Regulatory Challenges to Successful Global Clinical Studies

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What We Will Cover

- Keys to Regulatory Success in Global Clinical Trials
- Case Studies on Key Issues – Selected Country Examples
- Focus on Enforcement – What Can Go Wrong
- Final Thoughts -- Lessons Learned
Keys to Regulatory Success in Global Clinical Trials
Why Go Global?

- Higher number of patients, especially naive patients
- Large patient populations with diseases of both developed and developing countries (e.g., HIV/AIDS)
- Multi-ethnic/multiracial populations
- Wide spectrum of diseases
  - Especially important for rare diseases
- Potential new markets (e.g., China)
- Competent/motivated PIs
General Considerations

- **Standards of care** -- differ around the world. In doing a clinical trial OUS, seek to ensure trials are (can be) done the same in each jurisdiction -- but, “the universal protocol” is extremely elusive
  - Can add to cost

- **Ethical standards** -- particularly as to informed consent are different -- know this issue

- **Hire the right CRO** -- if you lack a “presence” in the country, right CRO is crucial to getting good data

- **Follow-up** -- in developing countries, can be difficult. Subjects need access to the treatment facility -- you may need to ensure they get there
Essential Sponsor Procedures

- How they will deal with any reports of PI or CRO non-compliance.
- U.S. sponsors – be very careful about payments to doctors and others – in some cases, they are government employees and the payment could trigger Foreign Corrupt Practices Act concerns
  - e.g., Eastern Europe – may ask for payments to referring doctors
- Be aware of trend in some countries for continued duty to provide drug after study end
- Ensure that local requirements are heeded
- Adverse events – OUS or ex-EU adverse events still have to be reported back to FDA or EU competent authorities
Clinical Trial Agreement -- Keys

- **Sponsors** – make sure contracts with clinical investigators and CROs have adequate provision covering GCP compliance.
  - Require an immediate escalation of compliance concerns to the sponsor.
  - CRO agreements should have a detailed transfer of obligations form.
  - Make sure CRO is not also a SMO – site management organization – not unusual overseas and can create conflicts
  - Be careful with excessive payments – even if legal and not subject to disclosure under 21 CFR 54, might “taint” data
  - Audit your sites per U.S. GCP standards
Key Issues by Selected Regions/Countries
Europe

- **Scientific Advice** --
  - Difficult to balance going to Europe before hearing back from FDA on EOP2 meeting and Phase 3 protocol agreement (especially if using a SPA).
    - Timing – Scientific Advice is on a more rigid schedule – predict in advance if possible
    - EMA – may be a little off-put if you are late, however

- **Insurance issues**-- allow extra time for coverage and review (especially in Germany)
  - *Example:* Phase 3 study required an extra 6-8 months to get coverage before would be considered by Ethics Committee. *Result* -- sponsor could not use Germany in first global study; only able to include in a parallel second study.
India

- **Phase 1 studies**
  - Ethics Committee and regulatory agency have suspicion that we (U.S.) are going to India to test because it is less likely to have problems if the drug "poisons" the patients. Do not want the Indian people to be guinea pigs.

  - **SOLUTION:** convinced them that safety data about the product was sufficient by taking extra steps to document in the cover letter both the safety measures included in the study protocol and outline the key points from the investigator brochure rather than simply providing the investigator brochure.

- **Fraud is rampant** *(former FDA General Counsel)*
China

- **CDE evaluation meeting:**
  - Monthly meetings, over 3-4 days, held in Chinese (translators may or may not be acceptable). Need to bring subject matter expert (CMC, Tox, etc.).
  - CDE issues final evaluation ~ 2 months after the meeting.
  - Much of the information that we are used to submitting for a NDA is required as part of the CTA in China.
  - A strong, local regulatory person may get the questions before the meeting and feed them back to the sponsor.
  - Local QC testing of test article for biologicals required. Average > 5 months to complete testing.
    - Companies are concerned about method transfer for IP reasons.
China …

- **Challenges:**
  - CTA approval time ~ 15 months.
  - Lack of flexibility
  - Requires information about previous studies
  - Two different regulatory bodies:
    - Center for Drug Evaluation (CDE) reviews the trial scientifically while the SFDA approves the trial.
    - Sometimes, CDE reviews and OKs and then SFDA rejects the trial.
  - Fraud is rampant (former FDA GC)
A Deeper Look -- Indonesia

Advantages/Logistics:
- Large Country
- Government and investigators receptive to industry knowledge
- GCP implemented into national laws and guidelines governing clinical trials
- National Agency for Drug and Food Control is competent authority for clinical trial authorization

Disadvantages:
- Very few trials being conducted, but numbers are growing.
- ECs to be established at institutional, regional/provincial, and national levels according to need
- Lack of population-based registries
  - Example: Hospital based-cancer registries in 13 cities
Challenge: Designing a clinical trial to account for the specifics of the region

- Cultural issues
- Inclusion/Exclusion Criteria
- Trial Length and approval timings
- Infrastructure issues
- Investigator and Staff Training

Our (The Weinberg Group) approach:

- Trial designed to account:
  - Differences in medical practice (disease diagnosis, investigator-patient relationship)
  - Translation of study/regulatory documents
  - Validation of measurement scales (patient questionnaire)
- Understood need to apply “partnership approach” to build supportive relationships
Indonesia

- **Challenge: Identifying and vetting the appropriate CRO partner**
  - No local CROs
  - Only a handful of Regional CROs working in Indonesia

- **Our approach:**
  - Decided on one regional CRO
  - Worked on setting clear expectations on how the study should be conducted
    - Task distribution (assigning of responsibility)
    - Which SOPs were going to be used
  - Increased communication
  - Thorough training of CRO staff and co-monitoring visits
Indonesia

- **Challenge: Investigators and Staff experience**
  - Lack of clinical trial experience
  - Gaps between concept and reality in the field

- **Our approach:**
  - Incorporation of GCP, ethical practices, clinical management training into Investigator Meetings, CRA/interviewer training, monitor training
    - Special emphasis on informed consent process
    - The training methods paralleled the expected performance of the study team
  - Site based CRAs conducting source data verifications during patient recruitment process
  - Increased site monitoring
Indonesia

- **Challenge**: Local infrastructure and sites constraints
  - Lack computerized central patient database systems
  - Lack of secure storage space
  - Difficult internet and phone access
  - Understaffing

- **Our approach**:
  - Site auditing prior to contract signature
  - Financial investments made into resources and personnel
  - Regular monitoring
Indonesia

- **Challenge: Cultural Complexities**
  - Hierarchical social structure impacts recruitment
    - Investigator
    - Site
    - Patient

- **Our approach:**
  - Build trust and cultivate relationships
    - Principal Investigator
    - Key Opinion leaders
  - Involve hospital administration in site selection and start up activities
  - Train and inform on “foreign” practices and international expectations
Focus on Clinical Trials Enforcement – What Can Go Wrong Overseas?
Clinical Sites Investigators –
Inspections by The Numbers
(closed since 1977; as of 2009)

- U.S. – 7,920
- Canada – 159
- UK – 98
- Germany – 67
- France – 53
- Russia – 50
- Italy – 38
- Poland – 38
- Sweden – 38
- South Africa – 30
- Belgium – 28
- Netherlands – 27
- Argentina – 25
- Brazil – 20
- Mexico – 18
- Spain – 18
- Australia – 9
- India – 8
- China – 7
- Japan – 3

How FDA Is Enforcing GCP Compliance Overseas

- Very limited foreign examples – only a few warning letters aimed at foreign clinical investigators.
- But, if done under a U.S. IND, must meet all clinical study requirements
  - IND rules – Part 312
  - Informed Consent – Part 50
  - Financial Disclosure – Part 54
  - EC/IRB – Part 56
  - AE reporting
- Thus, U.S. enforcement activity provides clear guidance
Moscow City Hospital WL -- 2006

- You failed to maintain adequate and accurate case histories that record all observations and data pertinent to the investigation [21 CFR 312.62(b)]
  - For Subject #_, the baseline ECG recording obtained on June 21, 2004, and the Visit 4 ECG recording obtained on August 3, 2004, were identical except for the information hand-written on each ECG, including subject number and date of tracing.
  - For Subject #_, the baseline ECG recording obtained on June 21, 2004, and the Visit 4 ECG recording obtained on Aug 2, 2004, were identical except for the information hand-written on each ECG, including subject number and date of tracing.
  - Source records for Subjects #_ and #_, document that the same individual performed the baseline physical examinations on the same day (June 21, 2004) and at the same time (0900).
Moscow City Hospital WL – 2006 …

- You failed to maintain adequate records of the disposition of the drug including dates, quantity and use by subjects [21 CPR 312.62(a)] .
  - Dispensing records show 5 mg. given out to Subject X, but 2.5 mg. tabs returned by same Subject

- Length of inspection – 3 days
You failed to protect the rights, safety, and welfare of subjects under your care and failed to ensure that the investigation was conducted according to the investigational plan. [21 CFR 5 312.60]

- overdoses of the study drug interleukin-2 (IL-2) that were 22 to 25 times higher than the dose specified in the protocol
  - One death
- Cause – incorrect dosing form used that did not jibe with the protocol
Children’s Hospital of E. Ontario WL …

- You failed to ensure that the investigation was conducted according to the investigational plan. [21 CFR 312.60].
  - Subject hospitalized for three days, but not so documented.
  - Records did not say at all how long she was in hospital
  - CRFs submitted 4 months late; required under protocol to be filed in one week
  - No record of storage in refrigerated conditions as required by protocol

- Length of inspection – 5 days per WL

- Average length of U.S. inspections leading to WL’s – sampling of 10 from last two years, showed average number of days (measured start to finish) was 28 days
Adventrx

- Bioequivalence study in Argentina – pivotal to application
- FDA audited site -- retained samples of drug were thrown out
- FDA -- not clear which patients got Study drug vs. brand
- FDA – Complete Response Letter -- we can’t verify what drugs the patients got, thus the study results are not acceptable
- Company – the test drug was very different looking than the comparator (but do the CRFs, etc., reflect that)?
Final Thoughts
Lessons Learned

- Advance preparation and strategy development
- Thorough knowledge of local processes and operations
- Design trial with an implementable protocol
- Upfront dialogue and partnership-oriented approaches
- Identify a CRO that is suitable for you
- Know your limitations and how much you are willing to concede to your vendors
- Audit CRO, site and monitors
- GCP training before start of the study
- Close monitoring during the study
- What is your plan B? Have one!
Some Resources

- **International Compilation of Human Research Protections (OHRP) [new version coming soon]**
  - [http://www.hhs.gov/ohrp/international/intlcompilation/hspcompilation-v20101130.pdf](http://www.hhs.gov/ohrp/international/intlcompilation/hspcompilation-v20101130.pdf)

- **European Forum for Good Clinical Practice (EFGCP) – state by state info available**

- **Legislations, Regulations and Guidelines – from GCPHelpDesk – country by country links**

- **Reviewing Clinical Trials: A Guide for the Ethics Committee; Editors: Johan PE Karlberg and Marjorie A Speers**
Questions?

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About Your Speaker

Michael A. Swit, Esq., is a Vice President at The Weinberg Group, where he develops and ensures the execution of a broad array of regulatory and other services to clients, both directly and through outside counsel.

Mr. Swit has been addressing critical FDA legal and regulatory issues since 1984. His vast and multifaceted experience includes serving for three and a half years, from 1990 to late 1993, as general counsel of Par Pharmaceutical, a prominent, publicly-traded, generic drug company. Mr. Swit then served for over four years as CEO of Washington Business Information, Inc. (now known as FDANews), a premier publisher of FDA regulatory newsletters and other specialty information products. His private FDA regulatory law practice has included service as Special Counsel in the FDA Law Practice Groups in the San Diego office of Heller Ehrman White & McAuliffe and at McKenna & Cuneo, both in the firm's Washington office and later in San Diego. He first practiced FDA regulatory law with the D.C. office of Burditt & Radzius.

Mr. Swit has taught and written on a wide variety of subjects relating to FDA law, regulation and related commercial activities. A former member of the Food & Drug Law Journal Editorial Board, Mr. Swit also has been a prominent speaker at numerous conferences sponsored by such organizations as RAPS, FDLI, and DIA. He earned his A.B., magna cum laude, with high honors in history, from Bowdoin College, and his law degree at Emory University School of Law. Mr. Swit is admitted to the California bar and is an inactive member of the D.C. and Virginia bars.