EPSTEIN BECKER & GREEN P.C.

IDENTIFYING & MANAGING GCP COMPLIANCE RISKS FOR THE PHARMACEUTICAL, BIOTECH & DEVICE INDUSTRIES

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APPLICABLE REGULATIONS

21 CFR 312 - Investigational New Drug Applications

21 CFR 812 - Investigational Device Exemptions

21 CFR 50 – Protection of Human Subjects

21 CFR 56 - Institutional Review Boards

21 CFR 54 – Financial Disclosure by Clinical Investigators

APPLICABLE REGULATIONS

21 CFR 314 – Application for FDA Approval to Market a New Drug

21 CFR 601 – Application for FDA Approval of a Biologic License

21 CFR 814 – Premarket Approval of Medical Devices

21 CFR 11 – Electronic Records; Signatures

21 CFR 820 – Design Controls of the Quality System Regulation

APPLICABLE GUIDANCE

FDA Good Clinical Practices website
http://www.fda.gov/oc/gcp/default.htm

ICH E6 Good Clinical Practice Consolidated Guidance
http://www.fda.gov/cder/guidance/959fnl.pdf

FDA Information Sheets for IRBs and Clinical Investigators
http://www.fda.gov/oc/ohrt/irbs/default.htm

Guidance on IDE Policies and Procedures
http://www.fda.gov/cdrh/ode/idepolcy.pdf

ICH E3 Ethnic Factors in the Acceptability of Foreign Clinical Data
http://www.fda.gov/cder/guidance/iche3.pdf

Sponsor's Responsibilities for Significant Risk Device Investigations
http://www.fda.gov/cdrh/manual/sponsor.html

APPLICABLE GUIDANCE

Guidance for Industry: Guideline for the Monitoring of Clinical Investigations
http://www.fda.gov/ora/compliance_ref/bimo/clinguid.html

Guidance for Industry: Financial Disclosure by Clinical Investigators
http://www.fda.gov/oc/guidance/financialdis.html

Guidance for Industry: Computerized Systems Used in Clinical Studies
http://www.fda.gov/ora/compliance_ref/bimo/ffinalcct.htm

Guidance for Industry: Acceptance of Foreign Clinical Trials
http://www.fda.gov/cder/guidance/fstud.htm

Guidance for Industry: Information Program on Clinical Trials for Serious or Life-threatening Diseases
http://www.fda.gov/cder/guidance/4856FNL.PDF

KEY DIFFERENCES BETWEEN DRUG & DEVICE REQUIREMENTS

Significant/Nonsignificant Risk Device Distinction for Studies Under an IDE

- **Significant risk devices** include implants, devices used for supporting or sustaining human life or of substantial importance in the diagnosis or treatment of disease, and devices that otherwise present a serious risk to the health, safety or welfare of a subject

- Clinical trials of **significant risk devices** require prior submission of an IDE application for FDA approval and compliance with labeling, distribution, informed consent, monitoring and reporting requirements.

KEY DIFFERENCES BETWEEN DRUG & DEVICE REQUIREMENTS

Significant/Nonsignificant Risk Device Distinction for Studies Under an IDE

- **Nonsignificant risk devices** do not pose significant risk to human subjects

- "**Abbreviated IDE requirements**," including labeling, informed consent, monitoring and reporting requirements are applicable to **nonsignificant risk devices**.

KEY DIFFERENCES BETWEEN DRUG & DEVICE REQUIREMENTS

Adverse Event Reporting Requirements

Unanticipated Adverse Device Effect - Any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem or death was not previously identified in nature, severity or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

KEY DIFFERENCES BETWEEN DRUG & DEVICE REQUIREMENTS

Adverse Event Reporting Requirements

Serious Adverse Drug Experience – Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly or birth defect.

Unexpected Adverse Drug Experience – Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure or with risk information contained within the general investigational plan…an adverse event is unexpected if it has not been previously observed, though it might have been expected based on pharmacological evidence.

KEY DIFFERENCES BETWEEN DRUG & DEVICE REQUIREMENTS

Adverse Event Reporting Requirements - IDEs

- **Investigators must report Unexpected Adverse Device Events to the sponsor & the IRB within 10 working days of learning of the event.**
- **Sponsors must report Unexpected Adverse Device Events to FDA within 10 working days of receipt of notice from the investigator.**
- **Sponsors must conduct an immediate investigation into any Unexpected Adverse Device Event and if they determine that the event suggests an unreasonable risk to subjects, the sponsor must terminate the study within 5 working days of the determination and no more than 15 working days after receipt of notice of the event.**

KEY DIFFERENCES BETWEEN DRUG & DEVICE REQUIREMENTS

Adverse Event Reporting Requirements - INDs

- A written IND safety report is required for any adverse experience associated with the use of the drug that is both serious & unexpected.
- IND safety reports must be submitted to FDA within 15 days of a sponsor's receipt of notice of the event.
- If an unexpected adverse drug effect is fatal or life-threatening and is associated with the use of the drug, there is a further requirement for a telephone or fax report to FDA within 7 calendar days.

KEY DIFFERENCES BETWEEN DRUG & DEVICE REQUIREMENTS

Investigator Agreements

- **Under an IND, sponsor must submit FDA Form 1572 (Statement of the Investigator) for each investigator with an attached CV and a separate financial disclosure form.**

- **Under an IDE, each sponsor must devise an investigator agreement that covers the requirements of the statute, including:**

KEY DIFFERENCES BETWEEN DRUG & DEVICE REQUIREMENTS

Investigator Agreement Requirements

21 CFR 812.43

- The investigator's CV;
- A detailed statement of investigator's relevant experience;
- If investigator was involved in other research that was terminated, an explanation of the circumstances leading to the termination;
- A statement of investigator's intent to conduct the research according to the agreement, the investigational plan, applicable regulations and conditions imposed by the IRB, and to supervise all use of the device involving human subjects and to ensure informed consent requirements are met; and
- Financial disclosure in compliance with 21 CFR 54 and a commitment to promptly update this information.

KEY DIFFERENCES BETWEEN DRUG & DEVICE REQUIREMENTS

- Labeling requirements (21 CFR 812.5)
- Requirement for written monitoring procedures (21 CFR 812.25(e))
- Specific provisions for transferring obligations to CRO under IND regulations are not included in 21 CFR 812

FDA ENFORCEMENT ACTIONS

- FDA Form 483 – Inspection Observations
- Warning Letter
- Determination that violations noted upon inspection render study inadequate
- Investigator disqualification proceedings
- Sponsor inspection to determine need to terminate IND

FDA ENFORCEMENT ACTIONS

- Sponsor recall of investigational product
- Seizure
- Injunction
- Prosecution for adulteration/misbranding

FDA GCP COMPLIANCE PRIORITIES: INVESTIGATOR WARNING LETTERS

- **Failure to conduct the investigation according to the signed agreement with the sponsor, the investigational plan, & conditions of IRB approval**
- **Inadequate reporting of adverse device effects**
- **Failure to establish all elements of & adequately document informed consent**

FDA GCP COMPLIANCE PRIORITIES: INVESTIGATOR WARNING LETTERS

- **Failure to maintain accurate, complete & current records relating to the investigator's participation in the investigation**
- **Implanting investigational devices without an FDA-approved IDE**
- **Failure to prepare & submit complete, accurate & timely reports**

FDA GCP COMPLIANCE PRIORITIES: IRB WARNING LETTERS

- **Failure to prepare, maintain & follow adequate written procedures**
- **Failure to operate in compliance with IRB membership requirements**
- **Failure to provide adequate continuing review**
- **Failure to assure adequate information is presented to patients for informed consent**
- **Failure to prepare & maintain adequate documentation of IRB activities**

FDA GCP COMPLIANCE PRIORITIES: SPONSOR WARNING LETTERS

- **Failure to secure investigator compliance with the investigational plan, applicable regulations & conditions of IRB approval**
- **Failure to comply with reporting obligations**
- **Failure to ensure adequate monitoring of clinical investigations**
- **Failure to ensure adequate procedures for informed consent**
- **Failure to select qualified investigators**

RESPONDING TO AGENCY INQUIRIES

Before the Inspection

- Accommodate inspector's scheduling requests whenever possible
- Notify the sponsor/CRO and IRB of FDA's request to schedule an inspection
- Gather study records, including source materials, and review for completeness
- Ensure investigator and other study personnel are available to meet with inspectors and have reviewed the protocol and other relevant study materials

RESPONDING TO AGENCY INQUIRIES

During the Inspection

- **Have research coordinator or other personnel familiar with the study readily available to answer questions or retrieve additional documents as needed.**
- **Make all study records available for review and copying.**
- **Be aware that observation of significant regulatory violations affecting subject safety or data integrity may result in expansion of the investigation to other studies.**

RESPONDING TO AGENCY INQUIRIES

After the Inspection

- **Send written response to inspection observations, including steps taken to correct violations noted and a corrective action plan to prevent recurrence.**
- **Implement the corrective action plan and otherwise update written procedures and train research staff as necessary to prevent future violations.**

GCP COMPLIANCE & LITIGATION

- **How GCP noncompliance may arise in litigation**
- **How to minimize exposure to GCP-related litigation risks**