What Does FDAAA – Especially Title VIII – Mean For Industry and Publication Planning Professional?

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Clinical Trial Registry and Results Databank

Expanded Databank: Overview

- FDAAA expands existing NIH registry
  - More studies must be submitted
  - More information on each study must be submitted
- FDAAA creates a Clinical Trial Results Databank
  - Links to existing results information
  - Basic results databank
  - Expanded results databank

Expanded Registry: More Trials

- Information must be submitted for any "applicable clinical trial":
  - Applicable Drug Clinical Trial
  - Applicable Device Clinical Trial

- Studies must be:
  - Initiated after September 27, 2007 or
  - Ongoing as of December 26, 2007

"Applicable Clinical Trial"

- "Applicable Drug Clinical Trial" defined as:
  - Any controlled clinical trial, other than a phase I study, regardless of the disease or condition studied
  - Of a drug subject to section 505 of FDC Act or section 351 of PHS Act

- "Applicable Device Clinical Trial" defined as:
  - Prospective clinical study of health outcomes comparing a device subject to section 510(k), 515, or 520(m) with a control (other than trials to determine feasibility); and
  - Pediatric postmarket surveillance

Expanded Registry: Information

- Required Information
  - Descriptive Information: e.g., title, summary, study design
  - Recruitment Information, e.g., eligibility criteria, status
  - Location and Contact Information, e.g., sponsor, facility
  - Administrative Data, e.g., protocol and IND numbers
- Requires submission of most of the 20 data elements specified by the World Health Organization (WHO)
  - No mechanism for delayed disclosure for drugs
- Must be searchable by keywords and by category (e.g., disease or condition studied, safety issue studied)

Expanded Registry: Deadlines

Clinical trial information must be submitted by the last applicable date, as follows:

- December 26, 2007; or
- 21 days after enrollment of first patient; or
- For trials involving diseases or conditions that are not serious or life-threatening and are ongoing on September 27, 2007: September 27, 2008

Clinical Trial Results Databank

Three-Step Process:

- Links to Existing Results Information
- Basic Results Databank
- Expanded Results Databank

Links to Existing Results

- By December 26, 2007, the registry must contain links to information already made publicly available by FDA and NIH

- Applicable Studies
  - Phase III clinical trials that form the primary basis of an efficacy claim
  - All Phase IV clinical trials
- Required Results Information
  - FDA summaries from advisory committee meetings
  - FDA assessments of pediatric studies (drugs)
  - FDA public health advisories
  - FDA “action package” for drugs
  - Medline citations
  - Approved labeling on NIH’s DailyMed website

Basic Results Databank

- By September 27, 2008, NIH must establish a basic results databank

- Required Trials
  - "Applicable clinical trial" (i.e., controlled clinical trial other than a phase I study)
  - Initiated after September 27, 2007 or ongoing as of December 26, 2007;

  AND

  - Involves an approved drug product or a cleared or approved device

Basic Results Databank (cont'd)

- Required Information:
  - Tables of patient demographic data
  - Tables of primary and secondary outcome measure data
  - Point of contact
  - Information on any agreements restricting ability of the principal investigator to publish or discuss results
- Adverse Event Information
  - By March 27, 2009, Secretary must issue regulations determining the best method for reporting adverse event information for approved drugs
  - If regulations are not issued, requirement becomes self-executing

Basic Results Databank (cont'd)

- Submission Deadline: 1 year after the estimated or actual completion date, whichever is earlier
- Extensions
  - Drug or device not yet approved or cleared for any use: 30 days after approval or clearance
  - Drug or device not yet approved or cleared for studied use: 30 days after approval or clearance, non-approval or NSE, or withdrawal without resubmission for 210 days
  - Good cause: as necessary
- *No extension available for seeking publication in peer-reviewed journal*

Expanded Results Databank

- Expansion of Results Databank
  - Public meeting: March 27, 2009
  - Regulations: September 27, 2010

- Regulations must address the following issues, among others:
  - Whether to require results for unapproved drugs and devices
  - Whether to require study summaries (both technical and in lay language)
  - Standard format for submission of results
  - Procedures for quality control
  - Appropriate timing and requirements for updates

Expanded Results Databank

- Deadline same as for basic results databank
  - One year after the estimated or actual completion date of the study, whichever is earlier
- Same extensions and waivers as basic results databank

Additional Submissions

- Voluntary Submissions
  - Responsible person may submit information about
    - A phase I study
    - A phase II through IV study initiated before September 27, 2007 and completed prior to December 26, 2007
  - Must submit information about all related studies

- Required Submissions
  - Standard: "necessary to protect the public health"
  - Trials subject to special authority
    - An applicable clinical trial for an approved drug or device that is completed on or after September 27, 1997; or
    - An applicable clinical trial for an unapproved drug or device that is initiated after September 27, 2007

Databank Compliance Provisions

- Certifications
- Pilot Quality Control Project
- Public Notice of Violations
- Prohibited Acts
- Civil Money Penalties

Certifications

- Applications
  - NDAs, BLAs, INDs, PMAs, 510(k)s, etc., must include certification that all applicable databank requirements have been met
  - FDA is requiring certification for INDs, though law may not support this interpretation
- HHS Grantees
  - Grant and progress report form for trials funded in whole or in part by any agency of HHS (e.g., NIH, FDA) must include certifications
  - Before releasing grant funds, Agency head must verify compliance with databank requirements

Pilot Quality Control Project

- NIH and FDA must conduct a pilot quality control project until the issuance of regulations establishing the expanded databank
- Pilot intended to determine the optimal method of verification of results information to ensure it is not promotional or false or misleading
- If violations detected, Secretary must provide notice and 30 days to correct

Public Notice of Violations

- Registry and results databank must include information about non-compliance, including penalties imposed and whether violations were corrected
- FDAAA specifies content of public notices
  - E.g., “The entry for this clinical trial was found to be false or misleading and therefore not in compliance with the law.”
- It does not appear that notices will be deleted
- Violations must be searchable

Prohibited Acts

- The following violations are now "prohibited acts" under the FDC Act
  - Failure to submit a required certification of compliance (i.e., with NDA, PMA or IND) or submission of a false certification
  - Failure to submit required clinical trial information
  - Submission of clinical trial information that is false or misleading in any particular

Civil Money Penalties

- A person who commits a "prohibited act" as specified above is subject to a civil money penalty (CMP)
- Amounts
  - Not more than $10,000 for all violations adjudicated in a single proceeding
  - If violations continue more than 30 days after notice of non-compliance, not more than $10,000 per day after such 30 day period
- There is no maximum limit on CMP liability

Preemption of State Database Requirements

- State laws regarding clinical trial registries and results databases are preempted "upon the expansion of the registry and results databank" per the Secretary's regulations

- Preemption could be delayed 3 years or more, depending on how quickly the Secretary promulgates regulations for the expanded results databank

Rule of Construction

- Information submitted in compliance with databank requirements
  - Shall not be considered as labeling, adulteration or misbranding of the drug; and
  - Cannot be construed in any administrative or judicial proceeding as evidence of a new intended use
- This should provide some protections against claims that the databank is being used for off-label promotion

New Postmarket Authority

New Post-Approval Authorities

- Labeling
- Post-approval study authority
- Risk Evaluation and Mitigation Strategies (REMS)
- Civil Money Penalties
- Active Surveillance
- Direct-to-Consumer (DTC) Advertising Requirements

New Labeling Authority

- FDAAA gives FDA explicit authority to mandate safety labeling changes based upon "new safety information."
- Accelerated review process
  - FDA must notify the sponsor regarding new safety information
  - Sponsor must respond within 30 days
    - Labeling supplement; or
    - Written statement why labeling supplement unnecessary
  - FDA must "promptly" review submission and initiate "discussions" if there is a disagreement
  - FDA may issue an "order" 15 days after the completion of discussions
  - Appeal available within 5 days of "order"

Postapproval Study Authority

- FDA may require postapproval studies or postapproval clinical trials to:
  - Assess a known serious risk related to the drug;
  - Assess signals of serious risk related to the drug;
  - Identify an unexpected serious risk
- Stepwise authority
  - Study may be required only if active surveillance and AE reporting not sufficient
  - Clinical Trial may be required only if active surveillance, AE reporting and post-market studies not sufficient

Risk Evaluation and Mitigation Strategies (REMS)

- FDA can require a REMS if necessary to ensure that the benefits of the drug outweigh its risks

- REMS Elements
  - Timetable for assessments
  - MedGuides and patient package inserts
  - Communication plan to physicians
  - Distribution and use restrictions

Distribution and Use Restrictions

- Restrictions Specified in the FDAAA
  - Required training or certification of HCPs
  - Special certification for dispensing sites
  - Limitations on dispensing sites (e.g., hospitals only)
  - Dispensing only upon evidence of safe use conditions (e.g., laboratory test results)
  - Patient monitoring requirements
  - Patient Registries
- Implementation system can be imposed

REMS Effective Date

- March 25, 2008, except . . .
- Drugs approved before the effective date will be "deemed" to have a REMS if they are subject to "elements to assure safe use"
  - Required under FDA's accelerated approval regulations
  - "Otherwise agreed to by the applicant"
- Companies should begin assessing whether any existing products will be subject to REMS requirement and prepare to submit proposed REMS

Penalties

- Misbranding: applies to violations of labeling, postapproval study and REMS requirements
- Civil Money Penalties (CMPs)
  - Applies to violations of labeling, postapproval study and REMS requirements
  - Before Notice:
    - $250,000 per violation
    - $1M for all violations adjudicated in a single proceeding
  - After Notice:
    - $250,000 per 30-day period, doubling every 30 days to a maximum of $1M per 30-day period
    - $10M for all violations adjudicated in a single proceeding

FDAAA Advertising Provisions

- Mandatory Pre-review of Television Advertisements
- Major Statement
- DTC Regulations
- 1-800 Number Disclosure
- Civil Money Penalties

Effective Date

FDA's new post-approval authorities, including REMS, safety labeling, postapproval studies and clinical trials, postmarket active surveillance, and advertising restrictions, become effective on:

March 25, 2008

Contact Information

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