JOURNAL OF CLINICAL RESEARCH BEST PRACTICES

Vol. 4, No. 10, October 2008 "Can You Handle the Truth?"

Investigator Disclosures of Financial Conflicts

By Norman M. Goldfarb

It has been ten years since the U.S. Code of Federal Regulations established a requirement for study sponsors to collect disclosures from investigators of financial interests that may bias the results of a study. (Financial Disclosures by Clinical Investigators (21 CFR 54) was published in the Federal Register on February 2, 1998, and became effective on February 2, 1999.) Investigators have now submitted hundreds of thousands of disclosure forms. What have they disclosed?

In simple terms, disclosable financial interests include:

- "Equity interest" (stock, options, etc.) in the sponsor greater than $50,000 in a security that is publicly traded or of any amount in a security that is not publicly traded.
- "Proprietary interest" in a patent, trademark, copyright or licensing agreement relating to the product.
- "Significant payments of other sorts" to the investigator or research site exceeding $25,000 for consulting, speaking, research grants, equipment, etc.
- Any other "financial arrangement" between the investigator and sponsor that could be influenced by the outcome of the study.

Sponsors collate and summarize this data and submit it to FDA in a New Drug Application (NDA) using two forms:

- **Form FDA 3454: Certification: Financial Interests and Arrangements of Clinical Investigators** certifies the absence of any financial arrangement between an investigator and the applicant for a marketing application for a new investigational product. The form is available at http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3454.pdf.
- **Form FDA 3455: Disclosure: Financial Interests and Arrangements of Clinical Investigators** details the specific status of any financial arrangement between an investigator or investigators and the applicant for a marketing application for a new investigational product. The form is available at http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3455.pdf

The forms are accompanied by attachments that list the investigators and provide other details. Because FDA does not specify the exact contents of these supporting documents, they vary substantially by sponsor.

On July 11, 2008, FDA responded to the author's Freedom of Information Act (FOIA) request for a sample of 3454 and 3455 filings. FDA supplied redacted copies of the disclosure filings in 49 NDAs. Table 1 lists the disclosure filings, dated from September 15, 1999 through June 14, 2004. FDA had "recently disclosed" these filings in response to previous FOIA requests by other parties. The filings cover more than 10,000 investigators in more than 271 studies by 44 sponsors. (It is impossible to determine the number of studies in five filings.) In general, the investigators' financial disclosure forms to the sponsors were not included.

Table 1. Disclosure Filings

NDA #	Applicant	Drug	3454/3455 Date
20-920	Scios	Natrecor	10/25/00
21-100	Pharmacia & Upjohn	Axert	09/15/99
21-106	Sensus Drug Development	Somavert	10/13/99
21-158	SmithKline Beecham Pharmaceuticals	Factive	12/13/99
21-169	Jansen Research Foundation	Razatmne	12/29/99
21-187	Organon	Nuvaring	12/03/99
21-196	Orphan Medical	Xyrem	09/20/00
21-223	Novartis Pharmaceuticals	Zometa	12/17/99
21-232	Swedish Orphan	Nitisinone	12/29/99
21-257	Alcon Research	Travatan	06/26/00
21-264	Mylan Pharmaceuticals	Apokyn	04/17/00
21-266	Pfizer	Vfend	10/19/00
21-272	United Therapeutics	Remodulin	10/15/00
21-286	Sankyo USA	Benicar	07/12/00
21-290	Actelion Pharmaceuticals	Tracleer	11/06/00
21-321	Baxter Healthcare	Extraneal	06/04/04
21-337	Merck & Co.	Invanz	11/09/00
21-341	G.D. Searle	Bextra	11/30/00
21-345	Fonda	Arixtra	01/24/01
21-348	Oxford GlycoSciences	Zavesca	08/14/01
21-361	Salix Pharmaceuticals	Xifizan	11/28/01
21-366	AstraZeneca Pharmaceuticals	Crestor	05/31/01
21-368	Lilly ICOS	Cialis	05/29/01
21-395	Boehringer Ingelheim Pharmaceuticals	Spiriva	10/17/01
21-400	Bayer Corporation	Letriva	09/24/01
21-411	Eli Lilly & Co.	Strattera	09/07/01
21-427	Eli Lilly & Co.	Cymbalta	09/17/01
21-436	Bristol-Myers Squibb	Ability	09/18/01
21-437	Pharmacia	Ispra	10/20/01
21-445	Merck & Co.	Zetia	02/11/02
21-446	Pfizer	Lyrica	02/25/03
21-455	Hoffman-LaRoche	Boniva	07/01/02
21-468	Shire Pharmaceutical	Fosrenol	04/19/02
21-476	Sepracor	Lunesta	01/14/03
21-487	Forest Laboratories	Namenda	07/19/02
21-549	Merck & Co.	Emend	08/17/02
21-565	Allergan	Elestat	11/25/02
21-567	Bristol-Myers Squibb	Reyataz	11/18/02
21-572	Cubist Pharmaceuticals	Cubicin	12/19/02
21-595	Indevus Pharmaceuticals	Sanctura	03/13/03

21-629	Aventis Pharmaceuticals	Apidra	06/18/03
21-654	Pronova Biocare	Lovaza	06/11/03
21-673	ILEX Products	Clofarabine	03/29/04
21-677	Nutritional Restart Pharmaceutical	Nutrestore	07/24/03
21-688	Amgen	Sensipar	08/11/03
21-743	OSI Pharmaceuticals	Tarceva	04/30/04
21-756	Eyetech Pharmaceuticals	Macugen	03/12/04
21-779	CoTherix	Ventavis	06/14/04
50-794	Pharmion Corporation	Vidaza	12/26/03

Although the varying contents and redactions of the filings prevent complete analysis, the following observations can be made:

- 26 (53%) of the NDAs disclosed financial conflicts. 23 (47%) of the NDAs disclose no financial conflicts. 23 (47%) NDAs disclosed 115 significant payments of other sorts. 14 (39%) NDAs disclosed 111 equity interests. No proprietary interests or other financial arrangements are disclosed. No more than 1% to 2% of investigators disclosed financial conflicts. Five (10%) of the NDAs accounted for 151 (67%) of the disclosed conflicts. One NDA accounted for 50 (22%) of the 226 disclosed conflicts, including 40 (36%) of the equity interests.
- Sponsors described a variety of steps taken to minimize any effects of bias. These steps included review of disclosure requirements with investigators; diligent collection of disclosure forms; site monitoring and audits; data analysis to identify aberrant data; use of an independent data monitoring committee; exclusion of investigators from interim reports; use of multiple investigators; review of disqualified, restricted and assurances lists; subject randomization; double-blinding; GCP compliance; consistent protocol implementation across sites; and SOPs for handling irregularities such as protocol violations, subject withdrawals, missing data, and unblinding. Retroactive considerations included investigators who enrolled no subjects or only a small fraction of subjects, financial conflicts that occurred before or after the study period, and disclosures of amounts below the regulatory thresholds.
- There is no evidence of sponsors searching their own databases for information about conflicts, except to clarify ambiguous or erroneous reports of conflict.
- Many of the investigators are located in developing countries where the monetary thresholds for disclosure are relatively high compared to physician incomes.

From the FOIA documents, it is impossible to determine:

- How many investigators were rejected by sponsors because of financial conflicts
- How many financial conflicts were eliminated to make study participation possible
- How many investigators did not disclose financial conflicts intentionally or inadvertently
- FDA's reaction to the financial conflicts disclosed, including exclusion of data
- How many financial conflicts existed in studies that did not result in an NDA

Provided that investigators comply with the regulatory requirements for financial disclosures, and given standard precautions to prevent conflicts from influencing study results, financial conflicts do not appear to jeopardize the objectivity of clinical research data. However, there is no mechanism to verify the absence of conflicts such as equity investments in public companies. In addition, it is unclear whether study sponsors verify the absence of consulting and other relationships that are known to them.

The reporting system consumes substantial time and effort. These costs could be reduced if sponsors were to rely on their own data for consulting and other relationships known to them. Further, the reporting requirements are well suited for automation through a web-based application. Not only would such a system save time, but it would provide more complete information to FDA in a more consistent format.

Author

Norman M. Goldfarb is Managing Director of First Clinical Research LLC, a provider of clinical research best practices information, consulting and training services. Contact him at 1.650.465.0119 or ngoldfarb@firstclinical.com.

