February 11, 2008

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

Re: Request that CMS Recognize the NCCN Compendium as an Authoritative Compendium for Medicare Coverage Purposes

Dear Dr. Phurrough:

The American Society of Clinical Oncology (ASCO) requests that CMS add the National Comprehensive Cancer Network Drugs & Biologics Compendium (NCCN Compendium) to the list of compendia specified in Section 1861(t)(2)(B)(ii)(I) of the Social Security Act. ASCO is the national organization representing physicians who specialize in the treatment of cancer, and Medicare coverage of new drug uses, which that section addresses, is extremely important to ensure the proper care of cancer patients. As discussed below, the NCCN Compendium meets CMS's definition of a compendium and largely satisfies the desirable characteristics for compendia identified by CMS in the Federal Register on November 27, 2007.

Background

Section 1861(t)(2) of the Social Security Act (the Act), in conjunction with Sections 1812(a)(1), 1832(a)(2)(B), 1861(b)(2), and 1861(s)(2), establishes a special Medicare coverage rule for drugs used in cancer chemotherapy regimens. The provision requires Medicare to cover drugs administered in physician offices and hospitals when used for indications approved by the Food and Drug Administration (FDA), and in the case of unapproved uses of approved drugs, when the uses are supported by citations in the compendia listed in Section 1861(t)(2)(B)(ii)(I) of the Act. This Section currently lists certain compendia and allows CMS to identify additional authoritative compendia.

CMS has established a formal process to consider requests for additions and deletions to the list of compendia in the Act. Interested parties are invited to submit these requests for a 30-day period beginning January 15th of each year. Requests must document that a particular compendium meets CMS's definition of a compendium and satisfies the desirable characteristics for compendia, discussed in detail below. By submitting this letter, ASCO is acting under CMS's formal process to request that the NCCN Compendium be recognized as an authoritative compendium for purposes of Section 1861(t)(2)(B)(ii)(I) of the Act.

ASCO has reviewed the online version of the Drugs & Biologics Compendium published by NCCN, which is available at http://www.nccn.org/professionals/drug_compendium/login/login.aspx. The NCCN Compendium is derived from the NCCN Clinical Practice Guidelines in Oncology™ (NCCN Guidelines), each of which covers a different type of cancer and provides an algorithm or decision pathway, a manuscript detailing significant issues related to the algorithm, and references to support NCCN's recommendations.

Definition of compendium

The NCCN Compendium meets CMS's definition of a compendium, which is "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."[1] A compendium must (1) include "a summary of the pharmacologic characteristics of each drug or biological and may include information on dosage" and recommended uses in specific diseases; and (2) be indexed by drug or biological.[2]

The NCCN Compendium, while a specialty compendium, is a comprehensive listing of anti-cancer drugs and biologicals that is indexed by drug and biological. Compendium users can access a detailed description of the pharmacologic characteristics of a particular drug by clicking on a link attached to the drug's brand name, which takes users directly to the drug's labeling. In addition, the NCCN Compendium itself provides information about the drug's pharmacologic class, recommends uses tied to a specific disease and histology, and provides information about dosage and route of administration. Therefore, the NCCN Compendium meets the CMS definition.

Desirable characteristics of compendia

CMS indicated that it will consider whether a compendium satisfies the desirable characteristics of compendia as identified by the Medicare Evidence Development and Coverage Advisory Committee (MedCAC) in reviewing requests for changes to the list of compendia in the Act. Desirable characteristics include:

- extensive breadth of listings;
- quick throughput from application for inclusion to listing;
- detailed description of the evidence reviewed for every listing;
- use of pre-specified published criteria for weighing evidence;
- prescribed published process for making recommendations;
- publicly transparent process for evaluating therapies;

[1] Medicare Program; Revisions to Payment Policies Under the Physician Fee Schedule, and Other Part B Payment Policies for CY 2008, 72 Fed. Reg. 66222, 66304 (Nov. 27, 2007).

[2] *Id.*

- 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 compendia's parent and sibling organizations, reviewers, and committee members, with an established procedure to manage recognized conflicts.

The sections below describe in detail how the NCCN Compendium and the Guidelines from which it is derived satisfy these characteristics.

Extensive breadth of listings. The NCCN Compendium is a comprehensive specialty compendium that includes all cancer drugs recommended in the NCCN Guidelines, covering an estimated 97 percent of cancer patients.[3] The listing for each drug includes a thorough set of recommended uses, both FDA-approved and unapproved.

Quick throughput from application for inclusion to listing. The NCCN Compendium is reviewed and updated continually in conjunction with updates to the NCCN Guidelines, each of which is updated at least annually following review by an expert panel, but often more frequently to incorporate new evidence and innovative therapies.[4] For example, the NCCN Soft Tissue Sarcoma Panel updated the Soft Tissue Sarcoma Guideline three times in 2007 alone, and the NCCN Compendium was updated to reflect new recommendations in the Guideline related to drugs. In version three of the 2007 Soft Tissue Sarcoma Guideline, published September 11, 2007, the Panel added to the decision pathway for gastrointestinal stromal tumors (GIST) a recommendation that practitioners consider adjuvant imatinib for patients completely resected after surgery. This recommendation was based on an abstract presented only months earlier at the June 2007 ASCO Annual Meeting, presenting the interim findings of a Phase III trial.[5] The NCCN Compendium also reflects this addition and lists as a recommended use for imatinib mesylate "[a]djuvant treatment following complete resection of primary GIST."[6] This example demonstrates that NCCN updates its Compendium to reflect new scientific and clinical developments in a very timely manner.

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[3] NCCN. About the NCCN Drugs & Biologics Compendium. (Accessed at http://www.nccn.org/professionals/drug_compendium/content/about.asp) [hereinafter About the Compendium].

[4] *Id.*; Winn RJ, Joan McClure J., About the NCCN Clinical Practice Guidelines. March 2007. (Accessed at http://www.nccn.org/professionals/physician_gls/about.asp).

[5] NCCN. Soft Tissue Sarcoma Guideline V.3.2007. Sept. 11, 2007. (Accessed at http://www.nccn.org/professionals/physician_gls/PDF/sarcoma.pdf) (citing DeMatteo R, Owzar K, Maki R, Pisters P, et al. Adjuvant imatinib mesylate increases recurrence free survival (RFS) in patients with completely resected localized primary gastrointestinal stromal tumor (GIST): North American Intergroup Phase III trial ACOSOG Z9001. 2007 ASCO Annual Meeting. Abstract 10079).

[6] NCCN. Imatinib mesylate. (Accessed at http://www.nccn.org/professionals/drug_compendium/MatrixGenerator/HTML/Imatinib%20mesylate.asp).

Detailed description of the evidence reviewed for every individual listing. The recommended uses listed in the NCCN Compendium correspond directly with NCCN Guidelines, which explicitly reference the evidence used to support NCCN recommendations. For example, the NCCN Compendium lists as a recommended use for bevacizumab the treatment of certain patients with invasive breast cancer in combination with paclitaxel, an off-label use. In the Breast Cancer Guideline, NCCN cites a randomized, phase III clinical trial in support of this recommendation, describes the results of the trial in the manuscript section, and provides citations to both a 2003 and updated 2005 abstract discussing the trial. These citations are linked to relevant text in both the algorithm and the manuscript.[7] Notably, the trial cited by NCCN was the only phase III trial regarding this combination of drugs identified by researchers conducting the Technology Assessment commissioned by CMS.[8]

When multiple sources support a particular recommendation, NCCN intentionally limits the number of references cited to direct users to the most useful, comprehensive, and relevant sources. As reported by Bill McGivney, the Chief Executive Officer of NCCN, in testimony before MedCAC, "NCCN committees purposely and purposefully limit the references used to one, two or three, in order to provide references that really define most definitely the recommendations for care, and secondly, point out and identify the optimal management regimen in terms of combinations to be used, the drug doses and the schedule for administration."[9] Thus, while not all reviewed sources are listed in the Guidelines, NCCN has a clinical justification for its decision to limit the number of sources cited.

Use of pre-specified published criteria for weighing evidence. For each recommended use of a particular drug, the NCCN Compendium includes a ranking to designate both the strength of evidence available to support the recommendation and the level of consensus among panel members that the recommendation is appropriate.[10] Users may link from the Compendium to a description of NCCN's process for determining these rankings.

NCCN labels the strength of evidence either "high" or "lower." A ranking of "high quality" indicates that supporting evidence consists of randomized controlled trials (RCTs) or meta-analysis of trials. A ranking of "lower quality" may include phase II trials, large cohort studies, or clinical experience from practitioners at NCCN member institutions.

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[7] NCCN. Bevacizumab. (Accessed at http://www.nccn.org/professionals/drug_compendium/MatrixGenerator/HTML/Bevacizumab.asp); NCCN. Breast Cancer Guideline V.2.2008. Jan. 3, 2008. (Accessed at http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf).

[8] Agency for Healthcare Research and Quality, Technology Assessment Program. Compendia for coverage of off-label uses of drugs and biologics in an anticancer chemotherapeutic regimen: final report. Rockville, MD: Agency for Healthcare Research and Quality, 2007:19. (Accessed at http://www.cms.hhs.gov/determinationprocess/downloads/id46TA.pdf).

[9] CMS. Transcript of a Medicare Coverage Advisory Committee meeting. Mar. 30, 2006. (Accessed at http://www.cms.hhs.gov/FACA/downloads/id33d.pdf?origin=globalsearch&page=/mcd/viewmcac.asp&mid=33&where=index) [hereinafter CMS Transcript].

[10] About the Compendium, *supra* note 3.

NCCN ranks the level of consensus among panel members as either uniform, non-uniform, or major disagreement. A uniform ranking means that all panel members agree that a particular recommendation is indicated. A ranking of non-uniform means that there is minor disagreement among panel members, and thus institutions may reasonably adopt different approaches. A ranking of major disagreement indicates that panel members have major disagreement over the interpretation of available evidence. This ranking may be used when substantial data supports the use of two interventions, which have never been directly compared in a randomized clinical trial. It may also be used when panel members disagree about the extent to which trial data can be generalized. NCCN's rankings incorporating both the strength of evidence and the level of consensus are listed below.

- **Category 1:** High quality of evidence/uniform level of consensus.
- **Category 2A:** Lower quality of evidence/uniform level of consensus.
- **Category 2B:** Lower quality of evidence/non-uniform level of consensus.
- **Category 3:** Any quality of evidence/major disagreement.

Use of prescribed published process for making recommendations. The NCCN Compendium compiles all recommendations about the appropriate uses of drugs and biologics contained in the NCCN Guidelines. Compendium users have access to detailed descriptions of the process used to develop these recommendations, which is summarized below.[11]

Panel membership. NCCN has established over 40 expert panels, which develop both the recommendations contained in both the Guidelines and the Compendium. Each panel is composed of approximately 15 to 22 specialists from multiple disciplines with expertise related to the particular tumor for which a Guideline is being developed, as well as lay members. Panel members are selected by the NCCN Guidelines Steering Committee, whose members are nominated by each NCCN member institution.

Guideline development and continual review. To develop the recommendations contained in a Guideline for a particular type of cancer, the NCCN panel for that cancer type holds a meeting to discuss available data and any controversial issues related to treatment. Based on this panel meeting, NCCN staff develop a preliminary version of the Guideline, which is reviewed by the panel chair and then distributed to each NCCN panel member. Next, the preliminary version is circulated for institutional review by experts outside of the panel, who submit comments, which are collated by NCCN staff. The panel developing the Guideline then reconvenes to consider all comments, make revisions, and develop the final version of the Guideline. The recommendations for indicated uses of drugs contained in the NCCN Compendium are derived directly from the recommendations in each Guideline. Each NCCN panel conducts a review of its Guideline at least annually, and any updates made to the Guidelines related to drugs are simultaneously reflected in the Compendium.

[11] *Id.*; Winn, *supra* note 4.

Publicly transparent process for evaluating therapies. NCCN invites interested parties, such as non-NCCN affiliated community and academic physicians, patient advocacy groups, and industry members, to submit data and requests for specific changes to a particular Guideline for consideration at the relevant NCCN panel meeting. A submitting party receives written notification about the panel's decision related to the request at the time the Guideline is published, ensuring that the decisionmaking process is open and transparent.[12]

Explicit "Not recommended" listing when validated evidence is appropriate. A listing is only included in the NCCN Compendium if an NCCN panel has deemed use of a particular drug clinically appropriate.[13] Thus, while the Compendium is silent with respect to non-recommended uses, it is understood by users that if a use is not clinically appropriate, it will not be included in the Guidelines or the Compendium.

Explicit listing and recommendations regarding therapies, including sequential use or combination in relation to other therapies. The recommended uses listed in the NCCN Compendium are extremely detailed, describing whether a particular agent is appropriate as a first-line, adjuvant, neoadjuvant, subsequent, or recurrent therapy and whether a drug is recommended as a single agent or in combination with other listed therapies, and listing patient criteria. In addition, NCCN's ranking of recommended uses may vary based on sequence, combination, or patient characteristics. The examples in the chart below from the listing for gemcitabine hydrochloride demonstrate the specificity of NCCN's recommendations.[14]

Disease treated	Recommended use	NCCN Ranking
Bladder cancer	Neoadjuvant chemotherapy in combination with cisplatin** with or without paclitaxel or docetaxel for patients with clinical stage T2 and node-negative T3 disease **Carboplatin can be substituted for cisplatin in patients who have impaired renal function*	2A; except category 1 in combination with cisplatin without paclitaxel or docetaxel and category 1 for patients with clinical stage T3
Bladder cancer	Primary treatment in combination with cisplatin** with or without paclitaxel or docetaxel in the following clinical settings: • as selective bladder-sparing treatment option along with radiation therapy for patients without hydronephrosis following maximal transurethral resection (TUR) with clinical stage T2	2A; except in category 1 in combination with cisplatin without paclitaxel or docetaxel

[12] NCCN. Submission request to the NCCN Guidelines panels. (Accessed at http://www.nccn.org/about/industry_members.asp).

[13] Winn, *supra* note 4.

[14] NCCN. Gemcitabine hydrochloride. (Accessed at http://www.nccn.org/professionals/drug_compendium/MatrixGenerator/HTML/Gemcitabine%20hydrochloride.asp).

	or node-negative T3 disease • for patients with clinical stage T2 or node-negative T3 disease with extensive comorbid disease or poor performance status • with or without radiation therapy for patients with clinical stage T4 and node-positive T3 disease • following surgery in selected patients with node-negative T4 tumors **Carboplatin can be substituted for cisplatin in patients who have impaired renal function*	
Epithelial ovarian cancer	Recurrence therapy as a single agent for the following indications: • recurrence as evidenced by serially rising CA-125 in patients who have received prior chemotherapy • progressive or stable disease on primary chemotherapy • relapse after being in complete remission following primary chemotherapy • stage II to IV disease showing partial response to primary treatment	2A; except 2B for the management of serially rising CA-125 levels and relapse after a disease-free interval of 6 months or more

In addition, NCCN recommendations are based on a risk-benefit analysis conducted by panel members, who consider not only drug therapies but also surgical procedures, radiation therapy, and other management tools such as watchful waiting when developing recommendations for cancer treatment. Thus, recommendations for appropriate uses of drugs in the NCCN Compendium have been developed after an assessment of the full continuum of care.[15]

Explicit "Equivocal" listing when validated evidence is equivocal. An NCCN ranking of either 2B or 3, both of which reveal that the NCCN panel could not reach unanimous consensus, indicates that the evidence supporting a recommended use is equivocal. For example, NCCN ranks as Category 3 the use of capecitabine, doxorubicin hydrochloride, floxuridine, fluorouracil, and gemcitabine hydrochloride as first-line therapy as a single agent for patients with relapsed or medically unresectable stage IV kidney cancer with non-clear cell histology. In the manuscript of the Kidney Cancer Guideline, NCCN cautions that enrollment in clinical trials is preferable and explains that its decision to give a Category 3 ranking to chemotherapy as first-line therapy

[15] CMS Transcript, *supra* note 9.

for these patients is based on clinical trials that have shown only "minor or modest activity in patients experiencing progression after treatment with immunotherapy."[16]

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. The NCCN Compendium includes a description of NCCN's conflicts of interest policy. NCCN discloses organizational conflicts of interest on its website by listing all members of the pharmaceutical and biotechnology industry who have given financial support to NCCN during the previous two fiscal years.[17] NCCN manages these conflicts by using industry grants only to fund the distribution costs associated with disseminating the NCCN Guidelines; no grants are used to support the development of Guideline or Compendium content.[18]

NCCN also ensures that the conflicts of individual panel members are disclosed by requiring panel members to disclose orally and in writing any conflicts at the beginning of any panel meeting. Conflicts may include industry support for research, participation on an industry advisory committee or speakers bureau, and holding equity in an industry member. NCCN lists aggregate panel conflicts at the end of each Guideline, listing each industry member giving support to a panel member and stating whether conflicts were sufficient to disallow participation by any panel member. Panel chairs have the authority to disallow participation by any member whose conflicts are viewed as significant.[19]

Other factors

In addition to the listed characteristics, CMS suggested that it might consider additional factors, such as the accessibility of a compendium. The NCCN Compendium is available for free online without a subscription. Thus, it is well-positioned to reach a broad audience and result in widespread use among both patients and practitioners as they assess treatment options.

Conclusion

Given the evidence that the NCCN Compendium meets CMS's definition of a compendium, satisfies the desirable characteristics of a compendium described by CMS in its final rule, and is widely available, ASCO requests that CMS add the National Comprehensive Cancer Network Drugs & Biologics Compendium to the list of authoritative compendia specified in Section 1861(t)(2)(B)(ii)(I) of the Social Security Act.

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[16] NCCN. Kidney Cancer Guideline V.1.2008. Sept. 4, 2007. (Accessed at http://www.nccn.org/professionals/physician_gls/PDF/kidney.pdf).

[17] NCCN. NCCN wishes to acknowledge the support of the following organizations who share our goal of improving cancer care for patients we serve. (Accessed at http://www.nccn.org/about/financial_support.asp).

[18] NCCN. NCCN disclosure of organizational relationships. (Accessed at http://www.nccn.org/about/disclosure.asp).

[19] About the Compendium, *supra* note 3.

If you have any questions related to this request, please contact Bela Sastry at sastryb@asco.org or (703) 299-1050. Thank you for your consideration.

Sincerely,

Joseph S. Bailes, MD
Chair, Government Relations Council

cc: Louis Jacques, MD