Federal Agency for Medicines and Health Products

- 3rd Joint Conference of European Human Pharmacological Societies

- Dominique Delforge 21-22 May 2015, Brussels

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GCP and GMP inspections in phase I: what can be learned?

- **Introduction**
  - **Type of inspection**
- **GCP Inspector point of view : feelings and expectations**
  - **Inspector's feelings**
  - **Inspector's expectations**
- **Findings frequency, which conclusions ?**
  - **Systemic focus**
  - **Specific focus**
  - **Focus on Phase I in normal hospital departments**
- **Conclusions**

Introduction

Phase I units and/or BE (BioEquivalence) units are very specific units to cope with during a GCP inspection and in the GCP field.

It's actually not the same GCP inspection as an investigator one or a sponsor one.

And in this field, BE or Early phase GCP inspection focuses are different

Only 2 GCP inspectors till March 2015 for the FAMHP

Introduction

Main differences between Phase I and BE

	Phase I Unit	BE Unit
EU Regulatory EMA GCP WG guidances	*ANNEX V TO PROCEDURE FOR CONDUCTING GCP IN SPECTIONS REQUESTED BY THE EMEA : PHASE I UNITS EMEA/INS/GCP/197215/2005	*REFLECTION PAPER ON ADVICE TO APPLICANTS/SPONSORS/ CROS OF BIOEQUIVALENCE STUDIES EMEA/INS/GCP/468975/2007 *ANNEX VII TO PROCEDURE FOR CONDUCTING GCP INSPECTIONS REQUESTED BY THE EMEA : BIOANALYTICAL PART, PHARMACOKINETIC AND STATISTICAL ANALYSES OF BIOEQUIVALENCE TRIALS EMEA/INS/GCP/97987/2008
Purposes	Not only PK, PD but SAFETY	Essentially PK
Main focus of the inspection	Safety process, safety monitoring, safety devices / IMP administration <-> Dosage	Timing of Drug dosages administration Samples tracking PK Labs process, samples analysis

Introduction

2 types of GCP inspection :

- **Specific :**
  Inspection drawn up on by the control of the processes, the procedures of the inspectee regarding the current guidances/rules
- **Systemic :**
  Inspection drawn up by the verification of the data from the source documents to the CSR through all the study

Emphasizes on

Matrix of the type of inspection / type of unit	Phase I/Early Phase	BE unit
Systemic	Safety/IMP process	PK/IMP/Blood Samples tracking
Specific	Safety data vs IMP dosage administration data	PK data

GCP Inspector point of view : feelings and expectations

GCP Inspector feelings

- The area is complex, has got its own specificities
- Phase I unit/BE staff are specialists in both the protocol, the area (pharmacology) and their own procedures
- We do get sometimes intemidated – we just try not to show!
  - Presence of lawyers, prior audit by pharmacological university professors or experts!

BUT

GCP Inspector point of view : feelings and expectations

GCP Inspector feelings

- Experience is important – but we all have to start somewhere
- Common sense – and preparation (global view upon the trial)
- Remember our strenghts/competencies:
  - Cross-trial experience
  - We know how it ”generally” works at Phase I/BE sites
  - Different/Several purposes/focuses
  - Authority/legal basis to request all information
  - We are allowed not to be experts in all areas

GCP Inspector point of view : feelings and expectations

GCP Inspector expectations

- All the documents requested (following GCP and local laws) must be quickly (1 day max) available, readible and complete
  - SOPs, source documents, TMF, ...
- During the interview : answer to the point, tell the truth, avoid emotional answers, a good atmosphere is sought
- Inspectors are human being
  - We are not hostile, nor an enemy
  - ”Errare humanum est...”; we try to avoid misunderstandings, to clarify all issues encountered before the closing meeting. So we try to avoid the inspectee ”...perseverare diabolicum !”

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GCP Inspector point of view : feelings and expectations

GCP Inspection goals (personal opinion)

- To ensure that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

BUT ALSO

- To improve the quality of study, the quality of the different processes by the inspectee in the direction of the sentence above.
- An opportunity for the inspectee to have an independant point of view.

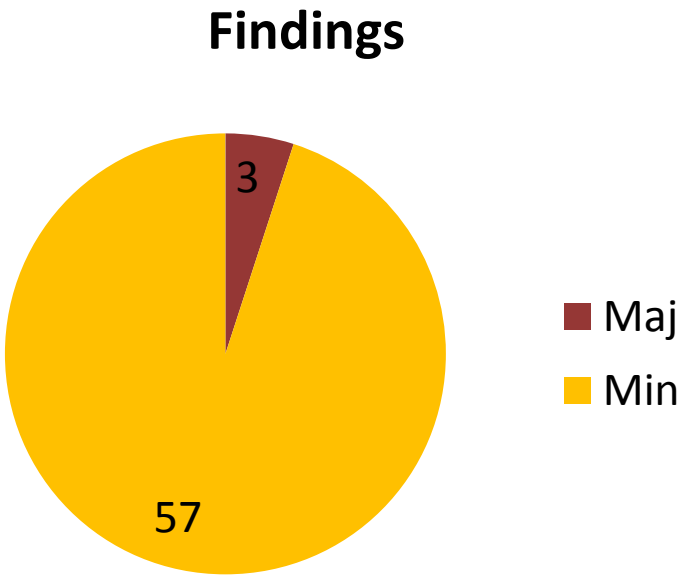
Findings frequency, Belgian experiences ?

Belgian GCP Inspection in Phase I / BE units

Object	Number
N° of Belgian GCP inspections in Phase I and BE units since 2010	12
Of which systemic GCP inspections in Phase I and BE units in Belgium since 2010	9
Of which specific GCP inspections in Phase I and BE units since 2010 (1 in Jordan, 1 in US and 1 in Belgium)	3
Of which specific EMA GCP inspections in Phase I and BE units (1 in Belgium, 1 in US)	2
Of which Belgian sites	9

Findings frequency, Belgian experiences ?

Findings in systemic inspections



Findings Rate/Site (Belgium)

Maj. = 3/9 = 1/3 = 0,33/site
Min. = 57/9 = 19/3 = 6,33/site

N° of Findings in systemic inspections

GCP and GMP inspections in phase I: what can be learned ?

General	Deficiency type	Critical	Major	Minor	# Insp. Deficiencies
General	Contracts/Agreements	0	0	3	3
	Access to Data	0	0	1	1
	Facilities & Equipm.	0	0	12	12
	Essential docs	0	0	2	2
	Qualification/Training & organization	0	0	16	16
	Randomization & IMP administration	0	0	3	3
	SOPs and Quality Management System	0	1	9	10
	Source Doc	0	0	4	4
Sponsor related	Monitoring	0	0	0	0
	ICF/Protocol/CRF/questionnaire design	0	0	0	0
	Data management/Stat/CSR	0	0	3	3
Investig. related	Protocol compliance	0	0	1	1
	ICF process	0	2	3	5

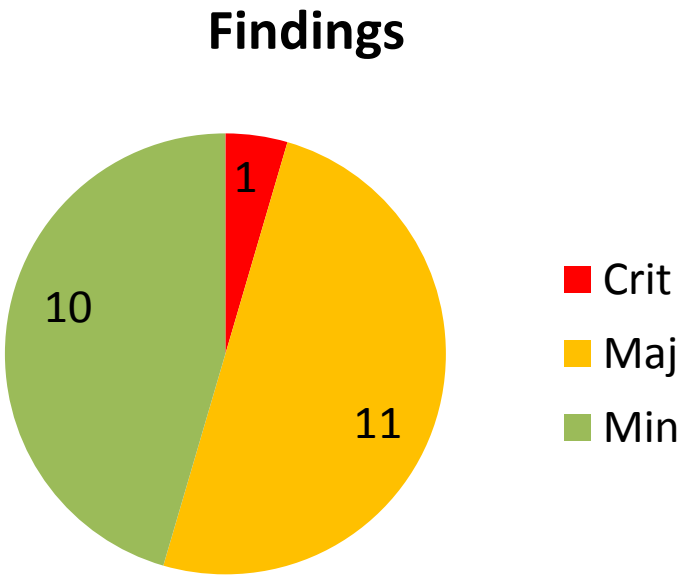
Type of Findings in systemic inspections

GCP and GMP inspections in phase I: what can be learned ?

Deficiency type	Examples
Contracts/Agreements	Vendor contracts not clear and complete, Deleg. Of Duty missing
Access to Data	Data confidentiality agreements
Facilities & Equipm.	Instrum. validation (labels, ...), emergency buttons missing, resuscitation trolley, non-sync. clocks, temperature monitoring, evacuation map
Qualification/Training & organization + essential docs	JD, CV, Training plan, Duty Log, records keepings, ...
Randomization & IMP administration	Mix up risks, fridge ID, ...
SOPs and Quality Management System	SOP missing, communication process; SOP keeping, distribution and process not always appropriate; ...
Source Doc	Medical history and communicat° with the GP, incomplete medical chart, ...
Data management/Stat/CSR	Mainly AE, SAE documentat°; ...
Protocol compliance	Samples (urine), tests not performed, ...
ICF process	ICF not well filled in, signed; amended ICF follow-up, ...

Findings frequency, Belgian experiences ?

Findings in specific inspections



Findings Rate/Site

Crit. = 1/3 = 0,33/site
Maj. = 11/3 = 3,66/site
Min. = 10/3 = 3,33/site

Type of Findings in systemic inspections (3 in BE)

GCP and GMP inspections in phase I: what can be learned ?

General	Deficiency type	Critical	Major	Minor	# Insp. Deficiencies
General	Contracts/Aggreements	0	1	0	1
	Access to Data	0	0	1	1
	Facilities & Equipm.	0	0	2	2
	Essential docs	0	0	1	1
	Qualification/Training & organization	0	0	3	3
	Randomization & IMP administration	0	0	0	0
	SOPs and Quality Management System	0	0	0	0
	Source Doc	0	1	1	2
Sponsor related	Monitoring/Audit	1	3	0	4
	ICF/Protocol/CRF/questionnaire design	0	2	2	4
	Data management/Stat/CSR	0	1	0	1
Investig. related	Protocol compliance	0	3	0	3
	ICF process	0	0	0	0

Findings frequency, Belgian experiences ?

Type of Findings in specific inspections (mainly BE)

Deficiency type	Examples
Contracts/Agreements	Contracts with the sponsor not GCP compliant
Facilities & Equipment	Personnel safety, standards certificates verification, ...
Qualification/Training & organization + essential docs	Duty Log, records keepings, ...
Source Doc	No Medical History, poor ID records for volunteers, uncompleted records, not matching with the CRF, ...
Protocol/CRF/ analysis method design	No concomit. medic. registration in CRF, bad wording in the CRF vs meal, elements missing in method validation, ...
Monitoring, audit	No monitoring, poorly organized monitoring by the sponsor, fake audit, ...
Data management/Stat/CSR	CSR missed an issue to discuss
Protocol compliance	Missing note to file, Schedule of dosage vs meal time, dosage schedule not appropriate, forget IS during a subject's samples analysis, ...
ICF process	ICF not well filled in, signed; amended ICF follow-up, ...

Findings frequency, Belgian experiences ?

Belgian GCP Inspection in Phase I trials in normal hospital departments

Object	Number
N° of Belgian GCP inspections in Phase I trial (hospital dpt)	3
Oncology	2
Major findings	**10**
Minor findings	**8**

Amongst those Majors findings: ICF process, SAE reporting, protocol compliance, good documentation practices, protocol design

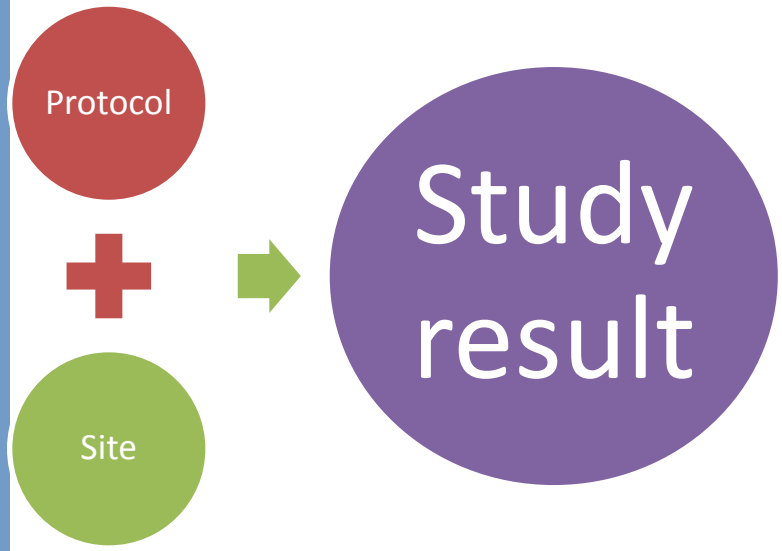
Findings frequency, Belgian experiences ?

Belgian GCP Inspection in Phase I /BE conclusions :

- In fact, there are some trends but reviewing all the reports, it seems that every inspection raises concerns very linked to each site and/or study inspected. Very dependant of the study and/or the site inspected.
- As inspectors we have also to work with the most objective and harmonized view.
- From a systemic point of view the Belgian Phase I/BE centers are rather of good quality => many minor findings, no critical.

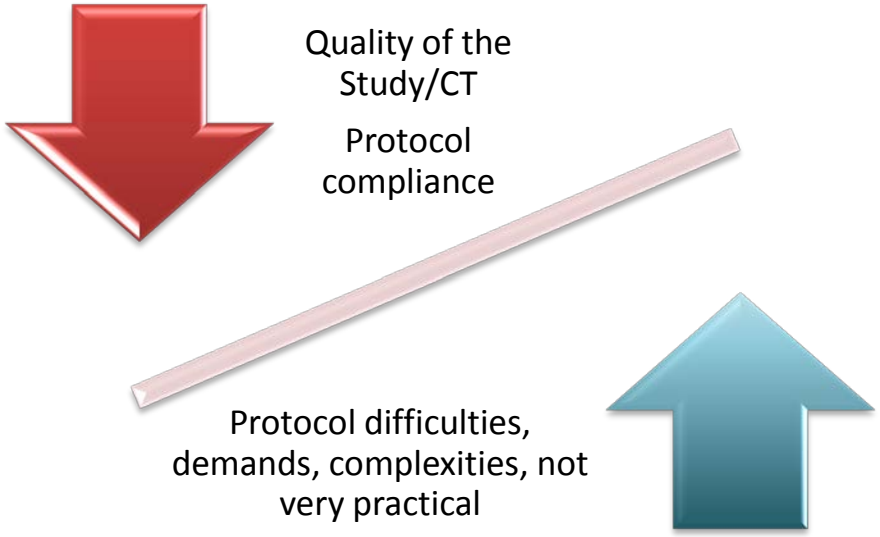
Findings frequency, Belgian experiences ?

Belgian GCP Inspection in Phase I /BE conclusions :



Obviousness but…
The quality of the site with the protocol compliance produce CSR of good quality

Obviousness but …
Importance of the Protocol Design



Contact

Federal Agency for Medicines and Health Products - famhp

Dominique Delforge
GCP Inspector
Place Victor Horta 40/40
1060 Bruxelles

tel. 0032 474859802

e-mail dominique.delforge@fagg-afmps.be

www.afmps.be

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