

ASHP Statement on the Use of Medications for Unlabeled Uses

The freedom and responsibility to make drug therapy decisions that are consistent with patient-care needs is a fundamental precept supported by ASHP. This activity is a professional duty of pharmacists not limited by language in Food and Drug Administration (FDA)-approved product labeling.

The prescribing, dispensing, and administration of FDA-approved drugs for uses, treatment regimens, or patient populations that are not reflected in FDA-approved product labeling often represent a therapeutic approach that has been extensively studied and reported in medical literature. Such uses are *not* indicative of inappropriate usage. Health-care professionals should appreciate the critical need for freedom in making drug therapy decisions and understand the implications of unlabeled uses. ASHP supports third-party reimbursement for FDA-approved drug products appropriately prescribed for unlabeled uses.

Definition of Unlabeled Use

The FDA approves drug products for marketing in the United States. Such a product approved for marketing is often termed an “FDA-approved drug.” FDA also approves each drug product’s labeling (container label, package insert, and certain advertising); the term “FDA-approved labeling” applies here. Drug uses that are not included in the indications or dosage regimens listed in the FDA-approved labeling are defined as “unlabeled uses.” For purposes of this document, unlabeled use includes the use of a drug product in (1) doses, (2) patient populations, (3) indications, or (4) routes of administration that are not reflected in FDA-approved product labeling.

It is important to recognize that FDA cannot approve or disapprove physician prescribing practices of legally marketed drugs. FDA does regulate what manufacturers may recommend about uses in their products’ labeling and what manufacturers can include in advertising and promotion.

The sometimes-used term “unapproved use” is a misnomer, implying that FDA regulates prescribing and dispensing activities. This term should be avoided.¹ Other terminology that is sometimes used to describe unlabeled use includes “off-label use,” “out-of-label use,” and “usage outside of labeling.”

According to FDA, unlabeled use encompasses a range of situations that extend from inadequate to carefully conceived investigations, from hazardous to salutary uses, and from infrequent to widespread medical practice. Accepted medical practice often involves drug use that is not reflected in FDA-approved drug-product labeling.²

Health-Care Issues Related to Unlabeled Use

Access to Drug Therapies. The prescribing and dispensing of drugs for unlabeled uses are increasing.^{3,4} In many clinical situations, unlabeled use represents the most appropriate therapy for patients. Failure to recognize this or, more importantly, regarding such use as “unapproved” or “experimental” may restrict access to necessary drug therapies.

Lack of Practice Standards. Well-defined medical practice standards that differentiate between experimental therapies and established practice will probably always be somewhat lacking, owing to the advancement of medical science and the dynamic nature of medical practice. Standards of practice for certain drug therapies, particularly biotechnologically produced drugs, cancer chemotherapy, and AIDS treatments, are continually evolving. The dynamic nature of these drug therapies makes it difficult for professional societies to review scientific data expediently and to develop standards that remain absolutely current.

Failure of Package Insert and FDA-Approved Labeling to Reflect Current Practice. For FDA-approved product labeling to be modified, scientific data must be submitted by a product’s manufacturer to FDA to support any additional indication(s) and dosage regimen(s). Once they are submitted, FDA must review the data and make a decision to permit alteration of the package insert.

Knowing that unlabeled uses are permitted, and knowing that the accumulation and submission of scientific data to FDA to modify labeling is a time-consuming and often expensive process, some pharmaceutical manufacturers elect not to pursue labeling changes. Therefore, a product’s labeling sometimes fails to represent the most current therapeutic information for a drug, and situations naturally occur when it is appropriate to prescribe drugs for unlabeled uses.

Pharmacist’s Role

ASHP believes that pharmacists in organized health-care settings bear a significant responsibility for ensuring optimal outcomes from all drug therapy. With respect to unlabeled uses, the role of the pharmacist should be to

1. Fulfill the roles of patient advocate and drug information specialist.
2. Develop policies and procedures for evaluating drug orders (prescriptions) and dispensing drugs for unlabeled uses in their own work settings. Such policies and procedures might address the documentation of scientific support, adherence to accepted medical practice standards, or a description of medical necessity.
3. Develop proactive approaches to promote informed decisionmaking by third-party payers for health-care services.

Role of Drug Information Compendia

The Medicare Catastrophic Coverage Act of 1988 (now repealed) included the statements that “in carrying out the legislation, the Secretary [of Health and Human Services] shall establish standards for drug coverage. In establishing such standards, which are based on accepted medical practice, the Secretary shall incorporate standards from such current authoritative compendia as the Secretary may select.”⁵ Specific compendia recommended were the *AHFS Drug Information*,

AMA Drug Evaluations, and USP Dispensing Information, Volume I. Despite the repeal of the Act, some third-party payers have adopted guidelines that endorse these three compendia as authoritative information sources with respect to unlabeled uses for drug products.

Positions on Unlabeled Use

FDA Position. A statement entitled “Use of Approved Drugs for Unlabeled Indications” was published in the *FDA Drug Bulletin* in April 1982 to address the issues of appropriateness and legality of prescribing approved drugs for uses not included in FDA’s approved labeling. This statement included the following:

The Food, Drug and Cosmetic Act does not limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. Such “unapproved” or, more precisely, “unlabeled” uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that have been extensively reported in medical literature.¹

Other Organizations. Other organizations that have published positions on the issue of unlabeled uses of drug products are the Health Care Financing Administration (HCFA),⁶ the Blue Cross and Blue Shield Association of America (BC/BS),⁷ and the Health Insurance Association of America (HIAA).⁸

The American Medical Association, American Society of Clinical Oncology, Association of American Cancer Institutes, Association of Community Cancer Centers, Candlelighters Childhood Cancer Foundation, Memorial Sloan Kettering Cancer Center, National Cancer Institute, and the National Institute of Allergy and Infectious Diseases jointly developed a consensus statement and recommendations regarding use and reimbursement of unlabeled uses of drug products.⁹

These statements are consistent with the ASHP position.

Reimbursement Issues

As a cost-containment measure, most third-party payers exclude coverage for experimental therapies. Drug therapy coverage decisions are complicated, because often it is difficult to differentiate among an accepted standard of practice, an evolving standard of practice, and investigational therapies. Data demonstrating medical necessity and improved patient outcome are often difficult to retrieve. Consequently, insurance carriers and managed care providers

have sometimes elected to cover only those indications included in FDA-approved drug-product labeling and have frequently denied coverage for unlabeled uses of drug products.

ASHP believes that such coverage denials restrict patients from receiving medically necessary therapies that represent the best available treatment options. A growing number of insurance carriers are following the BC/BS and HIAA guidelines that encourage the use of the three authoritative drug compendia, peer-reviewed literature, and consultation with experts in research and clinical practice to make specific coverage decisions. ASHP supports informed decisionmaking that promotes third-party reimbursement for FDA-approved drug products appropriately prescribed for unlabeled uses.

References

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