

## The Issue Is “Off-Evidence,” Not “Off-Label”

On March 30, 2006, a subcommittee of the Medicare Coverage Advisory Committee (MCAC) was convened by the Centers for Medicare and Medicaid Services (CMS) to evaluate the existing drug compendia and to identify the criteria that should guide compendia recommendations about the appropriate use of drugs. The meeting was called to specifically address issues regarding establishing coverage policies by CMS and its intermediaries and carriers for drugs and biologics in cancer care. The focus of these coverage decisions is an issue that has long been referred to as “use beyond FDA-approved labeling” or “off-label” use.

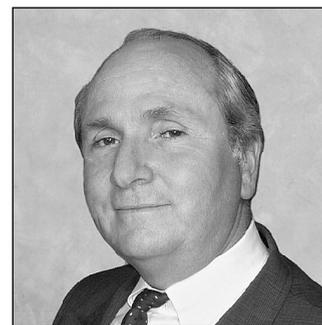
Approximately half of the use of drugs and biologic agents in cancer treatment is off-label. This fact should not be surprising in that drugs have historically been approved most often for a single indication and then used for others, not only in cancer care but also in other fields such as psychiatry. Further, in cancer treatment, one is dealing with both life-threatening diseases and fast-paced and abundant research advancement.

The U.S. Food and Drug Administration (FDA) has often stated the position that physicians, in the exercise of good clinical judgment, may prescribe drugs for indications other than those explicitly approved by the FDA. Indeed, the issue of “off-label use” attracted substantial attention only in the late 1980s, when insurance companies, as they morphed into managed care companies, began to scrutinize such use more closely. Increased scrutiny was further stimulated in 1987 when interferon was approved for the orphan indication of hairy cell leukemia. That this immunomodulatory agent with a high price tag would be used in a number of cancer diagnoses quickly became apparent. This situation caught the attention of insurers, who established coverage policies to describe the circumstances under which use of interferon would be reimbursed.

Interestingly, the term “off-label” seems to have assumed a negative connotation of perhaps surreptitiously trying to sneak the use of a drug through payors’ claims-editing processes. Instead, use beyond FDA-approved labeling appropriately proceeds from 2 principal concepts. First, as with other health care technologies such as devices and procedures, the uses of drugs and biologic agents evolve along a continuum of accumulating evidence about safety and effectiveness. Second, in the risk-benefit analysis of clinical decision making, the more serious and life-threatening the illness, the lesser degree of certitude about effectiveness and the greater risk of harm that physician, patient, and payor should be willing to accept.

The former concept is embodied in the substantial amount of phase IV (post-marketing) studies that are conducted by many companies to further evaluate uses not explicitly approved by the FDA. Also, the broad use of a drug after approval affords an opportunity to more precisely define its adverse effect profile and thus its therapeutic index.

Regarding the latter concept, it is important to note the guidance from CMS (Section 2049.4) to its carriers and intermediaries in their roles of establishing coverage policies for drugs and biologics on a locoregional basis. This guidance states that the following should be considered:



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“...the prevalence and history of disease when evaluating the adequacy of the number of subjects and the response rate. While a 20% response rate may be adequate for highly prevalent disease states, a lower rate may be adequate for rare diseases or highly unresponsive conditions.”

This guidance is often overlooked by, unknown to, or unused by those who make public policy decisions, including coverage. The CMS guidance information continues to discuss the appropriateness of study design in making coverage determinations. The recurring theme is that “the evidence,” evaluated in the context of severity of disease and available therapeutic options, should be the important basis for determining appropriate use whether in a clinical decision or in a coverage policy.

The primary question asked in the aforementioned MCAC meeting on compendia was:

*“How confident are you that the compendia adhere to evidence-based criteria and processes in making recommendations?”*

As an aside, we were interested to note that the MCAC subcommittee gave the *NCCN Drugs & Biologics Compendium* a positive ranking of 4.5 of 5.0, with the next closest score (of the other 5 compendia) being 3.58.

FDA approval is an evidentiary-based process that serves as the gateway for drugs and biologic agents to enter the marketplace. After a drug is approved, it should be the evaluation of accumulating evidence about its safety and effectiveness in a specific disease state that governs both clinical decisions and the coverage policies that will determine availability and access to these agents for patients. Indeed, this was the focus of the MCAC subcommittee and clearly it is the focus of CMS' guidance to carriers and intermediaries regarding establishing coverage policies on specific uses.

The bottom line is that decisions about the use, receipt, or coverage of a drug or biologic should be based on available evidence in the context of both the disease condition and individual patient characteristics. The singular, critical issue is whether such use is “on or off evidence” and not “on or off label.”