APEC Preliminary Workshop: Review of Drug Development in Clinical Trials

Session 1.4 - Clinical Trial Environment
United States (FDA) and European Union (EMEA)

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Disclaimer

The information within this presentation is based on the presenter’s expertise and experience, and represents the views of the presenter for the purposes of a training workshop.

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FDA's Mission Statement

The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation’s food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.
FDA Inspections

*Data Slide Presentation by Matt T. Thomas, FDA, DSI
FDA Inspection Results

Clinical Investigator Deficiencies
CDER Inspections - FY 2006

*Data Slide Presentation by Matt T. Thomas, FDA, DSI
European Medicines Agency - Structure
European Medicines Agency

Mission statement

The mission of the European Medicines Agency is to foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public and animal health.

Legal role

- The European Medicines Agency is the European Union body responsible for coordinating the existing scientific resources put at its disposal by Member States for the evaluation, supervision and pharmacovigilance of medicinal products.

- The Agency provides the Member States and the institutions of the EU the best-possible scientific advice on any question relating to the evaluation of the quality, safety and efficacy of medicinal products for human or veterinary use referred to it in accordance with the provisions of EU legislation relating to medicinal products.
HA Environment for Clinical Trials:
Who are the players?

- Procedures/processes
- Legal basis
- Audits
- Inspections
- Ethics Committees
- Inspectorates
- Competent Authorities
- Trials/Investigators/Sponsors/CRO's
- Full Compliance Area
What is Risk Perspective for HA?*

For whom?

**Trial subjects**
- May place subjects in that trial at possible safety risk
- May place future trial subjects at risk

**Patients**
- May place future patients or consumers at risk
- May delay availability of medicines

**Products**
- May place product(s) at quality/safety/efficacy risk
- Undermines business, availability of medicines

**Health Authority**
- Jeopardizes the reliability of submitted and/or published data
- Undermines the HA ability to protect and promote the public health
- Undermines trust of public in company/pharma industry
HA Requirements*:
Legalities

Legal basis is essential:
- Rights (protection and access)
- Requirements, standards (minimum, definite)
- Sanctions (professional, bureaucratic, punitive)
- Qualifications, processes and procedures

Types of legislation:
- National legislation
- EU legislation: Rules, regulations, directives, guidances, guidelines
- Third Country
- Professional standards

International complexities:
- Rights, requirements, sanctions, legislation differences, teams
HA Requirements*:

Responsibilities

Sponsor/applicant:
- Development process, Conduct clinical trials
- Composition and content of dossier
- Completeness of application dossier

Investigator
- Safety of subjects, quality of data,

Authorities
- Legal basis
- Assessment of dossier: verification of quality, safety and completeness of dossier, inspections of clinical trials and monitoring of Pharmacovigilance
- Licenses (manufacturing, marketing)
Inspection Practices *
General Approach in EU

**EMEA coordinates processes and procedures for CAP**

For decentralized/local inspections in MS: many similarities

Joint inspections versus single MS

*What is inspected:*

“ All that is deemed necessary by HA/Inspectors ”

= Re(Leg)ality

Inspectorates choices (annual plan, risk analysis, fashion)

MEB/CHMP choices

EMEA/CHMP

For cause, calamity, complaint
Inspection Practices *

Conduct

*Inspection format:*

- System directed, company (sponsor) and/or facility (site) directed
- Study/project directed
- Product directed (novel, generic, ...)
- Cause directed
- Ethics committees, safety committees
- For cause, routine, thematic

*Inspection activities (external):*

- Systems verification
- Data verification
- Educational activities


**Inspection Practices * 
When and How?**

*Inspection timing:*

- Pre-, post approval
- Obligations
- Before, during, after trial

*Inspection process:*

- Planning, preparing, **conducting**, reporting, follow up

*Inspection strategies:*

- Review, interview, access, test, re-analyze, recalculate
- Follow the process
- Evaluation

*EU Inspection frequency:*

- EMEA goal 15-30/annum (Sponsor/application/PhV)
Foremost EU Findings*
All Clinical trial and safety areas implicated

Patient safety, efficacy and data quality:
- EC approval, insurance, privacy (legal aspects/MS/third countries)
- IB, GLP (updates, present, IMPD)
- Protocol deviations (short cuts, trial vs. regular treatment)
- Contracts
- Responsibilities, work load (QP, QA, investigator, monitors)
- SAE/ADR reporting (CA, EC, Investigator)
- Information communication
- E-systems validation (awareness of users, new, archiving)
- No full Q-system (both GCP and PV ) coverage (sponsor global vs. local vs. CRO vs. site)
- Monitoring (training, planning, activities, follow up)
- IMP aspects (manufacturing, blinding, distribution, IVRS, accountability)
- Sources (definition, systems, documentation, filing, archiving)
  - SDV inconsistencies (sloppiness, misconduct, fraud)
- Fraud and misconduct
  (Directly detected fraud in NL inspections: 4 in 2006)
High Level Root Cause*: Conclusion From Inspection Findings

Common denominator: Sponsor

- Preparation for trial
- Timelines
- Grip on trial and participants
- Definition of responsibilities and terms
- Investigator versus “name”
-Evaluation of participants
- Processes and procedures
Use of Inspection Results*

As part of the entire evaluation process; adds/completes information

- Clinical assessment and inspection are two different aspects of verification of compliance and safety
- Inspection contributes to the verification of the quality of the data in the dossier
- Inspection will not enhance quality of data and dossier but enhance certainty on the quality
- There may be consequences for other notifications/applications/authorisations (positive/negative)
If Not*……..

What will happen in the event of observed non-compliance:

• Education, facilitation
• Inspection, re-inspection
• Suspension of clinical trial, EC approval withdrawn
• Warning
• Naming
• Urgent Safety restrictions, variation of MA
• Suspension of MA,
• Revocation of MA
• GMC, prosecution

Slides 9-19 adapted from a presentation entitled “A recent HA perspective –EU Inspections” Helena M. van den Dungen
Thank You

for your attention!

Questions?