

# 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-review journal*



## Expanded Results Databank

- Expansion of Results Databank
  - Public meeting: March 27, 2009
  - Regulations: September 27, 2010
  
- Regulations must address the following issues:
  - 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”:
  - 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



## 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

**Scott M. Lassman** is a Partner and Co-Chair of the FDA Practice Group in the law firm of Wilmer, Cutler, Pickering, Hale & Dorr (WilmerHale), where he specializes in FDA legal, regulatory and policy issues. Prior to joining WilmerHale, Mr. Lassman served as Senior Assistant General Counsel for the Pharmaceutical Research and Manufacturers of America (PhRMA), where he was responsible for FDA regulatory and policy matters. Mr. Lassman played a leading role in negotiating the \$400 million Prescription Drug User Fee Act (PDUFA) agreement with FDA, which recently was signed into law as FDAAA. Mr. Lassman's strong policy background at PhRMA is complemented by more than ten years of experience in private practice solving complex FDA legal and regulatory issues for pharmaceutical, biotechnology and medical device clients.

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