

Draft Guidance for the Public, FDA Advisory Committee Members, and FDA Staff on Procedures for Determining Conflict of Interest and Eligibility for Participation in FDA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 (Docket 2007D-0101)

Comment on Financial COI Guidance for Patient Advisors to FDA

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Context for Patient Advisors

Experts on clinical trials and the evaluation of new therapies for severe illness are increasingly alarmed by the crisis of confidence of the public in general and of potential research participants in human studies in particular. The ability of science to extend medical miracles of the last century to long term treatment of chronic illnesses that are the major challenges in the 21st century is being stretched beyond the applicability of the underlying assumptions of scientific models used for clinical tests of the acute illnesses.

A paradigm shift to ‘patient centered’ research and medical care is viewed by many as a vital element to regain the momentum of medical science. Patient centered health care emphasizes more active roles for patients in every aspect of research and application of evidenced based medicine, including self help actions ranging from exercise to significant involvement in regulatory and public policy decisions. Recognition of the value of obtaining the patient perspective on key decisions of the FDA, has prompted officials to gradually expand programs and roles for patient consultants and patient representatives on FDA Advisory Panels.

Now conflict of interest guidelines are being tightened as one means of regaining public trust. There is a public perception that experts on advisory committees can be biased in their recommendations due to financial conflicts of interest. Most frequently these financial conflicts of interests occur when highly specialized expertise is sought where only one or very few experts are available anywhere. Exemptions have been sought by FDA in these cases where the knowledge of a consultant is essential for a complete evaluation. Other possible conflicts of interests may occur in the more remote financial relations between an advisor and a sponsor of a therapy under FDA review.

Patient Advisors

The primary reasons patient consultants serve is to contribute unique insights from direct experience with their illnesses to the regulatory discussion, to advocate for the interests of patients in general, and to put a human face on the disease for others in the process. Patient consultants are dissimilar to paid consultants of sponsors in the pharmaceutical industry, in that they volunteer time and effort to the FDA (although they may be entitled to receive minimal daily stipends from the government to compensate for travel, food, and daily allowance). In

contrast, expert medical scientists consult with sponsors to earn income based on their extensive training and research activity. Often, by means of conflict of interest exemptions, they have also served as consultants to the FDA in its regulatory decision making. Given these significant differences in the nature of possible conflicts of financial interests, an argument can easily be made to evaluate potential financial conflicts of interest for patient consultants entirely differently from those for expert consultants from science and industry. That is to say, patient consultants should not be subjected to the same criteria as expert medical and scientific consultants whose income may be significantly dependent on the work they do with sponsors.

In addition, the major problem with the draft guidance document is that the procedures and criteria do not take into consideration the most rudimentary concepts of accounting, finance, or economics, in their calculation of cutoff criteria for determining COI. The result of applying these criteria as proposed at best would screen out very well qualified patients from participation on behalf of patients. Even worse, by overweighting the impact of assets on conflicts of interest, the draft guidance procedures would disproportionately disqualify people with experience in financial markets. These are individuals who, by virtue of their financial experiences, would be better equipped to understand the business ramifications of FDA decisions and their impact on patients' interests.

'Pilot' Patient Consultants for Parkinson's Disease

For 7 years I have been an FDA patient representative for Parkinson's disease (PD), which is considered a serious illness, and thus a priority among the central goals of the Agency. As a patient representative, I have been charged with the task of giving a voice to the interests of other patients like myself, who live with this progressive, degenerative condition 24/7 and are considered by most to be a primary constituency for the FDA role in regulation of the safety and efficacy of new medical therapies. The premise of the patient representative and patient consultant pilot projects (first in oncology and now in Parkinson's) is that patients or close family members who live with a disease all the time have unique insight into the condition that no outsiders can fully understand. Thus, there is singular value added by the inclusion of these points of view in achieving the most desirable results from the average 15+ years new therapies are in the pipeline.

The PD patient consultant program is a center piece in a comprehensive advocacy and outreach program called the *Parkinson Pipeline Project* (see www.pdpipeline.org) with active volunteer roles for highly qualified PD patients, who track the progress of all new therapies in the clinical phases of evaluation for PD and provide the patient perspective through education and consultation to all constituents in the process, including FDA, sponsors, clinical researchers and other patients

After seeking approval from the FDA to initiate the PD patient consultant program for more than 3 years, it has taken another 2 years to set up the activities, and at last the program is now underway. Highly qualified patient consultant volunteers have been recruited and trained. However, despite the extensive time and effort put into creating the PD patient consultant program and despite the virtually unanimous agreement of all involved that patient participation

contributes a unique and invaluable perspective to the regulatory process, actual patient involvement has been severely limited. Two issues in particular contribute to this impasse.

1. The procedures involved in assessing possible Conflict of Interest block meaningful inputs from patients to FDA decision processes.

Typically 6 weeks are required to clear a patient for COI and this must be done anew each time a patient consultant is slated to participate in a FDA review procedure. Since meetings are usually scheduled only 2 weeks in advance, necessary COI clearance could rarely be accomplished in a timely manner, thus, patient consultants would never get through the door. Alternative screening methods (such as pre-approval or changing screening procedures) were suggested to solve this problem but have been rejected as “diluting the process.” After many months delay, an approach to get started has been taken. The experiences with the COI procedure and the extent to which it actually blocks participation will be documented for a year and then the issue will be revisited with new information.

2. The financial conflict of interest criteria are problematic in several essential ways:

- a. The financial conflict of interest criteria and procedures proposed are overly simplified to the point that they make highly inaccurate assumptions about the actual relative values of different kinds of financial interests and greatly distort the extent of actual motivation to bias decisions derived from these financial interests. The financial gain to an advisor is far greater for consulting fees and other direct income such as stock options than for stock holdings, and even more so for holdings of competitors. By adding together equity assets with consulting income, the influence of assets is over weighted in determination of disqualification and the influence of consulting fees and other direct income are under weighted. This distortion will affect Patient Representatives more than other advisors because patients will not likely have consulting fees. Thus, a patient with a diversified portfolio could be screened out merely by the extent of his/her wealth, not by any inherent conflict. Also, past ownership of assets would not influence the future, whereas consulting in the past may effect the future motivation.
- b. The criteria do not adequately consider what the advisor actually has “at risk” and they do not account for other factors at risk that may balance the bias that may result from financial interests. The effect of diversification to manage risks that would cancel out any motivation for conflicts is not considered. More importantly, no consideration is made of the value of one’s own health as a counter weight to potential financial bias on the parts of patient consultants.
- c. The net result of these criteria and procedures is the arbitrary disqualification of dedicated and knowledgeable patients from participation in helping rid the world of their disease. Not only does this narrow unnecessarily the kinds of people available to perform the tasks of patient consultants, but it is also demoralizing to the patients.

I do not believe that the FDA intends to exclude well qualified patient representatives and patient consultants from full participation in their intended roles. But the conflict of interest criteria do just that. Below I will examine the criteria for their ability to screen out real financial conflicts of interest and suggest refinements to the concepts used to determine financial interest based on fundamental accounting rules familiar to anyone who fills out a tax return. If modified, this would go a long way towards ensuring that the resources provided by well qualified patient representatives and consultants are not lost. It goes without saying that the criteria can always be set at a level that few qualified people could make it through the screen. I do not think that would be in the public interest, however, and I will suggest reasonable criteria and rationale for a method of reporting financial information that will increase the power of screening by focusing only on essential material information.

Assessment of COI Guidance

The potential for conflict of interest in the draft Guidance is mainly related to decisions where the advice given has an effect on personal financial gain or loss of the advisor. The larger the gain or loss, the more personal interest could enter considerations (whether consciously or not) and create a bias which discounts public interest. The extent to which this motivation is real and substantial enough to outweigh other non-financial factors, such as professional ethics or, in the case of patient advocates, their own health, will clearly vary from person to person, depending on a range of variables, including personal financial considerations. It is imperative to counter these biasing factors, but the proposed COI criteria conflate and omit a number of crucial issues.

First, assets are different from income. The most fundamental accounting principles would not count assets (investments) as equivalent to income from a source of potential conflict of interest. Thus adding these together in comparison to an absolute benchmark (\$50,000) is not an appropriate procedure. An illustration of appropriate comparison of assets to consulting fees comes from the IRS code which taxes only the gain from sale of assets whereas consulting fees are 100% taxable. It is possible to compare these two sources of financial reward, but it requires some assumptions about such issues as risk and return on investment which can become a very complex conversion formula to be able to validly add the two together. Financial incentives are generally tied to income, and in most instances income return on investments is only a small fraction of the asset value, so by adding the two together the formula overweighs the influence of financial assets in surpassing the cutoff point. At the very least these two forms of financial resources should be screened separately with different upper limits to reflect the fundamental differences in financial value of each. .

How can a valid comparison be made? Other financial analysis concepts can be considered when picking a cutoff point. For instance, average financial assets yield on an average of 5-10% annual return for a moderately risky investment. A 5% to 10% return on a \$100,000 to \$500,000 of investment assets would be required to generate the same income as \$50,000 in consulting fees before taxes. (It is easiest to make moderate assumptions about return rates for the average case such as illustrated in the example, but it is possible assume higher returns as the norm, particularly in the case of smaller biotech firms where the net return of stock options could easily approach equivalence with a consulting fee.) Thus, a criterion of \$5,000 cutoff on consulting fees and stock options in direct payments would be similar to equity holdings in a sponsor above

\$50,000. The amount sufficient to bias an advisor is a judgment call, but the highest acceptable level for an expert consultant in an actual conflict of interest situation who may have on-going relations with the sponsor, will likely be quite different than for a patient who has his own health at stake when he represents patients' views.

It should also be noted that direct payments to the advisor are more likely to have a biasing effect on the expert than indirect payments to other parts of large institutions – unless, similar to asset positions, the institution is particularly dependent on that indirect payment, and /or the advisor is closely responsible for that part of the institution. Again it is only reasonable to scrutinize these indirect payments if they are very large in proportion to the size of the institution's total holdings. Certainly an indirect grant under 1 or 2% of the total revenue of an institution would not likely be noticed by an advisor in a different part of that institution, and should not be required to be reported.

Direct payment or asset positions are more important financially than competitive positions. For a decision made by an advisor to have an effect on his own competitive position to be comparable to the same asset or consulting position in the company directly involved, the competition who have to be head to head zero sum, win-lose choice between competitors. This kind of competition is rare with innovative products as complex as medical interventions.

Examination of competitive financial positions also raises issues of diversification and concentration of assets in sound portfolio management of assets. With a diversified portfolio of drug company stocks competitive interests tend to balance each other. Even with direct competition where one gains and the other loses, if you own both securities you would be indifferent to competitive advantage from a decision you made that impacted on the competitive position in the industry.

It is not unethical to have assets. In fact, looking at money as a motivator to alter ones objectivity (the harm of an actual conflict), screening out people with diversified assets is likely to eliminate those with the least motivation to violate the public trust. People who already have more assets than a \$100,000 or \$500,000 limit are likely to be less motivated by the effect of their decisions on the value of those assets than people with fewer assets (it's a smaller % of their wealth). Certainly if an asset is less than 1% of holdings, it should not be considered as a potential conflict if it is a competitor asset in a balanced portfolio, so these assets could be removed from the review and not be reported as consequential. Even assets directly held in a company of less than 0.5% in a balanced portfolio could be considered inconsequential if direct competitors are also held.

Finally, what is your health worth? It is hard, if not impossible, to imagine that patient representatives and consultants would be swayed by conflict of interest biases to actually vote against their own health interests. For patient consultants, the vote for health of themselves and fellow patients whom they represent is in line with the goals of the agency, and should be weighed as mitigating threshold to balance any decisions affecting investments and income

Recommendations

In summary I suggest that when weighing assets such as common stocks, different criteria should be used to establish cutoffs than for direct income payments received from a sponsor directly affected by the advisor. Criteria applied to consulting fees should be tightened, whereas criteria on assets should be loosened to a ratio of income equivalency between assets and direct consulting fees or other payments of at least 10 to 1 (e.g., at a 'market' rate of return of 10% per year, a \$500,000 of stock ownership translates to \$50,000 of consulting). In this formulation the earning power of the asset is compared with the earnings from consulting. Cutoff points as low as \$2,500 in consulting fees and \$25,000 in stock ownership would not be too tight as absolute upper limits for direct financial interests in the sponsor whose case is under consideration, even for an advisor for which these values are under 1% of their wealth. Cutoff points below \$1000 in direct payments and \$10,000 in stock ownership would not likely have a biasing effect on patient consultants and could be set as the practical lower limits for absolute disqualification of Patient consultants. I would tighten the cutoff in this instance to the lower end of these amounts to avoid appearances of conflicts because of assets in an institution directly affected by a decision. For competitive asset holdings in a diversified portfolio, advisors should only report assets in excess of 1% of their net worth; then after subtracting balancing interests from other competitors similar criteria could be applied as for direct stock holdings (e.g., a material COI exists if there is an unbalanced concentration of assets in a competitor of \$25,000 stock ownership).

These criteria provide reasonable checks on conflicts of interests by screening out real conflicts and allowing those with no real conflicts to serve – unlike the currently proposed criteria. While we can find people who have little or no financial assets to represent patients, considering that the FDA is regulating businesses that are heavily involved with financial markets, we will unnecessarily limit our advisors' experiences with these markets by arbitrarily excluding people who have even relatively low amounts of assets in these financial markets.