

CENTER FOR DRUG EVALUATION AND RESEARCH

SPECIAL INTEREST TOPIC

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

DATE: 09/30/91

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: SEP 30 1991

FROM: Deputy Director for Scientific and Medical Affairs

SUBJECT: Advisory Committees

9/30/91

TO: Carl C. Peck, M.D.
Director, Center for Drug Evaluation and Research

Gerald F. Meyer
Deputy Director, Center for Drug Evaluation and Research

The enclosed documents on Policy and Procedure in Selection of Issues for presentation to our Advisory Committees and on Conduct of Meetings have been drafted with substantial input from the CDER Office Directors and NDE Division Directors.

They were discussed at a CDER Policy Meeting and have been circulated for review and comment in two iterations. Although we have not achieved unanimity on all points, I believe they represent a consensus of the program directors.

I therefore recommend that they be signed and that we distribute copies to the Review Staff, executive secretaries of all committees, the current committee chairs and members and to the IOM contractor considering these issues.

D. Bruce Burlington, M.D.

Enclosures

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Policy and Practices in Selection of Agenda Items to be
Considered by Center for Drug Evaluation and Research Advisory
Committees

Issues under consideration by the New Drug Evaluation (NDE), Generic Drug Evaluation and Over the Counter Evaluation programs that are of major public health importance will ordinarily be discussed with one or more of the Center's standing advisory committees. Such discussion brings broader input to the decision making process, provides access to technical expertise that may not be available within the agency and opens FDA decision making procedures to broader scrutiny.

Range of Issues for Consideration

The range of issues that may be brought to a committee for such discussion is broad but includes:

I. Advice on the approvability of specific drugs:

1. Consideration of the overall data on safety and effectiveness submitted in support of a new drug application, most commonly a new chemical entity (NCE), but also significant new uses of already-marketed drugs. Particular issues could include:
 - a. Adequacy of the design and conduct of studies intended to provide substantial evidence of effectiveness.
 - b. Consideration of data to support the proposed dose and schedule.
 - c. Detailed consideration of critical studies.
 - d. Consideration of the appropriateness in particular situations of "surrogate" endpoints.
 - e. Adequacy of the overall safety data base.
 - f. Need for additional studies or special surveillance after marketing.
 - g. Need to limit indications to a particular subset of the overall potential treatment population.
 - h. Evaluation of the overall risk-benefit relationship of a new agent.

i. Consideration of special labeling features, such as boxed warnings, special limitations on use, monitoring requirements, or patient package inserts.

j. Evaluation of proposed prescription to OTC switches.

k. Primary review of selected portion(s) of NDA's.

II. Drug development

1. Guidelines for classes of drugs. Committee roles can range from review of a proposed guideline to actually writing a proposed guideline in conjunction with FDA staff.
2. Discussion of study design issues, including appropriate duration, endpoints, patient population, and analysis, for particular drug classes.
3. Specific safety issues arising in the course of development of particular drugs.

III. Marketed drugs

1. Consideration of ADR data emerging from either surveillance, new clinical studies or animal studies.
2. Class labeling, modifications of claims for classes of drugs.
3. Generic drug issues and evaluation methods.

IV. Management of the NDE Program

1. A periodic review, in closed session, of the status of important products under development especially where they may have important public health impact, the development is usually complex, or there is great public scrutiny.
2. A periodic review of the status of pending applications for approval of NCE's and major new indications for other drugs...

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3. A periodic analysis of the programs' assignment and allocations of resources to manage IND/NDA/ANDA applications and supplements to approved applications.

Advisory committees are composed of committed but busy leading scientists, most of whom are active researchers with academic appointments. Participation in FDA deliberations does not free them of their other obligations. As meetings are usually 2 days long, occur 2 to 5 times per year, and involve substantial pre-meeting preparation, it is clear that, for many committee members, current meeting schedules represent a substantial commitment. Therefore, we must select issues for discussion in ways that maximize the valuable contribution of our advisors as a public health resource, as well as makes efficient use of the agency's staff's time preparing for and participating in such meetings.

Selection of Issues for Consideration Within the Constraints of Available Meeting Time

The Center will attempt to select issues for advisory committee presentation as follows:

1. Applications for approval of the first entity in a pharmacological class will routinely be presented as well as any other new chemical entity whose evaluation poses special problems or raises issues of broad interest.
2. New drugs that are expected to have a major therapeutic impact, whether or not they are NCE's will ordinarily be presented. Similarly, major new uses of marketed drugs will ordinarily be presented to advisory committees. For drugs of particular urgency, this may require special or extra meetings. If these cannot be held, it may be necessary to present the advisory committee with reports of the agency's evaluation after the agency has taken action on the product.
3. Applications for initial Rx to OTC switches of a drug will routinely be presented to an advisory committee for their consideration.
4. Major safety concerns involving marketed drugs will usually be presented to advisory committees, if possible, before action is taken, although need for urgent action may require that the presentation take place after the agency's decision.

5. Clinical Guidelines will routinely be presented to the relevant committee for consideration before being adopted:

6. If the agency takes, or is planning to take, an action that conflicts with the explicit advice of an advisory committee on an important aspect of the committees' deliberations, the agency's position will ordinarily be summarized for the advisory committee with an explanation for the decision. Where the matter is likely to be controversial, this should be done before the action.

7. Other issues may or may not be presented at the discretion of the Chair and FDA staff, depending on the public health implications of the issue, the availability of time on the committee's calendar, and the need of the agency's review program for external advice on the issue. In general, requests by the Advisory Committee chair to have particular issues presented will be honored.

8. At least once a year, an NDE review division will present a program review of important and controversial drugs under development, and applications for NCE's that are pending. This shall specifically include an opportunity for the committee to advise the agency on the priority classification assigned to pending NDA's for NCE's.

Procedures:

1. The executive secretary of each advisory committee and the relevant review Office or Division Director will meet periodically to identify potential issues for upcoming advisory committee decisions. The potential issues identified and the plans for such meetings will ordinarily be discussed at Office Administrative Rounds.

2. All agenda items identified for consideration will be discussed with the chair to obtain his or her advice on which ones to discuss and how best to present them, choice of committee reviewers, etc.

3. The topics decided upon will then be published in the Federal Register.

4. On an annual basis, the executive secretary will report to the Center, through the Office, on the number of meetings held,

the topics discussed (classified as NDA, ANDA, IND, guideline, safety issues, and other); any recommendations by the committee that were: (a) not accepted, or (b) not yet implemented, and any difficulties or other matters of reference during the previous year.

D. Bruce Burlington, M.D.
Deputy Director for Scientific and
Medical Affairs

Gerald F. Meyer
Deputy Director

**APPEARS THIS WAY
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Director, Center for Drug
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Policy and Practices for the Conduct of Center for Drug
Evaluation and Research Advisory Committee Discussions

Advisory committees to CDER's New Drug Evaluation (NDE) Generic Drug Evaluation and Over the Counter Evaluation programs make a major contribution to application review by providing external advice on the safety and efficacy of new drugs proposed for marketing, generic drugs, non-prescription drug use and other issues. Although the committee's role is advisory, and the agency remains the final decision maker, the meetings of the committees provide a forum for discussion of scientific issues underlying the agency's judgment of whether products are safe and effective, thus in part providing public access to the review process. Meetings also provide public evidence that the agency draws on a wide range of expertise in trying to reach the best decisions possible. For the advisory committees to fulfill these functions adequately, committee members must be well informed about the issues under discussion, and equally important, must be, and appear to be, giving independent advice to the agency.

Agency staff need to be conscious of these twin goals in providing scientific or regulatory information and during all other interactions with advisory committee members, assuring the committee's independence while at the same time assuring that the committee is well informed and helpful to the agency.

Because each issue brought before a committee and the circumstances surrounding it is unique, it is hard to specify procedures that will assure these goals are met, but, certain principles are generally applicable.

It is never appropriate for either applicants or agency staff to lobby or negotiate with committee members about positions or conclusions the advisory committee should adopt on issues about to come before them. It is, however, appropriate for agency staff and corporate sponsors to provide members with background information on the issues at hand, and during meetings, to discuss the data and their own interpretation of the data with the whole committee.

Indeed, it is essential that the advisory committee collectively receive input from the agency regarding the staff's review of the data that will be presented to the committee. This provides committee members with the agency's expert analysis of the validity and organization of the data offered by sponsors, an analysis to which the agency usually brings more resources, expertise and experience than are available to the committee. It is also important that the committee have access to the agency's evaluation of the sponsor's data analyses, including the agency's evaluation of statistical techniques used, analysis of design

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issues, and assessment of the results of studies. Without such information, the committee may fail to address issues that will be critical to the agency's reasoning when it formulates a final decision on the issue.

In providing this input to the committee, the agency will usually send the committee copies of primary reviews, as well as statistical or other reviews, and reviews of supervisors. It is important to be sensitive to even the appearance of suppressing dissent or controversy, and, in general, it is preferable to provide all reviews, even if they present an extreme or poorly expressed view, and to add, as necessary, additional analyses so as to provide a fuller representation of the range of scientific thoughts in the division. In considering whether to withhold certain documents, it may be useful to carry out an internal peer review of them. If division or office management decides that the primary reviews do not provide an adequate representation of the data or are not sufficient in any way, it should take necessary steps to assure a more satisfactory presentation by omitting certain documents or supplementing them with additional material.

It is important to provide advisory committee members with appropriate background material in a timely fashion, generally at least two weeks before the meeting. In addition to the agency's materials, sponsors often provide additional data, sometimes with additional documentation to focus discussion or assist an identified committee member serving as a primary or secondary reviewer of the drug. In general the sponsor's background material should be submitted to the agency for review and may at times be supplemented by efforts to address issues raised in it by the agency. Usually, the sponsor's submission should be forwarded to committee members as provided, without editing or deletion.

Critical new information not received by the agency in time for review creates a special problem. While including data not previously reviewed by the agency in advisory committee presentations and briefing packets is generally discouraged, from time to time it is critical to understanding an issue at hand. Such material may be included with the recognition that it may lead to an outcome of a committee's deliberations that cannot later be accepted, e.g., if the data were not all they were purported to be. The agency recognizes that failure to use all available information is also wasteful. In many cases, the best course is to treat conclusions based on the new data as "conditional" and "pending review" and to attempt to establish whether the committee's conclusions are based on the previously reviewed data or rely on the data not yet reviewed.

Every effort should be made to be sure the sponsor understands the issues that will be raised for discussion by agency

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reviewers. There are many ways to do this, including deficiency letters to sponsors, pre-meetings between the sponsor and agency in anticipation of any advisory committee discussions (it is useful to offer the sponsor an opportunity for such a meeting) and communicating to the sponsor any questions to be posed to the committee in advance of the meeting.

The committee must be, and must be seen to be, offering advice that is meaningful to the decision making process and not endorsing a decision already made. Therefore, on pending issues, the views of the Division and Office Directors must be expressed with particular care so that both the committee members and public understand that the committee's deliberations are being taken seriously and will be given full weight in the agency's decision. Thus, for example, if there were a Division or Office Director's memo expressing a strong conclusion as to approvability (there is not usually such a document at the time of a meeting) it should be put into context with a clear statement that it is preliminary and subject to revision on the basis of the meeting. There are a few instances in which this approach seems especially appropriate. In some cases, NDA's are brought to committees where all parties share a clear expectation as to the outcome, but where, because the drug is novel or important, the committee is being consulted "just in case." In this situation there is no need to pretend that preliminary conclusions have not been reached. But the committee should be told that although the Division believes the data to be straightforward, the issue is nonetheless being brought to the committee to see if there are problems the agency has overlooked. This should be done with assurance that our preliminary conclusions are just that, preliminary, and that we will listen to the committee.

In some instances, NDA's have been brought to committees after an agency non-approval action, specifically to give the sponsor a chance to "make a case" before an outside review body. This is especially useful where the data are marginal and the decision was based on the agency's medical judgment. In that case the Division Director or Office Director will need to explain the past decision while emphasizing the agency's openness to reconsider the issue if so advised by the committee.

During the meeting it is essential that FDA staff at all levels be free to participate in the meeting by asking questions of presenters and committee members, raising or clarifying issues they feel need to be addressed and providing regulatory context or information on precedents. Given their familiarity with the data, agency officials should assist the committee in identifying and illustrating weaknesses and strengths in all presentations. While this active participation strengthens the advisory committee's deliberative process and the value of the advice rendered to the agency, it is important that such participation

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be conducted with discretion, so that the agency does not control, or appear to be controlling, the committee. To help ensure committee independence, participating agency officials should generally defer to the committee by raising scientific issues for discussion only after members have had an opportunity to do so.

In addition, the staff joining the committee at the table should be seated so as to promote independent discussion among the committee members. There should not be the impression that a principal purpose of the meeting is an opportunity for public discussion among the agency's staff. Therefore, the number of agency staff at the table should be limited and all but 1 or 2 should be seated peripherally.

The public, as well as the advisory committee members, understand and expect that sponsors will function as advocates for their drug. The role of the agency's staff is quite different. The agency is the decision maker, not an opposing advocate. The discussions and recommendations of the advisory committee do not take away the agency's judgmental role; rather the committee serves as a major source of expertise and a mechanism to weigh the issue in terms of the values and assessments of the larger medical community. This means, that while agency staff must raise and frame issues, identify flaws in the data or their interpretation, and even indicate their own views of particular matters, they must also acknowledge the valid points raised by the drug's sponsor. While a reviewer will surely have an opinion as to the approvability of an application after reviewing it, and may properly discuss that opinion, he or she, and other FDA officials nonetheless should be, and appear to be, open to alternative views and not engaged in an adversarial debate.

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Deputy Director for Scientific and
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