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CLINICAL TRIALS

LIFE SCIENCE INVESTIGATOR-INITIATED TRIAL GRANT PROGRAM COMPLIANCE

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Life sciences companies use investigator-initiated clinical trial grants as vehicles to encourage physicians and clinical investigators to study their products and publish or present findings. Investigator-initiated trial programs (IIT) go by a variety of different names, but are generally structured such that a pharmaceutical or medical device manufacturer provides a monetary grant to a physician or clinical investigator who, in turn, will design and conduct a clinical study on the manufacturer's product.¹ From the manufacturer's perspective, the manufacturer is not the "sponsor" of the clinical study; instead, the physician or institution acts as the author of the protocol, sponsor and principal investigator. In comparison to clinical trials that are sponsored by and conducted by manufacturers, a manufacturer should have very little control over the conduct and results of an IIT. In fact, clinical investigators will frequently receive grant funds from not only manufacturers but other governmental and non-profit sources.

These studies fall in a confusing area of the law at the intersection of regulation by the Food and Drug Administration (FDA) and the Office of Inspector General of the Department of Health and Human Services (OIG). Because of the general lack of regulation and guidance specific to IITs available to companies, it is important that a number of steps be taken to prevent possible violation of these laws and regulations. The key sources of regulation include the Food, Drug and Cosmetic Act (FDCA),

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1. IITs are also sometimes known as investigator-initiated studies (IIS), grant-in-aid studies (GIA), proof of concept funding and a variety of other names. However, the dominant title used by industry and investigators appears to be IIT.

the Federal Anti-Kickback Statute and the False Claims Act, in addition to guidance documents from the FDA and OIG. This article discusses each of these laws and regulations and their potential applicability to IITs, and provides general guidance to assist manufacturers in mitigating risk of violation of these laws.

APPLICABLE LAWS AND REGULATIONS

Food, Drug and Cosmetic Act

The FDCA prohibits the introduction of any drug or device into interstate commerce for an intended use that has not been approved as safe and effective by the FDA.² The FDA has consistently sought a broad interpretation of this restriction such that any promotion of a drug or device other than for a use that has been approved as safe and effective by the FDA is in violation of the FDCA. Despite this prohibition, manufacturers are permitted to engage in the “full exchange of scientific information” with physicians and clinical investigators.³ In recent years, the FDA has issued a variety of regulations attempting to restrict manufacturers’ efforts to publish and distribute information regarding off-label use, and an IIT program should not be structured to promote the use of a product for other than its intended use. If not designed and conducted with the intent to promote scientific exchange, a governmental investigator may interpret an IIT as intended to promote a product for off-label uses to physicians who are conducting the trials. As discussed further below, there have been a variety of settlements and cases related to manufacturers’ promotion of off-label use of a product.⁴

IITs must also be conducted in compliance with the wide variety of FDCA-related regulations regarding the conduct of clinical studies. These include the regulations which may require investigators to file an Investigational New Drug (IND) application with the FDA or seek an FDA waiver.⁵ In addition to meeting IND regulations, investigators must adhere to Institutional Review Board (IRB) requirements and human subject safety standards.⁶ In providing grant funding to an independently conducted study, manufacturers should be aware of the requirements placed on investigators and insist upon compliance with these regulations.

2. 21 U.S.C. § 355(a) & (d).

3. 21 C.F.R. § 312.7(a).

4. *See, e.g., Franklin v. Parke-Davis*, 147 F.Supp.2d 39 (2001).

5. 21 C.F.R. § 312.20 (IND requirements); 21 C.F.R. § 312.10 (IND waiver requirements).

6. 21 C.F.R. § 50 and 21 C.F.R. § 312.50 *et seq.* (FDA regulations governing protection of human subjects and clinical investigators), 21 C.F.R. Part 56 (FDA regulations governing Institutional Review Boards), and 21 C.F.R. Parts 50 and 56 (human subject safety requirements).

Federal Anti-Kickback Statute

The Federal Anti-Kickback Statute prohibits the knowing and willful offer or receipt of “remuneration” with the intent to induce a referral purchase order arrangement for the furnishing of a healthcare item or service that is reimbursable under Federal healthcare program.⁷ The definition of remuneration has been interpreted broadly to include any type of remuneration and not just overpayments or bribes.⁸ Even if a portion of a payment is intended to induce referrals then such payment could be in violation of the Anti-Kickback Statute.⁹ In an attempt to clarify the applicability of this broad statute the OIG has issued a variety of safe harbors which, if all of the requirements of the safe harbor are met, provide protection for certain conduct. Safe harbors include the personal services safe harbor which generally requires an agreement to be in writing and for a term of longer than one year and any payments to be consistent with “fair market value” for the services that are provided.¹⁰ The key risk presented by the Anti-Kickback Statute is that the intent behind the grant provided to a physician investigator will be determined to be to induce referrals from the physician for use of the drug. In compliance guidance for pharmaceutical manufacturers issued by the OIG, the OIG stated:

Pharmaceutical manufacturers sometimes provide funding to their purchasers for use in the purchasers’ own research. In many cases, the research provides valuable scientific and clinical information, improves clinical care, leads to promising new treatments, promotes better delivery of health care, or otherwise benefits patients. However, as with educational grants, if linked directly or indirectly to the purchase of product, research grants can be misused to induce the purchase of business without triggering Medicaid Best Price obligations. To reduce risk, manufacturers should insulate research grant making from sales and marketing influences.¹¹

As discussed further below, companies should use a variety of prophylactic steps to ensure that IIT programs are not interpreted as kickbacks in exchange for referrals.

7. 42 U.S.C. § 1320(a).

8. *United States v. Greber*, 760 F.2d 68, 69 (3rd Cir. 1985) *cert. denied*, 474 U.S. 988 (1985); *United States v. Kats*, 871 F.2d 105, 108 (9th Cir. 1989).

9. *See United States v. McClatchey*, 217 F.3d 823, 835 (10th Cir.) (“a person who offers or pays remuneration to another person violates the [Anti-Kickback Statute] so long as one purpose of the offer or payment is to induce Medicare or Medicaid patient referrals.”) (emphasis added), *cert. denied*, 531 U.S. 1015, 121 S.Ct. 574, 148 L.Ed.2d 492 (2000).

10. 42 C.F.R. § 1001.952(d).

11. OIG Compliance Program Guidance for Pharmaceutical Manufacturers, 68 Fed. Reg. 23736 (May 5, 2003).

False Claims Act

The False Claims Act (FCA) prohibits a pharmaceutical manufacturer from causing a false or fraudulent claim for payment to be submitted to the Federal healthcare program.¹² Federal prosecutors and courts have systematically expanded the type of conduct that can violate the FCA and incur significant civil penalties and damages equal to three times the amount of the false claims submitted to the government. Recent caselaw has set forth the concept that off-label promotion by a pharmaceutical manufacturer may cause the submission of false claims to the Medicare or Medicaid program.¹³ The significance of the FCA is heightened by provisions which allow third-party *qui tam* relators to file complaints against manufacturers under seal and, if successful, receive a portion of any recovery as a reward. This enables investigators, study sites and even a manufacturer's own employees to become whistleblowers if misconduct is detected.

RECENT SETTLEMENTS AND CASES

In 2001 the government prosecuted Warner-Lambert, now a Pfizer subsidiary, for conduct related to its promotion of the drug marketed as Neurontin, a drug which at the time had approved indications for the treatment of epilepsy patients.¹⁴ The government alleged that the promotion of Neurontin violated a variety of Federal and state restrictions including off-label promotion, the Anti-Kickback Statute and the False Claims Act. A *qui tam* case was filed against Warner-Lambert which disclosed internal documents that showed that Warner-Lambert maintained a detailed plan to promote Neurontin for off-label use in part through the structure of a clinical trial grant program which was intended to familiarize physicians with the use of Neurontin in various off-label situations. The government alleged that the program was not intended to support clinical investigator's exploration of the drug and its effects but instead was structured to directly encourage use in ways that had not been approved by the FDA. This conduct in combination with a variety of other unlawful kickbacks and promotional activities led to Warner-Lambert settling the allegations by paying criminal and civil penalties of more than \$430 million and entering into a Corporate Integrity Agreement (CIA) requiring large-scale compliance efforts to be undertaken.¹⁵ The CIA included the requirement that Warner-Lambert (now Pfizer) implement policies and procedures that address:

12. 31 USC §§ 3729-3733 (2007).

13. *U.S. ex rel. Franklin v. Parke-Davis, Div. of Warner-Lambert Co.*, 147 F.Supp.2d 39 (D.Mass. Jun 25, 2001).

14. *Id.*

15. Corporate Integrity Agreement between the Office of Inspector General of the Department of Health and Human Services and Pfizer, Inc., available at http://oig.hhs.gov/fraud/cia/agreements/pfizer_5_11_2004.pdf.

sponsorship or funding of research or related activities (including clinical trials, market research, or authorship of article or other publications) that are designed to ensure that Pfizer's funding or sponsorship of such activities complies with all applicable Federal health care program requirements and FDA requirements.¹⁶

In October 2005, Serono settled allegations that the company structured a grant program which provided payments to certain physicians to participate in "observational" studies. These studies required the physicians to collect data on patients and provide the data to Serono. The data was not used by Serono and the grants that were provided to physicians were intended primarily to encourage the physicians to use and gain experience with the Serono product. The program therefore allegedly violated the prohibitions of the Anti-Kickback Statute. The settlement included criminal and civil penalties of more than \$704 million and a long-term CIA requiring a variety of compliance initiatives including policies and procedures related to grant making functions.¹⁷

In 1994 Hoffman-LaRoche was charged with structuring a grant program that offered physicians grants to perform studies of the Hoffman-LaRoche product Rocephin. The grant program was alleged to lack scientific value and the program selected physician investigators less for their ability to conduct the study and gather quality data but more on their ability to recommend the product to patients. The government alleged that the grant program therefore was not truly intended to result in clinical studies and publications but instead to induce physicians to utilize and prescribe the Hoffman-LaRoche product. These allegations were settled resulting in the payment of significant civil and criminal penalties and a CIA requiring a variety of compliance initiatives.¹⁸

Genentec has also entered into a settlement agreement¹⁹ related in part to grant programs. In 1999, the government alleged that Genentec's Protropin grant programs violated the Anti-Kickback Statute and restrictions against off-label promotion. Protropin was approved as an orphan drug which, by definition had less than 250,000 potential users in the United States. Despite the fact that the approval for Protropin's primary indication included a dramatically low patient population, Genentec was alleged to have structured a grant program which awarded grants to prescribers to conduct clinical investigation into Protropin. The government alleged that the grants were actually awarded to physicians to induce them to prescribe Protropin for off-label uses. Genentec settled the

16. *Id.*

17. Corporate Integrity Agreement between the Office of Inspector General of the Department of Health and Human Services and Serono Holding, Inc., available at http://oig.hhs.gov/fraud/cia/agreements/SeronoHoldings_101405.pdf.

18. *Hoffman-La Roche to Pay HHS \$450,000 Settlement*, WASH. POST, Sept. 3, 1994, at C1.

19. Tamar Nordenberg, *Maker of Growth Hormone Feels Long Arm of Law*, FDA CONSUMER, September-October 1999, available at http://www.fda.gov/fdac/departs/1999/599_irs.html.

allegations for approximately \$50 million and a variety of other restrictions.

RECOMMENDATIONS FOR STRUCTURE OF IITs

With these statutes and regulations and history of settlements in mind, there are a variety of steps that pharmaceutical and medical device manufacturers may consider to help mitigate risk against violation of applicable laws. These steps include:

A. *Establish Proper Intent*

The primary protective measure that any company can take is to establish the proper intent behind the program. This can be done through a variety of steps. First and foremost, if an IIT is truly intended to result in a clinical trial and publication, it should not be driven internally by a company's marketing department. Historically, marketing departments had broad control over any relationship with a physician. This may have included control over grant programs for IITs and other grants. For example, with respect to continuing medical education, another area of scientific exchange, the OIG has now indicated that companies should include "effective separation" between marketing efforts and scientific exchange.²⁰

To establish this separation, and establish the proper intent behind an IIT program, an important step is to move the authority for grant funding from marketing or commercial operations to a medical affairs or research and development department. Putting medical affairs or R&D in charge of these grant activities helps to demonstrate that the goal of the program is not to promote the product but instead to produce effective scientific exchange. To achieve this, many companies have elected to establish grant committees and a structured IIT grant process for the review and evaluation of grant proposals. In this regard, it is helpful if any types of relationships between the marketing department and the company's grant structure be limited or subject to significant protective steps to restrict the involvement of marketing in IIT decision making. Additionally, establishing and adhering to a mission statement for the committee is an important step towards establishing that the intent of the program itself is not to induce physicians to prescribe the drug or to promote the drug off-label.

B. *Establish the Physician or Clinical Investigator and the Trial Sponsor*

To further help to establish the intent of the program and foster compliance with FDA regulations, it is important that manufacturers take steps to ensure that the physician or clinical investigator is the "sponsor"

20. OIG Compliance Program Guidance for Pharmaceutical Manufacturers, 68 Fed. Reg. 23736 (May 5, 2003).

of the study and is in control of the study.²¹ This risk presents itself if the study concepts are not generated solely by the physician but are instead planted by the company to encourage the physician to gain “experience” in using the drug or to learn about the drug. Second, there is a risk that if a manufacturer is overly involved with the trial, the involvement could be interpreted as making the manufacturer the true “sponsor” of the trial. If this occurs, the manufacturer could then be interpreted as required to meet all applicable regulations including IND, IRB and human subject safety regulations. Further, the trial outcome would not be independent and instead would be a manufacturer-sponsored trial that would need to be disclosed in publications, presentations and other discussions.

C. Establish Fair Market Value

As discussed above, to avoid violations of the Anti-Kickback Statute it is important for companies to establish that any relationships with physicians that involve payment to the physician are consistent with fair market value for the services provided. To establish fair market value manufacturers may consider utilizing a consultant or accountant to periodically review IIT budgets and assess whether amounts being paid to physicians and investigators are consistent with the fair market value for the services that are being performed by the physician. Note that in evaluating the fair market value of these services it is important to review all relationships in the IIT which may include not only the study budget but also any other support (whether financial or in-kind) that is provided by the company.

D. Avoid Influence of Sales Force in IIT Process

As discussed above, it is important to extract the activities of marketing from the IIT process. This includes the activities of the sales force. This is frequently difficult to achieve because the sales force is typically the primary communicator with physicians and clinical investigators. However, to avoid possible sales force abuses, which include improper use of trials to induce physicians to prescribe drugs, it is important that the sales force has a method to refer interested investigators to a medical affairs or research and development contact so that the investigator can obtain further information about the grant process. The sales force should not have any impact on the decision whether to award a grant and/or the recipients of a grant. Such influence could be used as evidence that the IIT program is actually intended to induce referrals and not to encourage clinical investigation.

21. 21 C.F.R. § 54.2.

E. *Limited Involvement in IIT Studies After Approval*

As demonstrated by the recent *Intermune* case, there is increased prosecutorial interest in the involvement of companies in clinical trials.²² In *Intermune*, the government alleged that the clinical trial registry and other communications were improperly used by the company to promote the Intermune product for off-label uses. With this heightened scrutiny in mind, it is important for companies to attempt to limit their involvement in IITs which are truly just granted funding by the company and not sponsored by the company. Steps should be taken to limit involvement in drafting protocols and trial documents, assistance provided to clinical study investigators during the trial should be limited and excessive communications with investigators and input on the conduct of the trial should also be limited. Any attempts to influence the outcome of a trial could risk portraying the company as the true sponsor. Instead of providing certain services such as technical/medical writers or Contract Research Organization (CRO) support directly, manufacturers may consider encouraging investigators to include funds for these services in budgets to allow for third-party providers.

F. *Promote Transparency and Disclosure*

Many companies and marketing departments may be inclined to establish a “publication strategy” which is intended to set goals for the manufacturer to have manuscripts and documents published on the use of the product. Many of these publications may address off-label use of a product. It is important that companies fully disclose any involvement in a publication and take steps to avoid allegations that the company’s publication strategy and involvements in publications were suspect. Recent scrutiny on manufacturer involvement in published articles and studies have raised concern in this area.²³

CONCLUSION

In summary, the IIT processes that are operated by many manufacturers are undergoing significant structural and procedural changes. These structural and procedural changes are driven by a need to establish proper intent for IITs, and maintain proper relationships with investigators. Being aware of the laws and regulations discussed in this article and taking certain of the recommended steps will help any pharmaceutical or medical device manufacturer establish a more compliant IIT program.

22. *Biopharmaceutical Firm Intermune to Pay U.S. Over \$36 Million for Illegal Promotion and Marketing of Drug Actimmune*, U.S. Department of Justice, available at http://www.usdoj.gov/opa/pr/2006/October/06_civ_728.html.

23. See e.g., *Tough-Talking Journal Editor Faces Accusations of Leniency*, N.Y. TIMES, Aug 1, 2006, at Section F.