

## Recent Developments in Medicare Coverage of Off-Label Cancer Therapies

### Overview

It is estimated that half of the uses of anticancer drugs can be considered “off-label”<sup>1</sup>; this is to say, they are used for indications that are not included in the labeling approved by the US Food and Drug Administration. The Medicare program covers uses of off-label drugs used in anticancer regimens when those uses are supported by at least one of the designated drug compendia. If an off-label use is not included in one of these designated compendia, then Medicare contractors are permitted to rely on peer-reviewed research published in one of 26 specified journals. During the past 18 months, the Centers for Medicaid and Medicare Services (CMS) has implemented a number of important changes regarding use of the compendia and journals for determining medically accepted off-label indications.

### Designated Compendia

The 1993 Omnibus Budget Reconciliation Act mandated that Medicare provide coverage for off-label uses of drugs in anticancer chemotherapy regimens if those uses were supported by designated compendia. The statute listed American Medical Association *Drug Evaluations*, American Hospital Formulary Service *Drug Information* (AHFS DI), and the United States Pharmacopeia *Drug Information* compendia, and gave the Secretary of the US Department of Health and Human Services (DHHS) discretion in updating the list. Since the 1993 statute was passed, publication of both American Medical Association *Drug Evaluations* and United States Pharmacopeia *Drug Information* has ceased.

With concerns that patient access to off-label therapies might be limited as a result of a change in the compendia landscape, several groups petitioned CMS to recognize additional qualified compendia. In March 2007, CMS convened a meeting of its Medicare Evidence Development and Coverage Advisory Committee (MedCAC) to consider the use of compendia and make recommendations about “desirable characteristics” for compendia that are recognized for the purposes of Medicare coverage. The attributes identified by the MedCAC (and later adopted by CMS) are listed in Table 1.

In fall 2007, CMS revealed its intent to use the Secretary’s discretion in reviewing the list of compendia that are available as references for off-label coverage. The agency announced an annual process whereby applications for the inclusion of new compendia could be considered, and requests to sunset the use of recognized compendia could similarly be addressed. CMS adopted the list of desirable characteristics generated by MedCAC as the basis for analyzing each of the compendia for which requests were submitted.

### Working with Your Medicare Contractor on Off-Label Issues

Contact your state society and/or the oncology Carrier/Contractor Advisory Committee (CAC) representative for your state to find out if others have encountered problems securing coverage for a particular drug, and if so, how they have addressed this issue. A list of state society and CAC contacts can be found at [www.asco.org/cac](http://www.asco.org/cac).

At the conclusion of its first review cycle in 2008, CMS added three new compendia to the list of designated publications: *the National Comprehensive Cancer Network Drugs and Biologics Compendium*, *Thomson Micromedex DrugDex*, and *Clinical Pharmacology*. CMS did not accept the request to recognize Thomson Micromedex *DrugPoints*, which is a distillation of *DrugDex*. CMS took no action to change the status of the statutorily identified AHFS DI, and therefore AHFS DI continues to be recognized. Table 2 lists the four recognized compendia and the CMS summary of covered and noncovered uses.

**Table 1. Desirable Characteristics for Compendia Used As References for Off-Label Uses of Anticancer Drugs and Biologics<sup>2(p60)</sup>**

Extensive breadth of listings
Quick processing from application for inclusion to listing
Detailed description of the evidence reviewed for every individual listing
Use of pre-specified published criteria for weighing evidence
Use of prescribed published process for making recommendations
Publicly transparent process for evaluating therapies
Explicit “Not recommended” listing when validated evidence is appropriate
Explicit listing and recommendations regarding therapies, including sequential use or combination in relation to other therapies
Explicit “Equivocal” listing when validated evidence is equivocal
Process for public identification and notification of potential conflicts of interest of the compendia’s parent and sibling organizations, reviewers, and committee members, with an established procedure to manage recognized conflicts

**Table 2. Compendia Recognized by Medicare As References for Off-Label Uses of Anticancer Drugs**

Compendium	Effective Date of Recognition	Access	Covered Uses <sup>3</sup>	Non-Covered Uses <sup>2(p257)</sup>
AHFS-DI	1993	Off-label reviews of cancer drugs available free online: <a href="http://www.thefebm.org">http://www.thefebm.org</a>	Narrative text is supportive	Narrative text is not supportive
NCCN Drugs & Biologics Compendium	June 5, 2008	Free online access: <a href="http://www.nccn.org">http://www.nccn.org</a>	Category 1 or 2A	Category 3
Thomson Micromedex <i>DrugDex</i>	June 10, 2008	Subscription required: <a href="http://www.micromedex.com/products/drugdex/">http://www.micromedex.com/products/drugdex/</a>	Class I, IIa, or IIb	Class III
Clinical Pharmacology	July 2, 2008	Subscription required: <a href="http://www.clinicalpharmacology.com">http://www.clinicalpharmacology.com</a>	Narrative text is supportive	Narrative text is not supportive

Abbreviations: AHFS-DI, American Hospital Formulary Service Drug Information; NCCN, National Comprehensive Cancer Network.

It is important to note that if any of the recognized compendia include a “Not Recommended” listing for an off-label use, then that use is not eligible for coverage even if the same use is listed as accepted in one of the other compendia. In addition, uses that CMS deems not medically appropriate (published, for example, in a Medicare National Coverage Determination) will not be covered even if support exists in one of the compendia.

### Peer-Reviewed Journals

In the absence of a compendium listing supporting off-label use, contractors may consider scientific evidence if published in one of 26 designated peer-reviewed journals (Table 3). Although Medicare contractors are required to provide coverage for accepted off-label uses published in the recognized compendia (with the exceptions noted above), they have discretion over coverage of off-label uses referenced in peer-reviewed literature. CMS recently updated its guidance on how contractors are to evaluate peer-reviewed journal articles when considering coverage decisions. In October 2008, CMS issued a revision to the Medicare Benefit Policy Manual stating that contractors will consider the following points:

- Whether the clinical characteristics of the beneficiary and the cancer are adequately represented in the published evidence;
- Whether the administered chemotherapy regimen is adequately represented in the published evidence;
- Whether the reported study outcomes represent clinically meaningful outcomes experienced by patients; and
- Whether the study is appropriate to address the clinical question.<sup>3</sup>

### On the Horizon

After many years with no new compendia players, CMS’s introduction of an annual review process and recent addition of three new publications will likely lead to more frequent engagement by both the provider community and compendia publishers.

Increasing attention to conflict of interest may ultimately have an impact on the current review process for off-label uses. CMS has requested the Agency for Healthcare Research and Quality to conduct an assessment of conflict of interest in

**Table 3. Peer-Reviewed Journals Recognized by Medicare for Off-Label Coverage of Anticancer Therapies**

<i>American Journal of Medicine</i>
<i>Annals of Internal Medicine</i>
<i>Annals of Oncology</i>
<i>Annals of Surgical Oncology</i>
<i>Biology of Blood and Marrow Transplantation</i>
<i>Blood</i>
<i>Bone Marrow Transplantation</i>
<i>British Journal of Cancer</i>
<i>British Journal of Hematology</i>
<i>British Medical Journal</i>
<i>Cancer</i>
<i>Clinical Cancer Research</i>
<i>Drugs</i>
<i>European Journal of Cancer</i> (formerly the <i>European Journal of Cancer and Clinical Oncology</i> )
<i>Gynecologic Oncology</i>
<i>International Journal of Radiation, Oncology, Biology, and Physics</i>
<i>The Journal of the American Medical Association</i>
<i>Journal of Clinical Oncology</i>
<i>Journal of the National Cancer Institute</i>
<i>Journal of the National Comprehensive Cancer Network</i>
<i>Journal of Urology</i>
<i>Lancet</i>
<i>Lancet Oncology</i>
<i>Leukemia</i>
<i>The New England Journal of Medicine</i>
<i>Radiation Oncology</i>

drug compendia reviews. Agency for Healthcare Research and Quality has drafted a white paper on this topic and is expected to issue a final version shortly. Congressional leaders have also been scrutinizing conflict of interest policies and

procedures for publications that are cited as evidence for off-label uses.

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### ASCO's Role in Advocating for Patient Access to Appropriate Off-Label Therapies

During the past 15 years, ASCO has played an instrumental role in advocating for access to off-label therapies supported by scientific evidence, starting with work leading to the passage of the 1993 Omnibus Budget Reconciliation Act requirement. In July 2006, ASCO published a policy statement entitled "Reimbursement for Cancer Treatment: Coverage for Off-Label Drug Indications" that called for the DHHS Secretary to use the agency's statutory authority to include all qualified compendia for use in the Medicare program; work with the cancer community to identify the full range of legitimate, peer-reviewed scientific journals that may be relied on by carriers in determining coverage decisions; and require Medicare contractors to take into account peer-reviewed literature from these reliable sources as they determine coverage.<sup>1</sup>

ASCO has been, in large part, successful on all three counts since this statement was published. The society wrote a series of letters to the DHHS calling for expansion of the list of qualified compendia between 2006 and 2007, and then actively participated in CMS' first annual review cycle for the compendia in 2008. After the announcements in summer 2008 regarding expansions to the list of accepted compendia, ASCO reached out to each of the Medicare Part B carriers and Medicare Part A/B administrative contractors to urge immediate implementation of the policy changes. ASCO also initiated the request to the CMS Coverage and Analysis Group to expand the list of peer-reviewed scientific journals to which Medicare contractors may refer, and provided specific recommendations regarding the journals that should be recognized. This action led to CMS' 2007 expansion of the list from 15 journals to 26 journals. ASCO continues to closely monitor policy developments related to the coverage of off-label therapies.

### References

1. American Society of Clinical Oncology. Reimbursement for cancer treatment: Coverage of off-label drug indications. *J Clin Oncol* 24:3206-3208, 2006
2. Centers for Medicaid and Medicare Services: Covered medical and other health services. Medicare Benefit Policy Manual. <http://www.cms.hhs.gov/manuals/Downloads/bp102c15.pdf>
3. Centers for Medicaid and Medicare Services: Compendia as authoritative sources for use in the determination of a "medically accepted indication" of drugs and biologicals used off-label in an anti-cancer chemotherapeutic regimen. <http://www.cms.hhs.gov/transmittals/downloads/R96BP.pdf>



## EARLY REGISTRATION DEADLINE APPROACHING FOR THE 2009 GENITOURINARY CANCERS SYMPOSIUM

The 2009 Genitourinary Cancers Symposium (February 26-28, 2009, Orlando, FL) will offer educational sessions and abstract oral and poster presentations focused on prostate, penile/urethral, testicular, bladder, and renal cell cancers from national and international opinion leaders. This is your best opportunity to learn about the newest strategies on prevention, screening, diagnosis, multidisciplinary treatment, translational research, and current controversies in the field of GU cancers. Early registration deadline: January 23, 2009. To register, visit [www.gucasymposium.org](http://www.gucasymposium.org).

