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Managing conflicts of interest: a survival guide for biotechs

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Conflicts of interest in research can affect a company's ability to move a product through the approval process or attract investment. Avoid the pitfalls by taking pro-active steps to manage these risks.

The complexity of relationships in biomedical research among physicians, institutions, industry and other actors can lead to potential conflicts of interest. Possible conflicts could arise from the research itself, the relationships between a company sponsor and the physicians/researchers who act as investigators, the relationship between the company sponsor and clinical trial participants, the relationship between researchers and their institutions, or even between researchers and patients. Trends in biomedical research are likely to exacerbate these tensions.

Biotech companies need to be aware of these issues. In some cases, laws or regulations specifically detail proper conduct, such as informed-consent requirements. In addition, nongovernmental entities have relevant policies, for example, the American Medical Association's (AMA) Code of Medical Ethics (see Box 1).

Although there could be several potential conflicts in a research endeavor, this article highlights several scenarios in which possible conflicts may arise specifically from the relationships between life science companies and the clinicians they hire as investigators or the participants in their trials. We describe federal law and other applicable rules, and provide advice on how companies should proceed.

None of the relationships described in this article are prohibited by law. However, companies should pay close attention to the rules governing these matters as they affect how to operate. The ramifications of ignoring these issues can be severe. A conflict of interest—or the perception of a conflict—may cause the US Food and Drug Administration (FDA) to question the reliability of a company's data or bring unwelcome scrutiny in the media. Both could affect a company's ability to attract investment or move a product through the approval process. It might also make it impossible to collaborate with the physician or institution of a company's choice. Moreover, the potential for lawsuits based on existing or novel theories of liability in this area may be increased. Addressing these issues early on will help avoid these pitfalls.

What are the rules?

Generally speaking, federal law only applies to those potential conflicts that could affect the reliability of the data in a marketing application submitted to the FDA. Federal law does not prohibit—or even define—a conflict of interest. Rather, FDA regulations address issues surrounding financial disclosure by investigators. They focus on the bias that could arise from an investigator's financial interest in the outcome of a study because of the way payment is arranged, because the investigator has a proprietary interest in the product or because the researcher has an equity interest in the company sponsor of the study[1].

These regulations require disclosure, by the sponsor, of financial arrangements between the sponsor and clinical investigators and certain interests of the clinical investigators in the product under study or in the sponsor of the covered study. Companies must disclose or certify "information concerning the financial interests" of a clinical investigator.

Specifically, the company must disclose

- any financial arrangement with an investigator performing the trial if the value of the compensation could be influenced by the outcome of

the study;
- any significant payments of other sorts from the sponsor which are payments that have a cumulative monetary value of $25,000 or more beyond the cost of the study, such as grants to fund ongoing research, a retainer for ongoing consultation, honoraria or compensation in the form of equipment;
- any proprietary interest in the tested product held by a clinical investigator involved in a study;
- any significant equity interest in the sponsor held by any clinical investigator involved in the study; and
- any steps taken to minimize the potential for bias resulting from any of these arrangements, interests or payments[2].

FDA will use this information as part of its assessment of the reliability of the clinical data presented[3]. If FDA determines that the financial interests of any clinical investigator raise a serious question about the integrity of the data, FDA will take any action it deems necessary to ensure the reliability of the data, including initiating agency audits of the data derived from the clinical investigator in question; requesting that the applicant submit further analyses of data, for example, to evaluate the effect of the clinical investigator's data on the overall study outcome; requesting that the applicant conduct additional independent studies to confirm the results of the questioned study; and refusing to treat the covered clinical study as providing data that can be the basis for an agency action[4].

Companies need to be aware of other rules as well. For example, the US Department of Health and Human Services (DHHS) issued a final guidance in May 2004 that addressed conflicts of interest[5]. In this document, DHHS provides advice to institutions, institutional review boards (IRBs) and clinical investigators (see Box 2).

Individual institutions often have their own rules and procedures governing conflicts of interest. In fact, the accreditation standards from the Association for the Accreditation of Human Research Protection Programs specifically require that the entity seeking accreditation "has and follows written policies and procedures to identify, manage and minimize individual conflicts of interest"[6]. Although these policies vary, they directly affect the activities of life science companies. For example, Stanford University's Faculty Policy on Conflict of Commitment and Interest addresses issues such as investments in startup companies involving university faculty, technology licensing, intellectual property and faculty financial interests in outside entities doing business with the university[7].

Thus, companies must do their homework before doing business with investigators and faculty from various institutions as well as choosing sites for clinical trials. They should take steps to manage conflicts as well as address perceived conflicts. They must also be sure to comply with the FDA's disclosure requirements and other applicable rules imposed by professional organizations, accrediting bodies and individual institutions.

The rules in practice

So how might this work in practice? Let's examine a few hypothetical scenarios. Note that these are meant to be illustrations and should not be interpreted as legal advice.

Example 1. Umbrella Biotech is performing a late-stage clinical trial for its product, a recombinant therapy to treat cancer. It has identified Dr. Brilliant, a noted oncologist and researcher at Ivy University, as a possible principal investigator and Ivy University Hospital as a trial site. As part of her compensation arrangement with Umbrella, Brilliant asks for company stock. What should Umbrella do?

First, Umbrella should familiarize itself with the requirements governing these arrangements imposed by federal regulations. The company also must research whether Ivy has policies and procedures that may apply. These policies may prohibit certain financial arrangements between faculty and outside industry, or they may detail specific ways the company must manage the conflicts of interest created.

Despite the possible conflict, there may be compelling reasons to use Brilliant as the lead investigator (such as her reputation for high-quality work and her ability to publish articles in leading scientific journals) and compensate her with stock (not adding to the company's burn rate). As it continues to evaluate the hiring of Brilliant, Umbrella should keep in mind that the fundamental objectives of federal and private rules governing conflicts of interest are to protect the research participant and to ensure the accuracy of clinical data.

If it chooses to hire Brilliant, therefore, in addition to complying with FDA regulations and Ivy University's rules, Umbrella should take steps to address these matters. Specifically, it should include language in the informed consent documents that clearly discloses its financial relationship with Brilliant. These details should also be disclosed to Ivy through its IRB. Other steps could include committing to publishing the results of the trial as soon as practicable or seeking an opinion from outside ethicists. Resources to obtain such opinions may be sought from the AMA, the Biotechnology Industry Organization (which has a bioethics committee), nonpartisan think tanks such as the Hastings Center or law firms and outside consultants that focus on matters involving compliance, conflicts and bioethics.

Example 2. Biotech company MedEx wants to conduct a clinical trial for its new drug developed to treat a common neurological disorder that currently

has no cure. In animal studies, the company had discovered that although the drug provides many benefits, in a small number of cases, it also caused heart damage. If that happens in humans, MedEx may want to halt the trial but may face the claims of numerous participants that they should be entitled to continue the experimental treatment due to its beneficial effects. What can MedEx do to ensure that it does not find itself in a conflict between those who wish to continue participating and the potential for harm from such participation?

This situation is counterintuitive to the typical claims seen from clinical trials —those where the participant alleges harm from participation, not from being prevented from participation. Here, MedEx should be proactive when planning the trial and prevent the conflict. How? By ensuring that its informed consent form specifically notes that the company retains the right to terminate the trial at any time, without obligation to the trial participants. MedEx should be sure that this right is spelled out clearly and concisely, in understandable terms. It should also take steps to ensure that its investigators clearly explain this provision of the consent form to research participants.

Example 3. Dr. Wise is a leading researcher at Ivy University and has been hired to advise Warbucks, a national investment bank. From time to time, Wise will be called by Warbucks' investment advisers to comment on a clinical trial being conducted or to address potential issues raised by the FDA in connection with an experimental drug. As noted above, Ivy University is often a clinical trial site. Is this a conflict of interest for Wise? For Ivy? What if Umbrella wants to hire Wise to be an investigator for a trial or a clinical adviser to the company?

Clearly, Dr. Wise cannot comment on any trial being conducted by Ivy University or any product he is researching personally or in tandem with others. This is tantamount to insider information. But what about a drug that is not being studied at Ivy but is manufactured by Umbrella and being studied elsewhere? Is Ivy's connection to Umbrella through a separate clinical trial enough to raise a potential conflict of interest? Here again, the issue is the perception of the public and the media. It is likely that the connection among Umbrella Biotech, Ivy University and Dr. Wise would be of interest to someone considering Wise's opinions. Disclosure would provide the transparency necessary for that individual to assess whether the connection would or could affect the insights offered.

If it seeks to hire Wise, Umbrella may ask him to sever his relationship with Warbucks. If it doesn't do that, the company must take steps to make sure that Wise is not providing advice or information to Warbucks about its trial at Ivy or the rest of the company's work. It should also ensure that Wise discloses to Warbucks, Ivy, the FDA and others his relationship to Umbrella.

Conclusions

Conflicts of interest in research are not illegal, but they can influence decisions and actions. Moreover, the perception that the conflict affected the judgment of companies, their employees, or clinical investigators will have severe ramifications. Taking pro-active steps is the best way for biotech companies to manage these issues.

As with other legal and ethical issues confronting life science companies, it is critical for the company to understand the relevant law, gather the relevant facts about the rules governing their particular situation and take necessary action. Companies should proceed with transparency and maximum disclosure when managing conflicts of interest or the perception of conflicts.

References

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Box 1: The AMA says...

The AMA's Code of Medical Ethics, and opinions interpreting the Code, provide both general policies and specific answers to particular situations. Code Sections 8.03, 8.031 and 8.0135, for example, address conflicts of interest generally, in clinical research and in the conduct of clinical trials. Some of the policies and restrictions noted in the clinical research area follow.

- A clinical investigator who is involved or knows he/she will be involved in a research project cannot ethically buy or sell the company's stock until the involvement ends and the results of the research are published or otherwise disseminated to the public.
- Any remuneration received by the researcher from the company whose product is being studied must be commensurate with the efforts of the researcher on behalf of the company.
- Clinical investigators should disclose any material ties to companies whose products they are investigating, including financial ties, participation in educational activities supported by the companies, participation in other research projects funded by the companies and consulting arrangements.

In the clinical trials area, some of the guidelines noted in the Code include the following:

- Physicians should be familiar with the ethics of research and should agree to participate in trials only if they are satisfied that an Institutional Review Board has reviewed the protocol, that the research does not impose undue risks upon research subjects, and that the research conforms to government regulations.
- When a physician has treated or continues to treat a patient who is eligible to enroll as a subject in a clinical trial that the physician is conducting, the informed consent process must differentiate between the physician's roles as clinician and investigator.
- Any financial compensation received from trial sponsors must be commensurate with the efforts of the physician performing the research. Financial compensation should be at fair market value and the rate of compensation per patient should not vary according to the volume of subjects enrolled by the physician and should meet other existing legal requirements.
- It is unethical for physicians to accept payment solely for referring patients to research studies.
- Physicians should ensure that protocols include provisions for the funding of subjects' medical care in the event of complications associated with the research.
- The nature and source of funding and financial incentives offered to the investigators must be disclosed to a potential participant as part of the informed consent process. Disclosure to participants should also include information on uncertainties that may exist regarding funding of treatment for possible complications that may arise during the course of the trial. Physicians should ensure that such disclosure is included in any written informed consent.

Box 2: The DHHS says...

According to DHHS, this guidance applies to “human subjects research conducted or supported by HHS or regulated by the FDA.” Because FDA requires human subjects research to be reviewed by an IRB, the provisions in the guidance directing the IRB to consider actions regarding financial interests apply to company-sponsored trials. These include:

- examining how the research in question is financed and where and by whom the study was designed;
- examining the interests created by the financial relationships involved including whether the individuals or institutions receive any compensation that may be affected by the study outcome, whether they have any proprietary interests in the product, an equity interest in the research sponsor or receive significant payments of other sorts;
- determining whether methods used to manage the financial interests of parties involved in the research protect the rights and welfare of human subjects;
- determining what other actions are necessary to minimize risk to subjects, such as any or a combination of the following: reduction or elimination of the financial interest, disclosure of the financial interest to prospective subjects, additional oversight or monitoring of the research, and use of an independent data and safety monitoring committee or similar monitoring body;
- determining the kind, amount, and level of detail of information to provide to research subjects regarding the source of funding, funding arrangements and financial interests of the parties involved in the research; and developing policies and procedures addressing IRB member potential and actual conflicts of interest.