

CENTER FOR DRUG EVALUATION AND RESEARCH

SPECIAL INTEREST TOPIC

**TITLE: MEMO FROM DR. TEMPLE REGARDING ADVISORY
COMMITTEE**

DATE: 07/08/92

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: JUL 8 1992

FROM: Director, Office of Drug Evaluation I, HFD-100

SUBJECT: Comments on the Industry Liaison Panel to the IOM Committee
to Study the Use of Advisory Committees by the FDA

TO: Dick Rettig, Institute of Medicine

The industry liaison panel has provided a thoughtful report. Nevertheless, many of their proposals require further comment. These are my personal thoughts. They do not necessarily represent a CDER consensus or viewpoint.

I. Preface and General Comments

It is important to note the panel's general conclusion that the system is more or less appropriate for the FDA's needs as well as those of the public and regulated industry and that the changes proposed are thus in the way of tune-ups. Some of the proposals, however, raise major issues of feasibility, practicality, and desirability.

II. Administration

A. While I would not dispute the idea that in general the function and overall policies of the committees ought to be similar for drugs and biologics, a central office can only accomplish a certain amount: assuring timely mailings, making sure room arrangements are comfortable, etc. But how committees operate is a much more complex problem and has little to do, I believe, with the administrative office. It has a good deal to do with the specific fields involved, the particular division directors, group leaders, and medical officers who formulate the questions, choose the subjects, etc., the committee chairs and members, and the overall direction coming from the Center. These are not primarily administrative matters but scientific ones and, to a degree, matters of tone and behavior. That said, I think there is no doubt at all that the central office can play a role in such very critical matters as making sure materials are delivered on time, making sure room and audiovisual requirements are adequate, being sure committees are staffed, sending out requests for nominations, etc.

B. Formal Orientation Sessions

This has often been suggested as important, and it seems almost undeniable, but I admit to some skepticism about expending major resources on it unless it is possible to identify very specific matters that need attention. Too much of what might be useful will be very difficult to transmit outside the context of specific drugs. One should also not underestimate the level of effort involved, given the large number of Committees. Actually, the only identified matter of training that concerned the panel was a need to make sure that the committees know their job to render "scientific, not regulatory judgments, and that they are not to be influenced by policy, 'political' or economic issues." I am not sure what the intended distinction between scientific and regulatory matters is. Committees often deal with such questions as to whether they believe certain additional studies should be done before or after approval, obviously a "regulatory", but still a scientific, matter, whether certain studies should be considered adequate and well-controlled, whether to approve a treatment IND, whether to accept a surrogate end point, etc., all matters that are both scientific and self-evidently "regulatory". I do not believe the distinction is clear; perhaps it needs to be clarified. On the other hand I agree totally that it is not the committee's place, nor indeed is it the FDA's place, to make judgments about the costs of therapy or even the comparison of the benefits of therapy to its economic cost. It is difficult enough to get the scientific and medical matters correct without having to worry about economics as well. To the extent that committees do wander into this area, and they occasionally do (although I doubt any decision has turned on this), they should be told unequivocally by FDA staff that this is not their business (or FDA's). The panel did not suggest any other important matter for communication to the committees. If this is really the panel's major concern, we should be readily able to respond to it without significant cost. Committee members can certainly be reminded of this in writing, perhaps supplemented with consciousness raising efforts directed at executive secretaries and division staff.

In any case, if in fact orientation is to be enhanced, there needs to be a very clear idea as to exactly what we want to communicate. The panel report does not help much.

- C. Enhancing the role of Executive Secretaries as suggested troubles me, as the panel seems to want the executive secretaries to monitor the tone and quality of scientific presentations, making them, in effect, monitors of the Division's activities. There is no question that executive secretaries need to be well trained and competent in dealing with such matters as conflict of interest, obtaining the necessary waivers, making sure that materials are presented on

time, and so on. I do not think it is reasonable, however, to expect the executive secretary, who is not possessed of the same level of training and scientific reputation as the division medical staff, to "manage" the "group dynamics" of the meeting, to prevent committees from moving beyond their mandate, to be sure that presentations and questions are unbiased, etc. For them to be alert to such problems seem reasonable, but it should be clear that they cannot be given responsibility for dealing with them. This should be the Division staff's responsibility.

I should add that "managing the group dynamics" is a potentially troublesome concept. Group dynamics are important, of course, in shaping the outcome of the meeting, but "managing the group dynamics" can look to outside observers very much like managing the outcome of the meeting, something FDA has sometimes been said to do (I do not accept the charge, but it is made and is one that the Panel warns about.)

I have no difficulty with the suggestion of having Executive Secretaries be connected with both the division and a central committee management office. Indeed, to a degree that is the way the system already works. I do not believe, however, that the Executive Secretaries should maintain "independence" with respect to critical aspects of meeting preparation and conduct. It must be appreciated that Advisory Committees interact principally with the review divisions and that the most critical element in how well they work is the quality of that interaction. Anything that divides the committee from the people it must interact with most can only be harmful. Efforts to assure that meetings are constructive, free of bias, independent, etc. must be made primarily through the Divisions themselves. Where a meeting is expected to be very sensitive and broader input is felt to be needed for arrangement of the meeting, the right way to do that is to have the division staff meet with office, center or Commissioner level people as appropriate.

III. Membership

A. Review Group for Membership

It does not appear realistic or desirable to have choices of committee members go through an additional body of people such as the IOM. The Divisions best know their specific needs for expertise and must be the primary selectors, and their choices should be monitored for quality by the Offices or Center. On the other hand, were the IOM to provide a periodic review of the members chosen, giving great attention to people's feelings in such matters, that might be useful. It is also time we faced up to the issue of whether committee expertise is affected by the distributional requirements, geographic, gender, racial, etc., that are imposed.

- B. I very much like the idea that some committee members might be chosen at least partly because they are skilled clinical investigators experienced in the conduct, interpretation and analysis of drug or medical device trials. Exactly what the Panel intended here is not clear (they do not seem to want more statistical/design input) and it may be that my enthusiastic response is not related to what the panel actually has in mind. I believe, however, that drug development and analysis of clinical trials is a legitimate subspecialty and that by no means all of the people on our advisory committees are particularly expert in that discipline, even though they are highly expert in particular areas of medicine.
- C. One of the most radical proposals the panel makes is custom tailoring the members for each committee meeting. Although the general idea is attractive, I would like to disagree with the way the panel proposes it be done. The proposal involves giving each committee a small core of people related to the discipline, that core to be supplemented by additional members chosen from a larger pool of people. The general idea of enhancing committees' expertise to deal with specific needs is an excellent one, but I would strongly disagree with reducing the size of the current core committees because that would essentially eliminate the standing committee. There is much that is gained from the continuity a committee attains as it grapples with a variety of specific problems and trains its own members. I have observed in the Cardio-Renal Committee, for example, that new members may appear uncomfortable with the regulatory/scientific enterprise they have joined for a few meetings, but then gradually come, through the experience of dealing with a variety of problems, to like and respect the process and to contribute to it. I think there is a significant benefit from having a sizable core of people who become comfortable with each other, are able to talk freely with each other, and become familiar with the regulatory process and the tasks before them. Such committees are able to be innovative, strong, and flexible, all of which require a certain degree of assurance and familiarity with the area. I would suggest, then, that committees stay at approximately the same size as they are now, with the same broad range of disciplines that is covered, but that we be much more prepared to expand the committee as needed with members or consultants who provide particular expertise, either drawing them from other committees or from groups of epidemiologists, biostatisticians, or toxicologists that would be identified as available to join other committees when their expertise seemed important.

My only reservation about this approach, which on the whole I would endorse, is that it is possible to manipulate a committee, or to seem to be manipulating a committee, when additional members are asked to join a standing panel for a particular issue. One of the visible public virtues of having

the same group of people dealing with issues week after week and month after month is that you obviously cannot adjust the committee easily to deal with a particular issue; the same committee, prospectively identified, deals with drug approvals, drug withdrawals, and so on, and it is hard to say that anyone is manipulating it (except perhaps by putting certain members on it in the first place). This potential problem should be considered seriously when we consider any arrangement that might alter the composition of the committee. I should note that, as I understand the OTC committee, which has a changing composition, it is not susceptible to this charge. What we have there is a constant core of OTC specialists that is then supplemented by most of whatever standing committee seems relevant. It is very hard to argue that that arrangement is manipulated.

The suggested inclusion of industry "nominees" in the central roster of committee members is a tricky matter. Those members would, according to the proposal, be ordinary committee members, with the usual voting rights, conflict of interest limitations, etc. Certainly, sponsors often know who are capable investigators in a variety of areas. If, during the nominating process, industry "threw names into a hat," just as academic societies and others now do, and if there were no suggestion at all that FDA had to accept some fraction of those suggestions, I would see no problem. Indeed, I am certain that many members of our current committees are highly recognized and regularly relied upon by industry, and might well be nominated by industry.

On the other hand, the suggestion that sponsors ought to have an opportunity to object to the composition of the committee that will deal with a particular issue troubles me considerably, on both theoretical and practical grounds. The committee is to serve the Commissioner and his designated representatives, not the needs of industry, and objections to composition by industry seem facially inappropriate. Moreover, as a practical matter, we often do not know who is attending a committee meeting until one or two days before the meeting, given the current conflict of interest situation. In many cases the people excluded are excluded because of their interactions with industry, presumably something sponsors would not find good, and it may well be that industry would find their deletion at the last minute a significant problem (we often do too, but we generally press on with the meeting). Apart from practical problems, as I indicated, I am quite uncomfortable with any suggestion that industry should have more than an informal commentator's role with respect to the adequacy of committee's scientific expertise.

- D. I have some sympathy with the comments about consumer nominated members. These members have ranged from scientifically competent to not expert at all, despite the requirement for relevant expertise. We should perhaps pay more attention to assuring a high level of technical expertise in these members. It is important to recognize that consumer nominated representatives are not meant to be a special interest group. They are not intended to represent consumers but to be individuals that consumers feel comfortable with and they do not, in my experience, function as a "consumer advocate group."
- E. I have great difficulty understanding what an industry liaison person, voting or non-voting, could do with respect to advising these committees. The committees invariably include individuals who are quite familiar with industry. The sponsor is at the meeting to explain his point of view on specific matters, and almost invariably makes the longest presentation. Remembering that the committees are scientific advisory committees dealing with specific issues, I have difficulty seeing what the role of a generic industry liaison person would be. In addition, it is critical to note that we do not choose members of committees to represent points of view. Even a liaison representative member would undermine the distinction between a committee of experts struggling with data and difficult decisions and a committee of committed points of view involved in a negotiation process, not at all the same thing and not at all what we want.

IV. Special Issues Committees

It is very tempting to agree with the idea of having special issues committees, e.g., one to deal with risk assessment (translate carcinogenicity) questions. My principal reservation about that panel, probably the one we could use most, is that it is all too easy, once you choose the members, to have a good idea in advance what point of view you are going to get, because so many experts have chosen sides on these issues. This is not, I think, a matter of commercial bias, but the result of a field of which there are distinct schools of thought. I am concerned that it will be difficult to choose an expert panel that would be credible and not thought to be chosen for its viewpoint. If in some way that problem could be overcome, we would find such a committee useful.

V. Conflict of Interest

Our conflict of interest rules are a major problem, too often focusing on trivial matters. The recent need to consider a person in conflict (routinely granted a waiver, of course) because the person's hospital uses a pharmacy that dispenses drugs is perhaps the ultimate unhelpfulness, but there are many others. On the other

hand, I believe the rules are sensible in addressing some non-financial conflict situations, such as the need to avoid judging your own efforts.

All suggestions that would improve the current situation are welcome. It would surely be reasonable to place minimums on the compensation that should be considered a conflict. Specifically, I would endorse recommendation A. Some of the other recommendations, however, seem much more debatable. A committee member who played a significant role in a product's development, either as investigator or consultant, (recommendations C, D, and E) should not, in my view, participate as a committee member in review of the product, not because of financial conflict but because a committee member should not review and pass judgment on his own efforts. It is not reasonable to consider a member neutral about the product under those circumstances and he should not be advising FDA. I do not have significant reservations, on the other hand, about that person's participating as a sponsor representative under those circumstances. Some have not felt comfortable about that arrangement, but I am willing to accept the risk that the member, even as a sponsor representative, would have an unusual degree of influence over the committee because the arrangement would be wholly public, and because I believe that committees are capable of dealing with that problem. Suggestion F, involving work on a closely competing product must be handled case-by-case. There could, in such cases, be an appearance of bias against the product being considered.

VI. Role of Advisory Committees

The panel has given thoughtful advice on the role of advisory committees and I agree completely with paragraphs A and B. I also have no reservations in theory about carrying out end-of-phase 2 conferences before a full advisory committee or a subcommittee (Paragraph C). That level of endorsement might help deal with the somewhat difficult problem of having FDA give its best advice in an end-of-phase 2 conference and having the committee, some years later, feel no obligation to agree with that advice. I am worried, however, about the ability to have such participation be timely and I further doubt whether committees can actually meet often enough to do it more than occasionally. It is certainly important that agreements reached at end-of-phase 2 conference before advisory committees or anywhere else be formally documented and signed, but this is required under current regulations. The suggestion (Paragraph D) that companies be able to request review by advisory committees of clinical holds is reasonable, so long as there is no implication that they can insist on this. In fact, clinical holds that were controversial and difficult have on occasion been brought to FDA's advisory committee. This does not seem a timely or efficient way to deal with this sort of problem as a rule, and I believe internal resolution is much more practical and is usually effective. Paragraph E suggests progress reports to Committees, a step we have recently initiated.

VII. Presentation to Advisory Committees; Avoiding Intentional and Unintentional Influence of a Committee

A. Material for Committees

Under current practices companies prepare materials for the advisory committee. It is unusual for FDA to disagree with the choice of materials but FDA should be able to do so, asking, for example, that materials related to a matter that is not being brought to the committee, or materials not yet reviewed, be excluded. As such disagreements have been relatively uncommon I see little reason to make a change in policy here.

We certainly should attempt to provide materials three weeks prior to committee meetings but where that is not possible what is the panel proposing? That the meeting be canceled? It is not realistic to think that the final version of the questions will always be available three weeks ahead of time, although one would like this to be so. [There have been problems with "leaks" of the questions and possible securities violations; early availability could increase this problem.] More important than the exact questions is the area of FDA's concern, and I believe we all agree that it is critical that the company have no doubt at all as to what FDA thinks the major issues are. My own view would be that it would be preferable to get questions out and distributed widely, as we used to do, so that people can comment on the questions and raise issues about them.

It is not reasonable to expect the company to regularly receive questions for comment nor should FDA be obliged to negotiate on them with the sponsor. The questions posed are the ones FDA needs answers to in order to take action.

The suggestion that internal FDA documents should consist only of "information on data provided and FDA analyses of those data and its concerns, if any, [but] no opinions on whether substantial evidence of safety and effectiveness have been provided" is not sensible. First of all, this would often be hiding the obvious. The usual biostatistical and medical analyses of studies and their design and problems leave no question as to whether these studies are considered adequate and well-controlled, whether the "Conclusions" section is left in or not. Further, the idea that FDA is supposed to enter a Committee meeting "in neutral," with no prior view to offer the Committee, is one with which I disagree completely. What FDA is obliged to do, should say it is going to do, and should make every effort to do, is listen closely and seriously to the committee's advice and try to be sure the committee is able to give an independent view. The committee may be asked to advise in situations where FDA has no view at all about what to do, but that is not the only possible circumstance in which advice is sought.

In many situations our review has led to a conclusion that approval is appropriate (the majority of drugs taken to committees), and in some that it is not. If approval is straightforward, there may be no need for a lengthy presentation of data and "sanctification" of the obvious by the committee, which instead may be asked to address only certain aspects of the application (dose, a labeling issue, need for post-marketing studies). In such a case, the committee must be made aware of the Division's view. Similarly, if the division feels data are not adequate, and that non-approval is the correct course, the committee must be made aware of the reasons so that it can deal with them. Failure to address those reasons, if the committee disagrees, may render the advice of the committee extremely difficult to use. We need reasoned views from the committee, not just an up-or-down vote. How, e.g., can a Division or Office Director even consider reversing the view of a primary reviewer to accept a committee's recommendation without a clear reason for doing so, and, in particular, a clear explanation of why the committee did not find the reviewer's concerns critical or correct.

It is perfectly possible to go to a committee with a division view and tell the committee honestly that this is FDA's initial view or that certain members of FDA staff feel one way and others disagree, and to tell the committee that their input into these questions is crucial and will be taken very seriously. There is plentiful history to support such an assertion. Committees are willing to disagree, in my experience, in whole or in part with such FDA preliminary judgements, and when they do, it is critical that FDA staff be able to help clarify their reasons, explain possible contrary views, etc. Indeed, this may be very much in the sponsor's interest, as in the case where the sponsor took FDA's advice in pursuing an approach the committee is unhappy with. In sum, committees should be made aware of the full views of reviewers where these views are complete. As office director, I will often not have reached a conclusion at the time of a committee meeting, and the Division Director also may not have done so, but if either of us does, that should be made honestly known, and we should make sure that the committee knows it can influence those views. How we feel we should deal with this matter is very well described in the policy documents (you have them) we generated some months ago. Those documents are an excellent balance of the need to make sure the committee gives us the advice we need and the concurrent need to be sure that excessive staff influence does not occur.

I want to add a few further thoughts on this. I believe the proper role of the committee is not being properly understood by the panel. An advisory committee is not a judicial body or jury, designed to listen to arguments from one side (the FDA) and the other (industry) and then render a decision. In the first place, FDA and the industry agree in the majority of

cases and there is no debate to decide. Further, there is no doubt that the committee is advisory to FDA who remains the decision maker. The role of the committee is thus not that of a judge, but of an expert advisor, specifically, an expert advisor to the FDA in the form of the Commissioner, Center Director, Office Director, or Division Director, whoever happens to be making use of it at that time. It is the job of the advised party to pose the questions and indicate the areas in which it needs, and is seeking, help, because that party will be the ultimate decision maker and is best able to determine what help it needs. If, for example, the judge (us) is prepared to say that it is ready to pass an adverse judgement, what it needs from the committee is expert consideration of the wisdom and basis of that judgement. The committee might rebut it, suggest modifications to it, suggest considerations and analyses that are lacking, etc. In the course of carrying out this function, the expert body can ask for the testimony of people who have opinions on the matter, including the sponsor, FDA staff who have analyzed data, FDA staff who can be informative as to relevant law or precedent, and its own consultants, and can probe this testimony. As experts, of course, the panel also brings its own wisdom to the matter, in addition to its capacity to ask hard and intelligent questions. The committee may therefore pose questions of its own, improve FDA's questions, etc.

Given the ultimate judicial role of the FDA, and its intent to seek expert advice, FDA should not be, or appear to be, lobbying or directing the expert witness to produce a particular point of view. It must, however, be sure that its expert advisor is dealing with all relevant view points, not sidestepping difficult problems (which even experts may do), and making its reasoning clear. This is especially critical because the FDA is, in one respect, in a difficult and sensitive situation, in that it has its own staff of experts who are also offering opinions. While I would not wish to contend that a division director is completely independent of his staff, I do believe that at each level of decision, the division director, group leader, and office director, an independent determination is made as whether to agree or not agree with the recommendations made up to that point. It is perfectly fair to have an expert outside advisor serve as an additional expert witness, which is what the committee does, but it is essential that if the committee does not concur in staff recommendations, the basis for the difference be crystal clear.

- B. This section simply states that companies should routinely be given the opportunity to make oral presentations at committees. We of course agree with that. I would argue that they should be able to comment even during committee deliberations, perhaps more than is now usually permitted.

C. Atmospherics

This section probably seeks the impossible by trying to limit running in and out of meetings and the use of cellular telephones. It does not seem at all likely that we can control these matters without producing an unacceptably stifling environment.

D. Avoiding the Appearance of Influencing a Committee

1. Questions posed to committees should be neutral.

This is probably the most critical section and the most difficult. I have addressed the issue several paragraphs above and note again that the Panel does not see the role of the committee correctly, at least in my view. Committees exist to give the Food and Drug Administration independent advice on problems the Food and Drug Administration has identified. There are some circumstances in which a committee does actually function as an administrative law judge, rendering a decision that the Commissioner may or may not accept. In that sort of case, where a sponsor is appealing a final CDER decision, the committee must be treated as a completely independent judicial body, with ex parte communications forbidden, etc. In most circumstances, however, the committee is, as indicated above, an expert advisor to the decision maker (in practice, the Division or Office Director). That is not to say there should not be clear separation of functions between FDA and the expert advisor. The advisor is useless if not independent. It is not the committee's job to try to support the FDA position, whether it agrees with it or not, to help the FDA by avoiding embarrassing disagreements, etc.

While it is critical to be certain the committee is independent in answering our questions, it is not necessary to pretend that FDA has no viewpoint. While FDA may have reached conclusions in some cases, it may still have other critical questions for the committee. For example, we do not necessarily need to ask an advisory committee whether studies are adequate and well-controlled. We have usually given studies far greater scrutiny than the committees can and may have reached the conclusion that they indeed are well-controlled. On the other hand, having concluded that studies are well-controlled is not the same as saying that the effect shown is of value or that the adverse reactions elicited are acceptable in view of the risks. We thus might well go to a committee believing that the studies themselves are well-designed and acceptable but asking the committee about the persuasiveness of the outcome. In that case there is no reason to pretend that FDA has no view as to

the adequacy of the studies. In other cases, we might believe that studies were fatally flawed, e.g., not long enough. We would need to know the committee's views on this, which is obviously a matter of judgment. Our questions for the committee need to pose the question clearly, so the committee can provide a clear viewpoint, agreeing or disagreeing.

It is not leading the committee merely to tell the committee where FDA stands. Knowing FDA's initial view does not prevent the committee from reaching a different conclusion and FDA is prepared to revisit even conclusions it thought it had reached.

I thus strongly disagree with the recommendation that questions posed to the committee should be neutral in all cases. It is reasonable to take a question to the committee that indicates a point of view by the agency so long as it is also entirely clear that the committee is invited to express a different view if that is what it believes and to explain its reasoning to the agency.

2. FDA should not ask committees whether a drug should be approved.

I fail to understand the distinction between asking the committee whether substantial evidence of safety and effectiveness has been provided and asking whether or not the drug should be approved. The two are equivalent. (Technically the substantial evidence requirement does not apply to safety. That requirement applies only to effectiveness. The critical safety issue is whether benefits outweigh risks.) Once a committee has said that there is substantial evidence of effectiveness derived from adequate and well-controlled studies and that the benefits outweigh the risks, it is being unduly coy to suggest that we should not ask whether the committee recommends approval.

- 2b. Committees should be able to rephrase questions.

Committees do in fact have the option of rephrasing questions; at least most committees do, and there is no reason not to explain to committees that if they think questions can be improved, they can certainly suggest improvements. In some cases, however, FDA may feel that it is particularly critical to get an answer to the question they originally posed and should feel free to press that point.

3. FDA's guest speakers and consultants should provide fair balance of the issues and be held to the same data standards as are companies and the FDA.

It is not entirely clear what problem is being addressed here or what remedy is proposed. FDA as a rule does not knowingly pick individuals who are biased, but picks people who are particularly knowledgeable in an area where that knowledge is needed, generally as a supplement to its own or the committees expertise. If the panel is suggesting that FDA presentations (staff plus speakers) are more likely to be biased than industry presentations, they are, I believe, on very shaky ground. If the panel thinks that drug companies and their consultants regularly provide fair balance, and are, in effect, neutral, they are offering a very naive view. Indeed, neutrality and balance is not a behavior that should be anticipated from a sponsor. While occasionally, and not unwisely, industry brings consultants who feel free to say whatever is on their mind, most industry presentations are well-rehearsed and highly targeted, part of an overall presentation that is directed at securing an approval recommendation. That is not to say presentations are not truthful; they usually are, but they are, nonetheless, efforts in advocacy. In general, in my experience; FDA presentations do seem to be balanced, as we are very mindful of the need to avoid behavior that seems to be pushing the committee toward a particular conclusion.

It is no doubt true that FDA speakers and consultants, like industry consultants, and sponsors themselves, from time to time present anecdotal data. Such anecdotes generally are to be avoided, but telling anecdotes is something that experts often do and wishing will not make it go away. Advisory committees should be well able to distinguish anecdotes from controlled data.

It appears perfectly reasonable to let industry know what consultants and speakers FDA intends to utilize, once their participation is established.

4. FDA staff should not give its own opinions on the matters on which the committee's advice is being sought.

For reasons described above, I strongly disagree with that suggestion. It is absolutely crucial that FDA staff not badger the committee to attempt to persuade it to a particular point of view (and, in my experience, this does not occur), but it is not necessary to hide staff conclusions about the matters under discussion. The FDA reviewer has often carried out a detailed critique and analysis of the studies and the results of this review should be known. Sometimes the results of that review identify flaws that cause the reviewer to consider the study less than well-controlled. The committee could

certainly examine the same findings and reach a different conclusion and that would be perfectly appropriate, but they should be aware of what the reviewer thought.

In my experience the advisory committees are composed of independent, well-respected academics, who have no difficulty at all in telling FDA staff, including FDA division and office directors, that they do not agree with them. The very idea of expert advisory committees has to be reconsidered if committees can readily be manipulated by FDA staff into abandoning their views.

5. Make the basis of FDA disagreements with advisory committees publicly available.

I am inclined to agree that FDA should publicly state its reasons for disagreeing with the committee, but one should recognize that it will often not be able to do this. If a committee's approval recommendation is rejected and a not approvable letter issues, this information would not be publicly available. I would have no objection to having it be available, I should add.

6. Committees should not meet, even for social purposes, outside of official meetings.

I suppose I understand the purpose of this, but I regret the suggestion and do not agree with it. The specific contents of the meeting must not be discussed outside of the meeting itself in accordance with what I understand to be the provisions of the Federal Advisory Committee Act. It is, however, an important part of a committee/division interaction for the people involved to get to know each other and to develop a relaxed set of interactions. Advisory committee members are helpful to the agency in many ways, including being willing to participate in end-of-phase 2 meetings, being available for occasional curbside consultations, and the like, and it is extremely helpful to the committee to understand and get to know the people involved. I believe it is completely possible to avoid any discussion of the specific issues that will be coming before the committee and have always sought to make sure that rule is followed. I have been at a great many social occasions with committee members that were informal, relaxed, and did not in any way violate the law; I would urge that it be possible to continue to do this.

7. Guidelines should be developed by FDA staff to avoid the appearance of influencing the committee.

I believe the current guidance goes a long way toward doing just that and I am not sure it needs to be adjusted further. The IOM might like to consider those documents and see whether they think they do the job. They do, in my view, provide a good balance of assuring that FDA staff views will become known to the committee and making sure that the committee does not appear to be unduly influenced.

8. An appeal process should be available when bias may have entered into the advice given by a committee.

I disagree with this suggestion. The committee is not the deciding body. The FDA is. Any complaints about the conduct of the meeting or the advice given can go to the FDA. The FDA itself has numerous avenues for appeal at all levels and these should be sufficient. The only example provided is obviously a matter of great concern to the members of the panel, but is not a matter of bias. It concerns a committee responding to the question of whether an expensive product is actually needed. If this issue is arising regularly (the Panel clearly perceives that it is), FDA certainly ought to do something about it, as well as about other non-scientific considerations that creep into committee discussions from time to time.

Committees and committee members have the flaws of all public bodies and will from time to time make mistakes. It is perfectly reasonable for a sponsor to complain about the outcome of a meeting and it would be my very strong view that sponsors should be allowed to, and urged to, rise in the course of the meeting to object to inappropriate considerations of that kind. FDA staff should also be prepared to make it absolutely clear to the committee that such matters as the cost of therapy, the need for yet another example of drug class X, and the like, are not within their purview. Nonetheless, I do not feel that a formal appeals process is necessary or would be useful. Again, my principal reason for this is that it is possible to appeal any FDA decision. It is unnecessary to appeal the elements of the process of reaching that decision.

Robert Temple, M.D.