# Recent Developments in FDA Regulation of Clinical Trials:

## ClinicalTrials.gov and Future FDA Proposals

International Pharmaceutical Regulatory and Compliance Congress and Best Practices Forum

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# Overview

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- Globalization of clinical research
- Regulatory Background
  - 21 CFR 312.120
  - Declaration of Helsinki
  - 21 CFR 314.106
  - FCPA
- Government Reports
- FDA Action and Future Plans
- Congressional Action - FDAAA

# Globalization of Clinical Trials

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- Companies under pressure to deliver innovative medicines more quickly, but also pressure to ensure safety
  - FDA seeking more information for approval
  - Need more trials enrolling more subjects for more time
    - But recruitment in western markets is difficult and costly
    - Emerging markets with improving medical infrastructure – well-trained doctors and willing subjects
- 10% of trials registered on ClinicalTrials.gov involve countries outside North America, western Europe, and Japan (as of January 2008; likely higher as companies comply with FDAAA registration requirements)
  - Studies conducted in more than 140 countries
  - Estimates that as many as 20-25% of trials of FDA-regulated products occur abroad
- 29% of PIs registered with FDA are based outside US and W. Europe (up from 5% in 1997 – fastest growth: India, China, Russia, and Argentina)

# Additional Complicating Factors

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- Janet Woodcock, Head of CDER:
  - New trial methods and designs
  - Electronic data capture
  - New arrangements between sponsors and various contractors, among investigators, among institutions, among IRBs, and rise of free-standing for-profit study centers
  - Delegation to parties not directly regulated by FDA
  - Larger trials where contribution of single site may be small, but where study-wide systems of data control and management may be very significant
  - Greater number of studies in children and other vulnerable populations
- Regulatory program must modernize as practices change – need regulatory guidance, and potentially new regulatory scheme to encompass modern trial arrangements, without inhibiting innovation

# FDA Will Accept Foreign Data: Non-IND Studies

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- Facilitate product development through avoidance of research duplication
- **21 CFR 312.120** (Foreign Studies *Not* Conducted Under IND)
  - Newly Revised Rule – 73 FR 22815, April 28, 2008
    - Effective date: Oct. 27,. 2008; applicable to all foreign clinical studies regardless of status of subject enrollment (but waivers available)
  - Non-IND trials must now be:
    - Conducted in accordance with GCPs
      - Standards for "design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials in a way that provides assurance that the data and reported results are credible and accurate and that the rights, safety, and well-being of trial subjects are protected."
      - Includes review and approval by independent ethics committee (IEC)
      - Includes documentation of freely-given informed consent
    - And data must be able to be validated through on-site inspection

# FDA Will Accept Foreign Data: Non-IND Studies

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- **21 CFR 312.120** cont'd
  - Must submit significant documentation of compliance (and keep records):
    - Investigator qualifications and GCP training
    - Research facilities
    - Summary of protocol and results, plus background records if necessary
    - Description of product
    - Demonstration that trial is adequate/well-controlled (if supporting efficacy)
    - IEC information
    - Informed consent information, including recruitment incentives
    - Monitoring
  - If standards not met, study not acceptable in support of application (IND or marketing application) – *but still reviewed for safety*

# FDA Will Accept Foreign Data: Non-IND Studies

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- **21 CFR 312.120** cont'd
  - Prior rule required non-IND trials to be
    - Performed by qualified investigators, and
    - Conducted in accordance with more stringent of 1989 Declaration of Helsinki, or laws of host country
  - Similar standards now, but:
    - Some disagreement with current Helsinki requirements
    - Avoid reliance on document outside FDA's control (same reason to avoid reference to ICH E6)
    - Note: FDA believes GCPs do require compliance with local laws
- 21 CFR 814.15 – Similar regulation for non-IDE device trials (but still relies on Helsinki)

# Declaration of Helsinki

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- Conform w/ generally accepted scientific principles/adequate pre-clinical data
- Independent ethical review of protocol
- Qualified personnel
- Risk-benefit analysis (including benefit to host population); subject's welfare prevails over interests of society; termination if hazards outweigh benefits
- Adequate and voluntary informed consent
- Tests against best current methods (placebo only if no proven method exists, with certain exceptions for compelling reasons or minimal risk)
- Every subject assured access to best proven therapy identified in study <u>following completion</u>
  - *NOTE: Final two requirements NOT found in FDA regs – Why?*
    - *Placebos may be necessary for trial to be adequate/well-controlled*
    - *FDA mission limited to determination of safety/efficacy – not access*

# FDA Will Accept Foreign Data: Exclusively Foreign Studies

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- **21 CFR 314.106** (Foreign Data)
  - Application based exclusively on foreign clinical data – gathered from trials conducted under IND or satisfying 21 CFR 312.120 – may be approved if:
    1. Application meets US standards for marketing approval
    2. Foreign studies performed by clinical investigators of recognized competence
    3. Data may be considered valid without need for onsite inspection
    4. ***Foreign data is applicable to US population and US medical practice***
       - Not assumed – must explain why ethnic differences or differences in diagnosis/management will not alter conclusions about product's effect
       - Almost always need US "bridging" data
  - Sponsors encouraged to meet with FDA in pre-submission meeting if approval will be sought under this section
- 21 CFR 814.15(d) – similar regulation for devices

# Serious Issues Raised

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- Protection of human subjects
  - Use of placebo controls
  - Coercion
    - Outright lack of informed consent
    - Participation only option for access to medical care
  - Post-trial access
- Quality of data
- Extrapolation of data to different regions
  - ICH E5 Guidance on Ethnic Factors and the Acceptability of Foreign Clinical Trial Data (June 1998)
  - ICH E5 Q&A (Sept. 2006)
  - Guidance: Collection of Race & Ethnicity Data in Clinical Trials (Sept. 2005)

# Serious Issues Raised

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- Compliance with **Foreign Corrupt Practices Act** (FCPA):
  - **Anti-bribery provisions**
    - Apply to:
      - Business entities formed under US laws, and US citizens
      - Companies/individuals who take any action in furtherance of FCPA violation in US
      - Companies with securities registered in US/required to file reports with SEC
    - Make it illegal to pay, offer, authorize, or promise to pay anything of value to non-US gov't officials (broadly defined) to influence any official act or decision in order to obtain or retain business
    - Wide reach: covers actions occurring, and companies based, outside US
  - **Also accounting and recordkeeping provisions**
  - Narrow exception for "grease" payments to facilitate performance of "routine governmental action" – does NOT cover discretionary decisions, and must be permitted by local law

# Serious Issues Raised

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- ***Clinical investigators may qualify as non-US "public officials" under FCPA***
  - Persons who fill non-clerical, non-laborer positions, having some authority within a foreign government entity, including government hospitals
  - Ex. Physicians employed by government and involved in purchasing/formulary decisions
- Any payment made to inappropriately influence decisions concerning new or existing business may be considered an illegal bribe – applied very broadly:
  - Provision of free medical equipment, infrastructure, or personnel
  - Paying for conference attendance
  - Referral Fees/Enrollment incentives
- Ask:
  - Is it necessary for conducting the trial?
  - Is it fair market value?
  - Or is it intended to induce potential gov't purchaser to recommend sponsor's products?
- Also consider local anti-corruption laws, Federal Anti-Kickback law, False Claims Act, Stark law

# Serious Issues Raised

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- FCPA Affirmative defenses (very narrow):
  - Payments that are “lawful under the written laws of the foreign country”
  - Limited reasonable and bona fide expenditures directly related to promotion, demonstration, or explanation of products or service; or execution or performance of contract with foreign government
- FCPA Penalties:
  - Anti-bribery: Criminal fines up to $2 million per violation for companies; $100,000 for individuals + 5 years in prison
  - Recordkeeping: Criminal fines up to $25 million per violation for companies; $5 million for individuals + 20 years
  - Civil penalties: Fines up to $10,000; injunction; forfeiture of assets; disgorgement; and suspension/debarment
  - May impact FDA review – raising questions of data integrity
- Enforcement priority for DOJ and SEC

# Government Status Reports Re: Clinical Trials

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- OIG Report, **Globalization of Clinical Trials**: A Growing Challenge in Protecting Human Subjects (Sept. 2001)
  - Findings:
    - FDA oversees an increasing level of foreign research
    - Sponsors have expanded sites into countries with limited trial experience
    - FDA receives minimal information on performance of foreign IRBs
  - Recommendations:
    - Obtain more information about performance of foreign IRBs by working with foreign regulators and through foreign inspections
    - Help foreign boards build capacity
    - Encourage sponsors to obtain attestations of compliance from foreign investigators
    - Encourage greater sponsor monitoring
    - Develop a database to track the growth and location of foreign research

# Government Status Reports Re: Clinical Trials

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- OIG Report, **FDA's Oversight of Clinical Trials** (Sept. 2007) - Findings:
  - Data limitations
    - Lack complete, internal (non-public) clinical trial registry, and lack IRB registry
    - Lack FDA database with complete info on all Bioresearch Monitoring (BiMo) inspections
    - Result: inspected only 1% of clinical trial sites total between 2000-2005, and only 6% of IRBs each year
  - Other limitations
    - Inconsistency classifying inspections as NAI, VAI, or OAI (and failure to follow-up)
    - Inspections focus on retrospective reviews to verify clinical data supporting applications (rather than current and prospective reviews while trials are ongoing)
    - Guidance and regulations do not reflect current clinical trial practice
      - Do not address delegation of investigator tasks to colleagues or subordinates (limited to action against clinical investigator or sponsor)
      - Limited authority over foreign trials (often unaware they are taking place, and limited to disqualifying data from consideration)

# Government Status Reports Re: Clinical Trials

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- OIG 2007 - Recommendations:
  - Develop a comprehensive clinical trial database to more effectively identify and target ongoing trials for inspection (distinct from ClinicalTrials.gov)
  - Create an IRB registry to more effectively target IRBs for inspection
  - Create a cross-center database that allows complete tracking of BiMo inspections
  - Establish a mechanism to provide feedback to investigators to improve consistency
  - Seek legal authority that covers all stakeholders in management and conduct of clinical trials – particularly colleagues and subordinates of PIs if participating in conduct of a trial

# Government Status Reports Re: Clinical Trials

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- Congressional Report: **FDA's Faulty Safeguards Against Corruption**: Concerns Over Debarment Use and Authority (Feb. 2008)
  - Rep. Barton's Minority Committee Staff Report, House Committee on Energy and Commerce
  - Stressed FDA's failure to adequately (and consistently) pursue disqualification and debarment of clinical investigators and sponsors involved in trial misconduct
    - Disqualification of investigator can lead to major problems for sponsor, including reexamination of data from all trials with which investigator was involved
  - Called for additional FDA authority to debar brand name drug companies for trial misconduct (currently limited to debarring generic companies)
- OIG will investigate FDA's failures to act and assess adequacy of current monitoring system

# Agency Response

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- FDA acknowledges lack of resources and limited authority in foreign countries as constraints
- Inspections just one part of BiMo and human subject protection (HSP); protocol review most important component
- Focus on prospective protocol assessment and assessing quality of data supporting approval (review completed trials, but ensure proper systems in place for all ongoing research at site)
- Focus resources on high-risk sites/IRBs, rather than arbitrary percentage of sites/IRBs inspected
- Plan to develop timelines to take action against violators of clinical trial regulations/assign more case managers and hire more staff to expedite disciplinary action

# HSP/BiMo Council

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- FDA initiative started in 2004
  - Previously chaired by Janet Woodcock
  - Started as “steering committee” – now permanent council
- Representatives from each center and office to scrutinize current clinical trials programs and develop policies
- Key issues: coordination, training, tracking mechanisms, guidance/regulations
- Overarching theme: difficult to inspect for quality – so must *build* quality in from the start

# Recent FDA Guidance Documents

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- Use of Clinical Holds Following Clinical Investigator Misconduct (Final, Sept. 04)
- Waiver of IRB Requirements for Drug and Biological Product Studies (Final, Jan. 06)
- 5 Info Sheets for Clinical Investigators, IRBs, and Sponsors (inspections of investigators and IRBs, medical device studies, waiver of IRB review) (Jan. 06)
- Using a Centralized IRB Review Process in Multicenter Clinical Trials (Final, Mar. 06)
- Establishment/Operation of Clinical Trial Data Monitoring Committees (Final, Mar. 06)
- Exceptions from Informed Consent Requirements for Emergency Research (21 CFR 50.24) (Draft, Aug. 06)
- Process for Handling Referrals to FDA Under 21 CFR 50.54: Additional Safeguards for Children in Clinical Investigations (Final, Dec. 06)
- Adverse Event Reporting – Improving Human Subject Protection (Draft, Apr. 07)
- Computerized Systems Used in Clinical Trials (Final, May 07)
- Protecting the Rights, Safety, and Welfare of Study Subjects – Supervisory Responsibilities of Investigators (Draft, June 2007)

# Recent FDA Guidance Documents

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- **Ex. Draft Guidance on Adverse Event Reporting**
  - Regulatory Background:
    - Investigators must promptly report all adverse effects to drug sponsor
    - Investigators must promptly report all **"*unanticipated problems*"** to IRB
    - Sponsors must notify investigators of new observations regarding adverse effects/safe use (reports on significance of current adverse experience)
    - Note: Device sponsors must evaluate unanticipated adverse effects - report to investigators *and IRBs*
  - Problems Experienced by IRBs:
    - Receiving large volumes of individual AE reports lacking context and detail – incomplete and unanalyzed
    - Often receive reports of events that were anticipated to occur
    - Inhibiting ability to protect subjects because unable to assess significance – need summary and evaluative information

# Recent FDA Guidance Documents

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- **Draft Guidance on Adverse Event Reporting**
  - All reports to IRBs should explain why event represents a "problem" for study and is "unanticipated"
    - Reports lacking evaluation of relevance to study should not be provided to IRB (cannot determine if individual AE is unanticipated problem if taken in isolation, even if event is unexpected)
    - Need reports explaining why info might affect IRB's view of study or require change to protocol or consent form
  - For unanticipated problems that are also adverse drug experiences, only report:
    - Any AE that even without analysis represents a serious unexpected AE because rare in absence of drug exposure (*e.g.*, agranulocytosis, hepatic necrosis, etc.)
    - Series of unexpected AEs that, after analysis, are not isolated occurrences and are significant to rights/welfare of subjects
    - Expected AE occurring at greater frequency or severity than expected
    - Any other AE that would lead to modification of investigator's brochure, protocol, consent form, or action by IRB

# Recent FDA Guidance Documents

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- **Draft Guidance on Adverse Event Reporting**
  - Sponsor in best position to process/analyze AE info from multiple sites and make determinations about unanticipated problems (and required by regulation to undertake such analysis)
  - But regs impose obligation on *investigators* to report unanticipated problems in drug trials to IRBs – instead of changing regs, guidance provides that:
    - Investigator may rely on sponsor's assessment and may provide unanticipated problem report prepared by sponsor
    - If investigator knows sponsor has reported unanticipated problem directly to IRB, FDA will exercise enforcement discretion (investigator need not provide duplicate report)
  - Device regs require investigators to report to sponsor and IRB, and *sponsor* must then report results of evaluation to IRB – paradigm working well
  - Bottom Line: drug sponsors already have to report <u>analyses</u> of unexpected events to investigators – encourage reporting of meaningful information to IRBs as well

# Future Goals of FDA Initiative

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- Response to 2007 OIG Report – FDA plans to:
  - Finalize proposed rule re: registration of IRBs (69 FR 40556, July 6, 2004, to create 21 CFR 56.106)
    - Require IRB registration with contact info, number of active protocols involving FDA-regulated products, description of products, IRB accreditation info
    - Goal: facilitate inspection of and conveyance of information to IRBs
  - Create cross-center database to allow complete tracking of BiMo inspections, develop risk-based inspection model, and hire more inspectors
  - Create mechanism for feedback to field district offices
  - Develop internal clinical trials database as part of creation of e-platform for all regulated product information
  - Continue to engage in rulemaking and guidance drafting to close gaps and address modern clinical trial practice

# FDA-Duke MOU (Nov. 2007)

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- Public-private partnership to modernize clinical trials – develop new standards and identify new methods/technologies to improve safety, quality of information derived from trials, and efficiency
  - Reagan-Udall Foundation established by FDAAA will also work to streamline clinical trials and other aspects of product development
- Representation from gov't, industry, patients, professionals, academia
- May initially focus on IRBs as low-hanging fruit
  - Asked to do too much
  - Duplication in multi-center trials
  - Delay initiation of research
- Creation of **Clinical Trials Transformational Initiative** - Jan. 30, 2008
  - Models of best practice from study design to metrics for evaluation
  - Primary focus on US studies, but consider global implications

# CTTI Goals and Projects

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## Initial projects:

- Best practices for enrollment, monitoring, and auditing
- Approaches to data quality and quantity
- Development of modernized approaches to informed consent
- Development of Smart Case Report Form (eliminate paper form and adopt electronic model to allow for real-time evaluation and remote monitoring; automated auditing for inconsistency, violations, etc.; expedite aggregation and data analysis)
- Additional standards for electronic data collection and management

## Long-term deliverables:

- Functional definition of clinical trial types w/ descriptions of optimal quality parameters
- Best practices for informatics, data standards, study plans, financial planning
- Best practices for minimizing delays in trial initiation (IRBs and contract negotiation)
- Clinical trial site accreditation program, and investigator/personnel credentialing
- Model for ideal clinical trial site
  - Roles of all key parties
  - Physical requirements
  - Best practices for site functionality and quality, including SOPs
  - Financial models
  - Best practices for interface between IRBs, sponsors, regulators, payers, subjects, etc.

# Congressional Action

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- **Food and Drug Administration Amendments Act of 2007**
  - Passed in September 2007
  - Shift from previous legislation focused on speeding review - now primary focus on safety
  - Reforms related to clinical trials:
    - Expansion of ClinicalTrials.gov database to include far more trials, as well as trial results
    - Post-market studies and clinical trials (and use of PDUFA funds)
    - Antibiotic trials
    - PREA
    - BPCA

# ClinicalTrials.gov Reforms

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- CT.gov established in 1997 - 42 USC 282(i)
  - Covered only serious or life-threatening disease drug trials
  - No enforcement mechanism
  - Trial results not required (and not accepted)
  - Goal: information for patients looking to enroll (so limited to purpose, eligibility, sites, contact info, and compassionate use policies)
- State of Maine moved to fill gap
  - Requires manufacturers and labelers conducting covered clinical trials in any jurisdiction initiated on or after Oct. 15, 2002, to register trial and post results
  - Applies only after product approved by FDA and dispensed, administered, delivered, or promoted in Maine
- ICMJE policy:
  - Registration upon trial initiation or will not be considered for publication

# ClinicalTrials.gov Reforms

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- **FDAAA Title VIII** – creating 42 USC 282(j)
  - Expanded goal: full disclosure of clinical trials (response to reports of suppression of unfavorable data by sponsors)
  - CT.gov no longer limited to serious or life-threatening diseases
    - ***In addition to previous requirements imposed by 282(i),*** now covers all controlled clinical investigations – other than Phase I (but including Phase IV) – of drugs subject to FDA regulation
    - Also covers device trials – other than small feasibility studies
  - Coverage of international studies
    - Not explicitly addressed by law – may be clarified by regulation
    - Conducted under an IND: subject to FDA regulation → covered
    - Not conducted under an IND:
      - Approved product – subject to FDA regulation → covered
      - Unapproved product – not subject to FDA regulation → may not be covered unless and until trial used to support regulatory approval in US

# ClinicalTrials.gov Reforms

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- CT.gov now requires far more content:
  1. **Initial registration information** (effective for most trials Dec. 26, 2007)
     - Descriptive information (title, summary, design, focus, dates, outcomes, etc.)
     - Recruitment information (eligibility criteria, site status compassionate use policies, etc.)
     - Location and contact information
     - Administrative data (protocol numbers, etc.)
  2. **Results posting**
- Posting by responsible party – sponsor (or PI, if so designated)

# ClinicalTrials.gov Reforms

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- Results Posting – Phases of Expansion:
  1. As of Dec. 26, 2007: Linking to existing results (no sponsor action necessary)
     - FDA Information: advisory committee materials, review documents, public health advisories
     - NIH Information: MedLine citations, labels from National Library of Medicine
  2. By Sept. 27, 2008: Results database expanded to include basic trial results (to be submitted by responsible party):
     - Demographic and baseline characteristics of patient sample
     - Primary and secondary outcomes
     - Point of contact for scientific information about results
     - Any agreements restricting publication

# ClinicalTrials.gov Reforms

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- Results Posting – Phases of Expansion (continued):
  3. By Mar. 27, 2009: Results database expanded by HHS regulation to include adverse event information (or by Sept. 27, 2009, should regs not be timely promulgated)
  4. By Sept. 27, 2010: Results database expanded by HHS regulation to include:
     - Lay and technical summaries of results
     - Protocol information
     - Will definitely apply to approved products – but regs must determine if also applicable to unapproved
     - ***State requirements for registration and results posting will be preempted upon this final regulatory expansion***
       - Maine's requirements likely to remain effective until 2010, if not later

# ClinicalTrials.gov Reforms

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- Deadlines
  - Initial registration: 21 days after first subject enrolled
    - Updates at least every 12 months
    - Changes to recruitment status: within 30 days
    - Notification of completion: within 30 days
  - Results (as requirements become effective): Within 1 year of actual or estimated completion date, whichever is earlier, with extensions for trials completed prior to product/indication approval, or for good cause
- Certification
  - As of Dec. 26, 2007, all NDAs, BLAs, and INDs submitted to FDA must be accompanied by certification that CT.gov submission requirements have been met
  - Draft guidance, available at http://www.fda.gov/oc/initiatives/fdaaa/guidance_certifications.html
  - FDA Form 3674, available at http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3674_508.pdf
  - Must also certify compliance on federal grant forms/reports

# ClinicalTrials.gov Reforms

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- Penalties
  - Failure to comply posted on site
  - Civil monetary fines up to $10,000 for all violations adjudicated in single proceeding for failure to post, or submitting false or misleading information
  - 30 days after notification of noncompliance: fine increased $10,000 per day until resolved
- Additional Implications
  - Significant impact on companies' ability to control proprietary data
  - Enable critical third-party meta-analyses (Avandia)
  - May impact medical journal policies regarding prior publication
- Watch for additional regulation/guidance regarding results posting
  - http://prsinfo.clinicaltrials.gov/
  - http://prsinfo.clinicaltrials.gov/s801-fact-sheet.pdf

# ClinicalTrials.gov Reforms

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- Ensuring Compliance
  - Which of your company's trials fall under law's new requirements?
  - Have all trials subject to Dec. 26, 2007, initial registration deadline been appropriately registered?
  - Who within your company will be responsible for ensuring compliance with future deadlines and serving as point of contact?
  - Will any registration responsibilities be delegated to PIs?
  - What are your company's priorities for public comment on regulations required by statute?
  - How are you ensuring compliance with Maine's requirements and ICMJE policy?

# Post-Market Studies and Trials

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- Until FDAAA, FDA's authority to require post-approval trials or studies limited to:
  - Accelerated approval based on surrogate endpoints for serious or life-threatening diseases – with post-approval trial(s) required to verify product's clinical benefit
  - Pediatric Research Equity Act requires pediatric studies for all new drugs or biologics, but FDA could allow a deferral until after approval
  - Voluntary commitment by sponsor as condition of approval
- Previous enforcement limited to drastic, resource-intensive measures: withdrawal of approval
- Extremely low compliance rates

# Post-Market Studies and Trials

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- **FDAAA Title IX** – Creating 21 USC 355(o)
- Authorizes FDA – before or after approving prescription drug or biologic – to require post-approval studies or clinical trials to:
  - Study known serious risk
  - Assess potential for serious risk
  - Identify unexpected serious risk when data indicates potential for such risk
  - Note: Not necessarily limited to safety issues – also failure of expected pharmacological action, so could require Phase IV efficacy study
- Requirement for post-approval study or trial must be based on scientific evidence, including information about chemically or pharmacologically related drugs
  - Difference between study and trial not defined
  - Study may refer to observational research or post hoc analysis

# Post-Market Studies and Trials

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- Limitations of FDA Authority:
  - Post-approval study may be required only if active postmarket risk identification system established in FDAAA and passive adverse event reporting system would be inadequate
  - Post-approval clinical trial may be required only if post-approval study would be inadequate
  - Post-approval obligations may be imposed after a drug is approved only if FDA becomes aware of new safety information, including info about serious/unexpected risks from broad range of sources, including new analysis of existing info
- Sponsors may appeal requirement for post-approval study through standard dispute resolution procedures

# Post-Market Studies and Trials

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- Must submit a timetable for completion and periodic reports
- May result in labeling change
- Penalties for failure to meet Phase IV commitments:
  - Product in question may not be introduced into interstate commerce, and would be misbranded
  - Civil penalty up to $250,000 per violation, not to exceed $1 million for all violations adjudicated in a single proceeding
  - If violation continues after notice, FDA may impose penalties up to $10 million
- Implementation and enforcement of these provisions may be supported by PDUFA IV fees

# Additional FDAAA Reforms

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- **PDUFA IV fees** will also be used to:
  - Enhance clinical drug development through new guidance documents covering:
    - Non-inferiority trials
    - Adaptive trial designs
    - Clinical hepatoxicity
    - End-of-phase II meetings
    - Enriched trial design
    - Multiple endpoints in clinical trials
    - Imaging standards as endpoints
  - Increase collaboration with scientific community to clarify regulatory pathways for new technologies and potential biomarkers for drug safety and effectiveness

# Additional FDAAA Reforms

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- **Clinical Trial Guidance for Antibiotic Drugs**
  - FDAAA § 911
  - By Sept. 27, 2008, FDA must issue guidance on conduct of clinical trials of antibiotic drugs, in particular indicating appropriate models and valid surrogate markers
  - By Sept. 27, 2012, FDA must review and update guidance to reflect developments in scientific and medical information and technology

# Additional FDAAA Reforms

HOGAN & HARTSON

- **Pediatric Research Equity Act** (PREA) – "Stick"
  - Reauthorized by FDAAA for additional 5 years
  - Maintains FDA authority to:
    - Require pediatric assessments in each application, and
    - Require pediatric studies for already approved products if:
      - Sponsor declined to comply with request for pediatric study under BPCA and
      - FDA determines that pediatric patients would benefit from studies or additional labeling
  - Sponsor may still request a waiver or deferral of pediatric assessment
  - Drug misbranded if sponsor fails to submit pediatric assessments within certain timeframes, and also if it fails to comply with pediatric labeling changes

# Additional FDAAA Reforms

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- **Best Pharmaceuticals for Children Act** (BPCA) – "Carrot"
  - Also reauthorized for additional 5 years
  - 6 month pediatric exclusivity if sponsor conducts and reports to FDA results of pediatric clinical studies in response to "written request"
    - Written requests may now cover preclinical studies
    - Agency will have 6 months to make pediatric exclusivity determinations, rather than 3 – and if determination made less than 9 months before expiration of existing exclusivity or patent, no extension will be awarded
    - Must submit pediatric studies earlier in lifecycle – at least 15 months prior to expiration of most valuable patent/exclusivity
  - FDA may now order labeling to include results of pediatric studies regardless of whether studies demonstrate safety or efficacy, or are inconclusive – all requested studies will make their way to label
    - Drug misbranded if sponsor fails to make ordered labeling changes

# Recent Developments in FDA Regulation of Clinical Trials:

## ClinicalTrials.gov and Future FDA Proposals

International Pharmaceutical Regulatory and Compliance Congress and Best Practices Forum

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