Regulatory Implications of Global Clinical Trials

Jurij Petrin, MD
PRS Clinical, Ltd
Where Can One Perform Clinical Trials

- USA
- EU
- Japan
- Canada
- Australia/NZ
- Emerging Markets
Europe

- The Clinical Trials Directive (Directive 2001/20/EC)
  - The Directive is in force since May 1st 2004.
  - Some Member States implemented the provisions later (and some are not completely done yet).
  - The Directive for the first time brings a specific rule on clinical trials at the EU level.
  - All clinical trials are concerned, except "non-interventional" trials.
Aims of the Directive 2001/20/EC

- Protection of subjects
- Ethics Committee procedures and timings (one per MS)
- Regulatory Authorities procedures and timings: notification/approval before initiating a clinical trial
- Conduct of trials, suspension of a trial.
- GCP compliance: trial process, manufacture of the product used in clinical trial, GMP, import, QC release, labeling
- Inspections
- Adverse events reporting
- Exchange of information
Main Points of the Directive

• Single Sponsor for all trials in the EU – has to be established in the EU (registered legal entity), or appoint a third party to serve as the legal representative

• Clinical supplies – GMP quality, and QC released in the EU (certification of every batch is required)
Main Points of the Directive

• **Principal Investigators** have to provide their qualifications and any GCP training or experience obtained from work with clinical trials to the local ethics committees for opinion on their suitability to conduct clinical trials.

• **Clinical investigative sites** have to submit to the local ethics committee an evaluation of the quality of the facilities (availability of adequate resources, personnel, and laboratory facilities) in which they plan to conduct a clinical trial.
Main Points of the Directive

• More information needs to be given to clinical trial subjects
  – Subjects have the right to know:
    • The name and address of the sponsor
    • The institutional affiliation of the investigator
    • The financial ties between the investigator and the sponsor
    • The source of finance for the study
    • Contact details of all personnel involved in the trial.
Main Points of the Directive

• Advertising for trial subjects:
  – Clinical research teams need to have written procedures for the management of persons responding to advertisements.
Main Points of the Directive

• Protection of children and adults incapable of giving legal informed consent:
  – **Old**: investigators were not obligated to describe the procedure for obtaining informed consent from a patient or his legal representative
  – **New**: information must be given to the subject’s parent(s) or legal representative, and the subject must be given information according to his/her capacity to understand.
Main Points of the Directive

- Protection of children and adults incapable of giving legal informed consent (cont’d):
  - No incentives are allowed in these populations and a direct benefit from the clinical trial for the group of patients is a must: in these populations, conducting a clinical trial is acceptable if essential only.
  - Provisions should be taken to minimizing pain, fear, risk, distress and an Ethics Committee with pediatric expertise or advice should be involved.
Main Points of the Directive

- Ethics Committees:
  - Single national ethics committee opinion in each Member State for proposed multicenter trials.
  - Protocol review: up to 60 days, with an extension of 30 days if there is a request for further information.
  - Amendments: 35 days for the EC; the Competent Authority may extend this if it wishes further information.
  - Review ongoing at the same time as the MOH review
Main Points of the Directive

• Non-commercial trials:
  – Investigators who wish to perform clinical trials without commercial backing must themselves become the study sponsors.
  – The administrative responsibilities will be exactly the same as those of the pharmaceutical industry for commercial trials.
  – In multicenter non-commercial trials, a “coordinating investigator” becomes the sponsor.
  – Monitoring of investigative sites in noncommercial trials is not specifically mentioned in the directive, but systems must be put in place by the principal/coordinating investigators for proper monitoring.
Main Points of the Directive

• Protocol amendments that meet the criteria for “substantial” amendments must be reported to the relevant competent authorities and ethics committees.

• The end of a trial must be notified to the competent authority via the Eudract database within 90 days of trial completion or 15 days of premature termination.
Safety Reporting

- Suspected unexpected serious adverse reactions (SUSAR) have to be reported to the CA via the EudraVigilance database
- SUSARs: A Suspected Unexpected Serious Adverse Reaction or SUSAR is defined as any suspected adverse reaction to an IMP that is both unexpected and serious
Steps in the Notification of a Clinical Trial

• The sponsor must register with the EUDRACT database (via the Internet).
• The sponsor then obtains a EUDRACT number.
• The competent authorities (notified by the sponsor) and the Ethics Committee (notified by the coordinator, sponsor or investigator) will be alerted about of the study—this can be done in parallel or sequentially.
• Regulatory authority inspectors are empowered to inspect all sites and resources involved in a clinical trial
• Sponsors should ensure they are always ready to be inspected
• Failure to comply with the Directive could lead to criminal prosecution of the violator.
  – Either an individual or an organisation or both.
  – In the UK, for example, a 2 year prison sentence can be imposed for infringement of the Directive!

Inspections
Definition of “Emerging Markets”

- Asia-Pacific
- Central & Eastern Europe
- Latin America
- Africa

- Only lately attracting global interest as potential contributors to global R&D, international regulatory issues, and even global business positioning
Emerging Needs in Clinical Research

- New patient pools
  - large number of available study subjects
  - treatment naive patients
  - certain disease types
  - high quality research
- Ethnical differences (bridging studies)
- Global dossier?

Answer: selected international (emerging) markets
Traditional Beliefs About the Emerging Markets

- Markets of the future
- Economic difficulties
- Business interest still mostly present in developed markets
- Good clinical research can only be done in the U.S. and Europe?
Traditional Beliefs About the Emerging Markets (con’t)

- Under-developed local research infrastructure
- Knowledge of western medicine not developed enough to enable top level clinical research
- Local regulations in most of the emerging markets an obstacle
Can and Should Good Clinical Research Be Done in Emerging Markets?

YES
Practical Difficulties in Conducting NCE Clinical Trials in the Emerging Markets

- Regulatory
  - IND vs. non-IND
  - export waivers
  - detailed and complicated CTA requirements in some markets
  - safety reporting
  - regulatory compliance (difficult source data verification)
Practical Difficulties in Conducting NCE Clinical Trials in the Emerging Markets (con’t)

- Regulatory (con’t)
  - CMC problems
  - need for a CFS from one or more countries
  - local regulations often do not give all necessary details about clinical research requirements
  - frequent changes of regulations
  - contacts with regulators often difficult or impossible
Practical Difficulties in Conducting NCE Clinical Trials in the Emerging Markets cont’d

• Clinical
  – time needed to start studies
  – written informed consent
  – multi-center multinational trials (timing, dose)
  – shipment and storage of study supplies
  – shipment of biological samples out of countries
  – monitoring difficulties (languages, travel, cost)
Practical Difficulties in Conducting Clinical Trials in the Emerging Markets (con’t)

• General
  – translations
  – timely start of studies
  – standards of local medical practice
    • comparators
    • adverse event reporting
    • cultural (patient-physician relationship)
    • informed consent
Practical Difficulties in Conducting Clinical Trials in the Emerging Markets
(con’t)

- General (con’t)
  - availability of experienced local staff
  - distance from sponsor’s main office
  - patent protection issues
  - political instability in some markets
  - ethical considerations
Availability of Experienced Local Staff and Needed Equipment

- Medical expertise not enough
- GCP knowledge
- Language skills
- Research Support
- Facilities
- Ethical committee composition and expertise?
Clinical Research Infrastructure

- Facilities
  - hospitals
  - labs
    - central vs. local
    - validated equipment/process/staff
    - reagent supplies
- Research support
  - no (or few) study nurses
  - support staff often not fluent in English
Clinical Research Infrastructure

• Source data
  – often do not exist or not available
  – local language
• Lack of experienced local CROs
Ethical Considerations

• Do potential study subjects in emerging markets really always volunteer?
  – Is any other treatment available if they don’t join the study?
  – What is the culture of physician-patient relationships in the particular country?
  – Have they received enough information before asked to sign the informed consent?
  – Do they understand what is going on?
• Pre-study inspection very important!
Study Conduct

• Recommended approach to a new site:
  – GCP training before the study start
  – Close monitoring during the study
  – Independent audit to validate both the investigator as well as the local monitor

• Signals to watch for:
  – Fast enrollment of large numbers of patients
  – No or very few adverse events
US Investigational New Drug (IND)

- Current US Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines.
- To ship investigational drug to clinical investigators across state lines, the sponsor must seek an exemption from that legal requirement.
- The IND is the means through which the sponsor technically obtains this exemption from the FDA.
Conducting Clinical Trials Outside the US

- If IND study, clinical supplies can be shipped under the IND regulations
- If non-IND study, Export Waiver may be required before shipping drug
Export Waivers

- Permission from the US FDA to export clinical drug supplies from the US to a foreign country

- US FDA Export Reform - 1996
  
  - Export Waivers no longer required to ship drug from the US to 25 “exempt” countries
Export Waivers

- Needed if:

  - study will not be conducted under US IND or if an IND does not exist
  - clinical drug supplies sourced from the US
  - drug is not an antibiotic
    - antibiotics (produced by fermentation process) can be exported without a waiver
  - recipient country is not one of the 25 exempt countries
The 25 Countries Exempt from Export Waiver Regulations:

- Australia
- Austria
- Denmark
- Finland
- Greece
- Iceland
- Italy
- Japan
- Netherlands
- New Zealand
- South Africa
- Spain
- U.K.

- Belgium
- Canada
- France
- Germany
- Ireland
- Israel
- Liechtenstein
- Luxembourg
- Norway
- Portugal
- Sweden
- Switzerland
Export Waivers

- Request may be submitted by
  - Sponsor
  - Authorized government official of the recipient country

- Sponsor request most common
Export Waivers

- Sponsor submits request to the FDA International Affairs Staff with:
  
  • protocol or protocol summary
  
  • statement that the drug will be used for investigational purposes only
  
  • adequate information that the drug may be legally used in the recipient country or that the recipient government has no objection to the importation of the drug for the proposed investigational use
Export Waivers

– Upon approval of export request from either sponsor or foreign government

• FDA notifies sponsor in writing

• copy of the approval letter sent to the foreign embassy and the foreign health authority

– Approval time approximately 8 weeks
Clinical Trials in China

- Required for introduction of a new drug
- Increasing interest from investigators
- Authorities are cautious
- Huge population
- Various unmet medical needs
Main Clinical Trial Regulations - China

- Drug Registration Regulation (2002)
- Drug Administration Law (2001)
- Work Rules for Clinical research of Drugs (2000)
- GCP for Pharmaceutical Products (1999)
- Regulation for Monitoring Adverse Drug Reactions (1999)
Recent Improvements in China

- Attempt for more transparency and internationalization:
  - references to ICH, GCP
  - timelines for the CTA review now outlined which adds to the transparency of the system
- Clinical Trial Application reviews – centralized (SFDA)
- Sponsor to select the right research institution from the list of qualified institutions
- “International Trials” included into Chinese regulations for the first time
Remaining Issues in China

• Clinical trials treated as a new drug submission – long reviews of detailed data
  – Minimum 195 days to review a CTA for a multinational study
  – 12 months to get a permission to do a study with an imported product
  – Data required are over and beyond data required elsewhere to do a study only (quantity, as well as details). Similar to an NDA reqs.

• Drug Specification Validation
  – Study drug samples tested (3 batches required!! – may not exist)
  – When Chinese standards are different, sponsors may be asked to revise the specification!! Even for a study-only drug!
Remaining Issues in China

- New PK requirement (details not clear – no guidance yet)
- Requirement for the latest formal package insert – assumes product will be already approved in the Country of Origin
Summary - China

- Complicated and demanding system with long reviews
- Difficult inclusion of Chinese sites into multinational trials
  - Delays
  - Extra requirements (sample testing, inserts..)
  - They require a Phase I trial in China first (before other phases can be started for a multinational trial)
Our Global Experience

- Several hundred sites
- Several thousand patients enrolled every year
- All therapeutic areas
- Both internal as well as external audits very positive
Summary

- Emerging markets have an important role in global drug development
- Need to align their local regulatory requirements with developed countries
- Need to increase local clinical research expertise
- Need to accept and enforce strong patent protection
SELECTED EMERGING MARKETS HAVE BECOME COMPETITIVE WITH MAJOR MARKETS
INCREASINGLY, SELECTED EMERGING MARKETS ARE A BETTER CHOICE TO CONDUCT CLINICAL RESEARCH THAN TRADITIONAL MARKETS