EUROPEAN MEDICINES AGENCY
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Compliance and Inspections

Classification and analysis of the GCP inspection findings of GCP inspections conducted at the request of the CHMP

(Inspection reports to EMA 2000-2012)

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1. Glossary

BE/BA	Bioequivalence/Bioavailability
CAP	Centrally Authorised Products
CRO	Contract Research Organisation
CHMP	Committee for Medicinal Products for Human Use
CIS	Commonwealth of Independent States
CRF	Case Report Form
CSR	Clinical Study Report
EEA	European Economic Area
EFTA	European Free Trade Association
EMA	European Medicines Agency
EU	European Union
GCP	Good Clinical Practice
GCP IWG	Good Clinical Practice Inspectors Working Group
GMP	Good Manufacturing Practice
IEC	Independent Ethics Committee/
IRB	Institutional Research Board
IC	Informed Consent
ICH	International Conference Harmonization on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human
IMP	Investigational Medicinal Product
IR	Inspection Report
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
NCA	National Competent Authority
RA	Regulatory Authority
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
UEC	Under Exceptional Circumstances

2. Introduction

Good clinical practice (GCP) is an international ethical and scientific quality standard for designing, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance 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.

Clinical trials, conducted within the European Union, must comply with the requirements of Directive 2001/20/EC (herein after 'Clinical Trial Directive') and Directive 2005/28/EC (herein after 'GCP Directive'). According to Directive 2001/83/EC all clinical trials included in marketing authorisation applications in the European Union, irrespective of their geographical location, are required to be conducted in accordance with the GCP and ethical principles equivalent to those of Directive 2001/20/EC. Any clinical trial included in the application could be subject to inspection.

Requirements for the conduct of clinical trials in accordance with good manufacturing practice (GMP) and inspections of these have been implemented in the GMP Directive for investigational medicinal products (IMP) for human use (Directive 2003/94/EC), the Clinical Trial Directive and the GCP Directive.

Compliance by an applicant or marketing-authorisation holder (MAH) with GCP and the other provisions of a marketing authorisation for medicinal products for administration to humans will be assessed by the EU/EEA Inspectorates when the Committee for Medicinal Products for Human Use (CHMP) considers it necessary. The CHMP may request inspections in EU/EEA and also in third countries (i.e. countries outside the EU/EEA).

The inspections are usually requested during the initial review of a marketing authorisation application (MAA), but could be raised post-authorisation (e.g. inspection of studies conducted or completed as part of the condition of a marketing authorisation, a new indication, a new pharmaceutical form or because of concerns arising from the studies previously submitted).

Different types of GCP inspections may be requested by the CHMP. The scope of these inspections may vary according to the objectives and the focus of the inspections. These inspections may be routine or may be triggered by issues arising during the validation of the pivotal clinical trials submitted to the European Medicines Agency (herein after 'the Agency') or during the assessment of the dossier by the assessors or by other information such as previous inspection experience.

A routine inspection is an inspection carried out as a routine surveillance of GCP compliance in the absence of specific trigger elements.

A triggered inspection is an inspection requested because there is a concern due to either the actual issues observed or the potential impact of deviations from GCP on the conduct of the study as a whole or at a particular site.

In general, the CHMP request for a GCP inspection is focused on the most important trials involved in the application. The objectives of a GCP inspection requested by the CHMP are:

- to determine whether the trial was conducted in accordance with applicable regulatory requirements which include local regulations and ethical standards, and the CPMP/ICH/135/95 Note for Guidance on GCP (ICH-GCP), Directive 2001/83/EC as amended and Directive 2001/20/EC;

- to provide answers to questions arising from the assessment process;
- to determine whether the data submitted in the dossier are credible and accurate.

Articles 2 and 15 of Directive 2001/20/EC further specify the locations where inspections shall be carried out in order to verify compliance with GCP standards. The sites concerned by a clinical trial include particularly, but not exclusively, the investigational site or sites, any laboratory used for analyses in the clinical trial, contract research organisation's and/or the sponsor's systems and premises.

The findings or failures to comply with GCP are presented formally to the representatives of the inspected entity and the sponsor/applicant of the trial in the inspection report (IR). Any response from the inspected entity and the sponsor is considered and the process is completed with the issuing of the IR and its addenda to the Agency.

If the outcome of the inspection is negative (GCP non-compliance and/or invalid data), the CHMP can take any necessary regulatory action, which may involve the refusal to authorise the product or the indication submitted, etc.

At the Agency, an important part of the work of the Clinical and Non-Clinical Compliance service involves harmonisation and coordination of GCP-related activity at EU level. This service is involved in coordinating GCP inspections for the centralised procedure for a MAA. The GCP inspectors' working group (GCP IWG) has developed procedures for the coordination, preparation, conduct and reporting of GCP inspections carried out in the context of the centralised procedure. Through the work of the GCP IWG the service is involved in the preparation and revision of guidance on GCP topics, coordination of advice on the interpretation of EU GCP requirements and related technical issues.

Between 2000 and 2012, a total of 398 GCP inspections of centralised products requested by the CHMP were conducted. These GCP inspections included investigator sites, sponsors, contract research organisations (CROs), and a few other types of sites including clinical laboratories and facilities dedicated to bioequivalence/bioavailability (BE/BA) studies.

In the inspection report each finding makes reference to the ICH-GCP guideline or other rules to which the non-compliance identified relates. However, this system is not practical to use for analysis from a statistical point of view, because the ICH-GCP guideline often refers to a particular aspect of GCP in more than one place. Therefore, a finding can refer to several points in the ICH-GCP guideline. The difficulty for analysis could be overcome by structuring the system using categories, so that one finding belongs to one single category. The GCP IWG agreed with a classification of 50 categories included in 11 main categories (annex 1). While providing less fine detail than an analysis based on each point of the GCP guideline, this system gives sufficient detail to provide a profound basis for an analysis.

The Agency decided to carry out a work project to classify the findings of all of these GCP inspection reports and provide a platform for categorisation of future IRs. The classification includes a verbatim of the finding, grading, category, responsibility and reference to the ICH-GCP and other guidelines and regulations. In addition, the identification details of the procedure, product, site(s) involved, dates of inspection and inspectors' details were also used for the analysis.

The primary purpose of this document is to describe the classification system, provide some examples of analysis and highlight the potential value of this system in identifying areas of concern.

3. Scope and aims

The information included in this report refers to the inspections carried out on behalf of the Agency from January 2000 to December 2012.

By publishing data on the inspection results that were conducted over the period stated above, it is the intention of the GCP IWG, as documented in its mandate, to communicate to the public details on its inspection activity and provide further information on the inspection outcomes for the centralised procedure. There is little information in scientific publications about the results of the GCP inspections carried out by the national competent authorities (NCA).

As this document provides greater transparency on the inspection process and findings, and highlights the areas that require more attention, it could support sponsors in applying a risk based quality management to their clinical trials (see also 'Reflection paper on risk based quality management in clinical trials') and thereby could contribute to improving GCP compliance.

Furthermore, the analysis of the findings provides support for discussion and harmonisation of findings and their grading at the level of the GCP IWG.

Finally, the analysis may help in prioritising areas for attention in future inspections, either in general or of specific company-types or sites.

4. Method

All the relevant records were captured in a database referred to as the Agency's Corporate GCP Database (herein after 'Corporate GCP Database') within this report.

4.1. Information about findings

The following information in relation to the findings is recorded in the Corporate GCP Database:

1. The wording of the findings is entered in the Corporate GCP Database as listed in the IRs.
2. The grading of each finding is entered as classified in the IR. The findings are classified by the GCP Inspectors as "critical", "major" and "minor" according to the classification of GCP findings described in the "Procedure for reporting of GCP Inspections requested by the CHMP":

    - **Critical**:

        - Conditions, practices or processes that **adversely affect** the rights, safety or well-being of the subjects and/or the quality and integrity of data.

        - Critical observations are considered totally unacceptable.

- Possible consequences: rejection of data and/or legal action required.
- Remarks: observations classified as critical may include a pattern of deviations classified as major, bad quality of the data and/or absence of source documents. Manipulation and intentional misrepresentation of data belong to this group.

- **Major**:
  - Conditions, practices or processes that **might adversely affect** the rights, safety or well-being of the subjects and/or the quality and integrity of data.
  - Major observations are serious findings and are direct violations of GCP principles.
  - Possible consequences: data may be rejected and/or legal action required.
  - Remarks: observations classified as major, may include a pattern of deviations and/or numerous minor observations.
- **Minor**:
  - Conditions, practices or processes that **would not be expected to adversely affect** the right, safety or well-being of the subjects and/or the quality and integrity of data.
  - Possible consequences: observations classified as minor, indicate the need for improvement of conditions, practices and processes.
  - Remarks: many minor observations might indicate a bad quality and the sum might be equal to a major finding with its consequences.

3. The classification of all findings is made according to the list of categories agreed by the GCP IWG (annex 1).
4. The reference of the findings to the GCP guideline and/or other guidelines and regulations specified in the IR are entered in the Corporate GCP Database.
5. The responsibility of each finding is entered according to the responsibility documented in the IR. When the responsibility is not specified by the inspector, the responsibility is taken according to the point of the ICH-GCP guideline chosen by the inspector. When there is no reference, the finding is classified as “not classified”. The system allows for the inclusion of more than one responsibility, for example, investigator and sponsor responsibility when both are referred to.

Work instructions with the keys to categorise the findings and the entering of the data were written to harmonise the procedure.

4.2. Information about the applications

The following information was included in the database:

- product (name, list A/B, orphan drug, therapeutic group);
- application (EMA code);
- MAH/Applicant.

4.3. Information about the clinical trial(s) inspected

The following information was included in the database:

- protocol number;
- title;
- number of investigational sites/patients;
- sponsor.

4.4. Information about the inspections

The following information was included in the database:

- inspection (EMA inspection number, dates);
- type of site inspected (clinical investigator, sponsor, CRO, clinical laboratory and sites related to BE/BA studies);
- site details (address, city, region and country);
- inspector details (names and NCA), and the reporting, lead, and supporting inspectorate involved in the inspection.

4.5. Information about the inspection outcome

The following information was included in the database:

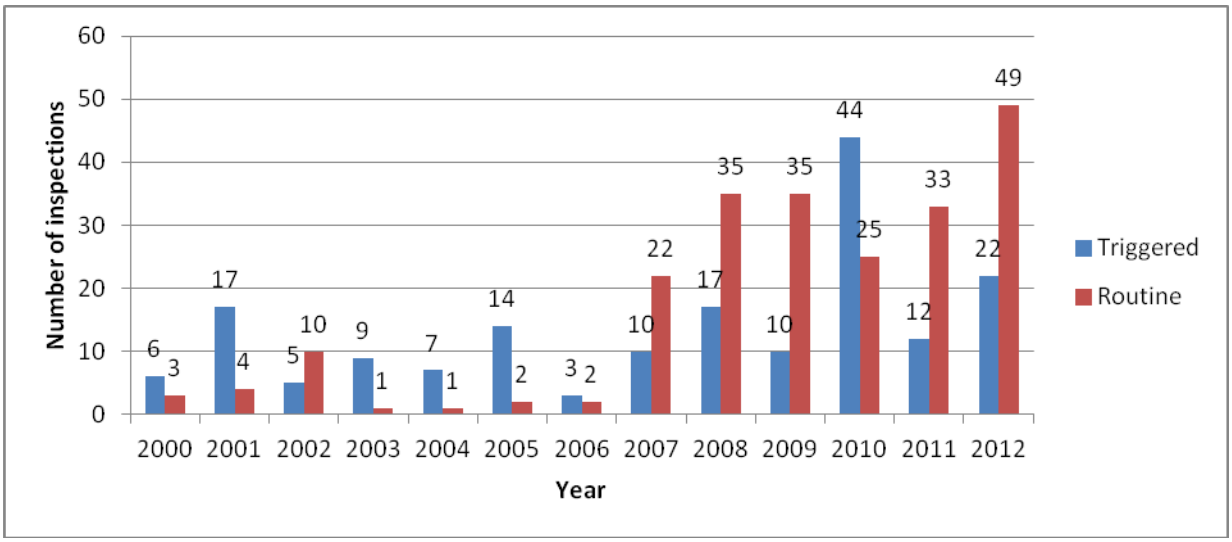
- GCP compliance;
- data validity;
- recommendations;
- assessment of the relevance of the findings for the full study.

5. Results

5.1. Overview of GCP inspections requested by the CHMP and carried out between 2000-2012

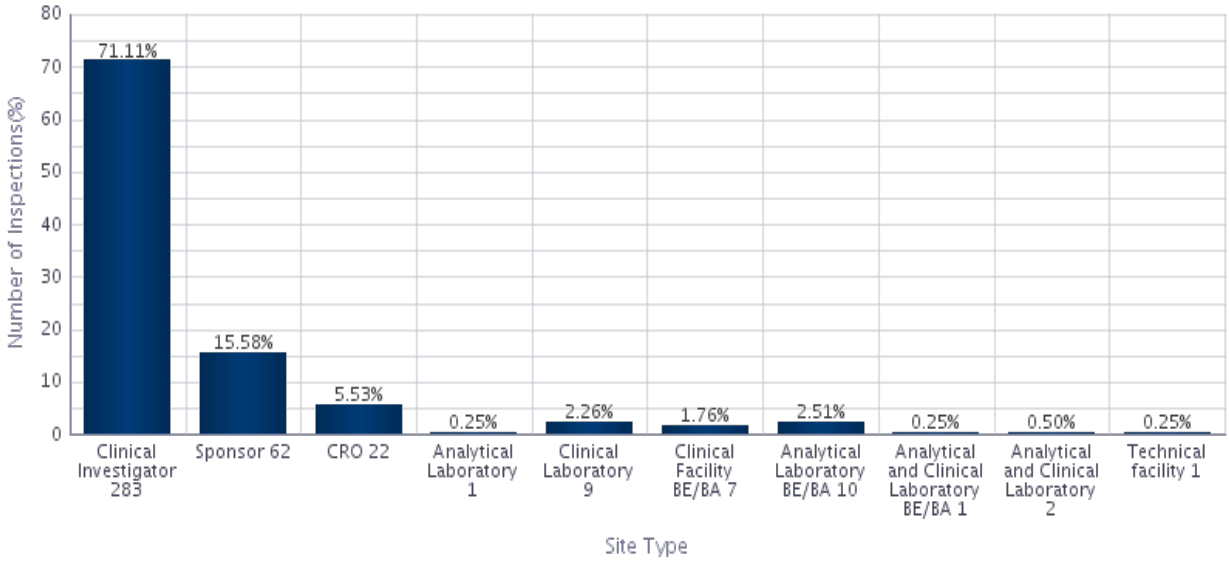
Between 2000-2012, a total of 398 site inspections were carried out. The distribution of the number of inspections classified as routine and triggered is shown in figure 1. It can be seen that the number of inspections has increased since 2006 mainly, due to routine inspections in line with the implementation of the GCP Inspection policy in 2006.

Figure 1. Number of inspections by type of inspection and year



As can be seen in figure 2, most of the inspections were carried out at the investigational site, followed by the sponsor site, CRO, analytical laboratory for BE/BA studies, clinical laboratory and the clinical facility of BE/BA studies.

Figure 2. Number of inspections by type of inspection site

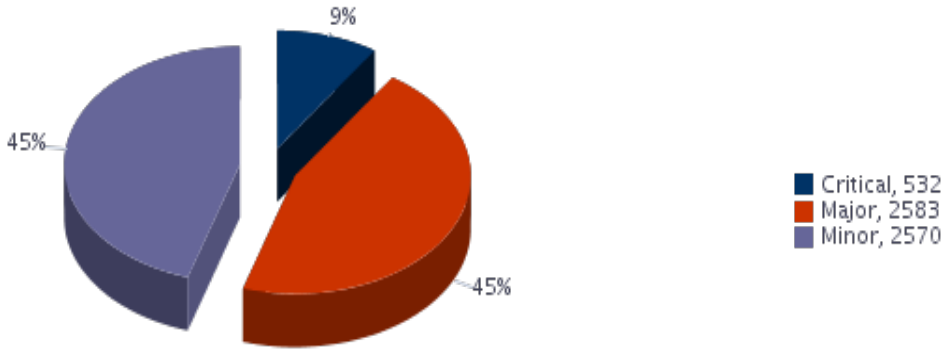


5.2. Analysis of the findings

5.2.1. Findings by grading and category

A total of 5685 findings, comprising 532 critical (9%), 2583 major (45%) and 2570 minor (45%) were recorded during the inspections conducted in the specified period (figure 3).

Figure 3. Number and percentages of findings by grading



The categorisation of the total number of findings reported for all sites is presented in annex 2. It can be seen in annex 2, that more than 80% of the findings are included in 4 main categories (general, trial management, investigational site and investigational medicinal product).

5.2.1.1. Critical findings

Overall there are 532 critical findings (9% of the total findings) in the Corporate GCP Database.

There are some categories where no critical findings were identified (design of the trial, insurance/ indemnity/compensation to subjects, manufacturing/importing authorisation, audit trail and authorised access, physical security system and back-up, certification/accreditation, normal values/ranges/updates, technical validation, facilities and equipment and contracts/agreements).

The following three categories, monitoring, data management and clinical study report (CSR), account for approximately one quarter of the total critical findings (table 1). The responsibility for the critical findings included in these categories is attributed to the sponsor although as mentioned before the majority of inspections were carried out at an investigational site. However, the percentage of the critical findings of each individual category is lower than 1% of the total findings.

The top 10 critical GCP findings represent 61.6% of the total number of critical findings and 5.8% of the total number of findings.

Table 1. Ranking of the top 10 critical GCP findings

Finding sub-category name	No.	% *	% **
Monitoring	49	9.2%	0.9%
Data management	48	9.0%	0.8%
CSR	47	8.8%	0.8%
Protocol compliance (selection criteria)	33	6.2%	0.6%
Source documentation	32	6.0%	0.6%
Protocol compliance (assessment of efficacy)	23	4.3%	0.4%
Protocol/CRF/diary/questionnaires design	21	3.9%	0.4%
IMP accountability	20	3.8%	0.4%
Protocol compliance (safety reporting)	19	3.6%	0.3%
Prescription/administration/compliance	18	3.4%	0.3%
Reporting in CRF/diary	18	3.4%	0.3%
Grand total	**328**	**61.6%**	**5.8%**

*Related to the total number of critical findings (No. = 532)

**Related to the total number of findings (No. = 5685)

Most of the critical findings included in the CSR category are related to:

- large number of major protocol deviations not reported in the CSR;
- SAEs not reported in the CSR resulting in an underreporting of the SAEs;
- inconsistencies between efficacy results observed at the sites and reported in the data listings.

Most of the critical findings included in the monitoring category are related to:

- inadequate monitoring activities performed at site;
- non-adequate corrective and preventive actions taken by the sponsor to prevent recurrence of non-compliance and to improve the quality of the site's performance despite receiving information of GCP problems at the sites.

Most of the critical findings included in the data management category are related to insufficient quality control (e.g. edit checks) performed on the data captured in the database taking into account that relevant inconsistencies in the data were not recognised and not followed up.

Although the number of critical findings is not very high, some differences are found when comparing the critical findings profile found in routine and triggered inspections. Monitoring and data management are placed among the highest first 3 categories in the two types of inspections. On the other hand, it is worth mentioning that the CSR category occupies the first place in triggered inspections and in routine inspections CSR is found in the ninth place.

During the time period 2000 to 2006, 84 inspections were conducted; 45 of the 84 inspections recorded a total of 249 critical findings, while no critical finding was recorded at 39 inspections. The most common critical findings were:

- IMP prescription/administration/compliance;
- CSR;

- protocol compliance (safety reporting).

During the time period 2007-2009, a total of 129 inspections were conducted; 44 of the 129 inspections recorded a total of 148 critical findings, while no critical finding was recorded at 85 inspections. The most common critical findings were:

- protocol compliance (selection criteria);
- source documents;
- monitoring.

During the time period 2010 to 2012, 185 inspections were conducted; 62 of the 185 inspections recorded a total of 135 critical findings, while no critical finding was recorded at 123 inspections. The most common critical findings were:

- monitoring;
- protocol compliance (selection criteria);
- protocol compliance (assessment of efficacy).

5.2.1.2. Major and minor findings

There are 1938 major (47.1%) and 1718 minor (41.7%) findings in relation to the total number of findings.

The top 10 categories for major and minor GCP findings are listed in the tables 2 and 3 respectively.

It is noted that the ranking of the categories found in annex 3 (ranking of total GCP findings for 2000-2012) and in table 2 (top major categories) is similar. This is in line with the fact that almost 50% of the total findings are graded as major. In those two tables source documentation, monitoring, supplying/storage/retrieval/destruction and CSR categories are among the greatest concerns. The top 10 major GCP findings represent 54.7% of the total number of major findings.

Table 2. Ranking of the top 10 major GCP findings

Finding sub-category name	No.	% *	% **
Monitoring	187	7.2%	3.3%
Source documentation	180	7.0%	3.2%
Data management	176	6.8%	3.1%
Supplying/storage/retrieving/destruction	138	5.3%	2.4%
Protocol compliance (selection criteria)	131	5.1%	2.3%
Essential documents	130	5.0%	2.3%
Reporting in CRF/diary	130	5.0%	2.3%
Standard operating procedures (SOPs)	127	4.9%	2.2%
Qualification/training	121	4.7%	2.1%
CSR	94	3.6%	1.7%
Grand total	**1414**	**54.7%**	**24.9%**

* Related to the total number of major findings (No. = 2583)

** Related to the total number of findings (No. = 5685)

In table 3 where the ranking of the top 10 minor GCP findings is shown, it can be seen that essential documents and reporting in CRF/diary head the list of minor findings representing 20.3% of the minor findings and 9.1% of the total number of findings respectively. The top 10 minor GCP findings represent 58.8% of the total number of minor findings and 26.7% of the total number of findings.

Table 3. Ranking of the top 10 minor GCP findings

Finding sub-category name	No.	% *	% **
Essential documents	322	12.5%	5.7%
Reporting in CRF/diary	200	7.8%	3.5%
Source documentation	160	6.2%	2.8%
Organisation and personnel	158	6.1%	2.8%
Qualification/training	134	5.2%	2.4%
Supplying/storage/retrieving/destruction	126	4.9%	2.2%
SOPs	117	4.6%	2.1%
Monitoring	108	4.2%	1.9%
Document control	95	3.7%	1.7%
Data management	92	3.6%	1.6%
Grand total	**1512**	**58.8%**	**26.7%**

*Related to the total number of minor findings (No. = 2570)

**Related to the total number of findings (No. = 5685)

5.2.2. Findings by type of site

Most of the findings have been reported at the investigational sites, even if many of the findings were attributed to sponsor responsibility (figure 4). However, there is only a slightly higher percentage of critical findings at the investigational sites, compared to the sponsor (figure 5).

Figure 4. Number of graded findings by site

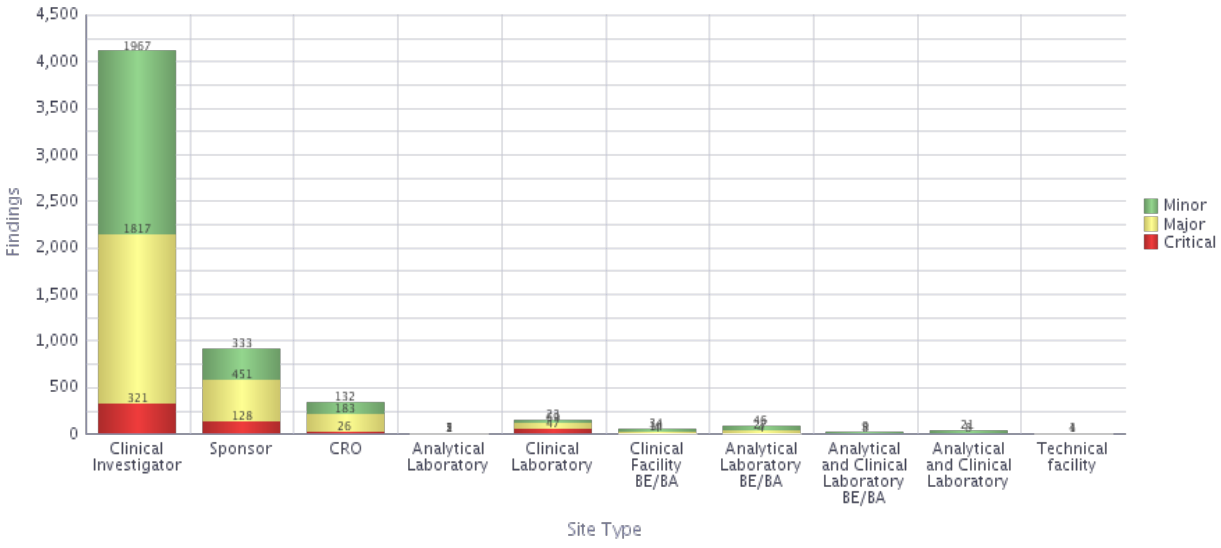
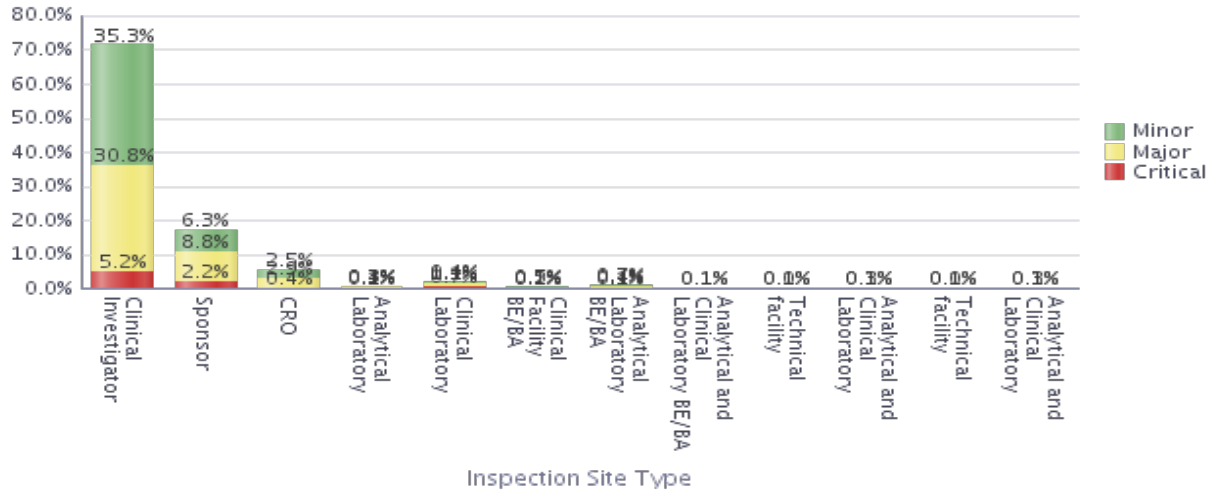


Figure 5. Percentage of graded findings by type of site



5.2.2.1. Findings at the investigator site

Annex 4 shows the total number of findings by category and grading (critical, major and minor) recorded for all investigational sites and annex 5 shows the ranking of total findings in those sites. In the top 10 categories with critical findings at the investigational site (table 4) it can be seen that there are some categories with findings related to the responsibility of the sponsor (monitoring, CSR, and data management).

Table 4. Top 10 categories with critical findings at the investigational site

Finding sub-category name	No.	% *	% **
Monitoring	31	9.7%	0.8%
Protocol compliance (selection criteria)	31	9.7%	0.8%
Protocol compliance (assessment of efficacy)	23	7.2%	0.6%
Source documentation	22	6.9%	0.5%
Data management	19	5.9%	0.5%
CSR	18	5.6%	0.4%
Prescription/administration/compliance	18	5.6%	0.4%
Protocol compliance (safety reporting)	17	5.3%	0.4%
Reporting in CRF/diary	17	5.3%	0.4%
IMP cccountability	13	4.0%	0.3%
Protocol/CRF/diary/questionnaires design	13	4.0%	0.3%
Grand total	**222**	**69.2%**	**5.4%**

*Related to the number of critical findings found at the investigator site (No. =321)

**Related to the total number of findings found at the investigator site (No. =4105)

5.2.2.2. Findings at the sponsor site

Annex 6 shows the total number of findings by category and grading (critical, major and minor) recorded for sponsor sites. The ranking of total findings at these sites is in annex 7 and table 5 shows the top 10 categories with critical findings at these sites.

Table 5. Top 10 categories with critical findings at the sponsor site

Finding sub-category name	No.	% *	% **
CSR	27	21.1%	3.0%
Data management	21	16.4%	2.3%
Monitoring	15	11.7%	1.6%
Protocol/CRF/diary/questionnaires design	7	5.5%	0.8%
Direct access to data	6	4.7%	0.7%
Statistical analysis	6	4.7%	0.7%
Manufacturing/packaging/labelling	5	3.9%	0.5%
Safeguard of the safety and well-being of subject	5	3.9%	0.5%
Supplying/storage/retrieving/destruction	5	3.9%	0.5%
IMP accountability	4	3.1%	0.4%
Randomisation/blinding/codes IMP	4	3.1%	0.4%
Grand total	**105**	**82.0%**	**11.5%**

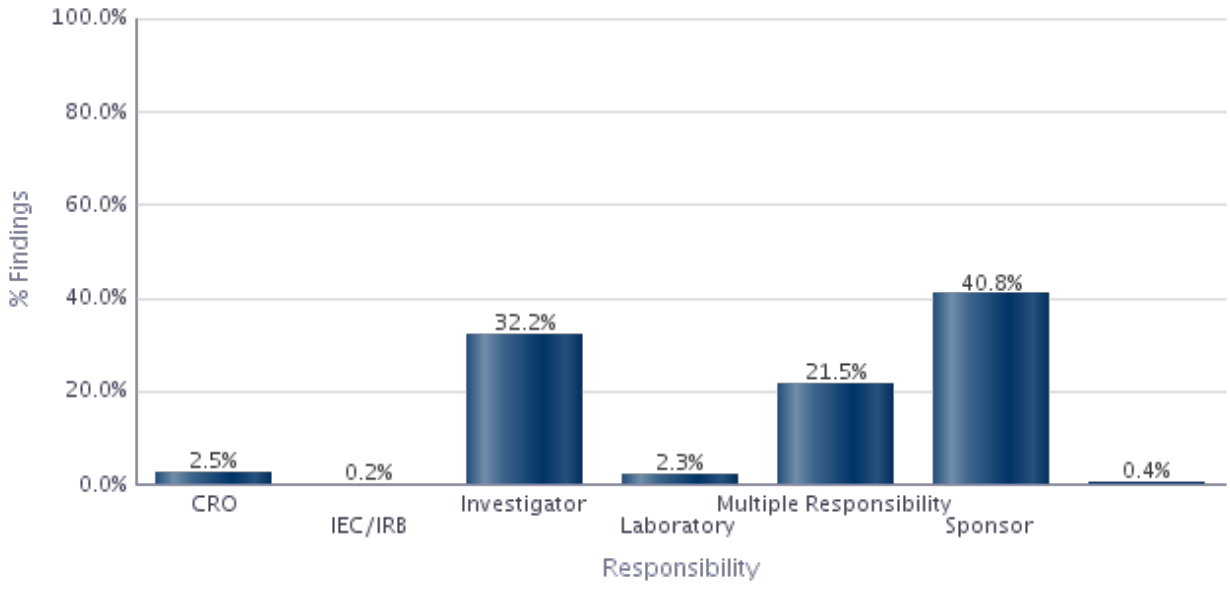
*Related to the number of critical findings found at the sponsor site (No. = 128)

**Related to the total number of findings found at the sponsor site (No. = 912)

5.2.3. Responsibility for the findings

The sponsor and CRO are responsible for 43.3% of the total findings (figure 6) although only 15.6% of the inspections were carried out at the sponsor site and 5.5% at the CRO site.

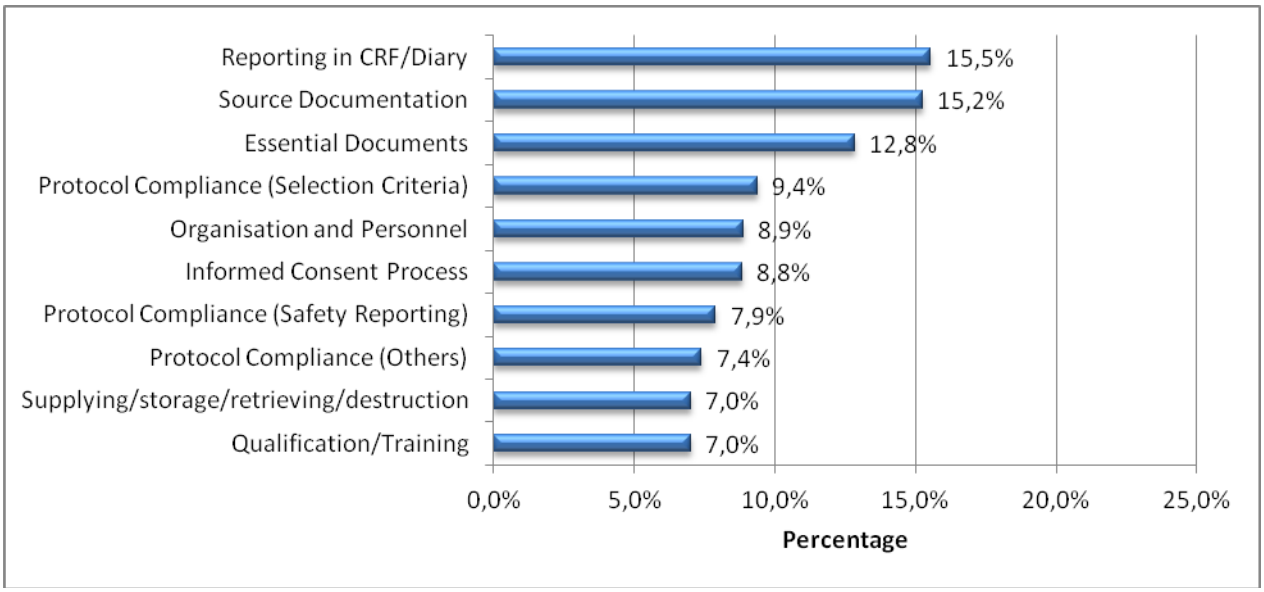
Figure 6. Responsibility of the findings from all sites



5.2.3.1. Investigator responsibility findings

The top 10 categories under investigator responsibility are tasks clearly related to the investigator (reporting in CRF/diary, source documentation, and essential documents; figure 7).

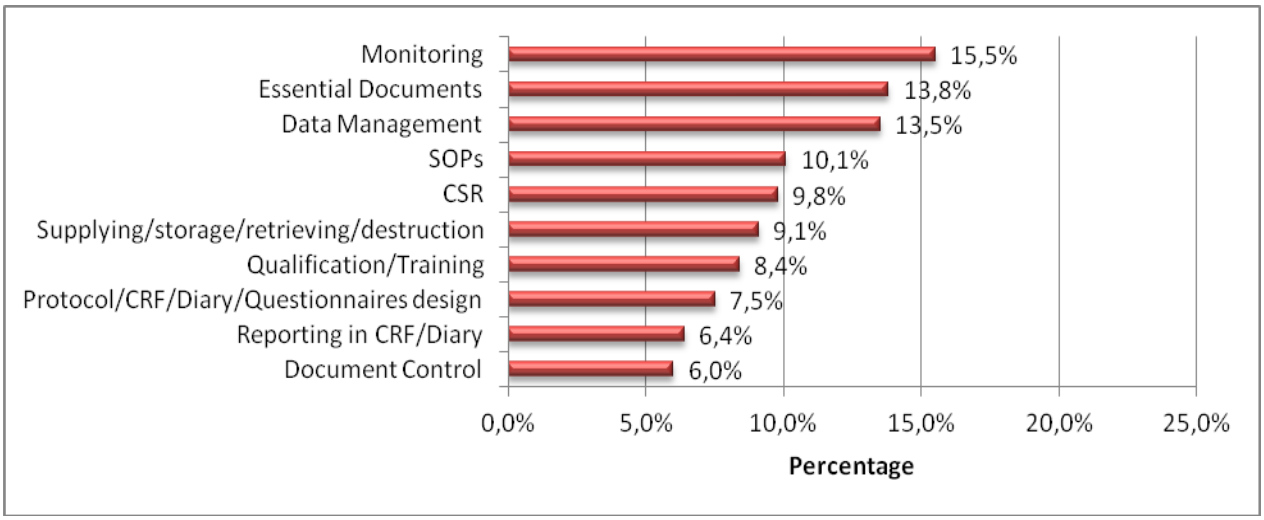
Figure 7. Investigator responsibility by category of the total findings



5.2.3.2. Sponsor responsibility of the total findings

The top 10 categories under sponsor responsibility are tasks clearly related to the sponsor (monitoring, essential documents and data management; figure 8).

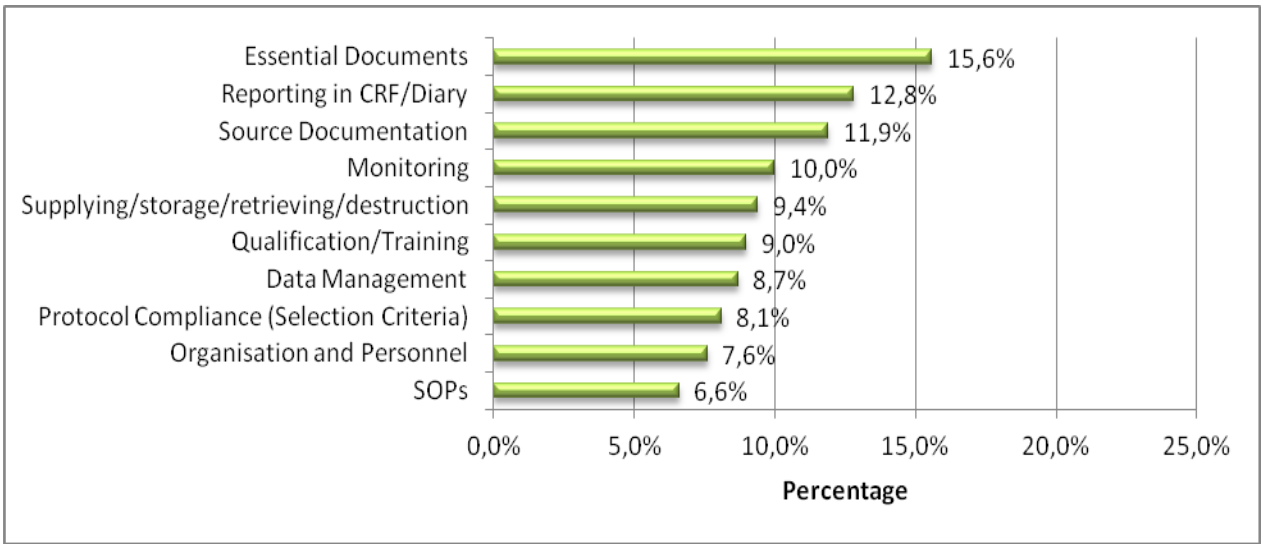
Figure 8. Sponsor responsibility by category of total findings



5.2.3.3. Sponsor and investigator shared responsibility findings

In some inspections there are findings with a shared responsibility between investigator and sponsor (figure 9).

Figure 9. Shared sponsor and investigator responsibility by category of total findings



5.2.3.4. Responsibility for the findings at the investigational site and at the sponsor site

In relation to the findings reported at the investigator site, the responsibility is shared between the investigator (42.9%) and the sponsor (32.1%) and 23.9% of the findings have combined sponsor and investigator responsibility (figure 10). The sponsor and CRO are almost fully responsible for the findings at their sites (figure 11).

Figure 10. Responsibility of the findings related to the investigator site

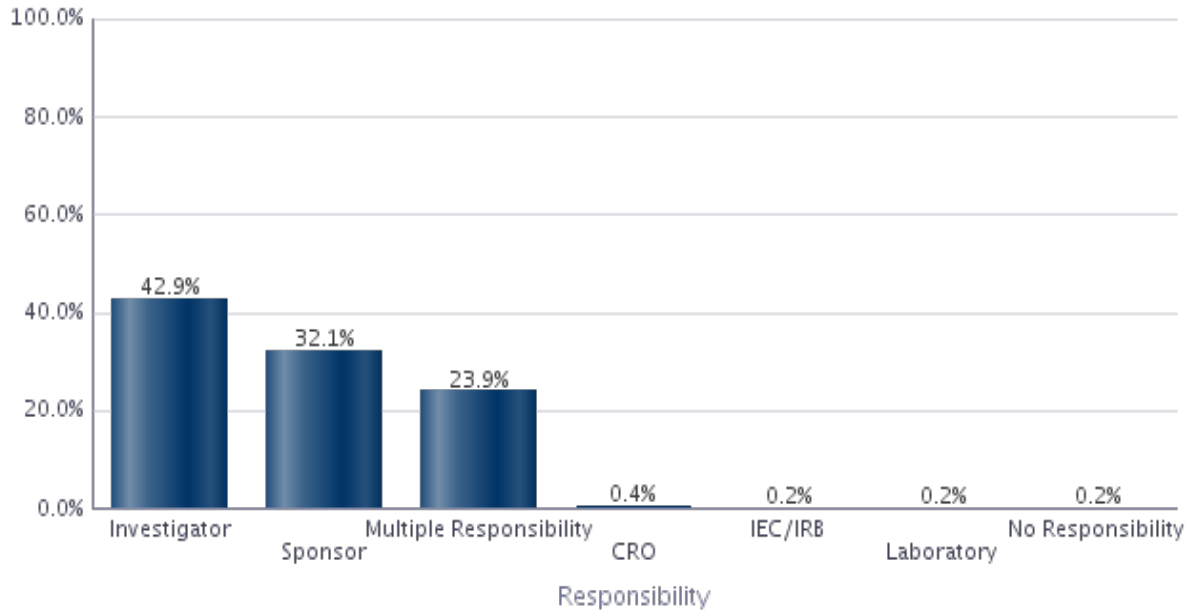
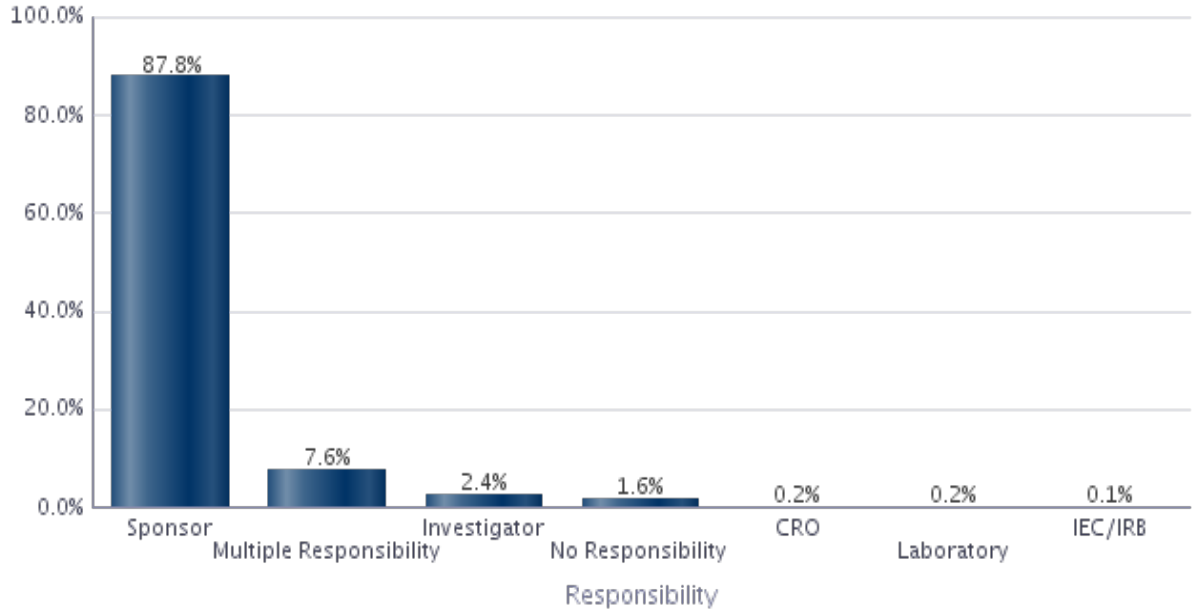


Figure 11. Responsibility of the findings related to the sponsor site



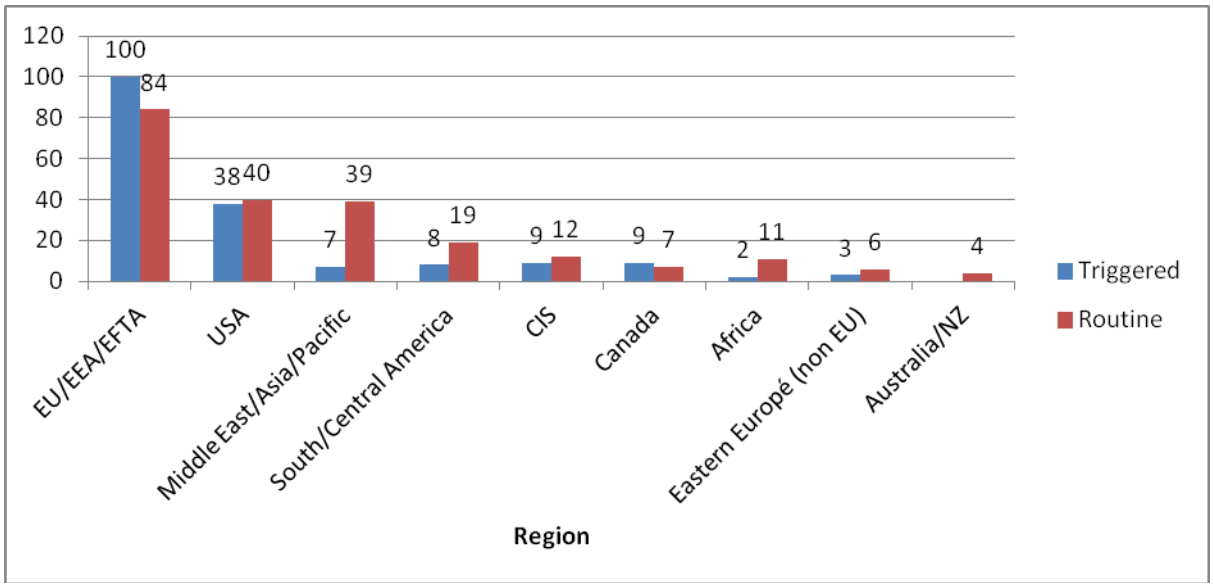
5.2.4. Findings by area of inspections

The classification of the world's areas is in line with the list used in other databases of the Agency:

1. EU/EEA/EFTA: countries of EU, EEA (Iceland, Norway and Liechtenstein) and Switzerland;
2. USA;
3. Middle East/Asia/Pacific;
4. Canada;
5. Commonwealth of Independent States (CIS), e.g.Russia, Ukraine;
6. South/Central America;
7. Africa;
8. Eastern Europe (non EU), (Turkey, Croatia, Serbia etc.);
9. Australia/New Zealand;
10. Japan.

Most of the inspections (65.8%) were conducted in EU/EEA and USA, (figure 12 and table 6). No inspection was carried out in Japan in this period.

Figure 12. Number of inspections by region



The average number of findings per inspection was very similar in all geographical areas (table 6).

Table 6. Average number of findings per geographical area

Country type	No. (%) inspections	No. (%) findings	Average of findings by inspection
EU/EEA/EFTA	184 (46.2%)	2677 (47.1%)	14.5
USA	78 (19.6%)	1091 (19.2%)	14.0
Middle East/Asia/Pacific	46 (11.6%)	555 (9.8%)	12.1
South/Central America	27 (6.8%)	430 (7.6%)	15.9
CIS	21 (5.3%)	317 (5.6%)	15.1
Canada	16 (4.0%)	203 (3.6%)	12.7
Africa	13 (3.3%)	211 (3.7%)	16.2
Eastern Europe (non EU)	9 (2.3%)	146 (2.6%)	16.2
Australia/NZ	4 (1.0%)	55 (1.0%)	13.8
Total	**398 (100%)**	**5685**	**14.5**

The percentage of graded findings in relation to the findings reported in each region is shown in table 7.

Table 7. Percentage of graded findings in relation to the findings reported by region

Region	Grade	No. inspection findings	% graded findings
EU/EEA/EFTA	Critical	243	9.1%
	Major	1309	48.9%
	Minor	1125	42.0%
Total EU/EEA/EFTA		**2677**	**47.1%**
USA	Critical	174	15.9%
	Major	514	47.1%
	Minor	403	36.9%
Total USA		**1091**	**19.2%**
Middle East/Asia/Pacific	Critical	27	4.9%
	Major	218	39.3%
	Minor	310	55.9%
Total Middle East/Asia/Pacific		**555**	**9.8%**
South/Central America	Critical	45	10.5%
	Major	165	38.4%
	Minor	220	51.2%
Total South/Central America		**430**	**7.6%**
CIS	Critical	14	4.4%
	Major	135	42.6%
	Minor	168	53.0%
Total CIS		**317**	**5.6%**
Canada	Critical	4	2.0%
	Major	78	38.4%
	Minor	121	59.6%
Total Canada		**203**	**3.6%**
Africa	Critical	7	3.3%
	Major	100	47.4%
	Minor	104	49.3%
Total Africa		**211**	**3.7%**
Eastern Europe (non EU)	Critical	18	12.3%
	Major	57	39.0%
	Minor	71	48.6%
Total Eastern Europe (non EU)		**146**	**2.6%**
Australia/NZ	Critical	0	0%
	Major	7	12.7%
	Minor	48	87.3%
Total Australia/NZ		**55**	**1.0%**

5.2.4.1. EU/EEA/EFTA

The total number of inspections conducted in the EU/EEA/EFTA area was 184 and a total of 2677 findings were found representing 47.1% of the total findings. The 243 critical findings found were seen in 75 of the 184 inspections and hence 109 inspections did not record any critical finding. Most of the critical findings are related to monitoring, CSR, protocol compliance and data management in relation to sponsor tasks (figure 13), although 68.4% of the inspections were conducted in investigational sites (figure 14). The number of top major findings in the EU/EEA/EFTA is shown in figure 15.

Figure 13. Number of top critical findings by categories in EU/EEA/EFTA

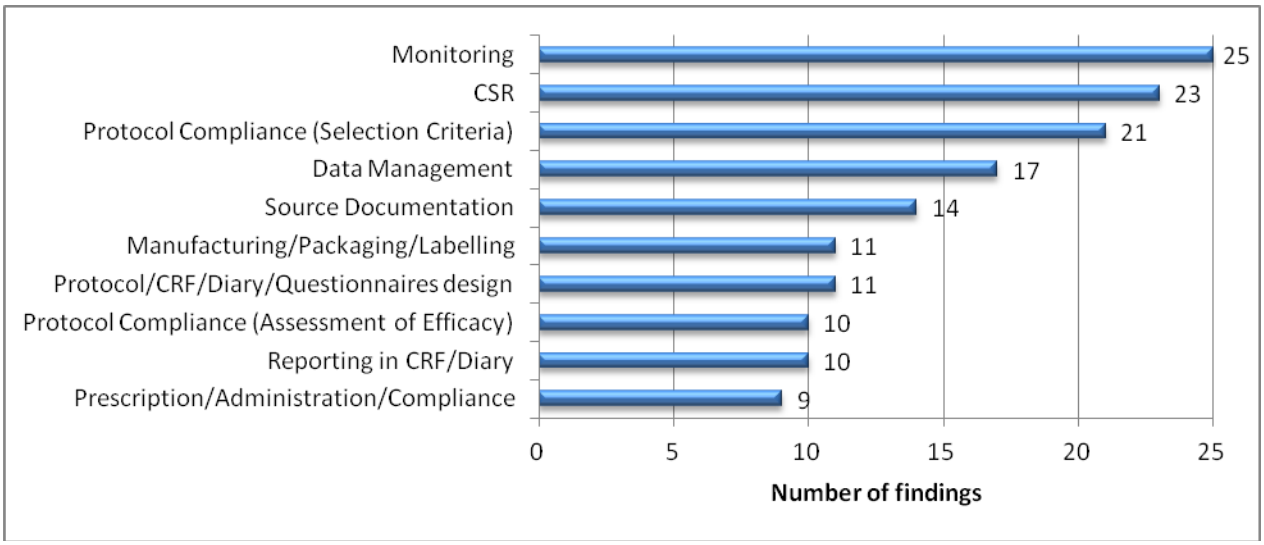


Figure 14. Percentage of sites inspected in EU/EEA/EFTA

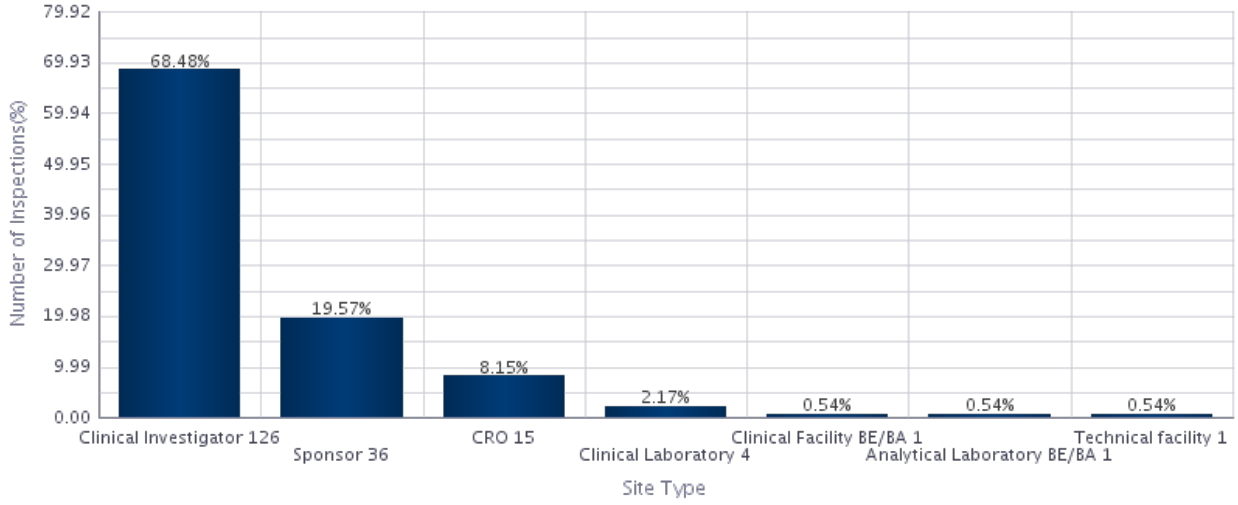
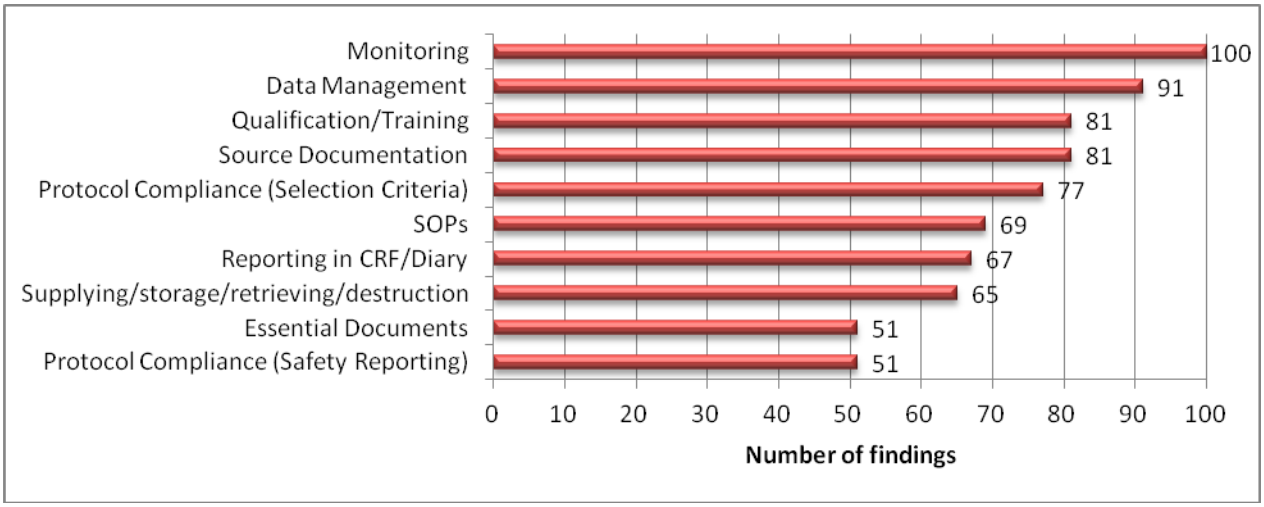


Figure 15. Number of top major findings by categories in EU/EEA/EFTA



5.2.4.2. USA

A total of 78 inspections were conducted in the USA and a total of 1091 findings were found representing 19.2 % of the total findings. The 174 critical findings found were seen in 39 of the 78 inspections and hence 39 inspections did not record any critical finding. Most of the critical findings are related to CSR, data management and monitoring in relation to sponsor tasks (figure 16), although 53.8% of the inspections were conducted at investigational sites (figure 17). The number of top major findings in the USA is shown in figure 18.

Figure 16. Number of top critical findings per categories found in USA

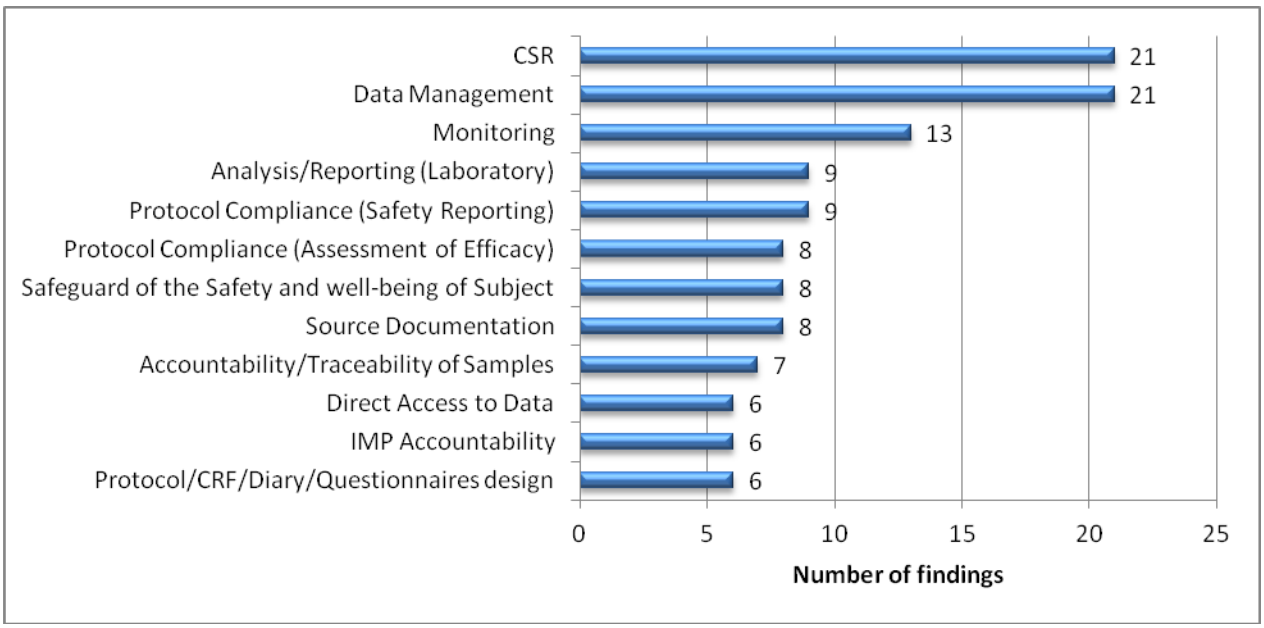


Figure 17. Percentage of sites inspected in USA

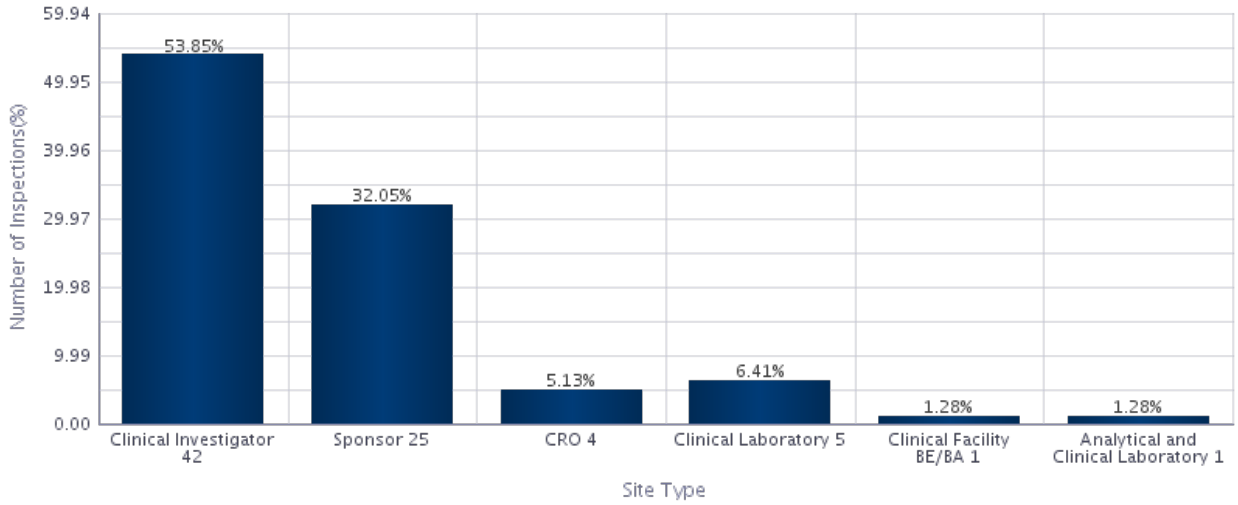
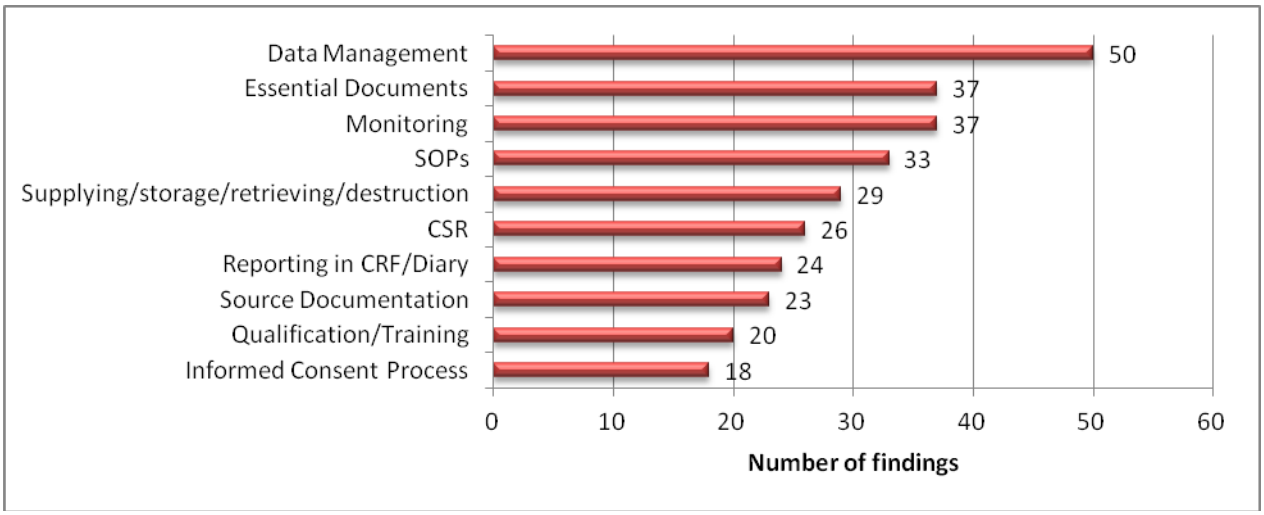


Figure 18. Number of top major findings per categories found in USA



5.2.4.3. Middle East / Asia / Pacific

A total of 46 inspections were conducted in the Middle East/Asia/Pacific and 555 findings were found representing 9.8% of the total findings. The 27 critical findings found were seen in 13 of the 46 inspections and hence 33 inspections did not record any critical finding. Most of the critical findings are related to source documentation, informed consent (IC) and protocol compliance (figure 19). Most inspections in this area were either at investigator's site or BE/BA facilities (figure 20). The number of top major findings in the Middle East/Asia/Pacific is shown in figure 21.

Figure 19. Number of top critical findings per categories found in the Middle East/Asia/Pacific areas

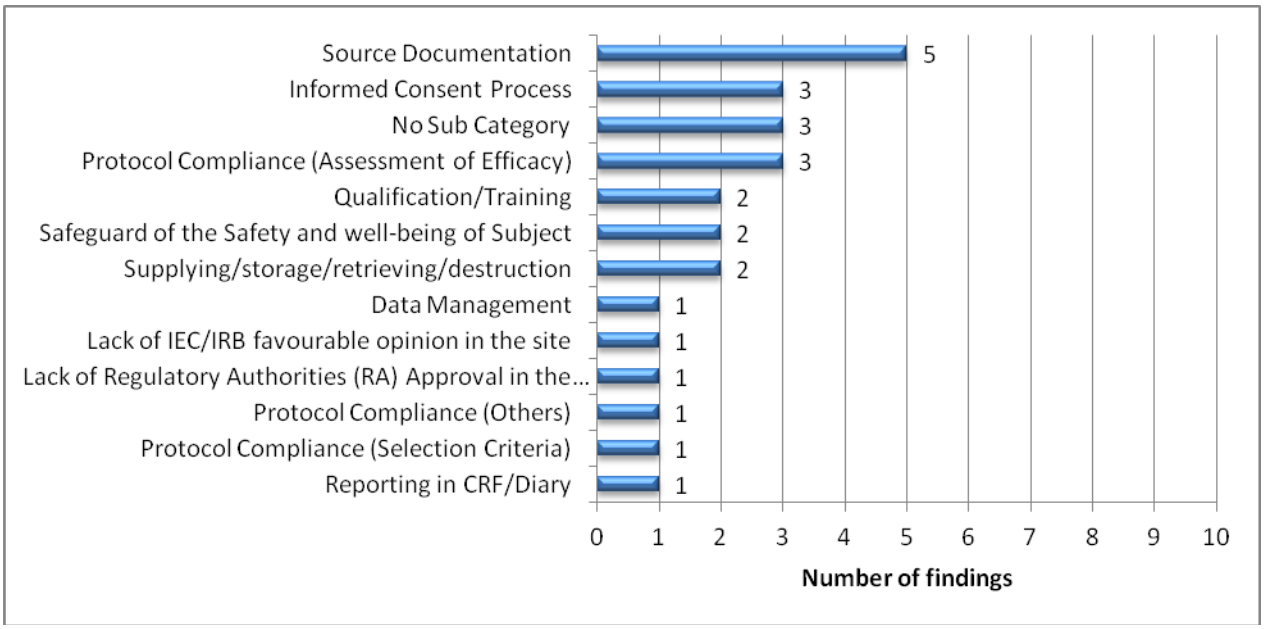


Figure 20. Percentage of sites inspected in Middle East/Asia/Pacific

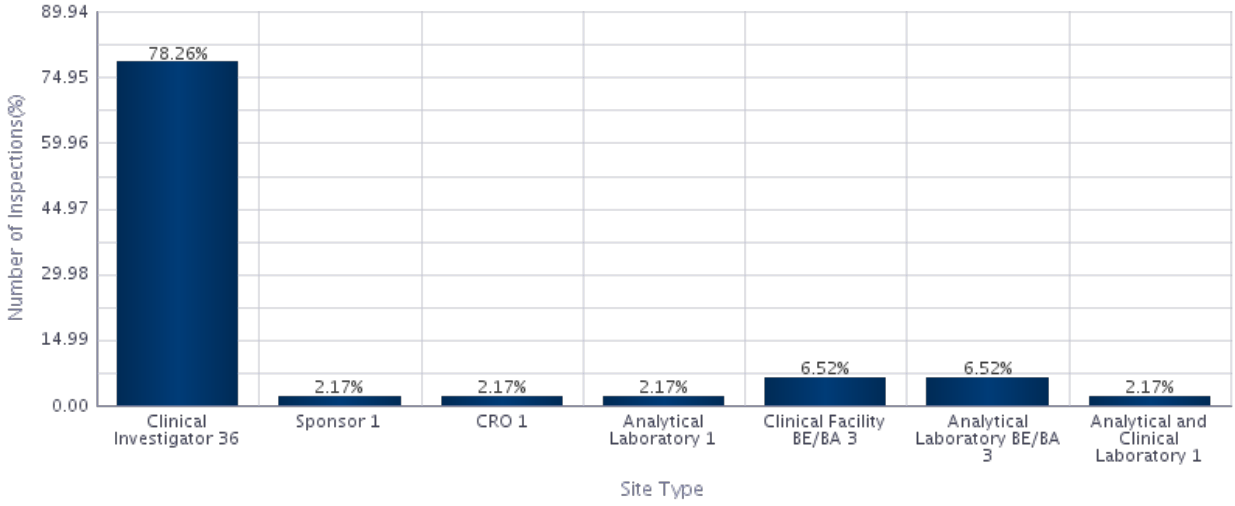
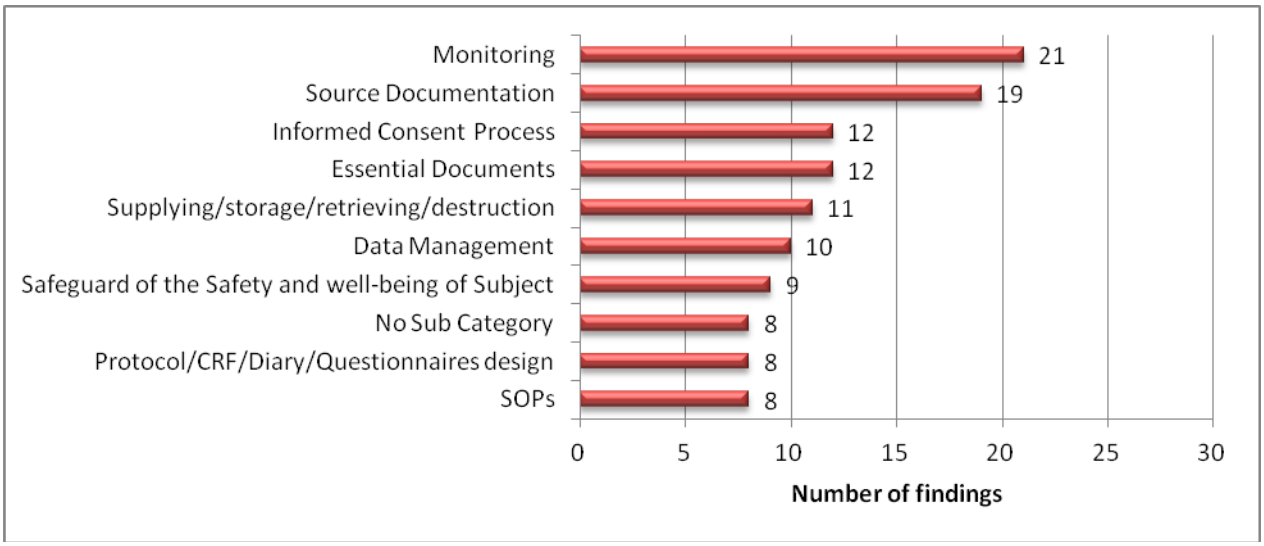


Figure 21. Number of top major findings per categories found in the Middle East/Asia/Pacific areas



5.2.4.4. Canada

In this area only 16 inspections have been carried out, reporting 203 findings, 4.0% of the total findings. Four critical findings were reported in this area in two of the inspected investigational sites (figure 22). In both cases the findings included the CSR and monitoring. All inspections in this area were either at investigator's site or BE/BA facilities (figure 23). The number of top major findings in Canada is shown in figure 24.

Figure 22. Number of critical findings per categories found in Canada

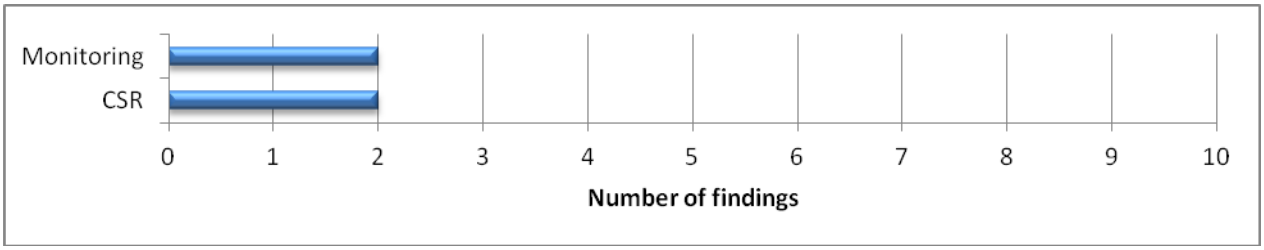


Figure 23. Percentage of sites inspected in Canada

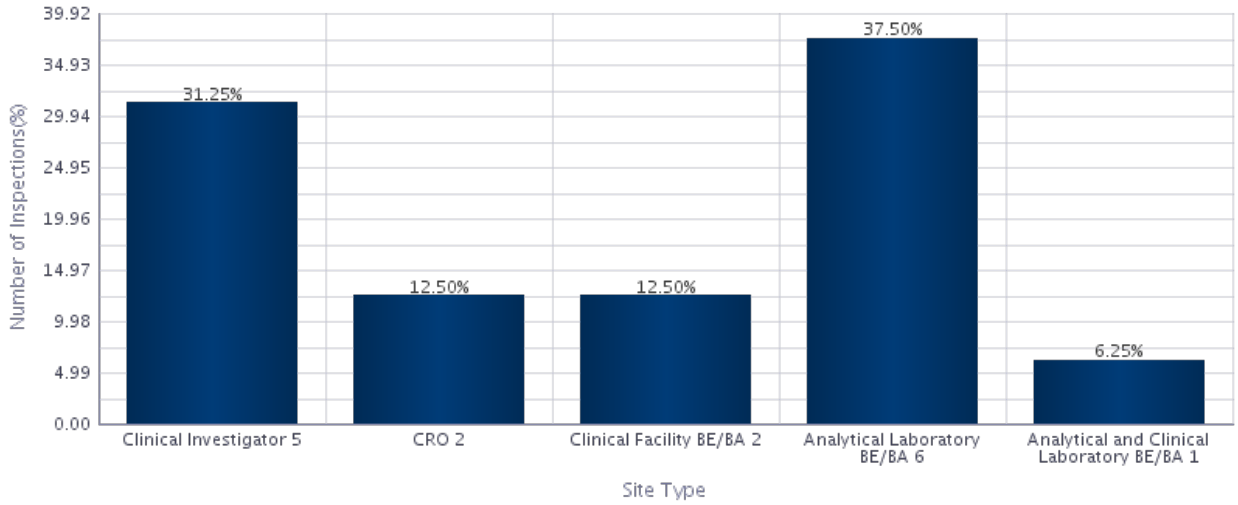
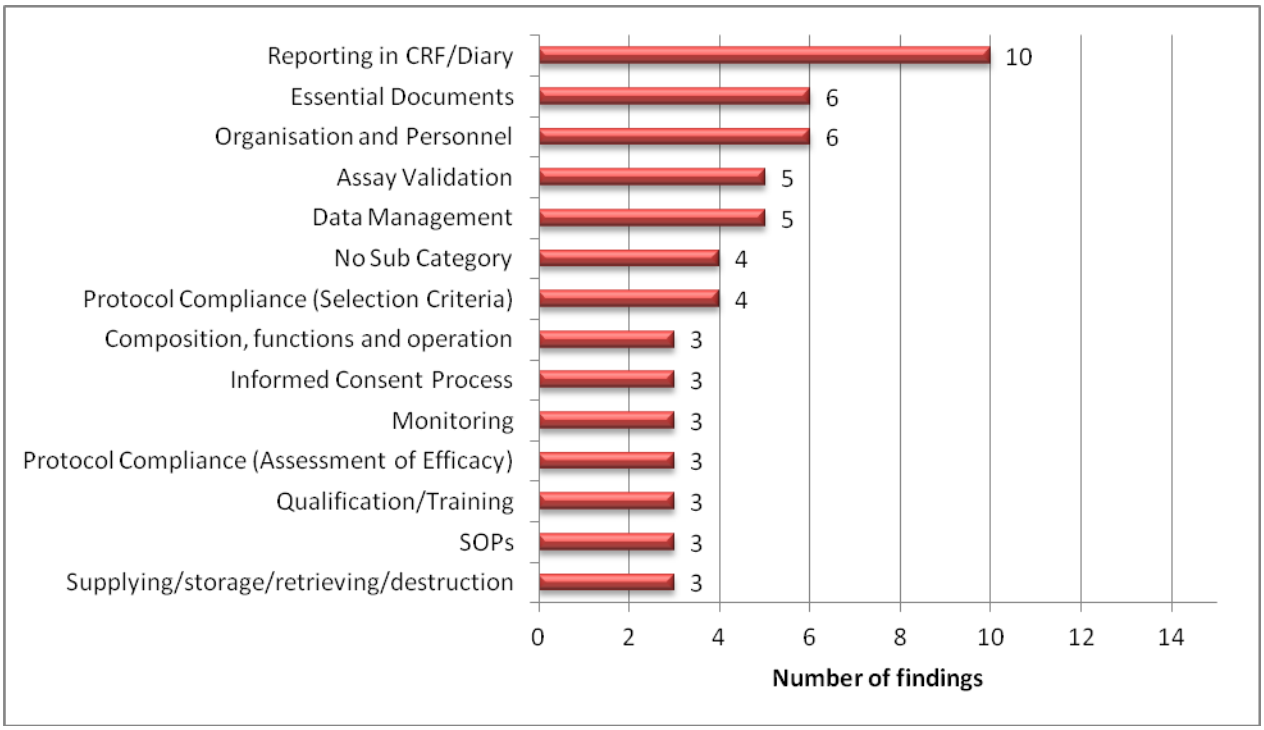


Figure 24. Number of major findings per categories found in Canada



5.2.4.5. Other regions

CIS, Africa, Eastern Europe (non EU), South and Central America and Australia are combined because they have in common that 100% of the inspections conducted in those areas were investigational sites.

5.2.4.5.1. CIS

In this area 317 findings have been reported, 5.6% of the total findings found in the 21 inspections carried out. 14 critical findings were reported in 6 of the inspected investigational sites in this area and hence 15 inspections did not record any critical finding. Most of the critical findings are related to handling of investigational product and training (figure 25). The number of top major findings in CIS is shown in figure 26.

Figure 25. Number of top critical findings per categories found in CIS

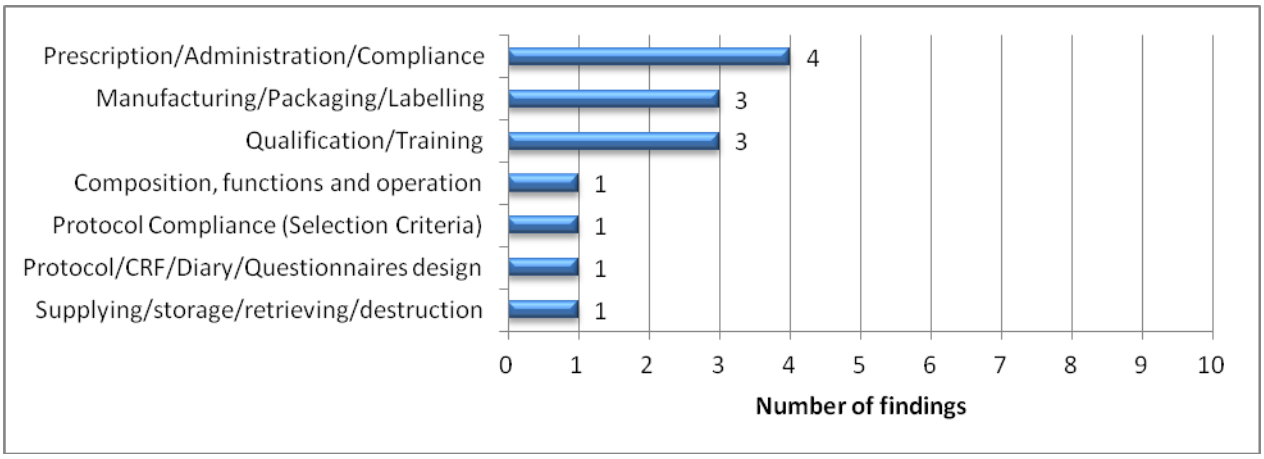
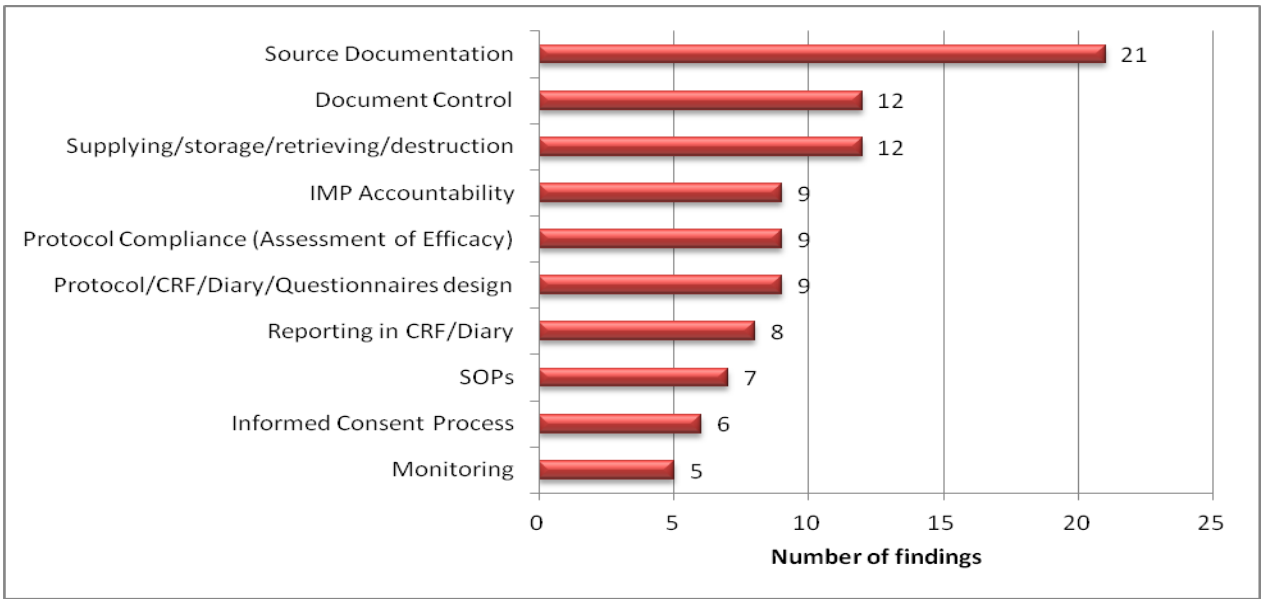


Figure 26. Number of top major findings per categories found in CIS



5.2.4.5.2. Africa

A total of 211 findings (3.7% of the total findings) were identified in the 13 inspections carried out in this area. 7 critical findings were identified in 4 of the inspected sites and hence 9 inspections did not

record any critical finding. Most of the critical findings are related to data management and handling of investigational product (figure 27). The number of top major findings in Africa is shown in figure 28.

Figure 27. Number of top critical findings per categories found in Africa

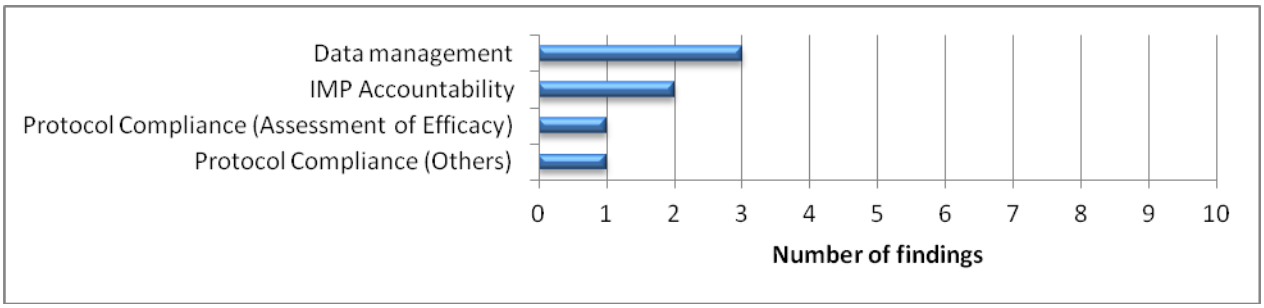
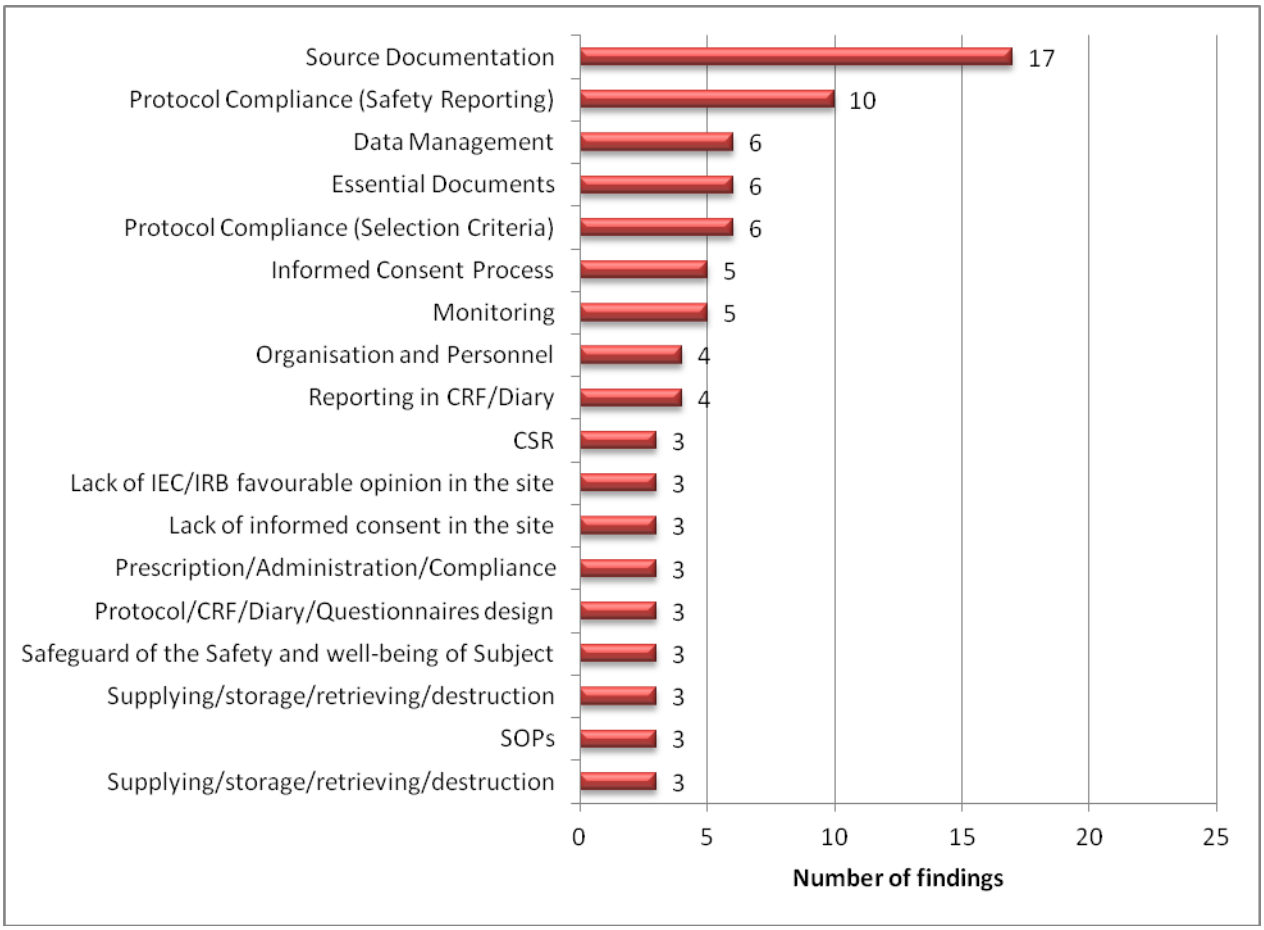


Figure 28. Number of top major findings per categories found in Africa



5.2.4.5.3. South/Central America

In this area 430 findings have been found, 7.6% of the total findings found in the 27 inspections carried out. A total of 45 critical findings were reported in this area in 8 of the inspected investigational sites in this area and hence 19 inspections did not record any critical finding. Most of the critical findings are related to monitoring and data management (figure 29). The number of top major findings in South/Central America is shown in figure 30.

Figure 29. Number of top critical findings by categories found in South/Central America

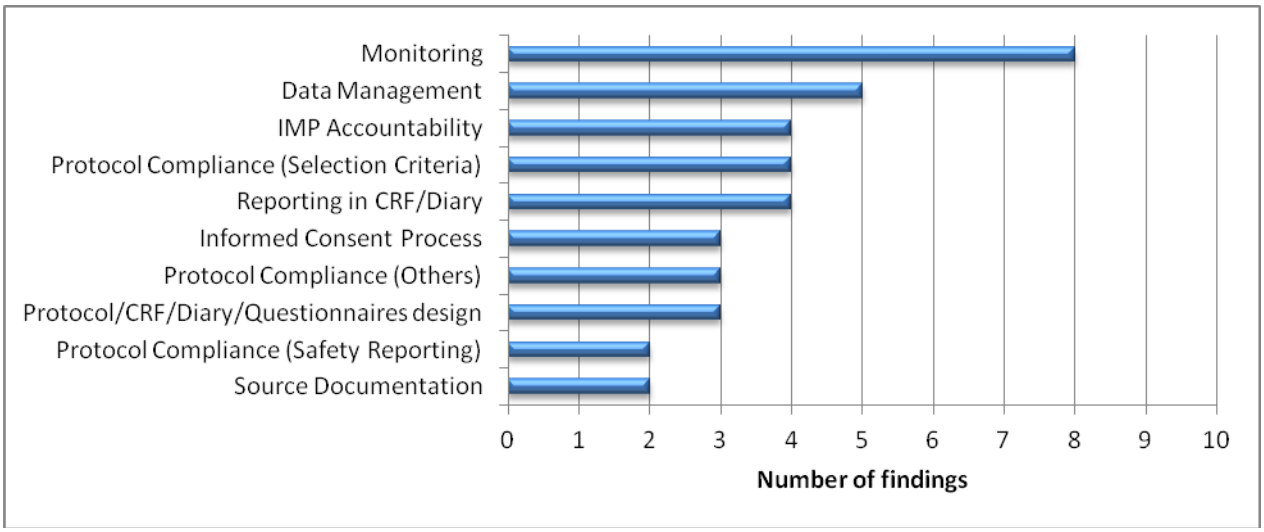
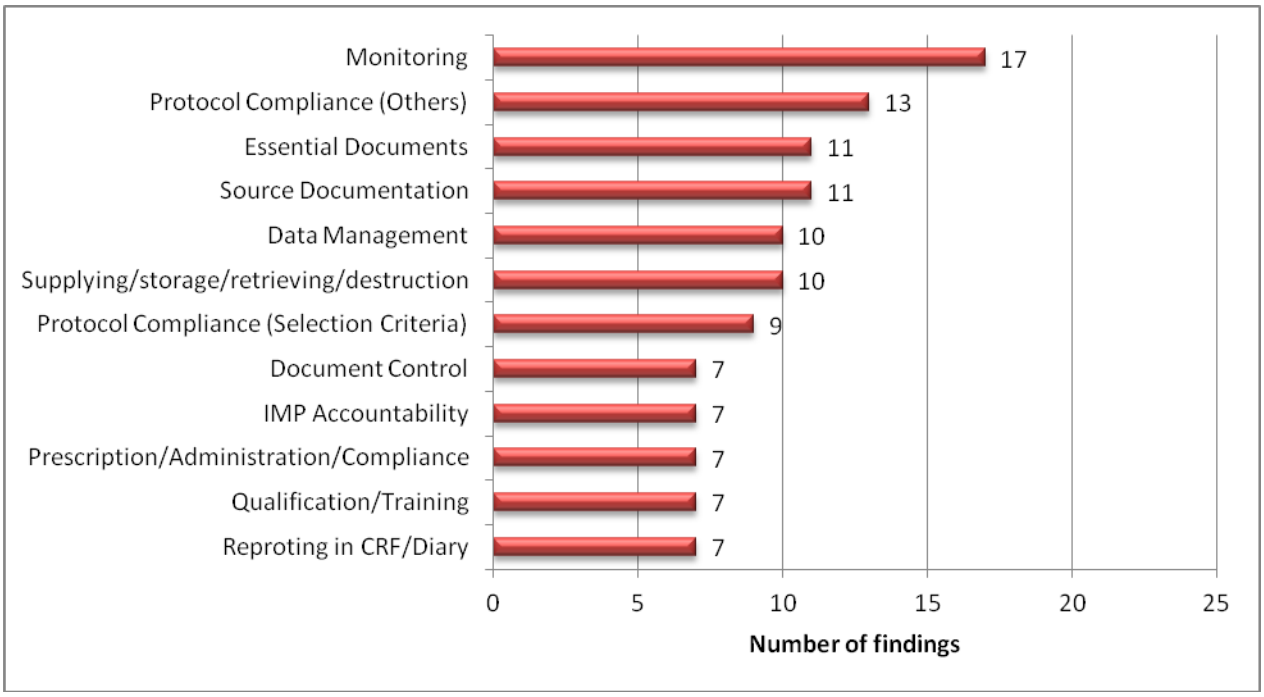


Figure 30. Number of top major findings by categories found in South/Central America



5.2.4.5.4. Eastern Europe (non EU)

A total of 9 inspections have been carried out in this area, reporting 146 findings, 2.6% of the total findings.

A total of 18 critical findings were reported in this area in 4 of the inspected investigational sites in this area and hence 5 inspections did not record any critical finding. Most of the critical findings are related to source documentation (figure 31). The number of top major findings in Eastern Europe is shown in figure 32.

Figure 31. Number of top critical findings by categories found in Easter Europe (non EU)

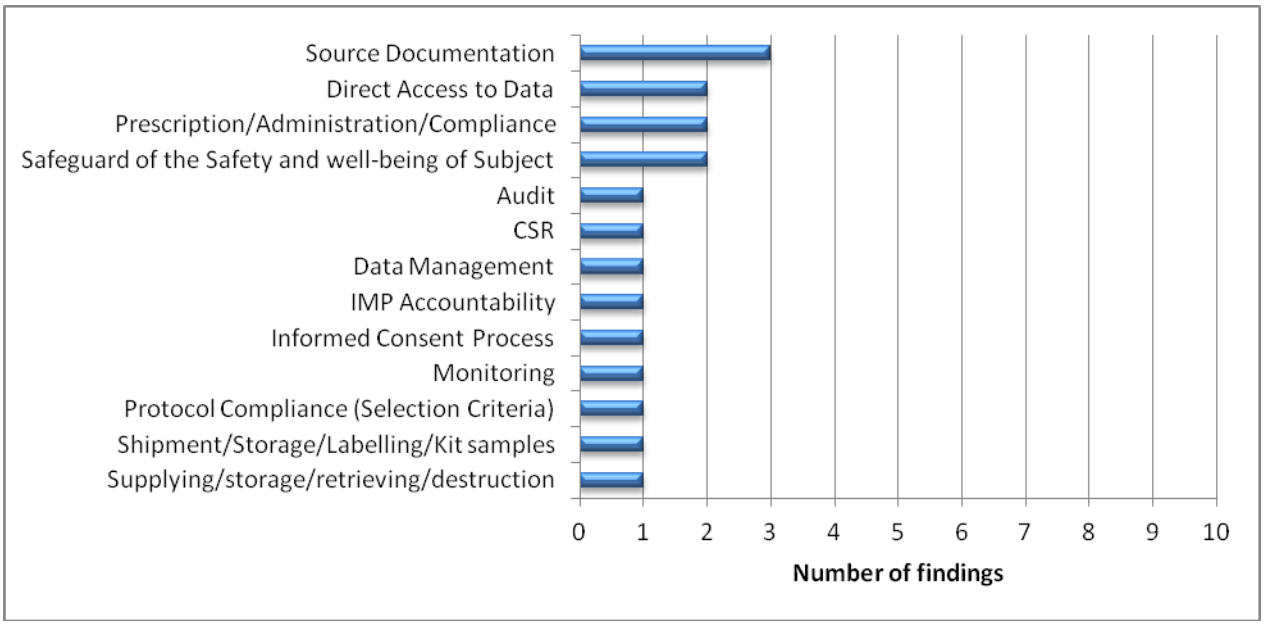
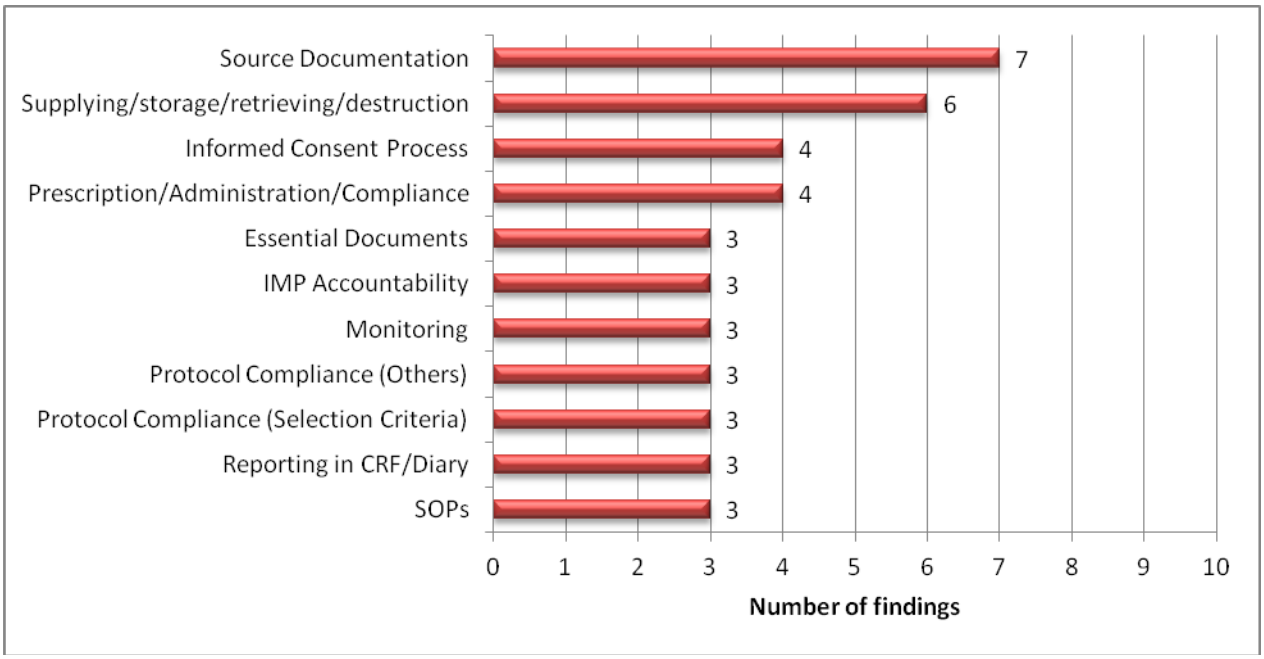


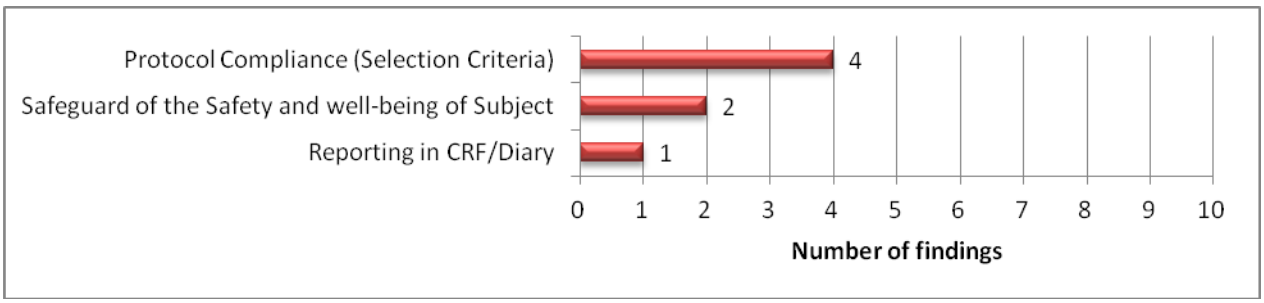
Figure 32. Number of top major findings by categories found in Easter Europe (non EU)



5.2.4.5.5. Australia / New Zealand

A total of 4 inspections have been carried out in this area (all in Australia), reporting 55 findings, 1.0% of the total findings. No critical finding was recorded in this area. The number of top major findings in Australia is shown in figure 33.

Figure 33. Number of top major findings by categories found in Australia



6. Conclusions

The primary purpose of this document is to describe the classification system, some examples of analysis of the inspection findings and the potential value of this system in identifying areas of concern.

- A total of 398 GCP inspections of products from centralised marketing authorisations or their applications (379 pre-approval and 19 post-approval) requested by the CHMP have been conducted from 2000 to 2012.
- During the last 3 years the number of inspections has increased particularly in routine inspections in line with the implementation of the GCP Inspection Policy in 2006.
- Most of the inspections (71.2%) were carried out at the investigational site, followed by the sponsor site (15.5%), CRO (5.5%), clinical laboratories (2.3%) and the sites related to the BE/BA studies (5.1%).
- A total of 5685 findings, comprising 532 critical (9.4%), 2583 major (45.4%) and 2570 minor (45.2%) were recorded during these inspections. More than 80% of the findings are included in four main categories (general, trial management, investigational site and investigational medicinal product).
- Three categories of critical findings account for 27.0% of the total critical findings (CSR, monitoring and data management) which are related to sponsor responsibility, although as mentioned before the majority of inspections were carried out at an investigational site. However, the percentage of critical findings of each individual category finding is lower than 1% of the total findings.
- In the top 10 categories with critical findings found at the investigational site it can be seen that some categories related to the responsibility of the sponsor (monitoring, CSR, and data management).
- In the top 10 categories with critical findings found at the sponsor site, there are categories related to the responsibility of the sponsor (CSR, data management, monitoring).
- The sponsor and CRO are responsible for 43.3% of the total findings although only 15.6 % of the inspections were carried out at the sponsor site and 5.5% at the CRO site.
- Sponsor and CRO are almost fully responsible for the findings at their sites. However, at the investigator site the responsibility is shared between the investigator (42.9%) and the sponsor (32.1%) and 23.9% of the findings have combined sponsor and investigator responsibility.
- Most of inspections (65.8%) were conducted in EU/EEA and USA. No inspections were carried out in Japan or New Zealand in this period.
- All the sites inspected in Africa, CIS, Eastern Europe (non EU) and South/Central America were investigator sites.

The average number of findings per inspection was relatively similar in all parts of the world, ranging from 12.1 to 16.2. Of the 398 inspections conducted 151 inspections had one or more critical findings recorded, or in other words 37.7% of the inspections recorded critical findings. The highest percentage of number of sites with critical findings was reported from the USA (50.0%) followed by Eastern Europe (non EU) with 44.4% and EU/EEA/EFTA with 40.8%. That EU/EEA/EFTA and USA had a high

number of critical findings might be due to the higher number of sponsor inspections, and sponsor inspections are more often triggered inspections.

7. Acknowledgments

We acknowledge that the data presented in this paper were generated by all EU/EEA inspectors who contributed through their valuable work in the centralised procedure to the preparation of this report. The staff of the Clinical and Non-clinical Compliance service at the Agency who has coordinated all the GCP inspections, categorised all the findings and prepared this report are also acknowledged.

8. Annexes

8.1. Annex 1 - List of categories used in Corporate GCP database.

No.	Main categories	References
	IMP	**01**
1	Supply/storage/retrieval/destruction	01.01
2	Prescription/administration/compliance	01.02
3	IMP accountability	01.03
4	Manufacturing/packaging/labelling	01.04
	IC	**02**
5	Lack of IC in the site	02.01
6	IC process	02.02
7	IC form	02.03
	IEC/IRB	**03**
8	Lack of IEC/IRB favourable opinion in the site	03.01
9	Opinion/amendments/notifications to the IEC/IRB	03.02
10	Composition, functions and operation	03.03
	Subject protection	**04**
11	Design of the trial	04.01
12	Personal data protection	04.02
13	Safeguard of the safety and well-being of subject	04.03
14	Insurance/indemnity/compensation to subjects	04.04
15	Payment to trial subjects	04.05
	Regulatory issues	**05**
16	Lack of regulatory authorities (RA) approval at the site	05.01
17	Approval/amendments/notifications to the RA	05.02
18	Manufacturing/importing authorisation	05.03
	Trial management (sponsor)	**06**
19	Protocol/CRF/diary/questionnaires design	06.01
20	Data management	06.02
21	Monitoring	06.03
22	Audit	06.04
23	Document control	06.05
24	Statistical analysis	06.06

No.	Main categories	References
25	CSR	06.07
	Computer system	**07**
26	Computer validation	07.01
27	Audit trail and authorised access	07.02
28	Physical security system and backup	07.03
	Investigational site	**08**
29	Protocol compliance (selection criteria)	08.01
30	Protocol compliance (assessment of efficacy)	08.02
31	Protocol compliance (safety reporting)	08.03
32	Protocol compliance (others)	08.04
33	Reporting in CRF/diary	08.05
	Laboratory / technical facilities	**09**
34	Certification/accreditation	09.01
35	Assay validation	09.02
36	Normal values/ranges/updates	09.03
37	Shipment/storage/labelling/kit samples	09.04
38	Accountability/traceability of samples	09.05
39	Analysis/reporting (laboratory)	09.06
40	Technical validation	09.07
	General	**10**
41	Organisation and personnel	10.01
42	Facilities and equipment	10.02
43	Qualification/training	10.03
44	SOPs	10.04
45	Randomisation/blinding/codes IMP	10.05
46	Source documentation	10.06
47	Essential documents	10.07
48	Direct access to data	10.08
49	Contracts/agreements	10.09
	Others	**11**

8.2. Annex 2 - Number of findings by main category

Rank	Category name	No.	%
1	General	1,786	31.4%
2	Trial management (sponsor)	1,279	22.5%
3	Investigational site	1,038	18.3%
4	IMP	653	11.5%
5	IC	238	4.2%
6	Laboratory/technical facilities	193	3.4%
7	IEC/IRB	177	3.1%
8	Subject protection	129	2.3%
9	Others	78	1.4%

Rank	Category name	No.	%
10	Regulatory issues	77	1.4%
11	Computer system	37	0.7%
Grand total		**5,685**	**100.0%**

8.3. Annex 3 - Ranking of total GCP findings

Deficiency sub-category name	No.	%
Essential documents	461	8.1%
Source documentation	372	6.5%
Reporting in CRF/diary	348	6.1%
Monitoring	344	6.1%
Data management	316	5.6%
Supplying/storage/retrieving/destruction	279	4.9%
Qualification/training	263	4.6%
SOPs	252	4.4%
Protocol compliance (selection criteria)	223	3.9%
Organisation and personnel	222	3.9%
CSR	211	3.7%
IC process	185	3.3%
Protocol compliance (safety reporting)	178	3.1%
Protocol compliance (others)	175	3.1%
IMP accountability	170	3.0%
Protocol/CRF/diary/questionnaires design	163	2.9%
Document control	160	2.8%
Protocol compliance (assessment of efficacy)	114	2.0%
Prescription/administration/compliance	112	2.0%
Opinion/amendments/notifications to the IEC/IRB	105	1.8%
Contracts/agreements	99	1.7%
Manufacturing/packaging/labelling	92	1.6%
Safeguard of the safety and well-being of subject	85	1.5%
No sub-category	78	1.4%
Approval/amendments/notifications to the RA	62	1.1%
Randomisation/blinding/codes IMP	61	1.1%
Audit	51	0.9%
Analysis/reporting (laboratory)	49	0.9%
IC Form	44	0.8%
Shipment/storage/labelling/kit samples	44	0.8%
Facilities and equipment	43	0.8%
Assay validation	42	0.7%
Lack of IEC/IRB favourable opinion in the site	40	0.7%
Statistical analysis	34	0.6%
Composition, functions and operation	32	0.6%
Certification/accreditation	30	0.5%
Personal data protection	19	0.3%

Deficiency sub-category name	No.	%
Computer validation	18	0.3%
Audit trail and authorised access	17	0.3%
Insurance/indemnity/compensation to subjects	15	0.3%
Direct access to data	13	0.2%
Accountability/traceability of samples	11	0.2%
Design of the trial	10	0.2%
Lack of IC in the site	9	0.2%
Normal values/ranges/updates	9	0.2%
Manufacturing/importing authorisation	8	0.1%
Technical validation	8	0.1%
Lack of regulatory authorities (RA) approval in the site	7	0.1%
Physical security system and backup	2	0.0%
Grand total	**5,685**	**100.0%**

8.4. Annex 4 - Total number of findings by category and grading at investigational sites

Deficiency category name	Deficiency sub-category name	No. critical deficiencies	% Critical inspected deficiencies	No. major deficiencies	% Major inspected deficiencies	No. minor deficiencies	% Minor inspected deficiencies	No. deficiencies
Computer system	Audit trail and authorised access			3	60.0%	2	40.0%	5
Computer system	Computer validation					2	100.0%	2
Computer system	Physical security system and backup			1	100.0%			1
Computer system total				**4**	**50.0%**	**4**	**50.0%**	**8**
General	Contracts/agreements			17	44.7%	21	55.3%	38
General	Direct access to data	3	60.0%	2	40.0%			5
General	Essential documents	7	1.8%	88	23.2%	285	75.0%	380
General	Facilities and equipment			16	44.4%	20	55.6%	36
General	Organisation and personnel	5	2.7%	44	23.5%	138	73.8%	187
General	Qualification/training	5	3.2%	70	44.3%	83	52.5%	158
General	Randomisation/blinding/ codes IMP	2	5.3%	22	57.9%	14	36.8%	38
General	SOPs	1	1.0%	43	43.0%	56	56.0%	100
General	Source documentation	22	6.7%	163	49.8%	142	43.4%	327
General total		**45**	**3.5%**	**465**	**36.6%**	**759**	**59.8%**	**1,269**
IEC/IRB	Composition, functions and operation	2	8.7%	5	21.7%	16	69.6%	23
IEC/IRB	Lack of IEC/IRB favourable opinion in	3	10.7%	16	57.1%	9	32.1%	28

Deficiency category name	Deficiency sub-category name	No. critical deficiencies	% Critical inspected deficiencies	No. major deficiencies	% Major inspected deficiencies	No. minor deficiencies	% Minor inspected deficiencies	No. deficiencies
	the site							
IEC/IRB	Opinion/amendments/ notifications to the IEC/IRB	7	8.8%	41	51.3%	32	40.0%	80
IEC/IRB total		**12**	**9.2%**	**62**	**47.3%**	**57**	**43.5%**	**131**
IC	IC form	4	11.1%	13	36.1%	19	52.8%	36
IC	IC Process	10	5.7%	78	44.3%	88	50.0%	176
IC	Lack of IC in the site	1	11.1%	4	44.4%	4	44.4%	9
IC total		**15**	**6.8%**	**95**	**43.0%**	**111**	**50.2%**	**221**
IMP	IMP accountability	13	8.7%	62	41.3%	75	50.0%	150
IMP	Manufacturing/ packaging/labelling	5	11.6%	25	58.1%	13	30.2%	43
IMP	Prescription/ administration/ compliance	18	16.8%	63	58.9%	26	24.3%	107
IMP	Supplying/storage/ retrieving/destruction	9	3.9%	116	50.0%	107	46.1%	232
IMP total		**45**	**8.5%**	**266**	**50.0%**	**221**	**41.5%**	**532**
Investigational site	Protocol compliance (assessment of efficacy)	23	20.5%	65	58.0%	24	21.4%	112
Investigational site	Protocol compliance (others)	8	4.8%	76	46.1%	81	49.1%	165
Investigational site	Protocol compliance (safety reporting)	17	10.4%	81	49.4%	66	40.2%	164
Investigational site	Protocol compliance (selection criteria)	31	14.8%	123	58.6%	56	26.7%	210

Deficiency category name	Deficiency sub-category name	No. critical deficiencies	% Critical inspected deficiencies	No. major deficiencies	% Major inspected deficiencies	No. minor deficiencies	% Minor inspected deficiencies	No. deficiencies
Investigational Site	Reporting in CRF/diary	17	5.1%	123	36.6%	196	58.3%	336
Investigational site total		**96**	**9.7%**	**468**	**47.4%**	**423**	**42.9%**	**987**
Laboratory/ technical facilities	Accountability/ traceability of samples					3	100.0%	3
Laboratory/ technical facilities	Analysis/reporting (laboratory)			6	54.5%	5	45.5%	11
Laboratory/ Technical Facilities	Assay validation	1	20.0%	1	20.0%	3	60.0%	5
Laboratory/ technical facilities	Certification/ accreditation			2	7.1%	26	92.9%	28
Laboratory/ technical facilities	Normal values/ranges/updates			1	11.1%	8	88.9%	9
Laboratory/ technical facilities	Shipment/storage/ labelling/kit samples	1	3.6%	15	53.6%	12	42.9%	28
Laboratory/ technical facilities	Technical validation					3	100.0%	3
Laboratory/ technical facilities total		**2**	**2.3%**	**25**	**28.7%**	**60**	**69.0%**	**87**
Others	No sub-category	2	7.4%	11	40.7%	14	51.9%	27
Others total		**2**	**7.4%**	**11**	**40.7%**	**14**	**51.9%**	**27**
Regulatory issues	Approval/amendments/ notifications to the RA	3	6.4%	17	36.2%	27	57.4%	47
Regulatory issues	Lack of RA approval in the site	1	16.7%	3	50.0%	2	33.3%	6

Deficiency category name	Deficiency sub-category name	No. critical deficiencies	% Critical inspected deficiencies	No. major deficiencies	% Major inspected deficiencies	No. minor deficiencies	% Minor inspected deficiencies	No. deficiencies
Regulatory issues	Manufacturing/ importing authorisation			3	42.9%	4	57.1%	7
Regulatory issues total		**4**	**6.7%**	**23**	**38.3%**	**33**	**55.0%**	**60**
Subject protection	Design of the trial	2	25.0%	6	75.0%			8
Subject protection	Insurance/indemnity/ compensation to subjects			1	8.3%	11	91.7%	12
Subject protection	Personal data protection	3	23.1%	5	38.5%	5	38.5%	13
Subject protection	Safeguard of the safety and well-being of subject	9	13.8%	43	66.2%	13	20.0%	65
Subject protection total		**14**	**14.3%**	**55**	**56.1%**	**29**	**29.6%**	**98**
Trial management (Sponsor)	Audit	3	33.3%	2	22.2%	4	44.4%	9
Trial management (Sponsor)	CSR	18	16.1%	52	46.4%	42	37.5%	112
Trial management (Sponsor)	Data management	19	15.0%	70	55.1%	38	29.9%	127
Trial management (Sponsor)	Document control	2	1.9%	40	38.8%	61	59.2%	103
Trial management (Sponsor)	Monitoring	31	13.7%	123	54.4%	72	31.9%	226
Trial management (Sponsor)	Protocol/CRF/diary/questionnaires design	13	12.5%	54	51.9%	37	35.6%	104

Deficiency category name	Deficiency sub-category name	No. critical deficiencies	% Critical inspected deficiencies	No. major deficiencies	% Major inspected deficiencies	No. minor deficiencies	% Minor inspected deficiencies	No. deficiencies
Trial management (Sponsor)	Statistical analysis			2	50.0%	2	50.0%	4
Trial management (Sponsor) total		**86**	**12.6%**	**343**	**50.1%**	**256**	**37.4%**	**685**
Grand total		**321**	**7.8%**	**1,817**	**44.3%**	**1,967**	**47.9%**	**4,105**

8.5. Annex 5 - Ranking of findings at investigational sites

Deficiency sub-category name	No.	%
Essential documents	380	9.3%
Reporting in CRF/diary	336	8.2%
Source documentation	327	8.0%
Supplying/storage/retrieving/destruction	232	5.7%
Monitoring	226	5.5%
Protocol compliance (selection criteria)	210	5.1%
Organisation and personnel	187	4.6%
IC process	176	4.3%
Protocol compliance (others)	165	4.0%
Protocol compliance (safety reporting)	164	4.0%
Qualification/training	158	3.8%
IMP accountability	150	3.7%
Data management	127	3.1%
CSR	112	2.7%
Protocol compliance (assessment of efficacy)	112	2.7%
Prescription/administration/compliance	107	2.6%
Protocol/CRF/diary/questionnaires design	104	2.5%
Document control	103	2.5%
SOPs	100	2.4%
Opinion/amendments/notifications to the IEC/IRB	80	1.9%
Safeguard of the safety and well-being of subject	65	1.6%
Approval/amendments/notifications to the RA	47	1.1%
Manufacturing/packaging/labelling	43	1.0%
Contracts/agreements	38	0.9%
Randomisation/blinding/codes IMP	38	0.9%
Facilities and equipment	36	0.9%
IC form	36	0.9%
Certification/accreditation	28	0.7%
Lack of IEC/IRB favourable opinion in the site	28	0.7%
Shipment/storage/labelling/kit samples	28	0.7%
No sub-category	27	0.7%
Composition, functions and operation	23	0.6%
Personal data protection	13	0.3%
Insurance/indemnity/compensation to subjects	12	0.3%
Analysis/reporting (laboratory)	11	0.3%
Audit	9	0.2%
Lack of IC in the site	9	0.2%
Normal values/ranges/updates	9	0.2%
Design of the trial	8	0.2%
Manufacturing/importing authorisation	7	0.2%
Lack of RA approval in the site	6	0.1%

Deficiency sub-category name	No.	%
Assay validation	5	0.1%
Audit trail and authorised access	5	0.1%
Direct access to data	5	0.1%
Statistical analysis	4	0.1%
Accountability/traceability of samples	3	0.1%
Technical validation	3	0.1%
Computer Validation	2	0.0%
Physical security system and backup	1	0.0%
Grand total	**4,105**	**100.0%**

8.6. Annex 6 - Total number of findings by category and grading at sponsor sites

Deficiency category name	Deficiency sub-category name	% Critical inspected deficiencies	No. critical deficiencies	% Major inspected deficiencies	No. major deficiencies	% Minor inspected deficiencies	No. minor deficiencies	No. deficiencies
Computer system	Audit trail and authorised access			5	71.4%	2	28.6%	7
Computer system	Computer validation	1	20.0%	3	60.0%	1	20.0%	5
Computer system total		**1**	**8.3%**	**8**	**66.7%**	**3**	**25.0%**	**12**
General	Contracts/ agreements			24	54.5%	20	45.5%	44
General	Direct access to data	6	100.0%					6
General	Essential documents	2	4.3%	22	47.8%	22	47.8%	46
General	Facilities and equipment			2	100.0%			2
General	Organisation and personnel	1	5.6%	9	50.0%	8	44.4%	18
General	Qualification/training	1	1.7%	29	48.3%	30	50.0%	60
General	Randomisation/ blinding/codes IMP	4	23.5%	8	47.1%	5	29.4%	17
General	SOPs	2	2.2%	49	55.1%	38	42.7%	89
General	Source documentation	2	13.3%	5	33.3%	8	53.3%	15
General total		**18**	**6.1%**	**148**	**49.8%**	**131**	**44.1%**	**297**
IEC/IRB	Composition, functions and					3	100.0%	3

Deficiency category name	Deficiency sub-category name	% Critical inspected deficiencies	No. critical deficiencies	% Major inspected deficiencies	No. major deficiencies	% Minor inspected deficiencies	No. minor deficiencies	No. deficiencies
	operation							
IEC/IRB	Lack of IEC/IRB favourable opinion in the site	1	12.5%	5	62.5%	2	25.0%	8
IEC/IRB	Opinion/ amendments/ notifications to the IEC/IRB	2	11.8%	7	41.2%	8	47.1%	17
IEC/IRB total		**3**	**10.7%**	**12**	**42.9%**	**13**	**46.4%**	**28**
IC	IC Form			2	50.0%	2	50.0%	4
IC	IC Process			2	66.7%	1	33.3%	3
IC total				**4**	**57.1%**	**3**	**42.9%**	**7**
IMP	IMP Accountability	4	30.8%	7	53.8%	2	15.4%	13
IMP	Manufacturing/ packaging/labelling	5	18.5%	15	55.6%	7	25.9%	27
IMP	Prescription/ administration/ compliance			3	75.0%	1	25.0%	4
IMP	Supplying/storage/ retrieving/destruction	5	15.2%	17	51.5%	11	33.3%	33
IMP total		**14**	**18.2%**	**42**	**54.5%**	**21**	**27.3%**	**77**
Investigational site	Protocol compliance (others)			1	33.3%	2	66.7%	3
Investigational site	Protocol compliance (safety reporting)	1	9.1%	6	54.5%	4	36.4%	11
Investigational	Protocol compliance	1	16.7%	4	66.7%	1	16.7%	6

Deficiency category name	Deficiency sub-category name	% Critical inspected deficiencies	No. critical deficiencies	% Major inspected deficiencies	No. major deficiencies	% Minor inspected deficiencies	No. minor deficiencies	No. deficiencies
site	(selection criteria)							
Investigational site	Reporting in CRF/diary			4	57.1%	3	42.9%	7
Investigational site total		**2**	**7.4%**	**15**	**55.6%**	**10**	**37.0%**	**27**
Laboratory/ technical facilities	Accountability/ traceability of samples	1	100.0%					1
Laboratory/ technical facilities	Analysis/reporting (laboratory)			5	83.3%	1	16.7%	6
Laboratory/ technical facilities	Assay validation			3	75.0%	1	25.0%	4
Laboratory/ technical facilities	Shipment/storage/ labelling/kit samples			1	100.0%			1
Laboratory/ technical facilities total		**1**	**8.3%**	**9**	**75.0%**	**2**	**16.7%**	**12**
Others	No sub-category	1	6.7%	6	40.0%	8	53.3%	15
Others Total		**1**	**6.7%**	**6**	**40.0%**	**8**	**53.3%**	**15**
Regulatory issues	Approval/ amendments/ notifications to the RA	2	18.2%	3	27.3%	6	54.5%	11
Regulatory issues	Lack of RA approval in the site					1	100.0%	1
Regulatory issues	Manufacturing/					1	100.0%	1

Deficiency category name	Deficiency sub-category name	% Critical inspected deficiencies	No. critical deficiencies	% Major inspected deficiencies	No. major deficiencies	% Minor inspected deficiencies	No. minor deficiencies	No. deficiencies
	importing authorisation							
Regulatory issues total		**2**	**15.4%**	**3**	**23.1%**	**8**	**61.5%**	**13**
Subject protection	Personal data protection	2	40.0%	2	40.0%	1	20.0%	5
Subject protection	Safeguard of the safety and well-being of subject	5	50.0%	5	50.0%			10
Subject protection total		**7**	**46.7%**	**7**	**46.7%**	**1**	**6.7%**	**15**
Trial management (sponsor)	Audit	1	5.6%	9	50.0%	8	44.4%	18
Trial management (sponsor)	CSR	27	34.6%	28	35.9%	23	29.5%	78
Trial management (sponsor)	Data management	21	16.9%	68	54.8%	35	28.2%	124
Trial management (sponsor)	Document control	2	5.7%	11	31.4%	22	62.9%	35
Trial management (sponsor)	Monitoring	15	16.3%	48	52.2%	29	31.5%	92
Trial management (sponsor)	Protocol/CRF/diary/ questionnaires design	7	18.4%	26	68.4%	5	13.2%	38
Trial management (sponsor)	Statistical Analysis	6	25.0%	7	29.2%	11	45.8%	24
Trial		**79**	**19.3%**	**197**	**48.2%**	**133**	**32.5%**	**409**

Deficiency category name	Deficiency sub-category name	% Critical inspected deficiencies	No. critical deficiencies	% Major inspected deficiencies	No. major deficiencies	% Minor inspected deficiencies	No. minor deficiencies	No. deficiencies
management (sponsor) total								
Grand total		128	14.0%	451	49.5%	333	36.5%	912

8.7. Annex 7 - Ranking of findings at sponsor sites

Deficiency sub-category name	No.	%
Data management	124	13.6%
Monitoring	92	10.1%
SOPs	89	9.8%
CSR	78	8.6%
Qualification/training	60	6.6%
Essential documents	46	5.0%
Contracts/agreements	44	4.8%
Protocol/CRF/diary/questionnaires design	38	4.2%
Document control	35	3.8%
Supplying/storage/retrieving/destruction	33	3.6%
Manufacturing/packaging/labelling	27	3.0%
Statistical analysis	24	2.6%
Audit	18	2.0%
Organisation and personnel	18	2.0%
Opinion/amendments/notifications to the IEC/IRB	17	1.9%
Randomisation/blinding/codes IMP	17	1.9%
No sub-category	15	1.6%
Source documentation	15	1.6%
IMP accountability	13	1.4%
Approval/amendments/notifications to the RA	11	1.2%
Protocol compliance (safety reporting)	11	1.2%
Safeguard of the safety and well-being of subject	10	1.1%
Lack of IEC/IRB favourable opinion in the site	8	0.9%
Audit trail and authorised access	7	0.8%
Reporting in CRF/diary	7	0.8%
Analysis/reporting (laboratory)	6	0.7%
Direct access to data	6	0.7%
Protocol compliance (selection criteria)	6	0.7%
Computer validation	5	0.5%
Personal data protection	5	0.5%
Assay validation	4	0.4%
IC form	4	0.4%
Prescription/administration/compliance	4	0.4%
Composition/functions and operation	3	0.3%
IC process	3	0.3%
Protocol compliance (others)	3	0.3%
Facilities and equipment	2	0.2%
Accountability/traceability of samples	1	0.1%
Lack of RA approval in the site	1	0.1%
Manufacturing/importing authorisation	1	0.1%
Shipment/storage/labelling/kit samples	1	0.1%
Grand total	**912**	**100.0%**