

Featured Article

Sponsors Beware: FDAAA Creates Compliance Challenges for Drug and Medical Device Clinical Trials

Article contributed by

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In response to concerns of incomplete or delayed reporting of drug safety data,¹ the Food and Drug Administration Amendments Act of 2007 (FDAAA or the Act), Pub. L. 110–85, 42 U.S.C. § 282(j), as amended, was recently signed into law, becoming the first federal legislation to mandate device companies to disclose clinical trial information and to require both drug and device companies to disclose clinical trial results through a publicly-available database. FDAAA creates new disclosure requirements that may have a significant impact on drug and device sponsors. Sponsors need to be aware that the Act's requirements may expose them to greater liability under the False Claims Act, 31 U.S.C. § 3729, Health Insurance Portability and Accountability Act of 1996 (HIPAA), Pub. L. 104-191 (Aug. 21, 1996), Securities and Exchange Commission (SEC) rules, Food and Drug Administration (FDA) product labeling and advertising rules² and product liability claims. Sponsors need to be familiar with the Act's requirements and be cautious of how the Act can affect proprietary information, inventions, publication, insurance coverage and agreements with institutions.

Summary of Database Requirements

The Act greatly expands the FDA's authority to regulate drug safety and ensure transparency of clinical trial data. Title VIII of the Act requires the Secretary of the Department of Health and Human Services (HHS), acting through the Director of the National Institutes of Health (NIH), to establish and administer through the Internet a clinical trial registry database and a clinical trial results database for drugs, biologics and devices. The databases apply to both privately and publicly-funded clinical trials. Prior to enactment of the Act, sponsors had to register clinical trials only for studies of drugs (including biologics) to treat life-threatening diseases. FDAAA expands this registry database to include all except Phase 1 drug and biologics studies and all device trials that either compare a device against a control or involve pediatric postmarket surveillance device studies. The Act exempts "small" (which the Act does not define) feasibility device trials. The results database will apply to trials conducted on approved drugs, cleared devices and those trials that primarily test efficacy.³

The responsible party for submitting such information to the database is the "sponsor" of the Study, as that term is defined in the FDA Regulations.⁴ In the case of an investigator-initiated

study, the principal investigator (PI) bears responsibility for compliance, but only if the PI has access to and control over the clinical trial data and has the right to publish the results of the trial.⁵

The sponsor is required to list descriptive information about the trial on ClinicalTrials.gov, an online registry of federally and privately sponsored clinical trials. The registry will also have a link to the results database. Clinical trial information for drugs and devices will need to be submitted to the registry database for all ongoing clinical trials other than Phase I studies. In addition, results information for completed trials will be added to a results database in stages over a three-year period. FDAAA also requires that the results of pivotal studies the FDA used in approving a drug, as well as results of post-market studies, be included in the results database.

Registry Database Elements

Sponsors should be aware that FDAAA requires many more data elements than under previous law.⁶ The descriptive clinical trial information required for the FDAAA registry database includes study design, recruitment information, eligibility criteria, demographic information, information on the primary and secondary outcomes, contact information for details about the trial, start date and the target number of enrollees. For a trial involving an unapproved drug, the sponsor must also indicate whether expanded access to the drug⁷ is available for subjects who do not qualify for the trial.⁸

Results Database Elements

The results database will include any FDA assessments of the trial results, FDA advisories regarding the drug or device, citations to any publications focused on the study results, detailed information about the patient sample, endpoints and outcomes and whether any agreements exist between the sponsor and the PI that restrict the PI from publishing or discussing the trial results. Sponsors also must submit periodic updates to the registry and results database.⁹

Upon approval of a drug, data from that drug's earlier trials will be added to the results database. This information will include summaries of FDA committee meetings, advisories, assessments and links to relevant journal articles and publications. The bill requires HHS to determine how to include detailed summaries of the results in language that the public can understand along with the full protocol. The Act also authorizes HHS to expand the database to require submission of results for drugs not approved and devices not cleared or approved.

Timing of Submission and Posting

In general, sponsors will be required to submit data to the registry database for ongoing or new studies within 21 days after the first patient is enrolled. In the case of a study that

was ongoing as of September 27, 2007 and does not involve a serious or life-threatening disease or condition, sponsors have until September 27, 2008 to comply. For the results database, sponsors must provide the required information to NIH within a year of completing the study, or 30 days after FDA approves the product, whichever is earlier.¹⁰

The Director of NIH will then post the registration information for a drug trial within 30 days of its submission, which may occur prior to approval. Presumably as a result of successful lobbying efforts by the device industry, submitted information for a trial of a device that has not yet been cleared or approved will not be posted until after or on the date of the device's approval. For a previously approved device, the Director has until October 27, 2008 to post the information.¹¹

Adverse Event Information

FDAAA also requires HHS to issue a regulation mandating sponsors to submit adverse event information to the databases in a way that is not misleading to patients or doctors. If such a regulation is not issued by September 27, 2009, sponsors will nonetheless be required to submit adverse event information to be included in the databases. The information to be submitted includes tables for all anticipated and unanticipated serious adverse events and tables for "frequent" adverse events that occurred at a rate of more than 5 percent within any arm of the trial. Interestingly, the adverse event requirements currently only apply to drug trials.¹² "Devices" were likely inadvertently left out of this section, so an amendment or corrections bill is likely needed to clarify that device trials are also subject to the requirements.

Penalties for Noncompliance

The Act authorizes civil monetary penalties of up to \$10,000 for all violations adjudicated in a single proceeding plus, if the violation is not corrected within 30 days of notice, up to \$10,000 per day. Noncompliance with the Act for trials involving federal funds may result in the withholding or recovery of grant funds. In addition, all new human drug, biologics and device submissions required to be submitted to the FDA¹³ now need to include certification of compliance with the Act's registration and submission requirements. Noncompliance may be found for failing to submit clinical trial information, submitting false or misleading trial information or failing to submit the certification. In addition, notice of that violation will be publicly posted in the database.¹⁴ The legislation specifically preempts states or state agencies from requiring sponsors to include information in any similar database, so any current state registration requirements will be preempted by the FDAAA.¹⁵ This is an important requirement because sponsors will now only need to comply with one set of regulations as opposed to the FDAAA and potentially fifty state registration requirements.

Compliance Issues and Tips

Sponsors should be aware of several important issues raised by the Act. Most obvious is that sponsors will need to establish new policies, procedures and data management software systems to address the submission of data to the registry and results databases. Since it is the company's ultimate obligation to ensure that complete and accurate data is submitted to the registry and database, sponsors are advised to re-evaluate their policies and procedures regarding clinical data collection and closely monitor and audit sites conducting trials on the sponsor's products. The failure to submit information to the registry or results databases may be argued as a fraudulent or negligent act. Sponsors are encouraged to examine their insurance policy and determine whether to add or increase Errors and Omissions insurance to cover this type of exposure.

Potential Liability for Submitting Inaccurate or Incomplete Data

If a sponsor submits incomplete or inaccurate results and the product is approved based on these results, liability could be found for fraud and abuse or for a violation of the False Claims Act. Any claims submitted by providers to the Centers for Medicare and Medicaid (CMS) for the erroneously approved product would likely be found to be in violation of the False Claims Act. In parallel, sponsors may also have liability for criminal restitution to private insurance companies under an expanded authority created by HIPAA. Although not well-publicized, HIPAA created federal criminal offenses under Title 18 of the U.S. Code for fraud and theft in connection with the provision of healthcare services and supplies.¹⁶ By doing so, the definition of "healthcare benefit program"¹⁷ expanded federal jurisdiction to fraud perpetrated against private insurers. This applies to providers who fraudulently bill private insurers for drugs or devices. Again, if a sponsor submits false results to NIH and the FDA approves the product based on these false results, providers may unknowingly submit false claims to private insurers. Liability for violations of the False Claims Act or HIPAA may extend to the sponsor for submitting the incorrect results that led to product approval and ultimately the submitted false claim.

Reporting of Adverse Events

Current regulations require sponsors to report serious unanticipated adverse events.¹⁸ FDAAA indirectly expands the reporting requirement by mandating disclosure of information for both anticipated and "frequent" adverse events. To account for these additional requirements, sponsors need to ensure that sites immediately report each and every anticipated and unanticipated adverse event to the sponsor and regulatory authorities. To do so, sponsors will need to revise their reporting mechanisms and policies to address what kind of adverse

events sites need to report. Sponsors also need to include language in the protocol and clinical trial agreement to ensure site compliance and minimize liability. Greater transparency in clinical research data and results may also result in greater transparency on product liability. Patients (and their attorneys) will have access to almost every adverse event – this access may facilitate more product liability claims from patients who experience any of the listed adverse events.

Publication of Registered Clinical Trials and Protection of Research Data

Although many drug and device companies have registered clinical trials on a public database in accordance with the International Committee of Medical Journal Editors (ICMJE) requirements, sponsors, particularly device companies who were not subject to FDAMA's disclosure requirements, need to consider how the new FDAAA disclosure requirements will affect publication. Since the public will have access to all results, sponsors will be under even more public scrutiny to publish all results, including negative findings. In accordance with ICMJE requirements, the Committee does not consider results posted in clinical trials registries as previous publications, but only if the results are presented in the form of a brief structured abstract or table.¹⁹ Therefore, if NIH publishes in accordance with FDAAA the results of a study prior to publication, a medical journal may not accept a proposed publication submission on these results.

Sponsors will need to disclose whether any agreement exists between the sponsor and a PI that restricts the PI from disclosing the trial results. This will be crucial to sponsors that want to protect proprietary information and intellectual property. Sponsors should execute non-disclosure agreements with each PI and include necessary language in clinical trial agreements with institutions and PIs to safeguard proprietary information and any inventions that may result from the clinical trial. In addition, each agreement should allow disclosure of the existence of the agreement to government and regulatory authorities. Sponsors concerned about potential threats to intellectual property or the disclosure of proprietary information can always take advantage of the time extension provided by the Act. An extension of the deadline for submitting information to the databases may be granted if the sponsor provides a written request to the Director of the NIH showing good cause for such extension.²⁰

FDAAA allows sponsors conducting clinical trials to delegate the Act's requirements to PIs, but only if certain conditions are met. These conditions are that the PI has access to and control over the clinical trial data and has the right to publish the results of the trial. While these are rights that institutions commonly request, institutions performing the research will likely leverage this requirement to obtain more

favorable contract terms. As a result, sponsors that delegate the responsibility to the PI need to be cautious of language in the clinical trial agreement restricting the company's rights to data and inventions. Companies should secure from the institution adequate representations and warranties that the institution will comply with the Act's requirements. As such, sponsors will need to include appropriate indemnification and remedy language to cover a breach by the institution of the representations and warranties.

Risk of Violating SEC Rules

Public companies need to be aware that disclosing results could put them at risk of violating SEC Rules by providing "forward-looking statements"²¹ that promote an unapproved product. If a sponsor is conducting simultaneous studies of its product and posts positive results from the first study completed and then completes a second study that does not support the first, the company may be accused of misleading investors and fraudulently promoting the product. Another problematic situation occurs when the sponsor completes a postmarket trial that fails to show the product's benefit. If the sponsor continues direct-to-consumer advertising about that product during the period between when results are available to the sponsor and disclosure of results to the database, the advertisements could be construed as misleading statements in violation of FDA labeling and advertising regulations. A recent example of this issue is the House Committee's investigation of Merck & Co. and Schering-Plough Corp. The companies continued direct-to-consumer advertisements showing the benefit of Vytorin for almost two years after the companies obtained trial results demonstrating the drug had no increased benefit to patients.²² Therefore, sponsors should have counsel review the information to be submitted to the results database.

Disclosure of Early Phase Trial Results

If HHS elects to expand the database to require submission of results for unapproved drugs and devices not approved or cleared, there is a potential threat not only to intellectual property, but also the advancement of research in general. Most companies protect their early phase research to prevent their confidential information from reaching competitors. Sponsors are generally concerned about disclosing information on unapproved products that never make it to the market, and on exploratory studies that are not designed to provide evidence of safety and efficacy. Disclosing early phase trial results related to effectiveness could reveal analyses or end points derived from significant negotiation with FDA and international regulatory authorities. This is a particularly sensitive issue for the device industry, where competitors can easily circumvent device patents with basic engineering or design changes. The iterative nature of device development means that early-

phase results are often useless to physicians and patients, but priceless to device competitors. This information would inevitably be invaluable to competitors. In addition, since many of these drugs and devices fail in early phases of development, companies often use the data from these trials to improve backup drug candidates. This process enables companies to learn from their failures and promote future research. If competitors have access to the data from these early studies, there is little incentive for a company to use these failed drugs or devices to conduct further research

Conclusion

Sponsors should closely watch for HHS's rulemaking process regarding requirements for the clinical trial registry and results database. This process will be critical to defining the requirements for the registry and database. In the meantime, sponsors should carefully review their policies, procedures and contracts to maintain data integrity and ensure compliance with these new standards.

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²² http://energycommerce.house.gov/Press_110/110-ltr.011608.ScheringPloughMerck.pdf (last visited Jan. 17, 2008).

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¹ See http://energycommerce.house.gov/Press_110/110nr35.shtml (last visited Jan. 16, 2008)(the House Committee on Energy and Commerce investigated reports that GlaxoSmithKline suppressed data that showed a significant increase in the risk of heart attack and heart-related deaths in patients taking Avandia); see http://energycommerce.house.gov/Press_110/110nr35.shtml (last visited Jan. 16, 2008)(a House Committee is investigating whether Merck & Co. suppressed clinical trial data showing an increased risk of heart attack and stroke in patients taking its drug Vioxx); see http://energycommerce.house.gov/Press_110/110-ltr.011608.ScheringPloughMerck.pdf (last visited Jan. 16, 2008)(a House Committee will explore whether Merck and Schering-Plough withheld results from a clinical trial on their cholesterol-lowering drug, Vytorin, showing the drug was not effective in reducing fatty deposits in arteries).

² 21 C.F.R. Parts 201, 314, 601 and 801.

³ Food and Drug Administration Modernization Act of 1997, Pub. L. 105-115 (Nov. 21, 1997) at § 113.

⁴ 21 C.F.R. § 3.2 (defining sponsor as "Any person who submits or plans to submit an application to the Food and Drug Administration for premarket review").

⁵ 42 U.S.C. § 282(j)(1)(A)(ix).

⁶ See Food and Drug Administration Modernization Act at § 113.

⁷ Under Section 561 of the Federal Food, Drug, and Cosmetic Act.

⁸ 42 U.S.C. § 282(j)(2)(A).

⁹ 42 U.S.C. § 282(j)(3).

¹⁰ 42 U.S.C. § 282(j)(2)(C).

¹¹ 42 U.S.C. § 282(j)(2)(D).

¹² 42 U.S.C. § 282(j)(3)(l).

¹³ See 21 U.S.C. §§ 355, 360e, 360(m), 360(k); 21 U.S.C. § 262.

¹⁴ 42 U.S.C. § 282(j)(5)(E).

¹⁵ 42 U.S.C. § 282(j)(5)(B).

¹⁶ See 18 U.S.C. §§ 669, 1035, 1347 and 1518.

¹⁷ 18 U.S.C. § 24(b).

¹⁸ 21 C.F.R. Part 312.

¹⁹ <http://www.icmje.org/#over> (last visited Jan. 19, 2008).

²⁰ 42 U.S.C. § 282(j)(3)(E).

²¹ See Private Securities Litigation Reform Act of 1995, Pub. L. 104-67, 109 Stat. 737 (Dec. 22, 1995).