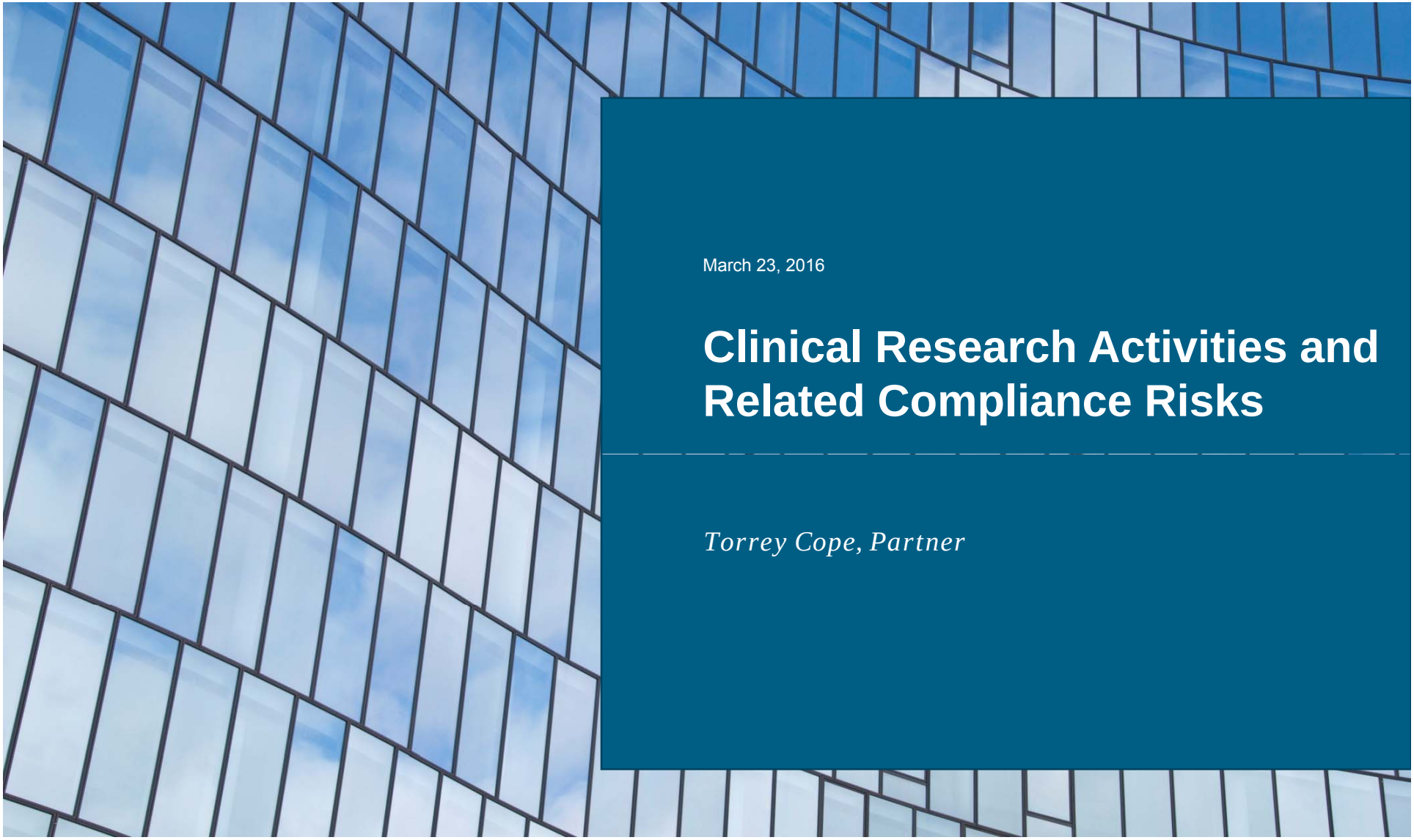


March 23, 2016

Clinical Research Activities and Related Compliance Risks

Torrey Cope, Partner

SIDLEY AUSTIN LLP
SIDLEY

Agenda

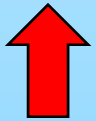
- Areas of focus for FDA and DOJ enforcement
- International considerations
- Emerging compliance issues
  - Data privacy: Why should you care about what's going on in the EU?
  - Spotlight on fulfillment of post-market study commitments
  - Transparency considerations beyond ClinicalTrials.gov
- Putting it all together: a compliance checklist

FDA Oversight: Highlights of CDER BIMO Metrics FY 2015

BIMO inspections decreased slightly overall, with fewer inspections of investigators and sponsors, but more bioequivalence and PADE inspections

International inspections increase in both absolute terms and as a share of total inspections

CRO inspections increased over 300%, returning to 2010 levels (21), even as sponsor and sponsor-investigator inspections decreased



Warning letters at lowest level in 10 years (6 in FY 2015, down from a reported 16 in FY 2014)

BIMO FY 2016 Action Plan

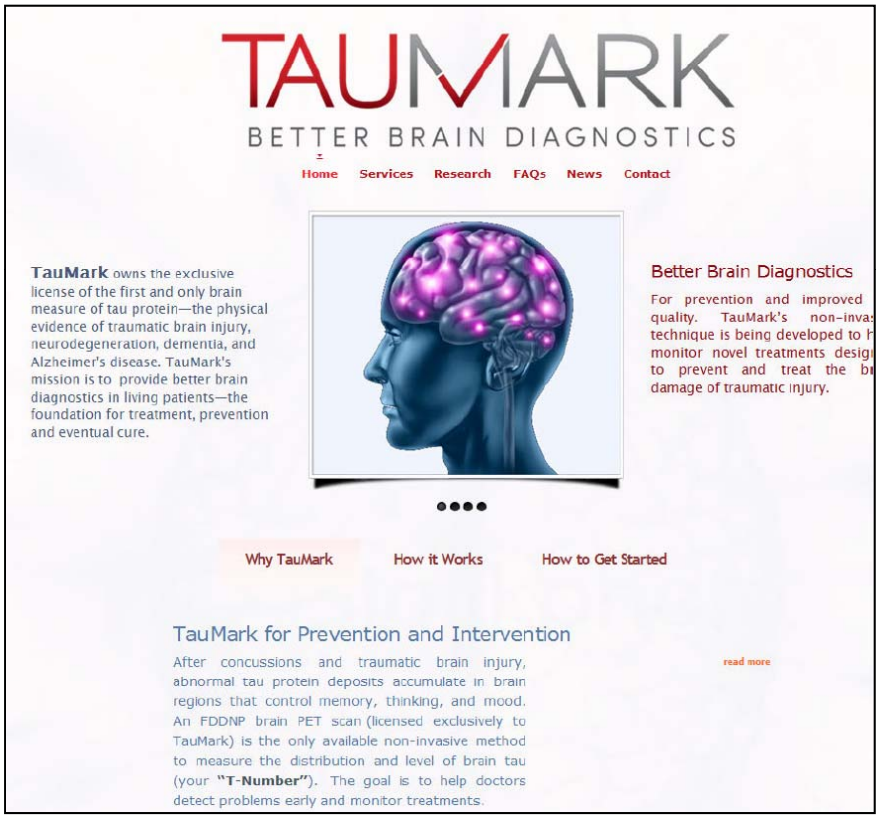
- Continued efforts relating to launch of a stand-alone BIMO Program in FY 2017
  - Currently, inspectors are commodity-specific investigators (whose primary program area typically is not the BIMO program)
  - The new BIMO program will involve a dedicated corps of inspectors based in the Office of Regulatory Affairs (ORA) who specialize in the BIMO program
- Work in FY 2015 was largely analytical/reflective in order to develop a vision for a stand-alone BIMO Program
- Focus in FY 2016 is on establishing the infrastructure needed to support the program, defining and beginning to monitor success metrics, developing common practices and communications across the program, and redefining work planning activities
  - Analyze current and historic data to establish resource and staffing needs
  - Establish BIMO Curriculum Committee to oversee development and execution of a consolidated training and development program
  - Develop a plan for revising/updating CPGM within BIMO program

BIMO Warning Letters to Sponsors

- AB Science (6/16/2015)
  - Failure to ensure proper monitoring
- CXL-USA (4/1/2015)
  - Failure to submit an IND
  - Failure to ensure proper monitoring
- Brava, LLC (8/28/2014)
  - Failure to adequately monitor
  - Failure to secure compliance or discontinue shipments of the device
  - Failure to notify FDA of IRB withdrawal of approval
- Rogerio A. Lobo (4/18/2014)
  - Failure to ensure proper monitoring
- Impladent, Ltd. (3/28/2014)
  - Failure to submit IDE and obtain IRB and FDA approval
  - Inadequate consent and failure to obtain IRB review of ICFs
  - Failure to obtain signed agreements from participating investigators and failure to maintain product disposition records
- AMKS Time Release Laboratories, LLC (4/10/2014)
  - Failure to submit an IND
  - Failure to ensure proper monitoring
  - Failure to maintain adequate records showing the receipt, shipment, or other disposition of the investigational drug
- Advanced Magnetic Research Institute International LLC (1/16/2014)
  - Failure to maintain IRB approval
  - Failure to adequately maintain records

Pre-Approval Promotion

- OPDP Untitled Letter to Dr. Gary Small, Semel Institute for Neuroscience & Human Behavior at UCLA (Feb. 2015)
  - "After concussions and traumatic brain injury, abnormal tau protein deposits accumulate in the brain regions that control memory, thinking, and mood. An FDDNP brain PET scan (licensed exclusively to TauMark) is the only available non-invasive method to measure the distribution and level of brain tau (your "T-Number"). The goal is to help doctors detect problems early and monitor treatments."
  - "The FDDNP compound (licensed to Taumark) contains a small amount of a rapidly disappearing radiation tag. For the PET scan, about a tablespoon of FDDNP preparation is injected into the patient's arm vein, allowing the chemical marker to reach the brain. The PET scan measures brain radioactivity accumulation for about 45 minutes, thus pinpointing areas where any tau protein deposits are present."



Pre-Approval Promotion

- OPDP Untitled Letter to CBA Research, Inc. (April 2013):
  - "ADMINISTERED ORALLY Oral delivery of CBT-1® prior to and during the administration of chemotherapy, achieves the required therapeutic concentration necessary to reverse multidrug resistance in the clinical setting."
  - "NO SIGNIFICANT OR LASTING TOXIC SIDE EFFECTS CBT-1® demonstrated no significant or lasting side effects in the clinical setting, and had a very favorable adverse event profile."
  - "MULTIPLE CANCERS Eight Phase I and II clinical trials, with patients that had failed conventional chemotherapy treatments, showed efficacy of CBT-1® in multiple cancers."

CBA Pharma Inc.
Many Minds, One Heart

Company Info | CBT-1® | Multi-Drug Resistance | Contact Us

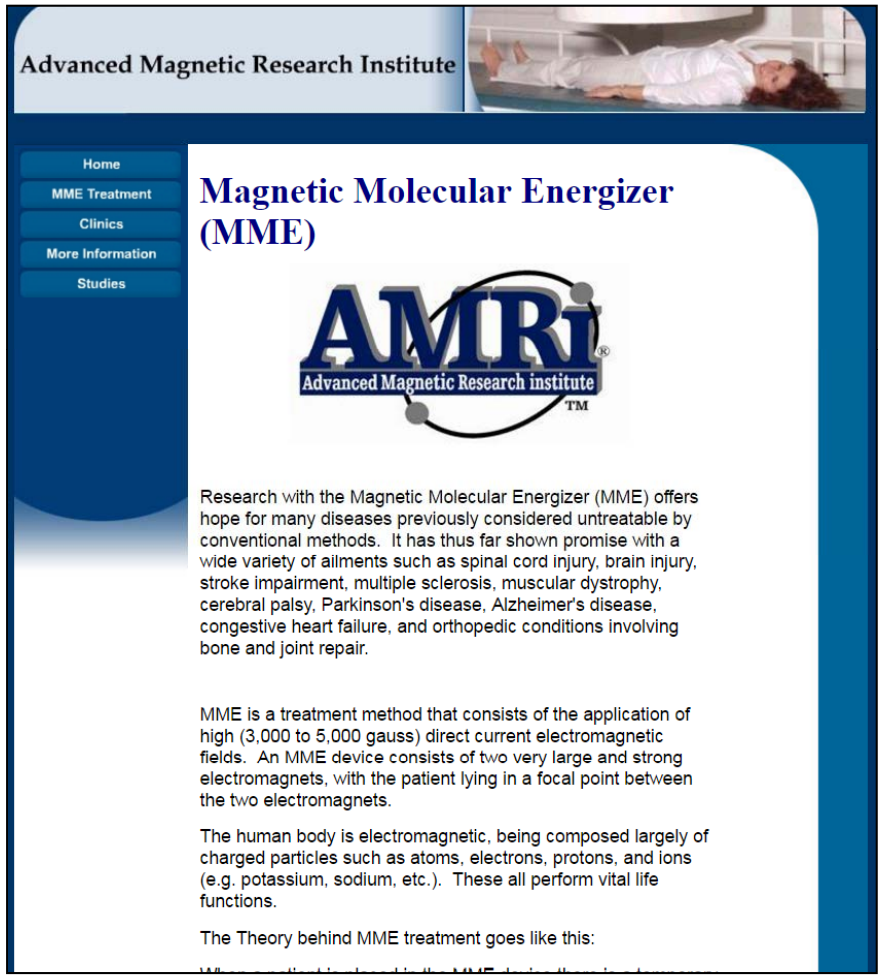
CBT1® Highlights
CBT1® Preclinical
CBT1® Clinical Trials
Phase I Trials
Phase II Trials
Phase III Trials
Publications
Medical Director
Moving Forward

CBT-1 HIGHLIGHTS

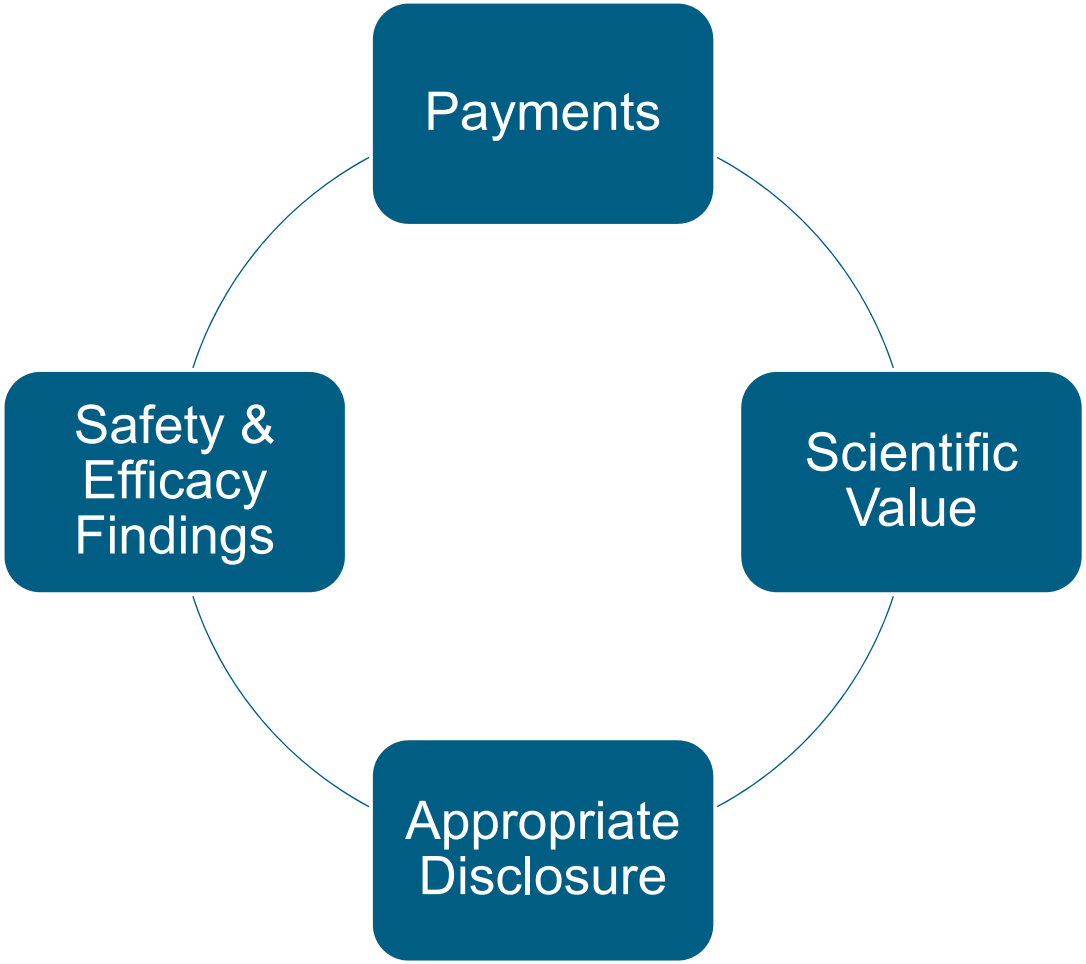
HIGHLIGHT	DESCRIPTION
NEW DRUG APPLICATION SUBMITTED	CBA Pharma, Inc. has submitted its New Drug Application (NDA) to the FDA for the use of CBT-1® as an adjunct to chemotherapy in all cancer types. Result of 22 years of basic science, animal and human research, including 18 years of clinical trials. Tested at 38 leading cancer treatment centers in 21 states.
RESISTANT MODULATION	CBT-1® has demonstrated the potential in preclinical and clinical trials to be an effective treatment for cancer that exhibits multidrug resistance (MDR) to chemotherapy as a multidrug resistant modulator
UNMET MEDICAL NEED; LIFE-THREATENING DISEASE	Multidrug resistance in cancer is responsible for a majority of cancer deaths, and to date there is no FDA approved treatment for it.
SMALL MOLECULE	CBT-1® is a small stable molecule with broad pharmacological effect.
STABLE PHARMOCKINETICS	CBT-1® has proven in clinical trials to not significantly alter the pharmacokinetic profile of chemotherapy agents.
ADMINISTERED ORALLY	Oral delivery of CBT-1® prior to and during the administration of chemotherapy, achieves the required therapeutic concentration necessary to reverse multidrug resistance in the clinical setting
NO SIGNIFICANT OR LASTING TOXIC SIDE EFFECTS	CBT-1® demonstrated no significant or lasting side effects in the clinical setting, and had a very favorable adverse event profile.
MULTIPLE CHEMOTHERAPY AGENTS	CBT-1® has demonstrated in preclinical and clinical trials the potential to enhance the effectiveness of leading chemotherapy agents when multidrug resistance occurred. Various substrates for MDR have tested positive including Doxorubicin, Vineristine, Vinblastine, Etoposide, Daunorubicin, Mitoxantrone, Taxol, Paclitaxel, and Carboplatin.
NATIONAL CANCER INSTITUTE	CBA Pharma, Inc. has collaborated with the National Cancer Institute in preclinical and clinical studies for multiple cancer types, and is working toward a clinical trial for AML (acute myelogenous leukemia).
MULTIPLE CANCERS	Eight Phase I and II clinical trials, with patients that had failed conventional chemotherapy treatments, showed

Pre-Approval Promotion

- CDRH Office of Compliance warning letter to Advanced Magnetic Research Institute (Jan. 2014):
  - "Research with the Magnetic Molecular Energizer (MME) offers hope for many diseases previously considered untreatable by conventional methods. It has thus far shown promise with a wide variety of ailments such as spinal cord injury, brain injury, stroke impairment, multiple sclerosis, muscular dystrophy, cerebral palsy, Parkinson's disease, Alzheimer's disease, congestive heart failure, and orthopedic conditions involving bone and joint repair."
  - "The rate of healing can be accelerated to be much faster than the typical healing rate of the human body. For example, a bone fracture that typically requires 6-8 weeks to heal may require only a few days with MME treatment."
  - "The safety of the induction of high strength magnetic fields was well established during toxicity studies performed for the FDA approval of the MRI."



DOJ: Factors for Enforcement Risk



Allegations Related to Research

After clinical trials for specific use showed drug was ineffective or associated with increased adverse events, promoted drug for that use

Failed to accurately report and disclose the results of clinical trials

Concealed studies that were unhelpful from a marketing perspective

Caused the submission of false and medically inappropriate claims to federal health care programs

Allegations Related to Research

To retain business or to convert from competing products, solicited participation in studies and paid for each patient enrolled

Exclusion and inclusion criteria for certain studies were ignored, and sales representatives completed study-related paperwork on behalf of participating physicians

The more clinical trial patients were enrolled, the greater the sales representatives' compensation

Used post-market studies and registry as vehicles to pay kickbacks to participating physicians

Results of Recent Investigations

Sample CIA Requirements

- Policies and procedures regarding the conduct, authorship, and disclosure of post-marketing clinical trials, observational studies and/or investigator-initiated studies (IIS)
- Internal auditing of clinical researcher and investigator arrangements, including review of needs assessment documents, proposal and/or protocol documents, contracts, payments etc.
- Independent third party review of research and publication activities
- Ensuring that there is a scientific need for research activities
  - Policies prohibiting sales and marketing directed research
  - Approval of research activities by medical or science functions
- Disclosure of clinical trial results on www.clinicaltrials.gov
- Disclosure of postmarketing commitments on the company website

Settlements with GCP Provisions

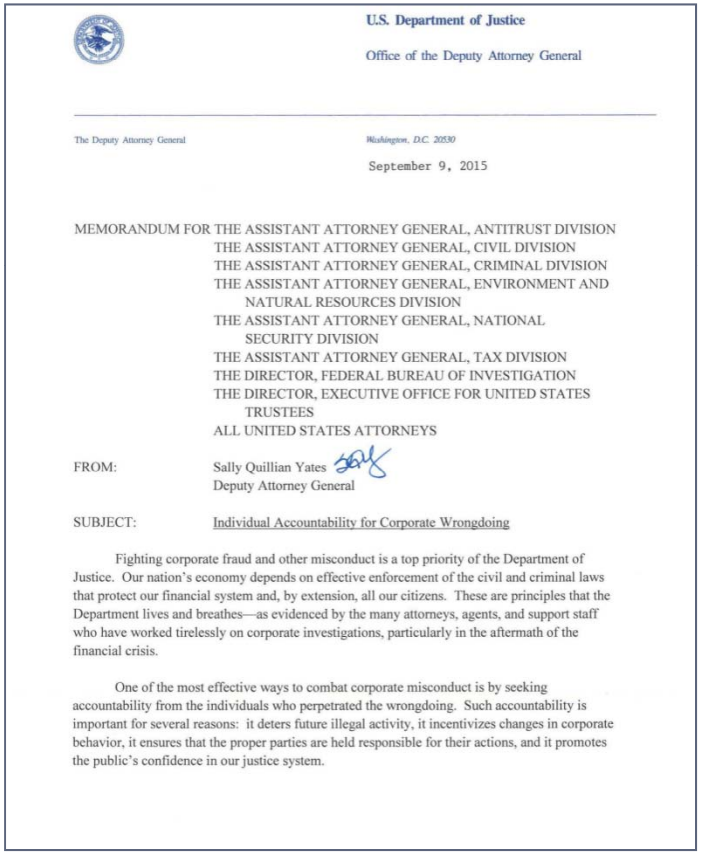
- ✓ Sanofi 2015
- ✓ Daiichi Sankyo 2015
- ✓ Shire 2014
- ✓ Endo 2014
- ✓ Johnson & Johnson 2013
- ✓ Par Pharmaceutical 2013
- ✓ Amgen 2012
- ✓ Boehringer Ingelheim 2012
- ✓ GSK 2012
- ✓ Orthofix 2012
- ✓ Abbott Laboratories 2012
- ✓ Merck 2011
- ✓ UCB 2011
- ✓ Novartis 2010
- ✓ Synthes 2010
- ✓ Forest Labs 2010
- ✓ Allergan 2010
- ✓ Ortho-McNeil 2010
- ✓ AstraZeneca 2010
- ✓ Pfizer 2009

PFP Enforcement by the Numbers

2010	Pilot Program
2015	Pharmaceutical Fraud Program (PFP) funded at $3.4 million
120	Criminal investigations since PFP began
17	Allegations of clinical trial or application fraud in FY 2015
12	Allegations of clinical trial or application fraud each in FY 2014 & 2013

Individual Liability

- "Yates Memorandum" (9/9/2015)
- Renewed focus on individual liability for corporate wrongdoing
- Six "Key Steps"
  1. To qualify for cooperation credit corporations must provide relevant facts relating to responsible individuals
  2. Corporate investigations should focus on individuals from the inception
  3. Routine communication between criminal and civil attorneys handling investigations
  4. No releasing culpable individuals from liability absent extraordinary circumstances
  5. No resolving matters with the corporation absent a clear plan for related individual cases
  6. Civil attorneys should focus on individuals as well as companies and consider more than just ability to pay



U.S. Department of Justice

Office of the Deputy Attorney General

The Deputy Attorney General

Washington, D.C. 20530

September 9, 2015

MEMORANDUM FOR THE ASSISTANT ATTORNEY GENERAL, ANTITRUST DIVISION
THE ASSISTANT ATTORNEY GENERAL, CIVIL DIVISION
THE ASSISTANT ATTORNEY GENERAL, CRIMINAL DIVISION
THE ASSISTANT ATTORNEY GENERAL, ENVIRONMENT AND NATURAL RESOURCES DIVISION
THE ASSISTANT ATTORNEY GENERAL, NATIONAL SECURITY DIVISION
THE ASSISTANT ATTORNEY GENERAL, TAX DIVISION
THE DIRECTOR, FEDERAL BUREAU OF INVESTIGATION
THE DIRECTOR, EXECUTIVE OFFICE FOR UNITED STATES TRUSTEES
ALL UNITED STATES ATTORNEYS

FROM: Sally Quillian Yates
Deputy Attorney General

SUBJECT: Individual Accountability for Corporate Wrongdoing

Fighting corporate fraud and other misconduct is a top priority of the Department of Justice. Our nation's economy depends on effective enforcement of the civil and criminal laws that protect our financial system and, by extension, all our citizens. These are principles that the Department lives and breathes—as evidenced by the many attorneys, agents, and support staff who have worked tirelessly on corporate investigations, particularly in the aftermath of the financial crisis.

One of the most effective ways to combat corporate misconduct is by seeking accountability from the individuals who perpetrated the wrongdoing. Such accountability is important for several reasons: it deters future illegal activity, it incentivizes changes in corporate behavior, it ensures that the proper parties are held responsible for their actions, and it promotes the public's confidence in our justice system.

Individual Liability

- Synthes/Norian and former executives conducted clinical trials of a significant risk device without an approved Investigational Device Exemption
  - In 2009, four executives pleaded guilty as responsible corporate officers in 2009 to misdemeanor (Park doctrine liability)
  - In 2012, excluded from participation in federal healthcare programs (permissive exclusion)

Foreign Corrupt Practices Act

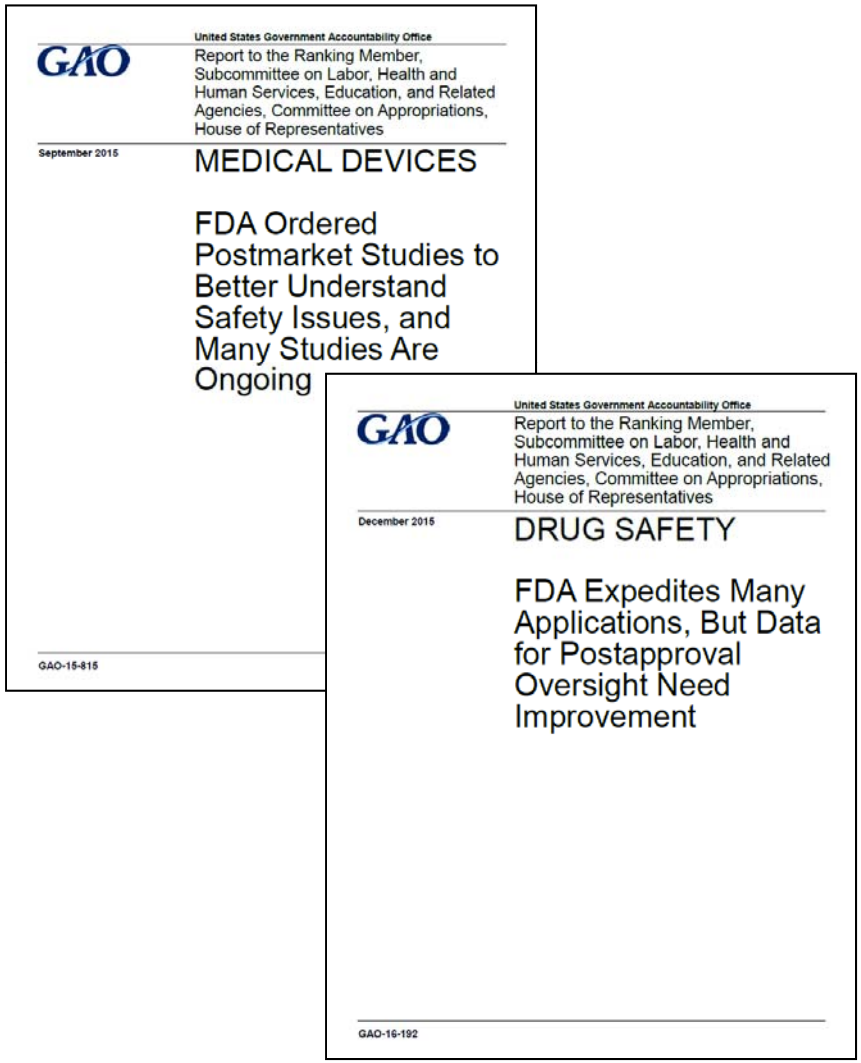
- June 2010 report by the HHS's Office of Inspector General drawing attention to risks associated with foreign clinical trials
- DOJ and SEC are focusing on Clinical trials in their sector probe of the pharmaceutical industry
  - Johnson & Johnson settlement for $21.4M (DOJ) and $48.7M (SEC) – 2011
  - Merck declination from DOJ regarding potential FCPA violations – Feb. 27, 2014
- DOJ has identified inappropriate "consulting fees" and travel and entertainment provided to doctors conducting clinical trials in China
- SEC has identified improper transactions booked as "Clinical Grants/Clinical Trials"
- Risk areas include:
  - IIS and PMS
  - Local regulatory approvals
  - Importation of equipment and supplies
  - Engagement of investigators, CROs, IRBs
  - Use of government facilities

Key Privacy Considerations in Clinical Trials

International Transfer of Clinical Trial Data

- EU Data Protection Directive prohibits transfer of personal data out of Europe except under certain exceptions (e.g., with consent of data subject)
  - Many CT sponsors relied on the "EU-U.S. Safe-Harbor Framework"
- *Shrems* case (October 2015)
  - Court of Justice of the European Union held that European Commission on adequacy of the Safe-Harbor Framework was invalid
  - Bottom line: sponsors of EU clinical trials may no longer rely on the Safe-Harbor Framework as a valid legal basis to permit transfer of data to the U.S.
- Recent Developments
  - "EU-U.S. Privacy Shield" framework proposed by European Commission on February 29, 2016
  - Framework undergoing review now
  - If approved, would replace and strengthen the former Safe-Harbor Framework

Spotlight on Fulfillment of Post-Market Study Commitments



- Warning Letter to Argo Medical Technologies, Inc. (9/30/2015)
  - Failure to submit a revised post-market surveillance study plan synopsis that addresses previously noted deficiencies
  - Failure to design an adequate PS study plan
  - Failure to timely commence surveillance under FDCA Sec. 522

Pressure for Data Transparency from Patient Groups and FDA

- *Treatment Action Group v. FDA* (D. Conn.)
  - Plaintiffs filed FOIA request and lawsuit seeking to compel FDA to make raw clinical trial data for Hepatitis C drugs public "so that doctors and patients can make informed treatment decisions and cost-benefit determinations"
    - FDA filed motion seeking a 14-month stay to process the TAG's FOIA request in accordance with first-in, first-out multi-track FOIA processing system (11/12/2015)
    - Responding to motion for stay, parties have filed cross-motions for partial summary judgement as to TAG's claim for expedited processing of its FOIA request
- Genervon / GM604
  - In April 2015, FDA responded to pressure to expedite approval Genervon's drug candidate for Amyotrophic Lateral Sclerosis (ALS) by publicly calling on the company to release the full data from its Phase 2A trial:

"We call upon Genervon to release all the data from their recently completed trial in order to allow a more informed discussion of the trial findings among ALS stakeholders."

JAMA Study:
Research Misconduct Uncovered by FDA Goes Unreported

- Reviewed publicly available documents from January 1998 through September 30, 2013
- 57 published trials for which FDA inspections identified 1 or more of the following:
  - Falsification or submission of false information (39%)
  - Problems with adverse event reporting (25%)
  - Protocol violations (74%)
  - Inadequate or inaccurate recordkeeping (61%)
  - Failure to adequately protect subjects or otherwise monitor the trial (53%)
- Only 3 of the 78 publications resulting from these studies mention the objectionable conditions or practices identified by FDA
- Calls for increased transparency from FDA regarding the clinical trials affected by their inspectional observations
  - "Is this fraud that is definitely affecting all the drugs in our medicine cabinet? No. But is this an issue that is affecting the quality of the peer-reviewed literature? You definitely can say that."

Charles Seife, "Research Misconduct Identified by the US Food and Drug Administration: Out of Sight, Out of Mind, Out of the Peer-Reviewed Literature," JAMA INTERN MED. (Feb. 9, 2015)

A Checklist of Compliance Considerations

- ✓ Regulatory requirements
- ✓ Payments
- ✓ Scientific value
- ✓ Safety and efficacy findings
- ✓ Appropriate disclosure
- ✓ Privacy

Questions

Torrey Cope

tcope@sidley.com

+1 202 736 8803

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