Inspections conducted by foreign Regulatory Agencies: lessons and experience

PRAHEALTHSCIENCES

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Agenda

- Introduction
- Comparison of Inspection Processes
- Trends and Observations
- Best Practices

Introduction

- The complexities of multiple submissions to local and national competent authorities make the inspection and approval process more time consuming and difficult
- As the joint inspection process continues, the understanding of the similarities and differences between regulators will help with the success of clinical trials
- The same trials are being used to support Marketing Authorization Applications (MAAs) in the EU and New Drug Applications (NDAs) or Biologics License Applications (BLAs) in the US, often as parallel assessments
- Regulations in the US and Europe have similar aims to ensure that trials are being run according to ethical principles, subjects' safety and well being are properly managed, studies are run according to the protocol, regulatory requirements and properly reported.

Comparison of Inspectional Processes

Activity type	EMA	FDA	MHRA
Notification	Formal notification	Prior notification is not usually given unless specified by center	Formal notification
Opening Meeting	Opening discussion is held	FDA investigator(s) presents credentials and issue a FDA482	An agenda is agreed prior to inspection
Number of inspectors	Usually 2 or 3	Work alone unless directed or for cause	Usually 2
Document Requests	Maintain a formal tracking log	Makes formal verbal requests for documents (could make notes)	Maintain formal tracking log

Comparison of Inspectional Processes (continued)

Activity type	EMA	FDA	MHRA
Facility tour	Inspector(s) walk through facilities used for the study and ask questions to confirm and evaluate equipment and overall facility as appropriate to work being conducted		
Closing Meeting	List of findings doesn't provided, but verbally announced	Present and issue the firm an FDA483. Questionable observations are required to be described in the Establishment Inspection Report (EIR)	List of findings doesn't provided, but verbally announced
Findings / outcome classification	Critical Major Minor Other	NAI – No Action indicated VAI – Voluntary action OAI – Official Action	Critical Major Other

Legal Authority Actions

Authority Name	Actions
EMA	Does not have a role of enforcement like FDA. Any enforcement actions are responsibility of the individual Member States concerned and are subject to each country's local laws and regulations.
MHRA	Enforcement and Intelligence Group (E&I) has responsibility for enforcing medicines legislation in England and does so in Scotland and Wales on behalf of the Scottish Parliament and Welsh Assembly.

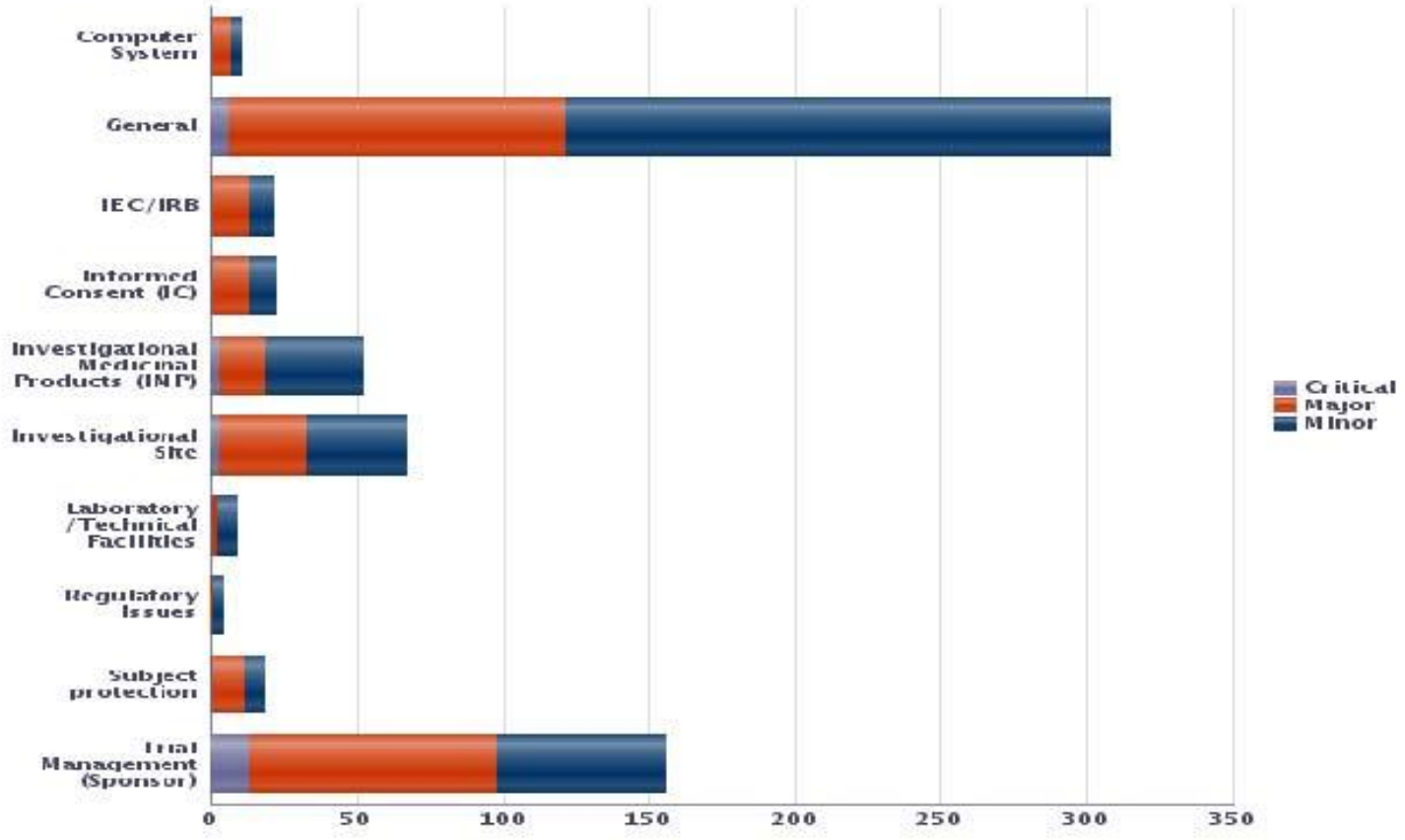
Legal Authority Actions

Authority Name	Actions
FDA	1. Warning and Untitled Letters. 2. Re-inspection 3. Termination of an exemption 4. Refusal to approve or license 5. Withdrawal of approval 6. Seizure of test articles 7. Injunction 8. Federal statutes 9. Debar (or prohibit) persons who have been conducted of specific felonies or misdemeanors from participating in certain FDA-regulated activities

Inspections conducted per type of site*

* Annual report of the Good Clinical Practice Inspectors Working Group 2014

Trends and Observations*



* Annual report of the Good Clinical Practice Inspectors Working Group 2014

General Observations

Essential documents:

• lack of essential documents e.g. receipt of IMP shipment to site, records of blood samples shipment to the central laboratories;
• incomplete documentation (e.g. incomplete screening list);
• lack of contemporaneous independent copy of the CRF filed on site.

SOPs:

• lack of evidence that sponsor SOPs have been followed and used;
• SOPs not updated as required;
• sponsor failure to implement an efficient quality management system.

Source documentation:

• discrepancies between source data and data reported in the CSR;
• missing source documents;
• lack of document specifying location of source data.

Qualification/training:

• incomplete training documentation and lack of training of study personnel on trial related procedures.

Organization and personnel:

• incomplete site personnel signature log and/or tasks performed by staff not authorized to do so.

Trial Management Observations

Data management:

- inappropriate system for reporting protocol violations;
- laboratory reports were submitted late to the site;
- data management activities were only undertaken after the clinical conduct of the trial was completed;
- the decisions made by the DMSB were not communicated to the site.

Monitoring:

- monitor has not identified number of deficiencies on site;
- lack of escalation process to resolve issues identified by monitor;
- monitor not following monitoring plan;
- investigator's training was done over the phone.

Document control:

- lack of version/date on the document;
- late introduction of amendments in the study.

Investigator Site Observations

Protocol compliance (selection criteria):

- violation of a number of inclusion criteria for some patients;
- final decision about eligibility not always documented in hospital records.

Reporting in CRF/diary:

- several discrepancies between source data such as medical history, concomitant medication etc. and the CRF for a sample of subjects;
- corrections on CRF not signed and dated;
- data not reported in CRF in a timely manner.

Protocol compliance (others):

- IMP and concomitant medication protocol deviations;
- protocol visits were not performed within the visit windows specified in the protocol;
- the sponsor established and used a system of prospectively accepting deviations from the protocol;
- insufficient maintenance of blinding of IMP.

Investigator Site Observations (continued)

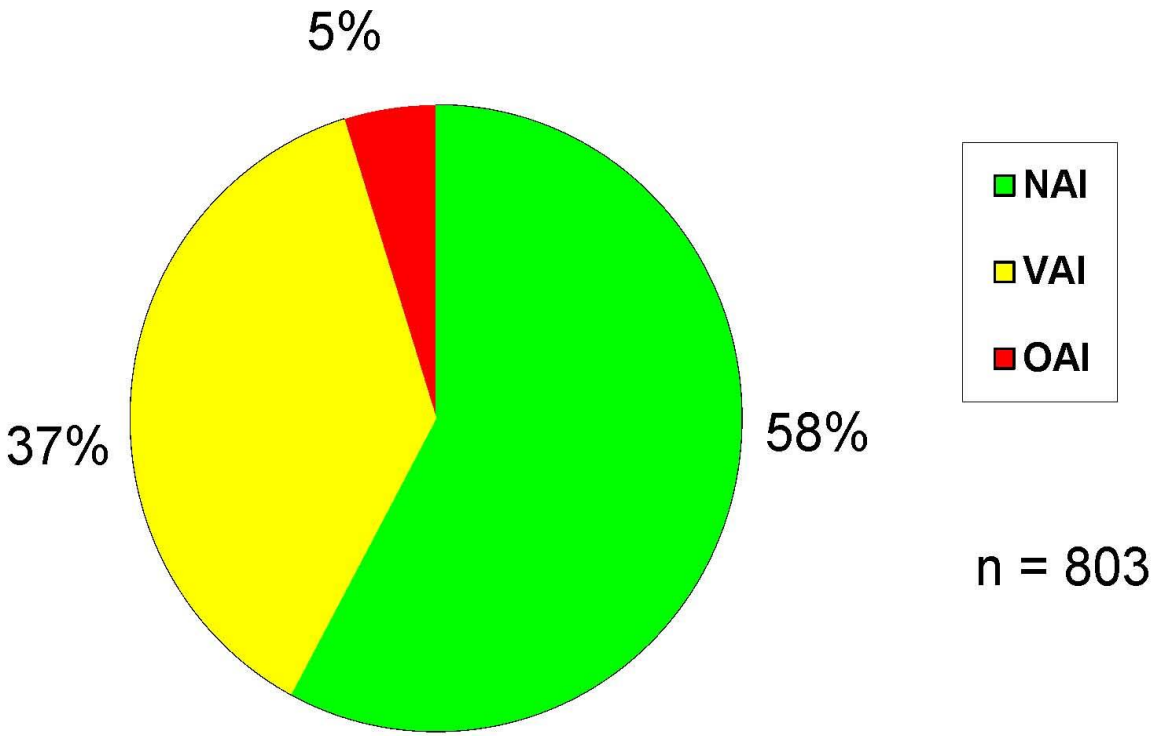
Protocol compliance (safety reporting):

- not all adverse events reported to the sponsor as required per protocol;
- instructions for SAE follow-up reports not followed;
- inadequate SAE documentation and reporting.

Protocol compliance (assessment of efficacy):

- site did not strictly follow the protocol criteria that had to be used to assess the disease status;
- the procedures for the primary end point assessment for patients were not always strictly followed as required by the clinical protocol.

FY'14 CI Inspections Classified All Centers*



*Inspections classified by all Centers in FY'14. Some inspections may have occurred in a different FY.

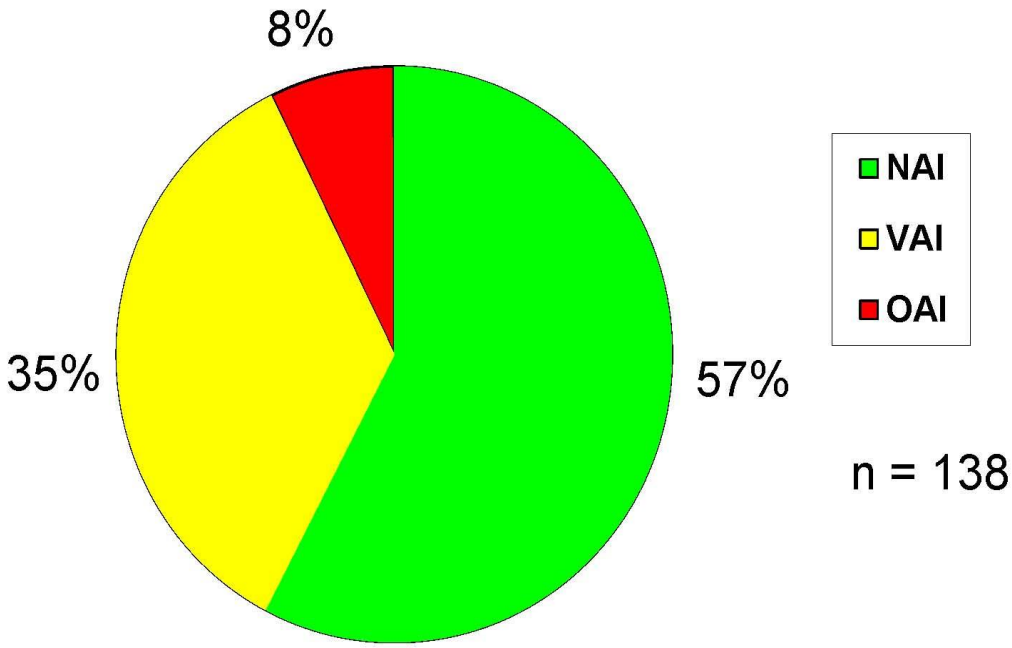
FDA

Most Common CI Deficiencies:

- Failure to follow the investigational plan and/or regulations
- Protocol deviations
- Inadequate recordkeeping
- Inadequate accountability for the investigational product
- Inadequate communication with the IRB
- Inadequate subject protection – failure to report AEs and informed consent issues

http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RunningClinicalTrials/UCM443775.pdf

FY'14 Sponsor/Monitor/CRO Inspections Classified - All Centers*



*Inspections classified in FY'14 by CBER, CDER, CDRH and CVM. Some inspections may have occurred in a different FY. Includes Sponsor-Investigator inspections.

FDA

Most Common Sponsor/Monitor Deficiencies:

- Inadequate monitoring
- Failure to bring investigators into compliance
- Inadequate accountability for the investigational product
- Failure to obtain FDA and/or IRB approval prior to study initiation

http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RunningClinicalTrials/UCM443775.pdf

Best Practices

The following four-step systems approach recommended by FDA can be extrapolated and considered by companies and sites for their best practice:

1. **Say what you do:**

The sponsor should have a qualified and responsible management team to provide governance of the whole clinical trial process. There should be a robust oversight of the outsourced trial and excellent coordination among the project team members, to ensure good decisions. The policy and SOPs should define procedures and responsibilities for all key clinical trial processes, from protocol development to preparation of the clinical study report. The SOPs should also focus on the potential anticipated risks.

2. **Do what you say**

This step largely describes education and training of all sponsor staff, CRO staff, and site staff uniformly about the trial protocol, study requirements, policies, and procedures. All the teams should be aware of their responsibilities. For the sponsor and CRO, the monitor is the main resource for ensuring the site quality. The quality depends a lot on how the site conducts the study. The sites should understand that documentation is the heart of GCP compliance. The quality of a trial requires an assurance of protection of subjects.

Best Practices

3. **Prove it:**

This step requires new approaches such as risk-based monitoring and trend analysis. Risk-based monitoring focuses on process management and verification of critical activities, including quality control, to ensure that they are carried out as planned. The trend analysis looks at data as compliance intelligence.

4. **Improve it:**

Improving quality will require actions — effective CAPA. For CAPA to be effective there should be an in-depth analysis of the root cause and its impact on the quality, and a search for an action plan that can provide long-term and sustainable solutions.

Meeker-O'Connell A. Enhancing clinical trial quality: CDER perspective. [Last accessed on 2011 May 2]. Available from: http: / / www.fdanews.com / ext/ files / Conference / FIS10Presentations / MeekerOConnell-HarmonizingRegulatoryApproaches.pdf .

Questions