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White Paper:

Potential Conflict of Interest in the Production of Drug Compendia

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Potential Conflict of Interest in the

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All of the investigators are affiliated with Duke University which is an NCCN Institution. Dr. Abernethy currently serves on the fatigue guideline panel (though this group has no relationship to chemotherapy drugs). There are no other conflicts to disclose.

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1.0 Introduction

This white paper, which was commissioned by the Agency for Healthcare Research and Quality (AHRQ), with sponsorship from the Centers for Medicare & Medicaid Services (CMS), explores the concern that conflict of interest may potentially influence the inclusion/exclusion decisions, editorial processes, production, and content of current drug compendia. Drug compendia – pharmacopeia providing information on drugs, their effectiveness, safety, toxicity, and dosing – are frequently used to determine whether a medication has a role in the treatment of a particular disease; these roles include both therapeutic uses approved by the U.S. Food and Drug Administration (FDA) and off-label indications. Policy enactments have also resulted in use of the compendia to inform reimbursement decisions made by CMS and other third-party payers.

The pages that follow provide: (1) a description of compendia processes, delineating points at which conflict of interest may arise; (2) an ethical framework for evaluating the potential presence and influence of conflict of interest in compendia; (3) results of an investigation into the policies and practices of four specific compendia (those officially approved for use in making Medicare coverage determinations) with regard to conflict of interest; and (4) a discussion of the adequacy of compendia approaches to conflict of interest, problems with conflict of interest that have been reported, and opportunities for minimizing conflict of interest in the compendia to ensure an objective and impartial system.

Results presented in this white paper do not constitute a critique of existing compendia. Rather, the investigators explored specific questions with the

intention of: identifying, if warranted, potential areas for improvement; assisting AHRQ and CMS in developing a systematic approach to the understanding of conflict-of-interest-related bias in drug compendia; and contributing to the effort to hone the compendia system such that it provides a digest of accurate, timely, unbiased, and complete evidence to clinicians as a reference for clinical decision-making.

2.0 Background

2.1 Use of Drug Compendia in Coverage Determinations

A compendium is a listing of drugs and biological agents which summarizes evidence on the effectiveness of each drug or biologic, and provides information regarding clinical indications and proper dosing. Compendia may recommend uses of a drug or biologic other than those approved by the FDA if scientific evidence supports those uses; in such cases, the use is termed an "off-label" indication.

For the past 15 years, off-label prescribing in oncology has been facilitated by Medicare insurability of off-label uses of anticancer drugs and biologics, as stipulated under Social Security Act Section 1861(t)(2)(B)(ii)(I) and (II), under the Omnibus Budget Reconciliation Act of 1993. This statute recognized certain compendia as authoritative sources for determining a "medically-accepted indication" of drugs and biological agents used off-label in an anticancer chemotherapeutic regimen, unless the Secretary of Health and Human Services determines otherwise. The statute originally indicated that medically-accepted indications would be determined by three designated compendia: American Medical Association Drug Evaluations (AMA-DE), American Hospital Formulary Service Drug Information (AHFS-DI), and United States Pharmacopeia Drug Information (USP-DI). Of the three originally approved compendia, only one, AHFS-DI,[1] still exists as of the writing of this report.

Due to the reduction in the number of originally approved compendia, and propelled by requests for the addition of new compendia to the approved list,

CMS commissioned AHRQ to conduct a Technology Assessment reviewing the structure and processes of several published compendia. The resulting Technology Assessment, prepared by the Duke and Tufts Evidence-based Practice Centers (EPCs) and entitled "Compendia for coverage of off-label uses of drugs and biologics in an anticancer chemotherapeutic regimen," compared five compendia for their practices regarding off-label anti-cancer drugs.[2, 3] It found that the compendia often did not cite the most current or best performed clinical trials as part of their evidence base. There were large variations in whether, and how quickly, off-label indications were added to the compendia included in the study. DRUGDEX[4], for example, tended to include more indications as substantiated by evidence than the other compendia, but did not consistently utilize the best designed or most timely available studies as the evidence underlying its decisions. The limited number of cited studies made it difficult to evaluate the basis of the recommendations made by all five compendia studied. DRUGDEX listed the most off-label indications, and AHFS-DI[1] the fewest. Given the lack of evidentiary citations, it was impossible to ascertain which set of indications (i.e., which compendium) most accurately reflected current best evidence.

In 2006, CMS convened the Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) to hear a formal presentation of findings from the Duke/Tufts EPCs' Technology Assessment, and to make recommendations regarding desirable characteristics of compendia that would be used to identify appropriate indications for drugs and biologics in cancer treatment. The

MEDCAC recommendations[5] included several items relevant to public transparency and minimization of conflict of interest: (a) “detailed description of the evidence reviewed for every individual listing”; (b) “use of prespecified published criteria for weighing evidence”; (c) “use of prespecified published process for making recommendations”; (d) “publicly transparent process for evaluating therapies”; and (e) “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.”

In 2008, CMS approved three compendia in addition to AHFS-DI, which had been approved by statute in 1993.[1] The new compendia were: the National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium[6], DRUGDEX[4], and Clinical Pharmacology[7] – raising to four the total number of compendia viewed as authoritative sources of information on “medically-accepted indications.”

While the original statute that stipulated which compendia were approved pertained specifically to CMS, most other third-party payers and state legislatures have followed suit.[8] The four approved compendia thus heavily influence, if not determine, treatment decisions for many cancer patients. The quality of their evidence and the impartiality of their methods are thus of paramount importance. In order to address these concerns, Congress has recently enacted legislation to further reduce conflicts of interest in compendia.

2.2 Definition of Conflict of Interest, and its Relation to Drug Compendia

A conflict of interest exists when an individual or corporate entity possesses more than one motivation for trying to achieve an objective. A formal definition is presented by Thompson in the New England Journal of Medicine in 1993: "A conflict of interest is a set of conditions in which professional judgment concerning a primary interest (such as a patient's welfare or the validity of research) tends to be unduly influenced by a secondary interest (such as financial gain).[9]

As described above, certain drug compendia have become regarded as authoritative sources of information to support coverage determinations of off-label uses of anti-cancer drugs and biologics. By definition, drug compendia include information that has major financial implications for drug manufacturers. Listing of a product in an approved compendium confers a financial advantage to industry. The basic motivation to attain listing in the compendia introduces potential for conflict of interest in ongoing compendia development processes. This potential conflict of interest exists at multiple levels, as experienced by various entities involved with the compendia and their development.

2.3 Entities Involved in Compendia Development and their Potential Conflicts of Interest

Multiple parties are affected by decisions made during the development of drug compendia. These parties include the public, health care providers,

pharmaceutical companies, private insurers, compendia staff, editorial boards of compendia, and compendia publishers. For each of these parties, the compendia and their entries have distinct reasons for importance (Table 1); thus each party may have specific – possibly conflicting – interests with respect to compendia development.

Pharmaceutical manufacturers have a direct interest in maximizing the number of accepted indications that are listed in approved compendia, and thus eligible for payment. Given this basic motivation, industry could be expected to favor policies that accept marginal data on a drug's effectiveness as evidence justifying reimbursement for that agent.

Compendia writers who are also practicing physicians have many reasons to favor a more liberal listing approach. For example, nephrologists who own or depend on dialysis centers have financial reasons to favor higher hemoglobin standards in chronic renal failure since those centers may be reimbursed at an above-cost rate for the relevant medications to increase erythropoiesis.[10] In most cases, it also behooves practicing physicians to have more, rather than fewer, treatment options available to offer to their patients. This is particularly the case with rare diseases where specific FDA-registration for the indication may not occur but the available evidence supporting the drug-orphan disease indication may be mentioned in the compendia, in which case the lack of FDA-registration does not correspond with the lack of need for therapy. Practicing physicians may be concerned that the seemingly slow process for FDA registration of a product for a specific indication limits access of potentially therapeutic treatments; this is

particularly urgent in settings of life-limiting illness. In addition, some physicians offer treatments as a mechanism to maintain hope in late-stage diseases such as cancer, even without an evidence base to support these uses of the treatment agents.

Insurance companies have a direct financial interest in limiting the number of accepted indications listed in approved compendia, while generally agreeing to pay in situations where the evidence is meaningful and secure. For the insurers, the financial incentives are clear, since every additional indication implies additional costs that must be covered – particularly an issue given the expense of some newer and less scientifically established therapeutic agents. The financial pressure to limit the size of the accepted indication list is particularly a factor for profit- or margin-seeking entities (which may be structured as non-profits under tax laws). At the same time, insurers have a public interest reason to avoid a *carte blanche* approach for therapeutics, since this approach drives up the aggregate cost of health care and, unless evidence-based, may or may not improve health outcomes. But despite these pressures, there are market reasons for an insurance company to cover a wider number of therapies so that their customers are more pleased with the company's service. In addition, using the best available therapy may be cost effective in the long term, since it may have the potential to avoid future treatment expenses.

2.4 Examples of Conflict of Interest in the Development of Clinical Practice Guidelines

Most of the general academic literature relevant to conflict of interest in compendia focuses on guideline-writing groups, which are very analogous. The NCCN compendium is, for example, explicitly based on the work of NCCN guideline writing committees. The degree of the concern about conflicts of interest was made clear in 2002, when Choudhry and co-authors found that 87% of guideline authors had some relationship with a pharmaceutical manufacturer; the mean number of companies with whom guideline authors had financial conflicts of interest was 10.5.[11] Fifty-nine percent of authors had relationships with companies whose products were considered in the guideline. Two prototypical situations that have been very actively debated are the "Surviving Sepsis Campaign" and the development of guidelines regarding erythropoiesis stimulating products.

2.4.1 rhAPC and the Surviving Sepsis Campaign. The basic issue in the Surviving Sepsis case was the approach that Eli Lilly took to marketing its drug, recombinant human activated protein C (rhAPC; brand name Xigris®). Eichacker and colleagues published an editorial in the New England Journal of Medicine[12] which closely echoed an editorial published by Christian Wiedermann in Wiener Klinische Wochenschrift in 2005.[13] Both noted that Lilly contracted with a public relations firm to market the concept that failure to use Xigris® was unethical, despite its cost. This public relations firm created the "Values, Ethics and Rationing in Critical Care Task Force" (VERICC). VERICC recruited well-known bioethicists as members in order to provide credibility. The second element to

their marketing effort was to support an existing guideline-writing group, the International Sepsis Forum (ISF), which looked favorably on rhAPC as a therapy. Lilly was one of the seven corporate sponsors for the ISF. The ISF, European Society of Intensive Care Medicine, and American Society of Critical Care Medicine (SCCM) joined together to lead the "Surviving Sepsis Campaign," for which Lilly was the largest sponsor. The campaign endorsed the use of rhAPC, based on a study known as the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis Trial (PROWESS).[14] In contrast to the Surviving Sepsis Guideline position, the FDA and the European Medicines Agency (EMEA) limited the license of the drug based on concerns regarding the PROWESS data. In particular, subgroups of trial participants receiving rhAPC had higher mortality than those receiving placebo. The Surviving Sepsis group was criticized for their relatively uncritical endorsement.

The Surviving Sepsis controversy illustrates several aspects of conflict of interest relevant to compendia. As an evidence source, the Surviving Sepsis Guidelines were accused of ignoring subsequent studies that were less favorable to rhAPC, such as the Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis (ADDRESS) and Researching Severe Sepsis and Organ Dysfunction in Children: a Global Perspective (RESOLVE) trials, both of which were terminated early because they were deemed unlikely to show benefit in their primary endpoints, while demonstrating significant toxicities associated with rhAPC.[15, 16] The studies considered in the product endorsement were all sponsored by Eli Lilly; their outcomes suggest that they were performed fairly, if

interpreted generously. Additionally, the interpretation of the data raised questions about conflict of interest, since some critics stated that the resulting guidelines were much more positive about rhAPC than the data justified.[17]

In an editorial supporting the Surviving Sepsis Campaign, Charles Durbin (President of the SCCM) took a differing set of positions.[18] First, he defended Lilly's support for disseminating the guidelines, arguing that without such support most guideline documents are not widely read or used. He made the point that there is little public funding for publicizing guidelines, and that the guideline writers applied for industry sponsorship. He noted that the fact that Lilly funded a large portion of the budget was never hidden, nor was there any attempt to camouflage Lilly's reason for interest. Dr. Durbin stated that the societies' rules meant Lilly could not have influenced the actual guidelines, claiming that "such influence has not been and cannot be substantiated."

2.4.2 Guideline development for erythropoiesis-supporting proteins. A second recent illustration of controversy regarding the influence of commercial interests on guidelines surrounded the use of erythropoietin and erythropoiesis-supporting proteins (ESPs) for anemia in chronic renal disease. In this case, financial conflicts of interest were transparently disclosed. The guideline committee made a controversial, even surprising, recommendation aligned with the interests of the pharmaceutical manufacturers. Public and professional skepticism about the value of the guidelines was profound.

The guidelines in question, published in 2006, were written under the aegis of the National Kidney Foundation.[19] The concerns were clearly defined by nephrologist Daniel Coyne in 2007.[10, 20] He noted that the guideline committee recommended the use of ESPs to maintain hemoglobin between 11 and 13 gm/dL, although the previous target range had been 11-12 gm/dL. The higher target range stood to benefit several groups: the makers of ESPs, nephrologists, dialysis facilities, and, potentially, patients. Coyne posited that the National Kidney Foundation also stood to benefit from an ESP-favorable report, since it received much of its support from corporations linked to ESPs. Amgen itself was the principal financial sponsor of the guideline, despite oversight of the National Kidney Foundation. Coyne noted that 14 of the 16 members of the guideline committee had personal financial relationships with companies that stood to benefit from higher hemoglobin targets.

The element in the guideline-writing process that raised the most concern was that of conflict of interest in evidence selection; specifically, the review process neglected to include data from two major studies, the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Trial (CREATE)[21] and the Correction of Hemoglobin and Outcomes in Renal Insufficiency Trial (CHOIR).[22] Both studies demonstrated increased risk of cardiovascular events in patients assigned to higher hemoglobin targets (13 to 15 in CREATE, 13.5 in CHOIR). The guideline-writing committee was given early access to the outcomes of these studies, although the formal presentation of the two studies did not occur until the same meeting in April 2006 where the guidelines were

announced. The committee rules specified that reviews would be limited to published results and that, where the information in publications was insufficient:

> In the absence of strong or moderately strong quality evidence or when additional considerations did not support strong or moderately strong evidence-based guideline recommendations, the Work Group could elect to issue CPRs [clinical practice recommendations] based on consensus of expert opinions. These recommendations are prefaced by "In the opinion of the Work Group," and are based on the consensus of the Work Group that following the recommendations might improve health outcomes.[19]

The upper bound for hemoglobin was judged to be insufficiently elucidated by randomized controlled trials, so a clinical practice recommendation was made on the basis of expert opinion. The fact that the opinions might soon be swayed by well-conducted randomized trials of which the committee was aware did not change the recommendations.

Controversy has surrounded the question of whether process policies or conflict of interest drove the final recommendations regarding ESPs.[20, 23, 24] Regardless, the presence of potential conflicts of interest clearly created skepticism about the validity of the recommendations. In addition, the situation pointed out the difficulty for the end user of evaluating guidelines created in a process which included conflicted individuals; it is nearly impossible for the guideline user to ascertain the role that conflict of interest may have played in the

committee process and the final recommendations. A guideline that is based on a mixture of opinion and clinical trial data poses a challenge to interpret; compendia are faced with the difficulty of evaluating "generous" interpretations that favor industry and their influence on clinical practice guidelines.

2.5 Rationale for this Study

A core function of drug compendia is to use evidence from systematic, scientific studies to make a determination on whether or not to include an indication in their drug summaries. Compendia face the objective task of evaluating the evidence for the novel use of a drug or device, amid the competing pressures of: (1) a desire to limit prescriptions for the drug to situations where evidence is sufficient to justify its use; (2) a desire to make products available to everyone who could clinically benefit; and (3) the fact that CMS approval of payment can have major financial ramifications. The evidence used by the compendia writers may be as complete as a large randomized controlled trial published in a respected peer-reviewed journal, or as limited as a meeting abstract describing a small case series that has yet to be fully peer reviewed.[3] Each publisher has distinct criteria and standards for inclusion of evidence in their compendium.

There are several concerns regarding the use of compendia as reimbursement guidelines, some of which have been recently summarized.[2] This role was developed to meet the need for a standard to assist with coverage determinations regarding the many off-label uses of FDA-approved drugs. In

oncology, this need is particularly important given the high cost of many new treatments and the authority of physicians to write prescriptions for any approved medication, regardless of whether the particular indication is part of the FDA-approved package insert.

Compendia approved by CMS purport to evaluate clinical trial evidence from many sources, use experts to assess the validity of that evidence, and publish summaries in a clear and concise format. Concerns have been raised that financial conflicts of interest may affect decisions made by compendia producers.[25] This paper explores the standards and policies that compendia use to minimize the impact of conflict of interest, and the application of those policies. It describes the processes through which compendia add new drug/biologic indications, the points in these processes at which conflicts of interest could enter, the current conflict-of-interest policies of the four compendia used by CMS, and the evidence that the compendia uphold these policies.

2.6 Purpose of this Study

This study was designed to explore the following research questions:

1. What potential conflicts of interest exist in the production of drug compendia?
2. What practices and policies have drug compendia instituted to protect against bias introduced by conflict of interest?

3. Does available evidence from medical literature, as well as mainstream media, suggest that these policies and practices are effective in minimizing the influence of conflict of interest on compendia?

These questions were addressed within the context of an ethical framework developed upon review of the literature on conflict of interest; the ethical framework serves as a structure that can be applied across compendia to evaluate the objectivity and impartiality of these reference sources.

3.0 Methods

This study comprised two main components: (1) development of an ethical framework for consideration of conflict of interest in drug compendia; and (2) review of compendia policies, practices, and experiences with regard to conflict of interest.

The first component – development of an ethical framework for consideration of conflict of interest in drug compendia – was conducted through the following steps:

- Identification of the most relevant literature regarding conflict of interest from the field of medical ethics. The literature search encompassed peer-reviewed journals listed in MEDLINE® and published in the English language. We initially identified articles pertaining generally to conflict of interest; these were then screened for more specific relevance to the development of clinical practice guidelines and/or compendia.
- Summarization of the results of the literature review. Key points, and elements of conceptual frameworks for addressing conflicts of interest that have been reported in the literature and that have relevance to compendia, were abstracted from the included articles.
- Creation of an ethical framework for consideration of conflict of interest in the production and development of drug compendia.

The second component – review of compendia policies, practices, and experiences with regard to conflict of interest – was conducted through the following steps:

- Retrieving the compendia's stated conflict-of-interest policies from their websites, focusing on the four compendia described above.
- Obtaining copies of the compendia's conflict-of-interest policies from the relevant legal or administrative departments.
- Summarizing the compendia's conflict-of-interest policies in tabular format.
- Creating a script for teleconferences with compendia "key informants," to gather parallel information directly from compendia personnel with regard to conflict-of-interest policies, implementation of these policies, and corporate experiences with conflict of interest.
- Conducting teleconferences with a senior editor or other high-level personnel (i.e., key informant[s]) at each of the four compendia, in accordance with the teleconference script.
- Presenting the information gathered by teleconferences.

4.0 Results

4.1 Components of an Ethical Framework to Approach Conflict of Interest in Compendia

The first component of this project resulted in the development of an ethical framework for considering conflict of interest in drug compendia.

Review of the literature on conflict of interest – which covered the general literature in medical ethics, guideline development, and compendia, as well as known cases where medical marketing affected guideline development – identified four primary areas in which conflict of interest might intrude in the process of compendia development. These categorical areas, presented in Figure 1, are:

1) Conflict of interest in the evidence sources;
2) Conflict of interest in the process of making study data available;
3) Conflict of interest leading to biased selection of indications to review, and of evidence sources; and,
4) Bias in the interpretation of evidence.

Two of these areas – conflict of interest in evidence sources, and conflict of interest in the process of making study data available – lie beyond the control of the compendia publishers. The remaining two areas – conflict of interest leading to biased selection of evidence, and bias in the interpretation of evidence – fall within the domain of the compendia publishers and under the jurisdiction of compendia's institutional policies.

4.1.1 Conflict of interest in evidence sources. No scientific research is ever totally free of conflict of interest. It is reasonable to assume that investigators publish papers in order to disseminate vital information, in order to deliver on agreements made with the research sponsor, because they care about a subject, and/or because they believe that their data and opinions convey some value. However, the act of publishing also confers personal benefits such as exposure, credibility in one's field, and "academic capital" that enters into decisions regarding promotion. Peer-reviewed medical journals typically seek to publish manuscripts that will be viewed as "contributions" to the field or to science more generally. Thus, investigators may face an underlying pressure – consciously or subconsciously – to present any finding in the most noteworthy fashion possible. Authors have liberty to present their analyses and their interpretations, often with considerable latitude under "Discussion" sections.

Investigator conflict of interest occurs when the researcher stands to benefit from one outcome of the research more than he or she would benefit from other possible outcomes. The nature of that benefit might be financial, professional, or personal. In a related way, investigator conflict of interest can also arise when the investigator has a significant relationship with a sponsor or other interested party who stands to benefit from one outcome more than another.

Most medical journals require authors to disclose all relevant substantive financial relationships as the standard mechanism for managing conflict of interest in their publications. This disclosure is usually printed in the

acknowledgements of an article, or in a separate footnote. Recent evidence, however, demonstrates that such disclosure is inconsistent and unreliable.[26]

Underlying the challenge of conflict of interest in evidence sources is the fact that most clinical trials of new drugs in the United States and throughout the world are sponsored by pharmaceutical companies, rather than by more neutral parties such as the National Institutes of Health or European Union. It is expected of industry that sponsored studies are designed with market-driven goals, for example: (1) to advance the drug toward licensure (by the FDA, the EMEA, or other agency); (2) to increase the number of indications for a licensed (or soon-to-be licensed) drug; (3) to expand knowledge of a drug's side effect(s); (4) to increase market awareness (i.e., Phase IV, post-licensure studies as a marketing device); and (5) to compare the benefits of one drug against another. With regard to the last category of study, pharmaceutical companies typically initiate comparative studies only if they possess a certainty that their drug has some clear advantage over a competitor product. The exception is when there is an accepted standard of care for a given situation and new drugs must compete with that standard.

The primary accountability of pharmaceutical companies is to their shareholders, rather than to public agencies. In this context, they have a fundamental motive to generate profits for distribution to shareholders. In our society, there is not a mechanism by which manufacturers are directly rewarded for developing better drugs *per se.* Thus, pharmaceutical company-sponsored studies need to be evaluated with potential *sponsor conflict of interest* in mind.

Relevant information for assessing potential conflict of interest includes the identification of the sponsor, determination of whether an independent team reviewed the raw data, and determination of whether conclusions were formulated independent of sponsor interests. Because investigators/authors on industry-sponsored studies frequently receive payment for their work, industry-sponsored evidentiary papers inherently carry the risk of conflict of interest.

Psaty and Kronmal present a recent case study illustrating the problem of sponsor conflict of interest, based upon their review of Merck archives related to rofecoxib (Vioxx®) litigation.[27] They describe how Merck failed to report important mortality information regarding rofecoxib in three studies evaluating its potential use to delay the onset or ameliorate the symptoms of Alzheimer's disease. While the study was designed as "intent-to-treat," the data presented to the FDA were "as-treated." This designation allowed Merck to discount many of the fatalities in rofecoxib patients that occurred after the end of the active treatment period. In addition, in 2001 Merck apparently performed an internal analysis that demonstrated a clear risk of increase in mortality (approximately threefold) with rofecoxib, but the company did not release the analysis externally – a decision made by corporate employees, i.e., individuals with a clear financial conflict of interest.[*]

[*] As a side note, the Psaty and Kronmal article itself exhibits conflict of interest. One of the authors was paid by plaintiffs' attorneys to research the Merck decision. In addition, the authors mention only briefly that Merck did publish the result of protocol 078, which demonstrated that patients receiving rofecoxib had a higher rate of Alzheimer Disease progression than placebo recipients.

4.1.2 Conflict of interest in data availability. One of the major manifestations of conflict of interest, which causes bias in clinical data, is the censuring of results by study sponsors when the results do not meet their expectations. Positive results are generally favored, even at the level of meeting abstracts. Withholding of data such as negative findings leads directly to *publication bias*. For example, a recent analysis found that 31% of 74 FDA-registered studies of antidepressant medications were not published.[28] Thirty-eight of the 74 studies were viewed as positive by the FDA, of which 37 were published. Of the 36 studies viewed as negative or questionable by the FDA, three were published, 22 were not published, and 11 were presented as if they had positive, rather than negative, results. Overall, this translates to a 12-fold higher probability that a positive study would be published than a negative one. A reader evaluating, or an investigator performing a meta-analysis of, published results would find that the drugs under study had a consistently beneficial effect, a misleading conclusion.

While the FDA has access to all of the data in Investigational New Drug (IND)-related trials, the public at large does not. Much of the data presented to the FDA is maintained as proprietary information not accessible to external parties. The increasingly common practice among journal editors of requiring prospective registration of clinical trials in the federal database, ClinicalTrials.gov, promises to improve availability of data. The expectation of ClinicalTrials.gov is that key elements of a registered study, including design and results, will be

available for review, thus making the complete range of experiences with any given drug more transparent.[29]

A well-known example of publication bias is the Pharmacia CLASS Trial, which presented a portion of the known clinical data as if it were the complete data set.[30] The CLASS trial was designed as a 12-month study of celecoxib (Celebrex®) to test whether there were fewer ulcers and gastrointestinal problems compared to treatment with alternative non-steroidal anti-inflammatory drugs (NSAIDs). The 12-month data failed to show an advantage to celecoxib over NSAIDs, but the 6-month data did show a differential benefit to celecoxib. The company published the 6-month data, rather than the 12-month data, in the primary publication.[31] The selective reporting was eventually discovered, and Pharmacia's decision to publish a *post hoc* analysis was generally condemned. Nonetheless, this case study justifies the concern that reviewers of data for compendia's purposes might not be able to determine when complete, rather than biased, data are being presented.

4.1.3 Conflict of interest in selection of indications and evidence.

Conflict of interest in evidence selection pertains to individuals reviewing any scientific literature, as well as to compendia processes. A first stage at which conflict of interest might arise is that of the decision regarding which indications to review. A prior review of compendia, their content and practices, found that new indications were frequently reviewed based upon requests from compendia

users or publicity about a drug – which can often be started by the drug company.[2]

Once the indication has entered the review process, the investigator reviewing data – and selectively highlighting certain data as important – applies his/her subjective filter to the information presented; in reading an article, a physician or other provider makes a decision as to whether the article is "good" or not, based to a certain extent on an internally generated set of norms, personal experience and understanding, and evaluation of the quality of the study and its conclusions. Systematic review presents a technique for evaluating evidence that uses a more formal set of specifications. In all cases of evidence review, however, subjectivity can enter into the selection of evidence, either through the creation of formal rules that favor one type of evidence over another, or through personal biases that enable the rejection of some evidence.

An area of potential conflict of interest in evidence selection with particular relevance to compendia is the decision regarding whether or not to include data from ClinicalTrials.gov. As a general rule, this information is likely to be more inclusive of negative outcomes, for reasons outlined in the previous section (4.1.2). If compendia authors are inclined to be positive about a drug – if, for example, they have of a conflict of interest (financial or otherwise) that leads them to favor inclusion of studies reporting positive results about that drug – they would be likely to implement review standards that did not include non-published studies. They might, hence, be more likely to institute editorial policies that did not include retrieval of information from ClinicalTrials.gov.

Another route by which bias can enter the evidentiary process for the compendia is through the inclusion of meeting abstracts. Abstracts tend to be smaller and less complete in their analyses than published papers. It is harder to use purely objective criteria to accept or reject an abstract, thus allowing for the introduction of competing interests. Factors that affect the usability of an abstract include issues such as the extent of the analysis, the degree of completeness of the study (clinical research abstracts are often periodic updates on studies designed with a long duration), or presentation of a subset of the originally designed study population. These caveats bear consideration, alongside recognition that many abstracts present important results well in advance of the final study publications. Particularly problematic is when compendia present information in abstracts as an evidentiary source, and do not update the information when the full published, peer-reviewed report becomes available.[3]

4.1.4 Conflict of interest in interpretation of evidence. Interpretation of evidence takes place at the level of individual reviewers, any of whom may have conscious or unappreciated conflicts of interest as described above. Conflict of interest can arise when there are no clinical trials directly relevant to an indication under consideration. In these situations, guideline committees (and compendia) may substitute consensus expert opinion. In many other cases, the interventions under review are so obviously appropriate that formal testing is never performed – nor should it be, given the inability to achieve equipoise in the two arms of clinical trials studying those interventions. And in some cases, the initial studies

involve a bundle of interventions, making it difficult to determine the specific contribution of any one drug or therapy, or to determine whether similar outcomes can be achieved using parts of the intervention bundle and/or differing doses of component interventions. In any of these scenarios, lack of clarity in the evidence requires that interpretation be applied, and this reliance on interpretation opens the door for potential conflict of interest to influence the conclusions.

4.2 Compendia Development, Review Processes, and Conflict-of-Interest Policies

The second component of this project entailed review of compendia policies, practices, and experiences with regard to conflict of interest, and yielded the following results.

A literature search was conducted to inform the development of an ethical framework. This review sought to identify: (1) previously developed ethical frameworks for conflict of interest, or components thereof, that might pertain to conflict of interest in compendia; and (2) published reports of conflict-of-interest issues with regard to the writing of guidelines and compendia generally, or to their decision-making, editorial processes, production, and content specifically. Thirty-six articles were included and abstracted for the study (Appendix A).

4.2.1 The process of compendia development. A basic process of compendia development – including potential sources of conflict of interest, and

points at which these potential conflicts may arise – was articulated (Figure 1). This model can be applied generally to any compendium, with minor modifications made for compendium-specific elements. In most cases involving update of the compendium, the publisher begins with a current chapter. Alternatively, new topics are introduced and a *de novo* chapter is begun. A team of researchers (who may be compendia employees) reviews the literature for new clinical trials presented in papers, meeting abstracts, guidelines, or review articles. The editorial team evaluates sources of new data, ideally using an explicit and uniform set of standards. A decision is made about whether to include the new results in the updated chapter. Depending on the particular compendium publisher, this decision may involve the use of external consultants.

Once a draft is prepared, most compendium publishers ask external reviewers (often consultants) to review the draft. The editors subsequently decide how, and whether, to incorporate the reviewers' comments. A final draft is then prepared, approved, and published.

The interval between content updates varies across the compendia. Some compendia focus on internet presentation, with updates performed on an almost continuous basis. Other, more print-oriented compendia perform fewer updates and have a more regular schedule of review. The specific editorial process for each of the four compendia included in this study is discussed in Section 4.2.2, immediately below.

4.2.2 The review processes of compendia. We reviewed the websites of each of the four compendia under consideration here for information about their review and editorial processes, and their policies on conflict of interest (Table 2).

One of the four compendia, Clinical Pharmacology, utilizes a review process that is almost entirely in-house; its stated methods allow for the possibility of peer review, but its standard process involves only internal company staff. Corporate policies prohibit staff members from having financial relations with industry. If financial conflicts of interest do occur, the company publishes them on its website.

The other three compendia – AHFS-DI, NCCN Drugs & Biologics Compendium, DRUGDEX – use external reviewers as an essential component of their document creation processes. They vary, however, in their mechanisms for ascertaining reviewers' conflicts of interest, and in the limits they set as a consequence of the conflicts of interest they find (Table 2).

AHFS-DI uses internal staff members to accomplish the primary writing of articles; these staff are required to be free of conflicts of interest. AHFS-DI also has an Oncology Expert Review Committee made up of external evaluators, who review the materials prepared by the internal staff; all Oncology Expert Review Committee members are unpaid volunteers. AHFS-DI has a conflict-of-interest policy for these external personnel. They must declare their conflicts initially, and report on them again at the beginning of each review process. Involvement with both the applicants (i.e., pharmaceutical companies requesting consideration of an indication) and their competitors (i.e., pharmaceutical companies that produce

drugs competing for that indication) are considered conflicts. If a Committee member's financial interests in the involved companies exceed $50,000, that individual will not be allowed to participate in the determination process. Committee members with a relationship of less than $50,000 can serve in an advisory capacity, but they cannot be primary reviewers and cannot vote on a final determination ballot. In addition, AHFS-DI includes information about committee member's conflicts in their published determinations [see http://www.ahfsdruginformation.com/off_label/determination_tables.aspx]. The information about reviewer conflicts is provided in a clear and transparent manner (although the individuals with conflicts are not publically identified).

A conflict-of-interest concern specific to AHFS-DI arises as a result of the unique mechanism by which indications for drugs/biologics may enter this compendium's review system. While AHFS-DI selects some therapies that need to be evaluated for off-label use, it also offers an expedited review. In order to obtain an expedited review, the products' manufacturers submit a request for consideration of the indication to the Foundation for Evidence-Based Medicine (FEBM). The FEBM is a non-profit, 501(c)(3) foundation established in 2007; it is "the sole entry point for the application process [to AHFS-DI] and receives the applications and communicates with the applicants."[32] With an application to the FEBM, a drug company must provide a summary of the evidence and full copies of all references cited in support of the application. Only data in the public domain are considered; no proprietary data are allowed. In addition to a summary, the background research, and the references, applicants must also

pay the FEBM $50,000 for every new indication requested. A spokesperson for AHFS-DI stated that AHFS staff supplement the information provided by the companies, and make a point to include negative studies. In addition, they note that the final determinations for AHFS-DI are made by the Oncology Review Committee members, who are volunteers and so have no financial relationship with the AHFS-DI or the Foundation for Evidence Based Medicine.

The NCCN Drugs & Biologics Compendium differs from the other three compendia considered here in its intrinsic tie to, and reliance upon, information generated for NCCN guidelines. NCCN clinical practice guidelines are written by panels of volunteer experts who come from NCCN member institutions. Disclosure is the core principle on which the NCCN conflict-of-interest policy rests. As of July 2008, with each new clinical practice guideline, NCCN publishes the specific external relationships for the committee members involved in evidence review for, and formulation of, that guideline. According to a teleconference interview between NCCN compendium staff and Duke project personnel, as of 2009 NCCN will also report the amounts of money involved in disclosed relationships (Appendix B). By rule, a panel member with a "direct relationship" should by default not participate in panel discussions. To quote the NCCN policy, "Any panel member who is identified as having a Conflicting Interest shall not attempt to influence the Panel's action with respect to the matter."[33] As of 2009, the threshold for considering potential conflicts of interest will be $10,000 (Appendix B).

Inquiries conducted for this study and by other investigators suggest that NCCN reviewers hold a substantial number of conflicts of interest. On August 27, 2008, one of the investigators on the current study (REM) accessed the NCCN website to evaluate the conflict-of-interest declarations for 22 guideline panels[34] (Table 3). Two additional guidelines had been published by the *Journal of the NCCN* with complete conflict-of-interest disclosures; these disclosures were reviewed separately (NCCN Task Force: Prevention and Management of Mucositis in Cancer Care, and NCCN Oral Chemotherapy Task Force). On the 22 guideline panels, a median of 24.5 external members served (range, 19-30).[†] As of August 27, 2008, a median 70% of the members of the guideline panels had disclosed their external financial interests (range, 32% to 80%). Fifty percent of the external members declared a conflict, with a range from 21% to 78% for each panel. For the two additional published guidelines, 53% and 75% of external members disclosed a conflict of interest. The specific types of conflicts, and the financial amounts involved, have not yet been published.

In addition to the issue of reviewer conflict of interest on the NCCN guideline committees and the effect that would have on compendia chapters, NCCN itself has significant relationships with industry. The network has a long list of sponsoring entities (http://www.nccn.org/about/financial_support.asp), although it does not publish the explicit levels of support from each donor. If this was to bias the compendia recommendations, it would probably be mediated either through the NCCN staff (who prepare materials for subject reviews), or through

[†] NCCN staff members were listed on the disclosure page but are not counted in these figures.

the editorial process when guidelines written by unpaid volunteers are converted into the NCCN Compendia.

Thomson Micromedex posts an explicit conflict-of-interest policy on the internet for its compendium, DRUGDEX. This policy focuses primarily on external advisors. The conflict of interest evaluation process begins with an initial disclosure of financial conflicts of interest by the reviewers, followed by annual updates of these disclosures. Advisors who refuse to disclose their interests are disqualified. Thomson states that its editors will review potential conflicts of interest, and "if possible, the editorial department will select advisors to assist with the content development without any pertinent financial relationships."[35]

In cases where it cannot identify advisors without conflicts of interest, Thomson has a series of rules:

1) Advisors who have been an employee or director of a pharmaceutical company will be excluded, as will individuals whose spouse has such a role.
2) Equity of less than $25,000 is considered *de minimis*, and full participation is allowed. Between $25,000 and $100,000 in holdings, the individual can participate, but their conflict(s) of interest will be disclosed on the Micromedex website. Equity holdings of greater than $100,000 disqualify the individual from participating.
3) Similar standards are in place for payments for consulting, lecturing, and other activities. Payments of less than $25,000 within one year

are considered *de minimis*, $25,000-$100,000 requires disclosure, and greater than $100,000 is disqualifying.

4) Research funding as a principal investigator from any pharmaceutical company within the year shall be disclosed. No one may review their own research (or that of his/her spouse).

5) Patent holders of drugs related to the current review are generally prohibited from participating in the compendia review. Royalty payments for non-related intellectual property from companies whose products are being evaluated will be considered in a manner similar to other payments (see #3, above).

Disclosure is managed by postings at the Micromedex.com website. As of August 31, 2008, there were nine members of DRUGDEX's Oncology Advisory Board. Of these individuals, only two had declared conflicts of interest.

4.3 Example of the Potential for Conflict of Interest in Compendia: DRUGDEX and Allegations of Conflict of Interest

The specific issue of conflict of interest related to the compendia was raised in a 2003 Wall Street Journal article by David Armstrong.[25] This article specifically considered Thomson Micromedex's DRUGDEX compendium, noting both potential conflict-of-interest issues and concerns about the breadth of DRUGDEX's recommendations. The article demonstrated a problem that is consistently present when assessing conflict of interest, namely, the final product (the list of evidence-supported indications) appears to be affected by both

corporate and personal conflicts of interest, but one cannot with certainty determine whether or not the process of judging the evidence was dispassionate or biased. As an example, DRUGDEX typically has more indications for each drug than the other compendia, but this does not necessarily reflect a cavalier approach to judging the data nor a tilt because of the effects of conflict of interest – it may simply be explained by the fact DRUGDEX has a larger, more active staff. Judging the presence or absence of an effect from conflict of interest on the basis of the work product alone is nearly impossible.

Armstrong's article noted several cases of conflict of interest in interpretation of evidence, where evidence appeared to be disregarded, particularly if it limited the number of indications for a given drug. As an example, the article pointed out that the FDA rejected Pfizer's request to label valdecoxib (Bextra®) for use in acute pain because the studies were "inadequate to establish safety and efficacy." DRUGDEX assessed the same studies and listed the drug as effective for the indication. Another example cited was gabapentin (Neurontin®), which was found in two studies to be no better or worse than placebo as adjunctive treatment for bipolar disorder. Yet DRUGDEX listed the indication. This was cited as an example of personal conflict of interest, since one of the authors on the Neurontin® chapter (who may only have been a reviewer) had a long-standing and well-compensated relationship with the company that originally developed and marketed Neurontin® (Parke-Davis, which was taken over by Pfizer in 2000). Shortly after this reviewer was identified, Thomson removed the list of reviewers and authors from its website.

Armstrong also questioned whether Thomson itself had a corporate conflict of interest. In addition to DRUGDEX, Thomson owns companies such as "Physician's World" and Gardiner-Caldwell, which produce continuing medical education (CME) events. In order to remain in good standing with the pharmaceutical industry, which sponsors most CME events, Thomson had an incentive to please drug makers, and thus a conflict of interest. However, in 2007 Thomson sold their branch that administered CME, Thomson Medical Education.

The issue of Thomson's conflict of interest was also raised by The American Society of Health-System Pharmacists, the owner of a competing compendium, AHFS-DI, in a letter to CMS during the process of reviewing Thomson's request to have DRUGDEX approved as an authoritative source for identification of medically accepted indications for off-label uses for drugs,[36] and as a compendium that can be used as the basis for Medicare coverage determinations.

4.4 Print and Electronic Information on Compendia Conflict-of-Interest Policies

Conflict-of-interest policies for each of four compendia considered here were ascertained through review of explicit, publicly available information. To reiterate, these four compendia and their respective publishers are: American Hospital Formulary Service Drug Information (AHFS-DI, produced by the American Society of Health-System Pharmacists),[1] Clinical Pharmacology (Gold

Standard, a subsidiary of Elsevier Reed),[7] NCCN Drugs & Biologics Compendium (National Comprehensive Cancer Network),[6] and DRUGDEX (Thomson Micromedex).[4] Summarized results appear in Table 2.

4.5 Teleconferences with Compendia Personnel

Teleconferences followed a prepared script developed by study investigators (Appendix C). Three of the four compendia (AHFS-DI, NCCN Drugs & Biologics Compendium, and Clinical Pharmacology) agreed to participate in a teleconference which included one or two editorial personnel from the compendium, a study staff person who conducted the interview, and a study staff person who recorded the teleconference. Study investigators were unable to schedule a teleconference with the fourth compendium included in this study, DRUGDEX; corporate policies prevented investigators from contacting appropriate company representatives and made it impossible to obtain verbal information by phone. [Following the posting of the draft report on the Agency website, we received a response from DRUGDEX which can be found as received in Appendix D.]

Results of the teleconferences are described in Appendix B. All of the editorial personnel who provided information reported that their compendium had experienced limited, or no, problems with conflict-of-interest episodes. AHFS-DI was the most precise in noting that they had encountered three instances in which conflict of interest was raised with their Oncology Review Panel. None of those experts was allowed to vote in the related determinations. Consistent with

their reliance on in-house staff members, Clinical Pharmacology noted no conflict-of-interest problems in recent company history. NCCN Drugs & Biologics Compendium noted three recusals; this information conflicts with reports of financial conflicts identified through review of the relevant literature (see section 4.2.2, above).

4.6 Evaluating the Impact of Conflict of Interest on Compendia

As a measure of the effect of conflict of interest on the final product (the actual compendia), an assessment could be made of the number of approved drugs and the quality of the evidence accepted for each indication. Here a reasonable assumption would be that a longer list indicates favoritism toward the manufacturers, patients, and physicians, rather than toward insurers (or perhaps toward science) (Table 4). Abernethy and colleagues, in a critique of the compendia performed in 2006 and updated in 2008, took essentially this approach; they counted indications and evaluated the quality of the evidence assessment in five compendia.[2, 3] Alternatively, one could argue that a longer list of indications may reflect not conflict of interest, but a more active program of evaluating new regimens. In either case, the quality of evidence should be evaluable.

The assessment by Abernethy and colleagues found that most of the compendia reviewed (or documented having reviewed) many fewer research studies than were available, as identified through an independent evidence review conducted by the study investigators. In such a situation, it can be hard to

determine whether there was bias in selection of evidence in order to achieve a desired end, an incomplete approach to finding all the evidence, or a reasoned set of criteria regarding which evidence should be evaluated. Regardless, for each indication there were clearly many opportunities for selective filtering of data.

Evaluating the four compendia studied in the present report in terms of the number of indications, Abernethy and colleagues found that DRUGDEX had the most listed indications, while AHFS-DI had the fewest (Table 4). After this 2006 review, AHFS-DI implemented their system where companies need to pay to apply to the FEBM in order to be considered for an expedited listing in AHFS-DI. Clinical Pharmacology and the NCCN Drugs & Biologics Compendium had very similar number of indications. It is unclear whether DRUGDEX's list of indications is more extensive because Thomson employs a larger or more aggressive staff, or because of the bias toward inclusion that the Wall Street Journal identified as a corporate conflict of interest. Clinical Pharmacology, which has the theoretically least conflicted approach, occupies the middle position in terms of numbers of listed indications.

Abernethy and colleagues also found that evaluating the use of evidence by the compendia as a measure of conflict of interest is an impossible challenge.[2, 3] The compendia do not provide enough detail about the evidence they chose to include versus the evidence they chose to discard in their review process to enable assessment of conflict of interest through this avenue.

5.0 Discussion

5.1 Compendia Play an Important Role in Health Care, Despite the Inevitable Challenge of Conflict of Interest

Physicians routinely prescribe FDA-approved drugs for "off-label indications," i.e., uses other than those for which the FDA has granted approval.[37] While off-label prescribing is common across all of medicine, it takes on particular urgency in oncology, where effective treatment options are often limited. In 1991, a U.S General Accounting Office (GAO) study reported that up to 33% of all anticancer drug prescriptions were written for off-label indications.[38] By 2005, the NCCN estimated that 50% to 75% of all uses of anticancer therapy were off-label.[39]

The compendia have an important role to play in providing information to clinicians regarding off-label indications for FDA-approved drugs. The significance of this role is compounded by the fact that CMS, and other third-party insurers who follow suit, consider compendia in their determinations whether to reimburse off-label indications.

Conflict of interest is an acknowledged, and largely unavoidable, factor in the development of drug compendia due to the nature of inputs to the process (data on drug effectiveness, safety, toxicity, and use, which requires selection and interpretation), the parties involved in the process (individuals with various relationships to drug manufacturers), and outcomes of the process (listing in a compendium, which has financial implications).

The public benefits if the compendia fairly and accurately assess the state of the evidence for a particular indication. Evidence from high-quality clinical trials

should, whenever possible, be the mainstay of review for new drug indications. Rare diseases will, unfortunately, remain problematic, since they are often beyond the scope of clinical trials; in those cases, expert opinion may be the only measure possible. Yet even in these cases, as in those where adequate data are available, compendia publishers should have in place, and enforce, meaningful conflict-of-interest policies that limit the interpretative contributions by conflicted editors and reviewers.

5.2 Compendia Differ in their Conflict-of-Interest Policies, and Likewise Exhibit Diverse Areas for Improvement

The purest approach to minimizing conflict of interest is to eliminate members of compendia writing and reviewing teams who have financial or personal conflicts (e.g., patents). This strategy is demonstrated by Clinical Pharmacology, which uses an in-house staff of professionals to prepare its reviews. This closed-shop approach has its own limitations; for instance, its staff may represent a shallow pool of expertise, or it may have limited input from physicians who actually see patients. Regardless, purely from a conflict-of-interest standpoint, it is the best possible option.

AHFS-DI is nearly as constrained as Clinical Pharmacology in terms of writer conflict of interest, although they allow reviewers to have up to $50,000 in financial interests. The single biggest issue, the impact of which is hard to define, is the relationship between AHFS-DI and the Foundation for Evidence-Based Medicine (FEBM), which functions as gatekeeper, as described above

(see section 4.2.2). The fact that all applicants must pay the FEBM $50,000 per expedited review of an indication could place the editors at AHFS-DI in a difficult position. In order to maintain the revenue stream for FEBM, AHFS-DI staff could feel pressured to approve the applicant's request for inclusion in the compendium.

The managers of the NCCN Drugs & Biologics Compendium appear to have very good intentions. The threshold for disclosure for the expert members (drawn from NCCN institutions) will soon be set at $10,000, a relatively stringent standard. However, a very high proportion of the expert reviewers currently have conflicts. Yet, as the only cancer-specific compendium, the NCCN Drugs & Biologics Compendium and its approach carry certain distinct advantages. NCCN review panels are large, comprising 25 to 30 individuals in most cases; for any given question there are likely to be an adequate number of unconflicted experts. There is also likely to be a leveling effect of peer pressure affecting the judgment of panelists whose conflicts are known and announced at the meetings.

DRUGDEX has the longest list of indications. Both the Wall Street Journal[25] and the Technology Assessment by Abernethy and colleagues[2, 3] questioned whether the evidence included in DRUGDEX was as carefully considered as in the other compendia. Thomson Micromedex did not respond to our requests for an interview, so we lack some of the background information that was available from the other compendia. [see Appendix D for response from DRUGDEX after this report was written] As posted, their conflict-of-interest policy allows reviewers to have more financial interests in the involved companies (up to

$100,000 before disqualification). However, only two members of their Oncology Review Panel reported conflicts, and for one of them the conflict was research support. Thus, the policy appears to be less desirable than the operational outcome, which on surface appears acceptable. The relatively liberal inclusion of indications remains an issue that could be affected by Thomson's non-compendium-related financial interests.

5.3 Conflict of Interest is Not Always a Straightforward Issue

At many points in the creation of compendia chapters, conflict-of-interest problems can perturb the desired scientific objectivity and balance. It is important to acknowledge that the individual with a conflict of interest is often unaware a problem exists. A typical rationalization concerning conflict of interest holds that the primary objective (in this case, the writing of the compendium) is of such importance that financial conflicts will have no meaningful effect. This belief, however, is often untrue.[40] In other cases, conflict of interest is quite explicitly understood and expected. For example, a company preparing a marketing brochure might choose to include the results from a small and favorable study rather than data from a more informative larger study that demonstrated more side effects. The conflict is between the company's primary goal (to sell more of its drug) and the public's interest in having maximally informed care providers.

Thus conflict of interest can be relatively subtle or quite overt. It may be the case that, at times, the appearance of conflict of interest is more of an issue than

the actual effect of that conflict on the performance of the conflicted individual. Given the inability to know the true effect of financial pressures on the decision-making of any one individual, in most cases a conservative approach is advisable, and appearance should be treated as reality.

Similarly, the potential for bias in compendia – due to inadequacies of their review processes, use of unsystematic methods, or intrusion of conflict of interest – is nearly impossible either to rule out or identify definitively. The 2006 Technology Assessment conducted by the Duke/Tufts EPCs[2, 3] found substantial room for improvement in compendia methodologies, and the present study underscores the fact that compendia's stated policies do not necessarily reflect the realities of their implementation. The reader of this report may well desire a final answer to the questions of whether or not compendia apply robust systematic methods in their review processes to reduce bias, and whether or not they uphold meticulous conflict-of-interest policies. Unfortunately, due to the largely subjective nature of conflict of interest, the presence or extent of (a) biased review, (b) conflict of interest, and (c) the relationship between the two, remains unclear. A matter of mental tendency or influence, sometimes conscious and sometimes unrecognized, conflict of interest cannot ever be completely quantified and defined. We again advise, therefore, the most conservative approach, namely, to require explicit, rigorous, systematic methods alongside explicit, strict, conflict-of-interest policies in order to minimize bias; and to prospectively evaluate the impact of these requirements on compendia content.

5.4 Each Compendium Faces Its Own Areas of Risk Where Potential Conflicts of Interest Might Arise

Each of the four compendia considered here, by virtue of its specific policies and practices, faces the risk of conflict of interest in distinct areas.

Among the four, Clinical Pharmacology has implemented the most conservative approach to conflict of interest in evidence review. By strictly limiting outside affiliations of its reviewers, who are internal staff rather than external experts, the company effectively minimizes the possibility of personal conflict of interest among its reviewers. This compendium, thus, appears fairly well insulated from personal conflicts of interest, though corporate conflicts of interest remain a possibility.

Clinical Pharmacology has recently changed ownership. In May 2006, Gold Standard was purchased by Reed Elsevier, a large Dutch publishing and information services conglomerate.[41] This large company contains a business services component that creates risk for corporate conflict of interest. There is potential concern that internal corporate policy could favor the products of Reed Elsevier's business services clients, in order to make working with Reed Elsevier more attractive. This study's teleconference interview with the staff at Gold Standard gave no indication that this concern is based on anything more than a structural possibility, but it should be noted.

The use of external reviewers by the other three compendia decreases their ability to control conflicts of interest.

AHFS-DI maintains a unique arrangement for obtaining evidence, namely, a requirement that applicants seeking expedited review of a new indication submit an application, with an application fee, to the FEBM. This arrangement may place the compendium at risk for influence by conflict of interest. Drug companies are not likely to look favorably upon the requirement to pay $50,000 to get their off-label indication listed in a compendium – especially if that compendium elects not to approve their indication. If AHFS-DI frequently fails to approve applications, the flow of applications will almost certainly cease. Drug companies will opt to seek listings of their indications in other compendia which do not charge a fee. Thus, there is a significant economic pressure on the FEBM for AHFS-DI to approve applications.

Although not specifically a conflict-of-interest question, presence of the $50,000 fee may also discourage requests for off-label uses of lower priced therapies and for those directed at low frequency conditions. The FEBM notes they may waive the application fee in the case of limited population therapies.[42]

Designation of the FEBM as a gateway to the AHFS-DI can be viewed as a strategy for skirting the issue of conflict of interest arising from the compendium's financial relationships with industry. Although the business reasons for the separation of AHFS-DI and FEBM may be legitimate, this configuration has the appearance of "plausible deniability."[32] This arrangement allows AHFS-DI to truthfully state that it does not receive payments from the pharmaceutical industry as part of their review process, and thus that their review remains "independent."

Yet their mandatory partner receives $50,000 from industry for every off-label indication request.

As a counter-balance to these structural concerns created by the fee system, a spokesman for AHFS-DI noted that the actual determinations of accepted indications are made by a volunteer committee. The members of that committee do not, therefore, have a direct financial COI as a result of the fee-based process. However it continues to be true that these reviewers would surely know that regularly rejecting new indications would have an impact on the revenue stream of the FEBM. What effect that knowledge will have on the reviewers cannot be determined.

The NCCN Drugs & Biologics Compendium process draws directly from clinical practice guidelines developed by expert committees convened by the NCCN. The NCCN maintains a clearly articulated commitment to transparency with regard to conflict of interest. It also maintains a commitment to engaging leading experts in its reviews of the evidence and development of clinical practice guidelines. In addition, it uses fairly large panels, which has the effect of diluting the effect of any one individual's conflict of interest. Because of the frequency with which widely known physicians and scientists at esteemed institutions in academia and research have some form of potential conflict of interest – whether it be research funding, speaker fees, consultant roles, or stock ownership – NCCN is open in acknowledging the difficulty of recruiting sufficiently experienced panels without conflicts of interest. Many external members have conflicts of interest; up to 78% of faculty have disclosed conflicts on some

panels. These disclosures call into question the objectivity and neutrality of the review process. Additionally, unlike with drug review articles, where the reader can consider the possible effects of known conflicts and decide whether or not to believe the writer's opinion, with guidelines that are used as a binary determinant by some payers (pay/no pay), knowledge of conflicts is of little use (see section 5.5, below). If the compendium approves a drug for a given indication, payment will be expected, regardless of knowledge regarding whether a majority of the panel members had potential conflicts of interest.

Another area of COI risk for the NCCN is the level of support it receives from external sponsors that include pharmaceutical companies, insurance companies, medical centers, and information providers [List available at http://www.nccn.org/about/financial_support.asp]. Since NCCN compendia entries are derived from NCCN guidelines, and the guidelines are produced primarily by external reviewers, the main risks by this pattern of sponsorship would seem to be either in information provided by staff to the committees (if staff members were aware of the sponsors), or in the process of converting the guidelines to compendia entries.

A third concern regarding NCCN is the fact that as a network it performs clinical trials sponsored by corporate entities. It is conceivable that both the volunteer faculty and the NCCN staff could be inclined to write more favorable guideline and compendia reviews in order to curry favor with potential research sponsors. The biases introduced by such a desire are probably small, given the size and diversity of the guideline writing committees, but should be noted.

Conflict of interest for the fourth compendium, Thomson Micromedex' DRUGDEX, was the subject of a pointed critique by the Wall Street Journal in 2003.[25] The first issue raised by the Journal was the fact that DRUGDEX has a much longer list of recommendations than the other compendia, a fact confirmed last year by a Duke evaluation of the compendia.[2, 3] Specific concerns were raised regarding the fact that other divisions of Thomson perform marketing services for the pharmaceutical industry. The impact of these institutional conflicts of interest can be nearly impossible to describe or quantify. For example, Thomson may have had an internal, unpublished, corporate policy of favoring its marketing clients, but this policy might not be discoverable. From the point of view of conflict of interest, Thomson ameliorated this concern by divesting itself of its medical education division in 2007. Although Thomson clearly and openly presents on the Internet its conflict of interest policies for DRUGDEX, this compendium may be at risk for intrusion of conflict of interest due to its cut-off points for disclosure. These thresholds are set substantially higher than are those of the other three compendia. Thomson's threshold of $100,000, beyond which reviewers may not participate in evaluation of evidence, may explain the relatively small number of conflicted individuals. The public could reasonably wonder if someone receiving slightly less than $100,000 per year might be biased. In addition, while the presence of a financial conflict of interest is disclosed on the website, the amounts of money, equity, or research support are not presented.

5.5 Problems when the Compendia's Approach to Conflict of Interest Relies on Disclosure

Interpretation of results is the component of the compendium-writing process where conflict of interest is least controllable. Although it is best to avoid the use of reviewers who have any connection with companies that manufacture products under consideration (or their direct competitors), conflict-free review is not always feasible and has its own drawbacks, as noted above. Transparency with regard to existing conflicts of interest thus becomes a next-level ideal, intended to enable the observer to ascertain whether the individual reviewer is or is not biased as a result of outside interests. There is little question that the reviewers will be poorly equipped to judge themselves. To quote George Lowenstein: "Conflicts of interest will inevitably bias physician behavior, however honorable and well-intentioned specific physicians may be. Bias may distort their choices, or they may look for and unconsciously emphasize data that support their personal interests."[43]

The four compendia considered here all rely heavily on disclosure as the mechanism for achieving transparency, and as a principal means of uncovering and monitoring potential conflicts of interest. Given the nature of compendia chapters, and the fact that the information in the chapters will be used both in clinical care decisions and reimbursement determinations, even valid disclosure does not seem adequate. How is the reader to adjust for the biases introduced by financial conflicts? In a typical journal article by a conflicted author, the reader can discount the result if he/she so chooses, or at least can attempt to match the

interpretation of the data with the data as presented. In contrast, biases by authors of review articles and meta-analyses may not be evident, even if conflicts are disclosed, and few readers have the ability to spend the time reviewing primary data sources as do authors of the compendia chapters.

Probably the largest difficulty in relying on disclosure as a means of managing conflict of interest relates to how the data are used by CMS and other insurers. When a compendium chapter is used as the reference justifying a drug's eligibility for reimbursement, that document becomes the final word, regardless of the chapter author(s)'s conflict(s) of interest. If conflict of interest induces the compendium or its evidence reviewers to deem almost all reported indications to be supported by evidence, and thus reimbursed, disclosure of the reviewers' conflicts of interest will not rectify the situation. Disclosure alone is, therefore, an inadequate form of management to control conflict of interest for the purpose of reimbursement decisions.

5.6 Other Mechanisms Could Help Curb the Influence of Conflict of Interest on Compendia

Mechanisms exist at the level of the compendia, the research community, and the FDA to minimize the influence of conflict of interest at various points in the compendia development process. First, compendia themselves can institute formal rules designed to prevent conflict of interest related to evidence selection; effectiveness of these rules depends on their consistent application. Ideally, these rules should allow inclusion of data that are presented in registries, peer-

reviewed papers published in biomedical journals, and abstracts – with criteria pertinent to each category of presentation. For example, compendia might set limits on a minimum sample size for studies that will be included in the evidence review (with distinction for orphan diseases), or articulate requirements regarding completeness of the data. The MEDCAC recommendations[5] articulate domains of action for ensuring transparency in the review processes used by compendia, and thus for minimizing conflict of interest. A logical approach that could be applied across compendia would be to require an articulated response to the MEDCAC recommendations, in which each compendium would clearly describe the manner in which it addresses each recommendation. This measure could help to institute accountability, with the compendia's responses providing a yardstick for their subsequent evaluation.

One possible strategy for overcoming the problem of faster publication of positive results than negative ones is to systematically follow the results of studies registered in ClinicalTrials.gov. All IND-related studies are required to be registered, and as of the FDA Modernization Act of 2007, there is also a requirement that the results of the study also be posted. Once the study is completed as designed and the results posted on ClinicalTrials.gov, the evidence could enter the compendium's review process, whether the results are positive or negative. The hope is that the posting of results on ClinicalTrials.gov will have less time-related bias than the publication review process.

Regardless of the strategy, in order to attend to the individual patient's need for options, compendia should enact secondary methods to allow explicit

exceptions to established rules (e.g., to allow consideration of the results of a published study which stopped early due to accrual problems but has particularly compelling Phase I/II study data with clear biological plausibility that an agent is efficacious in the disease), under the guidance of a review board with low and fully disclosed conflicts.

Clinical trials registration offers further mechanisms for reducing biases in the evidence, including biases introduced by conflict of interest. By publicizing the *a priori* designs and analysis plans of trials, registries have the potential to minimize the bias introduced by selective publication of trials and results, and to maximize the ability of reviewers to identify instances in which *post hoc* analyses may have been used to establish spurious statistical associations. In the future, when most clinical studies are registered, and when registry data include more uniformly reported results, reviewers in the scientific community as well as at the compendia will be able more easily to evaluate the completeness of evidence supporting a given drug or biologic. However, the process of reviewing registry data does take time; consequently, most reviewers have focused on published studies (which may be selectively published) and meeting abstracts (which are often submitted while data are still incomplete). Thus, it is important that compendia publishers set an expectation for completeness, including review of registries, since this step has the potential to ameliorate data availability biases.

To make the registry process most useful to compendia reviewers and publishers, registries must include data from Phase II as well as Phase III trials. Currently ClinicalTrials.gov limits its scope to Phase III trials. In certain medical

disciplines, such as oncology, information from Phase II trials is included in the compendia and is pivotal to clinical decisions.

Third, the FDA might play a role in efforts to limit the effects of investigator and sponsor conflict of interest on clinical research data. Because it reviews study designs, as well as data from IND-related clinical trials, the FDA could function as a balanced checkpoint affording an opportunity for data review by a body outside the compendia review sphere, and for secondary assessments of agents' efficacy. FDA oversight can help to assure that pharmaceutical companies work to improve best practices, rather than performing the minimum activities needed to obtain drug approval. However, the FDA is governed by complex rules that balance the need for companies to feel free to discuss proprietary issues (as opposed to hiding information), while at the same time providing sufficient transparency that the public can believe in the products over which the FDA has authority.

6.0 Authors' Commentary

The compendia play a vital role in our health care system today. Clinicians seeking the latest and most promising treatments for their patients frequently rely on the compendia as sources of information. Of interest and utility would be a survey of practicing clinicians, the ways in which they use the compendia, which compendia they consult, and with what frequency. While the compendia at present exhibit undeniable inconsistencies and shortcomings, it is important to acknowledge that they also do, effectively, get information out to practicing physicians who use that information to undergird clinical decisions. The system works, albeit imperfectly.

Potential for conflict of interest undeniably exists in current compendia, and will arguably always be present in any source of evidence review. There are, for example, non-financial pressures like the fact that it is easier to publish a positive result than a negative one that will bias how studies are presented and whether the results are published. The compendia included in this study are aware of the potential for financial conflicts of interest to influence their recommendations, and all have instituted policies intended to control and minimize this influence. The effectiveness of these policies is difficult to ascertain. The important facts are that a growing awareness surrounds the issue of conflict of interest, that steps are being taken to address it in the compendia, and that certain mechanisms already in existence might be strengthened to make the compendia more impartial, evidence-based, and comprehensive.

Areas of opportunity for improving the compendia through managing conflict of interest include:

- Standardization of disclosure processes, including reporting of conflicts (although, as noted, disclosure is of only marginal value in the context of compendia), and more consistent limits on the level of financial conflict of interest that is allowed.
- Greater standardization of the rules regarding evidence to be included in the compendia (which could limit some situations where conflict of interest could affect judgments regarding the inclusion or evaluation of studies). These rules could be established and used as part of the compendia selection process for CMS.
- Development of a process, potentially overseen by an appropriate government agency or designee, for secondary evidence review; it is more likely that a government agency would define process rules than actually perform the reviews. Evidentiary review of this type will not be inexpensive or easily achieved. One possible scenario would be an "enhanced evidence-based practice center" structure designed to achieve rapid-cycle synthesis and to produce updated reviews on a rolling basis. In this structure, highly qualified teams of experts, specially trained in evidence review and synthesis, would prepare evaluations and continuously modify as new evidence emerges. Simultaneously, teams of content experts would consider those reviews for relevance to clinical practice and comparative

effectiveness-based decision-making, and would provide recommendations which also are regularly and iteratively revised in light of new evidence and syntheses. Governance plans and oversight bodies – representing the perspectives of government, industry, third party payors, scientists, and the lay public – would serve to ensure the quality and timeliness of the centers' reviews, and the transparency and accountability of their processes. A system of full disclosure, combined with an open and explicit understanding that some level of conflicts of interest are inevitable, will ensure that best-qualified experts can contribute to the evidence review process, but that their potential conflicts of interest are factored into the review process. Because this process would entail substantial and continuous, coordinated, expert effort, the enhanced evidence-based practice center scenario would require substantial support from government or public/private sector sources.

- Development of a process for the annual assessment of compendia content, as well as of their disclosures and editorial policies, by an appropriate government agency or designee, or by the compendia themselves reporting to an agency/designee through a carefully designed mechanism.
- Use of registries such as ClinicalTrials.gov to improve capture of relevant evidence, and to minimize biases introduced by selective publication and *post hoc* analysis.

- Continuing and open public dialogue regarding the importance of recognizing and reducing conflicts of interest, while also acknowledging that some level of conflict will always exist and that these conflicts do not necessarily always erode safety or intent.

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Acronyms and Abbreviations

ADDRESS	Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis Trial
AHFS-DI	American Hospital Formulary Service Drug Information
AHRQ	Agency for Healthcare Research and Quality
AMA-DE	American Medical Association Drug Evaluations
CHOIR	Correction of Hemoglobin and Outcomes in Renal Insufficiency Trial
CME	Continuing medical education
CMS	Centers for Medicare & Medicaid Services
CPR	Clinical practice recommendation
CREATE	Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Trial
EMEA	European Medicines Agency
ESP	Erythropoiesis-supporting protein
FDA	U.S. Food and Drug Administration
FEBM	Foundation for Evidence-Based Medicine
GAO	U.S. General Accounting Office
IND	Investigational New Drug
ISF	International Sepsis Forum
MEDCAC	Medicare Evidence Development & Coverage Advisory Committee
NCCN	National Comprehensive Cancer Network
NSAID	Non-steroidal anti-inflammatory drug

PROWESS	Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis Trial
RESOLVE	Researching Severe Sepsis and Organ Dysfunction in Children: a Global Perspective Trial
rhAPC	Recombinant human activated protein C
SCCM	Society of Critical Care Medicine
USP-DI	United States Pharmacopeia Drug Information
VERICC	Values, Ethics and Rationing in Critical Care Task Force

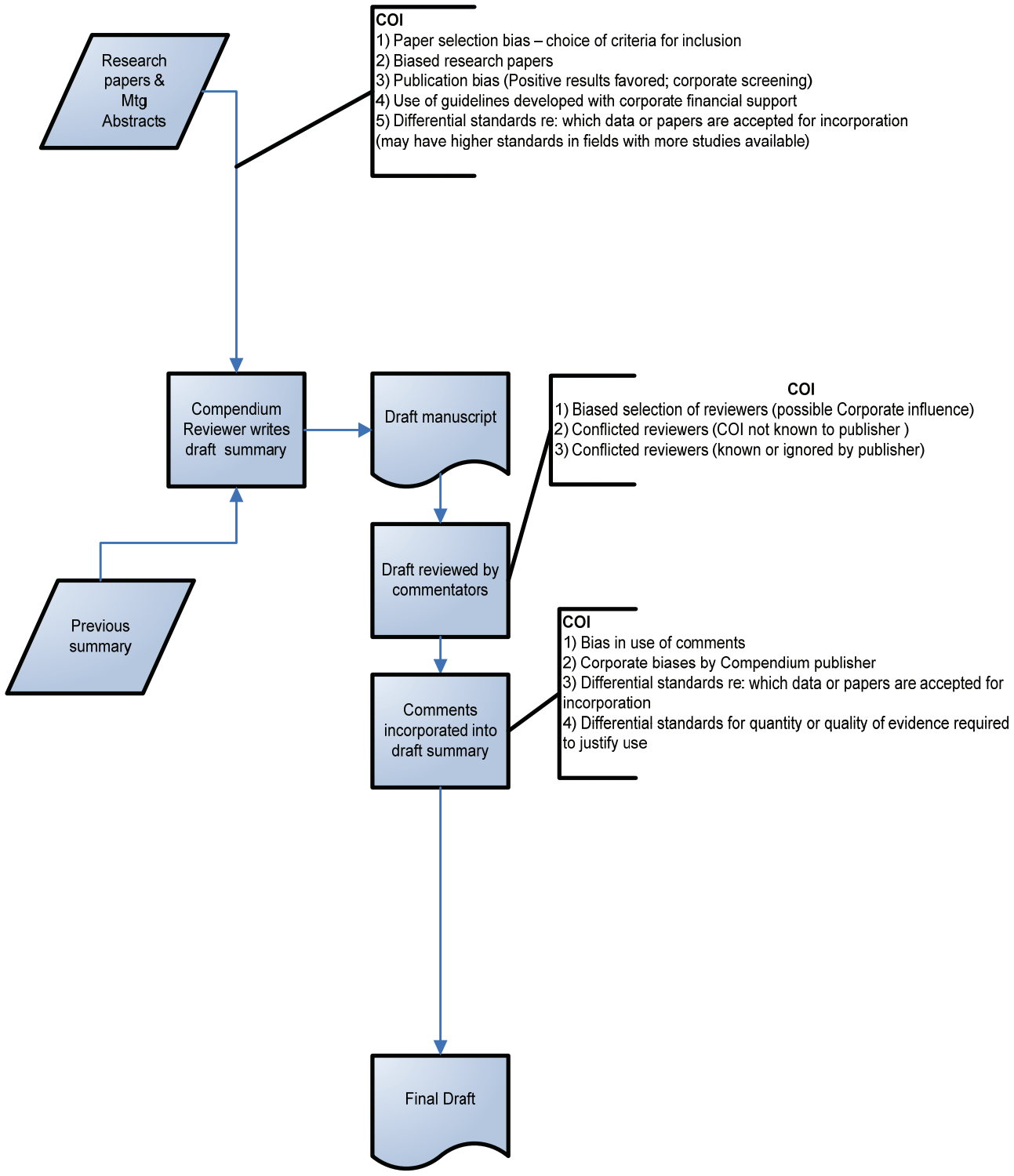

Figure 1: Editorial Flow and Potential Conflict of Interest Problems in the Preparation of Compendia Articles

Table 1: Positive Objectives for Producers and Users of Drug Compendia

Public

- More widespread use of evidence-based practices:
  - Vehicle for disseminating evidence-based practices and improving access to the latest/best available treatments
  - That compendia are used for payment decisions provides pharmaceutical companies an incentive to encourage the performance and publication of studies for secondary indications
  - "One stop" location for information about drugs
- The compendia become a mechanism to enforce standards of evidence
- Compendia provide a mechanism to obtain access to drugs for less common ("orphan") conditions, where there are insufficient patient numbers for FDA registration, and insufficient volume for companies to justify seeking an indication

Physicians and Other Care Providers

- A means to access summarized information about drugs, including effects, side effects, mechanisms of action, indications, and dosages.
- A means to determine which off-label uses are likely to be payable by insurance
- A means to determine which off-label uses have evidence to support them
  - In some cases, a mechanism to grade the quality of evidence in support of an off-label use
  - A means to set standards of evidence (as a screen filtering less well substantiated uses)

CMS

- A means to determine which off-label drug indications have sufficient evidence to support their use
- A means to let the private sector determine the quality of evidence supporting off-label uses
  - Reduces cost of determinations (to CMS)
  - Removes pressure on CMS to make determinations quickly
  - If evidentiary questions are raised, moves accountability away from CMS
- A means to provide information to medical providers regarding for which indications CMS will pay
- A means to motivate physicians and care providers to choose evidence-based practices
- Encourages the use of evidence-based practices, which should be cost effective

Private Insurers

- A means to determine which off-label drug uses have sufficient evidence to support their use
- A means to let an independent entity determine the quality of evidence supporting off-label uses
  - Reduces cost of determinations (to the insurers)
  - Removes pressure on the company to make determinations quickly
  - If evidentiary questions are raised, moves accountability away from the company
- A means to provide information to medical providers regarding for which indications the insurer will pay
- A means to motivate physicians and care providers to choose evidence-based practices, which should be cost effective
- Selection of compendia may provide a differentiating aspect between insurance plans (allowing use of more compendia may seem more patient friendly)
- May allow interaction between the insurers and compendia publishers to help set criteria and standards of evidence (it benefits the insurance company to assure that the evidence is solid)

Pharmaceutical Manufacturers

- Provides a clear pathway to acceptance of new drug indications (i.e. perform studies that provide adequate evidence of benefit to justify inclusion of the off-label use)
- Compendia standards provide guide to types of studies required to justify off-label use
- Can predict uses and thus market needs
- Can partner with compendia to make sure completed studies are publicized and used, and that the drug-specific articles are accurate
- Should provide an alternative model to the FDA for what drug company representatives can talk about (i.e. It should be permissible for the company to promote off-label uses for which there is evidence)
- Compendia are a means to market drugs without additional cost
- Can enhance product sales, when compendia are used as basis for reimbursement decisions
- Compendia provide a mechanism to obtain payment for the use of agents for less common ("orphan") conditions, where there are insufficient patient numbers for FDA registration, and insufficient volume for companies to justify seeking an indication

Compendia Editorial Board Members

- Enhancement of reputation by being selected for the Editorial Board
- Payment for participation in the editorial board
- Means to remain up-to-date on current literature for particular drug/drugs, to review current evidence
- Opportunity to influence patterns of drug use for particular diseases
- Opportunity to educate medical providers regarding drug options and corresponding evidence
- Opportunity to help advance evidence-based practice at the cutting edge of clinical care

Publisher

- Sell (or license) as many copies of the compendia as possible (not applicable to NCCN, which provides free access via the internet).
- Receive CMS approval for use as a criterion in payment decisions
- Provide up-to-date and accurate summaries of drug products
- Maintain a reputation for excellent, accurate, and unbiased information
- Maintain an efficient review process
- Minimize cost of production of the compendia

Table 2: Summary of Compendia Conflict-of-Interest Policies

	AHFS	Gold Standard	Thomson Micromedex	NCCN
Statement of purpose of COI policy	To ensure "that the information be authoritative, objective, and free of undue influence from pharmaceutical manufacturers, health insurers, pharmacy benefit managers, and other third parties who may seek to use the compendium to promote their own vested interests"	To provide "unbiased, complete, and accurate drug information"	To "help ensure individuals involved in literature evaluation and content development for Micromedex databases and products are free from financial conflicts of interest"	To “reach decisions objectively, without being influenced or appearing to be influenced by conflicting interests"
Initial disclosure (internal)	AHFS Oncology Expert Committee Members must complete initial disclosure form listing all financial and other interests for previous 12 months.	No mention of disclosure form or process	No mention of disclosure form or process	Not applicable
Initial disclosure (external)	Outside consultants must also complete the initial disclosure form.	No mention of disclosure form or process	External advisors must complete Financial Disclosure Form.	Prior to appointment to any panel, the individual must complete the Identification and Disclosure of Relationship with External Entities (IDREE) form.
Update of disclosure		Not applicable	Annually and prior to any new assignment (e.g., review of a particular monograph)	Annually; prior to participation in a guideline panel or task force; and within 2 weeks of any change of information
Public access to disclosure information	Individual interests and affiliations published, in aggregate and anonymously, on AHFS website as part of the specific determination	Information is "on file at Gold Standard"	Individual name, pharmaceutical company(ies), and nature of relationship provided on website	A list of panel members' external relationships is provided to every panel member prior to panel discussions. Content of IDREE forms is held by NCCN as confidential.

	AHFS	Gold Standard	Thomson Micromedex	NCCN
Cutpoint for participation in decision-making	Committee members who disclose > $50,000 are not allowed to participate in a particular determination. Committee members who disclose < $50,000 or other affiliations are not allowed to vote in a particular determination, but may advise based on expertise.	Editorial team members may have past relationships with industry, but may not have current, direct relationships with any pharmaceutical company or their representative."	Individual or spouse cannot have employment, or position as director/partner, in past 6 months. Where combined stock/equity value is ≤ $25,000, the individual can participate. Where combined stock/equity value is > $25,000 but < $100,000, the individual can participate with interest disclosed. Where combined stock/equity is > $100,000, the individual cannot participate.	Conflicting interest is defined as (1) being a director, employee, or officer of the organization; (2) owning equity in the organization; (3) receiving ≥ $10,000 per year for services from the organization; (4) having a debt relationship of any kind with the organization; (5) holding a patent (or interest in one) held, licensed, or utilized by the organization. Disclosure does not preclude participation on a panel or task force. Depending on magnitude of conflicting interest, a panel member may advise and participate, or may be excluded and asked to leave the room. Panel meetings should document a member's refraining from relevant discussions.
Policy regarding consulting, lecture/speaking fees, other payments	Not mentioned	Editorial team members may not be employees or receive payment, gifts, or benefits from industry. They may receive gifts extended to any participant in a conference or CE session.	Same cutpoints apply as above.	Not mentioned

	AHFS	Gold Standard	Thomson Micromedex	NCCN
Policy regarding research funding	Not mentioned	Not mentioned	If individual or spouse has received research funding as PI in past 12 months from pharmaceutical company, interest must be disclosed. No individual can participate in review of their own or spouse's research.	Noted as a concern in preamble, but not specifically addressed in the policy
Policy regarding patents or royalties	Not mentioned	Not mentioned	If individual or spouse has patent, IP, or royalty rights associated with content development, he/she cannot participate. If the patent, IP, or royalty rights are for content other than that under consideration, same cutpoints as above apply.	Not mentioned
Enforcement and resolution	AHFS staff review initial disclosure information, and select Committee Members without COIs using cutpoints above. No mention of enforcement practice if a COI is found.	Not mentioned	Not mentioned	Annually and as deemed appropriate, NCCN staff review relationships, compile data, and notify Governance Committee of potentially significant relationships. Governance Committee and Panel Chairs enforce policy. The Governance Committee can require an individual to terminate the conflicting activity or resign the panel, and if the individual does not comply, can remove him/her from the panel.
Waiver	If a Committee Member has a COI, AHFS staff will make final determination on whether that individual may advise (but he/she cannot vote).	Not mentioned	All waivers and exceptions must be reviewed and approved by Editorial and Legal Departments.	A panel member may appeal a decision of the panel chair regarding COI and participation; appeal is made to the Governance Committee.

	AHFS	Gold Standard	Thomson Micromedex	NCCN
Precautions regarding industry contact with editors/staff	Not mentioned	Single division of contact for all pharmaceutical queries/submissions; this division is not directly responsible for data/monograph production.	Not mentioned	Not mentioned
Update of COI policy	Not mentioned	Not mentioned	At discretion of Micromedex	Not mentioned

Table 3: NCCN Guideline Groups and Declared Financial Conflict of Interest (FCOI)*

Guideline Panel	N	Total Any Declared FCOI	Total Declared No FCOI	Total with Pending COI Dis-closure	% (of Disclosed) Reporting an FCOI	% with Pending Dis-closure
Acute Myelocytic Leukemia	21	9	5	7	64.3%	33.3%
Bladder Cancer	21	5	11	5	31.3%	23.8%
Breast Cancer	28	11	10	7	52.4%	25.0%
Cancer & Chemo Induced Anemia	20	7	8	5	46.7%	25.0%
Cervical/Uterine Cancer	23	7	7	9	50.0%	39.1%
Chronic Myelocytic Leukemia	19	5	4	10	55.6%	52.6%
Colon/Rectal/Anal	27	11	8	8	57.9%	29.6%
Esophageal/Gastric	27	7	12	8	36.8%	29.6%
Hepatobiliary	25	7	8	10	46.7%	40.0%
Hodgkins/Lymphoma	25	8	12	5	40.0%	20.0%
Kidney/Testicular	25	12	6	7	66.7%	28.0%
Melanoma	25	8	8	9	50.0%	36.0%
Multiple Myeloma	24	13	5	6	72.2%	25.0%
Myelodysplastic Syndrome	22	12	5	5	70.6%	22.7%
Myeloid Growth Factors	24	5	7	12	41.7%	50.0%
Non-Melanoma Skin Cancer	26	3	7	16	30.0%	61.5%
Non-small cell Lung Cancer	30	14	4	12	77.8%	40.0%
Occult Primary	21	3	11	7	21.4%	33.3%
Pancreatic Adenocarcinoma	27	8	11	8	42.1%	29.6%
Prostate	25	3	5	17	37.5%	68.0%
Senior Adult Oncology	20	4	11	5	26.7%	25.0%
Small Cell Lung Cancer	21	9	6	6	60.0%	28.6%
Oral Chemo	15	8	7	0	53.3%	0.0%
Prevention of Mucositis	12	9	3	0	75.0%	0.0%
Mean	23.9	7.8	7.8	8.4	49.0%	34.8%
Median	24.5	7.5	7.5	7.5	48.3%	29.6%
Min	19	3.0	4.0	5.0	21.4%	20.0%
Max	30	14.0	12.0	17.0	77.8%	68.0%

* Summary statistics on Guideline Groups only – does not include two JNCCN articles. Information compiled from NCCN Panel Disclosures tables (www.nccn.org/disclosures/default.asp); accessed 27 August 2008

Table 4: Discussion of agent-cancer combinations by compendia*

Agent-cancer	AHFS-DI	Clinical Pharma-cology	DRUGDEX	NCCN Drugs & Biologics Compendium	No. of Compendia
Bevacizumab – breast	No	No (Yes)[a]	Yes	Yes	2 (3)[a]
Bevacizumab – lung	No	Yes	Yes	Yes	3
Oxaliplatin – breast	No	Yes	Yes	No	2
Oxaliplatin – lung	No	No	Yes	No	1
Irinotecan – breast	No	No	Yes	No	1
Docetaxel – esophageal	No	No	Yes	Yes	2
Docetaxel – gastric	No	Yes	Yes	Yes	3
Docetaxel – ovarian	No	Yes	Yes	Yes	3
Gemcitabine – biliary tract	No	No	Yes	Yes	2
Gemcitabine – bladder	Yes	Yes	Yes	Yes	4
Gemcitabine – ovary	Yes	Yes	Yes	Yes	4
Rituximab – CLL	No	Yes	Yes	Yes	3
Erlotinib – head & neck	No	Yes	Yes	No	2
Erlotinib – pancreas	No	Yes	Yes	No[b]	2
No. of agent-cancer combinations	2	9 (10)[a]	14	9	-

*Adapted from Abernethy et al.[3]
[a] Indicates a change between the 2006 and 2008 reviews.
[b] A trial is discussed.

Appendix A: Included Articles from the Literature Search

The following 36 articles were included for data abstraction after full-text screening of citations retrieved by the literature search.

1. Abramson J, Starfield B. The effect of conflict of interest on biomedical research and clinical practice guidelines: can we trust the evidence in evidence-based medicine? Journal of the American Board of Family Practice. 2005;18(5):414-8.
2. Anonymous. Clinical practice guidelines and conflict of interest. [erratum appears in CMAJ. 2006 Jan 3;174(1):67]. CMAJ Canadian Medical Association Journal. 2005;173(11):1297.
3. Baily MA, Bottrell M, Lynn J, Jennings B, Hastings C. The ethics of using QI methods to improve health care quality and safety. Hastings Center Report. 2006;36(4):S1-40.
4. Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research: a systematic review. JAMA. 2003;289(4):454-65.
5. Billi JE, Zideman DA, Eigel B, Nolan JP, Montgomery WH, Nadkarni VM. Conflict of interest management before, during, and after the 2005 International Consensus Conference on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. Resuscitation. 2005;67(2-3):171-3.
6. Choudhry NK, Stelfox HT, Detsky AS. Relationships between authors of clinical practice guidelines and the pharmaceutical industry. JAMA. 2002;287(5):612-7.
7. Coyne DW. Influence of industry on renal guideline development. Clinical Journal of The American Society of Nephrology: CJASN. 2007;2(1):3-7; discussion 13-4.

8. Coyne DW. Practice recommendations based on low, very low, and missing evidence. Clinical Journal of The American Society of Nephrology: CJASN. 2007;2(1):11-2.

9. Davis D, Palda V, Drazin Y, Rogers J. Assessing and scaling the knowledge pyramid: the good-guideline guide. CMAJ Canadian Medical Association Journal. 2006;174(3):337-8.

10. Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. [erratum appears in Crit Care Med. 2004 Jun;32(6):1448 Note: Correction of dosage error in text]. Critical Care Medicine. 2004;32(3):858-73.

11. Detsky AS. Sources of bias for authors of clinical practice guidelines. CMAJ Canadian Medical Association Journal. 2006;175(9):1033.

12. Durbin CG, Jr. Is industry guiding the sepsis guidelines? A perspective. Critical Care Medicine. 2007;35(3):689-91.

13. Eichacker PQ, Natanson C, Danner RL. Surviving sepsis--practice guidelines, marketing campaigns, and Eli Lilly. New England Journal of Medicine. 2006;355(16):1640-2.

14. Eichacker PQ, Natanson C, Danner RL. Separating practice guidelines from pharmaceutical marketing. Critical Care Medicine. 2007;35(12):2877-8; author reply 2878-80.

15. Ferreira PH, Ferreira ML, Maher CG, Refshauge K, Herbert RD, Latimer J. Effect of applying different "levels of evidence" criteria on conclusions of Cochrane reviews of interventions for low back pain. Journal of Clinical Epidemiology.

2002;55(11):1126-9.

16. Frye CB. Disclosing conflicts of interest involving clinicians who prepare therapeutic guidelines. American Journal of Health-System Pharmacy. 2005;62(4):361-2.

17. Fye WB. The power of clinical trials and guidelines,and the challenge of conflicts of interest. Journal of the American College of Cardiology. 2003;41(8):1237-42.

18. Guo JJ, Wigle PR, Lammers K, Vu O. Comparison of potentially hepatotoxic drugs among major US drug compendia. Research In Social & Administrative Pharmacy: RSAP. 2005;1(3):460-79.

19. Hilbrich L, Sleight P. Progress and problems for randomized clinical trials: from streptomycin to the era of megatrials. European Heart Journal. 2006;27(18):2158-64.

20. Howlett MC, Lillie D. The Canadian Diabetes Association guidelines: putting the evidence first. CMAJ Canadian Medical Association Journal. 2006;174(3):333-4.

21. Ingelfinger JR. Through the looking glass: anemia guidelines, vested interests, and distortions. Clinical Journal of The American Society of Nephrology: CJASN. 2007;2(3):415-7.

22. Kassirer JP. Stacking the deck. Clinical Journal of The American Society of Nephrology: CJASN. 2007;2(2):212.

23. Kim SYH. Evidence-based ethics for neurology and psychiatry research. NeuroRx. 2004;1(3):372-7.

24. Landucci D. The surviving sepsis guidelines: "lost in translation". Critical Care Medicine. 2004;32(7):1598-600.

25. Laupacis A. On bias and transparency in the development of influential recommendations. CMAJ Canadian Medical Association Journal. 2006;174(3):335-6.

26. Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. BMJ. 2003;326(7400):1167-70.

27. Loewy EH. Ethics and evidence-based medicine: is there a conflict? Medgenmed [Computer File]: Medscape General Medicine. 2007;9(3):30.

28. Narins RG, Bennett WM. Patient care guidelines: problems and solutions. Clinical Journal of The American Society of Nephrology: CJASN. 2007;2(1):1-2.

29. Neale AV, Schwartz KL, Bowman MA. Conflict of interest: can we minimize its influence in the biomedical literature? Journal of the American Board of Family Practice. 2005;18(5):411-3.

30. Nissenson AR. Influence of industry on renal guideline development commentary: keeping our eye on the ball and improving chronic kidney disease patient outcomes. [erratum appears in Clin J Am Soc Nephrol. 2007 May;2(3):617]. Clinical Journal of The American Society of Nephrology: CJASN. 2007;2(2):205-6.

31. Papanikolaou GN, Baltogianni MS, Contopoulos-Ioannidis DG, Haidich AB, Giannakakis IA, Ioannidis JP. Reporting of conflicts of interest in guidelines of preventive and therapeutic interventions. BMC Medical Research Methodology. 2001;1:3.

32. Shiffman RN, Shekelle P, Overhage JM, Slutsky J, Grimshaw J, Deshpande AM.

Standardized reporting of clinical practice guidelines: a proposal from the Conference on Guideline Standardization. Annals of Internal Medicine. 2003;139(6):493-8.

33. Steinbrook R. Guidance for guidelines. New England Journal of Medicine. 2007;356(4):331-3.

34. Traynor K. Most clinical practice guideline authors receive drug industry support. American Journal of Health-System Pharmacy. 2002;59(6):509.

35. Van Wyck D, Eckardt K-U, Uhlig K, Rocco M, Levin A. Appraisal of evidence and control of bias in the kidney disease outcomes quality initiative guideline development process. Clinical Journal of The American Society of Nephrology: CJASN. 2007;2(1):8-10.

36. Van Wyck D, Eckardt K-U, Uhlig K, Rocco M, Levin A. Response to "Influence of Industry on Renal Guideline Development". Clinical Journal of The American Society of Nephrology: CJASN. 2007;2(1):13-14.

Appendix B: Results of Teleconferences with Key Compendia Editorial Personnel

Introduction

Each of four compendia – American Hospital Formulary Service Drug Information (AHFS-DI), Clinical Pharmacology, National Comprehensive Cancer Network Drugs & Biologics Compendium (NCCN Compendium), and DRUGDEX – was contacted to schedule an individual teleconference between project personnel and editorial managers and/or staff. The purpose of the teleconferences was to gather information regarding the compendia's conflict-of-interest policies, in parallel to information on these policies retrieved from published sources (websites, print materials). Project personnel first read an introductory script briefly describing the project, its purpose and format, and then queried the teleconference participants using a standard set of questions; these questions appear below in boldface type. Participants were informed that their identities would remain confidential.

Statements reported below from personnel at three compendia are presented in full, and are unedited (with the exception of minor changes, such as punctuation, to ensure clarity). The fourth compendium, DRUGDEX, did not participate in a teleconference; corporate policy with regard to the handling of unsolicited inquiries prevented project personnel from contacting an appropriate individual or scheduling a teleconference.

Results

What is your organization's conflict-of-interest policy?

AHFS-DI. AHSF-DI has several policies that apply to compendia activities. First, there is a board-approved editorial independence policy, which is available on the AHFS website. Content is developed by qualified editorial staff, therefore there is no risk of external bias. All editorial decisions must be evidence-based and made independent of third parties. All extramural reviewers participate on a voluntary basis, without recompense of any sort, and must provide full disclosure of interest. Staff must avoid participating in business discussions with industry; are required to disclose any potential conflicts of interests, financial or otherwise; and cannot solicit or accept gifts from parties that represent a conflict of interest. Staff must also avoid actions that might create the appearance of violating these principles of conduct. Questions unaddressed by this policy are to be referred to the Vice President of Publishing and Editor of AHFS.

Second, stringent firewall policies exist between applicants for off-label use and AHFS staff performing the evidence-based determinations as well as the Oncology Expert Committee. No direct communication is allowed between applicants and AHFS staff and committee members. There is no opportunity to appeal the final determination.

Third, members of the AHFS Oncology Expert Committee are required to complete a detailed disclosure of interest. Committee members, who are appointed for five-year terms by AHFS, are required to complete an initial disclosure form covering the past twelve months, including salary, grants, contracts, teaching, speaking, writing, expert witness, equity and other ownership rights, IP rights and nature of that interest plus affiliation of interest, who the affected person is (for example, self or spouse), and any

interests of other types (officer, director, trustee, employee). The amount of interest must be stated (categories are less than $10,000, $10,000 to $25,000, $25,000 to $50,000, and more than $50,000) modeled after FDA guidance. Committee members must also provide a full update of disclosure information every three years. Each time they participate in a particular determination, they must provide an update prior to the final vote. If they have an affiliation (for example, consultancy) that represents a conflict of interest, they will not be asked to serve as reviewer; they can serve in an advisory capacity, but cannot vote on the final ballot. Conflicts of interest are evaluated in the context of interests relating to potential competitors. If the amount of interest is greater than $50,000, the committee member is excluded from review. If the amount of interest is between $25,000 and $50,000, the committee member can serve in an advisory capacity. However, efforts are made to select committee members who do not have conflicts of interest. Occasionally, outside experts provide guidance to the committee, and they provide disclosure as well; a waiver may be granted if there is a conflict of interest, but that individual does not vote. Recusal is noted as part of public disclosure; examples can be found in current postings of determinations on the website. These Oncology Expert Committee policies are new this year (2008) and were developed following the MCAC and CMS final rule on key characteristics for compendia.

The full conflict-of-interest policy is not on the website. A summary is on the website. The full policy is distributed to committee members electronically. The editorial independence policy is posted in full on the website.

Clinical Pharmacology. The conflict-of-interest policy is posted on the Gold Standard website for the public to view. Clinical Pharmacology is a subscribed

compendium; its subscribers are individuals or institutions or corporate entities. A host of information regarding the editorial team, editorial processes, and policy summaries is on the website. There is a conflict-of-interest summary regarding the staff and the pharmaceutical industry. An annual disclosure summary informs users of the disclosure process and what it reveals regarding the staff. Base authoring is done by Gold Standard employees. Policy regarding those persons (for clinically oriented content) is very strict with regard to any direct pharmaceutical industry contact; speaking events, sponsored programs, and the like are highly discouraged. Employees are required to disclose annually and also any time a change may have occurred – either financially or through association. Forms are kept on file through Gold Standard.

The conflict-of-interest definition does not include personal associations (for example, family members); it would be nearly impossible to include personal relationships because everyone has them. This might present a conflict.

The editorial board requires disclosure of any dollar amount, even $1, if it is a direct payment (that is, disclosure is not limited to over $10,000 per year). Small gifts like pens are acceptable, if they are extended to everyone at a conference. Non-trivial gifts are not acceptable. No individualized gifts are allowed, even, for example a baby shower gift from a pharmaceutical representative.

The compendia industry is trying to do what's right in this arena. People do not put themselves in a place where the integrity of healthcare would be in danger. The compendia industry wants to make sure, for the sake of public safety and risk/benefit and reduction of medication errors, that they get best information out there. The

industry wants to be responsive to what Medicine needs, regarding information about drugs, with full disclosure.

NCCN Compendium. NCCN has 44 expert panels for their clinical practice guidelines. Since 2001, at the beginning of each meeting of these panels, each individual panel member discloses potential conflicts of interest including affiliations with organizations, NCI, cooperative groups, etc. Categories of interest include: equity, stock, patents, research funding, speaker bureaus, consultations, and advisory boards. The disclosed information is used as the basis to recuse individuals for specific issues under discussion. Staff associated with panel meetings also disclose their conflicts of interest.

Beginning in 2003, NCCN began listing all individual conflicts of interest at the front of the clinical practice guidelines and publishing them in JNCCN. In 2007, NCCN upgraded the conflict-of-interest process, responding to the need to continuously improve. NCCN reviewed and updated the policy to more specifically define what a conflict is, and developed a disclosure form that all investigators must submit annually and if there is a change of status.

NCCN has also promised a list of all panel members and their direct relationships to external entities by the end of 2008, and a list with financial ranges by the end of 2009. Specifically, by the end of 2008, NCCN will link, online and in tabular format, every panel member with organizations, for all the public to view. NCCN will probably have a listing of members with a direct link to this table. In 2009, NCCN will also have laid out, specifically, the amounts of dollars that panel members have received from outside organizations and the function that it was for. NCCN will consider $10,000 (received

from any one company) to be the cutpoint at which it will seriously look at an individual's affiliation. However, it will also look at the 2009 results of financial range disclosures, evaluate the landscape, and carefully review this cutpoint in light of the distribution of financial relationships. The figure $10,000 for any one company was chosen arbitrarily and may need to be changed.

NCCN will, in the future, consider conflicts of interest and potential for conflict of interest in recruiting new panel members. Heretofore, it has not done this. Potential new members will need to be reviewed by staff, and if any questions arise regarding conflict of interest, the question will go to the Governance Committee. This will go into effect by end of 2008. Right now the priority is to get all physicians on the list. Panelists tend to stay on a panel; the number of new ones each year is not large. Openings occur when a panel member leaves an NCCN institution or when standard of care changes and the panel needs a different balance of expertise.

How is this conflict-of-interest policy implemented in your organization?

AHFS-DI. The editorial independence policy is board-approved, and goes through the regular policy development process of the Board of Directors. Firewall policies, Foundation for Evidence-based Medicine policies, and ASHP firewall policies prevent direct communication between applicants and editorial personnel. Policies are spelled out on the Foundation for Evidence-based Medicine website.

AHFS receives no direct support from the pharmaceutical industry. AHFS-DI uses an appointed external expert committee, and requires disclosure statements that cover the prior twelve months, plus updates for each review that committee members

participate in. AHFS-DI staff review all disclosure forms and select for a particular determination members who have no apparent direct or indirect conflicts of interest. Staff are also instructed to consider investigational agents in this consideration.

Clinical Pharmacology. It is implemented first through the employment process: during the interview, prospective employees are asked if they have any current affiliations or financial interests that might present conflicts of interest. At that time they are informed that they will have to sever any potential interests that Gold Standard determines may represent conflicts (speakers boards, publishing). Second, there is annual disclosure: employees must file a conflict-of-interest disclosure form every year. This form covers any potential financial holdings, specifically related to pharmaceutical manufacturers, professional organizations, and other possibly interested parties. This includes speaking at professional organizations or on behalf of a pharmaceutical manufacturer. If an employee identifies a disclosed item, an internal peer review process exists through which the editorial team can determine that that person is not reviewing content related to potential conflict of interest. (This has never occurred at Gold Standard, their people are not speaking for pharmaceutical industry) The editorial team takes forms, summarizes them, reviews them, and posts them for the public as summarized results (not individual by individual, though the team wouldn't have a problem with doing so). Most editorial team members disclose that they have 401k's which may include a pharmaceutical holding. No one has held direct stock in a pharmaceutical manufacturer; one person did speak for the American Dental Association but was not sponsored by the pharmaceutical industry and did not speak on

a pharmaceutical subject – this was acceptable. If people want specific information on disclosures, they will share this.

NCCN Compendium. Nothing further added to comments provided above.

How well known is the policy to members of the staff?

AHFS-DI. It is a board-approved policy that all staff are aware of, and reminded of on ongoing basis (for example, at staff meetings). Policies apply sometimes to other ASHP staff and should be known by them. The policy is publicly accessible on the website. ASHP staff are provided periodic seminars on oncology initiatives, and a key item in these is importance of the editorial independence policy and the firewall. All committee members are provided with the conflict-of-interest policy as part of their introductory packet at the time of their appointment.

Clinical Pharmacology. It is extremely well known – a requirement of the staff. The staff is very well-versed on the policy, which is followed annually or with significant change. Compliance is universal.

NCCN Compendium. NCCN had the highest rating against CMS criteria for compendium quality. All recommendations in the NCCN compendium are derived directly from the well-known NCCN clinical practice guidelines. Thus, the clinical practice guideline policies and processes are those that determine the compendium content (with some editing to bring recommendation material into compendium format). Each panel chair verifies that the exact wording in the compendium faithfully and accurately represents what is in the recommendation of the guideline.

Other compendia that cover multiple diseases have a general cancer panel of 15-20 individuals, with only 2-3 individuals per major cancer type (e.g., breast). NCCN panels have 20-30 members each for every specific cancer. CMS and United both approved NCCN. See the pink sheet in which Lee Newcomer noted that the NCCN had the cleanest conflict-of-interest situation.[**]

In oncology, the NCCN recommendations are recognized as the most conservative, and also the most specific, so managed care orgs are comfortable using them for pre-authorization. This relates to the size of their panels and the expertise on each – they can look at performance status, histology, and a host of detail rather than just thumbs up or down on any given indication.

How was this policy developed? For example, was it created to address potential conflicts of interest specific to compendia development, or was it based upon a more general template?

AHFS-DI. The editorial independence policy was created through ASHP's policy development process to codify the publication's longstanding practice. As part of that process, it was first reviewed and approved by the Committee on Publications; following their review, the policy went to the Board of Directors. Firewall policies were developed to address potential conflicts of interest specific to compendia development. They were developed internally by staff in consultation with general counsel, looking at others' firewall policies to reflect best practices. The Oncology Expert Committee documents were developed by looking at existing conflicts of interest documents for ASHP, and

[**] The participant here refers to an article entitled, "UnitedHealth to Rely on NCCN Compendium for Off-Label Oncology Coverage," The Pink Sheet, FDC Reports, January 28, 2008.

relied on the FDA conflict-of-interest document (this provides guidance to the public for participation in FDA advisory committees). The ASHP general counsel reviews all of these documents.

Clinical Pharmacology. It was developed by the editorial team with approval by the Gold Standard management team. The policy then comes to management for approval. Once management approves the policy, it goes back to staff for administration and adherence. The editor-in-chief ensures that the policy is adhered to. (Not everyone at Gold Standard is in health care, so it's important to have the policy start with the peer group.) The editorial board has educated Gold Standard regarding how important this is to the public and why it's necessary to have a clean editorial organization and to rinse out any potential bias in content.

NCCN Compendium. The policy was developed through a staff-initiated discussion with the Governance Committee (which develops rules for specific NCCN programs). In April 2007, in consultation with outside lawyers, NCCN began development of the updated policy. This is now undergoing revision. (NCCN filed the updated policy with CMS, along with its disclosure form.) The Governance Committee made general recommendations which were reviewed at a board meeting. In early 2008, NCCN began to communicate the policy to all panel members. Of approximately 800–850 panel members, approximately 350 have filled out the form. All must have completed the form by the end of 2008, or they won't be allowed to remain on a panel.

NCCN's main interest is mitigation of bias, and this has guided the whole way they are set up, with large expert panels, institutional review, input from Board clinicians, and broad geographical distribution.

Who at your organization is responsible for addressing conflict-of-interest issues if/when they arise, and generally for implementing the conflict-of-interest policy?

AHFS-DI. The editorial independence policy is operationalized by the Vice President of Publications and Drug Information Services Offices, Assistant Vice President for Drug Info, and Editor of AHFS. The Oncology Expert Committee policy is operationalized by the Senior Drug Information Analyst, in consultation with the Assistant Vice President for Drug Information and, when necessary, with general counsel.

Clinical Pharmacology. The editor-in-chief is responsible. A key part of the editor-in-chief's job is to ensure that every member of the staff adheres to the policy without fail. For drug compendia especially, the editor-in-chief must represent both internally and externally the face of integrity, ethics in journalism, policy adherence, creation and format of content, and editorial policies across the board – not only for conflict of interest, but also for literary style, copyright and plagiarism, and so on. Editorial managers play this out under the editor-in-chief.

NCCN Compendium. Panel members at the meetings identify their conflicts of interest; these are recorded by audiotape and by staff. A senior staff person is the panel chair and logs conflicts reported. The panel chair will make the decision about whether an individual panelist should be recused. If a staff person leaves a significant issue with panel member, then the panel chair will decide whether that panel member should continue on the panel. That person then has a choice: to dispose of the interest

or leave the panel. If the individual disagrees, the dispute goes to the Governance Committee.

Have conflict-of-interest questions or issues arisen during the course of ongoing development and updating of your compendium?

AHFS-DI. Yes, since the application process was initiated at the beginning of this year, there have been three events on three different drugs. Each was handled according to policies and procedures. All were addressed in advance of balloting on the determination.

Clinical Pharmacology. There have been none. For at least the last ten years, no conflicts of interest have been driven through this policy. The editorial team is a tight-knit group, most of whom have been there more than five years. Clinical Pharmacology does not use outside authoring at all. There are 18 members on the team, but not all work on Clinical Pharmacology: 13 working on Clinical Pharmacology are pharmacists, 5-7 work on drug data alerts instead (there are also translators, etc.).

NCCN Compendium. This happens only infrequently, but it does happen. There are two or three examples of conflict of interest arising in which a panelist needed to be recused.

How was the conflict-of-interest policy applied to this (these) situation(s)? Could you give specific examples?

AHFS-DI. First, for azacytadine one committee member was identified as having direct conflict with the manufacturer. An outside consultant was used for expertise

instead of the committee member (rather than granting a waiver for the committee member); that expert did have a conflict of interest, but a waiver was granted with full disclosure so that his expertise could be used, and he did not vote. The final determination publicly notes that an expert consultant was used.

Second, for bortezomib, one committee member was chosen for essential expertise, but he had an indirect conflict of interest due to his affiliation with a competitor company. This individual was notified in writing that he could not participate in voting, and this was publicly noted in the final determination.

Third, for alendronic acid, one committee member was selected based on availability, but he was working with a Phase III investigational agent from a competitor. He could no longer participate in the balloting and voting process. His comments were not shared with other committee members.

Clinical Pharmacology. Not applicable

NCCN Compendium. One individual served as a consultant to a drug company that had obtained FDA labeling for the drug under panel consideration. The individual was recused from the discussion of that indication.

Is the conflict-of-interest policy reviewed on a regular basis? If so, by whom, at what time points, and through what methods?

AHFS-DI. Board policies are reviewed every five years. The editorial independence policy was last approved in December 2004, so it will be reviewed at the October 2009 meeting of the Committee on Publications, and if it needs revision, it will go to the full Board of Directors in December 2009. For the Oncology Expert Committee's current

policy, AHFS-DI is already in the process of reviewing some of the individual points within the policy to provide additional clarity (for example, for investigational agents, for which potential conflicts may not have been considered). In the long term, AHFS-DI will internally review the conflict-of-interest policy for the Oncology Expert Committee every five years. Revisions and changes to policies are all reviewed by the Assistant Vice President for Drug Information and the ASHP general counsel.

Clinical Pharmacology. The policy is reviewed annually with the editorial team members, at same time as disclosure updates. The policy has not changed in many years, because it is very comprehensive. The editorial board has not found a need to do anything more, unless CMS or another regulatory agency asks for an evolution of these policies.

NCCN Compendium. NCCN holds senior staff meetings once or twice per week and these meetings address the status of public disclosure, how to highlight this online, how to simplify the forms, and so on in ongoing discussion.

NCCN has planned conflict-of-interest policy updates through 2009. NCCN understands the importance and visibility of conflict of interest in the current environment. NCCN wants to be open, transparent, and public about who their physicians are and so on, so that end users can decide the extent to which they will rely on NCCN information products.

Has your organization attempted to study the effectiveness of the conflict-of-interest policy in preventing such conflicts from influencing compendium decisions or processes? If so, what were the results of the inquiry?

AHFS-DI. AHFS-DI has not yet studied the effectiveness of the editorial independence policy. It has been monitoring the Oncology Expert Committee with each determination. It will look, at the end of 2008, at which conflicts of interest were identified and consider if changes in policy could be made to prevent future conflicts and to determine if conflicts could be detected earlier. ASHP is exploring corporate mechanisms for monitoring, especially early on in the process.

Clinical Pharmacology. Because no one has disclosed potential conflicts, the editorial board has not felt the need to study it. If that situation did arise, the editorial board would probably want to study the policy's effectiveness, in order to eliminate unacceptable influences in the content stream. The editorial board has a strict way of going about evaluating the medical literature, information sources, and so on. If a client ever had a question regarding conflict of interest, the board would feel the need to investigate. (No one has ever raised a question.) People have asked about the evidence behind a recommendation, but not specifically about conflict of interest. The board has to re-evaluate the net that it casts regularly, because Medicine changes all the time.

NCCN Compendium. NCCN hasn't studied the effectiveness of their conflict-of-interest process formally. They have some expertise in-house, but would be happy to participate with project personnel [at Duke] or others if CMS would like to formally study it. They would be glad to open up their process. They feel that effectiveness of conflict-of-interest policies would be hard to determine, however.

Does your compendium ever give a waiver on the conflict-of-interest policy, or are there exceptions? If so, are they written into your policies?

AHFS-DI. Yes. Basically, AHFS-DI adapted its own waiver from the FDA's guidance document for advisory committees. If someone's expertise is considered essential for determination, a waiver is granted, but that individual is not included in the final vote and disclosure is made public. Waiver policies are written into the conflict-of-interest policy, and committee members are aware of those policies.

Clinical Pharmacology. There is no waiver policy.

NCCN Compendium. To date, no waivers or exceptions have come up.

Appendix C: Script for Teleconferences with Key Compendia Editorial Personnel

Introduction

Teleconferences will be conducted either with key individuals or with small groups of two to four individuals. Each teleconference call will solicit information from key information sources at a single compendium. We plan to conduct teleconferences with four compendia.

Verbal Script

[Read to all participants on each teleconference, at the outset of each call. In the case of a call with only one person, adjust the script accordingly.]

Hello, my name is […] and on the call with me is […; other project personnel say hello.] We are part of a team of investigators at Duke who are gathering input for a white paper that will assist the Center for Medicare and Medicaid Services (CMS) in evaluating the potential for conflict of interest in the development of drug compendia. This issue is of importance to CMS because, under current policy, Medicare may cover pharmaceutical products for off-label uses of drugs if those off-label indications are listed in specific, designated compendia. Information which we obtain through this teleconference today will supplement information which we are gathering through a literature review and through a review of compendia's policies, available in print or electronically, with regards to conflict of interest.

To verify information collected from these stated policies, and to collect additional information about compendia's experiences with implementing these policies, we are

conducting a series of teleconferences with individuals whom we view as “key information sources.” “Key information sources” are defined for this project as people in positions to have a sound knowledge base regarding their organization’s policies, practices, and experiences with respect to conflict of interest in the development of drug compendia.

It is important to understand that this is a policy project, from which the main output will be a white paper summary. The white paper will be delivered to CMS and the public for the purpose of elucidating issues regarding potential for conflict of interest in drug compendia processes. Its purpose is not to expose any particular compendium, nor to highlight any transgressions on the part of a specific compendium or of the compendia as a group. Rather, we are seeking to gain accurate information about the extent to which conflicts of interest may arise, and the methods by which compendia currently protect themselves against such conflicts of interest.

The salient points about the process of this teleconference are as follows:

- This teleconference will last approximately one hour, and will be digitally audio-recorded.
- The content of this teleconference will be used in development of a white paper, but otherwise statements provided by individuals will not become part of the public record.
- We will not name in any public way the specific individuals whom we have interviewed, although we will reference the names of the compendia whose policies we reviewed.

- We will maintain confidentiality by attaching no personal identifying information to any content provided; nothing that you say will be directly linked back to you within our report.
- If you say something quotable that we would like to use verbatim in the paper, we will ask your permission explicitly about using the quotation, either during this interview or subsequently.
- Digital audio-recordings will be stored on a secure server at Duke and will only be accessible only to the investigators to prepare the report. They will not be shared with CMS or become part of the public record, although they may be made available to members of the Duke IRB in the event of an internal audit. The digital audio-files will be destroyed six years after the project is complete.

Do you have any questions before we begin?

Leading questions to guide the conversation:

- What is your organization's conflict-of-interest policy?
- How is this conflict-of-interest policy implemented in your organization?
- How well known is the policy to members of the staff?
- How was this policy developed? For example, was it created to address potential conflicts of interest specific to compendia development, or was it based upon a more general template?
- Who at your organization is responsible for addressing conflict-of-interest issues if/when they arise, and generally for implementing the conflict-of-interest policy?

- Have conflict-of-interest questions or issues arisen during the course of ongoing development and updating of your compendium?
- How was the conflict-of-interest policy applied to this (these) situation(s)?
- Could you give specific examples?
- Is the conflict-of-interest policy reviewed on a regular basis? If so, by whom, at what time points, and through what methods?
- Has your organization attempted to study the effectiveness of the conflict-of-interest policy in preventing such conflicts from influencing compendium decisions or processes? If so, what were the results of the inquiry?
- Does your compendium ever give a waver on the COI or are there exceptions? If so, are they written into your policies?

Appendix D: Response from DRUGDEX following posting of draft report on Agency website

Thomson Reuters (DRUGDEX ®) Survey Responses
For
Potential Conflict of Interest in the Production of Drug Compendia

1. **What is your organization's conflict-of-interest policy?**

The editorial department within the Healthcare business of Thomson Reuters adheres to the conflict of interest policy as it is posted on our website. The policy is intended to ensure that staff and external advisors involved in literature evaluation and content development are not influenced by financial conflicts of interest. It is a three-tiered policy which provides that, for de-minimus levels of financial conflicts, disclosure of the conflict is not required. For increasing levels, disclosure is required but is not deemed to be disqualifying. For example, an individual disclosing a conflict between $25,000 and $100,000 will not be assigned to create or review content to which the financial disclosure directly or indirectly relates. They may, however, be assigned to create or review another topic unrelated to the potential conflict. Finally, disqualification of an individual from holding any position within the Thomson Reuters internal editorial group or on an external advisory board results from situations where there is a significant potential for conflict due to the size or nature of a financial relationship.

Our policy addresses conflicts with the pharmaceutical industry for the employee/advisor and his/her spouse/domestic partner arising from: employment or leadership positions, equity or stock ownership, advisory/consulting roles, lecture/speaking fees and payments of other sorts, research funding, and patents or royalties.

2. **How is this conflict-of-interest policy implemented in your organization?**

Employees within the editorial department are required to submit a Financial Disclosure Form at the beginning of their employment and annually thereafter. In addition, employees are obligated to inform their managers of any change in the information they provided on the disclosure form, which then requires further review.

External advisors are required to submit a Financial Disclosure Form prior to working on any content and annually thereafter. In addition, for the Oncology Board, the advisor must update the Financial Disclosure Form prior to each new assignment, such as review of a new indication packet.

If an employee or advisor discloses a financial interest valued between $25,000 and $100,000, editorial management will ensure such individual does not participate in content creation or review related to the conflict. They may, however, be assigned to another topic unrelated to the financial interest, and which does not create a conflict. If an employee or advisor refuses to provide information about his or her financial and other relevant interests, the person will be disqualified from participation in any content creation or review.

3. **How well known is the policy to members of the staff?**

   Employees and external advisors are provided a copy of our conflict-of-interest policy. The policy is redistributed and resigned annually. In addition, throughout the year the importance of our department maintaining editorial independence from any outside influence is emphasized at department and staff meetings.

4. **How was this policy developed? For example, was it created to address potential conflicts of interest specific to compendia development, or was it based upon a more general template?**

   The development of our conflict-of-interest policy for our editorial department has been an ongoing process. Initially, we looked to the market for best practice examples. We identified and reviewed a number of such policies including those from the FDA and ASCO.

   The intent of our policy is not specific to compendia development, but rather to prevent potential conflicts across all of our product offerings. The primary purpose of our DRUGDEX® product is to provide recommendations to clinicians making treatment decisions. Maintaining editorial independence is equally important in providing bias-free content to clinicians as it is to ratings assigned to drugs within a compendium. Our policy was developed to ensure editorial independence in all aspects of our content creation and review.

5. **Who at your organization is responsible for addressing conflict-of-interest issues if/when they arise, and generally for implementing the conflict-of-interest policy?**

   The Vice President of Knowledge Development (Editorial) is responsible for implementing the policy, ensuring adherence, and addressing issues if they arise. When necessary, internal legal counsel will also be consulted.

6. **Have conflict-of-interest questions or issues arisen during the course of ongoing development and updating of your compendium?**

   There has not been an instance of conflict. A small number of disclosures have warranted internal discussion in order to ensure those individuals were not assigned to content that would present a conflict. All potential conflicts have been addressed through appropriate selection of assigned topics, effectively avoiding conflict.

7. **How was the conflict-of-interest policy applied to this (these) situation(s)? Could you give specific examples?**

   A small number of members on our Oncology Review Board have disclosed potential conflicts. Before assigning a topic to anyone on this board, we review their Financial Disclosure Forms and select members who do not have any conflicts with the topic (either directly or indirectly with a competitor company). The board members are required to submit a new Financial Disclosure Form with

each assignment they complete. Upon receipt of the complete assignment, we review the newly submitted form to ensure the review remains conflict free.

8. **Is the conflict-of-interest policy reviewed on a regular basis? If so, by whom, at what time points, and through what methods?**

   We have historically conducted an annual review of the policy, but do not have a regular schedule; rather we review as necessary. Senior Management from Knowledge Development (Editorial), Product Management, and internal legal counsel are involved in all policy revisions.

9. **Has your organization attempted to study the effectiveness of the conflict-of-interest policy in preventing such conflicts from influencing compendium decisions or processes? If so, what were the results of the inquiry?**

   A study on the effectiveness of our policy has not been conducted. We would be interested in exploring a method to study the effectiveness and would welcome any suggestions.

10. **Does your compendium ever give a waiver on the conflict-of-interest policy, or are there exceptions? If so, are they written into your policies?**

    Our policy does allow us to grant waivers and exceptions. To date, no waivers or exceptions have been given.