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New Clinical Trial Registry Databank

The recently enacted Food and Drug Administration Amendments Act of 2007 ("FDAAA") adds new section 402(j) to the Public Health Services Act (21 U.S.C. § 282(j)), which requires the Director of NIH to create and operate a publicly available on-line data bank of information on clinical trials conducted on certain drugs and devices. These provisions expand upon the existing data bank of information concerning clinical trials for drugs to treat serious or life-threatening diseases and conditions, currently published at www.clinicaltrials.gov. Initially, only basic information about covered clinical trials need be submitted, but eventually, sponsors of clinical trials will be required to submit a great deal of information concerning covered trials and the results of those trials. The first submissions called for by the new provisions will be due as early as December 26, 2007.

Applicability

The new provisions apply to both drug and device trials. Specifically: (a) a controlled clinical investigation of a drug subject to section 505 of the Federal Food, Drug and Cosmetic Act ("FFDCA") or to section 351 of the Public Health Services Act, other than a phase I investigation, and (b) a prospective clinical study of health outcomes comparing an intervention with a device subject to the FFDCA against a control, other than a study to assess only the feasibility of a device, and (c) a pediatric postmarketing device surveillance, as required under new section 522 of the FFDCA¹ (collectively referred to as "applicable clinical trials").

Based on our analysis of the new provisions, we believe that the definition of "applicable clinical trials" includes drug bioavailability and bioequivalence trials, whether conducted under an IND or exempt from IND requirements and regardless of whether conducted in support of an NDA or ANDA filing. Similarly, with the exception of "feasibility studies," device studies appear to be included within the scope of the definition regardless of whether they involve significant-risk or non-significant-risk devices, whether they are covered by a submitted IDE or a deemed-effective IDE, or whether they are conducted in potential support of

¹ Section 307 of the Food and Drug Administration Amendments Act of 2007 amends section 522 of the FFDCA to enable FDA to order postmarketing surveillance of any class II or III medical device that is expected to have significant use in the pediatric population. The legislation requires the Secretary of the Department of Health and Human Services ("Secretary") to issue guidance by September 27, 2008 describing how the requirements of these provisions apply to pediatric postmarketing surveillance requirements that are not clinical trials.



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a PMA, a 510(k) notification, or an exempt device.² In contrast, the pre-FDAAA requirement to submit studies for posting on www.clinicaltrials.gov applied only to studies, conducted under FDA's IND regulations, testing the effectiveness of drugs for serious or life-threatening diseases or conditions.³

Basic Clinical Trial Information to be Submitted and Published by December 26, 2007

As initial disclosures, the sponsor⁴ of an applicable clinical trial must submit four categories of information, as follows:

- (1) a description of the study (e.g., a summary, the primary purpose, the study design and type, intervention name and type, disease/condition to be studied, anticipated start and completion dates, target number of subjects, and primary and secondary outcome measures);
- (2) recruitment information (e.g., eligibility criteria, including age and gender, overall recruitment status, individual site recruitment status, and for trials of unapproved drugs, information on any access under Section 561 of the FDCA for those not eligible to participate in the trial);
- (3) sponsor contact information; and
- (4) administrative information (e.g., any applicable protocol identification numbers).

This information must be submitted for applicable clinical trials that are initiated after September 27, 2007 (the date of enactment of the FDAAA) or that are ongoing on December 26, 2007 (90 days after the date of enactment). A trial is considered "ongoing" on a particular date if one or more patients have been

² The resulting broad scope of the newly-required disclosures indicates that the resulting database, particularly in the case of drugs, may advance significantly the point in time when firms become aware of products in their competitors' pipelines.

³ In guidance discussing these pre-FDAAA obligations, FDA broadly interpreted the phrase "trials for serious or life-threatening disease or condition" to include studies in HIV/AIDS, Alzheimer's disease, angina, heart failure, and cancer, as well as chronic illnesses that can have serious outcomes, such as inflammatory bowel disease, asthma, rheumatoid arthritis, diabetes, systemic lupus erythematosus, depression, and psychoses. See *Guidance for Industry: Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions*, March 2002, available on FDA's website at: <http://www.fda.gov/Cder/guidance/4856FNL.PDF>.

⁴ The obligations under these provisions fall to the "responsible party" defined as the sponsor or the principal investigator if so designated and if certain preconditions are met. For brevity, this summary will use the term "sponsor."

enrolled and the final patient has not completed the last examination or intervention for purposes of collecting data on the primary outcome measure. Information must be submitted by the later of: December 26, 2007 (90 days after enactment); or 21 days after the first patient is enrolled. However, this submission is deferred until September 27, 2008 (*i.e.*, one year from enactment) for clinical trials of drugs that are not for serious or life-threatening diseases or conditions⁵ and that were ongoing on the date of enactment.⁶

The submission date requirements for clinical trial information do not necessarily correlate with the date on which the information will be publicly disclosed. Information on drug clinical trials is to be posted to the on-line data bank by NIH within 30 days of submission. For devices not yet cleared or approved, however, information is to be posted within 30 days of clearance or approval. Information on trials of already cleared/approved devices is to be posted within 30 days of the date NIH posts basic information on clinical trial results, which is to occur by September 27, 2008 (see below).

The data bank must be readily accessible and allow the comparison of entries. It must be searchable by keyword and by at least one of the following: disease/condition studied, name of intervention (drug or device), location of trial, age group studied, study phase, sponsor, recruitment status, or study identification number. By March 27, 2009, the data bank must also be searchable by the safety issue (if any) being studied as a primary or secondary outcome.

Expansion of Data Bank to Include Results and Related Information

The FDAAA also includes a number of provisions that operate to expand the data bank to include information on the results of applicable clinical trials, as well as other related information. These provisions provide for a phased implementation, first requiring that certain existing information be linked in the

⁵ The scope of this one-year deferral will be limited if the FDA, as we expect, applies the same definition of "serious and life-threatening diseases and conditions" as it applied under the previous program (see footnote 3 above). The scope of the deferral is further narrowed by the fact that the deferral appears to exclude all studies of drugs intended to treat serious and life-threatening diseases and conditions – not just studies testing the efficacy of those drugs in those diseases and conditions. Thus, for instance, submission of information does not appear to be deferred for pharmacokinetic or bioequivalence studies of a drug that has any approved or investigational use in treating a serious or life-threatening disease or condition. Similarly, submission is seemingly not deferred for studies testing the efficacy of a drug in a non-serious or non-life-threatening condition, if the drug also has an approved or investigational use in a serious or life-threatening condition.

⁶ Based on the language, previously discussed, governing the general data submission requirements, a submission initially deferred under this provision will never be required if the study in question was ongoing on September 26, 2007 but is no longer ongoing as of December 26, 2007.



data base, next requiring sponsors to submit for inclusion in the data bank specified basic information concerning trial results and later, after rulemaking, requiring that sponsors submit further information.

First, beginning on or before December 26, 2007, NIH is to link certain existing publicly available information to data bank entries for clinical trials that form the primary basis for an efficacy claim or that are conducted after approval/clearance of the drug or device. Links to the following types of information must be included, if available:

- FDA summary documentation posted in connection with any advisory committee consideration of an applicable clinical trial;
- Any posted FDA assessment of a pediatric study conducted under Sections 505A or 505B of the FDCA;
- FDA public health advisories concerning the drug or device that is the subject of the applicable clinical trial;
- The FDA summary basis of approval (now called the “action package”) for any applicable drug clinical trial;
- The FDA detailed summary of safety and effectiveness information (for PMA devices) and the summary of safety and effectiveness data (for devices cleared via 510K procedures);
- Any Medline citations to publications focused on the results of an applicable clinical trial; and
- The entry for the drug that is the subject of an applicable clinical trial in the National Library of Medicine database of structured product labels.

These links are to be incorporated into the data bank within 30 days after they become publicly available, but not earlier than 30 days after approval/clearance of the drug or device that is the subject of the clinical trial. NIH is permitted, but is not required, to include links to these same sources for clinical trials submitted to the data bank prior to enactment of the FDAAA.

Second, beginning on or before September 27, 2008, NIH is to post the following four types of information for approved/cleared drugs and devices (referred to as “basic results”):

- (1) A table of the demographic and baseline data collected overall and for each arm of the trial, as well as information on the number of patients who dropped out of the trial or were excluded from the analysis;

- (2) A table of values for each of the primary and secondary outcome measures for each arm of the trial;
- (3) A point of contact for scientific information about the clinical trial results; and
- (4) Information on the existence of any agreements between the sponsor and the principal investigator limiting the principal investigator's ability to discuss or publish the results of the trial after its completion.

Subject to certain exceptions, the sponsor must submit the above information within one year⁷ of 1) the estimated completion date of the trial (as previously submitted), or 2) the actual completion date, whichever occurs first. For clinical trials completed before initial approval/clearance of the drug or device, submission may be delayed until 30 days after approval/clearance. If a sponsor is seeking (or will within one year seek) approval/clearance for a new use of an already approved/cleared product, submission may be delayed until 30 days after approval or rejection of the application for the new use, or withdrawal of the application (subject to an overall two-year limit on the length of the delay). Finally, the Director of NIH is authorized to grant an extension of the deadline for submission upon a showing of good cause.

Third, the Secretary is required to initiate a rulemaking to further expand the results information included in the data bank and enhance patient access to and understanding of the results. A public meeting must be held by March 27, 2009 to solicit input and rulemaking is required to be completed by September 27, 2010. For approved/cleared drugs and devices, the regulations must require posting of both a technical and a non-technical summary of the clinical trial and the results, if the Secretary determines such summaries can be included without being misleading or promotional. Additionally, the regulations will require posting of either the full protocol or information on the protocol sufficient to enable evaluation of the results. The regulations must also address whether or not this same information should be posted for unapproved products. Finally, the regulations are to address logistical issues, such as the timing for submission of this information for approved and unapproved products, the applicability to clinical trials submitted to the registry prior to the effective date of the regulations, the format for submission of clinical trial information, and requirements for updates to submitted information.

Fourth, the Secretary must also issue a regulation by March 27, 2009 specifying a method for including in the data bank information on serious adverse

⁷ The Secretary may increase this one year period to 18 months in the regulations described below.

events and frequent adverse events for drugs.⁸ If the regulations are not issued by September 27, 2009, default provisions of the FDAAA take effect requiring the inclusion of tables of adverse event information, along with additional information designed to enhance patient understanding of the information.

Accelerated Submissions

The legislation contains provisions enabling the Secretary to accelerate required submissions if the Secretary determines that posting of information on a particular clinical trial is necessary to protect the public health.

Informed Consent

FDA's IND regulations must be updated to require disclosure as part of the informed consent process that information concerning the clinical trial information will be submitted for inclusion in the data bank. Because the timing and potential retroactive application of these requirements is not certain, and because posting of information with respect to applicable clinical trials may begin before any changes are made to the IND requirements, we recommend that informed consent for applicable clinical trials be updated now to reflect the new submission and posting requirements, regardless of the status of any changes to FDA's IND regulations.

Compliance and Enforcement

The FDAAA includes a number of provisions designed to ensure sponsors timely submit accurate clinical trial information, as required by the legislation.

First, sponsors must include a certification regarding compliance with these new provisions when submitting an application for approval/clearance to the FDA and when submitting reports required by grants from the Department of Health and Human Services (for those clinical trials funded in whole or part by such a grant).⁹

Second, the Director of NIH must include in the data bank a notice of any failure to submit required information, or submission of information found to be false or misleading. The data bank must be configured to allow the public to search for entries that include such notices of noncompliance.

⁸ While the FDAAA as enacted refers only to adverse events for drugs, a technical correction pending before Congress would expand the requirement to apply to device adverse events. See H. Con. Res. 217, available at: http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_bills&docid=f:hc217eh.txt.pdf.

⁹ This requirement appears to apply to both new applications and to supplements to approved applications.



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Third, the legislation also amends the FFDCa to provide that the following are “prohibited acts”: (a) failure to include a certification of compliance with an application for approval/clearance, or the knowing submission of a false certification; (b) failure to submit required clinical trial information; and (c) submission of clinical trial information that is false or misleading. Violations are subject to civil monetary penalties of up to \$10,000 for all violations adjudicated in a single proceeding. The failure to timely correct a violation upon written notice may be further penalized up to \$10,000 per day until the violation is corrected.

Finally, the legislation provides that submission of clinical trial information concerning an unapproved use of a drug or device shall not be considered as evidence of a new intended use in any administrative or judicial proceeding. Similarly, the information in the data bank shall not be considered as labeling or to adulterate or misbrand the subject drug or device.

Preemption

Once the data bank is further expanded by rulemaking as described above (*i.e.*, the rule to be issued by September 27, 2010) no State may establish or continue in effect any requirement for the registration of clinical trials or for any database of clinical trial results.