

<b>CMS Manual System</b>	<b>Department of Health &amp; Human Services (DHHS)</b>
<b>Pub 100-02 Medicare Benefit Policy</b>	<b>Centers for Medicare &amp; Medicaid Services (CMS)</b>
<b>Transmittal 96</b>	<b>Date: October 24, 2008</b>
	<b>Change Request 6191</b>

**SUBJECT: 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**

**I. SUMMARY OF CHANGES:** CMS is recognizing four authoritative compendia and listing them in chapter 15, section 50.4.5 of the Medicare Benefit Policy Manual for use in the determination of a medically accepted indication of drugs and biologicals used off-label in an anti-cancer chemotherapeutic regimen.

**New / Revised Material**

**Effective Date: June 5, 2008 - NCCN Drugs and Biologics Compendium**

**June 10, 2008 - Thomson Micromedex DrugDex**

**July 2, 2008 - Clinical Pharmacology**

**Implementation Date: November 25, 2008**

*Disclaimer for manual changes only: The revision date and transmittal number apply only to red italicized material. Any other material was previously published and remains unchanged. However, if this revision contains a table of contents, you will receive the new/revised information only, and not the entire table of contents.*

**II. CHANGES IN MANUAL INSTRUCTIONS:** (N/A if manual is not updated)

R=REVISED, N=NEW, D=DELETED.

<b>R/N/D</b>	<b>CHAPTER/SECTION/SUBSECTION/TITLE</b>
<b>R</b>	15/Table of Contents
<b>R</b>	15/50.4.5/Off-Label Use of Anti-Cancer Drugs and Biologicals
<b>R</b>	15/50.4.5.1/Process for Amending the List of Compendia for Determination of Medically Accepted Indications for Off-Label Uses of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen

**III. FUNDING:**

**SECTION A: For Fiscal Intermediaries and Carriers:**

No additional funding will be provided by CMS; contractor activities are to be carried out within their operating budgets.

**SECTION B: For Medicare Administrative Contractors (MACs):**

The Medicare Administrative Contractor is hereby advised that this constitutes technical direction as defined in your contract. CMS does not construe this as a change to the MAC Statement of Work. The contractor is not obligated to incur costs in excess of the amounts allotted in your contract unless and until specifically authorized by the contracting officer. If the contractor considers anything provided, as described above, to be outside the current scope of work, the contractor shall withhold performance on the part(s) in question

and immediately notify the contracting officer, in writing or by e-mail, and request formal directions regarding continued performance requirements.

#### **IV. ATTACHMENTS:**

**Business Requirements**

**Manual Instruction**

*\*Unless otherwise specified, the effective date is the date of service.*

# Attachment - Business Requirements

Pub. 100-02	Transmittal: 96	Date: October 24, 2008	Change Request: 6191
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**SUBJECT: 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**

**Effective Dates:** Existing American Hospital Formulary Service-Drug Information  
June 5, 2008-National Comprehensive Cancer Network Drugs and Biologics  
Compendium  
June 10, 2008 -Thomson Micromedex DrugDex  
July 2, 2008-Clinical Pharmacology

**Implementation Date: November 25, 2008**

## **I. GENERAL INFORMATION**

**A. Background:** Section 1861(t)(2)(B)(ii)(I) of the Social Security Act (the Act), as amended by section 6001(f)(1) of the Deficit Reduction Act of 2005, Pub. Law 109-171, recognizes three compendia-- American Medical Association Drug Evaluations (AMA-DE), United States Pharmacopoeia-Drug Information (USP-DI) or its successor publication, and American Hospital Formulary Service-Drug Information (AHFS-DI)-- 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, unless the Secretary has determined that the use is not medically appropriate or the use is identified as not indicated in one or more such compendia.

Due to changes in the pharmaceutical reference industry, AHFS-DI was the only remaining statutorily-named compendia available for our reference; the AMA-DE and the USP-DI are no longer published. Consequently, the Centers for Medicare & Medicaid Services (CMS) received requests from the stakeholder community for a process to revise the list of compendia. In the Physician Fee Schedule final rule for calendar year 2008, CMS established a process for revising the list of compendia, as authorized under section 1861(t)(2) of the Act, and also established a definition for “compendium.” See 72 FR 66222, 66303-66306, 66404. Under 42 CFR 414.930(a), a compendium is defined “as a comprehensive listing of FDA-approved drugs and biologicals or a comprehensive listing of a specific subset of drugs and biologicals in a specialty compendium, for example, a compendium of anti-cancer treatment.” A compendium: (1) includes a summary of the pharmacologic characteristics of each drug or biological and may include information on dosage, as well as recommended or endorsed uses in specific diseases; and, (2) is indexed by drug or biological. See 42 CFR 414.930(a); 72 FR 66222, 66404.

In addition, CMS increased the transparency of the process by incorporating a list of desirable compendium characteristics outlined by the Medicare Evidence Development and Coverage Advisory Committee (MedCAC) as criteria for decision-making. The list of desirable compendium characteristics was developed by the MedCAC during a public session on March 30, 2006. The goal of this session was to review the evidence and advise CMS on the desirable characteristics of compendia for use in the determination of medically-accepted indications of drugs and biologicals in anti-cancer therapy. As a result of this meeting, the MedCAC generated a list of desirable characteristics to use when reviewing a compendium.

CMS generated one internal request to delete AMA-DE which is no longer published, and received four external requests from stakeholders for additions to the authoritative list: NCCN, Micromedex DrugDex, Micromedex DrugPoints, and Clinical Pharmacology. CMS staff conducted a review of specific compendia comparing the qualities with the MedCAC desirable characteristics.

**B. Policy:** CMS is recognizing the following as authoritative compendia and listing them in Pub. 100-02 of the Medicare Benefit Policy Manual, chapter 15, section 50.4.5 for use in the determination of a “medically-accepted indication” of drugs and biologicals used off-label in an anti-cancer chemotherapeutic regimen:

- American Hospital Formulary Service-Drug Information (AHFS-DI)
- NCCN Drugs and Biologics Compendium
- Thomson Micromedex DrugDex
- Clinical Pharmacology

Contractors shall recognize medically accepted indications as those that:

- are favorably listed in one or more of the compendia listed above, or,
- the contractor determines from a review of the peer-reviewed literature as described above that it is a medically accepted indication,

unless CMS has determined that the use is not medically accepted, or any of the listed compendia list the use as not medically accepted, or words to that effect.

CMS is aware that the listed compendia employ various rating and recommendation systems that may not be readily cross-walked from compendium to compendium. In general, a use is identified by a compendium as medically accepted if the:

1. indication is a Category 1 or 2A in NCCN, or Class I, Class IIa, or Class IIb in DrugDex; or,
2. narrative text in AHFS or Clinical Pharmacology is supportive.

A use is not medically accepted by a compendium if the:

1. indication is a Category 3 in NCCN or a Class III in DrugDex; or,
2. narrative text in AHFS or Clinical Pharmacology is “not supportive.”

The complete absence of narrative text on a use is considered neither supportive nor non-supportive.

**NOTE:** Referencing compendia for off-label anti-cancer chemotherapeutic drug use is an ongoing contractor instruction. The Secretary has the authority under section 1861(t)(2) of the Act to revise the compendia list as is appropriate for identifying medically acceptable off-label drug use. This instruction constitutes an update to the existing compendia list found at Pub. 100-02, Medicare Benefit Policy Manual, chapter 15, section 50.4.5.

**NOTE:** The contractor may maintain its own subscriptions to the listed compendia updates or peer-reviewed publications to determine the medically accepted indication of drugs or biologicals used off-label in an anti-cancer chemotherapeutic regimen. Compendia documentation or peer-reviewed literature supporting off-label use by the treating physician may also be requested of the physician by the contractor.

## II. BUSINESS REQUIREMENTS TABLE

Use "Shall" to denote a mandatory requirement

Number	Requirement	Responsibility (place an "X" in each applicable column)								
		A / B  M A C	D M E  M A C	F I	C A R R I E R	R H I	Shared-System Maintainers			
F I S S	M C S						V M S	C W F		
6191.1	Effective with the dates noted above in processing claims, contractors shall be aware of the additions and deletions to the list of 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, unless the Secretary has determined that the use is not medically appropriate or the use is identified as not indicated in one or more such compendia as described in Pub. 100-02, chapter 15, section 50.4.5.	X	X	X	X					

## III. PROVIDER EDUCATION TABLE

Number	Requirement	Responsibility (place an "X" in each applicable column)								
		A / B  M A C	D M E  M A C	F I	C A R R I E R	R H I	Shared-System Maintainers			
F I S S	M C S						V M S	C W F		
6191.2	A provider education article related to this instruction will be available at <a href="http://www.cms.hhs.gov/MLNMattersArticles/">http://www.cms.hhs.gov/MLNMattersArticles/</a> shortly after the CR is released. You will receive notification of the article release via the established "MLN Matters" listserv. Contractors shall post this article, or a direct link to this article, on their Web site and include information about it in a listserv message within 1 week of the availability of the provider education article. In addition, the provider education article shall be included in your next regularly scheduled bulletin. Contractors are free to supplement MLN Matters articles with localized information that would benefit their provider community in billing and administering the Medicare program correctly.	X	X	X	X					

#### IV. SUPPORTING INFORMATION

**Section A: For any recommendations and supporting information associated with listed requirements, use the box below:**

*Use "Should" to denote a recommendation.*

X-Ref Requirement Number	Recommendations or other supporting information:
	N/A

**Section B: For all other recommendations and supporting information, use this space:**

#### V. CONTACTS

**Pre-Implementation Contact(s):** Kate Tillman, coverage, 410-786-9252, [Katherine.tillman@cms.hhs.gov](mailto:Katherine.tillman@cms.hhs.gov), Brijet Burton, coverage, 410-786-7364, [Brijet.burton@cms.hhs.gov](mailto:Brijet.burton@cms.hhs.gov)

**Post-Implementation Contact(s):** Appropriate CMS RO

#### VI. FUNDING

**Section A: For *Fiscal Intermediaries (FIs), Carriers, and Regional Home Health Carriers (RHHs)* use only one of the following statements:** No additional funding will be provided by CMS; contractor activities are to be carried out within their operating budgets.

**Section B: For *Medicare Administrative Contractors (MACs)*, use the following statement:**

The Medicare Administrative Contractor is hereby advised that this constitutes technical direction as defined in your contract. CMS does not construe this as a change to the MAC Statement of Work. The contractor is not obligated to incur costs in excess of the amounts allotted in your contract unless and until specifically authorized by the contracting officer. If the contractor considers anything provided, as described above, to be outside the current scope of work, the contractor shall withhold performance on the part(s) in question and immediately notify the contracting officer, in writing or by e-mail, and request formal directions regarding continued performance requirements.

# Medicare Benefit Policy Manual

## Chapter 15 – Covered Medical and Other Health Services

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### Table of Contents *(Rev. 96, 10-24-08)*

*50.4.5 - Off Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen*

## **50.4.5 - Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen**

**(Rev.96, Issued: 10-24-08, Effective: 06-05-08 NCCN/06-10-08 Thomson Micromedex/07-02-08 Clinical Pharmacology, Implementation: 11-25-08)**

### **A. Overview**

Effective January 1, 1994, *off-label, medically accepted indications* of Food and Drug Administration-(FDA) approved drugs and biologicals used in an anti-cancer chemotherapeutic regimen are *identified* under the conditions described *below*. A regimen is a combination of anti-cancer agents clinically recognized for the treatment of a specific type of cancer. *Off-label, medically accepted indications are supported in either one or more of the compendia or in peer-reviewed medical literature. The contractor may maintain its own subscriptions to the listed compendia or peer-reviewed publications to determine the medically accepted indication of drugs or biologicals used off-label in an anti-cancer chemotherapeutic regimen. Compendia documentation or peer-reviewed literature supporting off-label use by the treating physician may also be requested of the physician by the contractor.*

### **B. Recent Revisions to the Compendia List**

Do not deny coverage based solely on the absence of FDA-approved labeling for the use, if the use is supported by *any* of the following *compendia* and the use is **not** listed as *unsupported, not indicated, not recommended, or equivalent terms*, in any of the *following* compendia:

*Existing* - American Hospital Formulary Service-Drug Information (*AHFS-DI*)

*Effective June 5, 2008* - National Comprehensive Cancer Network (*NCCN*) Drugs and Biologics Compendium

*Effective June 10, 2008* - Thomson Micromedex DrugDex

*Effective July 2, 2008* - Clinical Pharmacology

*The listed compendia employ various rating and recommendation systems that may not be readily cross-walked from compendium to compendium. In general, a use is identified by a compendium as **medically accepted** if the:*

- 1. indication is a Category 1 or 2A in NCCN, or Class I, Class IIa, or Class IIb in DrugDex; or,*
- 2. narrative text in AHFS-DI or Clinical Pharmacology is supportive.*

*A use is **not medically accepted** by a compendium if the:*

1. *indication is a Category 3 in NCCN or a Class III in DrugDex; or,*
2. *narrative text in AHFS or Clinical Pharmacology is “not supportive.”*

*The complete absence of narrative text on a use is considered neither supportive nor non-supportive.*

### **C. Use Supported by Clinical Research That Appears in Peer-Reviewed Medical Literature**

*Contractors may also identify off-label uses that are supported by clinical research under the conditions identified in this section. Peer-reviewed medical literature may appear in scientific, medical, and pharmaceutical publications in which original manuscripts are published, only after having been critically reviewed for scientific accuracy, validity, and reliability by unbiased, independent experts prior to publication. In-house publications of entities whose business relates to the manufacture, sale, or distribution of pharmaceutical products are excluded from consideration. Abstracts (including meeting abstracts) are excluded from consideration.*

In determining whether *an off-label use is supported, the contractors* will evaluate the evidence in published, peer-reviewed medical literature *listed below*. When evaluating this literature, they will consider (among other things) the following:

- *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.*
- *Whether the study is appropriate to address the clinical question. The contractor will consider:*

1. *whether the experimental design, in light of the drugs and conditions under investigation, is appropriate to address the investigative question. (For example, in some clinical studies, it may be unnecessary or not feasible to use randomization, double blind trials, placebos, or crossover.);*
2. *that non-randomized clinical trials with a significant number of subjects may be a basis for supportive clinical evidence for determining accepted uses of drugs; and,*
3. *that case reports are generally considered uncontrolled and anecdotal information and do not provide adequate supportive clinical evidence for determining accepted uses of drugs.*

The *contractor* will use peer-reviewed medical literature appearing in the regular editions of the following publications, not to include supplement editions privately funded by parties with a vested interest in the recommendations of the authors:

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

#### ***D. Generally***

*FDA-approved drugs and biologicals may also be considered for use in the determination of medically accepted indications for off-label use if determined by the contractor to be reasonable and necessary.*

If a use is identified as not indicated by *the Centers for Medicare and Medicaid Services (CMS)* or the FDA, or if a use is specifically identified as not indicated in one or more of the compendia *listed*, or if the *contractor* determines, based on peer-reviewed medical literature, that a particular use of a drug is not safe and effective, the *off-label* usage is not supported and, therefore, the drug is not covered.

**50.4.5.1 - Process for Amending the List of Compendia for Determination of Medically-Accepted Indications for Off-Label Uses of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen**  
*(Rev.96, Issued: 10-24-08, Effective: 06-05-08 NCCN/06-10-08 Thomson Micromedex/07-02-08 Clinical Pharmacology, Implementation: 11-25-08)*

**A. Background**

*In the Physician Fee Schedule final rule for calendar year 2008, the CMS established a process for revising the list of compendia, as authorized under section 1861(t)(2) of the Social Security Act, and also established a definition for “compendium.” See 72 FR 66222, 66303-66306, 66404. At 42 CFR 414.930(a), a compendium is defined “as a comprehensive listing of FDA-approved drugs and biologicals or a comprehensive listing of a specific subset of drugs and biologicals in a specialty compendium, for example, a compendium of anti-cancer treatment.” A compendium: (1) includes a summary of the pharmacologic characteristics of each drug or biological and may include information on dosage, as well as recommended or endorsed uses in specific diseases; and, (2) is indexed by drug or biological. See 42 CFR 414.930(a); 72 FR 66222, 66404.*

**B. Desirable Characteristics of Compendia**

*In addition, CMS increased the transparency of the process by incorporating a list of desirable compendium characteristics outlined by the Medicare Evidence Development and Coverage Advisory Committee (MedCAC) as criteria for decision-making. The list of desirable compendium characteristics was developed by the MedCAC during a public session on March 30, 2006. The goal of this session was to review the evidence and advise CMS on the desirable characteristics of compendia for use in the determination of medically accepted indications of drugs and biologicals in anti-cancer therapy. As a result of this meeting, the MedCAC generated the following list of desirable characteristics:*

- 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, and,
- Process for public identification and notification of potential conflicts of interest of the compendias' parent and sibling organizations, reviewers, and committee members, with an established procedure to manage recognized conflicts.

### **C. Process for Changing List of Compendia**

CMS will provide an annual 30-day open request period starting January 15 for the public to submit requests for additions or deletions to the compendia list contained on the CMS Web site at [http://www.cms.hhs.gov/CoverageGenInfo/02\\_compendia.asp](http://www.cms.hhs.gov/CoverageGenInfo/02_compendia.asp).

Complete requests as defined in section 50.4.5.1.D will be posted to the Web site by March 15 for public notice and comment. The request will identify the requestor and the requested action to the list. Public comments will be accepted for a 30-day period beginning on the day the request is posted on the Web site. In addition to the annual process, CMS may generate a request for changes to the list at any time an urgent action is needed to protect the interests of the Medicare program and its beneficiaries.

### **D. Content of Requests**

For a request to be considered complete, and therefore accepted for review, it must include the following information:

- The full name and contact information (including the mailing address, e-mail address, and telephone number) of the requestor. If the requestor is not an individual person, the information shall identify the officer or other representative who is authorized to act for the requestor on all matters related to the request.
- Full identification of the compendium that is the subject of the request, including name, publisher, edition if applicable, date of publication, and any other information needed for the accurate and precise identification of the specific compendium.
- A complete, written copy of the compendium that is the subject of the request. If the complete compendium is available electronically, it may be submitted electronically in place of hard copy. If the compendium is available online, the requestor may provide CMS with electronic access by furnishing at no cost to the Federal Government sufficient accounts for the purposes and duration of the review of the application in place of hard copy.
- The specific action that the requestor wishes CMS to take, for example to add or delete a specific compendium.
- Detailed, specific documentation that the compendium that is the subject of the request does or does not comply with the conditions of this rule. Broad, non-specific claims without supporting documentation cannot be efficiently reviewed; therefore, they will not be accepted.

A request may have only a single compendium as its subject. This will provide greater clarity to the scope of the Agency's review of a given request. A requestor may submit multiple requests, each requesting a different action.

## **E. Submission of Requests**

Requests must be in writing and submitted in one of the following two ways (no duplicates please):

1. Electronic requests are encouraged to facilitate administrative efficiency. Each solicitation will include the electronic address for submissions.
2. Hard copy requests can be sent to:

Centers for Medicare & Medicaid Services  
Coverage and Analysis Group  
Mailstop C1-09-06  
7500 Security Boulevard  
Baltimore, MD 21244

Allow sufficient time for hard copies to be received prior to the close of the open request period.

## **F. Review of Requests**

CMS will consider a compendium's attainment of the desirable characteristics specified in 50.4.5.1.B when reviewing requests. CMS may consider additional, reasonable factors in making a determination. For example, CMS may consider factors that are likely to impact the compendium's suitability for this use, such as a change in ownership or affiliation, the standards applicable to the evidence considered by the compendium, and any relevant conflicts of interest. CMS may consider that broad accessibility by the general public to the information contained in the compendium may assist beneficiaries, their treating physicians, or both, in choosing among treatment options. CMS will also consider a compendium's grading of evidence used in making recommendations regarding off-label uses, and the process by which the compendium grades the evidence. CMS may, at its discretion, combine and consider multiple requests that refer to the same compendium, even if those requests are for different actions. This facilitates administrative efficiency in the review of requests.

## **G. Publishing Review Results**

CMS will publish decisions on the CMS Web site within 90 days after the close of the public comment period.

*(This instruction was last reviewed by CMS in September 2008.)*