Drug Compendia in Oncology: Are They Flawed?

By Renee Twombly

Recent studies have raised concerns about the reliability of four compendia currently used by Medicare and other payers to help determine which cancer drugs will be covered for which off-label indications. Now, experts are looking for ways to improve the compendia, even as oncologists debate their usefulness to guide treatment decisions.

The studies, a series of reports funded by the Centers for Medicare and Medicaid Services (CMS) and conducted by the Agency for Healthcare Research and Quality (AHRQ), have found that the current compendia lack transparency, cite little current evidence, lack systematic methods to review and update evidence, and are replete with conflicts of interest issues.

The findings would seem to matter. Up to 75% of all uses of cancer therapies are off label, according to a 2005 estimate by the National Comprehensive Cancer Network (NCCN), whose own compendium was later chosen for use by CMS. Louis B. Jacques, M.D., who directs the division of items and devices coverage and analysis group at CMS, emphasizes that compendia—essentially lists of drugs for certain indications—are not a short-hand for coverage. Nevertheless, reimbursement issues were at least partly behind CMS’s decision last year to add more compendia to the one then in use for Medicare decisions (see sidebar).

The first AHRQ report, in 2006, compared six compendia for 14 off-label indications; examples include bevacizumab and oxaliplatin for breast and lung cancers, as well as docetaxel for esophageal, gastric, and ovarian cancers. Led by Amy Abernethy, M.D., a medical oncologist at Duke University Medical Center in Durham, N.C., the researchers compared 1,500 citations of evidence in the compendia with their own systematic analysis of the scientific literature. The second report, published in March in the Annals of Internal Medicine, added another 25 reports to the analysis of one indication, gemcitabine for bladder cancer, to see whether the compendia had improved.

Both analyses found that the compendia varied substantially in whether they listed any given agent and cancer combination and that they cited different literature for the same indication. The researchers found that DRUGDEX listed the most off-label indications and that AHFS DI, published by the American Hospital Formulary Service (AHFS), listed the fewest. The two other compendia were in the middle.

Abernethy’s newest study is a systematic review of the literature for 17 drug–disease combinations compared to current compendia, submitted to AHRQ in September. “We did this three times because no matter what we did we were always out of date and couldn’t keep up,” she said. “We need to come up with a real-time way to do this.”

Bill McGivney, Ph.D., chief executive of the NCCN, strongly disagreed that NCCN’s compendium is out of date. “To say that is ludicrous,” he says. The compendium is derived from information in the NCCN Guidelines, and both “are updated sometimes within days of a study being presented or published in the literature.”

Conflicts of Interest

AHRQ has also begun to focus on conflicts of interest, another major, and now high-visibility, issue for compendia producers. It’s not hard to see how conflicts of interest occur, said Ross McKinney, M.D., a Duke pediatrician who is chief author of a white paper on the subject, dated April 27 and posted on the agency’s Web site. Manufacturers have a direct

Not Up to Date

Abernethy said there was little agreement between the results of the team’s own systematic reviews and the evidence cited in the compendia, that the evidence cited was scanty and inconsistent across compendia, and that it was neither the most recent evidence nor the highest available level of evidence.

For gemcitabine for bladder cancer, for instance, the researchers identified 43 published phase I–III studies and 15 conference abstracts. The compendia, in contrast, referred to between zero and seven, Abernethy said. The 2008 review identified an additional 25 reports published in 2006 and 2007, but only one compendium increased its number of citations, adding three; the others had little or no change.

“We were looking at whether the compendia do what they say they are going to do, which is to be a synthesized evidence resource to assist with off-label prescribing. And in fact they don’t do a very good job of that,” Abernethy said. Although the compendia lack transparency, and lack systematic methods to review or update evidence, “the biggest problem is that they are not keeping up with the literature,” she said. “It is a monstrous task. The evidence moves so fast and the information is so hard to synthesize.”

Amy Abernethy, M.D.
interest in maximizing the number of accepted indications that are listed in approved compendia, which would then be eligible for payment, whereas insurance companies have an interest in limiting the number of those accepted indications. Furthermore, compendium writers are often practicing physicians who want to have more treatment options available to them in which to treat their patients, McKinney said.

CMS’s Jacques sees even more potential conflicts of interest that could influence compendium writers “from the time that people decide what kinds of clinical trials to do, to the publication or the suppression of the results of clinical trials, to the bona fide or biased way in which those published results might be interpreted by people, to even a physician’s decision to use one drug or to recommend one strategy versus another.”

Because of the potential for conflicts of interest, Congress included a provision in the 2008 Medicare Improvements for Patients and Providers Act that explicitly prohibits inclusion of compendia that do not have a publicly transparent process for evaluating therapies and identifying potential conflicts of interest.

AHRQ found that the four compendia used by CMS face the risk of conflicts ranging from potential corporate or institutional conflicts of interest (AHFS DI, DRUGDEX, and Clinical Pharmacology) to the difficulty of recruiting physicians to help draft compendia who do not have their own conflict of interest (NCCN Drugs & Biologics Compendium).

“Almost nobody was completely free from the potential of conflict of interest,” McKinney said. But he added that all the compendium developers are aware of the issue and some have instituted policies intended to control and minimize the conflicts. By January 2010, for instance, NCCN will post online the amount of money associated with specific relationships that its 834 expert panelists have with pharmaceutical and insurance companies, according to McGivney.

McKinney said that AHFS DI will now no longer require a $50,000 application fee to drug companies who seek an expedited review of a new off-label indication. AHRQ had cited this arrangement as a potential conflict of interest. However, AHFS strongly contests this point. The program was stopped not because of the white paper but because applications had “dried up as a result of a change in the compendial landscape [i.e., addition of three new compendia],” according to Gerald McEvoy at AHFS. “We had very strong firewalls in place to avoid potential conflicts,” he wrote in an e-mail. “The record simply does not support the hypothesis of the white paper authors about potential pressures for positive evaluations since less than a third of our determinations using this process were positive.”

The other two compendia also stand firmly by the integrity of their product. McKinney cited DRUGDEX as having the highest cutoff point ($100,000) for disclosure of potential financial conflicts beyond which external reviewers who contribute to the compendia may not participate in evaluation of evidence. “The public could reasonably wonder if someone receiving slightly less than $100,000 per year might be biased,” McKinney said in the report. The high figure accounted for the relatively few conflicted individuals listed on DRUGDEX’s Web site, he added. But Jill Sutton, vice president of product management for the Healthcare and Science business of Thomson Reuters, which publishes DRUGDEX, said, “our conflict-of-interest policy is consistent with industry standards” and that “Thomson Reuters is committed to providing unbiased, reliable, and evidence-based information products and services, and we believe DRUGDEX reflects this commitment.”

Clinical Pharmacology is the only compendium that uses a review process that is almost entirely in-house, and corporate policies prohibit staff members from having financial relations with industry. McKinney said that although this is the “purest” approach and best option to limit conflicts, Gold Standard, which publishes Clinical Pharmacology, was purchased by Reed Elsevier, a large Dutch publishing and information services conglomerate that owns a business services component. This purchase “creates risk for conflict of interest.”

That isn’t the case, said Karl Matuszewski, Pharm.D., an editor in chief who is responsible for the clinical content of Clinical Pharmacology. “We have very specific restrictions,” he said.

**A Practice Tool?**

Along with the conflict-of-interest and other issues in the compendia, the question

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**Compendia: A Primer**

A compendium is a comprehensive listing of drugs and biologicals that includes a summary of the dosing and characteristics of the drug and recommended uses for specific diseases.

But compendia have morphed into other uses, such as to aid reimbursement decisions. In the 1980s, payment for growing off-label cancer therapy deemed to be “experimental,” such as laetrile and shark cartilage, became an issue. So in 1993, Congress directed the Medicare program to refer to three existing published compendia, American Medical Association Drug Evaluations (AMA-DE), United States Pharmacopoeia Drug Information (USP DI), and American Hospital Formulary Service Drug Information (AHFS DI), to identify off-label but medically accepted uses of drugs and biologicals in cancer chemotherapy regimens.

Although the statute was specific to reimbursement by CMS, most other insurance payers and state legislatures followed the same criteria. The compendia essentially functioned as gatekeepers for off-label prescribing in oncology.

But the list of approved compendia shifted. AMA-DE and USP DI were discontinued. In response to concerns about the influence of the remaining single recognized compendium, CMS in 2007 established a process to revise the list.

Current CMS-approved compendia include the following:

- American Hospital Formulary Service Drug Information (AHFS DI)
- NCCN Drugs & Biologics Compendium
- DRUGDEX, published by Thompson Reuters
- Clinical Pharmacology, published by Elsevier Gold Standard
remains of what role they play, and how important they are, to the practice of oncology.

The question is a hard one, said American Society of Clinical Oncology President Douglas Blayney, M.D. Some oncologists may use the information in compendia and more will use guidelines, he said, but several rely on the opinions of their colleagues or institutions as well as their own reading of the medical evidence, taking into account the patient’s wishes and tolerances for various treatments.

“I have not read one of these compendia in 30 years, and I run a very big medical oncology group here that orders millions of dollars of drugs,” said Bruce Chabner, M.D., the former director of the National Cancer Institute’s Division of Cancer Treatment, who is now clinical director of the Massachusetts General Hospital Cancer Center and professor at Harvard Medical School. He said oncologists he knows rely on “local” policies and not on compendia. “Cost control is an important issue now in cancer, particularly with the most expensive new medications, and so institutions like ours have local review groups, which set policies about what we can do and what we can’t, and they’re evidenced-based,” he said.

“The only importance of the compendia is that insurance companies may limit use according to what the compendia say. But we’re even more restrictive than that. So a lot of the stuff that the compendia will say we may not allow,” Chabner said.

Compendia should not be used solely for reimbursement decisions, said Karl Matuszewski, from *Clinical Pharmacology*. “In my opinion, no compendium should be used exclusively by a health care payer to approve or deny access to a drug therapy that has been approved by the [U.S. Food and Drug Administration]. Numerous factors go into the choice for appropriate course of treatment, including things like stage or severity of disease, availability and past experience with alternatives, past comorbidities and risk tolerance, and prescribers’ familiarity and experience with the treatment.”

Others have much more positive views of compendia. McKinney said that even with their undeniable inconsistencies and shortcomings, they effectively get information out to practicing physicians “who use that information to undergird clinical decisions.” But he added that a survey is needed to find out how they actually use them.

Duke’s Abernethy said that she is a fan of compendia even as she uncovers their substantial flaws. She said the fact that four compendia exist, as opposed to one in 2007, offers her a broader “bandwidth” by which to capture beneficial information.

“In my mind, even though I think the compendia are a pretty unreliable resource, increasing the number of compendia is a very patient-centered strategy,” she said. It increases the chance that one of them will capture promising treatment information that will result in reimbursement of an off-label cancer therapy. “I have my own conflict of interest, because as a physician, I need to take care of the patient sitting in front of me,” she said.

But the CMS’s Jacques argues that the potential for conflicts of interest in compendia and beyond can result in patients being at the mercy of the system.

“It’s a hard time to be a patient,” he said. “It’s a hard time even to be an educated patient.”