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 DrugPoints Compendium as an Authoritative Compendium for Medicare Coverage Purposes

Dear Dr. Phurrough:

The American Society of Clinical Oncology (ASCO) requests that CMS add the DrugPoints 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, DrugPoints 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 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 DrugPoints 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 DrugPoints published by Thomson Micromedex. We believe that Thomson Micromedex will make the online version available to CMS for purposes of this review. The information contained in DrugPoints is derived from and summarizes more detailed information from Micromedex's DrugDex Information System (DrugDex). DrugPoints users who want more detailed information about a particular drug can click on a link that takes them directly to the corresponding section for that drug in DrugDex. DrugPoints is the successor publication to the U.S. Pharmacopoeia – Drug Information, which is one of the authoritative compendia specified in the Act.

Definition of compendium

DrugPoints 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]

DrugPoints is a comprehensive listing of over 1,400 drugs and biologicals that is indexed by drug and biological. Each drug listing contains information about pharmacokinetics, dosing, route of administration, indications, drug interactions, and toxicology. In addition, DrugPoints assigns rankings to each indication to help users determine whether the use of a drug for a particular indication is recommended. Therefore, DrugPoints 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;
- explicit "not recommended" listing when validated evidence is appropriate;

[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 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 DrugPoints (and DrugDex from which it is derived) satisfies these characteristics. Examples from DrugDex serve only to demonstrate the depth of information that DrugPoints users have access to and the source of content for DrugPoints; ASCO is not requesting that CMS add DrugDex to Section 1861(t)(2)(B)(ii)(I) of the Act.

Extensive breadth of listings. DrugPoints is a comprehensive compendium that lists over 1,400 drugs, including prescription, non-prescription, and investigational drugs, and provides recommendations for both FDA-approved and unapproved uses.[3] In a Technology Assessment commissioned by CMS, researchers found that DrugDex was the only compendium researched to list all 14 off-label agent-cancer combinations examined during the study. Ten of these combinations are included in DrugPoints.[4] This demonstrates the breadth and yet careful selection of drug listings contained in DrugPoints. To demonstrate the breadth of a single listing, the listing for gemcitabine hydrochloride in DrugDex provides information about 29 indications, 15 of which are included in the DrugPoints summary.

Quick throughput from application for inclusion to listing. The online version of DrugPoints is reviewed and updated weekly to incorporate new evidence and innovative therapies.[5] From August 2007 to November 2007 alone, Micromedex revised DrugPoints to add 8 new documents, update 127 documents, and retire one document.[6] Users can identify the specific documents that have been added or updated by clicking a link entitled "Content Updates." As an example, the DrugPoints and DrugDex listings for interferon alfa-2b were updated between August and November 2007 to include references to three studies published in 2007, including one abstract presented at the June 2007 ASCO Annual Meeting only months before.[7]

Detailed description of the evidence reviewed for every individual listing. DrugPoints contains a summary listing of the references contained in DrugDex, which are comprehensive

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[3] Thomson Micromedex. DrugPoints system. (Accessed at http://www.micromedex.com/products/drugpoints).

[4] 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) [hereinafter Technology Assessment].

[5] *Id.*

[6] DrugPoints.

[7] DrugDex listing for interferon alfa-2b (citing Gogas, H. A randomized phase III trial of 1 month versus 1 year adjuvant high-dose interferon alfa-2b in patients with resected high risk melanoma [electronic slides]. American Society of Clinical Oncologists. 2007. (Accessed at www.asco.org)).

and linked to relevant text. Each DrugDex listing cites numerous studies, with a detailed description of selected studies, for each indication listed for a particular drug. For example, DrugPoints lists as an indication for bevacizumab the treatment of metastatic breast cancer as first-line therapy in combination with paclitaxel. The corresponding DrugDex section cites five studies to support this indication and its DrugDex rating, describing the most recent study – a 2005 abstract presenting interim results of a phase III clinical trial – in some detail.[8] The 2005 abstract is also listed as one of seven references in the DrugPoints listing for bevacizumab. Notably, the trial described in this abstract was the only phase III trial regarding this combination of drugs identified by researchers conducting the Technology Assessment.[9]

Use of pre-specified published criteria for weighing evidence. For each indication listed for a particular drug, DrugPoints and DrugDex include a separate rating to designate (1) the strength of evidence, (2) the strength of recommendation for that indication, and (3) whether evidence favors efficacy. For each rating, DrugPoints indicates whether data is adult or pediatric. In DrugPoints, users access this rating by clicking on the information symbol next to a particular indication. Ratings appear under the "Therapeutic Uses" section in DrugDex. Users may link from DrugDex to a description of Micromedex's process for determining these ratings by clicking the link next to each rating entitled "Recommendation and Evidence Ratings." Micromedex ranks strength of evidence as follows:

- **Category A:** Data is derived from meta-analyses of randomized controlled trials (RCTs) with homogeneity or multiple, well-done RCTs involving large numbers of patients.
- **Category B:** Data is derived from meta-analyses of RCTs with heterogeneity, RCTs involving small numbers of patients, RCTs with significant methodological flaws, or non-randomized studies.
- **Category C:** Data is derived from expert opinion or consensus, case reports, or case series.

Micromedex provides recommendations as follows:

- **Class I:** Recommended. The test or treatment has been proven to be useful and should be performed or administered.
- **Class IIa:** Recommended in most cases. The test or treatment is generally considered to be useful and is indicated in most cases.
- **Class IIb:** Recommended in some cases. The test or treatment may be useful, and is indicated in some, but not most, cases.
- **Class III:** The given test or treatment is not useful and should be avoided.

[8] DrugDex listing for bevacizumab (citing among other studies Miller KD, Wang M, Gralow J. A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer. J Clin Oncol 2005;16(Suppl):[E2100]-). *See also* Technology Assessment, *supra* note 4.

[9] Technology Assessment, *supra* note 4.

- **Class indeterminate:** Evidence is inconclusive.

Finally, Micromedex ranks efficacy as follows:

- **Effective:** Evidence and/or expert opinion suggests that a given drug treatment for a specific indication is effective.
- **Evidence favors efficacy:** Evidence and/or expert opinion conflicts as to whether a given drug treatment for a specific indication is effective, but the weight of evidence and/or expert opinion favors efficacy.
- **Evidence is inconclusive:** Evidence and/or expert opinion conflicts as to whether a given drug treatment for a specific indication is effective, but the weight of evidence and/or expert opinion argues against efficacy.
- **Ineffective:** Evidence and/or expert opinion suggests that a given drug treatment for a specific indication is ineffective.

According to an explanation issued by Micromedex, an unapproved indication is listed in DrugPoints if the indication is rated (1) recommended (Class I), (2) effective or evidence favors efficacy and recommended in most cases (Class IIa), or (3) effective or evidence favors efficacy, recommended in some cases (Class IIb), *and* the strength of evidence is Category A or B.[10] In other words, if the unapproved indication is "recommended in some cases," the indication will be listed in DrugDex but not DrugPoints if the supporting evidence is Category C.

Use of prescribed published process for making recommendations. DrugPoints users can access detailed descriptions of the process used to develop listings and the DrugPoints ratings for indicated uses by clicking a link entitled "Editorial Info." This process, which is the same for all Micromedex products, is summarized below.

Literature searches and identifying topics for inclusion. Micromedex staff members conduct ongoing literature searches to identify new literature and conduct a full-text analysis of selected literature. For off-label indications, staff specifically look for negative or inconclusive findings to ensure that all relevant literature is identified. Senior editorial staff at Micromedex then select topics for inclusion in DrugPoints based on these literature searches, their own clinical experience, FDA approvals, suggestions from Micromedex editorial boards, policies from health organizations, external requests, and other sources.[11] Staff members forward literature that is relevant to the selected topics to clinical writers for further consideration for inclusion in DrugPoints.

[10] Compendium update: Changes to the USP DI Drug Information. Onc Issues 2007:8-9. (Accessed at http://accc-cancer.org/ONIS/articles/julaug07/issues.pdf).

[11] Thomson Micromedex. Editorial workflow. (Accessed at http://www.micromedex.com/about_us/editorial/ed_process.pdf).

Content development. Clinical writers assess the quality of the literature selected from literature searches, assessing both its methodological rigor and clinical relevance. If writers determine that it is appropriate to include the literature in DrugPoints, they summarize the literature using Micromedex's Content Management System, assign rankings, and forward the content they have created for internal review.[12]

Internal review. A senior clinical staff member reviews all new content to determine not only its clinical accuracy and the accuracy of ratings, but also whether it follows all Micromedex stylistic and other policies. This staff member provides feedback to the writer on an ongoing basis.[13]

Oncology Advisory Board review. The Oncology Advisory Board also reviews all new unapproved indications related to oncology, as well as significant ratings changes related to oncology. Members must be practicing physicians with at least five years of clinical experience and board certification in oncology or practicing pharmacists with at least five years of clinical experience and board certification and/or advanced training in oncology.[14]

Preparation for publication. A senior clinical staff member incorporates all feedback from the previous stages of review. Once this occurs, the content is available for publication in DrugPoints.[15]

Publicly transparent process for evaluating therapies. Interested parties may request that certain information be included in DrugPoints by following Micromedex's established procedures for making a request.[16] While Micromedex acknowledges all external requests, it does not provide requesters with any additional feedback or responses. However, the fact that the Micromedex's process for evaluating information for inclusion in DrugPoints is published, as described above, ensures that there is sufficient transparency.

Explicit "Not recommended" listing when validated evidence is appropriate. Micromedex has made the editorial decision not to include those indications with a rating of "not recommended" in DrugPoints. This ensures that users have access to indications supported by the best evidence. DrugDex, however, explicitly rates an indicated use Class III – not recommended – when validated evidence suggests that the treatment is not useful and should be avoided. For example, DrugDex rates as Class III the use of oxaliplatin for pancreatic cancer as first-line therapy in combination with gemcitabine. In support of this rating, DrugDex cites two

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[12] *Id.*

[13] *Id.*

[14] Thomson Micromedex. Off-label indications. (Accessed at http://www.micromedex.com/about_us/editorial/ed_Off_Label.pdf).

[15] Thomson Micromedex. Editorial workflow. (Accessed at http://www.micromedex.com/about_us/editorial/ed_process.pdf).

[16] Thomson Micromedex. Requesting inclusion of information in Thomson Micromedex databases. (Accessed at http://www.micromedex.com/about_us/editorial/ed_external_reqs.pdf).

large, phase III RCTs, both of which showed no additional survival benefit when oxaliplatin was added to gemcitabine to treat this patient population. Thus, DrugPoints users have access to "not recommended" listings even though these listings do not appear in DrugPoints itself.

Explicit listing and recommendations regarding therapies, including sequential use or combination in relation to other therapies. The therapeutic uses listed in DrugPoints indicate whether a particular use is appropriate as 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. Micromedex's rating of therapeutic uses may vary based on the sequence or combination. DrugPoints users also have access to a description of the comparative efficacy of a drug as compared to other drug therapies in DrugDex if there is support for a comparison from clinical trials. The examples in the chart below from the listing for rituximab and docetaxel demonstrate the specificity of the therapeutic uses listed in DrugPoints.

Drug	Therapeutic use	Micromedex Ranking
Rituximab	Chronic lymphoid leukemia, in combination for first-line treatment	Efficacy: Adult, evidence favors efficacy Recommendation: Adult, Class IIa Strength of evidence: Adult, Category B
Rituximab	Chronic lymphoid leukemia, relapsed or refractory	Efficacy: Adult, evidence favors efficacy Recommendation: Adult, Class IIb Strength of evidence: Adult, Category B
Docetaxel	Breast cancer, locally advanced/metastatic disease, as first-line chemotherapy	Efficacy: Adult, evidence favors efficacy Recommendation: Adult, Class IIb Strength of evidence: Adult, Category B
Docetaxel	Breast cancer, neoadjuvant treatment in combination with an anthracycline-containing regimen	Efficacy: Adult, evidence favors efficacy Recommendation: Adult, Class IIb Strength of evidence: Adult, Category B

Explicit "Equivocal" listing when validated evidence is equivocal. Micromedex explicitly ranks an indicated use as "class indeterminate" when staff are unable to provide a strength of recommendation ranking because evidence is inconclusive. Again, Micromedex has made the editorial decision not to include indications with this rating in DrugPoints, but these indications are included in DrugDex. For example, the use of abatacept to treat psoriasis vulgaris received a "class indeterminate" ranking where the only evidence supporting this use was a phase I trial. Micromedex also uses a ranking of "class indeterminate" to indicate that a drug is currently under investigation, as with the listing of abatacept to treat juvenile rheumatoid arthritis. In addition, an efficacy rating of either "evidence favors efficacy" or "evidence is inconclusive" suggests that 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. Micromedex maintains a written conflict of interest policy to ensure that those participating in content development are not biased. DrugPoints users can access this policy by clicking on a link entitled "Editorial Info." The policy establishes different rules depending on the type of conflict present, as described in the chart below.[17]

Type of conflict	Definition of conflict	Rule
Employment or leadership position	An individual (1) is currently or was within the past six months an employee of a pharmaceutical company; or (2) is or was within the past six months a director or partner of a pharmaceutical company. The individual's spouse is a director, officer, or partner of a pharmaceutical company.	Exclusion from participation.
Equity or stock ownership	An individual or the individual's spouse has stock or equity ownership in a pharmaceutical company and has direct control over the disposition of this ownership interest.	Individual can participate but must disclose conflict if ownership in any single pharmaceutical company between $25,000 and $100,000. Exclusion from participation if ownership in any single pharmaceutical company > $100,000.
Other payments	Payments to an individual or the individual's spouse for service as an advisor or consultant, lecture fees, and	Individual can participate but must disclose conflict if combined payments within the last 12 months

[17] Thomson Micromedex. Conflict of interest policy. (Accessed at http://www.micromedex.com/about_us/editorial/ed_ConflictofInterest.pdf).

	other honoraria from pharmaceutical companies.	from a single pharmaceutical company between $25,000 and $100,000. Exclusion from participation if combined payments within the last 12 months from a single pharmaceutical company > $100,000.
Research funding	Receipt of payment as a principal investigator in the previous 12 months.	Disclosure of conflict required. Participation prohibited if research is that of the individual or his or her spouse.
Related intellectual property rights	An individual or the individual's spouse holds a patent or other intellectual property rights in a drug that is the subject of current content development, or that is related to current content development as determined by the Editorial Department.	Exclusion from participation.
Unrelated intellectual property rights	An individual or the individual's spouse receives payments based on intellectual property rights in a drug that is unrelated to current content development as determined by the Editorial Department.	Individual can participate but must disclose conflict if combined payments within the last 12 months from a single pharmaceutical company between $25,000 and $100,000. Exclusion from participation if combined payments within the last 12 months from a single pharmaceutical company > $100,000.

Micromedex publishes all required disclosures on its website. DrugPoints users may identify the conflicts disclosed by each individual member of the Oncology Advisory Board and other editorial boards by clicking a name and linking to that individual's conflict of interest statement.[18]

[18] *See* Thomson Micromedex. Oncology Advisory Board. (Accessed at http://www.micromedex.com/about_us/editorial/boards/oncology_board.html).

Conclusion

Given the evidence that DrugPoints meets CMS's definition of a compendium and satisfies the desirable characteristics of a compendium described by CMS in its final rule, ASCO requests that CMS add DrugPoints to the list of authoritative compendia specified in Section 1861(t)(2)(B)(ii)(I) of the Social Security Act.

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

Sincerely,

Joseph S. Bailes, MD
Chair, Government Relations Council

cc: Louis Jacques, MD