- The government official (or other authorized official) responsible for the appointment must issue a written waiver before the employee takes any action in the matter(s).

- *The written waiver must be based on a determination that the disqualifying financial interest is not so substantial as to be deemed likely to affect the integrity of the employee's services to the Government.* The written waiver should describe the disqualifying financial interest, the particular matter or matters to which it applies, the employee's role in the matter or matters, and any limitations on the employee's ability to act in such matters. The waiver may apply to both present and future financial interests, provided the interests are described with sufficient specificity.

2. *(b)(2) Exemptions*

In implementing 18 U.S.C. 208(b)(2), OGE's regulations (5 CFR part 2640, subpart B) provide for exemptions to the general prohibition described in 18 U.S.C. 208(a). These exemptions allow participation without the need for individual conflict of interest waivers in the situations described below.

- Exemptions for Special Government Employees Serving on Advisory Committees

  An SGE serving on an advisory committee with a disqualifying financial interest based on his non-Federal employment or prospective employment may participate in any particular matter of general applicability affecting that interest if the matter will not have a special or distinct effect on the employee or his employer, other than as part of a class (5 CFR 2640.203(g)). This exemption does not apply to participation in particular matters involving specific parties (such as drug applications) and it does not apply to any stock ownership the employee may have in his employer or prospective employer.

  Under 5 CFR 2640.203(i), an advisory committee member may participate in committee matters concerning medical products if the disqualifying financial interest arises from (a) employment with a hospital or other similar medical facility whose only interest in the medical products is purchase of it for use by, or sale to, its patients; or (b) the use or prescription of medical products for patients.

  SGEs serving as nonvoting consumer or industry representatives on FDA advisory committees required by statute to have representative members may participate in any particular matter affecting a financial interest of the class that the employee represents (5 CFR 2640.203 (j)).

- Exemptions for all Government Employees[6]

  An employee may participate in any particular matter affecting one or more of the holdings of a diversified mutual fund or a diversified unit trust if the employee's disqualifying financial interest arises because of ownership in the fund or trust (5 CFR 2640.201(a)).

  If an employee's disqualifying financial interest arises from ownership in publicly traded securities that could be affected by the matter at issue, he may participate in a particular matter involving specific parties if the aggregate market value of his holdings and those of his spouse and minor children do not exceed $5,000, and may participate in a particular matter of general applicability if the aggregate market value of his holdings and those of his spouse and minor children do not exceed $25,000 in any one entity or $50,000 in all affected entities (5 CFR 2640.202).

An employee may participate in any particular matter affecting one campus of a State institution of higher education if the employee's disqualifying interest is employment in a position with no multi-campus responsibilities at a separate campus of the same institution (5 CFR 2640.203(c)).

3. *(b)(3) Waivers*

As discussed in section III.B, 18 U.S.C. 208(b)(3) was enacted as part of the Ethics Reform Act. Under this provision, a special Government employee serving on an advisory committee under FACA may participate in matters before the committee from which he would otherwise be disqualified if the official responsible for the appointment determines that *the need for the employee's services outweighs the potential conflict of interest created by the employee's financial interest.*

Under 5 CFR 2640.302(a), FDA may grant a (b)(3) waiver to a special Government employee serving on an advisory committee and to an individual being considered for appointment to an advisory committee. The granting official may consider many factors in determining whether to grant the waiver, including: the type of interest that creates the disqualification, the identity of the person whose financial interests are an issue, the uniqueness of the individual's qualifications, the difficulty of locating a similarly qualified individual without a disqualifying interest to serve on the committee, the dollar value of the disqualifying financial interest including its value in relationship to the individual's overall assets, and the extent to which the financial interest will be affected by the actions of the advisory committee (5 CFR 2640.302(b)).

The OGE regulations (5 CFR 2640.302(a)) also describe procedural requirements for granting a (b)(3) waiver, including:

- The advisory committee must be convened under FACA.
- The government official responsible for appointing the employee to his position (or other authorized official) must issue a written waiver before the employee takes any action in the matter(s).
- *The written waiver must include a certification that the need for the individual's services outweighs the potential for a conflict of interest.* The waiver should also fully describe the facts upon which the waiver is granted, including the nature of the financial interest and the particular matter(s) to which the waiver applies, and any limitations on the individual's ability to act in the matter(s). The waiver may apply to both present and future financial interests, provided the interests are described with sufficient specificity.

V. IMPACT OF THE FOOD AND DRUG ADMINISTRATION MODERNIZATION ACT OF 1997

Section 120 of the Food and Drug Modernization Act of 1997 (Pub. L. 105-115) includes additional requirements that apply to FDA advisory committees. One such requirement is that a committee member may not vote on any matter regarding the clinical investigation or approval for marketing of a drug or biologic if the member or the member's immediate family could gain financially from the committee's recommendations. Section 120 of the Modernization Act states that FDA may waive this conflict of interest requirement *if the member's participation is necessary to afford the committee essential expertise.* However, FDA may grant no waiver if the member's own work is involved.

When implemented together, three requirements in section 120 of the Modernization Act present conflict of interest challenges for advisory committees that review clinical investigations or approval for marketing of drugs and biologics.

- FDA may not grant a waiver allowing an advisory committee member to review his own work.
- There must be at least two members on the advisory committee who are knowledgeable about the disease that the product is intended to treat.
- Advisory committee members must be trained before participating in a committee meeting.

Of note, the pool of experts that serve FDA's Advisory Committees are special Government employees (SGE's).

VI. PROCEDURE FOR CONFLICT OF INTEREST CLEARANCE

The process for determining the eligibility of outside experts to participate in advisory committee meetings is a labor-intensive task that involves multiple levels of review. The process may involve as many as 11 steps. These steps are described below.

A. Review of Assignment to Assess the Potential for Conflicting Financial Interests

First, the agenda of the advisory committee meeting or individual assignment is assessed in light of the types of matters to be addressed. This assessment is critical because the eligibility and waiver rules (21 CFR part 2640) vary depending on the type of meeting or assignment. In general, there are three types of meetings or assignments: (1) a particular matter involving specific parties, (2) a particular matter of general applicability and (3) other matters such as committee member training or a review of intramural research.

If the meeting or assignment involves a particular matter involving specific parties, all entities with a financial interest in the meeting or assignment are identified to the extent feasible. For a meeting or assignment related to a product approval, the entities with a financial interest may include the sponsor and firms who will manufacture or market (1) the product being reviewed, (2) products that would be used in conjunction with the one being reviewed, and (3) products that would compete with the one being reviewed.

B. Preparation of Confidential Financial Disclosure Statement (Form FDA 3410)

It is critical that the FDA's financial disclosure form (FDA form 3410) be clear and accurate. In preparation for each advisory committee meeting, FDA's Center specific Advisory Committee Staff send each special government employee instructions and a summary of his or her previously reported financial interests in an effort to assist the SGE in updating his or her relevant information. The FDA staff is available to answer any related questions.

C. Completion of Confidential Financial Disclosure Statement by Outside Expert

The outside experts are expected to fill out the questionnaires to their fullest knowledge. There is no general requirement that they seek out additional information about interests of their employing institutions beyond their own personal knowledge. There is an exception to this provision in the case of Department heads. Department heads are expected to be knowledgeable about all research within their department and to obtain additional details on the research if needed.

D. Review of Questionnaire and Initial Determination

The FDA staff reviews the member's responses to the questionnaire and focuses on whether a conflict of interest exists. Based solely on the reported information it is often possible to determine: (1) there is no conflict of interest, (2) there is a conflict of interest that is minimal and a waiver can easily be justified or (3) there is a conflict of interest that is so great, recusal is the only course of action.

When clarification is needed, FDA staff may ask the outside expert to respond to additional questions.

If a conflict of interest exists, the details of the conflict are documented. FDA staff considers the factors described in the section on FDA's Modernization Act and uses the criteria tables in section three of this document in determining whether to recommend a waiver.

E. **Consultation with Review Division.**

Advisory committee meetings are scheduled to provide advice to the FDA official making a decision. Typically, the FDA official is an Office or Division Director. The official is notified of any significant conflicts of interest that are reported to enable a determination of the extent to which the member's expertise is important to the meeting. If the reported interest is significant and the need for the member's services is not great, recusal would be appropriate. If the member's services are important to the meeting because no one else with the expertise can be obtained for the meeting, a waiver may be appropriate. In making this determination, the review office and division must take into account the requirements of the FDA Modernization Act of 1997.

If it is not feasible to obtain other expertise, the review division and advisory committee staff will work together to provide the necessary justification for any waiver. Where the financial interest is relatively large it is essential that the justification be particularly strong.

F. **Preparation of Waiver and Justification**

Waivers are prepared using the standard Agency format. (See Appendix 1)

G. **Review by FDA's Ethics Staff**

The FDA Ethics Staff conducts an independent review of all conflict of interest waivers and makes a recommendation to the approving official concerning the waiver. If questions arise about the justification for the waiver, the Ethics Staff asks the recommending office for additional information. The Ethics Staff may also consult with the Office of General Counsel in the Department or the Office of Government Ethics.

H. **Final Approval by Appointing Official**

A proposed waiver and justification for the waiver receives multiple levels of review before reaching the appointing official for final approval. The official should have confidence in the vetting process and should feel confident in the recommended action.

The appropriate review division staff (including Office and Division Directors), appropriate conflict of interest staff, recommending official for the waiver, and appropriate Ethics Staff member are available to provide additional information and guidance to the appointing official.

If the appointing official does not approve a proposed waiver, the official notifies all affected parties and articulates the reason(s) for disapproval. The requesting official may choose to appeal the decision, may modify the agenda for the meeting, or may take another appropriate action. Every effort is made to resolve the issue expeditiously.

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[1]This guidance document represents the Agency's current thinking on policies and procedures for handling conflicts of interest with FDA advisory committee members, consultants, and experts. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

[2]*To Serve with Honor: Report of the President's Commission on Federal Ethics Law Reform (Commission Report)*, March 1989, p. 29.

[3]*Commission Report*, p. 30.

[4]*Commission Report*, p. 30.

[5]*Commission Report*, pp. 30-31.

[6]Please note that most full-time FDA employees are subject to a prohibited holdings regulation which prevents the ownership of financial interest in significantly regulated entities, notwithstanding the regulatory exemptions.

Conflict of Interest (COI) Criteria Guidance Table Working Definitions

Linked to the elements of the FDA Form 3410, the COI criteria guidance table merges the waiver criteria document and the interim section 502 guidance.

Working Definitions under Involvement Level:

NOTE: For convenience, the guidance table uses the categories of low, medium and high involvement to reflect the monetary levels involved. However, as the table demonstrates, the overall level of a conflict of interest is determined by more than one factor.

General Matters

Particular matter of general applicability means a particular matter that is focused on the interests of a discrete and identifiable class of persons, but does not involve specific parties. For example, a guidance document that affects an entire class of products and all similarly situated manufacturers is a matter of general applicability. In addition, the use of a potential product solely as a model or example for general discussion, the results of which will apply to a class of products may be a matter of general applicability.

Party Matters

Particular matter involving specific parties focuses on a specific product application or other matter affecting a specific manufacturer and its competing products/manufacturers (e.g., NDA, PMA, PLA/BLA, efficacy supplement for new indication). It focuses uniquely and distinctly on a given product/manufacturer.

Working Definitions under Expected Action:

Cover memo

The SGE's reported interests, including those that do not require a waiver, a written 502 or an exclusion, are explained to the Ethics Staff in a memorandum.

Decision (W)

This notation appears when it is most likely that a waiver will be granted. However, in all cases, each proposed waiver will be evaluated and judged on its own merits in light of all relevant factors during the review process, and it is understood that an approval is never automatic.

Decision (WC)

This notation appears when the extent of the interest must be examined and balanced against the need for the SGE's expertise. The decision to waive is not automatic and requires careful review. Before seeking a waiver in this involvement category, the Center may wish to consult with the Ethics Staff. When reviewing a waiver in this risk category, the Ethics Staff may consult with Center Officials, HHS General Counsel Ethics Division and the Office of the Senior Associate Commissioner to recommend the best course of action.

Decision (AC)

This notation appears for matters that may fall under the criteria for written 502s. In these cases, the Center will consult with the Ethics Staff to discuss the nature of the interest and determine whether it is necessary to prepare a written 502 (e.g., past financial interest is negligible, occurred over a year ago, but raises appearance concerns).

Decision (AE)

This notation appears when the SGE's interest will warrant a written 502 authorization or exclusion. The decision may require managerial prerogative. The Ethics Staff may consult with Center officials, HHS General Counsel Ethics Division and the Office of Senior Associate Commissioner to recommend the best course of action.

Exclusion

This notation appears when the SGE's reported financial interest and the conflict outweigh the need for the individual's services. However, the decision to exclude is always reviewed in context with the issues before the committee.

Definition of Institution Addressed in Section "I" of the Table

Institution means a nonprofit research center affiliated with academia. Research is defined as basic and applied research. The institution may also coordinate studies (clinical trials) at other research facilities. Institutional funding may be derived from government sources, private donations, industry donations, contracts and grants.

Net Worth

Net worth is defined as the value of an individual's total assets minus the value of the individual's debts (financial liabilities).

Related Issue

"Related" issue is defined as a matter surrounding a product(s) that competes or may potentially compete in the marketplace with the proposed product of interest.

Investigator

Investigator means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. "Sub-investigator" includes any other individual member of that team.[1]

Expected Action

Expected action is defined as the outcome that is anticipated in the majority of cases. It follows the course of action that weighs the Agency's need for expert advice against any appearance or actual conflict of interest.

Note on 502 Delegation of Authority

When an appearance or impartiality concern is present, the SGE should not participate in the

[1] http://www.fda.gov/oc/advisory/conflictofinterest/def.html

matter unless he has informed the agency designee of the appearance problem and received authorization from the agency designee. The COI Criteria Guidance Table identifies appearance and impartiality concerns related to various topics, e.g., contracts and grants provided by a sponsor that are unrelated to the product at issue, and provides resolution direction.

If the appearance issue is of a certain magnitude, a written authorization signed by the agency designee is required for the SGE to participate. For issues that fall below the threshold for a written authorization, Robert J. Byrd, Deputy Ethics Counselor, delegated authority (memo dated April 6, 1996) to the Ethics Staff located in the Division of Management Programs, Office of Human Resources and Management Services.

If the reviewing officials in the Ethics Staff concur with the Center's request for the SGE to participate, an authorization is noted on the cover memorandum. If the reviewing official questions the participation or believes based on the facts of the case that a written determination signed by the agency designee is warranted, the Center will be contacted and a dialogue will take place seeking appropriate resolution.

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[1] 21 CFR Section 312.3(b)

Office of the Commissioner
Food and Drug Administration
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