Expert Witness View of FDA-Regulated Companies: Information Trial Attorneys Must Know

(Insight from a former reviewer)

Joshua Sharlin, Ph.D.
Sharlin Consulting
cell. 410-231-8900
jsharlin@pipeline.com
www.linkedin.com/in/jsharlin/
www.SharlinConsulting.com

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Presentation Objectives

1. Learn an expert witness's view about common problems and errors in the processes FDA requires
2. Understand how information is collected and reported in today's FDA-regulated environment
3. Identify documents that add to a knowledgebase about the activities and results of FDA-regulated processes

About Dr. Sharlin

1. Former FDA reviewer
2. Expert witness on FDA regulatory isuues
3. 20 years of experience consulting with FDA-regulated companies (drugs, biologics, medical devices)
4. Skilled auditor of FDA compliance
5. Testified and been deposed in drug and medical device cases supporting plaintiffs and defendants

Bottom Line Up Front

1. Execution of FDA-required product development activities are complex and many errors are made affecting the accuracy and reliability of information
2. Root cause of errors:
   - Lots of people are involved (with differing priorities)
   - Lots of rules to follow
   - Work is outsourced
3. These errors can be discovered
4. These errors can be documented

Plaintiff vs Defendant

1. Attorneys for the plaintiff or the defendant should:
   - Identify errors in process and procedures
   - Determine their root cause
   - Establish their effect on facts of the case

Drug vs Medical Device

1. These general principles apply to all FDA regulated activities performed on behalf of drugs or medical devices
2. Drugs (and Class III medical devices) must be safe and effective
3. Medical devices cleared via a 510(k) must be substantially equivalent to a predicate device
4. Understand why errors occur and how they can be detected

Three Key Questions

1. What did the company know and when did they know it?
2. What should the company have known and when should they have known it?
3. What should the company have done and when should they have done it?

Who Has a Role in Committing, Detecting and Analyzing Errors?

1. FDA reviewers and inspectors
2. Drug or device company (a.k.a. the sponsor)
3. Contractors (a.k.a. Contract Research Organization or CRO)
4. Patients (a.k.a. subjects)
5. Clinical sites
6. Investigators
7. Monitors
8. Auditors
9. Quality Assurance (QA) group

The Process Supporting FDA Regulated Activities

1. Do you have a Standardized Operating Procedure (SOP)?
2. Is there evidence the SOP was followed?
3. Is there a quality check?
4. If an error occurred, is there evidence of actions to fix it?

Mistakes in each of these steps are common.

Sources of Requirements for FDA Mandated Processes

1. Legislation
2. Code of Federal Regulations (CFR)
3. The Federal Register - especially the Final Rule

Be sure dates of these documents are contemporaneous with key event dates of your case.

Sources of FDA's Recommendations and Insight About FDA-Required Activities

1. FDA's guidance documents
2. FDA's Compliance Program Guidance Manuals
3. FDA's Standard Operating Policies and Procedures (SOPP)

All of these documents change over time.

Sources of Commitments About FDA Required Activities

1. Contracts between pharma/device companies and their outsourcing partners (Contract Research Organizations or CROs). Who is responsible for what?
2. Standard Operating Procedures (SOPs) written by companies and their CROs
3. SOP topics
   - Adverse Event reporting and all regulated activities
   - Monitoring
   - Auditing
   - Quality
4. Companies and CROs over-commit in their SOPs. Did they follow their own procedures?

All of these documents should be requested during discovery.

Documents Containing Information About FDA-Required Processes

1. Drug/Device submissions (IND, NDA, 510(k), IDE, PMA)
2. Protocol
3. Informed Consent
4. Annual Reports
5. Adverse Event Reports
6. Auditing Reports
7. Monitoring Reports
8. CAPA (Corrective Action / Preventive Action) documentation
9. Emails

All of these documents should be requested during discovery.

Sources of Errors in FDA-Required Processes

FDA-regulated companies can have significant problems with process execution

1. **Different priorities between a company and its CROs**
2. **Outsourcing. Problems with CROs can include:**
   - **Confusion about the division of responsibilities**
   - **Weak skill and experience of CRO staff (Did the lowest price win the contract?)**
   - **Cost and schedule can be more important than quality of work**
3. **Work/submission due dates are locked. No time to find and fix mistakes.**
4. **Fatigue: Huge numbers of hours are worked during the final 3 months of submission creation. No will or resources to find and fix mistakes.**

Detecting Errors in an FDA–Required Process

1. What are the sources of requirements?
   - Contracts between the drug/device company and the Contract Research Organization (CRO)
   - FDA regulations
   - Standard Operating Procedures (SOPs)
2. Who finds mistakes and what is the process? Investigate:
   - Quality Assurance (QA) unit
   - Study monitoring
   - Documentation of protocol deviations

#1. What did the company know and when did they know it?

1. **Information sources that answer the question:**
   - **IND/IDE (Investigational New Drug/Investigational Device Exemption)**
   - **Study protocol**
   - **Annual Reports**
   - **Adverse event reporting**
   - **Patient registries**
   - **Email**

#2. What should the company have known and when should they have known it?

1. **Information sources that answer the question:**
   - **Articles in the scientific literature**
   - **Adverse event reporting database**
   - **Patient registries**
   - **Minutes from meetings with FDA**
   - **Email to and from FDA**

#3. What should the company have done and when should they have done it?

1. **Information sources that answer the question:**
   - **Content in the Code of Federal Regulations**
   - **Advice in FDA guidance documents**
   - **Information on the FDA web site (FDA.gov)**

Conclusions

1. Many documents contain information about FDA-regulated processes.
2. Processes are frequently incomplete and incorrect.
3. Differing priorities between drug companies and their outsourcing partners (Contract of Research Organizations or CROs) are a significant root cause of errors.
4. Errors can be detected and described.

Next Steps

1. Expand the types of documents sought during discovery
2. Understand the process, responsibilities, outcomes and differing priorities in all product development activities
3. Apply this knowledge to more thoroughly identify, investigate, and document errors