Role of Regulatory Authorities in GCP implementation

Gunnar Danielsson
Medical Products Agency
Role of Regulatory Authority

- Application for clinical trial licence
  - Pre-clinical data
  - Clinical data
  - Investigational product
  - Protocol – risk benefit
- Pharmacovigilance
  - Safety reporting
- Inspection
- Evaluation of results
Objectives of inspections

- Verification of patient safety and integrity
  - protection of patient who will or are participating in clinical trials

- Verification of data
  - protection of patients who will be treated with marketed medicinal products

- Adherence to laws and regulations
  - local and international

- Training and education
Compliance with GCP standard provides public assurance that:

- the rights, safety and well-being of trial subjects are protected
- the clinical trial data are credible
Trial subject

- Declaration of Helsinki
- Ethics Committee approval
- Confidentiality
- Informed consent
- Medical care and decisions by qualified physician
Data

- Can we rely on the credibility of the data
- Application to Regulatory Authorities for permission to start clinical trials
- Clinical Trial Report
- Application to Regulatory Authorities to obtain registration (market authorization)
Regulatory framework

- Declaration of Helsinki
- GCP (ICH, WHO or other)
- Local laws and regulations
  - Clinical trial
  - Ethics
  - Medical care and records
  - Secrecy and confidentiality
Audits in guidelines/regulations

- **FDA** - No requirement

- **ICH** - If or when sponsors perform audits as part of implementing quality assurance
  - ICH GCP 5.19

- **Local Requirement** - ?
Audit versus Inspection

- Sponsor/CRO
  - Focus on compliance and process review
  - Against laws, regulations and sponsor SOPs
  - Vested interest in ensuring study success

- Regulatory agency
  - Patient safety and data credibility
  - Sponsor SOPs usually irrelevant
  - Study “success” irrelevant
Inspecting clinical trials

Inspecting can be:

- Diagnostic to determine room for improvement
- Evaluation to confirm or refute compliance
- Surgical to delete improper data to ensure credibility
Risk Assessment

What is the best way to protect trial subjects and verify the quality of trial data? Given the limited inspection resources, some potential factors:

- Target those sponsors/investigators that perform the most trials
- Target trials that provide data for marketing authorisation applications
- Target high risk trials (e.g. number of patients, type of patient population, safety issues, issues relating to the sponsor)
- Target trials for which issues have been identified (Ethics Committee concerns, informants)
Intended outcome

- Improved quality
- By doing few achieve a lot
- Awareness by being seen
- Accepted as a source of information
- Appreciated by the pharmaceutical industry and academia
- Recognised by international society
Points to consider

- How many trials are conducted
- What types of trials are conducted
  - commercial/non-commercial
  - Early phase/late phase
  - Healthy volunteers/patients
  - Inclusion/non-inclusion of data in regulatory submission
- What oversight of these trials already occurs and by which government organisation
Points to consider

- What percentage of sponsors have offices in the country
- What resources would be required to address the agreed inspection strategy
- How will inspection be financed:
  - by sponsor, e.g. inspection fee, CT application fee
  - by marketing application authorisation holders
  - government funding
Points to consider

- What are the most efficient ways to protect trial subjects and verify the quality of the trial data with the available resource (risk assessment)?
- How frequent might the organisation be asked to participate in international inspections (at home and abroad)?
- What actions can be taken for GCP non-compliance?
- What are the expectations of stakeholders (patients, industry, government, academia)?
Inspection strategy

- Focus on achieving quality into the process in ongoing studies rather than finding faults in completed studies

- Inspection part of training and education
Inspection strategy

- Focus on completed studies?
  - data driven
- Focus on ongoing studies?
  - process driven
- Inspection part of training and education
Inspection strategy

- Clinical sites
- At least once a year to all major pharmaceutical industries
- Small companies and academia ad hoc
- Networking with the academic organisations
- Education and training
Lessons learned

- Improved quality
- By doing few achieve a lot
  - cascade effect
- Awareness by being seen
  - small country – few players
Lessons learned

- Accepted as a source of information
  - readily available
  - frequent contacts
- Appreciated by the pharmaceutical industry and academia
  - well-known and respected
  - communication and transparency
Objectives

- To develop a system for GCP inspection in respective country that ensures that inspections are:
  - conducted according to international standard
  - recognised as acceptable by the international society
  - conducted by qualified inspectors
System and procedures

Harmonisation and expertise through practical action and communication

- Implement standard policy and procedures
- Share experience; harmonize grading of findings; inspection reports
- Shared inspections
- Exchange of information
- Training

To be considered on a national and international level
System and procedures

Implementation of Standard Operating Procedures

- Preparation of inspections
- Reporting of inspections, including grading of findings
- Conduct of inspection
- Inspection records
- Sponsor/CRO, investigator/laboratory
- Pharmacovigilance
- Computer systems
- Phase I sites/Bioequivalence inspection
- Ethics Committees
- Investigational Medicinal Products

- INS-GCP-1 Procedure for coordinating GCP inspections requested by the EMEA Corr.
- INS-GCP-2 Procedure for preparing GCP inspections requested by the EMEA
- INS-GCP-3 Procedure for conducting GCP inspections requested by the EMEA
- INS-GCP-3 Annex I to Procedure for conducting GCP inspections requested by the EMEA- Investigator Site
- INS-GCP-3 Annex II to Procedure for conducting GCP inspection requested by the EMEA- Clinical Laboratories
- INS-GCP-3 Annex III to Procedure for conducting GCP inspection requested by the EMEA- Computer Systems Rev. 1
- INS-GCP-3 Annex IV to Procedure for conducting GCP inspections requested by the EMEA- Sponsor and CRO
- INS-GCP-3 Annex V to Procedure for conducting GCP inspections requested by the EMEA- Phase I Units
- INS-GCP-3 Annex VI to Procedure for conducting GCP inspections - File structure and archiving
- INS-GCP-4 Procedure for reporting of GCP inspections requested by the EMEA
- Principal Documents taken into account for the preparation of procedures for the GCP inspections requested by the EMEA
Inspection procedures

- Inspection made to suit inspection site/inspectees

- Different circumstances may require a different approach but all based on:
  - same set of legal requirements
  - same set of inspection activities
  - same set of inspection SOPs
  - inspection team: made to measure
  - fitted to regulatory environment
Types of inspections

- **for-cause inspection**
  - indication that something is not optimal in the study
  - the suggestions can come from
    - Regulatory Authority
    - Sponsor company
    - Head of Clinic or other staff at the clinic

- **routine inspection**
  - randomly picked clinical trials for inspection
Objects of inspections

➢ Individual studies
  • investigator
  • sponsor
  • CRO

➢ System inspections
  • sponsor
  • clinical trial center
  • CRO
Objects for inspections

- Sponsor
- CRO (various sites)
- Investigator
- Pharmacy
- Laboratory (special departments)
- Manufacturer, vendor
- Archives
- Ethics Committee
Objects of inspections

- Pharmacovigilance inspections
- Bioequivalence/bioavailability
Objects of inspections

- **All types of studies**
  - phase I-IV
  - academic or company sponsored

- **When**
  - ongoing studies
  - after completion
Inspection Goal

- A positive educational experience for Investigator, staff and sponsor personnel
Certification of inspectors

- Training in laws and regulations
  - local
  - International
- Training in other disciplines
  - GMP, GLP, GPP, GDP
- Internal instructions (SOPs), reporting, behavioural etc.
Certification of inspectors

- Appoint appropriately qualified inspectors
  - background education
    - Pharmacists, M.Sc., MD etc.
  - practical experience
    - pharmaceutical industry, clinical trials
  - personality
    - policeman or negotiator
  - language
    - international communication
Inspector characteristics

- Honesty
- Open-minded
- Interpersonal skills
- Professional skills
- Disciplined approach
- Proactive
- Leadership
Non-Inspector characteristics

- Aggressive
- Intimidating
- Stubborn
- Sneaky
- Uncooperative
- Nit picking
Certification of inspectors

- Standardized certification programme
  - depending on background but at least 6-12 months

- Participation in inspections in the country
  - observer
  - participant
  - leader
Certification of inspectors

- Develop an international inspection programme in collaboration with:
  - EMEA
  - FDA
  - WHO
  - Other relevant authorities