Practice Advisory on Unapproved Medications

Prescription and over-the-counter (OTC) drug manufacturers are required to complete the Food and Drug Administration's (FDA) approval process prior to marketing; however, for various reasons, there are currently medications marketed, prescribed and dispensed without this approval. The FDA estimates there are several thousand prescription and OTC drugs marketed illegally without FDA approval, accounting for two percent of all prescriptions filled, or about 72 million prescriptions a year.[1] Although the percentage of unapproved medications is small compared to those with approval, there are concerns about the safety, efficacy, quality and labeling of unapproved medications.

In 1906, the Pure Food and Drug Act required appropriate labeling of medications. Not until 1938 did safety become regulated when the Federal Food, Drug and Cosmetic Act (FFDCA) of 1938 required manufacturers to prove a new drug was safe. The FFDCA was amended in 1962 to require manufacturers to also demonstrate the efficacy of medications prior to their being marketed to the public. Medications marketed between 1938 and 1962 had to be re-evaluated for efficacy. This process is called the Drug Efficacy Study Implementation Review (DESI). The medications subject to this process are known as DESI medications. Some medications that gained approval from FDA prior to the 1938 and 1962 amendments are known as "grandfathered" medications. These medications have not changed in composition since that time and are exempt from the FDA approval process.[2] DESI and grandfathered medications make up a very small portion of the unapproved medications currently marketed. In addition, the majority of unapproved medications on the market have no current study or evaluation underway.[3]

All medications are identified with an individual National Drug Code (NDC). The NDC number is divided into three different sections. All pharmaceutical manufacturers must register their company with the FDA as a labeler and are assigned the first four or five digit section of the code. These four or five digits make up the first section of the individual 10-digit code, known as the NDC number, assigned to each medication. For example, every medication produced by a specific company will start with 12345-, followed by six different digits for the specific drug.

Health care professionals may assume that an NDC number implies FDA approval. However, this is not the case. Having an NDC number assigned to a specific drug does not indicate it has received FDA approval. Although pharmaceutical manufacturers are required to list product NDC numbers with the FDA, the NDC number does not mean the drug has gone through the FDA approval process. In addition, although manufacturers are required to register the 10-digit NDC numbers with the FDA, not all comply.

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[1] Ricardo Alonso-Zaldivar and Frank Bass. "AP Impact: Government Pays for Risky Unapproved Drugs," *San Francisco Chronicle*. November 24, 2008. http://www.sfgate.com/cgi-bin/article.cgi?f=/n/a/2008/11/23/national/w053222S92.DTL&type=printable (accessed August 12, 2009).

[2] Marketed Unapproved Drugs Compliance Policy Guide. Guidance for FDA Staff and Industry, Sec. 440.100, Marketed New Drugs Without Approved NDAs or ANDAs. The Food and Drug Administration, Center for Drug Evaluation and Research. June 2006. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070290.pdf (accessed on August 17, 2009).

[3] Ibid

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There are various examples of how unapproved medications became available on the market. For example, one manufacturer might have approval for the drug, but other manufacturers marketing the same product might not have approval, and therefore, are marketing the drug illegally. In another example, one manufacturer may be marketing an FDA-approved medication which is a combination of ingredients; another manufacturer might be marketing only a single ingredient from the approved combination. Additionally, some manufacturers claim their medications are "grandfathered in," but in most cases the term "grandfathered in" is being misused.[4]

Unapproved medications are being prescribed and dispensed on a daily basis, presenting a potentially significant public health issue. Most health care professionals are unaware that medications that have not undergone the FDA approval process may be unsafe, ineffective, lack quality standards or be labeled incorrectly. In addition, because these products have not been subjected to FDA scrutiny, their manufacturers do not have to report adverse events and product complications to the FDA, nor do they undergo post-marketing surveillance.[5]

Few health care professionals, patients and organizations involved in the distribution, sales or payment for medications are aware of this issue. No comprehensive list of currently marketed unapproved medication names and NDCs exists. The lack of information may be due to the multiple manufacturers marketing one drug. Some medications are marketed by more than 20 different manufacturers. It is difficult for the FDA to develop a comprehensive list due to the many different manufacturers and ingredients in unapproved medications.[6]

The FDA has removed a number of unapproved drug products from the market. Some products have been removed after numerous reports of adverse events. For example, in 2006 there were 21 reports of children under the age of two who died after taking unapproved cold and allergy medications containing carbinoxamine. The FDA banned all products that contained carbinoxamine in combination with other cold medications in 2007.[7] The FDA also banned injectable colchicine for gout in 2008 after 23 deaths were reported.

The FDA has focused its efforts on removing classes of unapproved drugs or on firms marketing these drugs. The FDA enforcement actions to date can be reviewed on the FDA website at www.fda.gov, within the Drugs tab follow the Guidance, Compliance, & Regulatory Information link to "Unapproved Drugs: Enforcement Actions."[8]

The issue presents a challenging situation for managed care organizations (MCOs). By analyzing federal data, the *Associated Press* discovered that from 2004 to 2007, Medicaid paid almost $198 million for 100 identified prescription drugs products that were not FDA-approved.[9] MCOs need to determine whether they will pay for medications that are unapproved. According to the Centers for Medicare & Medicaid Services' (CMS') Medicare Part D 2010 Call Letter, which sets requirements for Medicare prescription drug plan sponsors, beginning January 1, 2010, CMS will establish prescription drug encounter (PDE) edits to reject NDCs for drugs that are not appropriately listed with the FDA. In the Call Letter, CMS notes that determination of whether a drug meets the definition of a "covered drug" cannot be made readily unless drugs are listed with the FDA as required.[10] To accomplish this, CMS has worked in conjunction with the FDA to develop a "Non-Matched NDC List."

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[4] "The FDA Takes Action Against Unapproved Drugs." For Consumers: Consumer Updates, 1 Jan 2007. Food and Drug Administration.
[5] Ibid
[6] "Govt pays for risky unapproved drugs." 20 May 2009. Blue Cross Blue Shield Association. Available at: http://www.bcbs.com/news/national/ap-impact-govt-pays-for-risky-unapproved-drugs.html (accessed August 17, 2009).
[7] "The FDA Takes Action Against Unapproved Medications."
[8] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/SelectedEnforcementActionsonUnapprovedDrugs/default.htm (accessed August 24, 2009)
[9] Alonso-Zaldivar and Bass.
[10] Centers for Medicare and Medicaid Services, Medicare Part D 2010 Call Letter, issued March 30, 2009. http://www.cms.hhs.gov/PrescriptionDrugCovContra/Downloads/2010CallLetter.pdf (accessed August 12, 2009)

Medicare Part D sponsors are ultimately responsible for making medication coverage determinations based upon statutory and regulatory requirements and are not to cover medications not appropriately listed with the FDA.

To view information on FDA medication status and whether the medication is approved or unapproved, go to:

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/SelectedEnforcementActionsonUnapprovedDrugs/ucm119742.htm

Health care professionals within managed care pharmacy should:

1. Understand there are currently unapproved prescription and OTC medications being marketed, distributed, prescribed, dispensed and reimbursed;

2. Understand there is no comprehensive listing of the unapproved medications currently available in the marketplace. The FDA recommends health care professionals use the Approved Drug Products with Therapeutic Equivalents Evaluation (commonly known as the Orange Book), National Drug Code (NDC) Directory, or Drugs@FDA website to determine if a drug product is FDA approved;

3. Determine whether the FDA approval status of drug products should affect the coverage and reimbursement for these medications. MCOs should determine the best way to efficiently evaluate this issue based on the individual organization's pharmacy benefits structure. An MCO should seek input from its pharmacy and therapeutics (P&T) committee or equivalent body prior to making administrative coverage decisions. Additionally, health plans may need to seek support from their prescription benefit management company (PBM) prior to making coverage determination;

4. Be prepared to answer questions from patients/members regarding unapproved drugs. If MCOs decide not to cover an unapproved medication, then the MCO should be prepared to evaluate the market presence of FDA approved alternative(s) and to address member disruptions. MCOs should identify members taking unapproved medications and carefully communicate that the medications are not approved by the FDA; and

5. Educate health care providers (especially prescribers) and pharmacy networks on the issue. Many health care providers and pharmacies may not be aware of the issue but should be prepared to address questions from patients. MCOs can identify members taking unapproved drugs and convey that information to providers and pharmacies.