

May 21, 2007

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20857

Re: Docket Number 2007D-0101; Draft Guidance for the Public, FDA Advisory Committee Members, and FDA Staff on Procedures for Determining Conflict of Interest and Eligibility for Participation in FDA Advisory Committees; 72 Fed. Reg. 13805 (March 23, 2007)

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) is pleased to provide the following comments on the above cited draft guidance document. PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, healthier and more productive lives. PhRMA companies are leading the way in the search for new cures. PhRMA members invested an estimated \$39.4 billion in 2005 in discovering and developing new medicines, and industry-wide research and investment reached a record \$51.3 billion in 2005. PhRMA companies thus have a unique stake in the appropriate operation of the Food and Drug Administration's (FDA's) advisory committees.

**I. General Comments**

PhRMA members are committed to protecting the integrity of the Agency's advisory committee process. FDA advisory committees play a pivotal role in protecting and promoting the public health by providing expert, independent advice to the Agency on key scientific, technical, and policy matters. Given the importance of advisory committees, the conflict of interest rules governing participation of advisory committee members must be clear and should ensure that committee decisions have credibility with the public and scientific community. We commend the Agency for its effort to simplify the assessment of potential conflicts of interest of advisory committee members and support the Agency's intention to provide greater transparency, clarity, and consistency to the process.

***Pharmaceutical Research and Manufacturers of America***

The governing statutes and regulations (18 U.S.C. § 208(b), 21 U.S.C. § 355(n)(4), and 5 C.F.R. Part 2640) establish the applicable rules and factors to consider when handling conflicts of interest and granting waivers. The draft guidance is largely consistent with these statutes and regulations. As explained below, however, we are concerned that the Agency has proposed a simple and stringent policy at the expense of a qualified pool of experts available to advise FDA. We believe the proposed approach will ultimately decrease the quality and quantity of scientific advice. The comments that follow address these concerns.

**A. FDA Must Preserve Essential Expertise on its Advisory Committees**

Like FDA, the pharmaceutical industry draws upon scientific and medical experts for their technical knowledge and experience. The experts who serve as FDA advisory committee members are often pre-eminent scientists in their field. Typically, these advisors are active researchers at the forefront of their discipline or area of expertise in the pharmaceutical field. As would be expected, the pharmaceutical industry funds a substantial portion of innovative pharmaceutical research. Because there is a limited pool of individuals on the cutting edge of science, both industry and FDA frequently work with the same experts. As a result, financial interests are often unavoidable.

FDA must ensure that its conflict of interest rules appropriately take into account the inherent reality that many experts will have working relationships with the industry and recognize that not all relationships with the industry should translate into automatic disqualification from participation on an advisory panel. It is essential that FDA's conflict of interest rules are not so restrictive that they deprive advisory committees of expertise that is important to protecting the public health. Put simply, the Agency should strive for a balanced approach in crafting its new conflict of interest rules.

**B. The Current Conflict Review and Evaluation System Is Not Leading to Tainted or Unreliable Recommendations**

While we agree that FDA's approach to advisory committee conflicts of interest can be improved, there is no evidence to suggest that the current conflict of interest rules are producing biased decisions on issues of drug development. Last year, in an article published in the *Journal of the American Medical Association*, researchers analyzed all FDA drug advisory committee meetings from 2001 to 2004 and concluded that none of the voting outcomes would have changed had voters with conflicts of interest been excluded.<sup>1</sup> FDA expanded on this research in a comment on the article noting:

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<sup>1</sup> Peter Lurie, et al., "Financial Conflict of Interest Disclosure and Voting Patterns at Food and Drug Administration Drug Advisory Committee Meetings", *JAMA*, April 26, 2006; 295:1921-1928.

Advisory committee members and voting consultants with financial ties to pharmaceutical companies tend to vote *against* the financial interest of those companies. This result suggests that *fears that disclosed conflicts of interest are leading to tainted, unreliable recommendations are unfounded.*<sup>2</sup>

The JAMA article and the FDA comment reinforce the reality that the current conflict of interest rules are strong.

This empirical evidence shows that the more restrictive criteria in the draft guidance are not likely to result in a true increase in the reliability of advisory committee recommendations. At the same time, several aspects of the draft guidance will undoubtedly result in an increase in the number of experts disqualified from participation. In revising its policies and procedures, FDA should be careful not to sacrifice the expertise and reliability of advisory committee advice for an increased perception of process integrity. This caution is especially important given that the available empirical evidence suggests that conflicts of interest are not compromising advisory committee decisionmaking under the current rules.

## **II. PhRMA Responses to the Questions Posed in the Federal Register Notice**

In the *Federal Register* notice dated March 23, 2007 (Vol. 72, No. 56, pgs 13805-13806), FDA asks:

### **A. Question 1: Whether the draft approach, due to its stringency, could unduly restrict eligibility of needed experts for advisory committee meetings**

We find the approach to be unduly restrictive. Due to the extraordinarily stringent policy stated in the guidance and the complexity of financial relationships that may exist for advisors, we believe many will have conflicts (as defined in the draft guidance) that would restrict or prevent them from serving on advisory committees.

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<sup>2</sup> FDA, “Comment on ‘Financial Conflict of Interest Disclosure and Voting Patterns at Food and Drug Administration Drug Advisory Committee Meetings’”, available at <http://www.fda.gov/oc/advisory/analysis.html> (last viewed May 9, 2007) (emphasis added).

## **1. Divested or Past Financial Interests Should Not Disqualify or Limit Participation**

The draft guidance (Step 4a) disqualifies or limits the participation of an advisor based on financial interests divested in the past 12 months. The disqualification of an expert based on past financial interest is a significant departure from the prior conflict of interest guidance and has no basis in statute or regulation.

Under 21 U.S.C. § 355(n)(4), FDA may disqualify an individual if the individual or a family member “could gain financially from the advice.” Similarly, 18 U.S.C. § 208 also focuses on current financial dealings and applies if the individual “has a financial interest” in the matter. Moreover, the regulations explicitly state that an individual is authorized to participate in a particular matter if “the interest has been divested.”<sup>3</sup> The regulations also note that “[u]pon sale or divestiture of the asset or other interest that causes his disqualification from participation in a particular matter, an employee is no longer prohibited from acting in the particular matter.”<sup>4</sup>

FDA has provided no evidence that a past financial interest will influence an expert. Where there is no current financial interest, there would of course be no tangible basis for an individual to be biased in his or her participation on an advisory committee. The draft guidance nonetheless adopts a significant new rule, without including specific reasons for the policy change. The change seems to be designed simply to increase external perception of the integrity of advisory committees.

Requiring disqualification for prior financial interests will unnecessarily reduce the number of experts eligible to participate in advisory panels and consequently reduce the strength and reliability of advisory committee decisions. Past financial interests should not serve as the basis for limiting or prohibiting an expert’s participation in an advisory committee.

## **2. Specialized Expertise on Advisory Committees Should Be Preserved**

As noted above, the experts sought by FDA for participation in advisory panels are often active leading researchers in their field and the pharmaceutical industry is a primary sponsor of cutting edge research. To the extent that the proposed exclusions limit the participation of such advisors, the committees may be biased towards persons who lack experience in performing clinical trials, a key area of expertise for evaluating data presented to advisory committees. Advisory committees are commonly asked to provide guidance to the Agency regarding complex issues in drug development, such as the interpretation and application of potentially confounded

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<sup>3</sup> 5 C.F.R. § 2640.103(d).

<sup>4</sup> Id. § 2640.103(e).

trial results. Inexperience in conducting clinical trials will have a significant negative impact on the quality of advice provided by the committee.

We also have concern that frequent changes in advisory committee participation due to excessively stringent conflict of interest policies will diminish the strength and reliability of advisory committee determinations. It is hard to envision any “standing” advisory committees existing under these new rules since experts in every therapeutic area will likely have potential conflicts. This will necessitate that for each scheduled advisory committee meeting, the Agency will need to supplement the committee with non-conflicted persons who may participate and vote. In addition, it will be more difficult to identify a committee Chairperson, who must be an expert in the field and FDA approval processes, and not conflicted. Furthermore, we have noted an increasingly diverse and complex range of topics (e.g., serious safety issues, lack of effectiveness issues, newly discovered class issues) that advisory committees are asked to address. The lack of continuity in participation of any advisory committee member that may result from conflict standards may make it difficult for the advisor to provide credible and reliable advice.

### **3. Committee Members with Special Expertise Should Generally Be Permitted to Vote**

The draft guidance (Step 4a, Step 5, Step 6) generally limits voting participation to individuals with no financial interest (current or within the previous 12 months). Advisors with up to \$50,000 in current or recent (within the previous 12 months) financial interest would be permitted to participate, but not vote. The FDA Commissioner would be permitted to deviate from these general rules under certain circumstances. As the Agency acknowledges, these restrictions prohibit voting even in situations where voting would be permitted by the governing law. For the reasons outlined in the *JAMA* article and FDA’s comment, this policy is unwarranted.

The Agency should permit advisory committee members to vote except in extraordinary circumstances. Under the draft guidance, the decision whether to allow an individual with a qualifying financial interest to participate on the advisory committee will only arise where the financial interest is limited (\$50,000 or less) and the person has special expertise that is of value to the committee. The *JAMA* article suggests that present financial interests have not influenced the outcome of committee decisions. The same is presumably true of past financial interests, which by logic should present fewer issues than current financial interests. The restriction on voting thus sacrifices full participation by a key expert without any corresponding benefit. The Agency should permit an advisor with such value to the committee to vote on the committee’s recommendations.

#### 4. Need Waiver

In step 5 of the draft guidance, FDA may provide an outside expert a waiver to participate as a non-voting member of an advisory committee based on need for their expertise. As noted earlier, we believe that if FDA determines that an expert's knowledge is unique and necessary to the advisory committee, the individual should be permitted to vote on the panel. We find, however, that the draft guidance appropriately captures the criteria necessary to take into account when the Commissioner assesses whether or not to provide a waiver. In particular, the failure to find a similarly or better qualified candidate with fewer conflicts should be the most persuasive proof of need.

**B. Question 2: Whether the \$50,000 figure generally employed as the maximum amount for disqualifying financial interests, after applying certain exemptions, is appropriate, or alternatively, whether a different figure (higher or lower) should be used**

Under the policy described in the draft guidance (Step 4a, Step 5, Step 6), only individuals with no financial interest (currently or within the previous 12 months) generally would be permitted both to participate and vote as members of an advisory panel. Individuals with up to \$50,000 in current or recent (within the previous 12 months) financial interests would be permitted to participate, but not vote. Individuals with more than \$50,000 in current or recent financial interests would not be permitted to participate as a member of an advisory committee.

FDA's proposal assumes that \$50,000 of financial interests held within the preceding 12 months directly bear on the integrity of advisory services provided to the Agency. The \$50,000 threshold appears to be arbitrary, without any supporting evidence that this level of financial interest has significance. No threshold dollar amount is specified in any of the governing statutes or regulations. Furthermore, the 12-month period in FDA's proposal also appears arbitrary; no justification or rationale was provided as evidence that 12 months is an appropriate period of time to eliminate the conflict of interest. Considering the lack of empirical evidence suggesting the current rules compromise advisory committee decisionmaking, FDA should ensure any new approach to evaluating conflicts of interest is adequately justified.

**C. Question 3: Whether and what additional examples should be provided for the steps described in this draft guidance for determining conflicts of interest and eligibility for participating in an advisory committee meeting**

The draft guidance would benefit from clarification in the areas described below.

**1. Defining “Financial Interest”**

In Step 3 of the draft guidance, the reviewer of the potential conflict must determine if there is a disqualifying financial interest. The document, however, provides little if any guidance that would assist the reviewer in determining which types of financial interests are disqualifying.

Step 3 outlines the breadth of individuals associated with the member whose financial interests should be considered in this determination (spouse, children, etc.). However, the step fails to outline in any detail the types of relationships that would be considered potentially disqualifying financial interests (e.g., stocks, employment, etc.). In Section II of the draft guidance, there is a very brief discussion of financial interests, but that alone is insufficient to assist the reviewer in determining if a particular financial relationship is a disqualifying financial interest. If the Agency intends to apply 5 C.F.R. § 2640.103(b), it should state so explicitly in this step. Otherwise, the step should provide guidance to assist the reviewer in determining which types of financial relationships may be disqualifying financial interests. In particular, we suggest the guidance address the following:

Extended Relationships: It is not clear how "general partner" is defined. In addition, the discussion of institutional relationships should be expanded. We offer three aspects of this:

1. We agree that being a member of an institution that could benefit from a given product not being approved (under a nonapprovable decision) if the institution has an "interest" in a competitive product could be viewed as a potential conflict. This example should be more clearly described. For example, having someone serve from an institution that holds the commercial rights to a product that is competitive to the product under review may be considered a conflict of interest.
2. In an academic setting, would the conflict of a department member disqualify everyone in that department from serving on an advisory committee?

3. In addition, it is quite possible for the prestige value (publications, promotions) and future monetary value of an institutional grant or contract to be directly affected by a matter at an advisory committee. FDA may wish to consider this example as well.

## **2. The Relationship of Steps 3, 4a, and 4b**

The last paragraph of Step 3 directs the reviewer to the appropriate next step in the conflict of interest analysis based on whether or not the member has a disqualifying financial interest. The paragraph states:

If you determine that the member and persons or organizations whose interests are imputed to him do not have any disqualifying financial interests, then you may recommend that the individuals may participate in the meeting unless the member is disqualified for reasons unrelated to 18 U.S.C. 208. In this case you should proceed to step 4a. Alternatively, if you find that the member or persons or organizations whose interests are imputed to him has disqualifying financial interests, you should proceed to step 4b.

This paragraph could be clarified. In particular, we recommend replacing the sentence that now reads “In this case you should proceed to step 4a.” with the following: “In order to determine whether the member is disqualified for reasons unrelated to 18 U.S.C. 208, you should proceed to step 4a.” This change would make clear that the grounds for disqualification outside the statute are set out in step 4a, and that there is not some other set of unspecified criteria for disqualification.

### **III. Alternative Recommended Approaches**

As discussed in these comments, we believe the approach outlined by the Agency in the draft guidance may unnecessarily preclude the full participation of needed experts. We offer the following alternative, recommended approaches to assessing potential conflicts of interest and determining meeting participation.

#### **A. Universal Non-Voting Approach**

Regardless of the process for determining conflicts of interest that the Agency implements, including electing to keep its current method for screening conflicts, FDA could adopt a universal nonvoting approach to advisory committee meetings. Such an approach would enable FDA to move away from an advisory system in which experts formally vote on questions

to one in which experts merely advise and opine on topics/questions posed by FDA. We believe this approach has several potential benefits:

- It may address the public's erroneous perception that an advisory committee vote on an approval question is equivalent to or dictates an FDA action.
- It will focus more attention on the entire deliberations and not just the simplified vote that makes the news. Many times the advice offered during the discussion is much more meaningful than the vote taken.
- Frequently, the advisory committee changes the questions asked by the Agency to reflect the discussion during the meeting. Therefore, the vote taken does not necessarily provide the committee's response to the specific issue raised by FDA.
- If financial associations with industry are believed to affect the outcome of the vote, elimination of the vote should allow FDA to retain more valued consultants who have some association with industry.
- All advisory committee members, including consumer and industry representatives, may be seen as equal members of the committee and may fully participate in committee deliberations as such.

**B. Increase Transparency**

Finally, regardless of the approach FDA takes to determine conflicts of interest, we believe the Agency could increase transparency regarding such determinations. For example, FDA could use its website to make available the details of potential conflicts for the advisory committee roster at the same time that briefing materials are posted prior to an advisory committee meeting. Such an approach would go a long way towards increasing awareness of the potential conflicts and would enable attendees and participants to evaluate opinions and advice offered at the meeting in light of the stated potential conflicts.

If FDA determines that new procedures for assessing potential conflicts of interest and determining advisory committee meeting participation are warranted, we recommend that the Agency ensure the new policies do not have a significant negative impact on the advisory committee process. The approach should not be too complicated or onerous for the advisors, otherwise the conflict of interest process itself may deter experts from participating in advisory committee deliberations altogether.

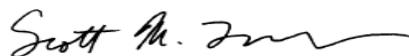
Furthermore, the approach should not hamper the Agency's ability to locate qualified experts who can participate and vote, as appropriate, at the meetings. We therefore recommend the Agency assess the potential impact of any proposed changes on the current robust advisory committee process. FDA should examine how the proposed changes would affect the participation of advisors at all advisory committees convened in a 12-month period. Because advisory committees are convened with varying frequency in a year, we believe an assessment that covers one year will adequately capture data from most – if not all – advisory committees. The results of this assessment should guide the Agency in its decision whether and how to amend current procedures.

The Agency also should determine the procedures it will follow if a sufficient number of advisors are not available to participate in an advisory committee meeting due to conflicts. Will the agency retain a general pool of non-conflicted advisors to draw from in the event conflicts are determined late in the process? If so, such advisors may not have adequate expertise to meaningfully participate in a particular meeting. Another approach could be to include extra advisors on the roster for each advisory committee and rotate participation at meetings. Such a system could prove difficult to administer, but will be more likely to ensure needed expertise during the committee meetings.

#### **IV. Conclusion**

PhRMA and its member companies are committed to ensuring the integrity of FDA's advisory committee system. In line with our comments, the Agency can simplify its approach to and enhance the consistency of the advisory committee conflicts of interest process without compromising the ability of the advisory committee system to provide genuinely expert input to the Agency on important questions.

Sincerely,



Scott M. Lassman  
Senior Assistant General Counsel