of Federal Regulations* Title 42 Section 482.25 [42 CFR §482.25] states that "...in order to provide patient safety, drugs and biologicals must be controlled and distributed in accordance with applicable standards of practice, consistent

with Federal and State law..."¹ It also states that "...the hospital must have pharmaceutical services that meet the needs of the patients. The medical staff is responsible for developing policies and procedures that minimize drug errors. This function may be delegated to the hospital's organized pharmaceutical service..."¹

Within the context of drug distribution, use, and monitoring in the inpatient setting, regulatory agencies (especially those responsible for licensing and recertifying inpatient facilities) often interpret this section to mean that with respect to high-risk drugs (i.e., drugs with black-box warnings), pharmacy departments, in consultation with appropriate hospital staff and committees, must develop and implement guidelines, protocols, policies, procedures, and systems that guarantee patient safety. These may include checklists, dose limits, preprinted orders, special packaging, special labeling, double checks, and specific written guidelines. In addition, the facility may be expected to incorporate external alerts or recommendations from well-respected national organizations (e.g., the FDA, Agency for Health Care Research and Quality, Institution for Safe Medication Practices, and the Joint Commission) into these systems. These activities may be part of the formulary inclusion process.

Recently, regulators in some states have created an additional expectation that drugs with black-box warnings require additional processes and systems before dispensing and use to minimize risks discussed in the warning. For example, the black-box warning for the antiemetic droperidol states that "...the drug should be reserved for use in the treatment of patients who fail to show an acceptable response to other adequate treatments...and that patients about to receive droperidol should first undergo a 12-lead electrocardiogram (ECG). Those patients with an ECG-detected prolonged Q-T interval should not receive the drug..."⁹ In California, three medical institutions that promoted the use of droperidol as a first-line drug on preprinted order forms did not adhere strictly to the warning and received immediate jeopardy citations with accompanying fines.¹⁰ Similarly, three other institutions in California also received immediate jeopardy citations for using transdermal fentanyl patches in a manner inconsistent with the black-box warning with respect to dosage titration, a contraindication in patients with acute pain, and a contraindication in opiate-intolerant patients. In both situations, pharmacists, physicians, and nurses were not aware of the black-box warning;

thus, there were no written policies or procedures in place to mitigate the inherent dangers of the drugs.¹⁰

Because additional time- and process-intensive surveillance may be required before dispensing a drug with a black-box warning, an unintended consequence is that clinicians may use these drugs reluctantly, or pharmacy and therapeutics committee members may refrain from placing them on formularies entirely.

To evaluate the effect of black-box warnings on physicians' prescribing practices, one group of authors conducted a survey of the members of the Society of Ambulatory Anesthesia. These physicians were asked about their use of droperidol, both before and after the FDA mandated a black-box warning due to potential QT-interval prolongation and subsequent ventricular tachyarrhythmias, to prevent or treat postoperative nausea and vomiting.¹¹ Of the 295 respondents to the survey, 92% did not believe the black-box warning was justified. Despite this, the percentage of physicians who prescribed droperidol as a first-line agent to prevent and treat postoperative nausea and vomiting decreased from 47% before the warning to 5% afterward, and from 38% to 8%, respectively. Conversely, the use of serotonin-receptor antagonists, dexamethasone, and combinations of agents that did not include droperidol nor carry black-box warnings, increased significantly.

Another risk management issue is that some black-box warnings include one or more prerequisites for prescribing the drugs. For example, clinicians must determine a patient's pregnancy status before prescribing numerous drugs, must perform an ECG before prescribing droperidol, and are supposed to determine opiate tolerance in the case of transdermal fentanyl. Because these prerequisites create a "duty" on the part of the prescriber and the institution, any breach of that duty, combined with proximate harm to the patient, is, by definition, negligence and may expose the prescriber and institution to significant liability.

Drugs Requiring Risk Evaluation and Mitigation Strategies

In recognition of the fact that certain drugs may be unsafe when used without certain caveats or restrictions, the Food and Drug Amendments Act (FDAAA) was signed into law on September 27, 2007.¹² One of the most significant aspects of the FDAAA was the establishment of formalized

risk evaluation and mitigation strategies (REMS) that serve to guide the safe prescribing, dispensing, administration, and monitoring of potentially problematic drugs. Some features of REMS resemble black-box warnings whereas others invoke the actual black-box warning as part of a wider risk management strategy. These strategies may include some or all of the following: specialty certification, training, or experience as a prerequisite to prescribe a given drug; specialty certification of the pharmacy or health care setting where the drug is dispensed and/or used; restrictions on the use of the drug to certain health care settings (e.g., hospitals); dispensing to patients only after evidence of safe use conditions (e.g., normal laboratory test results); specific monitoring requirements; and enrollment of patient in drug-specific registries. In addition, medication guides and package inserts are almost always part of the strategy. Effective March 25, 2008, all drug manufacturers with products deemed by the FDA to have safety concerns were required to develop REMS. As of late 2009, 81 drugs were deemed by the FDA to have approved REMS in place. In addition, all new drugs will require REMS if the FDA determines that this strategy is necessary to ensure that the benefits of any given product outweigh its risks. Although most drugs designated by the FDA for REMS are used almost exclusively in the outpatient setting, some of these drugs may be used in both inpatient and outpatient settings. As in the case of drugs with black-box warnings, it is important that when placing drugs that required REMS on hospital formularies, the duties of the physician, pharmacist, and institution are well defined as part of the formulary inclusion process and all necessary systems and processes are rigidly carried out by the institution.

Off-Label Use of Formulary Drugs

It is an accepted part of medicine that FDA-approved drugs are often used for other indications, and off-label use should always be contemplated when considering a drug for formulary inclusion. This is especially important given the fine line between deriving benefit from a drug whose safety and efficacy are supported in the literature and the potential for human experimentation. To protect the institution, it may be necessary to establish protocols guiding the use of an FDA-approved drug for a non-FDA-approved indication based on scientific evidence.¹³ Literature supporting off-label use should always be available for review in the pharmacy, and this

literature should be comprehensive and free of pharmaceutical industry bias, just in case a drug's off-label use is challenged either by payers or the legal system.

Guided-Use Strategies and the Formulary Process

One method used to improve therapeutic outcomes while mitigating the hospital's exposure to liability is the implementation of guided-use strategies when considering a drug for formulary inclusion.¹³ An example is when pharmacists obtain prior approval from a specialist (e.g., infectious disease, cardiology) before dispensing drugs that are prone to serious adverse reactions or drugs with a potential for misuse (e.g., antimicrobials that should only be used in the presence of documented antimicrobial resistance). In some cases, a formal consultation with the specialist may be necessary to predicate the use of a given drug. Another method is to restrict the use of an agent based on training (e.g., oncology, dermatology, anesthesiology) or a certain area of the hospital (e.g., intensive care unit, telemetry unit, operating room).

Some drugs may also require specialized treatment protocols before dispensing and administration. For example, in the clinical program for dofetilide, patients must be hospitalized and monitored for a minimum of 3 days while treatment is initiated.¹⁴ Patients are to be withdrawn from previous antiarrhythmic therapy for a minimum of three half-lives of the antiarrhythmic and anticoagulated as indicated. The patient's creatinine clearance is calculated and, if above a certain threshold, a pharmacist dispenses the required dosage of dofetilide. Subsequent dosages are based on the corrected QT interval (QTc) recorded on the patient's ECG. The patient is then discharged with 14 capsules of the prescribed dosage.

Another program restricts the use of alvimopan,¹⁵ a peripherally acting μ -opioid-receptor antagonist used to accelerate the time to upper and lower gastrointestinal motility after bowel resection with anastomosis.¹⁶ In this program, alvimopan may be administered only in a hospital that is enrolled in the program and has systems, order sets, protocols, and any other necessary measures in place to limit the use to no more than 15 doses. The program further requires that the drug not be used on an outpatient basis nor can the patient be transferred to any hospital not registered with the program.¹⁵

In both the dofetilide and alvimopan programs, the pharmacy department acts as the de facto gatekeeper. Placing either of these drugs on a formulary without the ability or desire to enforce these controls and restrictions constitutes a serious breach in the standard of care and leaves the hospital vulnerable to legal action should a mishap occur. Some future drugs will undoubtedly require the same types of controls and restrictions.

Role of Clinical Pharmacy Services

Clinical pharmacists must be involved in every step of the formulary process. Their involvement begins with the introduction of the drugs to the pharmacy and therapeutics committee for possible inclusion. This requires meticulous unbiased research regarding acquisition cost, cost versus therapeutic outcome (cost-effectiveness), cost versus actual money saved when a formulary drug is used (cost-benefit), and safety. Their research should always serve as a counterbalance to any representations made by the manufacturers of these drugs so as to make the process clinically based rather than financially based, thus avoiding the pitfalls exposed in the Wickline case.

Once a drug is included in the formulary, clinical pharmacists must ensure that all necessary steps are adhered to when a potentially problematic drug is dispensed (i.e., drugs with black-box warnings, drugs with REMS, and drugs requiring guided-use strategies). In addition, pharmacists must monitor the ongoing use of these drugs to make sure that everything has been done to guarantee their safety and effectiveness and report back findings to the pharmacy and therapeutics committee as necessary.

Another method that clinical pharmacists may use to mitigate the potential risk of formulary decisions is performing a modified failure mode and effect analysis before adding any drug to the formulary.¹⁷ In this analysis, a drug receives one numeric point for every potential problem identified during the evaluation process. Based on the total point score, drugs are then placed in three different categories that range from simple professional education required before formulary inclusion to establishing the need for protocols, specialist-prescriptive authority, enhanced education, and specific drug safety processes before dispensing.

Conclusion

To mitigate risk with respect to the formulary process, considerable thought must be given to

both the formulary inclusion process and how the drugs are to be used once placed on the formulary. The former is facilitated by using a fair inclusion process, having an appropriate array of agents for physicians to choose from, and performing rigorous pharmacoeconomic versus safety analyses whenever possible. Decisions should never be made strictly for financial reasons. Use of formulary drugs may require specialized dispensing policies and procedures for drugs with black-box warnings, REMS, and guided-use strategies. These policies and procedures are inviolate and serve to insulate both the prescriber and the institution from unnecessary liability. Furthermore, the entire formulary process must be owned by both the medical staff (through the pharmacy and therapeutics committee) and the pharmacy department, neither of which can function apart from the other.

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