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Submission Request

Full Identification of Compendium: ***The NCCN Drugs and Biologics Compendium***
Publisher: The National Comprehensive Cancer Network
Edition: Continual updating of electronic online publication of NCCN Compendium at www.nccn.org (available free of charge; registration required)
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Action Requested: ***The National Comprehensive Cancer Network (NCCN) strongly urges the Centers for Medicare and Medicaid Services (CMS) to officially recognize The NCCN Drugs and Biologics Compendium as a mandated reference for Medicare coverage decisions about the appropriate use of drugs and biologics in cancer care. NCCN requests consideration by CMS for such recognition under the process (as described in FR notice Volume 72, Number 133, July 12, 2007) established by CMS for the listing of new compendia and the review of existing compendia. The NCCN and all its member institutions are not-for-profit organizations.***

The inclusion of the ***NCCN Drugs and Biologics Compendium*** as a mandated reference for Medicare is argued for persuasively by the results of the March 30, 2006 meeting of the ***Medicare Coverage Advisory Committee (MCAC).*** The experts on the MCAC (now the Medicare Evidence Development and Coverage Advisory Committee - MedCAC) identified many characteristics of a "good compendium". The voting members of the MedCAC gave the highest positive scores to the NCCN Compendium ***on all characteristics.*** On the very important issue of *"how confident are you that compendia adhere to evidence-based criteria and processes in making recommendations"*, the NCCN received an aggregate positive score of 4.5 out of 5 with the next closest score being a 3.58.

One of the NCCN's major objectives is to improve the effectiveness and quality of care for patients by developing and disseminating up-to-date, authoritative information to clinicians, patients and other decision-makers. The NCCN shares with our colleagues at CMS the objective of providing access to effective therapies to Medicare beneficiaries. In a rapidly advancing area like cancer care, the establishment of coverage policy based upon the evaluation of safety and effectiveness can be challenging. This is particularly true for decisions about drugs

and biologics. ***The NCCN Drugs and Biologics Compendium*** has been designed and developed as an evidence-based reference to facilitate and substantiate coverage determinations.

The following describes: how the ***NCCN Drugs and Biologics Compendium*** fulfills the definition and the needs of a compendium; how the NCCN Compendium specifically addresses all desirable characteristics of a compendium as defined by the MedCAC and described in documents (Federal Register, Volume 72, Number 133, July 12, 2007 and CMS-1395-C); and provides a summary of important and supporting points, including the broad support in the oncology community and in Medicine for recognition of the NCCN Compendium by CMS.

About *The NCCN Drugs and Biologics Compendium*

The NCCN Compendium provides recommendations about appropriate uses of drugs and biologics in cancer care from 44 multidisciplinary NCCN Guidelines panels with 20-24 experts on each panel participating on an unpaid, volunteer basis and representing different specialties (e.g., medical, surgical, radiation oncology, pathology), subspecialties, clinical professions and patient advocates on certain panels. The panels have geographically diverse representation from across the United States (please see attached list of NCCN Guidelines panel members). Compendium recommendations are evidence-based and are derived directly from the ***NCCN Clinical Practice Guidelines in Oncology*** that are widely recognized and applied as the standard for clinical policy in oncology in the United States. The NCCN Guidelines are being used and cited by private and public payors, including CMS, in coverage policies and determinations. Importantly, on January 16, 2008, UnitedHealthcare announced that the NCCN Compendium would be the basis at United for coverage determinations about drugs and biologics in cancer care (please see attached press release).

The recommendations in the NCCN Compendium are based upon a scientific evaluation of available scientific evidence integrated with expert judgment of the aforementioned more than 800 expert clinicians and patient advocates. The NCCN Compendium is continually updated and is the most up-to-date source of evaluative information and recommendations. A more expanded description of the Compendium and the Guidelines is attached.

Compendium: CMS Definition and Needs

The NCCN Compendium is a comprehensive listing of the drugs and biologics and the recommended uses for such agents in the treatment and management of patients with cancer. The NCCN Compendium is organized by and presented as an alphabetized index of drugs and biologics by generic name. The NCCN Compendium also has a multifactorial search function that allows searching by generic and brand names, histology, pharmacologic class, general indication, etc. Additionally, the NCCN Compendium includes a comprehensive summary of the pharmacologic characteristics of each drug and biologic by direct links from a specific agent in our electronic system to the up-to-date FDA labeled information. As such, information on

clinical pharmacology, warnings, cautions, adverse events, drug interactions, dosing, schedule of administration, etc. is accessed by a single click on the link.

Importantly, the NCCN Compendium is available online at www.nccn.org ***free of charge*** to clinicians, patients, managed care companies, CMS and all other decision-makers. Thus, Medicare beneficiaries and providers have freely available access to NCCN's evaluative information and recommendations that serve as the basis for therapeutic decisions and coverage determinations. In addition to the Compendium, other important and complementary references such as the ***NCCN Clinical Practice Guidelines in Oncology*** for clinicians and the ***Treatment Guidelines for Patients*** also are available free of charge. The NCCN also is developing a set of standard order templates for prescribing drugs and biologics based directly on the NCCN Compendium. The combined guidance available through the NCCN Compendium and its complementary reference resources can serve to better inform decisions, help to assure that patients receive more appropriate, safer and effective care, and enhance the efficiency of care through a systematic evaluative approach.

MedCAC Recommended Desirable Characteristics

The NCCN has included the scores of the MedCAC voting members from the March 30, 2006 meeting evaluating existing drug compendia. The NCCN Compendium received the best score from the voting members on each of the desirable characteristics. The following describes further how the NCCN Compendium meets the desirable characteristics identified by the MedCAC for a drug compendium:

1. *Extensive breadth of listings*: The NCCN Compendium lists 196 drugs and biologics that cover all major tumor types including infrequently occurring cancer diagnoses. The Compendium covers all major supportive care areas and covers agents used in primary and secondary prevention. The recommendations for these drugs and biologics are drawn from 110 NCCN clinical practice guidelines. One advantage of this complementary publication is that NCCN recommendations about the use of drugs and biologics can be viewed in the context of the continuum of care (e.g., surgery, radiation therapy). The exhaustive list of agents in the Compendium is continuously updated. Also, the agents have been mapped to appropriate ICD 9 codes. Further mapping is available to J codes for use by payors.

2. *Quick processing from application for inclusion to listing*: The NCCN has the most efficient system for the tracking of information relevant to NCCN Compendium recommendations. This system results in timely updates to the Compendium. Updates usually occur within two to four weeks of a major new study being published, a major action by the FDA, or other events such as the stopping of a national trial for positive or negative reasons. NCCN has a doctoral level staff charged with prospectively tracking the literature, FDA ruling (e.g., approvals, label changes), and other activity areas as defined by tumor type, supportive care type, or area of prevention (please see attached list of NCCN Guidelines Department staff). Additionally, members of the

NCCN Guidelines panels proactively notify the panel chair and/or NCCN staff about specific clinical issues that need to be addressed. Importantly, NCCN Guidelines panels meet every year. Urgent issues are addressed by additional phone conferences within days of the issue being raised.

The NCCN also has a formal process for processing requests for change to the NCCN Compendium and Guidelines. All interested constituencies of the cancer community are encouraged to submit concise letters of request with concise packets of supporting documentation. NCCN receives requests from pharma/biotech companies, managed care companies, patient advocacy groups, individual clinicians, NCCN member institutions, etc. These requests are evaluated by staff and then the panel chair. Depending upon the cogency of supporting evidence, the issue/request may be placed on the agenda for consideration by the expert panel. It should be noted that annually NCCN member institutions review each of the guidelines and submit comments for consideration regarding possible changes; thus, internal NCCN review extends beyond the hundreds of clinicians on the panels to the thousands of clinicians in NCCN institutions. Importantly, the process for submission of requests for change is outlined on the NCCN web site.

3. *Detailed description of the evidence reviewed for every individual listing*: The NCCN Compendium explicitly categorizes each recommendation by the level of evidence available to support a recommendation for use for that specific agent. The assignment of a category (e.g., high level, lower level) of evidence is achieved through discussions of the results, study design, etc. by the full panel of 20-24 multidisciplinary experts. The NCCN Guidelines cite specific studies that are the basis for recommendations, including those for drugs and biologics. Cited studies are to be found in guideline footnotes and, particularly in the guideline manuscripts that discuss the evidenciary bases for recommendations. Cited studies for individual drugs and biologics tend to be seminal works that have helped define the appropriateness of the specific indication and the appropriate dosing and schedule of administration. The manuscripts also discuss the appropriate place for the use of drugs and biologics in the continuum of care. Finally, evidence supporting FDA-approved indications and other important issues is also described in the FDA labels that the NCCN Compendium links to specifically for each drug or biologic.

   The NCCN will release its Guidelines User System at the end of 2008. This system will be interactive and provide the actual abstracts (and, where available, the studies) that underlie the recommendations for use of drugs and biologics. Additionally, the NCCN is developing a set of standard order templates that specifically define the regimens (including indicated supportive care and monitoring and hold criteria) and cite references supporting such drug/biologics regimens.

   NCCN staff monitors the full literature in oncology on an ongoing basis to identify key new studies for citation and discussion. NCCN panel members are the leading clinical

researchers in oncology and report on important new studies underway or nearing completion.

As indicated above, on the important issue of "how confident are you that compendia adhere to evidence-based criteria and processes in making recommendations", the NCCN Compendium received the best score of 4.5 compared to the next highest score of 3.58 at the MedCAC meeting on March 30, 2006.

4. *Use of pre-specified published criteria for weighing evidence:* The NCCN publishes (below) an explicit and real-world definition of the criteria for weighing and categorizing the evidence that supports the recommendations for drugs and biologics and other health care technologies for specific indications. Clearly, the published criteria directly guide the process for decision-making leading to recommendations in the NCCN Compendium about drugs and biologics. The information is available online for all to read and is provided within the context of an outline and discussion of the evidence-based process that is the foundation for all NCCN recommendations about clinical interventions, including drugs and biologics.

NCCN Categories of Evidence and Consensus:

When studying the recommendations on a pathway, the NCCN Guideline user should be given information about how the recommendation was derived. In order to provide this critical information, the NCCN Guidelines Steering Committee has devised a set of Categories of Evidence and Consensus. These annotations contain two dimensions: the strength of the evidence behind the recommendation and the degree of consensus about its inclusion.

Category of Evidence and Consensus	Quality of Evidence	Level of Consensus
1	High	Uniform
2A	Lower	Uniform
2B	Lower	Non-uniform
3	Any	Major disagreement

Category 1: The recommendation is based on high-level evidence (i.e., high-powered randomized clinical trials or meta-analyses), and the NCCN Guidelines Panel has reached uniform consensus that the recommendation is indicated. In this context, uniform means near unanimous positive support with some possible neutral positions.

Category 2A: The recommendation is based on lower level evidence, but despite the absence of higher level studies, there is uniform consensus that the recommendation is appropriate. Lower

level evidence is interpreted broadly, and runs the gamut from phase II to large cohort studies (Cook, 1992) to case series to individual practitioner experience. Importantly, in many instances, the retrospective studies are derived from clinical experience of treating large numbers of patients at a member institution, so NCCN Guidelines Panel Members have first-hand knowledge of the data. Inevitably, some recommendations must address clinical situations for which limited or no data exist. In these instances the congruence of experience-based judgments provides an informed if not confirmed direction for optimizing patient care. These recommendations carry the implicit recognition that they may be superseded as higher level evidence becomes available or as outcomes-based information becomes more prevalent (Baillard, 1993).

Category 2B: The recommendation is based on lower level evidence, and there is nonuniform consensus that the recommendation should be made. In these instances, because the evidence is not conclusive, institutions take different approaches to the management of a particular clinical scenario. This nonuniform consensus does not represent a major disagreement, rather it recognizes that given imperfect information, institutions may adopt different approaches. A Category 2B designation should signal to the user that more than one approach can be inferred from the existing data.

Category 3: Including the recommendation has engendered a major disagreement among the NCCN Guidelines Panel Members. The level of evidence is not pertinent in this category, because experts can disagree about the significance of high level trials (McNeill, 2001). Several circumstances can cause major disagreements. For example, if substantial data exist about two interventions but they have never been directly compared in a randomized trial, adherents to one set of data may not accept the interpretation of the other side's results. Another situation resulting in a Category 3 designation is when experts disagree about how trial data can be generalized. An example of this is the recommendation for internal mammary node radiation in postmastectomy radiation therapy. One side believed that because the randomized studies included this modality (Woolf, 1997), it must be included in the recommendation. The other side believed, based on the documented additional morbidity and the role of internal mammary radiation therapy in other studies, that this was not necessary. A Category 3 designation alerts users to a major interpretation issue in the data and directs them to the manuscript for an explanation of the controversy.

5. *Use of prescribed published process for making recommendations:* The process for the development of the NCCN Guidelines, from which the NCCN Compendium recommendations are derived, is published online for any user to review and comment on. This online description outlines the process from which all recommendations about drugs and biologics are derived. The NCCN has published this process as articles in ***Oncology*** and thus, these articles with the full description of the process are available in the indexed medical literature (see three citations below). Further, senior NCCN staff make many public presentations every year describing the process or updates to the process for developing recommendations.

Winn RJ, Botnick W, Dozier, N: The NCCN guidelines development program. *Oncology* 10 (suppl 11):23-28, 1996.

Winn, RJ, Botnick, WZ: The NCCN guideline program: A conceptual framework. *Oncology* 11 (suppl 11A):25-32, 1997.

Winn, RJ, Botnick, WZ, Brown, NH: The NCCN guideline program – 1998. *Oncology* 12 (suppl 11A):30-34, 1998.

6. *Publicly transparent process for evaluating therapies:* As discussed above, the full process for the development of recommendations for the NCCN Drugs and Biologics Compendium, as based upon the NCCN Guidelines, is publicly available online and in journal publications. All recommendations and aspects of the NCCN Drugs and Biologics Compendium and the NCCN Guidelines are open for comment and suggestions by all constituencies of the health care community. These comments are carefully and fully considered by NCCN senior staff and by the panel chairs. Upon publication online of every new version of an NCCN Guideline, the third page catalogs and describes all changes and updates as compared to the previous version. Clearly, the published Compendium and guidelines represent the recommendations of the expert panelists after consideration of available evidence and comments and information provided by a variety of constituencies. The content and recommendations of the Compendium and the guidelines are made available at www.nccn.org free of charge for all to view and ultimately comment on. NCCN lists all panel members online at the beginning of every NCCN Guideline. Further, NCCN holds national conferences (with published proceedings) and regional symposia to allow for broader presentation, discussion and input on controversial issues or innovative technologies.

7. *Explicit "Not recommended" listing when validated evidence is appropriate:* The NCCN Compendium and Guidelines use a process of delisting when available evidence validates the deletion of an indication. Examples of deletions or delisting of indications for drugs include: interferon no longer listed for first line use in chronic myelogenous leukemia; gefitinib no longer listed for non-small cell lung cancer; erythropoietic stimulating agents no longer indicated for use in patients not on active treatment or for improvement of quality of life.

8. *Explicit listing and recommendations regarding therapies, including sequential use or combination in relation to other therapies:* The NCCN Compendium is the most specific of all Compendia regarding the appropriate patient population and appropriate circumstance and time (e.g., sequence) for the use of a drug or biologic alone or in specified combination therapy. This fact is best illustrated by specific examples from the NCCN Compendium.

   a. Bevacizumab in colon cancer:

   (i) Neoadjuvant chemotherapy in combination with FOLFOX, FOLFIRI, 5-FU/LV, or CapeOX regimens for patients with synchronous or metachronous liver or lung metastases

   (ii) Adjuvant chemotherapy in combination with FOLFOX, FOLFIRI, 5-FU/LV, or CapeOX regimens for patients with resected synchronous or metachronous liver or lung metastases

   (iii) Initial therapy in the following regimens for patients with unresectable advanced or metastatic disease:

   - in combination with FOLFOX, FOLFIRI, 5-FU/LV, or CapeOX regimens for those who can tolerate intensive therapy

- in combination with infusional 5-FU/LV, or capecitabine for those who cannot tolerate intensive therapy

NCCN Compendium indications above discuss the timing (e.g., neoadjuvant, initial therapy), the combinations (e.g., with FOLFOX), sites of metastases, etc.

b. Cetuximab in colon cancer:

(i) Therapy as a single agent or in combination with irinotecan or FOLFIRI regimen after first, second, or third progression of disease for patients with unresectable advanced or metastatic disease. Not recommended for patients with disease progression on panitumumab. Single agent recommended only for patients not able to tolerate cetuximab plus irinotecan

(ii) Single agent (PS 0-2 patients) or in combination with cisplatin (PS 0-1 patients) for the following indications:

- unresectable locoregional recurrence or second primary in patients who have received prior radiation therapy

- distant metastases

NCCN Compendium indications above specify the combination, the line of therapy in the metastatic setting and, in the latter cetuximab indication, performance status (PS); thus indicating that the recommendation pertains to patients with a PS of 0-2 and not to patients with a status of 3 or 4. As noted, NCCN Compendium recommended indications are clearly the most specific.

The sequencing of drug recommendations can be followed directly in the relevant guideline as the algorithm provides a sequential pathway for the delivery of drugs, biologics, surgical procedures, radiation, etc. Finally, as mentioned above, the NCCN is developing an information product directly complementary to the NCCN Compendium. The set of NCCN standard order templates will specify the chemotherapy regimen with doses, routes of administration, time frames and delivery days. These templates will also specify appropriate antiemetic and supportive care treatments, monitoring and hold parameters (e.g., liver function tests, hydration needs) and safety parameters, as well as provide supporting references.

9. *Explicit "Equivocal" listing when validated evidence is equivocal*: The NCCN Compendium specifies with particularity the indication for which a drug or biologic should be used. For example, a few drugs for a few indications are recommended to be prescribed only in the setting of a clinical trial. The NCCN Compendium takes a consistent approach in recommending drugs only in a specific setting.

10. *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 has a specific policy and process (please see attached) for the identification of potential conflicts of interest and a notification process to communicate to the NCCN staff, fellow panel members, payors and to the public at-large these potential conflicts. Additionally, the policy and

processes address specifically the management and handling (e.g., recusals) of particular types of potential conflict.

The NCCN policy defines pertinent terms such as "conflicting interest", "direct relationship", "indirect relationship", "external entity", etc. The policy directs the processes for disclosure, for consideration of potential conflicts, for participation and exclusion from meetings and discussions, for internal and public disclosures, and for sanctions. The actual disclosure form has been attached.

The NCCN publicly discloses a listing of all potential conflicts of interest (e.g., managed care companies, pharma/biotech, patient advocacy groups, government entities) with the publication of each relevant NCCN Guideline online. Additionally, each publication of an NCCN Guideline in ***JNCCN*** has the same listing of potential conflicts. Also, NCCN provides a full disclosure of every organization that has provided funding to the NCCN at www.nccn.org.

The open, direct and complete provision of such information is important for the end user of NCCN resources to inform the decision-making process.

Summary of Supporting Points

- The ***NCCN Drugs and Biologics Compendium*** is a comprehensive listing of the drugs and biologics used in cancer care and their recommended uses/indications. The NCCN Compendium provides an alphabetized listing indexed by the generic names of the drugs and biologics, full search capacity, and a complete description of pharmacological characteristics and actions through links to the most recent FDA labels.

- The NCCN Compendium received the best scores from the voting members of the MedCAC on the desired characteristics including the evidenciary basis of the NCCN process, the transparency of the process and our handling of potential conflicts of interest.

- All NCCN information products, including the NCCN Compendium, are available ***free of charge*** at www.nccn.org.

- The recommendations in the ***NCCN Drugs and Biologics Compendium*** represent the standard for clinical policy in the United States as they are derived directly from the ***NCCN Clinical Practice Guidelines in Oncology.***

- ***All major oncology organizations (e.g., ASCO, ACCC, ONS), the AMA, and a host of other organizations (e.g., NPAF) have written in strong support of the recognition by CMS of the NCCN Drugs and Biologics Compendium as a mandated reference for the determination of coverage policy regarding the use of***

drugs and biologics in cancer care. Letters from these organizations have been included.

- NCCN panels have over 800 unpaid volunteer expert participants and perspectives, are multidisciplinary in nature, have broad geographic distribution, and follow a formal conflict of interest identification, participation/exclusion and disclosure process. All this minimizes bias in the recommendations.

- UnitedHealthcare announced on January 16, 2008 that it would base its drug coverage policies in cancer care on the NCCN Compendium beginning on March 15, 2008.

- The NCCN Compendium has 10,420 registered online users (most likely the largest number of any Compendium). Of the registered users, 3755 identify themselves as physicians, 1924 as nurses, 645 as affiliated with managed care companies, 534 as affiliated with employers, 1866 as educators, etc.

- As indicated on page 38219 of the July 12, 2007 FR notice and in CBO scoring of the House S-CHIP/Medicare Bill (Section 224), addition of compendia through the CMS process will have a "negligible cost" or "zero" cost impact.

- The evidence-based, authoritative, comprehensive and specific recommendations in the NCCN Compendium, NCCN Guidelines and NCCN standard order templates are complementary in improving the quality of cancer care. The specificity of Compendium recommendations will provide direct and clear guidance to intermediaries and carriers.

- The use of the NCCN Compendium in combination with the NCCN standard order templates by clinicians will serve to improve safety for patients.

- NCCN, in collaboration with the American Cancer Society, makes ***Treatment Guidelines for Patients*** available to patients. These patient guidelines are translated directly from the NCCN professional guidelines and, of course, are available free of charge. Patients also are free to view the NCCN Clinical Practice Guidelines for professionals online at www.nccn.org.

- NCCN will establish a proactive electronic process to transmit all changes and updates to CMS and to its intermediaries and carriers. The NCCN will communicate such revisions to the NCCN Compendium well within the 45-day time period suggested in the July 12, 2007 FR notice.

- The NCCN and all its member organizations are not-for-profit organizations.