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CENTERS FOR MEDICARE AND MEDICAID SERVICES
Medicare Coverage Advisory Committee

March 30, 2006

Centers for Medicare and Medicaid Services
7500 Security Boulevard
Baltimore, Maryland

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Panelists

Chairperson
Alan M. Garber, M.D., Ph.D.

Vice Chairperson
Alexander H. Krist, M.D.

Voting Members
Deborah S. Cummins, Ph.D.
Deborah Schrag, M.D., M.P.H.
Robert S. McDonough, M.D.
Mark Fendrick, M.D.
Clifford Goodman, M.D.
Daniel D. Foley, M.D.
Norman S. Kato, M.D.
Alexander Emyr Ommaya, Sc.D., M.A.
Nora A. Janjan, M.D.
Catherine A. Glennon, R.N.
Nancy Davenport-Ellis, B.A.

HCFA Liaison
Steve Phurrough, M.D., M.P.A.

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Panelists (Continued)

Consumer Representative
Linda A. Bergthold, Ph.D.

Industry Representative
Kim K. Kuebler, M.N., R.N.

Guest Expert Panelist
Richard W. Whitten, M.D., F.A.C.P.

Executive Secretary
Michelle Atkinson

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PANEL PROCEEDINGS

(The meeting was called to order at 8:11 a.m., Thursday, March 30, 2006.)

MS. ATKINSON: Good morning and welcome, committee chairperson, members and guests. I am Michelle Atkinson, the executive secretary for the Medicare Coverage Advisory Committee. The committee is here today to discuss

the evidence, hear presentations and public comments, and make recommendations regarding the desired characteristics of published compendia that may be utilized by CMS and other insurers to determine the medically accepted indications of drugs and biologics used in an anti-cancer therapeutic regimen.
The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employer's financial interests. Each member will be asked to disclose any financial conflicts of interest during their introductions. We ask in the interest of fairness that all persons making

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statements or presentations also disclose any current or previous financial involvement in any drug compendia or any manufacturer of anti-cancer drugs or biologics. This includes direct financial investments, consulting fees and significant institutional support. If you haven't already received a disclosure statement, they are available on the table outside of the room.
We ask that all presenters please adhere to their time limits. We have numerous presenters to hear from today and a very tight agenda, and therefore cannot allow extra time. There is a timer at the podium that you should follow. The light will begin flashing when there are two minutes remaining and then turn red when your time is up. Please know that there is a chair in front of the stage for the next speaker, and proceed to the chair when it is your turn.
For the record, voting members present for today's meeting are: Alex Krist, Deborah Cummins, Nancy Davenport-Ennis, Deborah Schrag, Robert McDonough, Cliff Goodman, Daniel Foley, Norman Kato, Alexander Ommaya, Nora Janjan, and Mark Fendrick. A quorum is present and no one has been recused because of conflicts of interest.

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The entire panel including nonvoting members will participate in the voting.
If anyone is requiring a taxi, please sign up at the registration desk during the break or lunch. I would ask that all panel members please speak directly into the mike, and you may have to move the mikes since we have to share.
And lastly, please remember to discard your trash in the trash cans located outside of the room.
Now I would like to turn the meeting over to Dr. Steve Phurrough.

DR. PHURROUGH: Thank you, Michelle. I'm Steve Phurrough, director of the coverage and analysis group here at CMS and the government representative here on this particular advisory committee. We welcome you to this forum, we think this is an important topic. As we have done in some of our recent MCAC contact meetings, we are not focusing on a particular coverage determination that's underway now, we are attempting to define some of the current evidence around particular topics, in this case the use and validity, accuracy of some of the compendia that are currently part of the Medicare system or would

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like to be part of the Medicare system. I want to particularly thank the panel for taking part today. This is not just one day in the life of these panel members. We have provided them a lot of information, they do a lot of investigation on their own, and we appreciate the hard work that goes into this meeting. With that, I'll turn it over to the chairman, Dr. Garber.

DR. GARBER: Good morning and welcome, everyone. Welcome, panel members. I am Alan Garber, chair of the Medicare Coverage Advisory Committee. I'm a staff physician with the Department of Veterans Affairs and a professor at Stanford University. What I would like to do is have each of the panel members introduce themselves and state their conflicts. I will begin by stating mine. I am not a voting panel member, I should just note, as chair. I don't have any relevant stock holdings. I am on the board of directors of a biotech company that does not currently have a product that might be assessed but might at some point in the future, and I have in the past consulted for AmDen, which does have products that are relevant.

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Alex.

DR. KRIST: My name is Alex Krist. I am a family physician and associate professor at Virginia Commonwealth University and I have no conflicts of interest.

DR. CUMMINS: I'm Deborah Cummins, director or research and evidence analysis at the American Diabetic Association and associate professor at the University of Illinois College of Medicine, and I have no financial conflicts.

DR. SCHRAG: My name is Deborah Schrag, I'm a medical oncologist at Memorial Sloan-Kettering Cancer Center, and my institution, I personally do work in collaboration with the

MCCN for which we do receive some research support, which has been disclosed.
DR. MCDONOUGH: I'm Bob McDonough, and I'm a medical director at Aetna. I have no financial conflicts of interest to disclose.
DR. GOODMAN: Cliff Goodman, vice president of The Lewin Group. My 401(k) mutual funds and retirement funds may include stocks in some healthcare product companies. As a salaried employee for The Lewin Group, which is my sole source of income, I have not received financial

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support directly from any drug compendia or any manufacturer of anti-cancer drugs or biologics. As part of my salaried employment, I have worked on studies, done teaching and other work under contracts between my employer and the sources of some drug compendia as well as manufacturers of biologics and related products. This list is extensive, but some of them are National Conference of Cancer Networks, Eli Lilly. Bachelor Healthcare, Glaxco Wellcome, SmithKline, Johnson & Johnson, and others. My firm has also worked with physician groups and patient advocacy groups that may have an interest in this issue.
DR. FOLEY: I'm Dan Foley, I'm an emergency physician and medical director of the Allina Health System, and I have no conflicts.
DR. KATO: My name is Norm Kato. I am in the private practice of thoracic surgery in Encino, California. My conflicts are that I own stock in a pharmaceutical company that does manufacture anti-cancer drugs and I have received previous consulting support from two manufacturers of anti-cancer drugs in the past but have not received any (inaudible).
DR. OMMAYA: I'm Dr. Alex Ommaya, I'm

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director of the Garth Forum at the Institute of Medicine, which is part of the National Academy of Science. No conflicts.
DR. JANJAN: My name is Nora Janjan. I'm a professor of radiation oncology at M.D. Andercon Cancer Center, an NCCN-designated facility. My institution does a wide variety of clinical trials with anti-cancer agents and occasionally I do some consulting work with a wide variety of pharmaceutical firms as well. I have no personal holdings with any pharmaceutical firms.
MS. GLENNON: Catherine Glennon. I am a nurse at the advanced practice department at Duke University and I am a stockholder in various pharmaceutical companies and I also appear on the speakers bureau for different pharmaceutical

companies.
DR. FENDRICK: Good morning. I'm Mark Fendrick, professor of internal medicine at the University of Michigan, an NCCN institution. I have consulted for numerous pharmaceutical companies, pharmaceutical benefit managers, health plans and advocacy groups, but I have not worked in the cancer area for any of these firms.

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MS. DAVENPORT-ENNIS: I'm Nancy Davenport-Ennis, CEO of the Patient Advocate Foundation. We're a nonprofit patient services organization. I do have a 401(K) and a 403(B) and they do have mutual funds and may indeed had pharmaceutical stocks; however, I do not own pharmaceutical stocks directly as a singular person. I am an employee of the Patient Advocate Foundation, I am salaried as an employee of Patient Advocate Foundation. That organization does solicit from and receive unrestricted grant funding from a number of pharmaceutical companies in America in order to support direct patient services that we deliver to 4.1 million Americans.
MS. KUEBLER: My name is Kim Kuebler. I'm a medical scientist for Eagle Pharmaceuticals and I have received PhRMA support in the past.
DR. BERGTHOLD: I am Linda Bergthold. I am a consultant with Watson Wyatt Worldwide, an employee benefits consulting firm. I personally hold stock in a biologic firm and I'm currently doing some consulting work concerning investigational anti-cancer drugs.
DR. WHITTEN: Good morning. I am Dick Whitten, internist and medical director for

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Medicare Part B for Washington, Alaska and Hawaii, and no financial conflicts.
DR. GARBER: Thank you very much. Just a few brief statements. I want to reiterate what Michelle had said about the importance of timing. These meetings always have less time available than we feel that we could use to fully consider the topics, and we also often feel that we would benefit from more input from the speakers, whether they're designated in advance or people from the public which speak at the meeting and come up to the microphone during the meeting. But I have to reiterate that because of the time constraints, we will be absolutely strict and when your time is up you will be cut off, even if it's midsentence. I apologize in advance for that, but you do get the warning light and we will expect everyone to adhere very strictly to the time limits in order to ensure that everyone who wants to speak has the opportunity to speak during the designated times.

We have an unusual topic before us today. It's one that is, I would say a little more complex than what MCAC has typically dealt with. Some might say that the problem is in some ways amorphous, but it's not really amorphous and

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we tried to put a lot of structure on the way we will consider today's topic and how the voting will occur. This may be a little different from what anybody in the audience is used to, whether you have been here before or not. We have a set of voting questions, which I hope everybody has in front of them, and the panelists will be voting on two different boards for some of these voting questions. They have cards on which they will be marking their votes and they will hold that up so that the audience can see. We will not have extended discussion about this, but these scores will be compiled and if all goes as planned, we will have some summary statistics, basically, about how the votes have gone.
The procedure of this, we will be reviewing Question 1 before the presentation of the technology assessment. Question 1 is a sort of ground-setting question about what's important and what's desirable among the characteristics that drug compendia have. I want to just say that as we approach our task, we might think a little bit about the context, and we will hear more about this during the presentation that will follow next by Tara Turner.

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But the way that the statute is written, and Tara can correct this if I'm incorrect, there are three compendia listed, and an off label indication must be covered by the Medicare program if it is listed as an appropriate indication in any one of the compendia. The issue, I think, can be thought of as a type 1 and a type 2 error problem. By that I mean a type 1 error would be listing an indication as appropriate when in fact the particular indication for this drug does not provide a health benefit. A type 2 error would be failure to list when it is effective, or saying that it's not effective when it really is effective.
Because of the way the law is written, if it's listed in any one compendia it gets covered, even if there is disagreement between the compendia. So having more compendia increases the chances of a type 1 error but decreases the chance of a type 2 error, assuming that they don't agree 100 percent of the time and we will find out that that is the case, they don't always agree. And from the point of view of making decisions, a

failure to comment on an indication is the equivalent of saying it doesn't work in this kind

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of context.
So, I think that as we go through this rather complex assessment of the characteristics of the compendia, you might want to keep in mind at all times how this would be used, what the consequences are of these different kinds of errors. So remember that whether a compendium fails to list an indication or says that there is weak evidence or no evidence that it works, will have the same effect in a decision context, that is, if it's used at least in one compendia as not working, whereas if any compendia says it works, it will count as basically being covered. So specifically, the more compendia that CMS chooses to work with, the greater chance of type 1, the less the chance of a type 2 error.
So let me turn now to Tara Turner, who will be presenting on behalf of CMS.
LCDR TURNER: It's great to see such a large turnout this morning. Good morning and thank you. Chairman Garber, panelists, invited guests, members of the public, I am Lieutenant Commander Tara Turner of the coverage and analysis group. On behalf of the Centers for Medicare and Medicaid Service, welcome to today's Medicare

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Coverage Advisory Committee on compendia and off-label uses of drugs and biologicals in anti-cancer treatment.
The CMS panel for today's presentation includes Dr. Jim Rollins and Dr. Lori Paserchia, both medical officers; myself as lead analyst; Captain Michael Lyman as analyst; the MCAC executive secretaries, Michelle Atkinson and Kimberly Long; Dr. Louis Jacques, director of the division of items and devices; and Dr. Steve Phurrough, director of the coverage and analysis group.
Today's agenda includes a statutory background and overview of the compendia issues which I am presenting, the technology assessments conducted by the Duke and New England Medical Center evidence-based practice centers, presented by Dr. Amy Abernethy, Dr. Douglas McCrory and Dr. Ethan Balk. We will also hear presentations from the six compendia reviewed in the technology assessment and from other members of the public. Following the presentations, the panel will discuss and vote on the questions posed by CMS.
In preparation for this meeting, the panel was asked to review the materials listed here. With

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the exception of the written testimony of presenters, all of the documents are publicly available.

According to the Cancer Trends Progress Report, 2005 update, the projected number of new cases of cancer in 2005 was over 1.3 million. You can see the breakdown by the most common cancer types, prostate, female breast, lung and colorectal, which combined represent 55 percent of the projected new cases. In 2004, cancer treatment accounted for an estimated $72.1 billion. This is just under five percent of total United States medical spending for medical treatment.

Coverage of drugs and biologicals used in anti-cancer treatment is dictated by Section 1861(t)(2)(B)(ii) of the Social Security Act. This states that Medicare will provide coverage for an anti-cancer drug or biological used for a medically accepted indication. This is defined in two ways. First, it includes any use which has been approved by the Food and Drug Administration as stated in product labeling. Second, it also includes off-label uses if the following criteria are met: The off-label use must be supported by a

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citation that is included and listed favorably in at least one of the designated compendia, or the off-label use is determined to be medically accepted based on supportive clinical evidence in the peer reviewed medical literature.

The three compendia that are named in the statute for this purpose are the American Medical Association Drug Evaluation, the United States Pharmacopeia Drug Information, and the American Hospital Formulary Service Drug Information. Medicare-instructed contractors should cover an off-label use if that use is supported by at least one of these compendia.

It's important to note that these cannot be listed as not indicated in any of them. In other words, one positive listing results in coverage, while one negative listing results in noncoverage.

Now to give a little background on each compendium. In both the AMA and AHFS-DI compendia, information concerning indications are provided in each monograph, including both labeled and unlabeled uses. However, the text must be analyzed to make a determination as to whether a particular use supported. In the USP-DI, indications are rated as accepted, unaccepted, or

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insufficient data. An indication is considered to be a medically accepted use only if the indication

is listed as accepted.
When an unlabeled use does not appear in any of the compendia or is listed as insufficient data or investigational, the CMS relies on peer reviewed medical literature for coverage determinations. In the Medicare Benefit Policy Manual, 15 publications are listed for this purpose. Carriers are not required to maintain copies of these publications. If a claim raises a question about an off-label use that is not included in the compendia, the physician is typically asked to submit copies of relevant supporting literature.
There have been changes affecting the availability of two of the deemed compendia. The AMA Drug Evaluation is no longer in publication. Thomson Micromedex purchased the content of USP-DI in 1998 and took over responsibility for editorial control in 2004. Under Thomson's agreement with USP, the name USP-DI may not be used after 2007. This posed a problem with the recent enactment of the Deficit Reduction Act of 2005 which requires CMS to recognize and deem any successor

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publication of the USP-DI. Therefore, AFHS and the successor of USP-DI will be the only statutorily named compendia available for CMS's reference for determining coverage for anti-cancer drugs.
This was the problem. Prior to the new legislation, CMS was faced with the possibility of having to rely on only one compendium. This led to our consideration of whether there is an optimal number of compendia which should be available for determining medically accepted indications. Internally we have discussed several options for addressing this issue.
The Social Security Act allows the Secretary of Health and Human Services to revise the list of compendia as is appropriate for identifying medically accepted indications of drugs. Under this authority, CMS could recommend that the Secretary add one or more authoritative compendia to the current list. Alternatively, CMS could recommend that the Secretary reconsider the current list and designate one or more compendia instead of the AHFS and USP-DI. Finally, CMS could continue to use the AHFS and USP-DI as the only sources.

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I would like to note here that CMS recognizes the value of external expert input in the transparent process. Rather than making a decision internally, we decided to bring this issue to the public domain via the MCAC.

To better inform the process, CMS commissioned an external technology assessment through the Agency for Healthcare Research and Quality to assess the quality level of available compendia. In a moment you will hear the results of the reviews performed at the Duke and New England Medical Center evidence-based practice centers.
If CMS decides to reconsider the current list or to simply add compendia, we questioned the most desired characteristics of a compendium and the quality of the available compendia as judged by the desired characteristics. We will ask the panel to review and evaluate the evidence on these two factors.
Before I turn the meeting over to Dr. Garber, I will now present the nine questions that we would like the panel to address.
Question Number 1. A good compendium should be evidence-based. What additional

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characteristics are desirable and of high priority in a robust evidence-based compendium? We have developed a list of 18 characteristics and we are asking the panel to rate each one on the desirability, which is represented by the D score, and on its priority, which is represented by the P score. Those rating scales are listed here.
Please refer to your handout for the 18 characteristics to be rated. Note that this list is provided as a reference, and the panel may amend the list.
Question 2 asks panel members to rate their confidence that the currently designated compendia have adequately stated evidence-based criteria and processes.
Question 3 asks panelists to rate their confidence that the currently designated compendia adhere to evidence-based criteria and processes in making recommendations.
Question 4 asks panel members to consider separately each of the other available compendia and to rate their confidence that those compendia have adequately stated evidence-based criteria.
Question 5 again asks panel members to

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consider separately each of the other available compendia and to rate their confidence that those compendia adhere to evidence-based criteria and processes in making recommendations.
Question 6, considering each compendium separately, please rate its performance on each of the desired characteristics. For this question, we're asking the panel to apply the R scores

listed here to the characteristics that were addressed in Question 1. Please refer to your handout for this list.
Question 7 asks the panel members if they believe that the interests of the Medicare program and its beneficiaries are best served by having a particular number or type of available published compendia on the off-label use of anti-cancer drugs or biologicals for cancer treatment.
If the answer to Question 7 is yes, what is the minimum and/or maximum number or type of compendia that should be available?
Question 9 asks the panelists to rate their confidence that prescribers can rely on currently available published compendia to determine appropriate off-label uses of drugs and

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biologicals for anti-cancer chemotherapy.
Dr. Garber will now lead the discussion of Question Number 1.
DR. GARBER: Yes, Mark? Thank you very much, Tara.
DR. FENDRICK: Can I just ask a question of clarification? I understand the point that was discussed that if one compendia indicated it, that it would lead to coverage. I wasn't clear what you said about when one said it was not indicated, I thought you said if one compendium says it is not indicated, does that mean you don't take it?
LCDR TURNER: Yes. If there is one not indicated out of the three, then that means that it is not covered.
DR. GARBER: However, as Steve just pointed out to me, that is a rare occurrence, for one, and my understanding is, and Steve and Tara, correct me if I'm wrong, if the compendium says there is equivocal evidence or something to that nature, that does not lead to that sort of veto; isn't that correct? Okay.
So just for the, to explain how we will proceed with the discussion and voting on

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Question 1, we have a large number of characteristics. I hope that everyone has a copy of the voting questions, and these are characteristics that CMS has asked us to consider for their desirability as characteristics of compendia. This is obviously going to be complicated.
The D scores refer to basically, is this a desirable characteristic or not for a compendium, and the P scores are about how much weight to place on it, is it high priority or does

it not matter that much, whether it satisfies whether it's desirable or not. We are going to compile the votes in the following way. When an individual gives it, gives a particular characteristic a D score, we then apply their P score as a weight to the D score. So if somebody says high priority, we assign three points to their vote for whatever desired rating they give it; if they say that it's an intermediate priority we give it two points; and if it's low priority we give one point. So they get more weight on their desirability characteristics if they say this is high priority, and that's the meaning of those numbers one, two

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and three that you actually see next to the score. I hope this becomes clearer as the session goes on. So let me first ask if there are any questions from the panel about the voting before we get into the substantive question. So if there are no questions, let me re-read Question 1. A good compendium should be evidence-based. What additional characteristics are desirable and of high priority in a robust evidence-based compendium? Rate each characteristic below on its desirability and on the priority of that desirability rating. This list is provided for reference. The MCAC may amend this list. Now I'm first going to read each one, ask if there are discussions. I think most of these are self-explanatory and the main emphasis will be in your vote, but nevertheless, a discussion may be appropriate for some of these, particularly if in your view the characteristic is worded in an ambiguous way or there is some uncertainty about how to interpret the characteristic. So, A, extensive breadth of listing. Any discussion? If there is no discussion, I

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would like everyone to vote. People will be writing their votes on these cards, and please hold them up and make sure Kim can see in the front over there.
(Votes displayed and recorded by staff.)
DR. GARBER: Question 2, quick throughput from application for inclusion to listing. Does the compendium reactively incorporate the new evidence or does it rapidly incorporate the new application? Any discussion?
(Votes displayed and recorded by staff.)
DR. GARBER: Why don't we move to

discussion of the third one, then. The third one is detailed description of the evidence reviewed for every individual listing.
(Votes displayed and recorded by staff.)
DR. GARBER: Why don't we just collect them. Leave them up so the members of the public need to be able to see the scores at least briefly, and then we will be collecting these and there will be a spreadsheet made available. Yes?
DR. WHITTEN: I have a comment,

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Dr. Garber. We're just rating these on sort of a single scale as noted, but just to pick an example, even though a single compendium would have a clear desirability to have extensive breadth and direct throughput, it might still be valuable in one of several compendia, even if smaller and even with a much smaller segment. So I assume these are the things that staff will look at afterwards, that we're grading these kind of in the abstract as if this were to be a single compendium to be used. But just to pick an example, if two were very broad but one were very narrow, it might still be a valuable supplement to the other two. So just to comment, in a way we're forced to rate these on a single scale, and it doesn't mean necessarily that one that didn't meet all these criteria might still not be a valuable contributor. Thank you.
DR. GARBER: Yes, Mark.
DR. FENDRICK: Alan, can you just comment quickly, if we feel something is highly undesirable, would the P score be -- actually it would almost be preferable to be a negative, and I'm trying to figure out how you're going to in your quantitative analysis --

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DR. GARBER: The way that you should rate it if you think it's undesirable in an important way is give it a priority score of three, so you give it a one and a three. You can't give negative points in this scheme, but -- oh, I'm sorry, you're right. So, let me just add one thing. When you're counting up within categories of desirability, you're not putting in any specific desirability so it will show as more undesirable votes, right?
DR. FENDRICK: So you're taking care of it?
DR. GARBER: Yes.
DR. FENDRICK: All right. But how would you recommend we vote the P score for things that we think are highly undesirable, or should we not vote at all, should we not give it a P score?

DR. GARBER: No. If you believe it's extremely undesirable in an important way, you give it a D score of one and a P score of three.
DR. FENDRICK: Okay.
DR. GARBER: And that will show as three votes in the undesired category.
DR. FENDRICK: Thank you.
DR. KATO: Although technically if

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you're tallying up the numbers, then I understand your question, because technically you should probably give a one because if you're going to multiply the D score by the P score, then technically --
DR. GARBER: We're not adding up the D scores, it is just a constant category of D scores. That may be a little misleading, but the numeric scores are just the P scores weighting for the categories of D scores. So if something is really bad from your point of view, give it a P score of three and it shows up as three votes in the undesired category.
Okay. So now we're going to move to, display your votes, so pass your votes on C to the right, and display your votes on D, use of prespecified published criteria for weighing evidence.
(Votes displayed and recorded by staff.)
DR. GARBER: And I will read E, use of prespecified published process for making recommendations. I think you can pass your Ds, and pass them to the right, and put up your votes for E.

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(Votes displayed and recorded by staff.)
DR. GARBER: F is a publicly transparent process for evaluating therapies.
(Votes displayed and recorded by staff.)
DR. GARBER: Please pass your E votes to the right and put up your scores for F. Let me know if I'm going too fast.
G is explicit "not recommended" listings when validated evidence is appropriate, that is to not be science but actually state that it is not recommended for that indication.
DR. KRIST: Is that for, if there is evidence that it doesn't work or evidence that there is harm, for G?
DR. GARBER: I think that from CMS's point of view, if it's ineffective it does not merit coverage, whether there is harm or not.
Okay, so F gets passed down and G is put up.

(Votes displayed and recorded by staff.)
DR. GARBER: And I will read H. Bias toward "recommended" when validated evidence is equivocal. In other words, does the compendium

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itself make a type 1 error or is it likely to make a type 1 error in that situation? So please pass on your Gs and put up your votes for H.
(Votes displayed and recorded by staff.)
DR. GARBER: I, bias toward "not recommended" when validated evidence is equivocal, in other words, tending toward a type 2 error. Please pass on your Hs and put up your Is.
(Votes displayed and recorded by staff.)
DR. GARBER: J, explicit listing of combination of therapies. Please pass on your Is and put up your J scores.
(Votes displayed and recorded by staff.)
DR. GARBER: Please pass on your Js. K, explicit recommendations on the sequential use of a therapy or combination in relation to other therapies.
(Votes displayed and recorded by staff.)
DR. GARBER: Does everybody have their Js up? I'll read K, and please pass your Js to the right. Explicit recommendations -- I'm sorry,

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pass on your Ks. L -- you can pass on your Ks, and then L. Silence, i.e., no listing when validated evidence is equivocal. Now I think in answering this one, it's important to keep in mind how it's used by CMS, but that means if it's silent, that means it's the same action as saying not recommended, but it's saying the same as them saying, in other words, its not a default, but it will only be covered then if it is in that circumstance such that it is indicated.
(Votes displayed and recorded by staff.)
DR. GARBER: Okay. Pass on your Ls and we are on M. Explicit equivocal listing when validated evidence is equivocal.
(Votes displayed and recorded by staff.)
DR. GARBER: Okay. N, public identification of the members of the advisory/scientific review committee. Please pass on your Ms and put your N votes up.
(Votes displayed and recorded by staff.)

DR. GARBER: O, public notification of reviewers' and committee members' conflicts of

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interest, including institutional funding sources. Please pass your Ns to the right and put your O scores up.
(Votes displayed and recorded by staff.)
DR. GARBER: P, public notification of all funding sources of the compendium and its parent and sibling organizations, including unrestricted grants and gifts. Please pass on your O scores and put up your P votes.
(Votes displayed and recorded by staff.)
DR. GARBER: Q, net benefit analysis based on potential harm and potential benefit. Please pass on your P scores and put up your Q scores.
(Votes displayed and recorded by staff.)
DR. GARBER: R, explicit stratification of the risks of available therapies. Please pass your Q votes to the right.
(Votes displayed and recorded by staff.)
DR. GARBER: After you put these scores up and we pass them to the right, I think what we

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will need to do is allow some time to compile these and if people are comfortable with that, we can move up to the next agenda item and come back to this after we have the compiled scores and have a discussion for variations and any comments you want to make. Is everyone comfortable with that? Okay. So we may have further discussion after we see the compiled scores. Now actually, are the TEC presenters ready? Great. Is everybody comfortable with delaying the break until after the presentation of the technology assessment? Okay.
We will move ahead with the TA with investigators from Duke and New England Medical Center. I don't know in what order they will be speaking, but go ahead. Doug McCrory from Duke will be the first presenter.
DR. MCCRORY: Good morning. I'm Doug McCrory. I'm going to be presenting concerning the technology assessment. There will actually be three of us presenting some of their work. The second will be Amy Abernethy, one of my colleagues, and the third will be Ethan Balk from the New England Medical Center.
The team that we put together for this

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project included several of our colleagues at Duke, including people with wide backgrounds including oncology pharmacists, general internists, people with a background in health services research and research assistants that you see here. I think the background of the project has been covered. Let me describe a little bit about what we took away as our message or what we were trying to summarize.

First of all, what we wanted to analyze was the method which the compendia used to collect and evaluate evidence, specifically focusing on anti-cancer drugs and biologics, and specifically for off-label indications, so that the first thing when we were looking at the methods was more generic, not tied to particular drugs or indications per se. We subsequently went to another part of the project where we identified 14 specific drug indications and combinations, all of which were not FDA-approved, and analyzed the compendium listings. We then compared that with what their statement was for the indication or combination, or what they thought about it. And then finally, we conducted our own independent literature review. We used a method consistent

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with what we would generally do for an evidence-based center project, you know, structured a wide literature review followed by selection of literature with prespecified criteria to develop a current set of evidence bearing on the question. And finally, I think you will see by the end of the presentation that this gives us a rich set of data from which to present to the committee evidence as well.

So, the compendia that we selected for this analysis included the ones named in the statute, the AHFS, as well as USP-DI at the bottom, and while certainly not the (inaudible) publications. In addition, we selected several other drug information resources and we did this in a way to get a representative, a broader representation of the drug information process, since they don't all share some of the characteristics, so we looked purposely for the relationships between things like Clinical Pharmacology and other publications such as DRUGDEX and USP-DI, the Micromedex publications. We also looked at Facts & Comparisons and then the National Comprehensive Cancer Network, which is a compendium as well as some practice guidelines.

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Again, those two were evaluated as compendia, though.

Now I'm going to focus for a moment on our first goal, which was our evaluation methodology. We had a five-step sequence of events. We would initially go to the publications and abstract their descriptive information, and their methods section was usually contained in the foreword or some other printed material. We initially planned to submit our initial abstract to the editors of the compendia before interviewing them. However, time constraints led us to schedule the interviews first and then move to step four later, sending the completed table to the editors for their comment. During the interview, we verified the information that we had in the abstract, and additionally delved a little more deeply into the areas about the compendium, not only those that we covered in Question 1 a few moments ago, but also outline characteristics. And finally we prepared a report that summarized, this was the first part of the draft report, which was publicly available for review.
In looking at the characteristics of each compendium's use of the off-label indication,

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we were guided by two instruments. One was the AGREE instrument, which is an instrument used to evaluate quality of (inaudible). We felt that the compendia were like guidelines because they do endorse certain drugs for particular indications, which is particularly true for off-label indications. We were also guided by the QUORUM statement, which ascribes desirable characteristics for medical use, such as a systematic review and meta-analysis, so looked to see if they identified a drug as such-and-such, and then a body of evidence.
This approach does lead to a problem because a compendia is none of those things, and we recognized that we were as part of our evaluation looking at small parts and were maybe not getting a complete view of what the compendia were, so we looked at what we considered to be a reasonable approach. So for the next few slides I'm going to show you certain information that we took out of the compendia. These are abstracts of tables that are more completely reported in the draft report, so for those of you that have access to the draft report, there is certainly more detailed information, and we sort of abbreviated

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them, and you may refer to the draft report to fill in where the information on the table is lacking.
So these are the various compendia listed across the top, and we'll go through some

of the information in each row. For the publisher list, we looked at both print and electronic editions of the compendia where those were available and found the most recent version, went to the library and pulled the books off the shelf. And the print cycles are such that some were just getting ready to be updated on some we saw. The update cycles on the print editions was annual for most that were put out, but NCCN is probably more frequent since they have updates posted by topic. We looked at electronic editions where those were available for each of the compendium, and in many cases there were multiple flexible types of editions, sometimes only on CD-ROM and some had various on-line editions. They varied in terms of the update cycle, and by update cycle here I mean how soon after new information was available and approved by the editors does it make it into the on-line vision. So most of these updated the information very quickly, in some

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cases it varied between the print and on-line version and so forth. The dates listed on this table are the dates that we pulled the information, so in some cases we looked again for more recent information, but in general it was all collected in January and February.
And finally, the information we evaluated included the published information both in print and electronic, and we did interviews and in a number of instances we got additional information either from the editors or were directed by the editors to the corporate web site.
This slide, the purposes of the compendia, this is the overall purpose, not just for off-label use of the medications. We paraphrased very liberally in this slide and there are more complete quotes from the materials available in the report, but I wanted to point out just the highlights of their stated purposes.
So AHFS-DI describes evidence-based as being one of the key points in their purpose statement. Clinical Pharmacology emphasizes usability and conciseness. DRUGDEX and F&C are similar, and highlight an unbiased approach to prescribe, order or dispense. The NCCN perhaps is

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a little bit unique in that their clinical practice guideline was the initial product, and the compendia I believe was envisioned as the second step, and they emphasized the decision-making aspect as I think being the most emphasized aspect.
And USP-DI emphasized safe and effective use once a drug is prescribed, so if

there is a possible exception, they emphasize the selection between the alternative drug products. The scope varied as well. Many included prescription as well as over the counter, and some included investigational drugs. NCCN also was different in that it listed only anti-cancer drugs and was even more so specific to those that were listed in the NCCN clinical practicing guidelines.
The final important point for this project was whether non-FDA-approved indications were included in the compendium. We only selected compendia that did, and in some circumstances that included off-label indications. There were various ways the compendia characterized their policies to include non-approved medications. There were a few concepts here that I want to

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point out. One, many compendia noted that they evaluated current practice and the degree of interest in a particular agent for a particular indication as one of the things they considered when deciding whether to approve a medication, and that is obviously in addition to the evidence. Some of them didn't provide precise criteria or situations when they would include or exclude, and we will come back to some of these things a little bit later.
The strength of evidence scales varied and these would be scales that described the number, quality, the magnitude of effect, so the overall pharmacological effect. AHFS-DI described a scale that divided it into four categories, DRUGDEX used a similar four-category scale. Actually, I guess NCCN used a three-category scale. The precise wording for definitions of A, B and C are identified or contained in the draft report, and I think the difference is not quite so important as the fact that they used one or didn't use one.
Grading recommendations was slightly lower in contrast. As opposed to ratings, the number of studies to the magnitude of effect, the

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grade of the recommendations would include not only the strength of evidence but also the belief about how important the risk versus benefit might be. And in the case of NCCN for example, how much agreement there was, whether it was uniform or not uniform. Again, only one compendium used a rating scale alone, the others used a variety. We also heard that USP-DI used accepted, acceptance but not established, or not accepted. Some of the other scales were a little more explicit in terms of whether there was agreement on whether the

indication should be used. In fact in comparison, the F&C addresses safety concerns and specific reasons why the drug might not be recommended. The other point about the grading recommendations, the point I wanted to make was that a grading, a grading recommendation that a certain medication is not accepted, or insufficient or poor, would allow a compendia to put in an off-label request and qualify it as being equivocal evidence or even negative evidence. So conversely, the inability to use an insufficient or poor grading recommendation makes it a little bit more difficult for a publication to list something and then qualify it as not

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desirable or equivocal. That point's going to come up later in specific indications. A further point I wanted to make is contrasting the links between the recommendations and evidence. We looked as thoroughly as we could to find out how a specific off-label indication was linked to a general strength of evidence by references to the same, you know, citations, and we found that with no exceptions, those are contained in the electronic versions only, so we related that almost entirely to that phase of the project. The editors were asked to provide an assessment for the validity of studies that were identified and cited in the compendia. All of them used a subjective process by editorial staff. Some of them were more formal than others as to items which were published or included in the supplemental materials that we received. Several of them describe their procedure as some of the more accepted critical techniques, and some of them more extensive than others. The NCCN publication had a permanent editorial staff that evaluated the materials and others were done by staff, either permanent staff or that hired by the

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committee. The specific criteria for selecting items to be published in the compendium, almost all of them emphasized well designed and published controlled studies, and there was some difference in whether they would include lower level studies and particular case reports. So one of the factors for comparison, for example, some of them said that they did not include case reports, and others allowed almost any study to be included. Several of the others described the process where there was some sort of discretion such that if they found little good quality, they would look at maybe lower level of data for pharmacology, but

for some of the others, basically were phased into whether two studies would be just as effective and would result in a routine evaluation. Finally, we had difficulty in addressing what would be the policy on equivocal evidence. We initially thought we had a handle on that but once we fed it back to the editors and what we gleaned from our discussions, each of them had some comments that it didn't quite work that way, so this is a revised version. One thing we found was that the policy is difficult to state,

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and often the technique of the compendium on a case-by-case basis will make a decision based on their validity assessment, their evidence ratings and their grading criteria, but I think that we ended up taking it if they have a grading or recommendation scale that will allow them to list an indication with the appropriate amount of evidence and qualify it, I mean, the quality that the data would generate, so I think it's maybe more constructive to look and see what the compendia actually did, which we will look at in a few moments. But I wanted to make a point that all three of these issues required a great deal of subjective analysis. So to sum up, common themes that we elicited from our initial undertaking, the print and electronic versions were different. One thing that will come out I think a little bit later was the dates of publication, either when it was printed or the date of last update in the electronic versions didn't always correspond to, it was difficult to determine when the last search for evidence was conducted and how a given topic was assessed within this editorial process. An interesting result of the

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interviews, each of the editors of the compendia recognized that the landscape for medical decision-making is becoming evidence-based and each of them has plans to become more evidence-based, and there were various points in terms of implementing these changes. And finally, as we'll see later, I think the recency of the reviews wasn't always determined. I think in the interest of time I'm going to skip over and just briefly show the appearance of some of the on-line versions that we were looking at, which don't really project particularly well, but each of them would describe fairly clearly and sometimes with Word documents, off-label indications. And with that, I'm going to turn it over to Amy Abernethy. Thank you.

DR. ABERNETHY: I'm number two in speaking on this discussion, but I'm going to talk to you about compendia listing and our findings from Duke. And as I venture into this topic, I'm going to address for you three things. First, I'll tell you a little bit about the methodology that both the Duke and New England Medical Center EPCs used. The second thing that I will do is

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give you an example of what we observed as we were doing our analyses. And then thirdly, what I will do is give you a snapshot view across all the compendia.

To make sure that everybody is comfortable with what it was that we were asked at Duke to do, let me first show you our three key questions that we were asked to address in this part of the project. First, for chosen drugs and biologics and their off-label indications, evaluate the published compendia on the following: Level of detail on the evidence reviewed; any recommendations that were made; silence, in other words, no listing when the evidence is equivocal; and then presence of bias, for example, recommended when the evidence is equivocal or not recommended when the evidence was equivocal. And as you can see, this issue of equivocal evidence is a recurring theme.

Our second question is: Is there an analysis of potential harms and potential benefits in the assessment of biologics and chemotherapeutic agents included in the compendia, and if yes, what components are used and how are they quantified?

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Our third question: Which compendia have listings on the off-label use of drugs and biologics? Specifically considering the compendia and the drugs and disease combinations that we talked about within this report, and if these drug combinations and specified off-label indications are included in the compendia, how do the compendia compare to their own stated methods? Also, how do they compare to the other compendia? And thirdly, how do they compare to the EPC's review of the evidence?

So in order to address these three key questions, we had the following methodology that walked through these five steps. First, we identified each cancer agent singly or in combination, covering a range of different variables. So we were looking at new versus old agents, we looked at common cancers and more rare cancers, and drugs and biologics. What we were trying to do was address a broad combination or at

least within the scope of what we could get done before this MCAC meeting.
Secondly, we identified the compendia and the clinical practice guidelines, and that was done as just presented to you.

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Thirdly, we abstracted the agreed-upon information from the compendia, so we identified what the compendium had to say about each of these combinations. Then we performed an evidence-based practice center search, an EPC search, and looked at how much these two searches agreed, the compendia matters and the EPC.
I would like to highlight for you as we look at the EPC methodology, we are talking about an abbreviated EPC methodology and I'll explain to you why in a moment. So in order to address that score, which was getting the EPC methodology completed, first we conducted a MEDLINE search. We did limit this to MEDLINE in an attempt to maintain efficiency, and we looked at this through January 20, 2006. We focused on studies in English that dealt with people, agents and the diseases of interest, we specifically focused on those. We looked at any study design from phases I through IV, and we also looked through the abstracts from the American Society of Clinical Oncology focusing on 2004 and 2005, assuming that things in 2003 and backwards had had the opportunity to be presented.
Importantly, we extracted these data

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into tables and within these tables we tried to lay out the main information. And here we were abbreviating what we were doing, we were trying to get things in the table that we could look globally across the compendia. So we looked author and publication year, dose of the agent for the indicated use, the co-interventions that were evaluated, the comparator that it was evaluated against, a brief description of the cancer stage where these were evaluated in, an indicated line of treatment therapy, study design. Outcomes, we put in tumor response rate, survival, duration of survival, progression-free survival, quality of life and symptoms. And then finally, adverse events, which we evaluated by time, severity, organ, and frequency.
We think about how this is an abbreviated methodology, and here are some of the things that we did not do. For example, I mentioned that we limited ourselves to MEDLINE, that we only looked at the American Society of Clinical Oncology as a source of abstracts and did not look at other venues. In addition, we did not

have the opportunity or the time to assess methodological quality of all the studies, which

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would normally be incorporated into an EPC assessment. We also did not quantify the magnitude of the outcomes, so we were not trying to give you an efficacy endpoint for these different combinations, but rather look at what was the breadth of information out there and in the different categories.
At Duke we looked at these combinations. As I mentioned before, we were trying to get a different kind of grouping of different drugs and diseases. So we looked at bevacizumab, also known as Avastin, for both breast and lung cancer. So this was a new product for use on common cancers, breast cancer is approximately 32 percent of all cancers in women, and lung cancer is 13 percent in men and 12 percent in women. Bevacizumab was FDA-approved for colorectal cancer in February 2004.
One of the other drugs we looked at was oxaliplatin, also known as Eloxatin, and we looked at oxali in both breast and lung cancer. This drug was FDA-approved in February 2004.
Next, irinotecan or Camptosar, this time looking at breast cancer, and this drug was FDA-approved in October 1998 for colorectal

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cancer.
I suspect you're seeing a trend here, looking at common cancers and looking at drugs that had other FDA indications.
The other drug that we looked at was docetaxel or Taxotere, and we evaluated it in gastric, esophageal and ovarian cancer. Taxotere was FDA-approved in May of 1996 for breast cancer, and later received an FDA indication for lung and prostate cancer, and I think as maybe some of you know, just last week it received an indication for gastric cancer, which was one of the topics here.
These were some of our less common cancers that we were looking at, and we specifically focused on esophageal and gastric, and did not focus so much on ovarian, given the time line for this project.
Tufts New England Medical will tell you about these agents and these combinations.
So at Duke for the drug bevacizumab directed at breast and lung, oxaliplatin directed at breast and lung, irinotecan at breast, and docetaxel at esophageal, gastric and ovarian, we identified a total of 798 specific citations in MEDLINE, pre-MEDLINE, the Cochrane database and the ASCO abstracts. Of those individual reviews,

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19 percent met our initially stated criteria for inclusion and were actually abstracted into tables.
This completes the first point that I wanted to make, which was how we were doing this.
And now what I'm going to do is move forward into an example. As I've mentioned, we got a number of different drugs in these combinations, and you can go to the current version of the draft report to look at these in complete tables as to what we have for the evidence and how this evidence is matched to the compendia. There were a number of themes that emerged during this project, and I think that bevacizumab in breast cancer and lung cancer presents from the Duke EPC side a good example of some of the themes that we were finding during this project, and so I'm going to focus on this combination in this next segment.
So here we're looking at the compendia publications for bevacizumab for breast cancer.
The yellow across the top are the six compendia evaluated and you see there the various abbreviations I'm using for those compendia, and down across the left-hand column, you're seeing actually the row headings for the different topics

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that we were evaluating the compendium on as we moved across compendia. We actually have a number of other rows that are included within the tables and certainly the tables have much more detail, but for the purpose of today's discussion I am going to focus on these points.
So first we see in the first row whether or not an off-label indication was discussed and/or indicated in these different compendia. As you can see, only two of the compendia, DRUGDEX and NCCN actually present information about an off-label indication for bevacizumab in breast cancer. DRUGDEX says it's Level III or inconclusive, and NCCN says it's Level 2A, so that they felt like there was uniform information when it was not completely conclusive.
They do give us information on stage and whether or not it should be given as monotherapy or in combination, and DRUGDEX mentioned the outcomes that they're basing this on.
Importantly, consistent with our findings among almost all of our drug-disease combinations, the compendia actually do pretty much always represent toxicity data when we're looking at this, although these toxicity reports

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may not be specific to this particular disease.
Here these two compendia where they did

have information on off-label usage actually indicated a dose, and they both start to give us information about where they base this evidence. And DRUGDEX specifically states one citation which was from 2001, and NCCN states one citation from 2003. The DRUGDEX citation actually is of a Phase II trial that was presented in abstract form only and as you will see in a moment, this information was cited in DRUGDEX from 2001 and indeed, there was actually a 2003 abstract later presented updating this information. The NCCN single abstract that was cited in 2003, and as you will see, there is a 2005 abstract that has now updated this information.

There are, these data as identified by the EPC, it's a difficult table to read and believe it or not is actually quite abbreviated, so let me quickly tell you that what you see here is that we've got a total of 10 citations across these that addressed bevacizumab's use in breast cancer. Of these, two were Phase III studies, three were Phase II, two Phase I/II, and three in other groupings.

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This table highlights for you several points. First of all, that Phase II and Phase III studies did exist and indeed, there were two Phase III studies. That importantly, sometimes it can be difficult, so there were three studies were other, and actually looking at those, they included patients who had cancers and received bevacizumab for other indications, including non-FDA indications, and that there was both new adjuvant and metastatic disease represented across these several studies.

We also see that in the Phase III studies, there is information about tumor response, survival, quality of life and symptoms, but otherwise, that information is not uniformly presented across the other studies, as you would expect.

Now let's compare that to what the compendia have for this particular combination. What we can see is that DRUGDEX and NCCN both had one citation each and neither of those citations were common with the EPC search. Why were they missed? Well, both of these were missed because there was actually updated information available. As I mentioned before, the DRUGDEX search had the

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2001 abstract, this was an abstract that was Phase II data with more recent information presented in another abstract two years later.

The second was the NCCN. Again, it had an abstract indication in one of the Phase III

trials, but that had been updated at the American Society of Oncology meeting last year in June, as well as the preceding (inaudible).
If we look at what were the main Phase III studies, just focusing on Phase III here, we see that there were two Phase III studies, both with the same first author. The first of these was actually published in full text in the Journal of Clinical Oncology last summer and there they looked at bevacizumab with capecitabine in late stage, heavily pretreated women who had metastatic breast cancer. It demonstrated statistically and clinically significant tumor response but no survival benefit, and this was demonstrated in the full text.
Secondly, again Miller in 2005, combined with paclitaxel in advanced breast cancer in the front line setting, and there were statistically and clinically significant improvement in tumor response, progression-free

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survival and overall survival, but importantly, the second study where the progression-free survival wasn't even an endpoint, they only submitted preliminary data in abstract form and the published study has not met its final endpoints.
These other four compendia, as you can see, have remained silent on the issue. If we compare back to what they had said about equivocal data or silence in listing, AHFS-DI said they would be silence or listing; ClinPhar, silence; DRUGDEX listing with qualifier, which is what they did do; Facts & Comparisons, silence, which is what they needed to do; NCCN, silence or qualifier, which is where they were; USP-DI, listing.
There were some similar discrepancies when you look across these, such as the update dates suggest data that wasn't there. Also, secondly, their stated methodology focused on the fact that they would present new advanced studies, especially those in Phase III, some even said Phase II and Phase III, but these data were not always available. And they also, if they didn't state the specific evidence for the indication,

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you did not know whether or not it was unexamined, inadequate, equivocal, there was no benefit or it was harmful.
The other thing I would like to point out here is the influence of time, so here is the time line for bevacizumab in breast cancer. So if we kind of imagine that back in the red is somewhere around 2001 when we didn't really have

any good information, and as we move into yellow it becomes more unclear, and as we move into green, some might argue that there's more information now to suggest the role of bevacizumab in breast cancer.
So as you see, and I've put some of the actual studies in here, we've got a Phase II in 2001 that was positive and it makes us perhaps think that there is equivocal evidence of a clear phase. Now there's a Phase III that did not meet its progression to survival, it didn't have evidence of improved tumor response, and that one was first submitted in abstract form in 2002, and then when we get to Phase III, it is not quite completed yet, which was first submitted and recognized by the NCCN in 2003, moving it into this area of more information for bevacizumab in

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breast cancer.
What we can see is DRUGDEX makes their first statement and their only statement about the evidence here is unclear, referencing an abstract from 2001, and NCCN is referencing an abstract from 2003, and this is where we are on that time line. And again, we have four other compendia that we don't know what they've done with this information.
As a comparison, and quickly I'll show you lung cancer with bevacizumab. As an example here, we have five of the six compendia stating an off-label indication for this, giving a setting predominantly of advanced or metastatic disease. They are more clearly inclusive and uniform, although the information may vary as far as how clear they are in their statement of the off-label indication.
We look at the citations and we see that across those five compendia, there are approximately zero to three citations indicated, most of them including at least one, except for Facts & Comparison which does not mention any citations, but the other citations are from 2004 and 2005. These citations that are uniformly

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included across the compendia are abstracts, and actually as you will see in a moment, the same abstract, which is nice to see, they're all finding the same one. The number of journal articles is also a little bit different by compendia.
Here's what we found. We found five citations, one Phase III, which is the same one that all the compendia are finding, two Phase IIs, and then so forth. And if we compare back and forth between the number of compendia citations

and the citations which were common with the evidence-based practice center, we see that for the most part we are finding the same group of citations. So that four of the six compendia are listing references, and all of them are listing the one same abstract which was presented at the American Society of Oncology meeting in 2005. Here we see that carboplatin/paclitaxel resulted in statistically and clinically significant improvement in tumor response, progression-free survival, and overall survival. Here we have a mature study that has gone to its primary endpoint and has not been published yet. Here is a table for equivocal data.

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AHFS-DI says silence or listing, while the others have been more clear with their listing, as you can see here as to what they state or they don't with respect to their methodology.
Finally, this takes me to part three and this is just going to be a quick snapshot and you can take a look at the rest of these data in our full report. First of all, the question about what we knew about study quality. We did not establish quality clearly across all these studies, but this is just a sense of what quality looks like for the Phase IIIs, and I think the most important part of the Phase III data that we do have are really the emerging data in abstract form, and it's really difficult to establish what quality these reports are. If we look at reporting quality for the published studies for bevacizumab and breast cancer, and docetaxel for gastric cancer, we see that they come up with a JADAD score of two to three, which is moderate quality.
If we look at off-label indications and now look across our drug-disease combinations, what we see is that bevacizumab for breast cancer, two compendia state information. I'm not saying

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to you whether or not they tell us if this is something that should be used and they advocate use, but I'm telling you that they state information. Five for bevacizumab in lung cancer, one for oxaliplatin in breast cancer, none for oxaliplatin in lung cancer, one for irinotecan in breast cancer, four for docetaxel in esophageal cancer, and five for docetaxel in gastric cancer. And as you can see, it's not uniform across the groups. So if we come back, the way they address equivocal evidence and the citations are similar to what we've seen earlier.
So my main observations as I complete this segment, there is a need to continue to work

on a clear rigorous method for how these drug-disease combinations are dealt with within the compendia. There is an issue about regular updating and I think there is also a risk of delay whether there is or is not regular updates. There is not much in the way of presentation of evidence pro or con on these indications. There is an issue about whether or not the purpose of the compendia are pharmacopeia or as clinical practice guidelines, as Doug has already touched on. We see variations across the compendia, as we've

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seen. We have a hard time figuring out what initiates evaluation of an off-label indication. We see here the influence of time is very important. When we look at the compendia, what we're seeing right now is a static snapshot in time, so we have not had the opportunity to figure out if there is some way we can see what has happened over time with the compendia and how they may have changed or not changed their approach to the indication. And finally, we don't know what silence means, and silence was very common.

DR. BALK: I'm Ethan Balk, I'm with the Tufts Medical Center EPC, and let me get this going. So, I worked on this with Gowri Raman, who has joined me here, and several other people, including the director of our EPC, Joseph Lau. I may skip over some of the slides for the sake of time, but briefly, again, we looked at gemcitabine for bladder, ovarian and biliary tract cancer, rituximab for chronic lymphocytic leukemia, and erlotinib for head and neck, and pancreatic cancer, again, a mix of common and rare drugs, common and rare cancers, newer and older drugs, and drugs and biologics.

Again, the literature search was done

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around the new year, and here's an example from one of our comparisons. Gemcitabine used for biliary tract cancer, with the gemcitabine combination, there tends to be a fair number of studies available. There were 29 peer reviewed articles that we found, plus four abstracts from 2004 to 2005. As with most of the combinations, the large majority of the articles were Phase II trials, and again as common with most of the combinations, tumor response, survival and adverse events were almost universally reported, quality of life and patient symptoms were rarely reported. Across all the different combinations that are listed over here, you can see, again, that for gemcitabine there are a fair number, 25 to almost 50 articles available, likewise for rituximab. For the two cancers with erlotinib,

there are a small number of studies. Again, Phase II trials are most common, and there were few Phase III trials in these agent-cancer combinations. For the gemcitabine actually, there were two articles, but they both represent the same trial, and for the ovarian cancer, there was one Phase III trial that we looked at in connection with the other trial, and that was

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published within the last couple of months, in 2006, so we wouldn't expect that to be included in a compendium.
Again, with the gemcitabine biliary tract combination, three of the compendia were silent, there was no discussion about this combination, three of the compendia, Facts & Comparisons, NCCN and USP-DI, did include a discussion of this combination. As you can see, the number of citations that were used varies widely across the compendia and again, this compares to the 29 that we found. USP-DI had the largest number on this combination, NCCN looked at just a couple, or included just a couple of citations, and for this combination, Facts & Comparisons did not list any citations. There was fairly good overlap in the citations that were used in the compendia and the citations that we found.
In this case, there were a couple of citations that we had missed that we ended up adding in that were in the USP-DI. Generally citations were common across the combinations. Several of the citations did not meet our criteria, mostly because they were either foreign

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language or they were review articles, textbooks and so forth. For this combination, most of the studies were relatively old, they were published in 1998 to 2003, but there continued to be publications in 2004 and '5, and I would expect to find them in the different compendia, depending on when they updated.
I realize that this will be more difficult to read than on my computer, but this is one of the examples of the tables that compares all the different compendia and the different factors, and reading this over I'm just going to get examples, again, for different combinations.
For whether the off-label citation was explicitly cited for gemcitabine in biliary tract cancer, again, these three compendia stated it. We actually had NCCN as unclear; they did state that there was some data; however, in our interpretation of data at the NCCN, NCCN doesn't differentiate FDA-approved and off-label uses, so

we marked that as unclear.
To give an example of toxicity reporting, all of the compendia except NCCN reported toxicity, adverse events, none of them for this combination reported a cancer-specific

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adverse event. They did all report severity of adverse events, frequency of events and what organ they had occurred in. The NCCN, the version that we looked at did not include any listing of the adverse events across all of the combinations. The adverse events were actually fairly uniform across all the compendia and from our reading, they seemed to rely primarily on the package labeling. And finally for this slide, again, the number of citations varied widely across the different compendia, and the years that the citations were from also varied across the different compendia.
So, this is a summary across the six compendia that we looked at and the six combinations about whether the off-label status was clearly indicated. And this slide, as stated, the NCCN, that it was clearly indicated. So the cells in gray, basically these compendia were silent about these combinations. For the most part, actually, overall there was agreement, at least among the compendia that discussed a combination. There was agreement only for the erlotinib for pancreatic cancer, wherever the combination was discussed, it was not an

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indication.
Again, across the compendia and the combination, looking at different numbers of citations that were given by the compendia, this column here shows the number of citations that we found in our search, so you can see that for USP-DI, they for the most part had the largest number of citations, which, it's not indicated here, but there was generally fairly good overlap with the citations that we found. NCCN and Clinical Pharmacology tended to study just one or two, occasionally a couple of additional citations. Facts & Comparisons at least across these examples tended not to give any citations.
One point of interest with DRUGDEX is that we actually found there were different versions of the electronic compendia, and the version that we were looking at as opposed to the version Duke was looking at, did not include any references.
So, here is just the Phase III trials.
As I said, for these combinations there were actually very few Phase III trials. There was one gemcitabine in bladder cancer and one prior to

2006 for gemcitabine in ovarian cancer. And again, across the compendia, AHFS and Clinical

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Pharmacology did discuss this well and fully, and NCCN cited it but there was no specific discussion of the trials. Facts & Comparisons and USP-DI did not discuss or reference this Phase III trial. And actually, we haven't looked to see if the other version of DRUGDEX did include this. This more recent trial from 2005 was not cited in any of the compendia.

This reviews the toxicity reporting across the different compendia. Again, NCCN does not, in our reading, did not include toxicity. Otherwise, toxicity was generally reported. The plus signs indicate that there was a cancer-specific toxicity reported, and this was a variable across the different compendia. One point is that two of the compendia were actually silent as to the use for the indication, but they did reference the same article regarding toxicity of rituximab as a specific indication for CLL.

An item that we were interested in reviewing is how do the different compendia make statements or possibly recommendations, but make statements about the combinations. And we came up with pretty much, we came up with this stratification for what kinds of statements might

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be made. First, it's a recommendation and it could be a strong recommendation such as a statement like it is recommended or something that should be used, or it might be a weak recommendation such as just a suggestion or indication or advisement. And then another approach would be just stating some observations or findings, and this could be an active process where they actually describe the articles that they cite with some description, or a passive statement such as this is used or not used without that much description, or silence, they might not cover the topic.

So, some examples of strong recommendations. NCCN has categories of consensus and they made specific recommendations based on these categories. USP-DI also, as discussed earlier, had different categories of accepted, acceptance not established. For statements about observations and findings, some examples, AHFS used some phrases like agent X is used for cancer Y, agent X is an active agent against cancer Y. In Clinical Pharmacology studies were discussed, but there was no specific statement about that indication. DRUGDEX and Facts &

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Comparisons categorized agents by whether they were labeled, being used for labeled or unlabeled uses.
Some further examples of some wording, just to show the differences across the different compendia, and again, the compendia were designed as was discussed earlier for different purposes, so it is not surprising that there are differences in style. So, some examples. From AHFS, gemcitabine is used, and five references are given, for the treatment of bladder cancer. Objective responses have been observed. And in this example, there was no specific description of any of these five references. Clinical Pharmacology says gemcitabine was evaluated in patients with ovarian cancer, and then there's a description of one of the studies showing complete responses and so forth. DRUGDEX had a simple comment stating non-FDA-labeled indications, neoplasm of bladder.
Another example from NCCN, this combination, gemcitabine with cisplatin, is considered a standard first line choice for most patients, so it is a specific recommendation that is given category 2A, and a description listed in

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the compendium in the section describing what that 2A means. In another section for salvage therapy, several drugs including gemcitabine is advised depending on patient's current status.
USP-DI, under the accepted category, state that gemcitabine is indicated based on response rates achieved in clinical trials, stating five references. Gemcitabine is indicated alone or in combination as reasonable medical therapy at some point in the management of patients. This was given an evidence rating of III-D. However, nowhere in this section anywhere was that described, although the reference given for this was the reviewer's consensus. And actually across all the other compendia, or across all the other combinations that we looked at, this was the only place where there was an explicit rating of any kind for the USP-DI.
Under the acceptance not established, again, USP-DI states use of gemcitabine has not been established due to insufficient data regarding response/efficacy, and lack of peer reviewed evidence. For this there were actually 20 citations.
We'll skip over that and get to some of

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our findings. In combinations of agents and cancers that we looked at, Phase III studies are

rare. References used by compendia are often not up to date with the current medical literature, they tended to include only the older studies, and as was discussed earlier, the date of the update does not necessarily mean citations were updated. One other thing that's not on here that I should add is that the references, the way that the reference is used varies across compendia. Sometimes they were just listed and sometimes they were described.
The next point is that there are large variations among the compendia in the citation of evidence. USP-DI generally has a high number of citations compared to others. DRUGDEX is available in two formats, one of which does not include citations. Facts & Comparisons, for the indications we looked at, rarely offered citations.
The discussions and the conclusions in the compendia often did not appear to be based directly on the citations. Instead, citations were provided seemingly as simple lists of studies, and it was unclear from our reading of

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these sections alone whether the citations were lists of all, what were thought to be all the available evidence, or suggested reading for example, or actually as another alternative, kind of a more standard way of using references as actually backing up the prior statements.
There is variation in the types of statements made as discussed, sometimes clouding the interpretation of whether a recommendation or indication was being made, and we actually found it was somewhat subjective from our point of view when we found that a recommendation was being made.
There is general uniformity of reporting of adverse events, which as I mentioned, tends to be similar to package inserts or labeling.
So in summary, the compendia differ across each other by which combinations of agents and cancers are discussed, or on the flip side, which combinations they are silent on, how they state whether an agent is indicated for a specific cancer, the level of detail regarding the agent's use, how the evidence is discussed and referenced.
In general, a small percentage of the available

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evidence is explicitly cited. And, citations frequently act more as lists of available studies than references to back up the statements made.
Thank you.
DR. GARBER: Thank you, Ethan. Thank

you all three presenters. I just want to make sure, Amy, Doug and Ethan, you will be available for the open discussion? Okay, terrific. At this point, what I would like to know is if any panel members have questions of a clarifying nature for the three people who just presented. We will be able to ask them questions relevant to our discussion of voting questions later on in our open session. Cliff.
DR. GOODMAN: Early on in the evidence and EPC write-up it says that use of a quorum and frameworks for evaluating the compendia, and you noted those typically used were meta-analyses and practice guidelines. How practical do you think it was to use those two instruments for this purpose, and did it serve our needs in evaluating these compendia?
DR. MCCRORY: We didn't use the instruments per se as they were designed, we used them to report the scores and then we used them

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more as a framework for how to think about what the compendia were doing in their roles of looking at evidence, evaluating evidence, and interpreting the evidence and coming up with a recommendation. So we used them more as a conceptual framework along with the questions that the MCAC committee designed, and we developed almost a questionnaire, if you will, that we used to guide our interviews. Ultimately what we, what the tables show in the report is what we ended up coming up with as a range of domains. We felt they agree and the quorums were pretty good because they were comprehensive.
DR. GOODMAN: So relative to your expectations for meta-analysis instead of practice guidelines, given that contest, what is your overall assessment of the quality of these compendia as a group? I know you tried to display it in these tables, but I'm wondering about the potential disconnect between the way you were evaluating these and the purpose of these compendia. It seems to be --
DR. MCCRORY: I agree there is a disconnect, and let me return to the blind man and the elephant analogy. We went in with blinders

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on, evaluated them for a purpose for which I don't think they were particularly well suited. In the report we described the staffing levels, we described some financial and some other aspects that go into the compendia. They are not staffed to do a comprehensive literature review, they don't have the numbers of staff to do that. So we weren't really trying to hold them to a standard

that they perhaps couldn't achieve, we were only trying to say what would be, you know, if you have a choice between going to a compendia or going to a recently released high quality review or guideline, you know, how do they stack up and compare to them perhaps.
DR. GARBER: Thank you. Alex.
DR. OMMAYA: I recognize you have specific views of the compendia based on the examples that you chose, but I just wanted to notice that later on when we address the question specifically, I would appreciate your views as to strengths and weaknesses of individual compendia based on the time that you spent analyzing the questions that you did.
DR. ABERNETHY: Is that for later or now?

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DR. OMMAYA: Later.
DR. GARBER: Okay, thank you. Some of you might have noticed that we had a scheduled ten-minute break at 9:35. I have been in a few meetings in this room and I have never seen a ten-minute break. And it's obviously pretty difficult to reconvene in ten minutes. So I want to ask the pleasure of the panel that we not take a break but encourage you to leave individually if you need to, but otherwise we continue with our proceedings. Linda.
DR. BERGTHOLD: I'm trying to stay awake, but isn't it a little warm in here?
DR. PHURROUGH: We've had a budget cut.
(Laughter.)
DR. GARBER: So the next is the invited guest speakers, and I think next up is Gerald McEvoy, are you here and available?
DR. MCEVOY: Yes.
DR. GARBER: And just so you're ready to go, the next speaker we have is Laura Moore, so as your time is approaching, please come up front so we can resume. Is Laura Moore here? If she's not here, the speaker after her is Jerome Osheroff.

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SPEAKER: He's here.
DR. GARBER: Okay. Just be ready to go up front then.
DR. MCEVOY: Unfortunately, I'm going to be talking today without slides. We found that this committee is different from the committees that we've given comments to in the past, usually FDA where you cannot use Power Point, and we found out too late in the process that Power Point was in fact the preferred method, so I apologize in advance, and I hope that people are not upset

watching this talking head. My name is Gerald McEvoy. I'm the assistant vice president of drug information at the American Society of Health System Pharmacists. The American Society of Health System Pharmacists is pleased to provide comments to the Medicare Coverage Advisory Committee regarding the use of authoritative drug compendia in determining medically accepted indications for anti-cancer or chemotherapy regimens. ASHP is a 30,000-member national professional association that represents pharmacists who practice in inpatient, outpatient, home care and long-term care settings. My presentation has not been paid for by any

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organization or pharmaceutical company. I am currently employed at ASHP, a nonprofit professional practice which is funded by our membership and independent sponsorship. ASHP is the publisher of the American Hospital Formulary Service Drug Information, which is one of the three compendia originally designated for making determinations about medically accepted indications for anti-cancer chemotherapeutic regimens under the Social Security Act, and AHFS is the only remaining federally recognized drug compendium published by a noncommercial professional entity. ASHP believes that the mission of pharmacists is to help people make the best use of medications, and ASHP supports a vision for pharmacy practice in hospitals and health systems in which pharmacists will lead evidence-based medication use programs to implement best practices. Publication of AHFS-DI is an important component in achieving this mission and vision, as are the activities of our commission on therapeutics. The mission of AHFS-DI is to provide an evidence-based foundation for safe and effective

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drug therapy, and that was noted in one of the slides. It is widely trusted for its established record in refuting unfounded efficacy claims, a rigorous science-based editorial process, independence from the influence of pharmaceutical manufacturers, and we've remained true to our mission for almost 50 years. We have been conducting this type of activity since 1959, which is a period that predates the beef-up or Harris amendment, which for the first time gave the FDA authority to actually make determinations about efficacy programs. Our publication was based on evaluating claims prior to there being a regulatory method for example of doing that, in

1959.
We're the most widely vetted drug compendium. Requested of the compendial authority of AHFS has extended over four decades, being proposed initially as a resource whose quality and scope met the goals for a proposed federal drug compendium in the 1960s and 1970s. However, the government ultimately decided not to pursue that. As a result of our demonstrated expertise in critically evaluating drug information, FDA actually contracted with ASHP to develop a class

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prescription labeling system for 20 major classes of drugs in the 1970s.
HCFA, now CMS, determined in 1989 that AFHS-DI met the compendial selection criteria established by Congress and adopted it as one standard in carrying out certain aspects of the Social Security Act, and then this precedent established AHFS as a compendial standard in subsequent legislative and regulatory initiatives for both Medicaid and Medicare. HCFA also established the expectation that such designation of any compendium in the future would require similar evaluation by the agency as to whether a compendium met established standards as well as publication in the Federal Register of their selection decision in the form of a proposed rule allowing for public comment.
AHFS is supported solely by subscriptions and licensing fees and receives no financial support from pharmaceutical manufacturers. ASHP maintains a strong policy regarding the editorial independence of our staff.
AHFS had its origins in the formulary system, which established a mechanism for pharmacists to formally communicate with medical

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staff and which serves as a sound therapeutic and economic basis for drug policy. Originally, AHFS was designed to assist the pharmacy and therapeutics committee of each hospital in preparing its hospital formulary. Although the publication has developed beyond its original purpose, the principal goal of promoting rational drug therapy through objective evaluations has remained.
Paramount to providing such information is the critical evidence-based evaluation of pertinent clinical data concerning drugs, focusing on assessing the advantages and disadvantages of various therapies, including interpretation of various claims of efficacy for pharmaceutical products.
Information shapes treatment decisions

made by clinicians and influences public and private healthcare policies and decisions and as a result, it is important that the information be authoritative, objective, and importantly, free of undue influence from pharmaceutical manufacturers, health insurers, pharmacy benefits managers, and other third parties who may seek to use the compendium to promote their own vested interests.

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Editorial decisions are evidence-based and made independent of any such third parties, and final decisions are made solely by the AHFS editorial staff, taking into account the advice of expert reviewers.

Information in the AHFS is prepared by professional staff, a professional editorial and analytical staff who critically evaluate published evidence. We do not solicit authorship of our material from external sources, nor do we accept submission of information for potential publication. Use of external volunteers in our process is limited to expert review, not of content development. The external review process utilizes appropriate advice from leading medical experts in the specific field of therapy, including experts in major research and clinical institutions as well as public bodies such as the NIH and the CDC.

Using an independent process, AHFS monographs incorporate information from pertinent references in the medical literature and expert therapeutic guidelines. Many factors influence the selection of an off-label use for consideration and possible evaluation by staff.

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We apply a systematic approach in identifying and critically evaluating clinical data, aided in recent years by the availability of an expansive array or resources available through the Internet. Decisions about what or what not to include are evidence-based, requiring support in the published medical literature and medical practice.

The analysis is an intramural process performed by a professional staff with strong scientific and therapeutic backgrounds. This provides a high level of quality control and consistency in content development. The process involves assessment of scientific merits of available data.

The principal influence on these decisions is the weight of the supporting evidence. The process is evidence-based with well-designed studies, specifically randomized clinical trials and systematic reviews of randomized clinical trials being weighted more

heavily than observational studies or case reports. The importance and severity of the disease, availability of alternative therapies and their relative toxicities, the number of patients affected by the disease, other patient population

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characteristics and other factors also are important considerations.
The review process for preliminary information involves a multi-step intramural evaluation and review by the editorial and analytical staff and the solicited external expert review. Reviewer participation is solicited but voluntary, and no honorarium or other benefit is provided. Full disclosure of interest, including any affiliation or financial involvement with the manufacturer of the drug under consideration is requested.
In 2003, AHFS initiated a process for developing a codified method for summarizing its evidence-based analyses. While the principles of the AFHS editorial development process had not changed, moving to a structured, codified format that would summarize ongoing staff assessments of new and changing evidence was initiated to aid analysis and evaluation of various drug uses. The development of the AFHS evidence rating system applied the principles of Fletcher and Sackett, as reflected in the work of the American College of Chest Physicians. FDA guidance documents for assessing clinical trials, levels of evidence

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applied by AHRQ, and the ASHP's commission on therapeutics, as well as several dozen other documents and resources --
DR. GARBER: I'm sorry, but your time is up.
DR. MCEVOY: Okay, thank you.
DR. GARBER: Thank you very much. Our next speaker will be Jerome Osheroff, or Laura Moore.
MS. MOORE: My name is Laura Moore. I'm with Thomson Micromedex and the senior director of editorial services there. As far as financial conflicts, I am an employee of Thomson Micromedex and I do own some stock in Thomson Corporation, a provider of compendia. I don't have any other financial conflicts of interest. I have had some preliminary conversations prior to this meeting with Dr. Whitten as well as (inaudible) that are within the confines of our written testimony that we supplied to you previously.
I do have a prepared Power Point presentation for this morning, but at the outset I

would like to begin by saying that yesterday we had the opportunity to review the report that was

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produced by Duke and Tufts University and we had a chance to walk through that, and as part of our review we identified some inconsistencies in their information. In particular, Dreibach, for example, is always cited, so that particular product is fully referenced in all cases in every electronic format that is available, and in reviewing the 14 indications, all 14 of those indications do appear in DRUGDEX. And my concern is that there is the possibility that in DRUGDEX, the product was not actually used as the source of information but perhaps Drug Point, which is an abbreviated drug information source that's available in the electronic version, might have been used instead.

As part of my presentation today, I want to present to you just a quick overview of the Thomson Corporation and Thomson Micromedex, as well as introduce you to our people on the editorial staff responsible for maintaining our drug information content, the processes that we use for maintaining that content, the updates on that information, and what we've accomplished last year in that regard.

The Thomson Corporation is a leading

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global provider of integrated information solutions for businesses and professionals. We provide must-have information, using technology and applications to help our customers reach better decisions faster in the course of their workload. Currently we serve over 20 million information users in the field of tax, law, accounting, higher education, corporate training, financial services, scientific research, and of course healthcare. Thomson is organized into different units, Thomson Legal and Regulatory, Thomson Financial, and Thomson Healthcare.

Thomson Micromedex was founded in 1974 by a physician, Dr. Barry Rumack. We were subsequently acquired by Thomson Corporation in 1991, and are currently a business unit of Thompson Healthcare. We employ 425 people in the Denver office and we provide electronic subscription-based products with the exception of the print version of the USP-DI currently in the areas of drug information, toxicology, as well as patient education.

Now I would like to move on to our people. In our Denver office we employ over 100 editorial staff members. Physicians, nurses,

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pharmacists and other allied healthcare professionals comprise the majority of our editorial team. They represent a wide range of specialties, including internal medicine, emergency medicine, toxicology, oncology, clinical research, the list goes on, and I'll just give you a few. In addition to their educational and professional training, they also are trained in literature evaluation and in literature identification techniques, in accordance with accepted practices. And then also of interest to this panel, we do have oncologists, pharmacists who do evaluations in that area. We also have a clinical research design expert who also is an expert in statistical analysis of indications and reviews. And then finally, we have a full medical library on site staffed by a medical librarian and numerous research staff, this number is up to seven right now, in addition to our medical librarian, and this group is responsible for continuing to monitor research studies, enhancing those and making sure that the appropriate information reaches our editorial process in an efficient and effective manner.
Moving on to our process, we have, our

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senior clinical staff is responsible for identifying and prioritizing topics for inclusion in our databases. They select topics based on a number of criteria, primarily based on their ongoing review of medical journals. We do have standardized searches conducted of MEDLINE on a weekly basis and the results of those searches are reviewed on a weekly basis by our senior staff as well. Based on clinical judgment, we look at national healthcare trends and changes in practices from various professional organizations, regulatory standards and compliance, FDA actions. And lastly, we do accept submissions from external sources, although it's not the primary mechanism by which we identify information for inclusion. We do have very explicit criteria that submitters must follow, and this includes sharing potential financial conflicts, who they are, who they're with. We require that they submit original copies of research, positive and negative findings. And once it reaches us, the fact that it's now in our hands, and we typically don't have communications back and forth with the requester. We take those steps to insure that our process is unbiased. Once we identify the topic for

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inclusion, we perform extensive literature searches, identification of relevant and quality

literature for inclusion. We look at breakthrough therapy, and patient safety is prioritized. And we evaluate the literature for methodological rigor, appropriateness of statistical analyses, and clinical relevance.
I know that I have ten minutes, but I was on the schedule twice, so could I combine those?
DR. GARBER: Is Dr. Osheroff not going to speak then?
MS. MOORE: He is available to assist in answering any questions when I'm done.
DR. GARBER: Okay, fine.
MS. MOORE: And I should point out too that these procedures are used both for USP-DI and for DRUGDEX, there is no variation between those two products as far as quality of information. So following the identification and verification of the product, the literature moves on to our writing staff, it goes to one of our clinical editors. They review that literature, they summarize the information, assign ratings. We have actually four ratings that are in use

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today. In DRUGDEX we use strength of evidence, strength of recommendation, and an efficacy rating. Within USP we use an acceptance rating, so at that point they give it a rating using guidelines and internal policy.
Following creation of the content, the information moves through what we generally call content review, where it is reviewed by senior clinical staff or peer review. In the case of off-label indications for oncology, all of our new oncology indications, off-label oncology indication do go out to our oncology board for expert review. They go to a minimum of four members who are responsible for looking at the literature, assessing our ratings associated with those indications, and providing feedback to us. Once it comes back from expert review the senior clinical staff once again reviews it, confers final approval, and the information is now available for inclusion in our products.
As far as timeliness of the availability of that information to our customers, it really depends on the type of subscription that an individual customer has. Some information is updated daily, we have versions of DRUGDEX that

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are updated on a weekly basis. The Internet gets at least a quarterly update, and this will occur in our publications as well.
The next one, I wanted to walk through the old USP process versus what we're currently

using. Until 2004, USP was responsible for maintaining the off-label indication information within USP-DI. In April of 2004, we took over that responsibility. At the point that USP had it, off-label indications required unanimous approval by their oncology advisory board, and also there was a requirement for a 90-day public comment period. With those two things combined, occasionally, and in many cases it could lead to a backlog of up to one year. And in fact when we took over in April of 2004, there was a significant backlog and we were definitely hearing about that.

In response to that we took a look at our processes, and based on that, the process today is that all off-label oncology indications do go through expert review, and they are required to be reviewed by a minimum of four members and not the entire board. And we don't require unanimous agreement amongst those members; rather,

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we have a chair of our oncology board, as well as our chief medical officer, who will try to resolve any conflict. And lastly, we no longer require a public comment period.

At this point I would also like to note that it was previously stated that we will no longer be publishing under the name USP-DI in the near future. We are developing a successor product and as part of rolling out the successor product, it is possible there may be changes in formatting for that product, although we haven't made any final decisions in that regard. One of the changes might be that we would move from an acceptance rating to the three ratings that we're using today at DRUGDEX, so that the strength of evidence, strength of recommendation is given rather than a single acceptance rating.

Where we're at today with off-label indications, again, we have established a board, we currently have ten board members and we're actively recruiting additional board members. Dr. Thomas Marsland, of the Florida Oncology Association, is currently our chairperson. In 2005 we published ten new off-label indications under an accepted rating. Four off-label

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indications were added with an acceptance not established rating. And we also added 16 additional indications based on product labeling changes last year.

Just in closing, I would like to leave you with a few key messages. We do have a fairly large dedicated staff on site who is responsible for maintaining our content. We have invested

significant time and resources in the last few years to improve our processes internally and revising what we do. We believe that our literature retrieval and evaluation processes are unsurpassed in this arena. And we have employed a conflict of interest policy to insure that our content remains unbiased. We have taken all of these things together, so our people, our processes and policies that have been put in place in the last two years really serve to protect our longstanding reputation for providing unbiased drug information. That's all I have.
Oh, Barry just reminded me, one of the things that I did want to point out, again, is that the 14 indications that were covered as part of the study are in DRUGDEX, and I can provide a copy of that information to the panel. In

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addition, the nine, there are nine indications that were covered in USP-DI; of the five that were not, two of them are actually in the final stages of expert review, and I can share that with the panel as well. Any questions?
DR. GARBER: We will have a question period later on. I hope you will be available for that during the afternoon.
MS. MOORE: We certainly will be, thank you.
DR. GARBER: Thank you very much.
Shanti Divvela will be the next speaker from Facts & Comparisons, and following her will be William McGivney, from NCCN. The final scheduled speaker will be MaryAnne Hochadel.
MS. DIVVELA: Good morning. My name is Shanti Divvela and I am a clinical actuary at Wolters Kluwer Health. The first thing I would like to say is I do not have any conflicts of interest and I am appearing on behalf of Wolters Kluwer Health.
Before I get into describing our compendium, I would like to give you some background information on Wolters Kluwer Health. WK Health has over 2,500 employees on four

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continents. Our major brands include Facts & Comparisons, Lippincott, Williams and Wilkins, Ovid Technologies, Adis International, and Medi-Span. WK Health is a provider of information for medical and health professionals and our customers range from hospitals to pharmacies, to healthcare professionals and students.
Facts & Comparisons 4.0 is a browser-based electronic version of our most popular products. To provide you with the most comprehensive information, I will give you some

portions of Facts & Comparisons that contain unlabeled uses. These include Drug Facts & Comparisons, Off-Label Drug Facts, and Cancer Chemotherapy Manual.
These products, Drug Facts & Comparisons, Off-Label Drug Facts, and Cancer Chemotherapy Manual are unbiased and not financially influenced by pharmaceutical manufacturers. Drug Facts & Comparisons has been the standard drug reference for almost 60 years. It provides a wide course of information on prescription and non-prescription products. Each individual full drug monograph includes the sections you see here. The

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indications section is where the unlabeled uses are found, along with the FDA-approved indications. Drug Facts & Comparisons also includes drug class monographs in a comparative format.
A drug monograph goes through multiple steps before publication. Drug monographs are chosen for review based on changes to the FDA-approved labeling. Each monograph is reviewed independently by two clinical editors who are all pharmacists. During these reviews, the clinical editors research and evaluate the literature related to off-label uses that are clinically significant and meet our criteria for inclusion. Various references such as primary biomedical literature and standard medical textbooks are researched in order to identify unlabeled uses. We include those unlabeled uses that are well documented from these references. If an unlabeled use is found in primary literature, then we ensure that the clinical study is of substantial size, using human subjects, and show positive results that are both clinically and statistically significant. We exclude animal data and case reports.

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For those off-label uses that do not meet our criteria for inclusion, our policy is to be silent and, therefore, not include the indications in our compendium. However, there may be a few cases in which we include unlabeled uses that do not meet our criteria because they aren't noteworthy.
I would like to mention that for the past year we have started including references to our electronic version and as each monograph gets updated, we are making these references available for viewing.
Our second reference that contains information on unlabeled uses is entitled

Off-Label Drug Facts. This describes off-label drug use that is not encompassed by FDA-approved labeling, including therapeutic indications, patient populations, dosage, dosage formulation, and route of administration. Each monograph in Off-Label Drug Facts summarizes information from published medical and scientific literature. Also included is an evidence-based rating that can be used in a clinical setting for decision-making. These ratings are assigned by an editorial panel that critically evaluates all monographs in order

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to provide an authoritative compendium of the clinical relevance of the published information. The rating scale ranges from one to five. And evidence-based rating of one signifies that the efficacy, safety risks and optimal dosage are clearly identified in appropriate populations, as evidenced by consistent favorable data from at least one well designed controlled trial, or dramatic results from uncontrolled experiments reported by our expert panel. An evidence-based rating of five signifies that the use is not recommended based on data that is considered unsafe or not effective.
Unlabeled uses are identified through a monthly review of approximately 250 medical journals, the compilation of data received from a managed care claims database, and inquiries into the University of Kansas School of Pharmacy Drug Information Center. After an unlabeled use has been identified, information is then compiled from human data published in primary literature. This may include controlled clinical trials, non-controlled trials, and case reports since 1990. Earlier data may be used in some cases. Monographs are then developed and

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reviewed by an editorial review panel, consulting reviewers and editors. The editorial review panel consists of physicians and pharmacists.
Individual monographs will be updated when significant new studies become available and new monographs will be added with each additional update.
The third reference on off-label uses is our Cancer Chemotherapy Manual. This product provides a wide variety of information on chemotherapy regimens for both healthcare professionals and patients. It is developed in collaboration with the University of Utah Hospitals and Clinics, including the Huntsman Cancer Institute.
Each individual drug monograph is included in the sections noted here. The

indications section is where the unlabeled uses are found, along with the FDA-approved indications. The drug monographs are developed and reviewed by an editorial review panel, consulting reviewers and technical editors. The editorial review panel consists of practicing clinicians, pharmacists, nurses and pharmacy technicians. The unlabeled uses are identified

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through the research and evaluation of various sources, including primary biomedical literature, standard drug information and medical references, practicing clinicians, and evidence that a manufacturer is seeking FDA approval for the specific unlabeled use.
To be included as an off-label use in this compendia, the use must be well documented from these sources and shown clinically and statistically significant results from clinical trials.
This concludes our presentation on Wolters Kluwer Health's compendia that provide information on unlabeled uses. Thank you.
DR. GARBER: Thank you. Our next speaker will be Bill McGivney, NCCN.
DR. MCGIVNEY: Members of the committee, good morning. I am Bill McGivney, the chief executive officer of the National Comprehensive Cancer Network, better known today as NCCN. NCCN is a not-for-profit alliance of the leading cancer centers of the world, and I invite you to take a look at the map specifically, because these centers like M.D. Anderson, Memorial Sloan-Kettering, Johns Hopkins, Stanford, the

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University of Michigan, et cetera, supply over 700 expert clinical professionals who constitute and make up our panels to develop our guidelines and develop our compendium recommendations.
Additionally, and relevant today, in a past life I have served as vice president for clinical and coverage policy at Aetna Health Plan, where I ran technology assessments, clinical guidelines, and national coverage policies, including drug policies. And finally regarding me, I am a member of the Medicare Coverage Advisory Committee.
In the following comments, the NCCN will use the NCCN drugs and biologics compendium as a reference point to discuss and evaluate characteristics of a compendium that can be used to make informed and timely coverage determinations under Medicare, and thus serve to provide appropriate access to effective drug and biologic therapy for Medicare beneficiaries.

So, let's talk about characteristic number one. Recognition and application of standard of care for oncology. The recommendations of the NCCN guidelines, and this is a very very important point, are based directly

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on the recommendations coming out of the NCCN clinical practice guidelines on oncology, so the drug compendium recommendations are directly based on NCCN guideline recommendation. I think this is important, an important point. This is to say with substantiation that the compendium recommendations, is that they are derived from a disease-based analysis that places the most appropriate therapy in line with the patient with not only consideration of drugs and biologics, but also surgical procedures, radiation therapy, watchful waiting, et cetera. It is a very important point.

NCCN guidelines, as I said, are widely recognized and applied as the standard of care for oncology in both the community practice and the academic setting. Our guidelines cover the managements of over 97 percent of all cancer patients, all major supportive care areas, and prevention screening and early detection. Our guidelines are widely referred to, as evidenced by the fact that in January of 2006, there were 110,000 downloads in one month of complete NCCN guidelines from our web site.

The recommendations of the individual

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NCCN compendium chapters, as I said, are derived directly from the NCCN guidelines. These recommendations are the result of an overall risk-benefit analysis regarding, again, the continuum of care with all the variety of care and management tools available for treatment of specific cancers. It is important also to note that the recommendations from the NCCN guidelines and from our compendium are already being used by Medicare regarding, for example, this January 28, 2005 decision memo on colorectal agents used as therapeutics, and by private payers, again referencing the many times that health plans have called us for our opinion on specific technology, be it a drug, device or procedure.

Characteristic two, that indeed, the recommendations must be based upon available scientific evidence. The NCCN compendium recommendations are based on explicit evaluation of scientific evidence, integrated with expert judgment in a consensus-driven approach. The NCCN communicates explicitly, as you've heard in the analyses presented by Duke and by Tufts New

England Medical center, specific categories that underlie, categories of evidence and consensus

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that underlie our recommendations. And this is an important point: Users of the NCCN compendium can track back to the same recommendations as the NCCN guidelines, to see their supporting references and to review discussions of supporting evidence or issues in management. And indeed, regarding references, NCCN committees purposely and purposefully limit the references used to one, two or three, in order to provide references that really define most definitely the recommendations for care, and secondly, point out and identify the optimal management regimen in terms of combinations to be used, the drug doses and the schedule for administration.
Characteristic three, input evaluation and development by multidisciplinary panels of experts. The NCCN compendium provides recommendations about the appropriate and effective use of drugs and biologics from 46 guideline panels that are disease or issue-specific. Each panel has 15 to 22 experts; they represent a broad variety of subspecialties, including medical oncology, surgery, radiation oncology, gynecologic oncology, et cetera, and other clinical professionals. And as I said at

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the outset, these are thought leaders from those 20 institutions.
The panels meet at least annually, sometimes they meet three or four times a year. The agenda for each meeting is based on new data that may have been presented at major oncology meetings or published in major journals, from panel member input and from broader expert input across all our institutions, not limited to just panel members. Additionally, other interested parties including patient advocacy groups, academic physicians from outside the NCCN, community physicians, industry, et cetera, may also submit data to NCCN for consideration.
Characteristic four, broad participation to diminish bias. The representation of different subspecialties and clinical professionals serve to diminish opportunity for dominance by a single faction. The broad geographic distribution of representation expands the perspective of the panel, the large number of experts provides for an exposition of analyses and interpretations based in evidence, with many clinicians with stature both nationally and internationally.

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And I just got back from Beijing, and the Chinese are adapting NCCN guidelines for use in China. The expansion of formal input beyond the panel for multidisciplinary experts based in NCCN centers expands the sources and interpretation of evidence and as such, the NCCN has established a process that enhances the expression of divergent views and identification of conclusive evidence and thus, the synthesis of broad-based and authoritative recommendations.
Characteristic number five, recommendations must be specific to be useful. Our recommendations are extremely specific. I would just ask you to take a look, and actually that was an example shown by Duke on one of its slides.
Characteristic six, information and recommendations must be up to date. Just very quickly, I think the fact is fairly obviously across all medicine, that we need to be current with our guidelines and to substantiate the most up to date of any analyses and recommendations out there.
Characteristic number seven, information and recommendations must be widely

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available. NCCN guidelines are made widely available free of charge across the United States and globally in a variety of informational and educational formats. The most prevalent, up-to-date and accessed format is the one that's on line. And very importantly, NCCN collaborates with the American Cancer Society to translate our guidelines into user-friendly patient guidelines.
Also, NCCN guidelines are presently serving as the centerpiece for the 2006 CMS quality demonstration project on oncology, and as mentioned above, CMS characteristically references NCCN guidelines in its national coverage determinations.
An important point, that CMS, when it awards the integration of processes for the setting of coverage policies, the establishment of reimbursement levels and the evaluation of the quality of care, it will be critical to insure that the decision-making for all three processes is consistent in terms of recommendations and the sources of such recommendations. So given the existing uses of NCCN by CMS, it's logical that the NCCN compendium be officially recognized as one of the settled references mandated for the establishment of coverage policies regarding drugs

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and biologics.
In summary, NCCN supports the efforts

of CMS and all of us in the room to insure the quality, effectiveness and efficiency of care that is made available to its beneficiaries and patients nationwide. And again, we believe that the NCCN compendium provides sound scientific recommendations to support decision-making by CMS and by its intermediaries and carriers, and thus, NCCN officially requests that we receive recognition for our drug and biologics compendium as a mandated reference for national and regional coverage decisions regarding the appropriate use of drugs and biologics in cancer therapy. Thank you very much.

DR. GARBER: Thank you. Next, MaryAnne Hochadel.

DR. HOCHADEL: Thank you, Dr. Garber and the committee. I'm MaryAnne Hochadel. I am the vice president and editor in chief of Clinical Pharmacology. You might want to refer to us as sort of the new kids on the block. Back in 1994 when the committee first started to get into this compendia-based system in the cancer arena, we were just getting started as a drug compendium

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organization and had a fairly good idea of what a drug compendium might be able to do in healthcare, which is very different, perhaps, from the typical referential or encyclopedic type of information that we might be used to from standard publications. So I think one of the issues, and I'm going to speak not only to our editorial policies -- and I will disclose the fact that I am of course here as a representative of Gold Standard as an employee. I am a shareholder in the company, I do also have an editorial staff, some of whom may be shareholders in the company, but outside of that, we have a very strict financial disclosure policy in which there must be no conflicts of interest in the compilation of drug information and the standards under which we operate.

When you talk about editorial policy, our editorial policies are not unlike those of others who have spoken here, very different from NCCN obviously, because of the focus of where their information is coming from, but it's very similar to the drug compendia, and we've been talking about that today.

I think what's important are what are

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some of the considerations of off-label drug use in oncology that are important when trying to address strength of the evidence and how, why are there these differences (inaudible) and drug compendia in regards to the listings or what might

be taken as being, why is this one different from that one, why is the reference base different, those types of things. And maybe some of these issues are important to a consideration of whether the drug compendium itself is an appropriate one in terms of helping to determine off-label reimbursement policy interpretations.
In terms of patient advocacy, we need a reasonable system to use in terms of providing patient care and providing reimbursement and providing access to treatment. One of the things that I think is very important in oncology is that in that drug approval process through the FDA, one of the interesting things about that process is that the accelerated improvement process has helped deliver access to patients who are new and (inaudible).
What's interesting about that process, though, is that often the drug receives accelerated approval within a certain stage of

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cancer or a certain indication, that type of thing, and then it awaits confirmatory evidence. And we've seen a lot of examples of this type of situation over the last couple of years, (inaudible) targeted treatments in cancer. What's interesting about that process is that it's kind of (inaudible) off-label drug use and fully approved and recognized evidence in oncology, particularly as it relates to taking one drug and then combining it with other drugs.
It's very uncommon to find a fully FDA-approved drug regimen used in a cancer patient throughout the United States. Usually they've got at least one drug, either being used in a different way, the drug administration, a different dosage regimen, a different stage of the cancer than has already been proven, it's very unusual to find this situation happening.
Now that (inaudible) drug compendia, particularly under a database structure that is intended to serve certain functions for the clients and healthcare professionals or patients that are using that data in actual healthcare, and I think in certain respects every drug compendium (inaudible) in that regard, and it may be very

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difficult to define standards by which all drug compendia should make their mark, for issues that are related to the drug approval and investigational use process, as well as the fact that there is proprietary issues raised.
Proprietary rating scales may not have so much meaning when you start looking at the strength of evidence ratings or particular levels

of evidence related to particular types and published data. Garnering that all together and then (inaudible) evidence in our compendia is a fairly difficult process as a result when you look at it overall.
Let me give you some examples of volume here. In our drug compendium situation, we have at least on average 500 drug information updates per month. That includes regulatory approvals, disapprovals if you will, or withdrawals from the market, Med-Watch alerts, published literature. Peer reviewed literature such as the ones you mentioned that are part of this off-label identification process for CMS, the peer reviewed is standardly accepted literature in a review. It averages 500 a month, and in the entirety of a month you may have 1,200 particular updates that

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must be researched, driven down, put into standardized format, and then provided in a timely manner to the patient and healthcare professionals.
So when you're looking at an update, to speak to that (inaudible), what does an update even mean? It's not always going to be a full review from top to bottom of the particular information that you find in the (inaudible), and I'm just being very honest here about how the processes work. Even though they are important healthcare policy decisions based on drug compendia, and (inaudible) necessarily to talk specifically about a standard process, which are identified as a standardized developed internal process, but to talk about some of the issues surrounding this data and how it should be interpreted, evaluated and put into the system.
At Gold Standard, we definitely welcome and provide an evidence-based process in drug information in providing the data, but this is an evolving field. When we look at criteria systems, rating systems, once again, they have usually been established and validated within a certain level of evidence. A randomized controlled clinical

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trial usually tops that type of evidence rating scale because it meets any criteria. And we find those publications through those committees, from us for example, making it very hard to take all that body of evidence, identify that evidence, and then evaluate if it is evidence-based evidence or whether it has been validated using the whole of the information.
What's very important too in drug information databases is the goal they serve. We were developed, for example, for a concise

actionable point of care level in various types of healthcare settings. That means that you don't necessarily expect to see Phase I and Phase II data in all of our listings. What we are concentrating on is the human clinical use of the drugs in the settings, and with reference to oncology, we may include Phase II trial data in that because of some of the accelerated approval process, so some of that data may be from Phase II and you have to consider it when you look at these entries.
So with that being said, we would love the committee to consider some of those unique details, particularly in light of patient

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advocacy, and we know that in oncology they frequently use combination drug use for the reasons I mentioned, in trying to establish newer and emerging regimens in the field to provide better tumor response, improved survival rates, and to not be too limiting in defining very rigid criteria for drug information compendia, because I think because of the evolution of this field, we're going to find ourselves in a whole new, maybe four or five years down the line, where we need to consider other factors that are going through this process of evaluating treatments, particularly as we get into more focused and targeted drug therapies.
The intended use of a drug is barely evident at the time of its initial approval, but oncologists are smart enough to figure out based on what we know about cellular dynamics, particular growth stages of various types of tumors, where a drug might have promise to start using case studies, which lead to pilot studies, which might lead to those next very large trials. But we have to (inaudible) participant's approval as well as in these processes. We're farming out a lot of information overseas to try to get the

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study numbers in order to get the required level of data. Not that that's a bad thing, but it prolongs the process, because if you can't get the right power of numbers in order to approve these sometimes very vague or indistinct endpoints, it becomes very difficult to move a drug from the off-label process to the labeled process.
And so I would ask the committee to consider those things as you consider this issue of drug compendia. A multiplicity of compendia probably helps the issue given the fact that it points to the appropriate citations to document uses which may prove effective for patients.
Thank you.

DR. GARBER: Thank you very much. I would like to thank all of the speakers who just spoke. In our deliberation, we find it very helpful to have presentations that not only present the point of view of the speakers but are directly germane to the voting questions the panel faces, and I think I can speak for the panel in saying these were extremely helpful presentations. So, we have a group -- we have begun, we have a compilation of the votes but I think what we're going to do next, if the next set of

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scheduled public speakers, we have four of them, are here now and ready, let's do that next, and then we'll return to voting question number one. The first person scheduled to speak is George Silberman. Are you here?
MR. SILBERMAN: I am.
DR. GARBER: And following him will be Keith Logie.
MR. SILBERMAN: Good morning, everyone. My name is George Silberman, I'm a self-employed consultant. I do not own stock in any of the companies that have an interest in today's proceedings. For the last eight years I have received almost all my support directly or indirectly from the pharmaceutical industry, largely around therapeutic drugs and oncology agents. No one paid for my transportation today, and a change from the submitted form, I was contacted by representatives of PhRMA two days ago to discuss my presentation, although they did not try in any way to influence that presentation. I put down in a very sort of self-aggrandizing way that I am speaking on behalf of the public interests, and I think I'm taking a fairly unpopular position, but let me just give

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you my qualifications. I directed the study that GAO did that served as the basis for the legislation for off-label drugs. For the past decade I've advised the industry on submissions for off-label indications, I've also worked with USP on developing their process for submission of off-label drugs. I have published in health technology assessments, developed a number of technology assessments. I worked in and published in JAMA and the New England Journal of Medicine, and I testified as an expert witness before Congress on health policy issues on at least a dozen occasions. I state these qualifications because as I say, I'm going to ask the committee to consider an issue that is not a very popular issue.
And for a moment I would ask you to

lift your heads away from the figurative trees that are certainly important regarding issues like whether or not it takes three weeks or three months of treatment to publish, or the relative number of citations, and to focus on the literal forest that we are in a healthcare crisis, and that healthcare crisis is likely to get worse. You are here today to define how cancer patients

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will be treated for decades to come, and you simply can't escape that reality. This isn't a technical decision that you're making but it is ultimately a societal clinical decision based on our input today, and ignoring the fact that as we have an increasing supply of therapeutics, you have increasing demand for these therapeutics and you have limited resources to pay for it, it's both short-sighted and irresponsible on your part. My recommendation is that what serves as the basis for healthcare decision-making in the oncology field as a compendia be encouraged to eventually include information on net value. By net value I do not mean the price of the drugs, but I do mean looking at the cost effectiveness of those products so that the constant battle that's occurring out there between insurers who are trying to avoid efficacious drugs simply on the basis of a dollar figure, and physicians who are really at a loss in terms of understanding true value, are helping those deliberations by information from objective third-party sources. We are certainly not ready for this yet. Publishing cost effective information in the

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compendia today would probably do more harm than good, but I would urge the committee to make a strong recommendation that we move to that position. I advise a lot of companies in how to structure clinical development processes to maximize market strategies, and certainly off-label compendia policy is a critical component of that. And I can tell you that if you make the statement that net value is important, it will influence drug development. If you don't, we're simply going to proceed down that road. Thank you for your time and interest in this issue and good luck with your deliberations.

DR. GARBER: Thank you very much. Our next speaker is Keith Logie. Following him will be Sharon Brigner.

DR. LOGIE: My name is Keith Logie. I am a practicing oncologist in Indiana. I am also a member of the ACCC, the Association of Community Cancer Centers. ACCC is a membership organization

whose members include hospitals, doctors, nurses, social workers, and oncology team members who treat the millions and millions of patients with cancer. ACCC is committed to insuring that Medicare beneficiaries have access to quality

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cancer care, including the innovative and cutting edge therapies our patients require to win their battles against this deadly disease.
Many of these treatment regimes involve new drugs already approved for other indications by the FDA. This off-label use of cancer drugs is a common medical practice that is critical to the treatment of these patients. I can't tell you how many times I've come across new data from ASCO presentations such as Perceptin for breast cancer chemotherapy, and it's clinical that it be rapidly introduced into clinical practice. It took five to six months before I felt comfortable giving it in my clinical practice in terms of being paid and reimbursed for it.
After the demonstration at an ASCO plenary session, three randomized clinical trials with a P value that was like 10 to the minus 12th in significance, 50 percent improvement in early stage breast cancer, that had to be given. It was a presentation given in May and we should have been able to use that drug in May. It's very critical to get these drugs into the market and to allow us to be able to use them.
Because off-label use is so critical in

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cancer delivery, ACCC believes it is important to have multiple sources of compendia. In addition, we would like to see the following criteria:
First, the compendia must include an extensive breadth of listings that reflect multiple treatment regimens for each of hundreds of types of cancers.
Second, the compendia must demonstrate a flexibility to rapidly integrate literature, and readily accessible updates. The delays of months and sometimes years between the announcement of significant clinical research outcomes and their inclusion in the compendia cannot disrupt Medicare's beneficiaries' access to care.
Third, the compendia must use a clearly described and transparent application and review processes for new listings and revisions to listings. Such a process will protect access to new treatments by making it easier for researchers, physicians and patients to request regimens to be included in the compendia.
Fourth, the compendia must consider the data from various types of trials. While

randomized control trials are recognized as the gold standard for clinical research, they cannot

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be performed for rare cancers. Importantly, the compendia must not limit their data to large randomized clinical trials but instead, must consider data from other studies such as Phase II trials as well.

Fifth, the compendia provide clearly written entries that describe the evidence for each use. A publication is useful to physicians and carriers only if it presents information on treatment options in clear language and an easily understood format.

Finally, the Secretary should continue to recognize at least two publications in Medicare coverage decisions. Medicare's recognition of multiple compendia will provide physicians and carriers with more data regarding current treatment options.

The ACCC also believes that several of the characteristics identified in your current committee questions are a little bit inappropriate. For example, the compendia should not establish explicit recommendations on the sequential use of therapies because different patients require different sequences. There may be individual characteristics of certain sequences

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that may elicit NCCN practice guidelines.

Additionally, the compendia should not provide net benefit analysis based on harm versus potential benefit because this analysis is impossible to perform meaningfully through variation among patients' comorbidities. For the same reason, the compendia should not provide any type of stratification of the risk of available therapies. ACCC also believes that the compendia should remain silent when the evidence on a particular drug is equivocal.

We are certainly not recommending listing (inaudible) deny coverage for that use in all patients, especially if one compendium is slowly updated where the other one gets new updates very rapidly and where one not recommended may disqualify a drug. Instead, carriers should continue to cover its use on a case-by-case basis until more data are available. Thank you very much.

DR. GARBER: Thank you. Our next speaker is Sharon Brigner, and she will be followed by Elizabeth Halpern.

MS. BRIGNER: Good morning. In way of full disclosure, I am a full-time paid employee by

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PhRMA, the Pharmaceutical Research and Manufacturers of America. My name is Sharon Brigner. I'm pleased to be here today as a representative of America's research pharmaceutical companies, but I'm also here as a registered nurse who cares for patients and who is a granddaughter of a victim of pancreatic cancer. It's out of that concern for cancer patients like my grandmother and a commitment to insure they receive the best possible care that brings me here today. If you have ever been in the situation of having a family member who has been diagnosed with cancer, you want them to have access to any and all possible medicines that have promise that your provider thinks would work in his or her particular case.

I was in that exact same position. I was a first-year nursing student when my grandmother was diagnosed, one of the 32,000 patients a year who were diagnosed and died of pancreatic cancer. I remember her clearly telling her doctor, Doctor, there's got to be some type of medicine that's available, even if it's experimental, that will give me two, three more months with my granddaughters, my sister and I. I

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remember her saying that back in 1995, and now I am happy to say that there are five new drugs that are approved for the treatment of pancreatic cancer. Even more interesting is the numerous clinical studies that show the possibility and uses of medicines off-label that can give a patient more time to be with family.

That is ultimately why we're all here today, to discuss how we can best assure cancer patients access to cancer care. These are the four items that I will cover briefly.

The important role of off-label use of medicines is well recognized by (inaudible) and clinicians. The National Cancer Institute said that off label represents the standard of care for patients with cancer. ACS said that only 15 percent of cancer patients receive off-label drugs, highlighting the critical importance of off-label medicines. ASCO said that off-label use of approved drugs are an important tool for advancing the good of cancer care. In 1991 a GAO report acknowledged widespread use of off-label use of oncology drugs, reporting that more than half of all those patients receive at least one off-label drug.

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In 2005 a study commissioned by ACCC, BIO and PhRMA, they interviewed 25 oncologists and

12 profit practice managers to get their insight on the current trends in off-label use of cancer therapies, and they found that the oncologists' uses do compare to the GAO findings. Although there are inherent limitations to this study because of the small sample size, there are several indications that suggest similar findings may be seen in a broader sample.
Our survey sought to examine these four questions. One thing that has changed since 1991 is the role of compendia in Medicare policy. In 1993, Congress mandated the use of recognized compendia. This policy has functioned well in general and insured the robust evidence-based compendia system. This is no less important today than it was in 1993.
As these findings suggest from the OBS survey, there are two things that I want to bring to your attention. One, recognized compendia play an important role in insuring coverage of and patient access to medically appropriate off-label uses of cancer drugs. Number two, compendia alone does not guide providers' clinical decision-

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making; compendia serve as one of a number of tools in the community as scientific evidence in support of clinical decision-making.
The majority of oncologists relied on peer reviewed literature while supplementing with compendia. In this study, 13 of the 17 oncologists used USP-DI. Similar to the GAO, many oncologists felt restricted in their treatment decisions by payer policies. The survey also found that payer policy caused them to alter their treatment decisions, similar to GAO findings.
The most interesting finding on this slide for me was this last one, to avoid potential payment denials, six oncologists state that they avoid other off-label therapies that might be eligible for coverage but lack affirmative policy.
Research and science in oncology is moving so rapidly, and you all know this, as a gold standard compendia system was developed in order to reduce the lapse between science and policy. To avoid unnecessary delay, there must be an adequate number of compendia, and these compendia must be updated in a timely manner.
So what is it that PhRMA recommends?
Number one, we would like continued recognition of

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USP-DI under Thomson, especially given the period of transition that we've heard. Number two, NCCN is just one of several compendia that merit evaluation by CMS for recognition and we welcome the opportunity to continue working with the

agency in this area. Number three, identify core characteristics that are important for a compendia. Number five is --
DR. GARBER: I'm sorry, your time is up. Thank you very much.
MS. BRIGNER: Okay.
DR. GARBER: Next speaker, Elizabeth Halpern.
MS. HALPERN: Mr. Chairman, members of the committee, my name is Beth Halpern. I am an attorney with Hogan & Hartson, speaking today on behalf of the California Healthcare Institute. By way of personal disclosure, I own stock in several biotech firms, pharmaceutical companies, and Hogan & Hartson represents several of those firms. CHI represents the full biomedical sector of the California economy and unites more than 250 of California's leading biomedical firms, universities, and private research institutes, in support of biomedical science, biotechnology, and

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pharmaceutical and medical device innovation. As the advocate for California's biomedical industry, CHI is committed to ensuring Medicare beneficiaries' access to much needed cancer therapies. We believe that access to quality care is best protected when coverage and treatment decisions are based on valid clinical evidence. For this reason, we support the Medicare statutory requirement to cover anti-cancer drugs and biologicals for indications not initially approved by the Food and Drug Administration when those uses are listed in the AHFS-DI, the USP-DI or its successor publications, or the now-out-of-print AMA-DE.
In response to the MCAC's list of questions, CHI believes the following criteria would be ideal for any compendia used in Medicare's coverage decisions. However, we understand that given the information available and the volumes of information included in each compendium, each publication may meet these standards with varying success for each drug or indication.
First, just as our members strive to address the diverse needs of cancer patients, the

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compendium must also reflect the extensive range of treatment options available for each form and stage of cancer.
Second, the compendium must keep up with the constant evolution of the standard of care by reviewing and publishing newly accepted treatment regimens in a timely manner.
CHI also recommends that the compendium

use a transparent and consistent application and review process for new and revised listings. This process should use pre-specified published criteria for weighing evidence and making recommendations. The compendium also must announce its deadlines for submissions, and publicly identify the members of its advisory, scientific and review committees.
Fourth, to help physicians and policy-makers understand the basis for each entry, the compendium should provide a detailed description of the evidence reviewed for each listing.
Fifth, we recommend the compendia be flexible about the types of research needed to support an entry, that it include promising treatment options that are being looked at in

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results of relatively small studies. This is particularly important for protecting access to care for rare cancers, where the treatment for those cancers are rarely on the FDA-approved label but often not included in the compendia.
We ask that this panel recommend that CMS quickly work to implement this system to improve access to those areas.
Moreover, because the statute clearly reflect Congress's intent for Medicare carriers to use at least three compendia, including the AHFS-DI and USP-DI or its successor publications, we recommend that Medicare continue to recognize these two compendia and add at least one additional publication to give the decision-makers more choices of evidence to consider in making treatment and coverage decisions.
We also believe that several characteristics identified in the MCAC's questions are not desirable. These are explicit recommendations on the sequential use of therapies, net benefit analysis, explicit stratification of the risks of available therapies, and explicit listing of appropriate combination therapies.

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Finally, we recommend that compendia remain silent when an indication is not supported by sufficient evidence. Thank you.
DR. GARBER: Thank you very much. Now, I need to ask the discretion of the panel again. It is now about 11:30. One option we have is to break for lunch, resume at about noon. I see a lot of heads nodding. Would anybody object to that change in the schedule? Okay. CMS won't like us for going down to the cafeteria this early, but it will work for us. So what we'll do

is resume at noon. We are waiting for the slides to be made from the morning, but just in case they aren't ready, could I ask the people who signed up for the open public session to be back here at noon, the speakers who signed up for the open session. Thank you.
(Luncheon recess.)
DR. GARBER: We're about ready to resume our deliberations, if I could ask everybody to take their seats as quickly as possible. The next agenda item will be the open public speakers. We have five open public speakers, who will speak for two minutes each, and then we will move on to the resumed discussions of Question Number 1 and

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consideration of the remainder of the agenda, panel deliberations and so on. So I would first like to welcome Steve Grossman.
MR. GROSSMAN: Thank you. I appreciate your distributing the short statement so I can impart to you very quickly my comments. My personal disclosure, I own drug stocks, both for my client for this and other issues. I do have drug and biotech clients. I have no particular focus on off-label uses of cancer products. Ultimate efforts to promote research and development of drugs are diminished if patients are not going to be able to access the new therapies or if the level of medical evidence supporting its particular use is not well-known. Thus, being listed in the compendium matters. It is a springboard to reimbursement as well as a tool by which new and innovative therapies gain acceptance.
We are asking MCAC to provide the following directions to CMS. MCAC recommends that the CMS work with patient groups, professional association and compendium publishers to assure Medicare beneficiaries with rare cancers have coverage and access to innovative state-of-the-art

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care on a comparable basis to beneficiaries with more common cancers.
In the statement you will see that our position rests basically on three points. The technology assessment highlighted the lag time and in getting information out and that lag time is magnified to rare cancers and alternative cancer drugs. We're concerned that there is a heavy reliance on random control trials, which we appreciate is appropriate, but we want to make sure that these more rare cases are not ignored because they aren't based on RCTs. And finally, the lack of transparency concerns us because if we can't predict when and where the reviews will

occur, what standards we use or whether all evidence is considered, then we really can't participate in the process and make sure that all indications were considered.
DR. GARBER: Thank you, Steve. We appreciate your comments and we distributed a copy of your handout to the panel members. Next is Ron Walters.
DR. WALTERS: Thank you very much and good afternoon. My name is Ronald Walters, and I am a practicing oncologist in the department of

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breast (inaudible) at the UNC Cancer Center and medical director for clinical operations. I have no conflicts of interest to disclose other than (inaudible) 15 years.
I support the addition of the NCCN compendium to the list of approved compendia for off-label coverage for decisions regarding chemotherapy. As you heard from Dr. McGivney this morning, the NCCN compendium is cancer-specific, expert-driven, evidence-based, timely and transparent in both content and process.
I would like to specifically address some of the issues I heard this morning about the concerns remaining for type 1 error. I think that is a legitimate concern, I agree that there needs to be proper controls put in place for that. If you've ever been involved in one of these consensus opinion forming processes, believe me, the conscientious nature and the purely self-critical nature of people sets in very quickly and type 1 error is extremely minimized. There is also very little concern with type 2 errors. If I'm sitting in front of a patient looking at the NCCN compendium and it's not on there, I should be putting that person on a

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clinical trial if the NCCN is not proposing that therapy.
I would also like to address the silence issue brought up this morning. Frequently, again, this is related to type 2 business, if the NCCN is silent on it, I probably don't have any business considering it.
I'm very tempted by the possibility of formal systematic reviews. Due to the sheer number of diagnoses as well as the rapidly changing environment that we are concerned about, it is important to keep people fully informed. Thank you very much again for the opportunity. I would like to have you seriously consider the addition of the NCCN compendium to the two that are currently recognized. Thank you.
DR. GARBER: Thank you very much. Next

will be Jayson Slotnik.
DR. SLOTNIK: Thank you very much, Dr. Garber, members of the MCAC. My name is Jayson Slotnik and I am director for Medicare reimbursement and economic policy at BIO. BIO represents more than 1,100 biotech companies, academic institutions, state-funded technology centers and related organizations in the U.S.

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For full disclosure, I own no stock in any of the compendia and unfortunately for me, am prohibited from owning any biotechnology stocks.
(Laughter.)
As a representative of the industry that is involved in the discovery of new therapies, innovation and access, BIO understands that the practice of medicine constantly evolves through the incorporation of new clinical evidence into the standard of care. It is imperative, therefore, that CMS and its contractors insure that coverage policies keep up with the pace of innovation and clinical discoveries to allow beneficiaries timely access to the most appropriate treatment options in their battles with these deadly diseases.
Because the statute clearly indicates the congressional intent for three compendia, we urge the MCAC to at least recommend adding NCCN and then to focus its efforts on identifying additional compendia that Medicare carriers should use in determining medically accepted indications.
BIO believes that existing and future use of compendia should continue to represent the versatile approaches of clinical information,

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accessibility and dissemination. However, each compendium should create a transparent and consistent application and review process for new and revised listings such that stakeholders have a clear understanding of how to submit requests for new or revised listings.
Compendia, since they are at the forefront of disseminating critical clinical information, should be continued to allow to employ the full range of validated sources available to inform new listings, including both prospective and observational data, data collected by manufacturers and specialty societies, and data on patient-reported outcomes such as quality of life and patient functionality and patient preferences as informed by patients and physicians.
Given that treatment options for rare disorders are very limited, the compendia should consider looking at putting in place a provisional

system that addresses such circumstances surrounding access to the innovative and new indications for various disorders.
DR. GARBER: Thank you, Jayson. Terri Deal.

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MS. DEAL: Good afternoon. Thank you for this opportunity to speak with you today. For disclosure, I am vice president in the area of policy and compliance at BioMed Pharmaceuticals. BioMed is a small biotechnology company located in the Southern California/San Diego area with about 500 employees. BioMed basically does research development and commercializes treatments for rare cancers and many other diseases. We currently have five products on the market dealing specifically with rare cancers.
I am here today as an example of an innovative small biotechnical firm in support of the National Organization for Rare Diseases, in support of the Biotechnology Industry Organization, and in support of the California Healthcare Institute's testimony this morning. As a small company, BioMed is trying to balance patient access with the need to fund our research and balance our business. Our limited resources are very similar to many other small companies in Southern California and throughout the country.
I researched within our company what people thought about compendia, I went to our medical safety liaisons, to our researchers, and

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tried to determine what people thought about the compendia that are in use today. And what I learned was that it is a black box, that what goes into it, no one is that familiar with, and what comes out of it, we're not sure. So I think the need for transparency is extremely important. We have very limited resources in small companies and so the need for a transparent system or transparent process is important.
I learned that when working with published medically -- when we first published medically relevant information from clinical trials in rare diseases, including cancer, that the time line between knowledge of medical evidence and appropriate off-label use can be greater than a year. This, you heard about this morning from a number of the speakers about that time line.
Well, think of yourself as a patient with a rare disease. That time line is extremely important and so we need to speed up the process a little bit, and make sure when setting criteria that you take a look at the particular situations

surrounding various disorders.
DR. GARBER: Thank you very much.

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Sorry to cut you off because we have such limited time, but the final open public speaker is Jerome Osheroff.
DR. OSHEROFF: Greetings. I'm Jerry Osheroff, the chief clinical informatics officer at Micromedex, so that's my potential conflict of interest. I just wanted to spend a very brief moment expanding on some of the comments that Laurie made trying to expand on the clarifications of how the USP-DI and DRUGDEX actually fare when compared to some of the things that were presented from the EPCs.
First of all, we have an underlying, for all of our content, we have an underlying process, policy, technology and staff that are consistent across all of these products. There's an underlying path whereby we create the knowledge and make recommendations that winds up in these processes. Underpinning that is a very extensive literature review process. We have over half a dozen librarians on staff to develop, maintain and execute a search, and those searches reflect a very robust analysis of the medical literature and include criteria of what pieces of that literature we review and what winds up in the database. It

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isn't that all of a sudden when we look back and when we didn't include them, why we didn't include them. So many of the studies are in USP where we did in fact look at them and we have reasons why we didn't include them in the database for one reason or another.
We also try to organize the results of those studies into what winds up being part of the recommendations, particularly about off-label utilization. So as Laurie mentioned, we look at the literature that has the greatest impact for care and for decision-making, and prioritize that for coverage. We actually have policies dealing with the literature that we have and that we have shared pieces of that with you today.
And then we take that information, include it in the DRUGDEX database and the other databases as well, and as Laurie mentioned, in fact all of the 14 different drug combinations that were discussed by the EPC are in fact in the DRUGDEX product and they are also in the USP. So, we do have these policies and we think if we shared the data that is in those databases, you'd see better how we decide what is to be published.
DR. GARBER: Thank you very much. Now

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we move back to, if I can find my agenda here, let me just explain to the audience that the panel members have now received copies of the votes on Question 1 which will be guiding our further deliberations, and what I thought we would do at this point is finish up our Question Number 1 discussion and then we can pose questions to presenters that will help us regarding our votes on the remaining questions. Okay? So all the panelists have copies of the voting sheets, and these will be made available to everyone in the audience, although I don't know if we can make them available in real time for you. We're going to try to find a way to put this up, though. So, let me read off what the panelists have been explained, the weighting scheme that was used here. In the handout that was distributed are three pages regarding Question 1. The first list gives raw counts of how many people -- oh, it's on the easel too -- raw counts on how many people voted desired, equivocal, and undesired for each of the A through R characteristics. Now the weight of desirability here is -- this is a little -- actually, Steve, do you want to explain? This one weights both the priorities and gives a

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numeric scale for desirability, and Steve can explain that.

DR. PHURROUGH: For each, the desirability, we provided a weighted score times the priority that was assigned to it in the P score and then just added those together. It's a somewhat complicated formula, but again, for each of the three scores, we used the priority weighting for that score, we assigned a weight of two to the desirable, one to the middle one, equivocal, and minus one to the undesirable, so that's how we arrived at these numbers. And then again, we'll make these available in the minutes and in the later publication.

DR. GARBER: So, I'm sorry. There are actually four pages on this handout and what it consists of is scores on Question 1 for all members as just described, then divided by, then just voting members, and the other two are the same things where they are ranked, they are reordered according to the weighted desirability. So the last two pages are just different orderings of the same information.

Now for the panelists, one of the things that we need to decide is if there is some

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characteristics that we do not need to consider in further deliberations, and there are a few ways

that you could go about thinking about this, but if you think it really doesn't matter at all, then probably we shouldn't include it in the further deliberations. Now when it's undesirable, you will have to make a decision to weigh the desirability as a large negative number. You might want to include it in peer review areas if the compendium in question has that characteristic. Okay? So one thing you might think about is low positive scores where there is not a lot of people who said it is desirable, but they said it was equivocal desirability and of low priority, that's probably the kind of thing that we really shouldn't be considering further. So one question is, you may just want to look at whether it's desirable and if the distribution unweighted is desirable or unequivocal and undesired. Mark, did you have a question?

DR. FENDRICK: No.

DR. GARBER: Okay.

(Dr. Phurrough and Dr. Garber held discussion off the record.)

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DR. FENDRICK: I was wondering if you wanted a practical suggestion regarding the undesirability as to at least those most undesirable, since that could change the opinion as to a compendium with equivocal results. I think what that's saying is that the panel, and maybe this will open the discussion, they want a statement of equivocal results stated as equivocal results, and there is no bias in either one direction or the other. You made a point saying, instead of keeping it in the negative, I think at least for the two most undesirable characteristics on the grid, you could make that a positive statement.

DR. GARBER: That it's freedom from bias?

DR. FENDRICK: It's a statement about how the compendia validates the equivocal.

DR. GARBER: But, can you just tell me what change in language you're suggesting? We don't need to be wired to this particular order.

DR. FENDRICK: Correct. I think that we should add a characteristic that basically says how the compendium deals with validated evidence that is equivocal, so there would be no bias when

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validated evidence is equivocal.

DR. GARBER: Okay. So, is everybody clear with what Mark is saying? Rather than have a couple things looking at bias, just making it a positive statement that you consider it desirable

that a compendium be free of a bias in the situation where the evidence is equivocal. That's the proposal on the table here.
DR. OMMAYA: Alan, in other words, eliminate H and I, but keep M; is that correct?
DR. GARBER: I think that's right, yes, H and I, that's correct.
DR. PHURROUGH: Our recommendation was that M is the statement that the other Mark was looking for.
DR. GARBER: So eliminate H and I, and keep M in.
MS. KUEBLER: I would like to make a comment about H and I, because we need to consider subpopulations where the data might not be significant but important, and also, it may have clinical significance, maybe not research significance.
DR. GARBER: Well, I think what you're talking about is how you interpret equivocal and I

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think that would be fair. I'm not sure which characteristic that might alter. Yes, Nancy?
MS. DAVENPORT-ENNIS: One of my concerns that I think we need to consider is we need to define equivocal if we indeed are going to eliminate H and I and we're going to adopt M as a standard. I think from a patient perspective, because we acknowledge that compendia are used as a foundation for making many of the reimbursement decisions around off-label, we don't want to adopt M and then have a definition of equivocal that within the construct of the compendia would ultimately result in less reimbursements for those therapies that might be dinged or identified as equivocal at a time when for that particular disease or stage of disease, that perhaps would be a better option than any other existing option available for the patient. So there is a concern here.
DR. GARBER: Well, I think you raise a very important point. There's just one tactical issue, which is that we've had entire meetings devoted to single topics for which there is a lengthy debate about when it's equivocal and when it is not. Though I think it's an important

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point, what I would suggest is as panelists vote for what they think is right, I don't think we'll be able to get down to a detailed discussion of the general principle of when evidence is equivocal. However, I do want to also add that CMS's guidance document to MCAC discusses evidence in detail, which gives a lot of discussion into this very point about when is there adequate

evidence, when is it equivocal and so on, so I think you might want to keep that document in mind, and that is also available on the web and I hope that you all had a chance to see that. Yes.
DR. CUMMINS: I just want to point out that if we're eliminating H and I and keeping M, we have to make a decision about L, because it says silence, when the validated evidence is equivocal. So if we're saying that we want it to be explicit, then we would have to reject the silence.
DR. GARBER: Yes, that's absolutely right, and I don't know how people voted, but hopefully that's reflected in your votes before. Now I just want to also point out another procedural thing. What was not distributed to you but I do have in front of me is

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the scores by category using the priority weights for desired and undesired. Unfortunately we don't have copies distributed for that, but we can give you those scores and, you know, the discussion of H and I, and K and L actually fit very well with the course that we've established too, because these were the ones where we had more than ten points in the undesired category for those four items. That's H, I, K and L. So let me just ask if we can take a formal vote. I take it, Mark, is that a formal motion, that we strike --
DR. FENDRICK: If you want it to be, yes.
DR. GARBER: So it would be strike H and I, and keep M as one of the criteria.
DR. FENDRICK: And L.
DR. GARBER: Right, strike, H, I and L, and keep M.
DR. PHURROUGH: Can I make one other addendum to that, because I think Nancy made an important point and at least clearly outlined it, but I think it would be highly desirable for compendia to clearly, in its process or methods statement, clearly identify how it, clearly describe how it identifies equivocal, so that

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there is a clear definition in the compendia as to how we categorize something as equivocal. Wasn't that your point?
MS. DAVENPORT-ENNIS: I think that is the real point because with that, we do need to provide to the payers of the country a very clear indication of our process, and I think a broader opportunity for acceptance and reimbursement on behalf of the patients. I would never want to see compendia that from the patient's perspective, I do believe if we could bring them all into this

room today, they would all say make it a living document, make it relevant to my disease today and tomorrow, and do not initiate a set of standards that will not allow flexibility moving forward in the reimbursement process. And I do think that the issue of equivocal is a foundational piece of that discussion, and Steve, I do agree with what you recommended.

DR. GARBER: Okay. So, there's been a motion and I see a second. All in favor of making the suggested change, striking H, I and L, and definitely keeping M?

(Unanimous response.)

DR. GARBER: Opposed?

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(No response.)

DR. GARBER: Okay. Now, I'm trying to amend my copy of the questions. So let me quickly go through the ones that got very high scores overall, and there was a huge amount of consistency between the numbers you have in front of you across voting and nonvoting members, and the ones where we assigned priority scores in the distribution, and pretty much A through E, or A through F all got very high scores by either measure. Does anybody have a problem with saying we definitely keep those as criteria?

(Negative response.)

DR. GARBER: Okay. Now as you see, there is a drop for G, and there are three people who actually gave G undesired. Let me just tell you about the distribution here in terms of weighted priority scores. So this would be the three if you said it was high priority, two if it was in between priority, and -- I'm sorry. Three high, two if it was not very important, and one if it didn't matter at all. And for G, there were 72 points for desired, 14 equivocal, and 8 for undesired, so it appears that the people who gave it undesired also tended not to give it a very

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high priority weight. So by votes ranking, this one also comes out as being fairly high. Is there a problem with keeping G in? And the people who said it was undesirable maybe should let us know if they think it's important that it not be used, or counted as a negative.

And let me make sure we are all on the same page as to what this means. I think it means that when there is appropriate evidence and it shows that it doesn't work or is harmful, that there would be an explicit nonrecommended listing. Is that everyone's understanding of this one?

Okay. Is there anyone that feels strongly this should not be a criteria by which to judge a

compendia?
(Negative response.)
DR. GARBER: So that will be included as a characteristic. Yes.
DR. WHITTEN: When we finished A through E, I know there was consensus on that, but I just wanted to make a comment. First of all, the extensive breadth of the listing, we talked as we went through it that that's clearly a good desirable characteristic of a compendium. But just to be sure there's no misunderstanding, if a

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single compendium met all the criteria and was very narrow in its breadth, let's just say for argument's sake that it dealt only with rare diseases, we didn't vote that in the negative. But I wouldn't want to see it conveyed somehow that because the compendium did not have extensive breadth, it might not still be valuable for treatment. It's a positive criteria, but I'm not sure there should be any inference that these would be a negative criteria in the reverse. Thank you.
DR. GARBER: I thank you for making that point. Let me ask about this. This is one of the tricky things about this, because in the end we're asked to make decisions in Questions Number 7 and 8 that have to do with how many compendia do we need, and presumably your answer to that will depend upon how comprehensive you believe each compendium is. So if we have compendia that focus only on small areas, you might say we need a larger number of those and a relatively small number of comprehensive compendia. So, I'm not exactly sure what's the best way to communicate that to CMS, so if people feel that way, I think we should have a more

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extended discussion about that when we deal with Questions 7 and 8. So, is there any disagreement, though, with what Dick says, that it would be nice to have more comprehensive compendia, but it's still going to be very useful if it meets all the other criteria we have now?
(Negative response.)
DR. GARBER: Okay. So now we move into more contentious territory. We are eliminating H and I, and J is explicit listing of appropriate combinations of therapy. Now I want to go back to my other list that has priorities. For all numbers with J, most people thought it was desirable, there were only two people who listed it as undesirable, or, I'm sorry, I don't know if it was two, one person who gave it a priority in the middle, so there's not much objection to using

combinations. So, do people feel comfortable keeping that question as a criterion?
(Affirmative responses.)
DR. GARBER: Any disagreement? Dick.
DR. WHITTEN: I suspect where people may be uncomfortable, if the interpretation of explicit listing implies that the drug can only be used in the way that it's listed, then you

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probably have a lot more negative opinion. If the explicit listing comes across as several of the presenters gave information, then what they are doing is providing the evidence on an explicit basis, so those who want to use it can look at the explicit issues, and I expect we would get a much more positive view of it. So I think a little bit of it, again, is in the interpretation, but my guess is the majority of the panel would be fairly comfortable if it was explicit for what the evidence showed but not explicit in terms of limiting the use of a specific combination.
DR. GARBER: Maybe we should interpret the question that way. Is everyone comfortable with that?
(Affirmative response.)
DR. GARBER: Okay. So we'll keep that in mind as we interpret the characteristics.
Nancy.
MS. DAVENPORT-ENNIS: Alan, just a very quick comment as to a couple of the ones before that, we are coming from the perspective that it would have to be a comprehensive concept of how we're going to look at explicit listings, because we don't want to limit the off-label application

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in that particular area, so I agree with the analysis that it does need to be comprehensive and it does need to be not limiting.
DR. GARBER: Thank you.
MS. DAVENPORT-ENNIS: You're welcome.
DR. GARBER: So, that takes care of J, K, L and M. N, let me read that again, public identification of the members of the advisory/scientific review committee, everybody felt that was desirable. It didn't get that -- or not everybody, but nobody thought it was undesirable. The weighted score for N was 111 desired, 4 equivocal, and no undesired, and it also got fairly high priority scores. So is there any question putting that on?
(No response.)
DR. GARBER: Okay.
DR. KRIST: You skipped K.
DR. GARBER: Yeah, thank you. I skipped K, explicit recommendations on sequential

use of a therapy or combination in relation to other therapies, and K was divided both by the priorities, 45 desired, 8 equivocal, and 13 undesired. And you see that the overall score was 20, so here there's some division between people

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who thought it was desirable and people who thought it was undesirable, so maybe I could ask someone who felt it was undesirable to express themselves. Alex.

DR. KRIST: I was going to say, I would be curious to see if we might reach more of a consensus if we reconsidered K in the same context that we considered J.

DR. GARBER: We might even consider folding those two together, because they have the same reference to the explicit issue. So, is everyone comfortable with that, we keep that interpretation?

(Affirmative response.)

MS. DAVENPORT-ENNIS: One comment on that, Alan. My concern in reaching the score that I did is the concern that we are now dealing in step therapy applications for formularies, and so that's a concern. When I look at explicit recommendations on sequential use of a therapy or a combination in relation to others, you may indeed have a patient that has an underlying comorbidity that would preclude their ability to be a logical candidate in this sequential use of a therapy, there may be a piece of that therapy that

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may not be appropriate for them. I don't want us to be so specific in what we're trying to do here academically that the role of the treating physician and the patient is completely lost as we're trying to determine what the sequence of therapy is, and therfore I scored that in the low area.

DR. GARBER: Deborah.

DR. SCHRAG: For related and similar reasons, I also scored it low. I think operationally it's just immensely complex and it's not going to be helpful for making coverage decisions to try to figure out what line of therapy, this is approved second line therapy, third line therapy. Simply defining second line therapy is extraordinarily difficult, is it really adjuvant, how do you call it second line, they couldn't get this agent so it's not really second line, et cetera. I think it's really creating an unnecessary mess and that's why I scored it low for CMS.

DR. GARBER: Well, a lot of how you interpret this is going to determine how CMS uses

it to make coverage decisions. And also, these may not be made at the national level, these may

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be local carrier decisions as well. But if this is interpreted that if it's in there, in a compendium that's on the list, it's covered, and it's a little bit hard to imagine a compendium that would say this particular sequence absolutely does not work and should not be used, and treating physicians would want to use it anyway. That's the only way in which I think this would make it hard to get coverage by explicitly discussing the sequence or a combination.

DR. PHURROUGH: I think the thinking was sort of the positive side, if you get it into the compendia, the likelihood of coverage is pretty good. So the more you're able to say this particular drug has adjuvant, second line, first line, whatever the particular terminology indications, versus just saying the only, a more narrow or broad discussion, I think the more information that is in there about the ways it can be used is a positive way, because then you get better guidance and direction.

DR. SCHRAG: Okay, it's an interpretation?

DR. PHURROUGH: The goal is, whether this says that or not, the goal is that if there

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is information on the sequential use, where the drug fits into the time line of the cancer, then it ought to be there, and it's helpful for it to be there.

MS. DAVENPORT-ENNIS: A point of clarity. Is this sequential use currently identified in a number of the compendia that we have evaluated?

DR. PHURROUGH: It is not an uncommon finding to see where they talk about it in various stages of use.

MS. DAVENPORT-ENNIS: So when you affirm that process and cast it in a positive light, certainly it's a benefit.

DR. GARBER: Alex.

DR. OMMAYA: I don't want to belabor the point but when I first read the question I was concerned. It might be useful from a clinical information perspective but not so much from a coverage perspective, and that's why I rated it low, but given the clarification, I think it's fine.

DR. JANJAN: One other issue. As a radiation oncologist, I reference these regularly in terms of, say, preoperative chemoradiation. Do

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the compendia include that, or are we restricting sequence only to a chemotherapeutic sequence? So I was also very confused about this thinking that the coverage might be limited depending on somehow you define sequencing of therapy. So it was just, it brings confusion and if we clarify it in the broad sense I'm more comfortable with it, but unless that broad umbrella of therapy is considered, then I have some confusion about it.

DR. PHURROUGH: Part of the problem I think is that, is your view of the use of the compendium. If a clinician is using a compendia, and I think someone made this comment, they in fact may be more interested in what's the clear evidence for the use in this particular setting of this particular drug but you may want more explicit and more, it may be looked at in a more negative light. In the coverage arena, compendia in almost all instances is a positive guide. It says you don't have to go to a medical literature contractor, just look in this book just like you look at the PDR or FDA labeling and if it's in either one of them, you're going to pay for it. There's obviously a bit more discretion than that, but in general, if it's there, we're going to pay

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for it. So the compendia from a coverage viewpoint is, should be looked at as a positive thing, and I think that's perhaps not necessarily the view that is always looked at outside the coverage arena.

DR. BERGTHOLD: Alan, I read this as, I looked at the word appropriate, and I assumed that you would explicitly list these things in J and K when there was pretty definitive evidence that the stuff was appropriate. And there are gold standards out there, there are lots of standards for what do you use for asthma for example, and there are sequential therapies that are pretty well accepted in the medical community. So I looked at it as if it's accepted within the medical community, the gold standard, that the evidence is appropriate for these kinds of sequences, therefore it should be explicitly describes. Would it help if we added some kind of language around the quality of evidence that supports these sequences?

DR. GARBER: Well, I think, if we go back to criteria D and E about having a published criteria and process, and I'm assuming that applies to sequences and combinations, so that

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would presumably be the idea, that they would apply the same standards across the board. Okay.

So as I heard the comments, people are comfortable with the revised language, and we combine those two into one, and when we get into Question 6, then we will be just rating a combined J and K. Everyone okay with that?
(Affirmative response.)
DR. GARBER: Then we turn to, I think we are on O now. O is public notification of revewers' and committee members' conflicts of interest, including institutional funding sources. I actually have a question about this, and I didn't get to vote. O and P are both about disclosure of conflict of interest, and there are a number of aspects about conflict of interest disclosure, and one of them is if it's disclosed in the editorial process, is there a formal requirement for recusal? So for example if you're a stockholder and you're on a committee for any one of these compendia considering the use of a drug that's produced by a company you consult for or hold stock in, are you required to recuse yourself?
And that doesn't appear explicitly

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here, but we might want to think about just having explicit processes for disclosure and appropriate recusal to insure that the recommendations are perceived as being free of financial bias. Would that sound -- first of all, I want to ask if that is the attempt of these questions and secondly, if that agrees with the direction of the panel.
DR. PHURROUGH: That is part of the intent, yes. The intent in general was to insure that the public, the users of the compendia were aware of any potential biases that may be present in the compendia at large and in the specific reviewers, and that there was a process in place to insure that only the least biased people possible were being used.
MS. GLENNON: Does that mean that if it's only an internal review and not an external consultant review, that those staff members make public their conflicts for an internal report?
DR. GARBER: Yeah, I think that would be the intent.
MS. GLENNON: For all, internal and external?
DR. GARBER: Right. If they are going to have some influence on the recommenation that a

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particular therapy is indicated, that their financial conflicts should not have influenced the decision, it doesn't necessarily mean that you can't participate in the process at all if you have a direct interest in the product being

discussed, but you are not involved in making the recommendations, and that's the intent I think, of virtually all conflict of interest regulations and disclosure requirements. Norm.
DR. KATO: One thing I just thought of is, there may be some difficulty with this idea of disclosure of parent and sibling organizations, particularly when one organization may have a parent organization that's a multinational corporation here, or let's say the NCCN which has 20 different academic institutions as part of that, would that those academic institutions be required to disclose their funding sources.
DR. GARBER: That's one of the reasons I suggested rephrasing the question. I should have known this, and I probably knew it, but I didn't realize until NCCN's presentation, and Stanford University is a member. Obviously there are some limits. I don't think most of us as individuals directly in oncology or something have

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a financial interest in NCCN, so it has to be some kind of reasonable standard, and there are plenty of precedence for this. I personally believe that knowing all your institution's conflicts, if you're in a large institution, is not even feasible, but I think the intent here is if you have a direct financial conflict. Alex.
DR. OMMAYA: Alan, you're talking about adding, that there are policies and procedures in place to manage identifiable conflicts of interest; is that correct?
DR. GARBER: Right, and that they use some standards that are broadly accepted.
DR. CUMMINS: Are we combining those into one?
DR. GARBER: Yes, with this rephrased language.
(Inaudible colloquy.)
DR. GARBER: My original comments were only as to O and P, but it could be, if you want to eliminate N to, I believe that that's going to be the major hurdle that any compendium needs to get over.
DR. PHURROUGH: That's not a good reason to eliminate it.

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DR. FENDRICK: So concerning O and P, talking about revising it, so I'm just crystal clear and concrete, are we saying that on each topic that the compendium reviews, that we want them to list the biases of everyone involved on that topic, or what I saw more in the technology assessment was a compendium listing what their process is for recusing people so that they limit

and prevent bias?
DR. GARBER: If the process is well described and explicit in detail, there is no necessity to individually reach the valuation. If it's vague, then there is a real problem, because then you should say it doesn't meet this criterion.
MS. DAVENPORT-ENNIS: Just for further clarification, as I look at N, O and P, currently we're calling for public identification and public notification. Your recommendation is that there be another step to the process that would essentially identify an appropriate action to be initiated or taken once the disclosure is made and there could be bias from the institution after the disclosure based on the disclosure; is that correct? Because my concern is, it feels like

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we're leaning a bit towards some form of formal regulation so that we can't just notify and inform what those potential conflicts of interest may be, but now we're going to recommend as an MCAC that there is an additional step to that.
DR. GARBER: For many processes, and it is consistent among organizations that if your are making the recommendations, some of the evaluations about a drug, for instance, if you have a direct financial stake, you are considered to have a bias and therefore the recommendation will not be taken with the same weight. And this is true, even if disclosed, that may not be adequate, especially if it's blanket for this whole compendium. So normally that would require recusal. And if the compendium specifies the conditions under which recusal is required, that would meet the criterion. But to say for example in this compendium that these people have all these conflicts with these companies without some sort of recusal process, for someone concerned about having unbiased recommendations, that won't be adequate. I wouldn't call it regulatory, that's fairly standard for this kind of activity for dealing with conflicts.

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MS. DAVENPORT-ENNIS: Thank you for the clarification.
DR. GARBER: Sure thing. So, are people comfortable with leaving in N, O and P, but in a combined way as described?
(Affirmative responses.)
DR. GARBER: Now Q and R had weighted overall scores of 50 and 45. One person, two people thought Q was undesired, and Q is net benefit analysis based on potential harm and potential benefit, in other words, describing

whether overall this therapy is considered beneficial. Yes, Deborah.
DR. SCHRAG: I just have a small motion which is, this is with respect to clinical issues, not economic issues; is that correct?
DR. GARBER: That's correct.
DR. SCHRAG: So my small suggestion would be to add the word net clinical benefit, because this is focused on reimbursement issues, and one of the speakers was addressing specifically the cost issues.
DR. GARBER: Okay. Any objection to that? Dick.
DR. WHITTEN: Mr. Chairman, not an

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objection, I agree with the principle. Mr. Silberman spoke to the issue, and it seems to me that you're in a position to make a recommendation to the agency at several different levels, one of which is the specific criteria for a compendium, and that may well be for the clinical benefit. What I heard Mr. Silberman speaking to was maybe asking CMS also to think at this time about trying to begin to initiate the process of facilitating and encouraging financial data that will enable these issues to be looked at over time, not from the point of view of the compendium itself, but from the point of view of allowing researchers over time to raise some of these cost-benefit issues. I think they are two different issues and I think it might be very appropriate for the committee to look at the recommendation of CMS, what it might do to facilitate the collection, preparation, use of, and long-term analysis of cost data on these things that Mr. Silberman addressed.
DR. GARBER: Well, I think that the purpose of today's meeting is really about using the compendia for off-label uses of cancer drugs, and knowing that it will be used in a particular

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way as specified by statute. As I understand Mr. Silberman's point, not that we're trying to reinterpret the law here, but that it might be good to send a message that it would be good for the compendia to provide this information, independent of dealing with this task at hand which relates to coverage. So I think it would be perfectly appropriate for the panel to say it would be a nice thing for the compendia to include, and I think the compendia have probably given that some thought on their own anyway and maybe they have decided to do it, maybe they decided not to, maybe they decided the time is not right. But to answer our set of questions today,

we really, I believe, we're not, in coming to our answers on those questions, bringing in cost issues in those contexts, because they aren't relevant. Would that, is that what you need from us?
DR. PHURROUGH: That's fine.
DR. GARBER: Okay. Just for the record, Steve said that's fine.
So, are people comfortable with this notion of adding the adjective clinical before benefits?

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DR. SCHRAG: Just for purposes of clarification, it's for purposes of clarifying that.
DR. GARBER: Okay, so it's for the purpose of understanding. Okay. So, are people in favor of keeping Q in, that it is desirable to have some description of that benefit?
(Affirmative response.)
DR. GARBER: Okay. R is explicit stratification of the risk of available therapies. Now this one, let me describe the weighting as being tepidly in favor on this one. The weighted number was 27 desired, 28 equivocal, and 1 undesired, so the person who thought it was not desired also didn't think it was high priority. I think this statement means comparison of what's known here and what's less typical.
MS. GLENNON: I have a question. Does that mean in like some of the examples that we had on toxicity, or does this mean just a general summary?
DR. KRIST: I was going to add to that, because I had a tepid response for sort of the same reason, because if I'm thinking of putting it into the context of the risk and benefits, it

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seems similar to Question Q to me, and so I was envisioning something different, I was thinking of listing of the side effects. And quite honestly, I don't think the compendia has to list the packing insert of all the side effects. I would be more in favor of wrapping R into Q, because it's the same concept and that to me is what's more important for a compendium.
DR. GARBER: Alex.
DR. OMMAYA: In the EU, you are required to weight essentially a level of risk for harm, including the label, and that was seen as a potential improvement for labeling, but it's not yet here in the U.S. I think you're absolutely right that we're covering this topic in another area, but I think that was the focus of this question.

DR. GARBER: While ever mindful of the mechanics of getting through so many, I have to say that I am favorably disposed to rolling R into Q so if the panel is amenable to that, that's what we will do.
(Affirmative response.)
DR. GARBER: Okay, great. We have finished the beginning of the agenda, Question 1.

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DR. BERGTHOLD: Are you going to summarize or are we going to renumber these things?
DR. GARBER: Well, when we do Number 6, Number 6 has a rating for R scores for each compendium. The characteristics that we decided to eliminate, you won't have to rate when we get there, okay? So this might be a good time to make sure that I have these down correctly, or that Michelle and I are in agreement. We eliminated H and I. We eliminated L, kept M. And we kept N, we replaced O and P with having a formal and rigorous process for dealing with conflicts of interest, and we folded R into Q, so we basically eliminated R.
DR. CUMMINS: And we combined J and K.
DR. GARBER: Right, so what I think we should do is cross off K. Mark?
DR. FENDRICK: You may want to kill me now, but I think it's worth mentioning here with all this talk about equivocal evidence, it brought me back to some discussions at the task force, which is, we really don't have, as the NCCN presentation mentioned, one is specifically conflicting, not equivocal data but actual data

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where one trial says yes and one trial says no, and then the task force has to say where the data is. So if we don't conclude they are equivocal, but there's also when they are conflicting and there is also a statement you might be able to make when you're just not sure, which is different in my opinion than equivocal.
DR. GARBER: What I would suggest is that when, even though technically you're correct, I think people should understand that when they evaluate equivocal.
DR. FENDRICK: You made the point about defining equivocal, and I just want to make sure we put on the record that we want to at least have an open discussion of what equivocal means, that it's not the narrow academic view, that it's the broader view.
DR. GARBER: Okay. Do you want a discussion or just make the statement?
DR. FENDRICK: Nancy, I think, stated

that it's prone to misinterpretation, that this is one of these terms depending on which context, equivocal may be used too narrowly, and I think if we use that statement about equivocal, we should basically say explicitly equivocal, conflicting or

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not sure, and that might be an easier way around this.
DR. GARBER: Or nonexistent.
DR. FENDRICK: Whatever the term.
DR. GARBER: Okay. I want to make sure that the panel agrees with interpretation as well.
(Affirmative response.)
DR. GARBER: Thank you. Now what we move into is, actually we are right on schedule now, questions to presenters. So at this point, now, before we start asking them questions, it might be good to refresh your memories about what the remaining questions are, so that your questions to presenters are a target for these. We're going to be asking about how confident are you that AHFS and USP-DI compendia have adequately stated evidence-based criteria and processes. The third question is also, do they adhere to those processes. And the fourth question is, how confident are you about, the fourth and fifth questions are basically identical but pertain to the other compendia. And then the sixth question is going to be where we rate each compendium for each of the characteristics that remain in the fold. Okay?

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So now I would like to open the panel to ask questions of the presenters. I see that the Duke and New England Medical Center presenters are in the second row, available here, so any questions for them? Alex? And by the way, other presenters this morning are for the most part available and you should feel free to call on them if you have questions for them.
DR. OMMAYA: I want to go back to the question I raised earlier, which is if you could give us your perspective on essentially good points and bad points of various compendia that you reviewed.
DR. BALK: I'm Ethan Balk from Tufts. I want to reiterate that because of the process that we went through, that we did not review the DRUGDEX, the full version of DRUGDEX, so my comments are going to be limited to the other compendia. The major differences, I think all of these have been brought up by us and by the different presenters.
I think the most obvious, the unique of the compendia is NCCN, which was the only one that

was set up as a guideline with recommendations, it was the only one set up, organized by cancer, by

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disease, as opposed to by agent, which all the other ones were. It was the only one, at least among the combinations that we looked at, that consistently graded the level of their recommendations.
However, it like all the compendia, did not clearly meet any individual write-up, individual sections, did not base their recommendation or clarify how their recommendations were based on the evidence. NCCD did that indirectly with a statement about the strength of the evidence, but there was nothing that you could look to and say oh, I see there are three studies that said this, two studies that said that, there was no way to compare their statements directly to the studies; even when there were references made, it was an indirect comparison.
USP-DI was the most complete in giving citations, although again, the same issue, that for the most part at least in the combinations we looked at, it was not clear exactly how those citations really had an impact on the recommendation's statements.
Let me see what else I have here. And

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also, I think one of the important questions in theory is how accurate each of the compendium are in terms of accuracy in any sense you want, but unfortunately one of the limitations of our review is we were not able to compare our systematic reviews of the evidence directly to the compendia, so I really can't make a comment as to which of the compendia did better or made more accurate statements about whether a drug relation should be indicated or not.
DR. GARBER: Amy, did you want to make a comment.
DR. ABERNETHY: I just wanted to follow up on that with several points. I need to make it clear that I'm a medical oncologist so I am offering a medical oncologist's thinking about this. I also need to clarify for the committee that while I don't have any financial relationships except for the fact that Duke is an NCCN center, and I do sit on a Duke panel, but that panel does not have any reference to the NCCN panel.
The important statement about the differences between the various compendia and the distinction between NCCN and USP-DI is very clear,

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and our colleagues have already stated this multiple times. It is important when talking about NCCN and thinking about the different compendia that you recognize the advantages of NCCN and the evidence-based guidelines, and so supposably NCCN does develop their guidelines in an evidence-based format and do not always have the ability to transfer that evidence base to their compendia. They do review that, but they do distinguish their evidence and do document their guidelines, and that is directly related to their compendium.

As we look through the other compendia, because I think importantly when you look through your decision making, you actually have , NCCN, AHFS, USP-DI and the other ones currently recommended listed in front of you, and you need to look through all six as you think about it. The AHFS is the one that was the most difficult for us to find the combinations that we were looking at. As a matter of fact, for those that Duke looked at, we were not able to find those at all listed within that compendium. So as a compendium to help us in decision making, we were not able to use that compendium for that role.

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Similarly in Facts & Comparisons, when looking at the referencing for that compendium, we were unable to clearly document their use of evidence and an evidence base that we would normally consider for the EPC.

So we looked at USP-DI and that compendium had the most citations. However, you will see within our evidence review report that sometimes that was inconsistent, they may have had the most number of citations, however, there was an inconsistency both in timeliness of citations as well as the appropriateness of citations such that, for example, when we looked at Taxotere for gastric versus esophageal, many of the esophageal references were actually the gastric references, and they weren't specified clearly that we were looking at a different disease, particularly within this drug disease combination, and so we tried to clarify that within the report.

So as you walk through each compendium, and I tried to do this very briefly, to come back and say that Amy Abernethy thinks A, B and C. I think you can see that NCCN is different from the other five, you can see that there are different uses of citations and different numbers of

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citations and different use of the literature across those five. And in addition, those six

have different volumes of evidence and indications and indication combinations, so it goes back to that issue of sometimes there are ones where they are very narrow, such as AHFS, but it may be important to have a distinction, and then there are ones that are broader such as DRUGDEX where we saw that for the most part, most of the combinations we were looking at were represented. So I think those are some of the differences across the group, and I'm happy to answer any questions as you think about that.

DR. GARBER: Dick ?

DR. WHITTEN: Just to follow up, let me put it in a different way. One of the problems in being able to access things is the currency, and neither of you addressed the currency issue or availability, and since this is web based, I think that availability and currency would be nice issues to be addressed.

DR. ABERNETHY: At least within the group that Duke looked at, NCCN tended to be the most current, although it did have a fairly restricted number of publications with NCCN as far

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as what was publicly available as far as their guidelines on the web, and that was a very important consideration. As we looked across the drug combinations at issue, the currency tended to change, both in terms of drugs and disease combination, and we were not necessarily always able to figure out why, and I wish we had some insight as to why, but unfortunately I can't bring that to you today.

DR. BALK: My only addition to that, it goes back a little bit to the difficulties we had trying to assess how the recommendations really connected with the evidence that was provided in terms of the references. There was great variation across compendia and also within compendia across combinations of how current the most recent citation was, but there was no clear consistent pattern we could find that really made clear to us that the recommendation is necessarily based on older evidence versus more recent evidence, so there was difficulty assessing that.

DR. GARBER: Cliff.

DR. GOODMAN: This question about the inclusion threshold by strength of evidence across the compendia, in other words, across the several

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compendia, which ones had the highest and lowest thresholds for entry of a study or a claim? And the example I would give is which ones are more or less likely to allow in their compendia, for example, a single abstract of a disease treatment,

which are less likely to include that, more or less likely, so which among the compendia, which have the highest and lowest thresholds for entry by strength of evidence.
DR. GARBER: And Cliff's question is predicated on the knowledge that we already heard that you can't make an overall statement, but just based on your sample, did you have an impression about that?
DR. MCCRORY: Let me try to answer that. (Inaudible) correlate what we actually observed. One of the things that severely limited us was the fact that AHFS-DI had so few indications that (inaudible) threshold is fairly high. We wanted to look at the quality of evidence and they listed very few off-label indications so we were unable to really analyze it. We couldn't figure out whether they didn't include it because they thought the evidence didn't rise to the level that they needed or

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simply because they didn't have any evidence available and so they didn't look at it, and that was the purpose of doing our empirical investigation.
The Thomson Micromedex publications, they identified a lot more indications in both DRUGDEX and USP-DI, they tended to describe more off-label indications. The evidence (inaudible) somewhere in the middle, it was difficult to tell precisely. DRUGDEX regularly allowed case reports in certain situation, they listed case reports and other lower levels of evidence that were cited were Phase I, II, and some Phase III studies.
DR. GOODMAN: So the phenomenon of entry into compendia based on having been reported at some meeting one time is an uncommon or common occurrence?
DR. MCCRORY: Well, the ASCO meetings are very, I think a lot of generally very good quality studies reported there.
DR. GOODMAN: They might be.
DR. MCCRORY: They might be, they might not be, but I mean, they're not talking about a lot of the prospective clinical trials, Phase I, Phase II, and sometimes Phase III.

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DR. GARBER: Alex.
DR. KRIST: I actually have a question, but I can mention one thing. I was just kind of tabulating everything with the different compendia and if you look at the number out of these 14 that they recommend for inclusion, AHFS is two, Clinical Pharmacology is eight, DRUGDEX is seven, Facts & Comparisons is seven, and NCCN is nine but

four have kind of an unclear rating, and USP-DI is eight.
And if you're looking at policy and which ones you would combine, and the way the current law goes, only at best, it would be two of these 14 that are covered. If you go back to the way it was before with AHFS and USP-DI covering, there are eight. If you said that all of these were covered, then 12 out of these 14 medications would be covered. So it's straightforward there, but very limited, because we only looked at 14 agents, for whatever that's worth.
I had a question because it seems, and I don't quite understand the law exactly, but I see in the assessment and the introduction material, if I'm reading it right, that USP-DI, the name of that is going to disappear and as

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written into the law, the next publication after that from Thomson Micromedex would also be a covered compendium.
And so I was curious, I had some questions for Miss Moore or Dr. Osheroff about Thompson Micromedex. And one of the first ones I had was, if you could give any insight as to what the plan is going to be, is it going to be a completely new compendium under a new name or are you going to be merging whatever you have in USP-DI, or is it DRUGDEX and DRUGDEX will be the compendium. That's sort of the first one.
And with two different compendia, I would imagine if there are two different publications, it's still going to based on the same information that the two compendia would make their conclusions, and maybe you can comment whether that's true or not.
And then just as a final point, I just want to make sure I understand things clearly. What I heard Miss Moore mention was that the DRUGDEX, that for the tech review they were looking at Drug Points and not DRUGDEX, and so the assessment can't necessarily say whether the references are correct for DRUGDEX and in some

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cases the recommendations may not be the same. I want to clarify that's true, and then maybe Ethan or Amy can clarify that after they do, maybe you can rebut what they say.
DR. OSHEROFF: I'll try to take those sequentially. A comment was made a second ago about the number of drugs that are listed in each compendium. When DRUGDEX lists a drug, we (inaudible) literature about efficacy, assign a level of recommendation to that, and also grade the evidence. That doesn't mean that we're

recommending it for off-label use, but we're accepting it and then through those three parameters we are providing information that can be used to decide if it's appropriate for patient use, or coverage or whatever. So that's an important clarification.
And as I said before and Laurie mentioned, DRUGDEX in fact discusses all 14 of those things and provides different levels of recommendations and evidence ratings and efficacy.
DR. KRIST: Well, when I said the number seven, it was based on you listed it and said it wasn't indicated, or at least based on the tech assessment, just looking through and counting

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up what it said.
DR. OSHEROFF: I think the tech assessment was describing if they found it at all in the compendia, and I think they said seven were found in DRUGDEX, whereas in fact all 14 are found in DRUGDEX.
DR. ABERNETHY: And gave some level of indication information, inconclusive or whatever, and when I speak, I'll talk about that.
DR. OSHEROFF: So in the broad sense about the issue of whether it's USP-DI information or DRUGDEX, you're sort of talking about two separate things, and I'll let Laurie go into more of the details of where things are and where they're going, but to reemphasize the point that I made earlier in my comments, there is an underlying knowledge management infrastructure that Thomson Micromedex has that oversees all development processes. So as of today the ongoing literature review and search, the policies that we use to decide how we're going to survey data, which data wind up in our repository, how that information gets translated into the different products, all of those policies, technologies, processes, the staff are the same across all of

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the Thomson Micromedex offers. Now today, there's two slightly different drug products that result from that, one is USP-DI and one is DRUGDEX. And going forward, I'll let Laurie speak to the specifics.
MS. MOORE: First of all, we are working on a successor product for DRUGDEX, I can't tell you its name yet because that's up to the marketing people. As far as the process, it will be similar to DRUGDEX because as Jerry indicated, the same people will be writing that content. The discussion of products will be more abbreviated, similar to what you see in USP today versus what you might see in DRUGDEX. We actually

survey information and we may sort of abstract out some of the details from the studies that supports that summary. On the USP side, more than likely it will be more of a summary approach, the rating system.
And in getting to the point about including information, DRUGDEX is really meant to be pretty inclusive, so the presence of an observation or indication in DRUGDEX alone should not be used to determine reimbursement, you need to look at the context of that listing, the data

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associated with it, so that we may have case reports in DRUGDEX just for informational purposes to meet the needs of our customer base for that product.
For USP, we may elect to exclude some of those case reports and esoteric stuff that really isn't enough to support reimbursement of the drug concerned.
DR. OSHEROFF: You had raised the question about seven points and what was that exactly. Because of the nature of DRUGDEX and by design, it is intended to be a very encyclopedic formulary compendium, but it is also something that is used by pharmacists and physicians at the point of care. Drug Points is basically a clinically oriented point of care extract of the DRUGDEX, and that's what the folks at the Tufts EPC had looked at.
So because of its point of care use, it does not have the references there, it has only a very synoptic statement about whether it's an FDA-approved indication or off-label, so that's why there were no citations there and why there was no evidence or recommendation or efficacy rating, all that stuff is in the linked

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information in the full DRUGDEX product.
MS. MOORE: It is just a subset of the data that would be included in the others, it is an entry point really into that product or indication.
DR. GARBER: Thanks. We're running a little bit short of time, so try to focus your questions and responses. Deborah.
DR. SCHRAG: I wanted to pursue Dr. Goodman's point about abstracts, and I know a few folks struggled to answer that question, but since you guys are up here, do you explicitly consider meeting abstracts as part of your definition? You said you rely on peer reviewed published medical literature. Is that somehow, and if it's in abstracts, is there an explicit process for doubling back and taking a look at

whether the full publications appear within a specified time frame and have there been any changes. You know, something may appear at first off-label and then it's pulled.
MS. MOORE: Part of our literature evaluation or identification process, we do rely heavily on MEDLINE searches and usual typical sources. We also have our database and restricted

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information which includes abstract information from meetings, you know, ASCO, AMO, other groups that we do track. The way our process works, we don't go back and update it like every year looking at specific topics. Rather, we just follow the primary literature so if we see something come out on a given indication, then we're going to take a look at that and update our database.
DR. OSHEROFF: The searches are incredible. As I mentioned, we have an army of librarians that run them, they're ISI evaluated for inclusion into the databases, so it's not just a hit or miss procedure, so presumably if somebody gets published in the peer reviewed literature, they will pick that up as part of the day-to-day surveillance.
MS. MOORE: Our numbers in this survey are incredible. We actually reviewed the citations and abstracts if they are available for almost 98,000 citations last year. We ended up ordering about 22 or 25,000 of those articles, of which 95 percent ended up in our databases. So we look at a lot and pare it down.
DR. GARBER: Thank you. Deborah.

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DR. CUMMINS: I have a question regarding access to your products, is it by subscription? Can you tell me how that works and how many people subscribe and how readily it's available?
DR. OSHEROFF: Well, most of the customers for the products are health systems, hospitals, organizations like that in North America and actually around the world, but in North America there are three or 400 health systems, so it's a very high percentage, most of the top hospitals, so there is a very deep penetration into health systems.
DR. CUMMINS: I guess what I'm getting at is, is the subscription cost burdensome to a small practice, or would it take a large number of people who might not have the resources?
MS. MOORE: It depends on the product that you're talking about. DRUGDEX is more of the premium priced product and you know, it may not be

affordable to a physician practice, versus USP-DI is a more affordable option.
DR. CUMMINS: And I just want to react to your 98,000. That's, we did 2,000 in the last year at ADA, so that's a monumental number.

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MS. MOORE: It is, and we're not reading all of those, I want to make that clear, but we're scanning that many.
DR. JANJAN: I have a question with regard to that. Am I correct that you have ten advisory board members and at any one time you have four making a decision, with the chair being the fifth, tie breaker I assume.
MS. MOORE: Yes.
DR. JANJAN: So if you look at 25 percent of those 98,000, are you telling me that your advisory board members look at those?
MS. MOORE: No, no, no. And out of those that we scan, we pare it down to 22 to 25,000 of those total. Our internal staff reads those and analyzes them, and what goes out to our board members is essentially a book. It contains our detailed analyses, statistical design analyses, our summary information, our sort of abstract if you will of the data, as well as a copy of the primary literature and a number of articles that they would review, which may range from three or four to maybe eight or ten, depending on what's available. Information that we've gotten back from our board members is that

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it's pretty easy for them to look through all that information and make a determination. Our turnaround times are pretty fast from the board, so once we do our analysis and get the information out, they typically get it back to us within a month or two.
DR. JANJAN: What are your criteria for recusal?
MS. MOORE: Our conflict of interest policy is three-tiered, we have looked at the policy in the industry to develop this. For involvement less than $25,000, it's nondisclosure; 25 to $100,000 will require disclosure; anything over a hundred, regardless of the source, the individual can't be on our boards. And for assigning topics to board members, we do look at those, every single time we look at those potential conflicts and we do not assign a drug to an individual who may have some type of stock or financial interest in the company, and each of the members are required to do periodic updates.
DR. GARBER: So let's say you have a $30,000 speakers bureau deal with some drug

company. Would you or would you not be a member of the group that's deciding on a drug sponsored

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by that company, or indication, would you be automatically excluded because you have this conflict?
MS. MOORE: We would typically exclude, but we leave the window open in case, there are going to be situations where you have an individual who possesses an identifiable skill set that would be difficult to find, so we leave that door open, but we have not taken advantage of that.
DR. GARBER: Is there a way for a reader of USP-DI or DRUGDEX to know on a particular recommendation whether this situation had arisen, that is that a person had a conflict but because they had this specific expertise, they were included in a decision process about whether this off-label indication was appropriate?
MS. MOORE: We are not disclosing at the individual indication legal, so what we do disclose with the board members on the web site is their potential financial conflicts. However, an individual who may have an interest in knowing who reviewed a particular indication, we will provide that to them if they request it.
DR. GARBER: Dick.

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DR. WHITTEN: One of the questions the panelists will be asked is, how confident are you that USP-DI adheres to evidence-based processes? As I understand when you put up your slide on the old versus the new process, you went from a situation where you had a requirement for unanimous consent to, if I understand correctly, what is now a panel of four, and basically you need three of those four, or two plus the medical officer, something of that nature, to make a decision. That seems like a fairly radical change in the process, which I gather took place fairly recently. And then if I understood correctly, you said this process is going to move again to that of DRUGDEX. So just from the point of view of consistency of the process, what's the assurance of closer to unanimous agreement that you used to have, what kind of assurance can you provide?
MS. MOORE: The process that we have in place now is the process that we intend to take going forward for both DRUGDEX and for the USP-DI. The requirement of four, we just felt that was a reasonable number to take a look, and really we're trying to let the literature drive what we present. We truly are. As far as the true

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evidence-based question, we're not doing a full meta-analysis for each indication, it's just not feasible for us to do so, and it is very time consuming in doing that.
DR. OWEN: If we make a recommendation whether or not something should be covered or recommended for use, there's two pillars that underpin it. One is the human expert and the other is the weight of the evidence, and often times neither are appropriate. So the USP-DI was looking at the literature and then a whole bunch of experts had to agree that it was something that should be used.
What's happening in the processes now and going forward is there's a much more stable foundation of evidence analyses, so the grading of these three things, the strength of the recommendation, the use of the agent, the analysis of the evidence according to a multilevel hierarchy, yields a much stronger evidence foundation. So, we were able to pull back some of that whole bunch of people to read every proposed indication, so hopefully that explains some of the evolution in the making of clinical recommendations.

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DR. GARBER: I just want to point out that we have, in addition to the two compendia representatives, there are four additional entities we will be voting on, and if you have questions that you want to put to the people representing the other compendia, that's fine.
Nancy, do you have a question?
MS. DAVENPORT-ENNIS: I have a question for Dr. McGivney from the NCCN. We heard a fair amount of discussion this afternoon concerning the process of how evidence is being evaluated, and earlier in your comments from the podium you referenced your 46 guideline panels and the disease-based analysis that you followed. Can you talk with us just a bit about the evidentiary process used by NCCN.
DR. MCGIVNEY: I would like to reemphasize, one of the points is that we, our expert panels number 15 and 22, and are mostly interdisciplinary, and they are looking at the continuum of care so they are looking at the vast management options such as therapeutics, et cetera. And you know, basically for each decision, there really is a risk-benefit analysis, and evaluation of net health benefit.

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Specifically with respect to evidence, what happens is we typically schedule a formal

in-person panel meeting after ASCO, so that all the latest data is available. Our staff collects that data and additionally, the panel is asked to submit specific articles for consideration. Additionally beyond that, each institution circulates the guideline, the existing guideline, and asks for input beyond the experts that are already on the panel.
So again, you know, you get input from a radiation oncologist, a clinical oncologist, a medical oncologist who don't sit on, say a breast cancer panel, they feed it in. And all that serves as a basis for the opening agenda, with specific recommended changes attached, specifically with evidence of new articles or new abstracts that might suggest that the guidelines be updated with regard to a specific recommendation, something needs to be changed, something needs to be highlighted, et cetera, so it's a fairly continual literative process that goes on.
One other point clearly that might be considered an advantage for us is not all the

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time, but very often when our panels are sitting there discussing, you know, the latest results of what's coming out, very often we have principal investigators on the national and international scene sitting on our panels. So even before these have been even submitted in abstract form, they are aware of the results and it is certainly a confidential forum that they have.
The other point too, our process is open to provision of data and results and comments by outside groups, be they any of the constituencies that should be interested in what the recommendations of the NCCN guidelines or NCCN compendium are. So as I indicated before, the data and comments are submitted to the community physicians, academic physicians outside of NCCN, patient advocacy groups, industry, et cetera. So it really is a broad-based process, an open process in terms of reception, evaluation and analysis of available data.
And then I think quite frankly, I do think that the process that they came up with for the exclusive exhibition of the underlying evidence and the expert judgment and uniform consensus that underlies each recommendation and

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guideline is indeed a simple yet eloquent communication of what the panel has done.
DR. CUMMINS: Your network of cancer institutions is certainly a strength in this case and this area, but could you say something about

your process of potential conflict of interests and how you deal with that issue?
DR. MCGIVNEY: Specifically right now for example, we publish it, so if you went on-line for the 2006 version of NCCN guidelines, at the end of the guidelines there is an explicit exposition of the potential conflicts of interest, the traditional ones we all talked about today, the pharmaceutical or biotech companies, and Blue Cross Blue Shield is one I just looked at. Additionally when we publish them in our journal as well, we do list aggregated companies and others, and relationships that might represent a conflict of interest, and these are published. Before each meeting, just as you did here today, the guideline panel sits there and they go around and they communicate again and update each other on what their potential conflicts of interest are in terms of their relationships are with pharmaceutical or biotech

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companies. These are all recorded and published later, and it's just a communication as to whether he should recuse himself entirely from the meeting or for discussions of particular issues. And I would say that recusal is extremely rare. Again, when you have a panel of 15 to 22 world leading authorities, they cannot be shrinking violets, who tend to, again, represent subspecialties very strongly, who tend to know the data cold and they tend to argue extremely vociferously about important points, eliminating any bias is impossible, but certainly I think this serves to diminish it to a great extent. But again, I think that any organization involved in this, and we're looking at it on an ongoing basis, we just had a discussion about it at our last board meeting, and we will submit this to our governance committee for further review, as to what NCCN is presently doing to communicate to any user of our information products the potential for bias based on the relationships our experts have with companies out there.
DR. KRIST: How do you feel about the bias of having the investigators involved in the

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study on your panel? I agree with that, but having done some studies myself, investigators tend to be wedded to their ideas. How do you deal with that?
DR. MCGIVNEY: Yeah. Well, again, I think it's diminished by the, first of all, I mean, evidence rules. Second of all, they are diminished by the discussions these individuals

participate in. Believe me, as I say, individuals who are familiar with specific studies are not shy about criticizing either the methodology, the power of the study, communication of results, whatever. So it is an advantage that I think outweighs the disadvantages, but I see your point.
DR. KRIST: You also said that for a lot of these studies, the data is not out, so there is only one person who has the information.
DR. MCGIVNEY: One or two, yeah, but many of these studies do emanate from cooperative groups, so there has been broader participation, for example, in the design of the study, in the prioritization of the study, et cetera, et cetera, et cetera.
DR. KRIST: And how about the data?
DR. MCGIVNEY: They may or may not have

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the data, no, but that is certainly a valid point.
DR. GARBER: Bill, if I could just make a comment, your answer is excellent and I think that both you and the Thomson people have made admirable efforts to insure the proceedings are free of conflicts. But I do have to point out that neither of you have developed your products, or in your case guidelines, specifically to guide coverage. And the standards that are typically applied in coverage situations are a little bit different from, say, guidelines situations where for example, I was sitting on a Blue Cross Blue Shield panel, and if I had some financial interest in companies that were being discussed, disclosure in that case is not sufficient, I have to recuse myself from the entire scene.
And similarly here, this particular assessment that we're dealing with today is very unusual for MCAC, this is not really about a specific product, so the conflicts application turns out to be a little trickier. So, do you have any comment on how NCCN based on the compendium, how you would handle a conflict?
DR. MCGIVNEY: I think it would be at the level they participate, but I think

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specifically we, as I just indicated, we are looking at this issue. You know, in terms of oncology, there is a very explicit individual investigator-based disclosure at the end of every article that we just talked about, in terms of actual level of dollars received by the companies. We are looking at how close to that we should get right now and that's actually irregardless of whether or not it will be taken to the compendium, because obviously having run a national coverage policy program, it's important to that, but I also

think every physician that's making a treatment choice for his patient, I think it's extremely important as well. The other point I would like to make too is interestingly, the guidelines clearly direct the clinical professional disease based, they cover the continuum of care specifically. So actually, our drugs and biologics compendium was developed specifically and directly to take those guidelines and put them into a format that payers used, be it the federal mandate or the mandate for the 39 state laws. So actually that's why it's so critical that there is this understanding. And what we did was we went to the

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payers, and the feedback we got was, we used guidelines, but if you could specifically delineate appropriate uses so the evidentiary standard right next to it with the recommended uses, this would be a very useful and important format for payers, and so that's why we did it and that's why it's so important. And we always tie that back to the guidelines and the discussion of risk profiles and the discussions as I say, I would call it therapeutic index, but you know, net health benefits, et cetera, et cetera.
MS. KUEBLER: One comment. Is my understanding correct that the NCCN does not differentiate between the FDA and off-label?
DR. MCGIVNEY: Well, basically I guess the answer to that is yes. Basically we specifically list what the FDA-approved indication is in the compendium right next to the NCCN recommended uses, so someone could compare directly what the FDA label is with what our specific recommended uses are for a very specific subpopulation of patients. The other comment I would make as an editorial, because I'm writing one right now, the issue to me is not off-label, it's off evidence, on evidence or off evidence.

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But anyway, the answer to your specific question, the FDA labeled indication word for word is listed right next to the NCCN recommended use, so it can be compared directly to each other.
DR. GARBER: Okay. This is the last question, and then let me make a suggestion. I'll let you ask your question, Alex, but we've kind of gone over into the time that we need for the voting questions. I want to ask if the presenters will be available, because I think it may be useful to ask them questions as we consider each individual voting question, so, can the people who are here representing the different compendia stay longer? Okay, great. So Alex, your question, and

then we will move on to the voting questions.
DR. OMMAYA: I just want to say I very much appreciate the presentations by the various compendia and find this very helpful, but just out of fairness, if we could maybe get from the other two compendia, Facts & Comparisons and Clinical Pharmacology, what do you think are the unique strengths of your publications?
DR. HOCHADEL: MaryAnne Hochadel. I think our unique attribute in a healthcare system is actually the way we positioned our data around

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some fairly unique indexing and also in our editorial process in terms of efficiency of the updating process, and that has occurred just really recently within the new system within the last couple of years and in particular since I have been editor-in-chief.
And what I mean by that is at any given moment, a physician could come into our system, for example, look for a disease state that they're interested in treatment, get a list of drugs, they could see very clearly by our citations whether that drug is used on label or off label. They could seek more specific information, or they can go into some advanced reporting features around the standardized formatting and indexing to say I've got an elderly patient with breast cancer who has this attribute in terms of his disease or her disease, what are some of the treatment options considering those conditions and some of the unique features of that patient that he may want more information for.
So I think in the context of that information, the way our database is set up, we are really speaking to the fact of how do you want your data to be used in the compendia and where

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would it be most useful in the healthcare setting. I think that's one of our unique attributes. And the other thing is our real-time editorial process which allows us to benchmark content on the backside in terms of date time stamping, which piece of information was actually touched, how long was it from point A, discovery of the need for update, to actually available for our users in the public. I think those are two very important features.
DR. OMMAYA: Thank you.
MS. DIVVELA: Our strengths are that we have been a standard in the drug information industry since 1945. We have been the primary reference for pharmacists. Our biggest strength is our comparative information, individual drug information that includes the off-label use along

with all other information you need regarding drug information, but also class information. So you can look at one drug in a class compared to another drug in that class.
Also, our timeliness. We have always updated monthly in our loose-leaf publication and our on-line version we are moving to a continual update. Our electronic Facts & Comparisons 4.0,

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you not only get the Drug Facts and Comparisons, but access to our Off-Label Drug Facts and our Cancer Chemotherapy Manual, so with one search you can go to whatever resource best meets your needs.
DR. JANJAN: Do you correlate those data among the three different products? How do you make sure that a new piece of information goes into all three products?
MS. DIVVELA: For Off-Label Drug Facts and Drug Facts & Comparisons, what stimulates an update in Drug Facts & Comparisons right now is a change to labeling information and FDA action, major warnings that come out, et cetera. And at that time the entire monograph is reviewed, including the off-label use information, and that's when our clinical editors do evaluate the primary literature not only for labeled uses, but they're also looking at how that information is presented in off-label indications, which is the one that has the rating scale of one to five, that's how off-label drug information is rated. And the fours and fives need more information or aren't safe, and those aren't included in Drug Facts & Comparisons, but the ones, twos and threes typically are included in Drug Facts &

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Comparisons.
DR. JANJAN: Do I understand that it's only an FDA change?
MS. DIVVELA: No, that's a main source for updates to Drug Facts & Comparisons. We also, if changes, the Off-Label Drug Facts is updated on a quarterly basis and when one, two or three get added to that, our general policy is that the off-label use will be added to Drug Facts & Comparisons at that time as well.
DR. GARBER: Thank you. Let's move on to the next agenda item. These are the voting questions. Number 2. How confident are you that the AHFS and USP-DI compendia have adequately stated evidence-based criteria and processes? Let me add that you should feel free to call representatives of the compendia for questions, but also please be mindful of the time. We could go into tomorrow if you want to get the complete explanation for these compendia and

unfortunately that's not going to be feasible. So please be very direct and pointed in your questions and we'll try to move through these. Cliff.
DR. GOODMAN: A question about how to

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interpret Number 2. You refer to adequately stated evidence-based criteria and processes. Do you mean that whether they are good evidence or bad evidence or processes, they've explained them very well, or does it mean they are solid evidence-based criteria and processes?
DR. GARBER: Well, let me get my notes that I had with staff.
(Inaudible colloquy.)
DR. GARBER: If you find that they clearly talk about what they did, but you didn't find that it was evidence-based, then you would give it the low rating on Question 3, but Number 2 is only about, can you determine what process they used based on the materials that are available.
DR. GOODMAN: So two is transparency, and three is the quality?
DR. PHURROUGH: But two is not a transparent bad process. If they have a process that is evidence based and a process that is used properly to arrive at a correct answer, so it's not just that it's a transparent process but a transparent good process.
DR. KRIST: And isn't three whether they stick to their process to do what they say?

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DR. GARBER: Based on Steve's interpretation, that's the only way it can work. So Cliff, I guess Steve is telling us we shouldn't interpret it the way I said. The second one is, are they high quality and also explicit, and then the third one is do they adhere.
DR. FENDRICK: And for two and three, are we going to be voting separately like in four and five? I think the cards suggest that we're going to be voting on each compendium separately.
DR. PHURROUGH: Yes. How confident are you that independently each compendia have, not combined.
DR. FENDRICK: Because they were both under the original statute, it could have been interpreted that they remained, but we're evaluating each of them separately, okay.
DR. GARBER: So, are you ready to vote or did you have further discussion or questions concerning AHFS or USP-DI? Okay, so after you give these ratings, one, two, three, four, five, display them in the holder.
(Panelists displayed votes which were

recorded by staff.)
DR. GARBER: Just for clarification,

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but when you looked at USP-DI, you should answer in terms of its current formulation, not your guess about what the future will be but the current USP-DI, what was the date of the report?
DR. ABERNETHY: The date of the report, the last evidence review was the end of January.
DR. GARBER: Okay. You can pass them to the right. So Question 3 is again, just to reiterate this one, it's about how confident are you that they adhere to the stated process, and that means good or bad, right, that's your interpretation.
(Panelists displayed votes which were recorded by staff.)
DR. GARBER: Okay, and pass them to the right. Question 4 is four compendia -- I apologize to the audience, you think you had trouble reading the last one, this is really going to strain your eyes. Four is the confidence that compendia other than AHFS and USP-DI have adequately stated evidence-based criteria, with separate ratings each for DRUGDEX, Facts & Comparisons, NCCN and Clinical Pharmacology. And I just want to add that you should feel free to ask any of the speakers if you have questions

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before you vote. I'm not trying to rush this through without you having adequate information.
(Panelists displayed votes which were recorded by staff.)
DR. GARBER: Okay, you may pass them to the right. Now Question 5: Again, considering each separately, this is analogous to Question Number 3, how confident are you that they adhere to the stated process in making their recommendations?
(Panelists displayed votes which were recorded by staff.)
DR. GARBER: Has everyone displayed their card? Okay. Please pass them to the right. Now, I believe that copies of the revised voting Question 6 have been distributed to the audience, excluding the characteristics that were not important enough to include in our evaluation of the compendia. And for six now, we're going to give a different score, well done, uncertain, or not well done, for each characteristic for each of the compendia.
DR. OMMAYA: Alan, could we go through seven, eight and nine first?
DR. GARBER: How do the other panel

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members feel about Alex's suggestion?
(Affirmative response.)
DR. GARBER: I see some nods, so we will do seven, eight and nine, and give the panelists a chance to rest. Okay. Seven, do you believe that the interests of the Medicare program and its beneficiaries are best served by having a particular number or type of available published compendia on the off-label use of anti-cancer drugs and biologicals for cancer treatment?
(Panelists displayed votes which were recorded by staff.)
DR. OMMAYA: Can you define particular.
DR. GARBER: We will, but you should have asked that before you voted.
DR. FENDRICK: I'm still okay.
DR. GARBER: So, do people want to revote and have a discussion first about what this means? If you have serious doubts what it means you should discuss it rather than just vote. Well, let's -- yes.
MS. GLENNON: I would like you to define type, because I would assume type has been discussed, but I was thinking more numbers, that we would have a minimum number and a maximum

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number, if that were the question. So we're looking at number and whether they include all the criteria that we have deemed important already?
DR. GARBER: Well, Steve, eight clearly is intended to follow on seven. Seven is intended to say if you answer yes, then there needs to be a specific number. Now as we discussed before, if your issue is you think in aggregate that the compendia need to be comprehensive and the number is not so important, then probably you should answer no to this one. If there is no specific type, but there is a specific aim that needs to be achieved, i.e., comprehensiveness, because if the answer is yes to seven, then you need to answer some numbers in eight.
DR. FENDRICK: What if one's allowable, then that statement doesn't hold, if there's a singular comprehensive compendium, you could still answer yes to that question.
DR. GARBER: It's not very helpful to CMS to say that we need at least one.
DR. FENDRICK: The way the question is written, a singular comprehensive compendium, you would vote yes, the way the question is written.
DR. GARBER: So you could answer yes,

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and one on eight, that's true.
DR. FENDRICK: I would interpret a no

vote to Question 7 if you do not believe in any compendium. That's what I read that question to say, and if there are in any lawyers here, you might help me out, but if you believe in one compendium, then you should answer yes.
DR. PHURROUGH: Okay. Let me tell you what we thought we were saying, regardless of what's written here in words. Should we aggressively attempt to insure that the compendia that are used to assess the use of anti-cancer drugs are sufficient in scope, type and numbers so that all of the characteristics that we are concerned about are met? For instance, if there is a rare orphan drug compendium that covers drugs that aren't covered in the other compendia, is that important? Or should we not go to that extent in our attempt to be aggressive about identifying a broad range of the compendia to identify the separate classes. That was the goal of that question.
DR. FENDRICK: So with all due respect, if there were a singular perfect compendium, you would vote yes to Question 7. So listening to

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what you said, so the chairman and I are disagreeing then. What you said if you find one you would vote yes, even if it's singular.
DR. PHURROUGH: We would then be investigating to see, does this single compendium answer all the questions.
DR. FENDRICK: And then we would vote five for all the attributes that we just voted on, or we will vote on for Question 6.
DR. PHURROUGH: Yes and one is an acceptable combination, I think, not a preferred combination, but it's acceptable.
DR. KRIST: In addition to the cards here, will we still have an opportunity to say what we think?
DR. GARBER: I think that will be helpful, very briefly, and we're going to role up seven and eight. So give your reasons and state both whether you think there needs to be a specific minimum or maximum number, state what they are.
DR. WHITTEN: It is exactly this confusion that some of us have. I think the way CMC should ask the question for what we're trying to achieve, the number should be flexible to be

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able to obtain certain criteria. CMS should set the criteria it wants to obtain, which is exactly what Steve mentioned, to be able to cover the breadth and the depth that's necessary. But if one of them all of a sudden doesn't have an

ethical statement or something else, then the number should be able to be flexible. So the idea was, I think what needs to be done is to set the criteria CMS wants to obtain over a period of time, because what's happened in just the last couple of years, this market is flexible, so rather than set a set number, I was just wanting certain criteria, and that's why I said no to the specific type or number.
DR. BERGTHOLD: That's exactly, independently of him, that's why I voted no, because I think CMS should have the flexibility. And I also think that the reason we have certain compendia in the law, I think that makes it very inflexible for CMS, and it's a product of industry lobbying, so I would encourage the flexibility of CMS.
MS. KUEBLER: I voted yes, that we should have a particular number and type with a minimum of two and a maximum of three.

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MS. DAVENPORT-ENNIS: I voted yes, and I certainly think that the minimum needs to be what the statute of 1993 calls for. We currently have two, I think our nation needs to have three to satisfy the statutory recommendation. Are we answering eight at the same time?
DR. GARBER: Yes.
MS. DAVENPORT-ENNIS: And I do think that the word type for me, as an English major reading that question, Mark, was a very important element in the question, because I think your point that we do need to lend the agency the flexibility so that when new ideas are presented or concerns about the population, we need to have a vehicle available for them to be included.
DR. FENDRICK: It's nice to sit next to someone who speaks English.
(Laughter.)
DR. FENDRICK: I agree with what you said in that all the compendia have to be good, and I would like at least two because one makes me uncomfortable.
MS. GLENNON: I answered no because I don't think there should be a set number, minimum or maximum.

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DR. JANJAN: I answered yes, but in the sense that we think, I think CMS needs to have a certain number of criteria to compendia or for compendia to evaluate. I'm not opposed to a single compendium and as we look at homogeneity of care to insure quality, it is very confusing to physicians who have so many different choices. If we're going to go for a single quality measure,

then it might be worthwhile to also have single criterion set up for use of these medications, albeit by a very respected group that looks at these in a very critical way. So I wouldn't be opposed to one but I would prefer to have more than one, and I think you need to have three for a tie breaker.
DR. OMMAYA: I answered yes, with two as a minimum and four as a maximum. You also have to have the ability to present published evidence so that it allows use and flexibility. But you need some quantification on them to get some clarity among the processes and also agreement among the payers.
DR. KATO: I voted yes because I believe that there have to be some guidelines someplace that identify which drugs can be used in

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what situations. I'm in favor of the market allowing these compendia to compete. Therefore, I like the idea of having three as a minimum, just as a tie breaker, and I put down a maximum of five plus, because I don't think we can identify and regulate how many compendia there may be, and as said before, there may be a need for orphan compendia at some point for a small number of drugs, but with data given in depth. So I would say minimum of three and let the market handle the rest.
DR. FOLEY: I voted yes also, and I stipulate a minimum of three. Somewhat similar to what Norman said, the max should be based on the criteria that is set, and if there are other quality compendia that will meet those criteria, then they will benefit.
DR. GOODMAN: Today and in the near future, no single compendium captures all of this desirable criteria but as a small group they may. Therefore, for now, I vote yes for at least three, no more than four or five, but eventually, if the market adjusts, one or two would do.
DR. MCDONOUGH: I think there should be a specified type and number of compendia. I

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believe in terms of type, we need to evaluate the quality of the compendia. And certainly in terms of the quality from a practical standpoint, it would be unwieldy to have numerous compendia, competing compendia, so you might say an upper limit of six is somewhat arbitrary, but we need to have some upper limit.
DR. SCHRAG: Again, in view of what's already been said, I think three is reasonable as a minimum and I think an upper maximum should be set with practicality, but to foster and encourage

competition among the various compendia to improve and upgrade their quality. And I think the key thing is a specific indication of the criteria is very clear and then you know, consistent evaluation of how the compendia are meeting those criteria. Add to that that each of them we heard from today have a slightly different rating scale or set of adjectives, or one, two, three meant to say acceptable, recommended, not recommended. We should see consistency across compendia, and it would make it much easier to compare them.
DR. CUMMINS: I voted yes and I specify one to any number of maximum. I think as long as they meet the criteria, that's what is important,

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and as long as CMS specifies what the criteria is, so that it can be inclusive of the rare disease types as people have spoken to today.
DR. KRIST: I'll echo the thoughts of everyone around me, I think peoples comments were very good. I voted yes, but my basic philosophical grounding was that I thought that if a compendium met the criteria that was specified, that should be the basis for deciding whether it's included or not. I think there are also practical realities in the way compendia currently are, it has to be more than one just the way they currently are. But I have a little concern that I'll just raise with the maximum number that people mentioned, because also looking at the practical reality of the way compendia currently are, you know, if you have these five, 12 of these 14 agents are covered. And so you'll hit a ceiling where you might as well say everything is covered for off-label use and just forget this whole process, but that's my thought.
DR. GARBER: Thank you, everyone. Let me just make a suggestion. Question 9, I think really very logically follows after you have gone through Question 6. That is, how confident are

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you that prescribers can rely on currently available published compendia to determine appropriate off-label uses of drugs and biologicals for anti-cancer chemotherapy?
We don't want the panel to consider any compendia that we haven't discussed today, so it's only the ones we've discussed today. So we will be going through these compendia characteristic by characteristic as you do Number 6, so, is there any objection to holding Number 9 until after you have done Number 6?
(No response.)
DR. GARBER: Take a deep breath. Would people be comfortable in doing them all row by

row? I mean, you're going to, you've got a separate card for each row. Do you want to just sit down and do them all and pass the whole stack to the right, or would you rather pause and discuss for example individual questions? Is there going to be any discussion, by the way? Do people have questions or points that they want to make before we proceed to voting on Number 6?
DR. GOODMAN: Maybe you could ask that question for each of the characteristics, A through K.

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DR. GARBER: That's fine. So let's do A first of all. If everyone's done it, please display your card.
(Panelists displayed votes which were recorded by staff.)
DR. GARBER: Actually, I don't believe anybody will be able to read these anyway, so you might as well pass it to the right when you're done.
DR. PHURROUGH: We will publish a summary of these either later this evening or first thing tomorrow on our MCAC web site.
DR. GARBER: Then after you're done, we move on to question B. Are there any questions on B?
(Negative response.)
DR. GARBER: Please put your scores down for B and pass them to the right.
(Panelists marked votes and passed them to staff.)
DR. GARBER: C, detailed description of the evidence reviewed for every individual listing. Any discussion?
(Negative response.)
(Panelists marked votes and passed them

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to staff.)
DR. GARBER: Move to D, use of prespecified published criteria for use of weighing evidence.
(Panelists marked votes and passed them to staff.)
DR. GARBER: E, use of prespecified published process for making recommendations. Please pass your Es to the right.
(Panelists marked votes and passed them to staff.)
DR. GARBER: F, publicly transparent process for evaluating therapies.
DR. GOODMAN: I'm sorry, I have a question on this one, the process described in a transparent way or the process is conducted transparently so people can participate, watch,

listen. I'm not sure.
DR. GARBER: Is the process described in a --
DR. GOODMAN: Publicly transparent means you can look up it up and it's described very nicely, or people can actually participate, sit in the room. The former?
DR. GARBER: Yes, I think -- yes, Steve

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says it's the former.
DR. GOODMAN: Okay.
DR. GARBER: If you're done with your Fs, please pass them to the right.
(Panelists marked votes and passed them to staff.)
DR. GARBER: G, explicit "not recommended" listings when validated evidence is appropriate. Pass your Gs to the right.
(Panelists marked votes and passed them to staff.)
DR. GARBER: H, and this is one of the characteristics that we combined. H is explicit listing and recommendations regarding therapies, including sequential use or combination in relation to other therapies. And pass your Hs to the right when you're done.
(Panelists marked votes and passed them to staff.)
DR. GARBER: I, explicit "equivocal" listing when validated evidence is equivocal. And you'll recall from our earlier discussions that this includes equivocal evidence as well, so it's sort of a class category.
(Panelists marked votes and passed them

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to staff.)
DR. GARBER: J, this is the conflict of interest one. It's phrased here, 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. And I would insert rigorous between established and procedure.
(Panelists marked votes and passed them to staff.)
DR. GARBER: Okay. K, net clinical benefit analysis based on potential harm and potential benefit.
(Panelists marked votes and passed them to staff.)
DR. GARBER: Well, we have time for a very serious discussion now of Question Number 9. This is, again, the question about the overall

compendia as a group, not about any single compendium. That is, how confident are you that prescribers can rely on currently available published compendia to determine appropriate off-label use of drugs and biologicals for

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anti-cancer chemotherapy? And again, this pertains to the compendia we have heard about today, not ones that we haven't heard anything about. So please put a score from one to five here and display your card in the card holder, with five being very confident and one is very unconfident.
Do you want some discussion first? We do, we will ask you to justify your votes as we go through, okay, but is there anything that you want to discuss or ask questions about before voting?
(Negative response.)
(Votes displayed and recorded by staff.)
DR. GARBER: Okay. Dick, do you want to go ahead an explain your vote?
DR. WHITTEN: We're explaining just on Number 9; is that correct?
DR. GARBER: Yes.
DR. WHITTEN: This question asks how confident are we that prescribers can rely on this, and I think the net process is such that they can't really rely on these very well at all because of timeliness, because (inaudible) so I view this more as a statement that there really is

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a problem but it's an opportunity to address, which we are attempting to do, and this process should go through.
DR. BERGTHOLD: I voted unsure, was that the middle answer? I don't know enough about how they receive these reports, and similarly, it's completely baffling and confusing to figure out which one of these compendia are the best from any perspective, and I think it would be very had to figure out.
MS. KUEBLER: I voted four. I believe the current compendia offers appropriate evidence-based resources and an opportunity for clinicians to go from different available compendia.
MS. DAVENPORT-ENNIS: I tried to look at this question through the eyes of professional case managers who are constantly having to make these decisions and can't find a compendium available or can't get reimbursed. And I also looked at the question and was reminded of discussions earlier today that indeed, many prescribers really do not rely on compendia to

make judgments about what type of treatment decisions they are going to be making, but they

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would refer to a larger body of evidence. So the compendia have become almost a prisoner rather than a facilitating reference for them. Considering all those factors, and reading into the question that published would include any of the compendia presented today and all compendia presented today, I answered that indeed I do think prescribers can rely on those current compendia and therefore, scored this answer a four.
DR. FENDRICK: I'm somewhat confident for similar and also additional reasons. One, the tech assessment report gave no confidence that the compendia could be used to decrease the amount of inappropriate off-label use, which hasn't been discussed very much, and people are looking for anti-cancer interventions that given the particular aspects of the disease, and often use them without other choices.
MS. GLENNON: I voted a four. I think that I'm somewhat confident that oncologists in practice rely on their clinical knowledge and their expertise in their practice, and they may refer to this as a mere resource or reference, so I'm confident, somewhat confident that they have the resources.

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DR. JANJAN: I voted four, but I think the thing that concerns me is the wide variation among the compendia and as a clinician, if you looked at the numbers that were shown earlier today with the yeses and nos, that concerns me, because which compendium do I trust, and that I think is a major problem that I noticed today.
DR. OMMAYA: I think the technology assessment pointed out areas of improvement that need to be taken, but I think the compendia taken as a whole and in view of the variety of compendia, you can get the information you need. The question is how efficient is it given the amount of information that you have to go through to reach a conclusion, and I think that's a challenge.
DR. KATO: I voted a three, being unsure, primarily because of the wide variety in the reports of the current compendia. I think in perhaps one or two more iterations of the compendia certainly there will be a breakout, at least I anticipate there will be a breakout of one or two that will be able to satisfy many of the criteria discussed today. But until we can improve that process, I'm keeping my vote as

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unsure.
DR. FOLEY: I also voted three. As a hospital medical director with a lot of physicians, I talked with a number of our oncologists before this meeting about what sources do they utilize. Obviously they do look at the compendium but they also have a network of other oncologists around the country either where they trained or who they are related to, and those private networks are usually saturated with off-label kinds of indications and directions that many of them are looking for. So my three is related to uncertainty specific to current compendia, but I have much more certainty and trust in the clinical judgment in the sort of private network of information that develops between the oncologists.
DR. GOODMAN: I voted a less sanguine two, somewhat unconfident, because I looked at that term appropriate in the context of trying to strive towards evidence-based medicine, and when I considered off-label uses of drugs and biologicals for cancer compared to the standard evidence-based medicine we're trying to promote for healthcare, I don't have a lot of confidence in that body of

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evidence as a whole. So it's not just in cancer, but how we try to provide healthcare today. So I don't have a lot of confidence.
And I also took the question literally as far as can rely on. If there are three compendia that have the diversity of evidence and processes and findings that we have today, and if a clinician tried to rely on that set of three, he or she couldn't reach a common denominator, so the end result is a highly inappropriate non-evidence-based application of care for cancer, and that's why I was somewhat unconfident.
DR. MCDONOUGH: I'm a bit more optimistic. I rated this a four. Obviously there are differences in one's ability to rely on different compendia. And I think the evidence report showed us, it identified some problems in terms of timeliness, in terms of identifying the strongest evidence, in terms of gleaning the evidence for the specific recommendations. But overall, I see that there is with all of these, an intent to identify appropriate evidence and use an evidence-based process, some better than not, but overall I feel somewhat confident in being able to rely on these compendia.

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DR. SCHRAG: Also four, similar comments. I think based on the TA, specific areas

that would be most helpful would be a common set of criteria, some commonality in terms of the terms across the different compendia. I gave that a four as a member of the panel, but in my day-to-day practice as a medical oncologist, it often feels like a two. And I say that because I think typically a week doesn't go by where I get five or six letters of exception. I get the sense that if these compendia really worked terrifically well, I wouldn't need to write to my patients' payers various letters trying to justify what I was giving them as being legitimate, because it should just be crystal clear from the compendia. See maybe some of these discussions pointed out by the technology assessment will help get you there.
DR. CUMMINS: I voted three, not sure, based on the technology assessment because of the wide variety among compendia.
DR. KRIST: I voted three, and same reason we've heard here before, the wide variation. A transparent evidence-based process should produce some consistency, more than we saw here, and that's a little bit concerning, although

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as Cliff was saying, this is a difficult topic and so maybe it just requires a more clear explanation between the compendia as to why there is some of those variations.
The other thing I would like to see is more references, quite frankly. A lot of the references were older references and maybe it helps a clinician, maybe it doesn't, but if somebody reads this and they're going to change the way they do things, in many cases it might be helpful to have a reference that they could really further explore, is this really valid that I change what I do.
DR. GARBER: Thank you everyone. Nora.
DR. JANJAN: I would just like to say that this is concerning to me as a clinician. I mean, not one of us gave this a five, and as a physician, I don't have the room to be this inaccurate in what I do every day. And I really think that, I realize it's a big volume, but I've got to be responsible for that big volume every day in my clinical decision-making, and I just think it's got to be done in a much better way, there's got to be much more consistency among these documents for them to be clinically

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reliable. And I have to say, I never look at a compendium, because I don't think they're reliable, and I think that's a charge to all of you who are creating these documents.
DR. FOLEY: One of the things I am

seeing is much more use of multidisciplinary prospectively designed tumor conferences where before therapy, from surgeons, radiation oncologists and oncologists, they use all of their minds and literature and discussion to actually design a particular therapy. That gives me a little better sense that people are taking a lot of this uncertainty more seriously, bringing more heads and more ideas together before they start doing things to people with cancer.

DR. GARBER: Well, thank you. I want to congratulate the panel and thank the panel for your very thoughtful deliberations. And I especially want to thank the speakers who have really helped us in our deliberations. Most of you have come and spent the day with us, it was less exciting than usual, we didn't prolong many votes, and unfortunately I don't have the results of Number 6 in real time here, so we'll wait for it. Steve has some comments.

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DR. PHURROUGH: Yes, and looking at the agenda, I have an hour and a half.

(Laughter.)

DR. PHURROUGH: First of all, particular thanks to the panel. This is arduous work and we appreciate your willingness to take part in it. For those of you who have not been part of MCACs before, over the last year we have very diligently moved MCAC from not just being an advisory committee as to what does the evidence demonstrate around a specific coverage determination that we're involved in, but more to an entity that helps us develop that evidence or helps us determine the different courses we may take or provides some guidance on what's the state of the evidence at the current time around broad topics that then may in the future result in our opening specific formal decision-making processes, and thus far we think that's worked well, we think that's a helpful move for this committee. For those of you who have not been at an MCAC, this running around and changing questions and figuring out how to vote hasn't changed, it is pretty common in that we bring together a group of very bright, intelligent and

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energetic people who have spent a fair amount of time individually looking at an issue and who have collectively decided that we sort of screwed up some of the questions. And we understand that and recognize that, and wish that wouldn't happen, but it always will, so we don't expect that part to change.

So let me get to sort of the crux,

where do we go from here with compendia? Well, I think we've heard today both from you and from the panel that perhaps there are some positive things that can occur from this. I think first of all, the panel spent a fair amount of time attempting to define what should make a good compendium. I think those of you who are responsible for that should listen closely. I think that is some advice that may serve you well.
Our current position is we have on the Part B side regarding cancer chemotherapy some legislative guidance, and two of the three compendia left. One of those two is undergoing some changes. Some congressional direction that says the successor of the one undergoing change should be covered, but in fact some comments have been made to us that the successor may not be the

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same entity. So what do we do in that case? So I think perhaps you could expect from us in the next several weeks to months some continuation of this discussion around what should our next steps be, and perhaps there should be a discussion around criteria and perhaps more formalization of those criteria and then some discussion as to whether we should open a formal process to more clearly define those criteria and define a process, a potential process for allowing a greater breadth of compendia to be involved if there is criteria to be met. We would love to hear your opinions on that as we move forward in the next several weeks.
The process that we should use in general when you're using secretarial discretion and conversation before you get to rule making, though we have done that in the coverage process also. Congress has given us some latitude to do that, but this probably fits more closely into the public comment process. So we would be interested in your input into that. And based upon what we have heard today, I think there is the potential for us to more clearly define what a good compendium ought to be and, two, a process for

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including various compendia to meet those criteria as part of the Part B process.
As I mentioned earlier, we will try to have the results of all the voting on line either later today or first thing tomorrow. If you're not familiar with our web site, we do have a web site at cms.gov/center/coverage, I think, and on that web site is a link to the MCAC page and that's where we will post those.
Thank you very much, and again, a special thanks to the panel, and we'll see you

back at our MCAC in May.
(Whereupon, the meeting adjourned at 3:03 p.m.)