# "Off-Label" Indications for Oncology Drug Use and Drug Compendia: History and Current Status

Amid oncologists' continuing concerns over Medicare coverage of new uses of anticancer medications, one of the authoritative drug compendia is undergoing administrative and editorial changes, and a new oncology drug compendium has been partially released.

*Michael Soares, RPh*

Medicare must cover off-label uses of anticancer chemotherapeutic regimens if they are supported by a citation in at least one of the following compendia: *American Hospital Formulary Service Drug Information* (*AHFS DI*), *United States Pharmacopoeia Drug Information* (*USP DI*) or *American Medical Association Drug Evaluations*.[3] The latter was merged into *USP DI* in 1996 and is now available only under that title.[3]

In this article, the *Journal of Oncology Practice* takes an in-depth look at the current state of affairs of the drug compendia and the processes for how they list new drug indications. Also included is the history of Medicare's coverage of drug uses that are not in the U.S. Food and Drug Administration (FDA) drug labeling—the so-called "off-label" uses.

## What's New

The National Comprehensive Cancer Network (NCCN) is seeking recognition from the Centers for Medicare and Medicaid Services (CMS) for what will be the only oncology-specific drug compendium when completed, said William McGivney, PhD, chief executive officer of the NCCN.

There is broad support from patients, providers and others in the health care industry for CMS approval of the NCCN *Drugs & Biologics Compendium*, McGivney said. The National Patient Advocate Foundation and the Association of Community Cancer Centers are among the organizations that have urged CMS to include the new resource with the drug compendia that the U.S. federal government already recognizes as sources of drug utilization review and reimbursement for unlabeled uses.[1,2]

The NCCN, an alliance of 19 cancer centers, began releasing chapters of the *Drugs & Biologics Compendium* on its Web site on October 22, 2004. Chapters published as of June 2005 include colorectal and anal cancers, kidney and testicular cancers, acute myeloid and chronic myelogenous leukemias, and non–small-cell and small-cell lung cancers. The chapter on growth factors is due out in mid-July, and non-Hodgkin's lymphoma is scheduled for release in mid-August, according to McGivney. He expects they will have released information covering drugs for 90% of all cancer patients by the end of 2005. It will include all appropriate off-label uses, he said. Currently, the NCCN is making the compendium available online free of charge. Print copies are available on request.

The *Drugs & Biologics Compendium* is derived from the NCCN Clinical Practice Guidelines in Oncology. The organization continually updates its guidelines and disseminates updates within 8 weeks of a major new study, he said. "It's a rapid process, which is why I think the NCCN guidelines are so widely used, applied and recognized," McGivney said. "Our guidelines are up-to-date, are comprehensive and have an authoritative source."

## What's Changing?

In other compendium news, Thomson Micromedex, which acquired the content of the *USP DI* six years ago, has made changes since assuming management of the review process from USP in January 2005.

One major change was to speed the review process by setting deadlines for reviewers to make their conclusions, said Michael Soares, RPh, vice president of editorial for Thomson Micromedex, a provider of evidence-based medical information. "We saw a backlog of submissions waiting for review, and some new indications for drugs were being approved by the FDA before we were getting responses," he said.

The review process remains similar to the former USP review process but, according to Soares, is now faster. He said the goal is to complete the process within three months of submission of solid clinical evidence identifying new therapeutic uses. Breakthrough cancer therapies receive an expedited review process.

Thomson Micromedex is licensed to use the *USP DI* name until the end of 2007. It is working with Congress to change the compendium title because the federal laws about reimbursement state the names of the approved compendia. "We don't perceive that there will be any problem with this going forward," Soares said. They have not yet determined a new name.

In addition to these changes, the company next year will make the format of the *USP DI* more user friendly. Format

**Table 1. Comparison of drug compendia**

| | AHFS DI | NCCN Compendium | USP DI |
|---|---|---|---|
| Staff actively gather, review and summarize evidence-based drug information before suggesting course of action | Yes | Yes | Yes |
| Content reviewed by multiple experts in the field who recommend course of action | Yes, all content | Yes, from NCCN member institutions | Yes, for off-label indications or specialized subjects |
| Contains information on off-label uses | Yes | Yes | Yes |
| Format | Intranet, print | Web, print | Web, print, CD-ROM |
| Frequency of updates to subscribers | Monthly online | Continual, as NCCN updates its guidelines | Monthly online |
| Authorized by statute | Yes | No | Yes |
| Approved by CMS | Yes | Working toward approval | Yes |
| Intended users in addition to health care professionals who authorize treatment | Hospital pharmacists | Case managers, managed care decision-makers | Retail and hospital pharmacists, health plan administrators, pharmacy and medical school faculty and students |
| Web site | *www.ashp.org/ahfs* | *www.nccn.org* | *www.micromedex.com* |

AHFS, American Hospital Formulary Service; DI, Drug Information; NCCN, National Comprehensive Cancer Network; USP, United States Pharmacopoeia; and CMS, Centers for Medicare and Medicaid Services.

modifications that Soares mentioned include making the most frequently used sections easier to find and putting related sections together. He assured users that these alterations will not conflict with Medicare legislation or the quality of data.

## Off-Label Drug Uses

The primary purpose of the *USP DI* and the *AHFS DI* is not to provide off-label drug uses, but they have become respected sources of that information, said Joseph S. Bailes, MD, co-chair of the ASCO Government Relations Council and *JOP* Editorial Board member. For example, if an unlabeled drug indication is listed as an accepted use in volume 1 of the *USP DI*, *Drug Information for the HealthCare Professional*,[4] it gets Medicare reimbursement, "which is why ASCO members find it so important," Soares said.

Bailes praised the speed of updates and the peer review process for both the USP and AHFS compendia (Table 1).

Strengths of the *AHFS DI* are its long history of objective evaluation of drug claims and its attention to maintaining editorial independence, according to Editor Gerald McEvoy, PharmD (case study[5-8]). "We have a well-vetted editorial process," said McEvoy, assistant vice president of drug information for the American Society of Health-System Pharmacists, publisher of the *AHFS DI*.

The number of reviewers the *AHFS DI* staff uses depends on the drug and the disease it treats. Rather than using predetermined review panels, staff members submit content submissions to people they identify as most expert in an area, McEvoy explained.

The review process involves actively searching for new drug information and uses. "It's not a passive process," Dr. McEvoy said. "We don't wait for someone to submit something to us before we evaluate the off-label uses of a drug."

Both the *AHFS* compendium and the *USP DI* strive to keep information free of influence from third parties who promote their own interests, according to information from the organizations. Thomson Micromedex asks its reviewers about potential conflicts of interest. Reviewers must have less than $25,000 of stock in pharmaceutical companies, cannot hold a drug patent, and cannot have an employment relationship with a pharmaceutical company, among other restrictions, Soares said. The *USP DI*, like the *AHFS DI*, does not solicit content submissions from pharmaceutical companies, but does accept them and gives them the same rigorous review.

Clinical staff members conduct an internal review of all new content in the *USP DI*. An additional external review is performed for certain off-label indications for drug therapy and for specialized disease and toxicology subjects.[9] For each content set in the *USP DI*, Thomson Micromedex has advisory boards composed of practicing physicians and pharmacists who are board certified in an applicable specialty area or, for pharmacists, who have advanced training in that specialty area.

## Background

The policy that Medicare must cover an off-label use of a cancer drug if it is in the drug compendia, or is supported by peer-reviewed articles in certain journals outlined by Medicare, became law 12 years ago with the passage of the Rockefeller-Levin Bill. Named after its sponsors, Senator Jay Rockefeller (D-WV) and Representative Sander Levin (D-MI), the bill passed as part of the Omnibus Reconciliation Act of 1993 (OBRA 93).

ASCO played a major role in helping craft this bill, Bailes said. In 1992, Bailes and other society leaders brought their concerns to Rockefeller that patients were not getting access to effective anticancer drugs that were not on the FDA labeling. Some Medicare carriers did not cover these drugs, even though clinical studies had found them effective, he said.

The problem was, and still is, that pharmaceutical companies often may not submit new indications to the FDA for approval, in part because of the expense involved, but also because the time involved with pursuing and acquiring FDA approval can potentially delay access to therapies for certain malignancies.

"Our concern was that if the medical literature supported a drug's use, there needed to be a more efficient way [to decide Medicare coverage] than the FDA label, which is not intended to be a compendium," Bailes said. Because the drug compendia have a turnaround time from drug submission to publication in months, not years, and because the compendia conduct an independent review process, ASCO wanted them to be the deciding factor for reimbursement.

ASCO's legislative efforts to improve patient access to cancer drugs succeeded in 1993. "We spent a lot of time and energy to make sure people got access to cancer drugs who otherwise wouldn't have had them," Bailes said.

**Case study: Proposed off-label use of anastrozole**

**The following is an actual example of the review process that the *American Hospital Formulary Service Drug Information (AHFS DI)* typically uses.**

**1. Information Tracking and Gathering. During their ongoing review of the medical literature, *AHFS DI* staff read a January 2005 article on drugs for breast cancer in Treatment Guidelines from the Medical Letter.[5] The article indicates that the aromatase inhibitor anastrozole (Arimidex) is used in combination with luteinizing hormone-releasing hormone (LHRH) agonists for hormone receptor–positive breast cancer in premenopausal women. This unlabeled use in premenopausal women also is cited as a therapy of choice in the most recent issue of "Drugs of Choice for Cancer" in Treatment Guidelines from the Medical Letter.[6] Labeled uses, however, are in postmenopausal women. The AHFS team then gathers more information to find if scientific evidence supports this statement.**

**2. Evidence-Based Information Analysis. A search of the medical literature finds a single study with a small number of patients.[7] An ASCO practice guideline states, "Aromatase inhibitors [alone] are contraindicated in premenopausal women."[8]**

**3. Drug Information Synthesis. In completing an internal review, staff members look at the role of the drug and determine that there is limited evidence to support the statement in the Medical Letter.**

**4. Review. The data are sent to an external group of 15 independent reviewers, primarily physicians, who are prominent and well published in the field of breast cancer and have disclosed any potential conflict of interest in any of the drugs under study. The experts are to determine whether combination therapy with anastrozole and LHRH agonists is the therapy of choice for premenopausal women with hormone receptor–positive breast cancer. Their answer: "No, it is still being investigated and, therefore, its role remains to be established."**

**5. Finalization and Maintenance of Published Information. The proposed off-label use of anastrozole in combination with an LHRH agonist is described in the *AHFS DI* as an investigational use. They will continue to monitor the data on this therapy in premenopausal women. Further experience (such as additional clinical study, accumulation of more patients, and longer follow-up) will be needed to determine whether there has been any change in the status of this investigational use.**

**Source: Gerald McEvoy, PharmD, AHFS.**

Today 50% to 75% of all uses of drugs and biologics in cancer care in the United States are off-label, according to NCCN estimates. Off-label uses are even more prevalent in the pediatric population, Bailes pointed out.

Since enactment of OBRA 93, he believes that "Medicare has tried to ensure the Act has been correctly administered."

However, problems remain. Medicare carriers still have discretion as to whether to cover an off-label use of a cancer drug that is not listed in the approved drug compendia or in certain peer-reviewed journals. The carriers can set their own

criteria to determine if drugs are medically accepted in these situations.

ASCO believes that CMS should issue uniform guidelines if the drug compendia do not list an off-label drug use. "Our position is that Medicare carriers and private insurers should use data in the literature if a drug is not in the compendia," Bailes said.

## References


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