



American Society of  
Health-System Pharmacists  
7272 Wisconsin Avenue  
Bethesda, Maryland 20814  
(301) 657-3000  
Fax: (301) 664-8877  
[www.ashp.org](http://www.ashp.org)

August 31, 2007

Centers for Medicare & Medicaid Services  
Department of Health and Human Services  
Attention: CMS-1385-P  
P.O. Box 8018  
Baltimore, MD 21244-8018

**Re: CMS-1385-P; RIN 0938-AO65; Medicare Program; Proposed Revisions to Payment Policies Under the Physician Fee Schedule, and Other Part B Payment Policies for CY 2008; Proposed Revisions to the Payment Policies of Ambulance Services Under the Ambulance Fee Schedule for CY 2008; and the Proposed Elimination of the E-Prescribing Exemption for Computer-Generated Facsimile Transmissions; Proposed Rule**

Dear Sir/Madam:

The American Society of Health-System Pharmacists (ASHP) is pleased to submit written comments pertaining to compendia for determination of medically accepted indications for off-label uses of drugs and biologicals in an anti-cancer chemotherapeutic regimen. ASHP represents pharmacists who practice in hospitals and health systems. The Society's more than 30,000 members include pharmacists and pharmacy technicians who practice in a variety of health-system settings, including inpatient, outpatient, home care, and long-term-care settings.

ASHP is also the publisher of AHFS Drug Information (DI), a comprehensive, independent reference on the clinical use of medications marketed in the United States. Published continuously for 49 years, AHFS DI is recognized through federal legislation and regulation as an official compendium for information on medically accepted uses of medications.

**DRUG COMPENDIA**

ASHP commends CMS for proposing a process to determine changes to the drug compendia list, and applauds CMS's interpretation of the Deficit Reduction Act (DRA)

regarding successor versus substitute publication for USP DI. ASHP also commends CMS's decision to consider whether a compendium contains the MedCAC-recommended desirable characteristics when reviewing requests for change to the list of compendia. However, ASHP recommends that the extensive breadth of listings characteristic not be a principal determinant in judging the merits of compendial designation; the quality of review and associated processes, not the quantity of listings, are most important in assessing compendial merits. Additionally, ASHP believes that, in addition to the MedCAC-recommended desirable characteristics, the compendia review process should include a strong emphasis on the need for appropriate processes, including editorial independence, which is essential to a designated drug compendium. Finally, CMS should ensure that its process for review is as rigorous as the Health Care Financing Administration's (HCFA) review was when AHFS became a recognized compendium.

ASHP is also concerned about any reliance by CMS on the Technology Assessment of drug compendia used to determine medically accepted uses of drugs and biologicals in an anti-cancer chemotherapeutic regimen commissioned from the Agency for Healthcare Research and Quality (AHRQ). ASHP submitted comments to CMS regarding the draft report (please see Appendix A, Peer Review Checklist); however, these comments were not addressed in the final report. Additionally, the report focused on the quantity of cited references and did not address the quality of those studies as evidence. Evidence quality should have been measured in order for the report to be considered a useful assessment.

ASHP makes the following specific recommendations to CMS:

- ASHP agrees with CMS that recognition of the USP DI compendium after its name change should not continue if the Secretary determines it is now a substitute publication.
- ASHP cautions CMS in its consideration of extending compendial status for Medicare Part B to Thomson's Drugdex database.
- ASHP strongly recommends that the proposed extensive breadth of listing characteristic not be used as a primary determinant in judging the merits of compendial designation.
- ASHP strongly recommends that CMS add the following characteristic to the list of MedCAC-recommended desirable characteristics of compendia CMS will consider when reviewing requests:
  - Inclusion of safety information for oncology drugs
- ASHP strongly recommends that, in addition to the MedCAC-recommended desirable characteristics, the review process include a strong emphasis on the need for an appropriate process, including editorial independence, which is essential to a designated drug compendium.

- ASHP strongly recommends that CMS add the following characteristics to the list of MedCAC-recommended desirable characteristics of compendia CMS will consider when reviewing requests:
  - High-quality, controlled content development
  - Well-established expert-review process
  - Demonstrated independence from pharmaceutical manufacturers, health insurances, and pharmacy benefits managers
  - Demonstrated evidence-based objectivity
- However, the Society also recommends that CMS ensure that its process for determining changes to the compendia list remains as rigorous as the process used by HCFA when AHFS DI was included as one of the three original drug compendia.
- ASHP strongly recommends that, because AHFS DI went through a rigorous review process prior to its designation, AHFS DI, as well as any other compendium approved under such a rigorous process, should be evaluated by CMS every five years, rather than every year.

### **Successor v. Substitute Publication**

ASHP applauds CMS's interpretation of section 6001(f)(1) of the DRA that amends both sections 1927(g)(1)(B)(i)(II) and 1861(t)(2)(B)(ii)(I) of the Social Security Act (the Act) by inserting "(or its successor publications)" after "United States Pharmacopeia-Drug Information." CMS interprets this DRA provision as explicitly authorizing the Secretary to continue recognition of the compendium currently known as USP DI after its name change, if the Secretary determines that it is in fact a successor publication, rather than a substitute publication.

- **ASHP agrees with CMS that recognition of the USP DI compendium after its name change should not continue if the Secretary determines it is now a substitute publication.**

In 2007, Thomson Healthcare announced that it was replacing the USP DI with its own previously existing DrugPoints database.<sup>1</sup> While Thomson chose to use the term "succeeded" in its press release announcing the change to subscribers,<sup>2</sup> DrugPoints clearly is not a "successor" database since it bears little resemblance to the previous USP DI database in content or editorial oversight by USP's Expert Committees, and it existed

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<sup>1</sup> Thomson Healthcare. Important notice: USP DI drug information for the health care professional. Greenwood, CO; 2007 May. Press release No. HC-4684b rev 05/07.

<sup>2</sup> Id.

simultaneously for many years in Thomson's drug database collection. If CMS is unable to determine whether DrugPoints is a successor or substitute publication, ASHP recommends that CMS contact the originator of USP DI, the United States Pharmacopeial Convention (USP), to advise CMS about the nature of DrugPoints relative to USP DI.

- **ASHP also cautions CMS in its consideration of extending compendial status for Medicare Part B to Thomson's Drugdex database.**

Unlike the original three compendia (AHFS DI, AMA DE, and USP DI), Drugdex was never subject to the same rigorous review by Congress and CMS or opportunity for public comment in the *Federal Register*.<sup>3,4,5</sup> Instead, it achieved compendial recognition for Medicaid by amendment to unrelated legislation and for Medicare Part D by reference to the Medicaid language.<sup>6</sup> While not a scientific analysis by any means, in an October 23, 2003 *Wall Street Journal* article, a prominent investigative reporter questioned Drugdex's editorial approach to evidence as well as connections with the pharmaceutical industry (one cited example in the report was the use by Drugdex of a paid pharmaceutical manufacturer consultant to author the gabapentin [Neurontin] monograph).<sup>7</sup> The policy implications on coverage decisions were substantial, costing state Medicaid programs considerable resources.<sup>8</sup> Drugdex subsequently deleted all author attributions in their database (fall 2005), so it is no longer possible to determine the extent to which such authors have been used and still remain. Unfortunately, neither AHRQ's Technology Assessment nor CMS's MedCAC public meeting on March 30, 2006, probed this editorial record.

### **MedCAC Desirable Compendial Characteristics**

ASHP generally agrees with the MedCAC desirable characteristics identified in the Proposed Rule. In addition, ASHP believes that sound, independent, evidence-based policies are the most critical element in establishing compendial merits.

In 2005, assessment of the loss of USP's evidence-based development process for off-label antineoplastic uses led ASHP to consult with oncology experts to develop a codified model for summarizing AHFS' evidence-based analyses of cancer uses for drugs. The

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<sup>3</sup> Armstrong D. How drug directory helps raise tab for Medicaid and insurers. *Wall Street Journal*. October 23, 2003:A1.

<sup>4</sup> Health Care Financing Administration. Medicare program; catastrophic outpatient drug benefit. 21 CFR Part 410. Proposed rule. [BPD-613-P; RIN 0938-AD91] *Fed. Regist.* 1989;54:37190-37208.

<sup>5</sup> Legislative History for compendial designation for Drugdex: 104<sup>th</sup> Congress Balanced Budget Act of 1995 (vetoed by President) 105<sup>th</sup> Congress H.R. 3507 Personal Responsibility and Work Opportunity Act of 1996 (not passed)

<sup>6</sup> Id.

<sup>7</sup> Armstrong D. How drug directory helps raise tab for Medicaid and insurers. *Wall Street Journal*. October 23, 2003:A1.

<sup>8</sup> Id.

goal was to develop a model that provided succinct codified conclusions about specific off-label uses that would be readily actionable. Background information was provided to CMS as part of the AHRQ Technology Assessment in 2006. In the intervening year, ASHP has continued to refine its model.

The characteristics of this codified AHFS model are consistent with those identified as desirable by MedCAC, including expanded coverage (listings); quick throughput; provision of detailed evidence tables in support of each individual assessment, including strength of end point; use of pre-specified criteria for weighing evidence; a well-defined expert-review process with clear strengths of recommendation; a publicly transparent process with editorial independence and firewalls; an explicit “not recommended” category that includes therapy considered inappropriate, obsolete, or unproven; an explicit “not fully established” category that includes equivocal evidence and uses with unclear risk/benefit; explicit recommendations concerning sequential and combination therapies; and a process for identification and notification of potential conflicts of interest. ASHP has received favorable comments from CMS, oncology experts, and others regarding this model. Current plans are to roll it out later this year.

### **Breadth of Listings**

ASHP commends CMS’s decision to consider whether a compendium contains the MedCAC-recommended desirable characteristics when reviewing requests for change to the list of compendia.

- **However, the Society strongly recommends that the proposed extensive breadth of listing characteristic not be used as a primary determinant in judging the merits of compendial designation.**

While ASHP recognizes the importance of expanding the coverage of off-label anti-cancer uses in its compendium (and has launched a program to address the gap created by USP’s exit from focused attention to this therapeutic area), the quality of review and associated processes, not the quantity of listings, are most important in assessing compendial merits. In fact, a principal flaw with CMS’s commissioned AHRQ Technology Assessment was its focus on quantifying study citations rather than on assessing the true quality of the evidence that these studies represented.

ASHP believes that a compendium should engage in evidence-based processes that are guided by objective evaluation of the level of evidence according to a well-defined process, and should not to be driven by goals of achieving extensive listings at the expense of quality assessment. The 2003 *Wall Street Journal* report on the effects of overly broad listings of uses documented the severe negative effects of this approach on government expenditures.<sup>9</sup> To require a compendium to have an extensive breadth of

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<sup>9</sup> Id.

listings will encourage the listing of off-label uses for which there may be insufficient evidence to either include or exclude.

In the AHRQ Technology Assessment, the emphasis seemed to be on cataloguing all available evidence regardless of quality and merit while discounting the value of editorial process, evidence analysis, expert review, and clinical judgment. Would this approach, i.e., cataloguing all available evidence, be a worthwhile consumption of considerable compendial resources versus emphasizing an ongoing method of reviewing research, evaluating evidence quality, soliciting expert advice about levels of evidence and strengths of recommendation, and then reporting what is relevant according to explicit criteria and reporting methods? ASHP thinks that it would not, and therefore encourages CMS to emphasize the qualitative not quantitative aspects of the process in determining compendial merit.

ASHP remains committed to expanding its timely coverage of off-label anti-cancer uses in a manner that fully embodies the desirable characteristics identified by MedCAC; However, this process should be driven by established principles of evidence-based quality review rather than arbitrary goals of citation quantity. To this end, ASHP's compendial staff is being expanded by at least five full-time employees, including recruitment of a Board Certified Oncology Pharmacist. The result will be an increased breadth of off-label oncology assessment but not one driven by numbers alone.

A basic value among health professionals and the public is that health care practices (including the use of prescription medicines) must be based on evidence of net benefit to the patient (positive outcomes exceeding negative outcomes). Any standard of care lower than this may result in harm to the patient's clinical condition, emotional state, or quality of life, as well as be wasteful of the patient's or society's financial resources. These issues escalate in importance as the cost of a therapy increases. With respect to drug therapy, a too-lax standard for assessing the evidence supporting off-label use could have real consequences for the patient such as delaying or precluding more effective treatment or fostering unfounded hope for improvement in health status.

### **Safety and Effectiveness**

One important desirable characteristic missing from the Proposed Rule that was discussed by AHRQ and MedCAC was inclusion of safety information. In the current environment of increased attention to safe medication use, it is critical, not just desirable, that drug safety issues be weighed in any therapeutic decision. In fact, the strength of recommendation for a given off-label use can be greatly affected by its toxicity profile relative to other therapies and potentially can obscure clinical evidence findings either positively or negatively.

- **ASHP strongly recommends that CMS add the following characteristic to the list of MedCAC-recommended desirable characteristics of compendia CMS will consider when reviewing requests:**
  - **Inclusion of safety information for oncology drugs.**

**Appropriate Process and Editorial Independence**

- **ASHP strongly recommends that, in addition to the MedCAC-recommended desirable characteristics, the review process include a strong emphasis on the need for an appropriate process, including editorial independence, which is essential to a designated drug compendium.**

An ideal source for drug information aimed at fostering safe and effective medication use should provide dependable, objective, authoritative information in the context of sound editorial policies; high-quality, controlled content development; a well-established expert-review process; independence from pharmaceutical manufacturers, health insurers, pharmacy benefits managers, and others who may seek to use the source to promote their own interests; an ongoing updating process; a mechanism for correction notification; and broad-based authoritative guideline incorporation. A key aspect of such a resource is the evidence-based objectivity that allows the inclusion of uses and dosages that are not included in the FDA-approved labeling (i.e., off-label/unlabeled uses).

- **ASHP strongly recommends that CMS add the following characteristics to the list of MedCAC-recommended desirable characteristics of compendia CMS will consider when reviewing requests:**
  - **High-quality, controlled content development**
  - **Well-established expert-review process**
  - **Demonstrated independence from pharmaceutical manufacturers, health insurers, and pharmacy benefits managers**
  - **Demonstrated evidence-based objectivity**

Recognition of the authority of a drug information source by professional, government, legislative, regulatory, and private-sector groups should be linked to the strength of its editorial process and the dependability of the information it provides. It also is important that the information be free of undue influence of pharmaceutical manufacturers and other third parties who may seek to use the publication to promote their own interests.

An appropriate process for developing authoritative drug information should involve several key steps: information tracking and gathering, evidence-based information analysis, drug information synthesis and development, a review process, and finalization and management of published information; the process should be well documented, transparent and independent. Maintenance efforts should include periodic updating to

accommodate new information and an assertive accessible alerting and correction-notification process.

AHFS DI applies all of these key steps in its process and is widely trusted for its established record in refuting unfounded efficacy claims, its rigorous science-based editorial process, and its independence from the influence of pharmaceutical manufacturers. (See Appendix B, policy relating to editorial independence of AHFS Drug Information approved by the ASHP Committee on Publications and Board of Directors).

### **Rigorous Review**

ASHP commends CMS for its proposal to create a process incorporating public notice and comment to receive and make determinations regarding requests for changes to the list of compendia used to determine medically accepted indications for drugs and biologicals used in anti-cancer treatment.

- **However, the Society also recommends that CMS ensure that its process for determining changes to the compendia list remains as rigorous as the process used by HCFA when AHFS DI was included as one of the three original drug compendia (See Appendix C, Overview of AHFS DI HCFA Review Process).**

This rigorous review by HCFA was an extremely important process, since it ensured that any approved compendium contributed to the information sources available to CMS to determine coverage for appropriate indications. Because of the process AHFS DI went through, CMS should maintain AHFS DI as an approved compendia, and require all other compendia to go through such a rigorous process prior to approval.

- **ASHP strongly recommends that, because it went through this process, AHFS DI, as well as any other compendium approved under such a process, should be evaluated by CMS every five years, rather than every year. In place of an annual review of approved compendia, CMS should consider implementing a certification process that requires approved compendia to certify maintenance of the desirable characteristics during the past year.**

### **Consensus Opinions vs. Evidence-Based Clinical Trials**

ASHP cautions CMS to carefully investigate the independence of a compendia's process, and ensure its process is not biased toward the consensus opinions of its members rather than a rigorous assessment of the evidence from clinical trials and scientific studies. CMS must carefully weigh the outcomes that such a potentially heavily opinion-weighted process may have on its own policies and goals for coverage of off-label uses of drugs and biologics in anti-cancer therapeutic regimens.

**CMS versus FDA Standards**

CMS should carefully review some of its current standards regarding off-label anti-cancer drug use. For example, as a result of the FDA Modernization Act of 1997, FDA has changed many of its previously stringent requirements for the quality and quantity of evidence required for approval of a new use.<sup>10,11,12</sup> As a result, CMS may be holding coverage of off-label uses for anti-cancer therapies to a higher standard than FDA does for actual approval of labeled uses (e.g., different regimens, different stages, etc).

ASHP appreciates this opportunity to present its written comments on the proposal for a process to determine change to the drug compendia list. Feel free to contact me if you have any questions regarding our comments. I can be reached by telephone at 301-664-8702, or by e-mail at [jcoffey@ashp.org](mailto:jcoffey@ashp.org).

Sincerely,



Justine Coffey, JD, LLM  
Director, Federal Regulatory Affairs

Enclosures/Appendicies

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<sup>10</sup> US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), and Center for Biologics Evaluation and Research (CBER). Guidance for industry: providing clinical evidence of effectiveness for human drug and biological products. (Clinical 6) 1998 May.

<sup>11</sup>US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), and Center for Biologics Evaluation and Research (CBER). Guidance for industry: FDA approval of new cancer treatment uses for marketed drugs and biological products. (Clin 7) 1998 Dec.

<sup>12</sup> US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), and Center for Biologics Evaluation and Research (CBER). Guidance for industry: Clinical trial endpoints for the approval of cancer drugs and biologics. Draft guidance. (Clinical/Medical) 2005 Apr.

# **APPENDIX A**

## **Peer Review Checklist**

**“Compendia for Coverage of Off-Labels Uses of Drugs and Biologics  
in an Anti-Cancer Chemotherapeutic Regimen”**

# Peer Review Checklist

## “Compendia for Coverage of Off-Labels Uses of Drugs and Biologics in an Anti-Cancer Chemotherapeutic Regimen”

Name of Reviewer:

Title:

Affiliations:

Preferred Mailing Address:

**Gerald McEvoy, AVP Drug Information, ASHP, 7272 Wisconsin Ave, Bethesda, MD 20814**

Principal ASHP reviewers:

Olin Welsh, Pharm.D., Associate Editor, AHFS

M.E. Ford, M.D., MPH, Contributing Editor, AHFS

Phone:

Fax:

E-mail:

Conflicts of Interest: Please disclose any potential conflicts of interest, such as research in progress, consulting arrangements, or other financial involvements.

All members of ASHP’s AHFS Drug Information publishing.

Please use this form to guide your comments. Return your separate written review and this completed form by **August 14, 2006 (N.B.: Extension granted by AHRQ because wrong version initially sent to ASHP)** to the attention of the Technology Assessment Program:

**E-mail: [ahrqtap@ahrq.gov](mailto:ahrqtap@ahrq.gov)**

If there are any questions, please contact Chuck Shih via e-mail [cshih@ahrq.gov](mailto:cshih@ahrq.gov) or by phone at 301-427-1969.

Name of Reviewer:

ASHP

Please indicate your answers to the following questions by placing an “x” in the appropriate column, and add a brief explanation of answers and comments in the space provided.

Questions	YES	SOME TIMES	NO
<b>General Comments</b>			
1. Is the purpose of the assessment clear?		X	
2. Is the technology assessment well structured and organized?		X	
Comments: The authors of the report clearly state what was done, but the underlying methodology is overly simplistic. Evaluation of item 3d on p. 6, presence of bias, depends on definition of “equivocal evidence”, which was not explicitly defined by authors according to study limitations section on p. 147.			
<b>Scope and Analytic Framework</b>			
3. Is the scope of the report clearly defined?		X	
4. Were all clinically important issues considered?			X
Comments: The report did not adequately address the quality of the evidence considered. Analysis seems to emphasize the number of study citations included more than the quality of evidence. Reporting which unlabeled uses and what supporting evidence was included by each compendium without analysis of <i>whether</i> all such information should have been included is not the most optimal measure of compendial quality. There also seems to be a misconception that a compendium is used to catalog all clinical studies for a drug instead of presenting clinically relevant information based on carefully selected studies. One could also argue the clinical impact of the off-labeled uses that were selected as examples.			
<b>Methods</b>			
5. Are the inclusion and exclusion criteria appropriate?			X
6. Is any published literature or work in progress missing?			X
7. Have we included materials that ought to be excluded or down-weighted?	X		
8. Is the method for grading the quality of individual studies appropriate?			X
9. Is the method for analyzing data appropriate and clearly explained?		X	
Comments: Not all studies conducted for a drug provide clinically relevant information. Searching the literature for all studies and checking that against which studies are cited in various compendia is not a valid measure of quality. Method of selecting agent-cancer combinations for study (new and older agents, common and rare cancers, etc.) is likely not consistent with criteria considered			

Questions	YES	SOME TIMES	NO
<p>important by compendia for prioritizing inclusion of unlabeled uses; i.e., high degree of therapeutic efficacy, lesser toxicity than current treatments, number of patients potentially affected, lack of alternative therapies. Also, many studies were reported as abstracts, which are not optimal for assessing evidence because of deficiencies in reporting of methods and may not be representative of final study results. (See attached references listed under “Problems with using abstracts to assess evidence from clinical trials”.) Editorial decisions regarding inclusion of information on unlabeled uses must balance the desire for expediency in reporting with the need for reliable evidence upon which to make recommendations for therapy.</p>			
	YES	SOME TIMES	NO
<b>Results</b>			
10. Are adverse effects adequately addressed?			X
11. Were the results stated clearly and were the figures, tables and evidence tables clear?		X	
<p>Comments: The various compendia offer information on the adverse effects of each drug based on its labeled uses. The cautions and adverse effects information for a drug is relevant when the drug is used for off-labeled uses too. In addition, when certain risks appear to be uniquely related to or affected by the underlying cancer being treated, they can be described. However, it should be recognized that establishing causal relationships, even from large studies, often is difficult. In the context of the often limited clinical data that is available for emerging off-label uses, establishing causal relationships would be even more difficult. NCCN guidelines are not strictly comparable to other compendia since they do not include adverse event information (Table 1F), which is important for clinicians to consider when deciding whether or not to use a particular drug for a given cancer.</p> <p>Data presentation is sometimes inconsistent or incomplete. For example, there is no summary table for the first 8 agent-cancer combinations as there is in Table 16 for the second 6 combinations. Also, text states that an evidence table was not done for docetaxel in ovarian cancer because the large number of citations (143 total, 57 meeting EPC criteria) “exceeded capacity” (?). However, a similar number of citations was found for some other uses yet they were included in evidence tables, e.g., docetaxel for gastric cancer (132 total, 72 meeting EPC criteria). See additional comments at end of this form.</p>			
<b>Conclusions</b>			
12. Are the major findings clearly stated?	X		
<p>Comments: The major findings are clearly stated, but not particularly helpful. A compendium should be judged on the rigor of its editorial process and the timeliness and clinical relevance of its content. The selection of off-labeled oncology uses for this report does not recognize that publication of certain off-labeled uses may be prioritized based on the strength of the available evidence and the impact the drug will have for the treatment of a particular cancer; there</p>			

Questions	YES	SOME TIMES	NO
<p>was no attempt to evaluate the quality/strength of evidence in the technology assessment. Many of the off-labeled uses selected for this report, including those for oxaliplatin, irinotecan, rituximab, and erlotinib, have not progressed to phase III trials. In the constraints of existing resources, editorial priority often is driven to add off-labeled uses that have progressed further in clinical trials because there is greater evidence of efficacy and safety to support these uses. There is also no recognition that keeping clinicians up to date on important cautions information on these drugs is an important mission of a compendium. Safety concerns on proper use and management of adverse effects of the drug generally should be given greater priority over citing unlabeled uses that have little or no supporting evidence. First, do no harm.</p>			

**On the following page, please provide:**

- **References for relevant studies that we have missed**
- **Any other comments and suggestions for improving the content and format of this review**

**Name of Reviewer:**

ASHP
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**Name of Reviewer:**

ASHP

## Peer Review Form

Please use this sheet to provide specific comments about the technology assessment below.

ASHP appreciates the opportunity to provide comments on AHRQ's Draft Report on Compendia for Coverage of Off-label Uses of Drugs and Biologics in an Anti-cancer Chemotherapeutic Regimen May 31, 2006.

### General Comments about AHRQ's Draft Technology Assessment

Quality of evidence: Reviewing and selecting studies based on the quality of evidence is more meaningful than citing all studies (phase I-IV) as done in this technology assessment. The authors of this report seem to make assumptions that all studies published for a drug are equally important (hence the searching and tallying) and that numbers of studies translate into clinical importance (not necessarily true). Their methodology seems overly simplistic. The table from the statistics web site (Bandolier: <http://www.jr2.ox.ac.uk/bandolier/band139/b139-2.html>) supports the arguments for selecting studies based on the quality of evidence. The parenthetically noted JAMA study (PubMed ID: 16014596) shows that an initial randomized trial that is widely cited might be contradicted by a second randomized trial, so confirmatory trials are important. In this study, a sizable percentage (16%) of second randomized trials contradicted the findings of the initial trial.

The technology assessment commented on the reference padding employed by Drugdex; it was notable that in 9 of 14 uses, references included in the bibliography were not cited in the text of the monographs. While not a scientific analysis by any means, a prominent Wall Street Journal investigative report (Armstrong D. How drug directory helps raise tab for Medicaid and insurers. WSJ. 2003 (Oct 23):A1) questioned Drugdex' editorial approach to evidence as well as connections with the pharmaceutical industry (one cited example in the report was the use by Drugdex of a paid pharmaceutical manufacturer consultant to author the gabapentin [Neurontin] monograph). Drugdex subsequently deleted all author attributions in their database (fall 2005), so it no longer is possible to determine the extent to which such authors have been used and still remain. Unfortunately, neither the current technology assessment nor CMS' MCAC public meeting on March 30, 2006 probed this. Table 1C of the Technology Assessment also acknowledges that Drugdex' evidence process is designed to be broad and includes case reports.

It is unclear how the authors of this technology assessment are using "tallying" of study citations, abstracts, and numbers of patients as a measure of efficacy and safety. Phase I trials are intended to establish activity of a drug for a particular cancer and dosing ranges and generally would not represent good evidence. Information on some studies is published at intervals in abstract form (e.g., ASCO abstracts) before publication as a full study, so simply "counting" all of these citations would falsely inflate the number of studies. As mentioned above, the use of abstracts as a sole source of evidence may be particularly troubling because of deficiencies in reporting methods in abstracts and because of possible discordance from final published results or other studies. The

section below on “Problems with using Abstracts to Assess Evidence from Clinical Trials” provides additional insights. This certainly is an issue that must be addressed in balancing expediency in reporting versus the need for reliable evidence and associated recommendations. This issue continues to be assessed as ASHP further refines its own evidence rating system.

Many factors, including the numbers of patients with a specific cancer, the stage of the disease, the risk/benefit ratio for treatment, and the presence or absence of standard treatment can affect the level of evidence that would be acceptable in a particular situation. That's why any systematic review of the evidence must recognize these complexities instead of reducing the process to a simple formula.

For some cancers, there are insufficient numbers of patients to conduct large randomized trials, so smaller phase II randomized trials may be acceptable. For some cancers, there is no current standard of therapy, so less rigorous studies, such as uncontrolled phase II studies showing high response rates and acceptable toxicity may be used as justification for further studies to establish efficacy and safety.

The citations and studies for an oncology drug need to be interpreted within the context of the cancer, stage of disease, patient population, existing therapies, and risk-benefit ratio, so a generic tallying of numbers of citations for each unlabeled use in this report as a method of evaluation seems overly simplistic. In addition, there may be other problems with selection of phase II or sometimes, phase III, trials. If many different combination chemotherapy regimens or differing dosage regimens are tested in phase II studies, it is difficult to clearly determine any "recommended" regimen or dosage schedule involving the study drug. Typically, the most promising combinations of agents and the dosage regimens that balance efficacy and toxicity are selected for further study. For this reason, it may be preferable to not cite all phase II studies for a drug in favor of following the progress of the research to identify a reasonable regimen or dosage schedule. Even some published phase III trials select a comparison with a nonstandard regimen or nonstandard dosage schedule for other drugs. In this situation, the comparative efficacy and toxicity of the study drug/regimen versus this non-established regimen does not offer clear benefit and it is difficult to apply the results to clinical practice.

Research versus clinical practice: Overall, this report does not make a distinction between research and clinical practice. The authors seem to discount the value of editorial process, expert review, and judgment. Is it the purpose of a compendium to consume considerable resources in simply cataloguing ALL available evidence or would those resources be better spent in an ongoing effort at reviewing the research, evaluating the evidence, soliciting expert advice about levels of evidence and strengths of recommendation, and then reporting what is relevant for clinical practice at that time? In addition, because there was no determination of the quality or strength of evidence nor on relative clinical importance, a process for establishing assessment priorities could not be developed.

While phase I/II studies are important in the research process, it is not until drugs are further along in phase II and phase III studies that we begin to obtain clinically useful information. Reporting all of those studies is not helpful to a clinician. Reporting the chemotherapy regimen and dosage schedule used in 25 patients in one phase II study and suggesting that clinicians use this information to start treating their patients would be a misrepresentation of the level of evidence and strength of

recommendation. The authors of this report are not recognizing the distinction between research and clinical practice.

By including studies of all design (Phase I-IV) and all studies conducted for a drug for a particular use, the authors of this report fail to acknowledge the diminishing return from less rigorous or irrelevant studies. A reader can simply search Medline or ASCO abstracts or other such sources to obtain unsynthesized information. Is it not an important role of a compendium to sift through the available material, analyze and synthesize it, and attempt to identify and assess what is most useful for the clinician? Unfortunately, the design and tone of the technology report seem to emphasize the tallying of all studies, regardless of quality, rather than this latter evaluative and synthetic process.

Purpose of a compendium: The point of a compendium is to provide a reference for clinicians in which experienced staff have carefully reviewed the medical literature, selected clinically important studies, and then summarized and synthesized this information into discussion that pertains to clinical practice. In this context, evidence tables for key studies can be a useful supplement. But simply pulling all studies and putting the information into evidence tables without any editorial process leaves all the work of evaluation to each clinician. This is an unrealistic expectation.

Despite the considerable time and effort that was put into carefully preparing the detailed evidence tables for all existing studies for each drug/off-label use combination (Appendix detailing the search strategies for the technology assessment), it is not clear how this presentation of the material alone benefits the reader/clinician or dictates what should be reported by a compendium. Unless it is used as a supplement to a discussion that results from an editorial review and synthesis of the literature, this material would leave each reader the unrealistic task of evaluating the entire body of evidence. A compendium is intended to itself serve as a reference containing a summary of the evidence and to provide the reader/clinician with selected bibliographic sources if they wish to pursue the topic in greater detail. While evidence assessments are integral parts of the compendial process in establishing levels of evidence in support of a given use and in soliciting strengths of recommendations from expert reviewers and clinicians, the emphasis on tallying studies (quantitative) in this technology assessment and general lack of assessing the evidence quality could provide the wrong message about the role of compendia.

NCCN is a guideline-based publication for oncology therapy only and distinctly different in approach compared with the other studied compendia. NCCN does not meet the conventional definition of a drug compendium. All of the other compendia provide monographs on the wide variety of prescription drugs in the US addressing a wide array of critical elements needed to safely and effectively use a drug. This is not an equivalent comparison. For example, NCCN does not provide detailed dosage information, information on adverse effects, precautions, warnings, contraindications, etc. In addition, there are other oncology guidelines besides NCCN, such as NIH consensus guidelines, ASCO guidelines, and others. If the intent was to extend the definition of a drug compendium to include to such guidelines, why weren't other such oncology guidelines included in the assessment?

General conclusions: There certainly are useful insights in this report that can be applied by each compendium in improving its process. The discussion section of the document is perhaps most

valuable in this regard. The difficulty in assessing methodological transparency is an important message.

What would have added greatly to the value of this report would have been greater discussion on the importance of assessing evidence quality and on the health policy issues involved, particularly in the context of competing expectations for expeditious evaluation of evidence and more clearly defining thresholds of evidence needed to establish reliable recommendations for therapy. For example, what is the role of a sole meeting abstract in this context? Is evidence truly driving the process or are expectation and opinion?

Perhaps the most valuable health policy conclusion is an implicit one about the overwhelming need for additional resources to address the formidable task of evaluating and synthesizing evidence. For example, what resources were consumed by CMS and AHRQ to simply tally the reported evidence, not even evaluate its quality and make specific recommendations about therapeutic roles, for only 14 uses involving 7 drugs? Now extrapolate this, particularly in the context of clinician and patient expectations.

### **Specific Comments about AHRQ's Draft Technology Assessment**

p 7 (pdf p 9): says source was AHFS 2006 but 2005 edition was used.

Therefore, two \*corrections\* should be made for unlabeled uses for bevacizumab that appear in January 2006 version of AHFS DI (PDF pages from AHFS can be provided on request.) This discussion is on pdf pp. 28-46 (document pp. 26-44) of the report.

- \*1. Bevacizumab (Avastin) for treatment of breast cancers - COVERED IN AHFS DI January 2006
- \*2. Bevacizumab (Avastin) for treatment of lung cancers - COVERED IN AHFS DI January 2006

Tables 2a-c:

bevacizumab - breast cancer

added for AHFS DI January 2006 citing the study of capecitabine vs bevacizumab and capecitabine (Miller J Clin Oncol 2005) and the NCI protocol for a phase III trial of bevacizumab with or without paclitaxel

The discussion in the report is inaccurate because AHFS DI does cover this use and provides current citations for phase III studies.

Tables 3a-c:

bevacizumab - lung cancer (non-small cell lung cancer)

added for AHFS DI January 2006 citing the 2005 ASCO abstract for the Sandler et al Phase II/III trial

The discussion in the report is inaccurate because AHFS DI does cover this use and provides one of the current citations mentioned as supporting evidence.

p 12 (pdf p 14): included all study designs (phase I, phase I/II, phase III or phase IV) - why include phase I studies in a review of evidence?

p 13 (pdf p 15): data extraction done from abstracts: abstracts often contain errors and full text should be requested and reviewed to confirm the information and fully evaluate the study

p 16 (pdf p 18): error - says AHFS DI uses number sign to identify unlabeled use when in fact a dagger is used

p 19 (pdf p 21): Table 1A states that AHFS-DI 2005 was used; why wasn't the 2006 edition, which was available in January, used instead?

Table 1F (p. 24): Clarify that references DO exist for most statements in AHFS monographs, just not published except in electronic version. Material sent for external review is always fully referenced and extensive archival documentation extends back to 1959.

Table 1F (p. 24): Methods for formulating recommendations: Add "External review for comment." This was described in the documentation provided to the Duke Center for Clinical health Policy Research. Unfortunately, this omission was overlooked in the draft reviewed by us in February 2006.

Table 1F (p. 24): Harms: Disagree with comment that harms are not considered in unlabeled uses. Information on adverse effects/precautions is discussed or cross-referenced in uses section when appropriate, e.g., when use in certain patient populations may be associated with increased risk of adverse effects or necessitate additional precautions. In addition, comparative toxicity is typically discussed in Uses section when such information from randomized comparative trials is available. Also, adverse effects info is available in Cautions section from labeled uses of the drug. Toxicity information often is not available if data has only been published in abstract form. Also see earlier discussion under question 10 above.

Table 13b (p. 125). Footnote b under "number of evidence citations" for AHFS DI doesn't correspond to footnote description.

Discussion, p. 144: Contrary to what is stated, AHFS DI often provides information on different therapies for a given condition when alternative therapies are available.

## Problems with using abstracts to assess evidence from clinical trials

JAMA. 2006 Mar 15;295(11):1281-7.

Comment in:

JAMA. 2006 Aug 9;296(6):653.

Transition from meeting abstract to full-length journal article for randomized controlled trials.

Toma M, McAlister FA, Bialy L, Adams D, Vandermeer B, Armstrong PW.

The Division of General Internal Medicine, University of Alberta, Edmonton, Alberta, Canada.

**CONTEXT:** Not all research presented at scientific meetings is subsequently published and, even when it is, there may be inconsistencies between these results and what is ultimately printed. Although late-breaking trials sessions are now integrated into several major scientific meetings and the results are often promptly and prominently communicated, no studies have examined the publication fate and degree of consistency between meeting abstracts or presentations and subsequent full-length article publications for randomized controlled trials (RCTs) presented at these sessions. **OBJECTIVE:** To compare RCT abstracts presented in the late-breaking trials session vs other sessions at a major scientific meeting and subsequent full-length publications. **DESIGN:** RCTs were identified by hand searching abstract proceedings booklets and related Web sites for the American College of Cardiology scientific meetings (1999-2002). Subsequent full-length articles were identified via electronic databases. **MAIN OUTCOME MEASURES:** Publication fate and degree of consistency between meeting abstract results and subsequent full-length publication results. **RESULTS:** The 86 late-breaking RCTs were significantly larger (median, 2737 patients vs 896;  $P < .001$ ), were more likely to be preceded by a published design paper (27 [31%] vs 13 [13%];  $P = .002$ ), had higher quality scores when eventually published (mean Jadad score 2.69 vs 2.19;  $P = .01$ ), and were less likely to report favorable results for the intervention than the 100 randomly chosen comparison RCTs presented in other sessions (50 [58%] vs 75 [75%];  $P = .01$ ; odds ratio 0.46; 95% confidence interval, 0.24-0.90). RCTs presented at the late-breaking trials sessions were significantly more likely to be published (79 [92%] vs 69 [69%];  $P < .001$ ) and appeared earlier after presentation (median 11.5 months vs 22.0 months;  $P < .001$ ) than RCTs presented in other sessions, an association that persisted even after adjusting for sample size, conclusion of study, and RCT design: adjusted hazard ratio, 1.80 (95% confidence interval, 1.24-2.61). **Sixty (41%) of the 148 RCTs that were subsequently published exhibited discrepancies between the efficacy estimate reported in the meeting abstract vs the one reported in the full-length article for the primary outcome. The mean change in effect was 0.44 SDs and in 20 cases (14%), the point estimate was statistically significant in only 1 member of the pair.** The discrepancy rate was the same for late-breaking RCTs as for RCTs presented in other American College of Cardiology sessions ( $P = .92$ ). **CONCLUSIONS:** Late-breaking trials were larger, more likely to be preceded by a design paper, and less likely to report positive results than RCTs presented at other sessions, but **discrepancies between the meeting abstract results and subsequent full-length publication results were common even for late-breaking trials.**

PMID: 16537738 [PubMed - indexed for MEDLINE]

J Clin Epidemiol. 2006 Jul;59(7):681-4.

Reporting of trials presented in conference abstracts needs to be improved.

Hopewell S, Clarke M, Askie L.

UK Cochrane Centre, Summertown Pavilion, Middle Way, Oxford OX2 7LB, UK.

shopewell@cochrane.co.uk

**OBJECTIVES:** To assess how trial information reported in conference abstracts differs to their subsequent full publication. **METHODS:** Randomized trials reported at the American Society of Clinical Oncology conference (1992) were identified. CENTRAL and PubMed (December 2002) were searched to identify corresponding full publications. A checklist (based on CONSORT) was used to compare abstracts for 37 trials with their full publication. **RESULTS:** Some aspects were well reported. Ninety-five percent of study objectives, 92% of participant eligibility, 100% of trial interventions, and 84% of primary outcomes were the same in both abstract and full publication. Other areas were more discrepant. **Forty-six percent reported the same number of participants randomized in the abstract and full publication; only 22% reported the same number analyzed (median number analyzed per trial was 96 for abstracts and 117 for full publications). Eighty-two percent of trials were closed to follow-up in the full publication compared to 19% of abstracts. Lack of information was a major problem in assessing trial quality: no abstracts reported on allocation concealment, 16% reported on blinding and 14% reported intention to treat analysis. These figures were 49, 19, and 46%, respectively, for full publications.** **CONCLUSION:** The information given for trials in conference proceedings can be unstable, especially for trials presenting early or preliminary results, and needs to be improved.

PMID: 16765270 [PubMed - indexed for MEDLINE]

JAMA. 1998 Jul 15;280(3):254-7.

Erratum in:

JAMA 1998 Oct 14;280(14):1232.

Positive-outcome bias and other limitations in the outcome of research abstracts submitted to a scientific meeting.

Callaham ML, Wears RL, Weber EJ, Barton C, Young G.

Division of Emergency Medicine, University of California, San Francisco 94143-0208, USA.

mlc@itsa.ucsf.edu

**CONTEXT:** Studies with positive results are more likely to be published in biomedical journals than are studies with negative results. However, many studies submitted for consideration at scientific meetings are never published in full; bias in this setting is poorly studied. **OBJECTIVE:** To identify features associated with the fate of research abstracts submitted to a scientific meeting. **DESIGN AND SETTING:** Prospective observational cohort, with 5-year follow-up of all research submitted for consideration to the major annual 1991 US research meeting in the specialty of emergency medicine. **PARTICIPANTS:** All research abstracts submitted for consideration at the meeting for possible presentation. **MAIN OUTCOME MEASURES:** Characteristics associated with acceptance for presentation at the meeting and subsequent publication as a full manuscript. **RESULTS:** A total of 492 research abstracts were submitted from programs in emergency medicine and other specialties affiliated with 103 US medical schools. A total of 179 (36%) were accepted for presentation and 214 (43%) were published in 44 journals. Of the 179 abstracts accepted for presentation, 111 studies were published. Scientific quality of abstracts or prestige of the journal in which the study was eventually published did not predict either of these outcomes. The best predictors (by logistic regression) of meeting acceptance were a subjective "originality" factor (odds ratio [OR], 2.07; 95% confidence interval [CI], 1.13-3.89) and positive results (OR, 1.99; 95% CI, 1.07-3.84), and, for publication, meeting acceptance (OR, 2.49; 95% CI, 1.49-4.35) and large sample size (OR, 2.26; 95% CI, 1.23-4.31). **Forty-nine percent (241) of abstracts did not report on blinding, and 24% (118) did not report on randomization.** Acceptance and publication were both more likely for positive outcomes (P=.03). Funnel plots showed the classic distribution of positive-outcome ("publication") bias at each of the submission, acceptance, and publication phases. Meeting acceptance predicted publication with a sensitivity of only 51%, specificity of 71%, positive predictive value of 57%, and negative predictive value of 66%. **CONCLUSIONS: Positive-outcome bias was evident when studies were submitted for consideration and was amplified in the selection of abstracts for both presentation and publication, neither of which was strongly related to study design or quality.**

PMID: 9676673 [PubMed - indexed for MEDLINE]

J Orthop Trauma. 2006 Feb;20(2):129-33.

The consistency between scientific papers presented at the Orthopaedic Trauma Association and their subsequent full-text publication.

Preston CF, Bhandari M, Fulkerson E, Ginat D, Egol KA, Koval KJ.

New York University-Hospital for Joint Diseases, New York, NY, USA.

**OBJECTIVES:** To determine the consistency of conclusions/statements made in podium presentations at the annual meeting of the Orthopaedic Trauma Association (OTA) with those in subsequent full-text publications. Also, to evaluate the nature and consistency of study design, methods, sample sizes, results and assign a corresponding level of evidence. **DATA SOURCES:** Abstracts of the scientific programs of the OTA from 1994 to 1997 (N = 254) were queried by using the PubMed database to identify those studies resulting in a peer-reviewed, full-text publication. **STUDY SELECTION:** Of the 169 articles retrieved, 137 studies were the basis of our study after the exclusion criteria were applied: non-English language, basic science studies, anatomic dissection studies, and articles published in non-peer-reviewed journals. **DATA EXTRACTION/SYNTHESIS:** Information was abstracted onto a data form: first from the abstract published in the final meeting program, and then from the published journal article. Information was recorded regarding study issues, including the study design, primary objective, sample size, and statistical methods. We provided descriptive statistics about the frequency of consistent results between abstracts and full-text publications. The results were recorded as percentages and a 95% confidence interval was applied to each value. Study results were recorded for the abstract and full-text publication comparing results and the overall conclusion. A level of scientific-based evidence was assigned to each full-text publication. **RESULTS:** The final conclusion of the study remained the same 93.4% of the time. The method of study was an observational case series 52% of the time and a statement regarding the rate of patient follow-up was reported 42% of the time. Of the studies published, 18.2% consisted of a sample size smaller than the previously presented abstract. When the published papers had their level of evidence graded, 11% were level I, 16% level II, 17% level III, and 56% level IV. **CONCLUSIONS:** Authors conclusions were consistent with those in full-text publications. Most studies were observational, less than half reported on the rate of patient follow-up. **Many abstracts followed by publication had a smaller sample size in the published paper. Half of all studies were graded level IV evidence.**

PMID: 16462566 [PubMed - indexed for MEDLINE]

## **General Comments About ASHP's Compendial Publishing**

American Hospital Formulary Service Drug Information (AHFS DI): ASHP is the publisher of AHFS DI, which is one of 3 drug compendia originally recognized for making determinations about medically accepted indications for anti-cancer chemotherapeutic regimens under Section 1861(t)(2)(B)(ii)(I) of the Social Security Act (SSA). AHFS DI is the only remaining federally recognized drug compendium published by a noncommercial entity—the American Society of Health-System Pharmacists—a nonprofit professional practice and scientific society.

ASHP supports a vision for pharmacy practice in hospitals and health systems in which pharmacists will lead evidence-based medication use programs to implement best practices. Publication of AHFS DI is an important component in achieving this vision.

The mission of AHFS DI is to provide an evidence-based foundation for safe and effective drug therapy. Widely trusted for its established record in refuting unfounded efficacy claims, its rigorous science-based editorial process, and its independence from the influence of pharmaceutical manufacturers, AHFS DI has remained true to this mission for almost 50 years and is the most widely vetted drug compendium. (Background included in documentation provided to Duke.) Recognition of the compendial authority of AHFS has extended over 4 decades.

ASHP holds in high regard the responsibilities attendant to the public and private trust placed in the evidence-based editorial deliberations of AHFS DI. As such, ASHP also considers it essential to protect the integrity and independence of the editorial decisions of AHFS staff by separating the Society's business activities with pharmaceutical manufacturers (e.g., exhibits at educational meetings, journal advertising) from the editorial activities of its drug compendium. Interactions between AHFS staff and pharmaceutical manufacturers are limited to the legitimate exchange of the scientific and medical information needed to fulfill the mission of AHFS DI. Communications are directed to the scientific and medical information areas within the companies; contact with marketing areas is avoided. An editorial independence statement (included in documentation provided to Duke), approved by ASHP's Board of Directors, outlines the principles that AHFS staff apply in ensuring such independence.

ASHP recognizes the challenges of the resource-intensive process involved in conducting evidence-based therapy assessments and remains committed to its vision of fostering evidence-based medication use and publishing its highly regarded drug compendium. The recent loss of USP's evidence-based development process for antineoplastic therapy has prompted the Society to explore opportunities for enhancing its own consideration of such uses via AHFS DI. The codified AHFS evidence rating system that makes use of levels of evidence to reflect strength and quality of existing data as well as recommendation grades is a major initiative aimed at enhancing this effort. As a nonprofit, professional practice and scientific society, resources needed to support such efforts remain a challenge, but our commitment to promoting rational drug therapy through compendial considerations remains steadfast. ASHP remains ready to continue to assist CMS through the Society's authoritative AHFS DI drug compendium in making determinations of medically accepted indications for drugs and biologicals used in anti-cancer chemotherapeutic regimens under Part B of Medicare.

To this end, ASHP continues to work with other nonprofit professional practice and scientific societies such as the Association of Community Cancer Centers (ACCC), American Society of Clinical Oncology (ASCO), American Society of Hematology (ASH), Oncology Nursing Society (ONS), and others in refining its evidence rating system described in the background information provided to the Duke Center for Clinical Health Policy Research.

## Appendix B

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### ■ Editorial Independence of AHFS Drug Information

**Approved by the American Society of Health-System Pharmacists Committee on Publications and Board of Directors**

The mission of *AHFS Drug Information (AHFS DI)* is to provide an evidence-based foundation for safe and effective drug therapy. Information included in *AHFS DI* shapes treatment decisions made by clinicians and influences public and private health care policy and decisions. As a result, it is important that the information be authoritative, objective, and free of undue influence from pharmaceutical manufacturers, health insurers, pharmacy benefits managers, and other third parties who may seek to use the compendium to promote their own vested interests. Editorial decisions are evidence-based and made independent of such third parties; final decisions are made solely by the AHFS editorial staff, taking into account the advice of expert reviewers.

Widely trusted for its established record in refuting unfounded efficacy claims, its rigorous science-based editorial process, and its independence from the influence of pharmaceutical manufacturers, *AHFS DI* has remained true to its mission for almost 50 years.

*AHFS DI* is the only remaining official drug compendium published by a non-commercial entity (i.e., by a tax-exempt [“nonprofit”] professional association). The American Society of Health-System Pharmacists (ASHP) is an IRS 501(c)(6) tax exempt entity. ASHP is the national professional association that represents pharmacists who practice in inpatient, outpatient, home-care, and long-term-care settings. ASHP has a long history of fostering evidence-based medication use as well as patient medication safety—efforts designed to help pharmacists improve their delivery of pharmaceutical care.

*AHFS DI* is published by ASHP under the authority of its elected Board of Directors. As such, the Board exercises oversight through its ongoing Society considerations as well as through its Committee on Publications. This oversight by the Board also involves review and approval of relevant recommendations originating from its appointed Commission on Therapeutics and the advisory and best practices developments of its Councils, House of Delegates, and other policy-recommending bodies.

In addition, hundreds of experts, principally physicians but also other clinicians, leading medical scientists, pharmacists, pharmacologists, and other professionally qualified individuals, participate in an ongoing extramural review process for *AHFS DI*. Participation is solicited but voluntary, and no honorarium nor other benefit (e.g., complimentary subscription) is provided. These experts must provide full disclosure of interest, including any affiliation with or financial involvement in the manufacturer of the drug(s) under consideration and directly competitive products.

ASHP considers it essential that interactions between AHFS and pharmaceutical manufacturers be limited to the legitimate exchange of the scientific and medical information needed to fulfill the mission of *AHFS DI*. To maintain independence from the undue influence of the promotional interests of pharmaceutical manufacturers, communications are directed to the scientific and medical information areas within the companies; contact with marketing areas is avoided.

ASHP holds in high regard the responsibilities attendant to the public and private trust placed in the evidence-based editorial deliberations of AHFS. As such, ASHP also considers it essential to protect the integrity and independence of the editorial decisions of AHFS staff by separating the Society's business activities with pharmaceutical manufacturers (e.g., exhibits at educational meetings, journal advertising) from the editorial activities of its drug compendium. AHFS staff apply the following principles of editorial independence in weighing the propriety of their conduct.

1. AHFS staff should avoid participating in business discussions with pharmaceutical manufacturers and other ASHP staff should avoid engaging AHFS staff in such discussions.
2. AHFS staff must disclose any potential financial conflicts of interest or other external activities that may affect their editorial decisions on specific drugs. AHFS staff should not hold financial interests that conflict or may influence the conscientious performance of their editorial duty.
3. AHFS staff may not solicit or accept any gift or other item of monetary value from any individual or entity seeking official action or influence from the compendium nor from those whose interests may be substantially affected by the performance or nonperformance of the staff's editorial duties.
4. AHFS staff have an obligation to act impartially and not give preferential treatment to any interested individual or organization that might influence their editorial decisions.
5. AHFS staff should avoid actions that might create the appearance that they are violating these principles of ethical conduct and editorial independence. Any such behavior shall be judged from the perspective of a reasonable individual in a similar situation with knowledge of the relevant facts. When necessary, the expert advice of other staff (e.g., professional practice, corporate counsel) should be sought.
6. On occasion, ASHP may determine that the Society's interest in the staff's participation in a particular activity or discussion outweighs any concern that a reasonable individual might question the integrity of the activity.
7. AHFS staff members with questions about their activities that are not addressed by these principles on editorial independence shall refer their questions to the Vice President of Publishing and Editor of AHFS.

## **APPENDIX C**

### **Overview of AHFS DI HCFA Review Process**

The mission of AHFS Drug Information (DI) is to provide an evidence-based foundation for safe and effective drug therapy. AHFS DI is widely trusted for its established record in refuting unfounded efficacy claims, its rigorous science-based editorial process, and its independence from the influence of pharmaceutical manufacturers. AHFS DI is one of the three Compendia listed under Section 1861(t)(2)(B)(ii)(I) of the Act that may be used in determining the medically accepted indications of drugs and biologicals used in an anti-cancer chemotherapeutic regimen.

In January 1989, HCFA began developing regulations to implement section 202 of the Medicare Catastrophic Coverage Act of 1988 aimed at establishing standards for prescribing outpatient drugs based on accepted medical practice. In establishing these standards, HCFA required ASHP to describe the extent to which AHFS DI met each of the criteria outlined in the Congressional Conference Report relating to the legislation.

HCFA was required by Congress to designate as official only those compendia that based such medical practice standards on review of published scientific and medical information, that provided for a public comment and review process, and that provided adequate assurances that the panelists who establish standards were free of financial (or other) conflicts of interest.

In March 1989, ASHP participated in a public hearing conducted by HCFA's Bureau of Eligibility, Reimbursement, and Coverage on the use of authoritative compendia to determine prescribing standards for the new Medicare outpatient drug coverage.

In September 1989, HCFA published its determination that AHFS DI, along with AMA-DE and USP DI, met the selection criteria as an official compendium in the Federal Register, and requested public comment, thus subjecting its determination to broad-based public scrutiny.<sup>1</sup>

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<sup>1</sup> Federal Register, Vol. 54, No. 172, Thursday, September 7, 1989, 37190, Medicare Program; Catastrophic Outpatient Drug Benefit; Proposed Rule.