Ninth Annual Pharmaceutical Regulatory And Compliance Congress And Best Practices Forum

How We Get to Where We Want to Be – Managing GCP Inspections Pre-Approval

Robert F. Church, Partner
Hogan & Hartson, LLP
Los Angeles

October 28, 2008

HOGAN & HARTSON

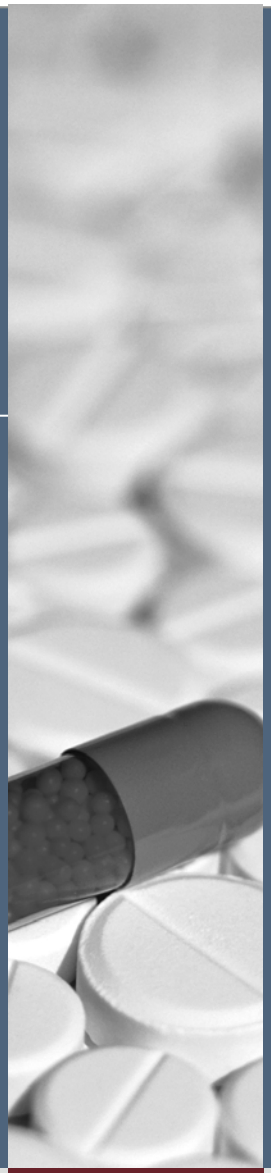
Summary

HOGAN & HARTSON

- Significance of GCP inspections
- How to successfully manage a sponsor GCP inspection
- How to successfully manage a clinical site inspection
- What to do after the inspection
- Recent areas of focus for FDA GCP Inspections
- Final recommendations

HOGAN & HARTSON

Significance of GCP Inspections



Q: What percentage of clinical sites does FDA inspect each year?

HOGAN & HARTSON

Q: What percentage of clinical sites does FDA inspect each year?

HOGAN & HARTSON

- A: Around 1% of clinical trial sites
- *Department of Health and Human Services, Office Of Inspector General's 2007 Report on "The Food And Drug Administration's Oversight Of Clinical Trials"*
  - "We estimate that FDA inspected 1 percent of clinical trial sites during the fiscal year 2000–2005 period. FDA conducted 2,855 BiMo inspections that required a clinical trial site visit during the FY 2000–2005 period."

Table 4: Centers' BiMo Inspections With Site Visits by Fiscal Year

Fiscal Year	CDER	CDRH	CBER	Total
2000	296	91	143	530
2001	186	113	79	378
2002	194	153	109	456
2003	226	167	103	496
2004	219	189	75	483
2005	221	183	108	512
Total	**1,342**	**896**	**617**	**2,855**

Source: OIG Analysis of CDER, CDRH, and CBER data, 2006.

Q: If FDA does so few GCP inspections, do they matter?

HOGAN & HARTSON

Q: If FDA does so few GCP inspections, do they matter?

HOGAN & HARTSON

- A: Absolutely.

Q: What are the consequences of a bad GCP inspection?

HOGAN & HARTSON

Q: What are the consequences of a bad GCP inspection?

HOGAN & HARTSON

- 483 Observations
- Untitled Letter
- Warning Letter
- Enforcement action against sponsor
- Clinical investigator disqualification / other enforcement action
- ***Removal of data from NDA / BLA***
- ***Refusal to continue application review***

Who does the work in a clinical trial?

- Sponsors
- IRBs
- Principal Investigators (PIs)
- Sub-Investigators
- Study Coordinators
- Other Study Staff (nurses, pharmacists, etc.)
- Clinical Trial Monitors
- Sponsor-Investigators
- Contract Research Organizations (CROs)
- Site Management Organizations (SMOs)
- Physician Practice Groups / Clinical Site Networks
- Cooperative Groups

Q: How do the FDA regulations govern the inter-relationship of all these parties?

HOGAN & HARTSON

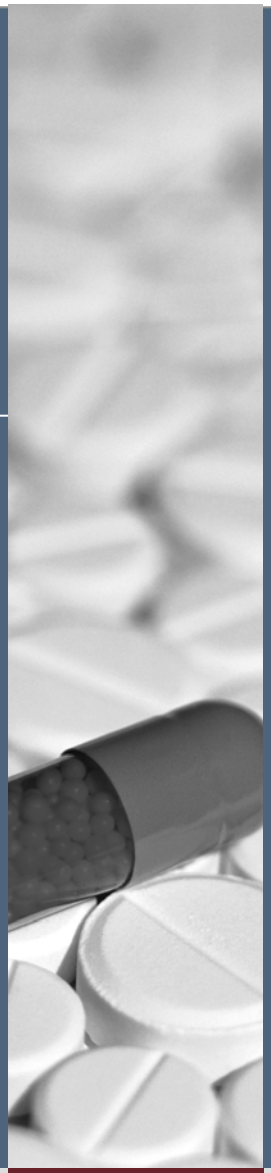
Q: How do the FDA regulations govern the inter-relationship of all these parties?

HOGAN & HARTSON

- A: Could be better.
  - FDA's regulations were written at a time when clinical research primarily consisted of Sponsors, IRBs, and Principal Investigators
  - FDA has struggled over the last several years to understand and regulate the complex web of parties involved in clinical studies

HOGAN & HARTSON

How to Successfully Manage Sponsor GCP Inspections



Preparation Before the Inspection

HOGAN & HARTSON

- Implement a GCP inspection management SOP and train relevant staff on the SOP
- Develop a GCP inspection management call tree and test it before the inspection
- Identify a GCP inspection management host
- Conduct a mock GCP inspection using your internal QA group or outside consultants
- Use mock inspection results to drive process improvements before the actual inspection

Basic Procedures for Managing FDA Sponsor Inspections

HOGAN & HARTSON

- Preliminaries
  - Greet inspectors
  - Determine scope of inspection
  - Provide the inspectors with an overview of the company
  - Send notification to staff
- Utilize 3 inspection rooms
  1. Meeting room with inspectors
  2. Operations room for inspection management team / document preparation
  3. Room for preparing company staff for interviews with inspectors
- Have 2 company staff with each inspector at all times
  1. One person who does the talking
  2. One person to act as scribe, taking notes of the discussion and keeping a log of all records that have been requested
  - "Runners" should also be available to retrieve documents for inspectors

Basic Procedures for Managing FDA Sponsor Inspections (cont'd)

HOGAN & HARTSON

- Companies should have an "Inspection Request" database that is used to log and track all requested documents. Inspection teams should:
  1. Keep a complete copy of all documents provided to inspectors, or
  2. Take other steps to clearly identify what company records have been provided to the inspectors

- Hold daily inspection de-brief sessions to update management, address open action items, and prepare for the next day of the inspection

- At the inspection close-out meeting with FDA, review any potential observations that have already been corrected and request that this be noted in the 483 (if applicable) or Establishment Inspection Report

Appropriate Conduct During Inspections

- Be polite and respectful to inspectors
- Fully and truthfully respond to any questions from inspectors
- Do not guess what the response to a question should be
- There is no requirement to volunteer information to inspectors
- While it is ok to put your best foot forward during an inspection, it is not acceptable to "cherry pick" documents with the intent to mislead the inspectors
- It is not acceptable to alter records or files. Examples include:
  - Removing specific records from a responsive file when those records are part of the file
  - Filling in blank date fields or back-dating documents
  - "Whiting out" information on documents
  - Falsifying data in records

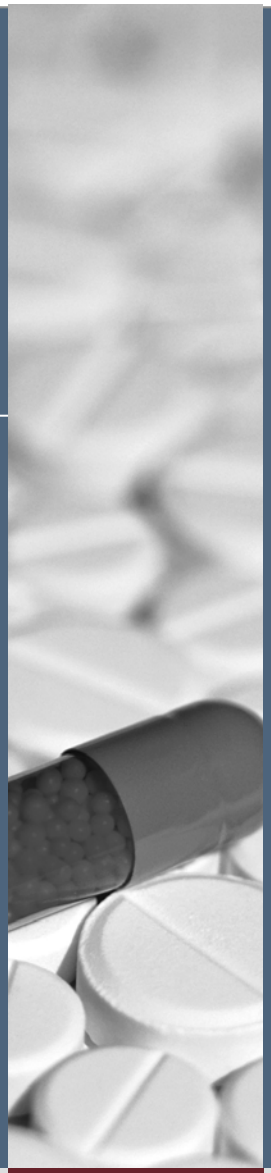
FDA's Access to Quality Assurance Audits

- Ordinarily, FDA will not request internal audit reports during an inspection. However, under Compliance Policy Guide Sec. 130.300, inspectors may request those reports in certain situations:

  - **POLICY**: During routine inspections and investigations conducted at any regulated entity that has a written quality assurance program, FDA will not review or copy reports and records that result from audits and inspections of the written quality assurance program …
  - FDA may seek written certification that such audits and inspections have been implemented, performed, and documented and that any required corrective action has been taken. …
  - FDA will continue to review and copy records and reports of such audits and inspections:
    - ***1. In "directed" or "for-cause" inspection and investigations of a sponsor or monitor of a clinical investigation;***
    - 2. In litigation (for example, and not limited to: grand jury subpoenas, discovery, or other agency or Department of Justice law enforcement activity (including administrative regulatory actions));
    - 3. During inspections made by inspection warrant where access to records is authorized by statute; and
    - 4. When executing any judicial search warrant.

HOGAN & HARTSON

How To Successfully Manage Clinical Site Inspections



Sponsors Play an Important Role In Ensuring Successful Site Inspections

HOGAN & HARTSON

- During the clinical trial:
  - Closely monitor and audit clinical sites
  - Invest in qualified GCP audit staff
  - Have a clear corporate policy on managing site non-compliance and investigator misconduct
    - Train all Clinical Staff on the policy
  - Have a system in place to promptly capture, document and respond to complaints of misconduct
  - Take immediate and effective action with non-compliant clinical sites

- If a CRO is providing monitoring services, either ensure that the CRO's policy on managing study site non-compliance is adequate, or mandate that CRO staff train on and follow your company's policy

Sponsors Play an Important Role In Ensuring Successful Site Inspections (cont'd)

HOGAN & HARTSON

- Ensure that there is a defined process for escalating concerns from the CRO monitor to the sponsor

- Review monitoring reports on an ongoing basis to identify problems in time to implement corrective action

- Immediately after a site has been notified about an FDA inspection:
  - If possible, assist the site in preparing for the inspection
    - Explain inspection process to clinical staff
    - Ensure all records are on-site and ready for inspection

Sponsors Play an Important Role In Ensuring Successful Site Inspections (cont'd)

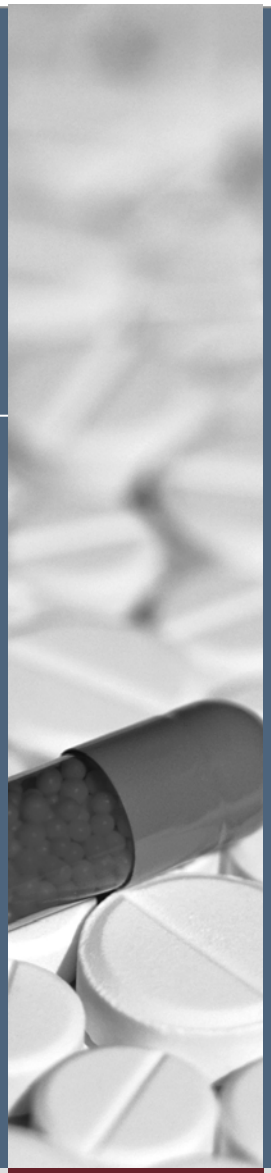
HOGAN & HARTSON

- During the site inspection:
  - Consider sending a sponsor staff member to the site to answer any questions FDA might have about the study
- After the inspection
  - Offer to assist the site in responding to the 483

- Common observations from clinical site inspections:
  - Failure to personally conduct or supervise the study
  - Failure to follow the protocol
  - Failure to maintain adequate/accurate case histories
  - Inaccurate/incomplete Drug Accountability or dosing errors
  - Inadequate subject consent form or inadequate consent procedures
  - Inadequate reporting and/or follow up of Adverse Events

HOGAN & HARTSON

What To Do After The Inspection



Appropriate Conduct After Inspections

- Avoid “victory celebrations” after the conclusion of a regulatory inspection
- A gathering where management thanks staff for their work during an inspection is acceptable
- Remind staff not to joke about, or make disrespectful comments about, inspections or inspectors

After the Inspection

HOGAN & HARTSON

- After the conclusion of an inspection, responsible staff should take prompt action to correct or remediate any significant verbal observations made by the inspector
- If the inspector issues a Form FDA 483, Inspection Observations, the company should make every effort to promptly respond
  - Many companies respond within 2 weeks of receiving a 483

Practical Advice for Responding to 483 Observations

HOGAN & HARTSON

- Best Responses to a 483 Observation
  - Problem fixed
  - Problem will be fixed by *[Fill in Date]*
- Less Successful Responses to a 483 Observation
  - FDA is wrong
  - The observation is trivial
  - The inspectors didn't understand our science
  - The inspectors misinterpreted the law
- In responding to clinical site 483 observations, many investigators either:
  - Say too little and fail to convince FDA that they take the observations seriously
  - Say too much and provide FDA with admissions of wrong-doing

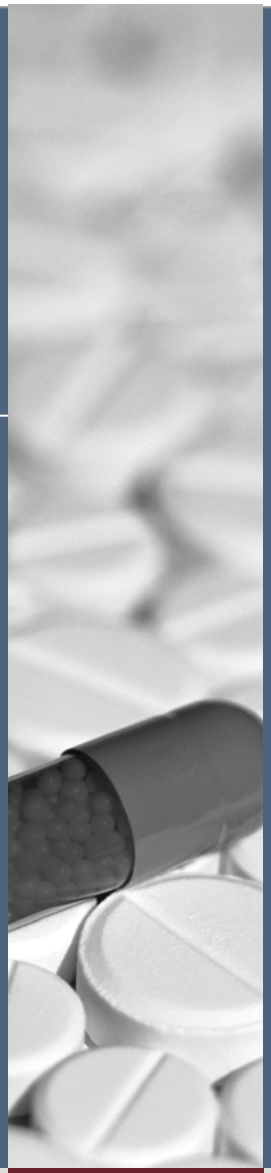
When It's Ok to Push Back on a 483

HOGAN & HARTSON

- You should correct factual inaccuracies in an observation
- It is also acceptable to supplement the record if the inspector did not have access to all relevant documents
- If an observation from a clinical site inspection second-guesses a physician's medical judgment, it may be appropriate to challenge the finding

HOGAN & HARTSON

Recent Areas Of Focus For FDA GCP Inspections



Recent Enforcement Trends

HOGAN & HARTSON

- FDA's recent GCP inspections seem to be focusing on the following issues:
  - Effective transfer of obligations to CROs
  - Satisfactory monitoring of principal investigators (PIs)
    - If PIs are not complying with GCP or the protocol, FDA expects that companies will promptly secure compliance
  - Integrity of data related to a study's primary efficacy endpoints
  - Safety reporting

FDA's 2007 Sanofi-Aventis Warning Letter

HOGAN & HARTSON

- In summary, our investigation found that Aventis did not adequately secure compliance of Dr. Kirkman Campbell. In addition, ***Aventis's method for securing compliance, (i.e., the generation of more than 125 memos to file for protocol and informed consent deviations noted at the site) was not adequate.***

- Our investigation found that Aventis failed to properly ensure monitoring of the study…. Under the original study protocol only 5 to 50 subjects were to be enrolled per center. However, in December 2001 ***Aventis permitted the number of subjects per site to be increased to a maximum of 500 per site, without amending their monitoring*** to adequately adjust for the increased enrollment during the time that subjects were actively enrolled into the study.

- Although Aventis had contracted with PPD to conduct monitoring visits, Aventis conducted its own QA audits and conducted co-monitoring visits with PPD of Dr. Kirkman Campbell's site. ***As the sponsor of the NDA, Aventis retains responsibility for ensuring proper monitoring***.

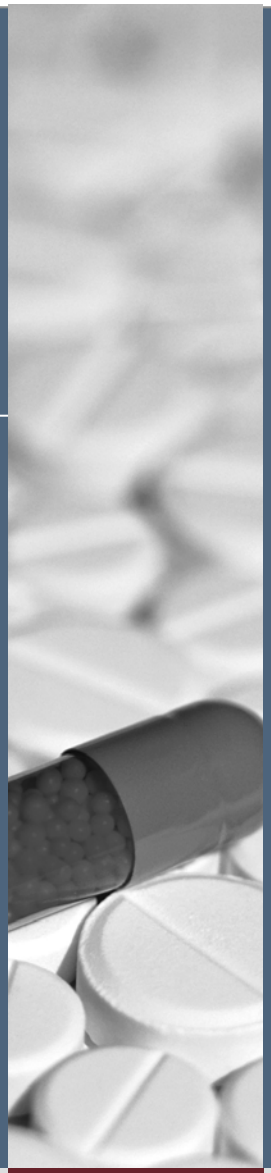
Final Thoughts

HOGAN & HARTSON

- Best Ways to Ensure a Positive Inspection Outcome
  - Carefully select your CROs and investigators
  - Put into place a clear transfer of obligations form, ideally incorporated by reference into the contract with the CRO
  - Consider putting in place a Quality Agreement or – at the very least – a highly detailed scope of services for any outsourced study
  - Invest the resources in an effective clinical trial monitoring plan
  - Have a robust Clinical Quality Assurance program to audit your sites ***and CROs***
  - If you're a sponsor outsourcing a study, remember that you have the ultimate accountability to ensure that the CRO is doing high quality work
  - Carefully document and take effective corrective action for any observed protocol or GCP deviations during the course of the study
  - Take the pre-approval GCP inspections as seriously as you would a GMP inspection

HOGAN & HARTSON

Questions and Answers



HOGAN & HARTSON

For more information on Hogan & Hartson, please visit us at:

www.hhlaw.com

ROBERT F. CHURCH, PARTNER

HOGAN & HARTSON LLP

1999 Avenue of the Stars, Suite 1400, Los Angeles, CA 90067

direct +1.310.785.4646 | tel +1.310.785.4600 | fax +1.310.785.4601

rfchurch@hhlaw.com

Abu Dhabi
Baltimore
Beijing
Berlin
Boulder
Brussels
Caracas
Colorado Springs
Denver
Geneva
Hong Kong
Houston
London
Los Angeles
Miami
Moscow
Munich
New York
Northern Virginia
Paris
Philadelphia
Shanghai
Tokyo
Warsaw
Washington, DC