R&D Compliance:
Prepare Now for Future Enforcement

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Agenda

- Growing Risks in R&D
- Third Parties and R&D
- Hypothetical Case Study

Growing Risks in R&D

- Regulator focus has shifted/shifting more to R&D; remember risk exposure in research prior to clinical trials
- Investigator Initiated Studies
  - Does research request and approval relate to an “appropriate” therapeutic area?
  - Does approval follow a standardized, well-documented process?
  - Are payments at fair market value? Any non-monetary items of value provided?
  - Are payments made prior to verifying attained milestones?
  - Do the investigators subcontract? Do the work through a government-owned institution?
  - Who is handling patient recruitment and informed consent?
- Post-approval studies / Research & Consulting Services / Scientific Publications
  - Documented, legitimate business purpose and need
  - Fair Market Value in connection with payments and other items that could be deemed of value
  - Author connected with data and analysis? Author meets requirements?

Growing Risks in R&D (continued)

- Limited pool of talent globally that understand the science, the business, the regulations, and the focus to conduct R&D in a risk-adjusted effective fashion
- Medical science liaisons (MSLs) and their activities are a growing focus
  - Who is making what request for information?
  - How are the requests tracked and documented?
  - How are off-label risks managed?
- Social media, crowd sourcing, telemonitoring: relationship to whistleblowing?
- Data security & privacy regulations; analysis “in the cloud”
- 3rd & 4th Party Risk; relationships among IRBs, investigators, sponsors and vendors
- Continued lack of integrated global IT infrastructure; continued M&A activity
- Comparative Effectiveness
  - Patient recruitment and potential gaps in site selection; increase in CRO subcontracting and foreign trials
  - Unexpected learnings and transparency
  - Managing data and new mining paradigms; predictive analytics

Third Parties and R&D

- Third-parties:
  - Joint collaboration partners (pre-clinical)
  - CROs, sub-CROs
  - KOLs and Investigators
  - Event Planners, travel agencies, etc.
- Emerging markets continue to represent the fundamental challenge to growth from a corruption perspective.
  - Roughly 60% of FDA regulated clinical trials are conducted in foreign markets.
  - Since 2002 the number of active Food and Drug Administration (FDA) regulated investigators based outside the United States has grown by 15% annually.

Hypothetical Case Study

- Acme Pharmaceuticals Inc. (“Acme”) is developing a diabetes drug and has completed Phase I and Phase II trials.
- Acme has developed the protocol for its Phase III global clinical trial and has received protocol approval from the FDA.
- After receiving protocol approval, Acme has hired a contract research organization, CRO, Inc. (“CRO”) to own and run the Phase III global clinical trial.
- After some negotiation and modifications, Acme and CRO agree on the protocol, including patient recruitment rates in each country.
- The primary end points are:
  - XXXX
  - XXXX
  - XXXX
- The global clinical trial is to start and be completed in 2.5 years at a total cost (revenue, grants, and pass-through costs) to CRO of $75 million.
- Any changes in scope and CRO fees will be agreed to in writing.

Hypothetical Case Study (continued)

- The following are details for the Phase III global clinical trial:
  - Recruit 1,000 patients, of which 900 patients will be included in the double-blind randomized trial.
  - Patients will be recruited from 20 countries, with 50% coming from Asia, 40% coming from Europe, and 10% from the United States.
  - Patient recruitment goals and rates:
    - China, 150 patients at 4.6 patients per month
    - India, 150 patients at 5.3 patients per month
    - Korea, 100 patients at 6.1 patients per month
    - Japan, 50 patients at 7.4 patients per month
    - Philippines, 50 patients at 3.2 patients per month
    - Poland, 150 patients at 7.2 patients per month
    - Czechoslovakia, 100 patients at 5.5 patients per month
    - France, 75 patients at 8.1 patients per month
    - Portugal, 75 patients at 9.2 patients per month
    - United States, 100 patients at 12.6 patients per month

Hypothetical Case Study (continued)

- Lets break up ourselves into 2 groups, where one side of the group is Acme and the other side is CRO.
- If you are Acme, what are your risks in connection with the Phase III clinical trial?
- If you are CRO, what are your risks in connection with the Phase III clinical trial?

Hypothetical Case Study (continued)

- Scenarios for discussion:
  - 5 months into the trial, CRO informs Acme that it cannot meet the patient recruitment rates in China, Czechoslovakia, and Poland. The patient recruitment goal was 50% too high in each of these countries.
  - 8 months into the trial, allegations arise of forged informed consent forms in China.
  - 12 months into the trial, allegations arise of fictitious patients in Poland.
  - 18 months into the trial, allegations arise of critical missing data in the trial master file in Korea.
  - 22 months into the trial, Acme realizes that data collected 20 of the patients from Czechoslovakia is not usable.
  - 23 months into the trial, the clinical trial cost has increased from the projected $75 million to $125 million.
  - The Phase III trial was completed at a total CRO cost of $145 million, the FDA approved the product, and Acme is now conducting post marketing / pharmacoeconomic studies.
- Under each of the above scenarios, what do you need to manage if you are Acme?,
- Under each of the above scenarios, what do you need to manage if you are CRO?

Q&A