ONCOLOGY C

Greater Transparency and Regulatory Attention at the Forefront

By Bryan Cote

As we enter an era of accountability and financial scrutiny, CMS is set to take a lead role with federal and state agencies to ensure compendia remain a vital resource for off-label treatment decisions—but that they become free of conflict.

Just three months after increasing its approved compendia to give oncologists and payers four options to aid their off-label reimbursement decisions, a Medicare official at the recently held Foundation for Evidence-Based Medicine's "Off-Label Therapy Forum" promised greater spotlight from Washington regulators into each compendium's business and financial practices.

In the pipeline, fraud control may start to tighten as early as 2009 as the Government Accountability Office (GAO) or the Office of the Inspector General (OIG)—which until now have been orbiting outside the compendia arena—could take on a more active investigative role. "Given recent Congressional and public interest in this issue, no one should be surprised if the GAO and OIG examine how each compendia organization and those with whom they do business account for conflicts of interest in their drug and biologic recommendations," said Louis Jacques, MD, Division Director of Items and Devices, CMS. However, an official in the OIG's audit office said there are no current plans to look at compendia. In September, the GAO issued a report on FDA conflicts of interest (http://www.gao.gov/products/GAO-08-640) so there is precedent.

Meanwhile, state prosecutors are positioning to move beyond the typical misbranding and pricing cases they typically take. "The next push in prosecutorial focus will be on the drug's science: Is it honest and are we getting true and accurate information that leads to compendia decisions from which physicians make treatment decisions," says Susan Winkler, Esq., Chief of the Massachusetts Health Care Fraud Section. To date, reports Winkler, misbranding or off-label promotion and pricing crimes have netted more than $3.1 billion in pharmaceutical fraud settlement. "And we're not done yet," she notes.

For its part, Medicare has already begun to influence compendia policies and push for transparency. During the compendia approval process in early 2008, several compendia publishers announced more stringent conflict of interest and disclosure policies. At the time, Dr. Jacques said that the agency strongly looked at the consequences of a system that didn't have any Medicare-approved compendia. "If [we] think about it, our local contractors can still rely on peer review and medical literature," Jacques said. "I can't tell the publishers how to do their business, but we hear that it's been frustrating for practicing oncologists to try to figure out what's recommended across compendia and what isn't and what they should do with a recommendation."

Conflict of Interest Requirements

CMS is hoping to better understand the extent to which compendia advisors and personnel are influenced by their relationships with outside groups, such as pharmaceutical companies. Case in point, Jacques inferred that CMS finds trials that have been

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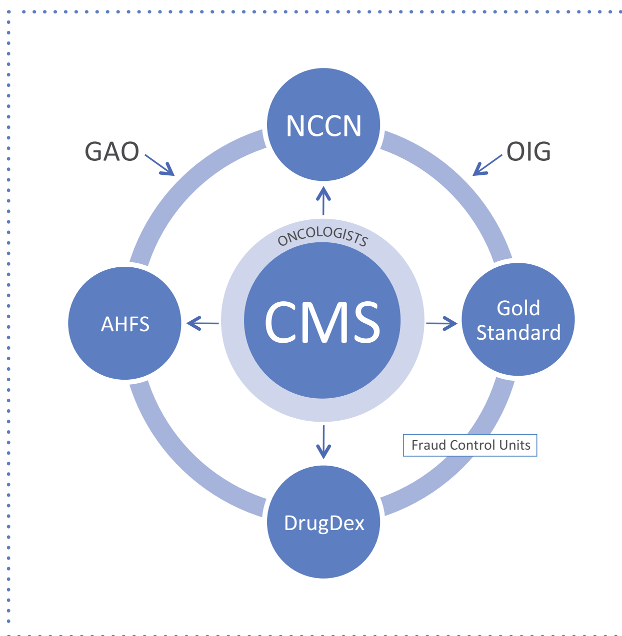
terminated, but that the results have never been publicized and he suspects that “people are slicing, dicing and publishing positive results.” He added that, “If the public loses faith in medical research that’s a big problem. There are rumblings from Capitol Hill and the Senate Finance Committee on that.”

CMS Administrator Kerry Weems received a letter February 14, 2008 from the Senate Finance Committee expressing concerns that conflict of interests in peer-reviewed research can have a significant impact on quality of care. As a result, expect greater disclosure of financial conflicts involving compendia staff, panels, and expert committees who make product recommendations. “I can tell you the GAO is going to be interested which means the OIG will be interested,” said Jacques. By January 2010, the regulators will implement the conflict of interest and public transparency provisions from section 182(b) of the Medicare Improvements for Patients and Providers Act (MIPPA) of 2008, added Jacques.

In light of the pending scrutiny, Jacques contacted all four Medicare-approved compendia—AHFS, DrugDex, GoldStandard, and NCCN—to understand how each planned to address conflict of interest in light of the MIPAA provisions. He’s heard from two of the four and expects to eventually hear from the other two. His goal is to construct rules for the compendia to identify information such as who’s involved in making decisions, who’s attending review meetings, and who’s voting or abstaining—since one way to get a vote to go a certain way is to abstain. “I would not be surprised if we put out a notice of rulemaking on conflict of interest [in 2009],” he said.



Future Compendia

The number of approved Medicare compendia may change next year, but any applicant should expect to answer a lot of questions about its conflict of interest and transparency practices. “We have had interest expressed from others,” said Jacques. “I would not be surprised if we review more compendia applications this coming January. If someone sends us a request and says that one of the approved compendia should be delisted, that it doesn’t meet the regulatory or conflict of interest requirements, we would review it.”

Beyond conflict of interest, Medicare is already receiving questions about how diagnostics and molecular profiling may be listed in future compendia. Jacques said CMS could look at pharmacogenomic profiling, but he would like the evidence to “ripen a bit more” since not all targeted therapies are without risk (a drug, for example, may have other effects even if it is aimed at a particular receptor). “Clearly things bind to things we don’t want them to.”

NCCN’s Kristina Gregory, RN, Vice President of Clinical Operations, said there may come a time when we need diagnostic compendia. cont. on pg 12 >>

"If it's for a specific genotype, the info would probably be listed in compendia currently," she said, but currently the Medicare statute limits approved compendia to drugs.

A Side-by-Side Comparison of Approved Compendia

CMS did not nor does it plan to assign ranking or weight to the compendia it approves. If oncologists or others want to challenge a compendia's process or decision, they should call the compendia and have that conversation about what's weighted and why.

The table illustrates how the four compendia stack up. All four as of January 2009 will be Medicare approved for the Part B and Part D programs, as well as for Medicaid.

Key Points of Distinction:

- NCCN differs from the other groups because of its multidisciplinary subspecialist panel approach to building its compendium. The compendium is based on its own clinical practice guidelines in oncology whereas the others use an in-house editorial process based more definitively on evidence-based literature.
- BioPharmaceutical companies may apply to have a drug reviewed for inclusion but only to AHFS and NCCN; acceptance or denial times are clearly inside 3 months. As publishers, DrugDex and GoldStandard do not have a formal application process. Beginning in April of each year, NCCN holds a 7-month institutional review of outside submissions from industry and others from the oncology community; if appropriate, submissions are further reviewed by a panel chair.
- Final decisions on which products are deemed recommended or approved vs. non-recommended vary greatly. AHFS holds the most specific system on paper with a multi-level ballot process, and NCCN uses a consensus process and if necessary a "simple majority" vote, said Gregory. DrugDex and GoldStandard do not vote, however both lean on outside reviewers to evaluate each publisher's findings and recommendations.
- AHFS may address the cost of an off-label regimen relative to existing or standard care. For example, drugs accepted with condition may come with this caveat: "relative cost, toxicity, and quality-of-life issues should be weighed in any decision to use such a regimen." NCCN says cost may play a role in its decision making at some point. DrugDex's and GoldStandard's compendia are not intended to drive reimbursement decisions, rather to be informational only. While each compendium is taking steps to improve its conflict of interest policies in the wake of government and industry pressure, there are already differences. AHFS set up its compendium process this year so that it does not have any direct communication with pharmaceutical manufacturers or other applicants. "The Foundation for Evidence-Based Medicine serves as a firewall," said Gerald McEvoy, PharmD, Editor-in-Chief, AHFS Drug Information. A panel chair reviews all financial conflicts at NCCN, which will soon break out financial affiliation into levels. According to Jill Sutton, Vice President of Knowledge Development, DrugDex, all clinical personnel are required to take biostatistics training and sign a conflict of interest agreement.

Compendia Recommendation Could Help Deter Government Investigation

For pharmaceutical companies, compendia listings are in some way an unwritten safe harbor protection in the event someone alleges illegal off-label promotion of a drug in question.

Case in point, Daniel Miller, director of Delaware's Medicaid Fraud Control Unit, said the state has nearly 150 current whistleblower cases it could investigate—most of them off-label related. "If we find out that the drug in question is recommended by the government-approved compendia, then we probably wouldn't take the case," he said.

According to Judy Waltz, a healthcare attorney with Foley & Lardner, it costs significant money to work up a case so sometimes the decision to prosecute is based on whether the state or federal government believes it can achieve a significant "return on investment." If the drug is "approved" for a particular use by the compendia, then arguably it has some merit and has not been demonstrated as danger-

Side-by-Side Comparison of Compendia

	AHFS	DrugDex	GoldStandard	NCCN
Government Program Approved as of 2009	Part B, Part D, Medicaid	Part B, Part D, Medicaid	Part B, Part D, Medicaid	Part B, Part D, Medicaid
Type	Evidence-based peer review; expert committee	Evidence-based peer review	Evidence-based peer review literature, field-based reports	Evidence-based guidelines integrated with expert medical judgment; 44 panels representing 800 cancer specialists
Process	Application submitted to Foundation for Evidence-Based Medicine, then to AHFS, which conducts its own literature review, prepares evidence tables, and submits to outside oncology expert committee	In-house editorial staff selects topic based on journals and trends; identifies clinical update, off-label update needed via literature searches. Scores literature, then outside oncology advisory board reviews. In-house senior clinical content specialists provide final review; also accepts manufacturer suggestions	Editorial staff identifies clinical update, off-label update needed, then outside reviewers provide feedback; also accepts submissions via manufacturer portal	Application; Institutional review process prior to panel meetingto assess changes affecting standard of care. Seeks papers from panel and accepts outside submissions. Disease-specific panels review relevant studies, make recommendations
Evidence & Recommendation Levels	**4 Evidence/Quality Levels:** 1-High; 2-Moderate 3-Low; 4-Opinion/ experience 4 Recommendation Levels: Recommended (Accepted); Reasonable choice (Accepted with condition); Not fully established (unclear risk or benefit, equivocal, inadequate data or experience); Not recommended (unaccepted)	**4 Levels:** **Class I:** Recommended **Class IIa:** Recommended in most cases **Class IIb:** Recommended in some cases **Class III:** Not recommended **Class Indeterminate:** Evidence inconclusive	Follows American Academy of Family Physician's Strength of Recommendation Taxonomy. **A**=consistent and good quality patient-oriented evidence **B**=inconsistent and limited quality patient-oriented evidence; **C**=based on consensus or opinion, or case histories	**4 Levels:** **Category 1:** high level of evidence and uniform consensus **Category 2a:** lower level of evidence and uniform consensus **Category 2b:** lower level of evidence and non-uniform consensus **Category 3:** disagreement on the evidence's relevance
Voting (Decisions)	Ballot sent to expert committee with proposed evidence, recommendations of each committee member; final ballot seeks simple majority	No formal voting; reviewer recommendations	No formal voting	Consensus development process (simple majority of panel)
Time from Request to Inclusion	90 days	Varies	Varies	6-12 week average (shorter for FDA use/indication approvals, significant scientitific advances)
Updates/Denials	Updated at least monthly; determinations posted as completed on website. Applicants can request educational conference call with reviewers within 30 days of determination (this is not an appeal)	Web site updates	Monthly summaries; real time updating online. Can get changes posted online within half day from change	Web site updates
Funding	Subscription fees	Subscription fees	Subscription fees	Member dues from 21 centers; Educational grants for distributing scientific information
Affect of Drug Cost on Decisions	Drug cost may impact recommendation strength, only after clinical data addressed. Expert committee may add language in final decision. "If therapy is 100x more expensive than comparable therapy, I doubt the committee would find it reasonable." —*Gerald McEvoy, PharmD, Editor-in-Chief, AHFS*	Compendia not designed for reimbursement decisions, only for informational support	Compendia not designed for reimbursement decisions, only for informational support	Currently not integrated, "but evaluating processes to include cost information in the future." — *Kristina Gregory, RN, Vice President of Clinical Operations, NCCN*
Conflict of Interest	No direct communications between AHFS and applicant; Foundation serves as "firewall." Expert committee conflict of interest policies and procedures modeled after FDA guidance on advisory committees.	Uses three tiered policy of financial disclosure disqualifying some if there is significant potential for conflict. Used outside legal team to develop	Policy on Web site	Individual disclosure available on website; level of financial compensation available before 2010

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ous to patients for the particular use; in addition, the particular drug may be approved by a Medicare contractor for coverage based upon its inclusion in compendia for a specific use.

"Both of those factors presumably result in fewer Medicare claims being paid inappropriately for that drug (at least that particular use), and consequently fewer false claims can lead to awards of treble damages," says Waltz. So while there may be improper off-label promotion, the damage to the beneficiaries and the government programs may not causally result if a drug has already been included in a compendium for a particular use. "Plus, how would one show that the decision to use the drug was related to the off-label promotion rather than reliance upon the compendia?" she asks.

Despite the financial realities existing today in government investigations, there are gray areas in whether a biopharmaceutical company can communicate compendia listings, such as a new favorable decision. "I think that it is a very gray area as to what a manufacturer can say to physicians about the drug's inclusion in a compendia relating to an off-label use," says Waltz. "If the information was solicited verbally, such as 'Is your drug recommended by NCCN?' then it's probably okay for a sales rep to give a yes or no."

Medicare contractors may ask for physicians to submit documentation to support off-label use and two of the four compendia—NCCN and AHFS—are okay with dissemination of relevant information, since few Medicare contractors have the budgets to pay for all the compendia. Keep in mind that if a local carrier decides not to cover a drug for a specific use and the drug's use is recommended by one of the four Medicare-approved compendia, Jacques said the carrier is "expected to have a reason beyond the absence of an FDA-approved label for that use." [See: Medicare Benefit Policy Manual, Chapter 15, section 50.4.5-Unlabeled Use for Anti-Cancer Drugs].

Gaps Remain

Despite progress in compendia this year, there are opportunities for improvement beyond conflict of interest transparency, such as in how payers, Medicare carriers, compendia, and oncologists handle treatment and coverage decisions for rare diseases.

For example, NCCN does not have any new drug recommendations for treating sacral chordoma—a rare spinal cord cancer—despite two recent case reports and a lab study suggesting that newer targeted therapies may be effective, according to Len Lichtenfeld, MD, Deputy Chief Medical Officer, American Cancer Society. So for physicians presented with rare diseases such as this—and Dr. Lichtenfeld faced three chordomas in a four-week span in September—compendia in some cases raise more questions than answers: Do physicians raise a family's hopes based on two case reports and limited overall research, and if so, who will pay for the treatment, and which doctor will take the risk? With rare diseases where total patient burden is low, perhaps a binary system or PET-like registry could solve these questions, said Lichtenfeld.

Conclusion

These are all fair questions to consider no matter how compendia are utilized, and no matter the patient population or tumor which is being targeted. But as compendia become a greater part of how government pays for oncology treatment, regulators seem far more interested in finding out where science and business ethics intersect. To reach answers, expect CMS to continue to engage compendia and the clinical community but with a warning: In no way will regulators allow unethical financial conflicts to dictate coverage. All stakeholders—not just pharmaceutical companies—but physicians and the publishing compendia are now on watch that the government is serious about restoring what it perceives to be waning public faith in the business of medical literature. BC

>>OBR DAILY NEWS FLASH

The recent failure of a Genentech lung cancer study highlighted the potential pitfalls of cancer drug combos—combining the targeted cancer therapies Avastin® and Tarceva® didn't extend lives any more than giving patients Tarceva alone.
(Wall Street Journal Health Blog, 10/7/08)