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SCIENCE MEDICINES HEALTH

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Compliance and Inspection

Annual report of the Good Clinical Practice Inspectors Working Group 2010

Adopted by the GCP IWG on 20 June 2012

The publication of this report has been delayed due to the migration of inspection data to our new database and the creation of our reporting tool to retrieve the statistics included in this report.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8595
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

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1. Introduction

This document is the third annual report of the GCP IWG[1]. This group was established in 1997 under the scope of Article 57(1)(i) of Regulation (EC) No. 726/2004.

The GCP IWG focuses on harmonisation and co-ordination of GCP related activities at Community level. The group's role and activities are described in more detail in its Mandate and Workplan and also in Volume 10, Chapter IV, of the Rules Governing Medicinal Products in the European Union. The group supports the co-ordination of the provision of GCP advice and maintains a dialogue with other groups such as CHMP[2], CVMP[3], PhV WP[4], CMD[5,] GMDP[6] IWG and other groups, as needed, on areas of common interest.

This annual report is set out in line with the format and objectives of the 2010 Workplan.

2. Meetings

The plenary GCP IWG took place on: 24 – 25 Feb 2010, 09 – 10 June 2010, 08 – 09 Sep 2010 and 01 – 03 Dec 2010. During 2010, the following GCP inspectors' subgroups were involved in the discussion of specific topics and drafting documents:

- GCP/CMD(h) (refer to section 7.4)
- GCP Computer Systems (refer to section 5, 1st bullet point)
- CTFG GCP Risk Based Quality Management (refer to section 7.3)

A joint meeting with CHMP clinical assessors took place on 2 December (refer to section 4.2a).

Delegates from this group are also involved in the Agency's multidisciplinary working group on 3rd country clinical trials (refer to section 7.6). A workshop with all stakeholders took place on 6-7 September 2010.

3. Inspections conducted in support of the centralised procedure and under national programmes

3.1. CHMP requested inspections

3.1.1. General overview

The CHMP requested 63 inspections in 2010 and 69 inspections were carried out by the inspectorates of the EU member states in the same year. The number of CHMP requested and conducted inspections is not consistent due to the fact that several inspections requested in the last 3 months of the year 2009 have been conducted in 2010 and some inspections requested in the last 3 months of 2010 will be carried out in 2011. The data in this report relates to inspections carried out..

In figure 1, the number of inspections carried out in 2010 is shown by region and type of inspection. Most inspections were carried out in the EU/EEA[10] (48%) followed by inspections in the USA (16%) and The Middle East/Asia/Pacific (10%).

Figure 1: Inspections conducted per region and type of inspection.

[1] Good Clinical Practice Inspectors Working Group
[2] Committee for Medicinal Products for Human Use
[3] Committee for Medicinal Products for Veterinary Use
[4] Pharmacovigilance Working Party
[5] Co-ordination Group for Mutual Recognition and Decentralised Procedures
[6] Good Manufacturing Distribution Practice Inspectors Working Group
[10] European Union/European Economic Area/European Free Trade Association

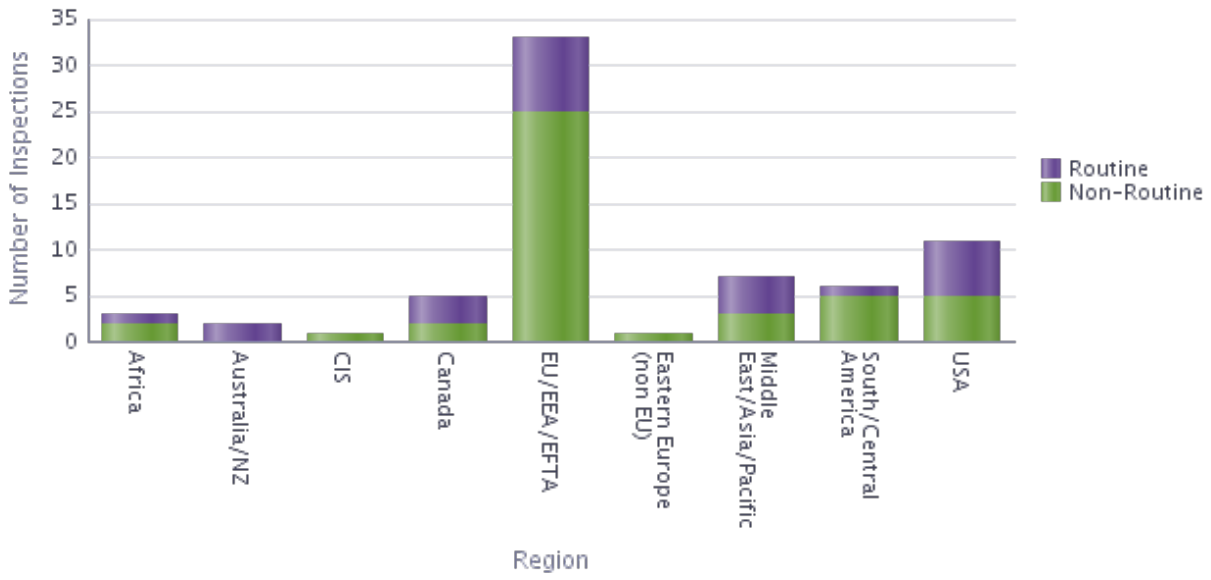


Table 1. Number of Inspections conducted per region and type of inspection.

Region	Non-Routine	Routine	Total
EU/EEA/EFTA	25	8	33
USA	6	5	11
Middle East/Asia/Pacific	4	3	7
South/Central America	5	1	6
Canada	3	2	5
Africa	2	1	3
Australasia/NZ		2	2
CIS	1		1
Eastern Europe (non-EU)	1		1

Figure 2: Inspections conducted per type of site and type of inspection.

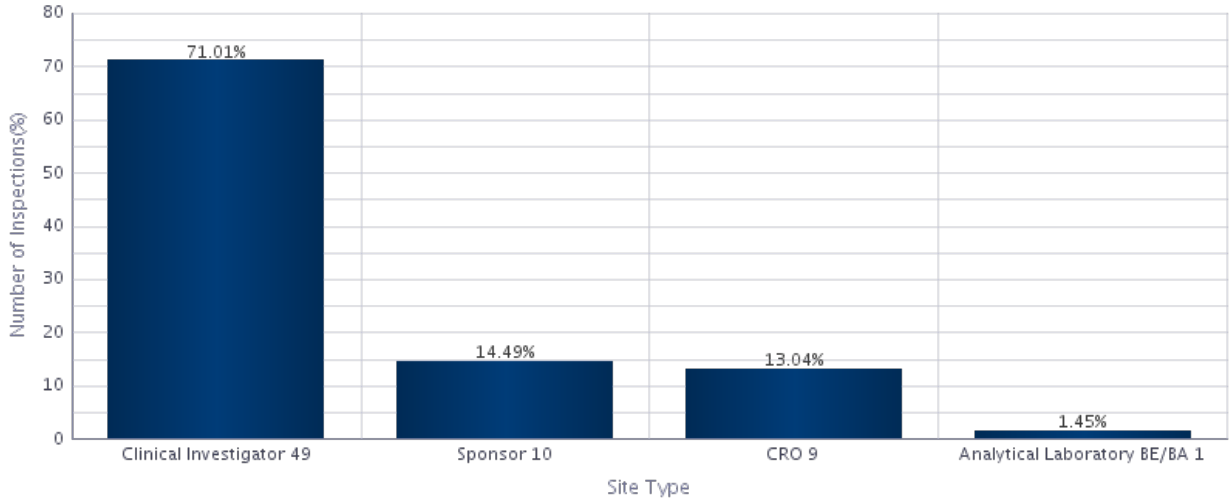


Figure 2 represents the number of inspections conducted per type of site. Most inspections were conducted at clinical investigator sites (71%).

3.1.2. Categorization of findings

A total of 1069 deficiencies, comprising 66 critical (6%), 465 major (43%) and 538 minor (50%) were recorded for the 69 inspections conducted in 2010.

The main findings observed in the 2010 inspections are detailed below in accordance with the GCP categorization of findings agreed by the GCP IWG.

Figure 3. Number of findings with regard to the main categories graded by critical, major and minor.

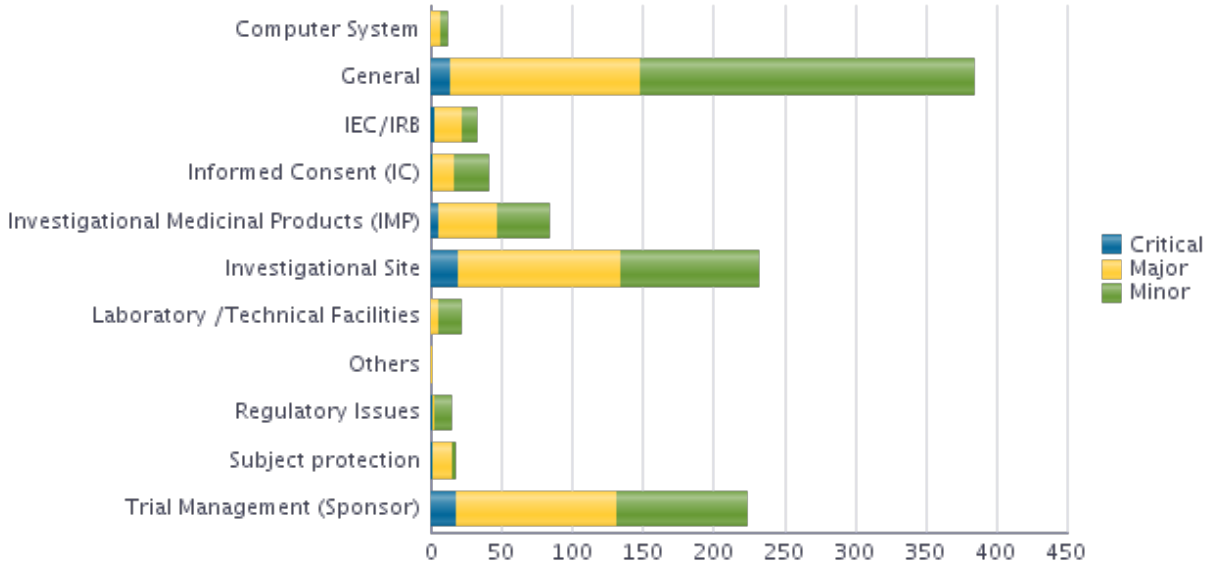


Table 2. Number of findings per sub-category of the top 3 main categories (general, investigational site and trial management) graded by critical, major and minor.

Number of findings per sub-category of the top 3 main categories (general, investigational site and trial management) graded by critical, major and minor					
		# Inspected Deficiencies			# Inspected Deficiencies Total
Deficiency Category Name	Deficiency Sub Category Name	Critical	Major	Minor	
General	Contracts/Agreements		9	10	19
	Direct Access to Data	2			2
	Essential Documents	2	36	82	120
	Facilities and Equipment		2	2	4
	Organisation and Personnel		13	33	46
	Qualification/Training	1	19	32	52
	Randomization/Blinding/Codes IMP	3	6	3	12
	SOPs	2	25	35	62
	Source Documentation	4	24	40	68
General Total		**14**	**134**	**237**	**385**
Investigational Site	Protocol Compliance (Assessment of Efficacy)	8	16	7	31
	Protocol Compliance (Others)	3	11	14	28
	Protocol Compliance (Safety Reporting)		8	13	21
	Protocol Compliance (Selection Criteria)	7	42	12	61
	Reporting in CRF/Diary	2	38	51	91
Investigational Site Total		**20**	**115**	**97**	**232**
Trial Management (Sponsor)	Audit		5	1	6
	CSR	4	12	11	27
	Data Management	4	50	23	77
	Document Control	1	6	17	24
	Monitoring	6	34	27	67
	Protocol/CRF/Diary/Questionnaires	1	5	12	18

Number of findings per sub-category of the top 3 main categories (general, investigational site and trial management) graded by critical, major and minor					
	design				
	Statistical Analysis	2	1	2	5
Trial Management (Sponsor) Total		**18**	**113**	**93**	**224**

3.2. GCP inspections performed under national programmes

The CHMP GCP inspections are just a small part of the total number of inspections performed by the EU/EEA inspectors as there are many others performed as part of their national programmes in the following contexts:

Oversight of the conduct of clinical trials in Europe.

Marketing Authorization Applications (MRP, DCP or national procedures).

The following statistics are based on information obtained from EudraCT.

Table 3. Inspections conducted per Region.

Region	Number of Inspections conducted in 2011
EU/EEA	563
North America	14
Rest of the World	45

Figure 4. Number of inspections per type of site.

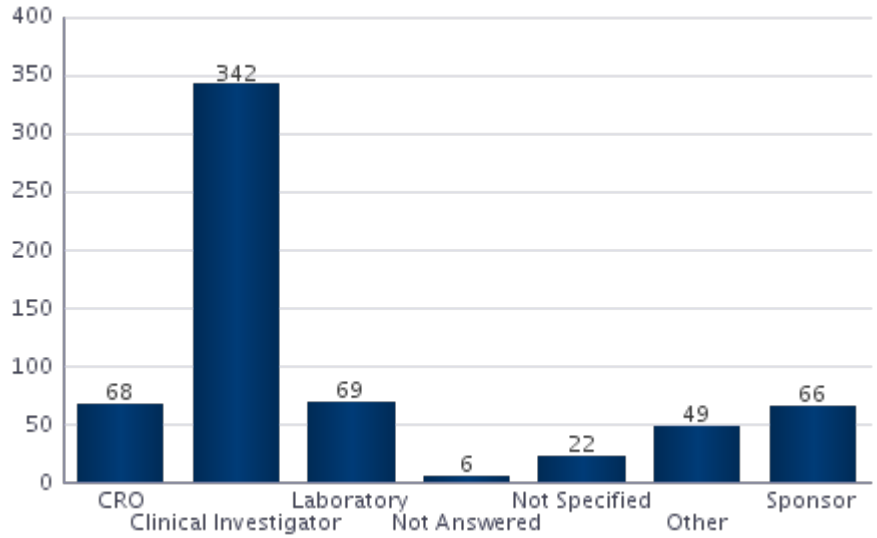


Figure 5. Trial specific vs non-trial specific conducted inspections

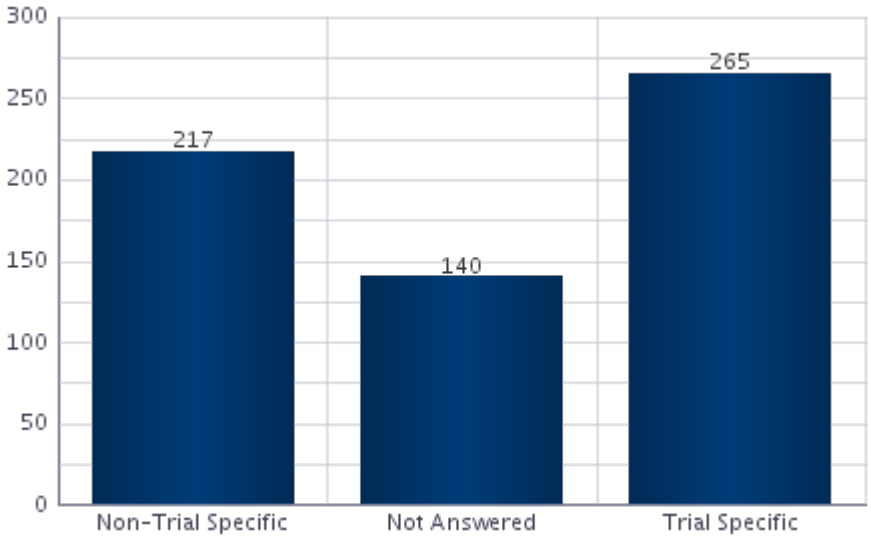
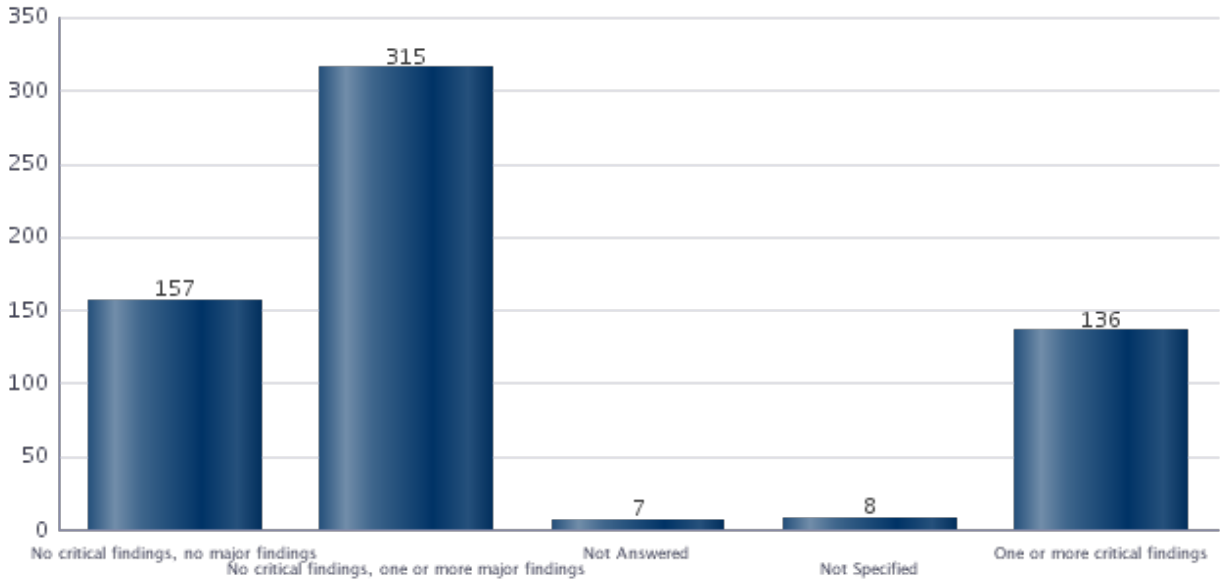


Table 4. Trial specific vs non-trial specific conducted inspections

Type of Inspections	Number of Inspections conducted in 2011
Trial Specific	265
Non trial specific	217
Not answered	140

Figure 6. Percentage of inspection in relation to the number of critical and major of findings.



4. Harmonisation topics

4.1. Procedures and guidance documents

The GCP Inspection procedures and/or guidance for GCP inspections conducted in the context of the Centralised Procedure have not been revised this year.

The following guidance on GCP Inspection required in accordance with article 29 of Directive 2005/28/EC and prepared by the GCP IWG is now publicly available in Chapter IV of Volume 10 of the Rules Governing Medicinal Products in the European Union:

- Record keeping and archiving of documents obtained or resulting from the Good Clinical Practice inspection.

The following guidance document required by the same article mentioned above is still pending and will be included in the Workplan for 2011:

- Actions taken after completion of Good Clinical Practice inspection.

4.2. Inspection cooperation

- Cooperation between the Member States:
  - In 2010 all the inspections requested by the CHMP were joint inspections involving inspectors from at least two Member States,
  - A joint meeting GCP IWG and CHMP assessors took place on 2 December 2010 with practical presentations from the inspectors' and assessors' perspective on the experience with some GCP inspections carried out for the centralized procedure. The issues discussed included the interpretation/understanding of findings, communication between inspectors and assessors during the procedure, difference in views, expectations and suggestions for process improvement.
- Cooperation with 3rd countries (see also section 7.6)
  - Observers from countries outside the EU have always been invited to observe the EU GCP inspections performed in those countries in the context of the centralized procedure. In 2010, at least 6 inspections were observed by FDA inspectors and 7 joint inspections were performed together with the FDA. In addition, 2 inspections were observed by TGA (Therapeutic Goods Administration, the Australian regulatory agency), 1 inspection was observed by FDA-Thailand, and 1 inspection was observed by Health Canada.

4.3. GCP training and development

The following activities have taken place during this year:

The 8th GCP IWG Training Course in London (EMA) on 03 – 05 Nov 2010. Participants included inspectors from EEA (Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, Malta, Netherland, Norway, Poland, Portugal, Romania, Slovenia, Spain, Sweden, UK) and from countries outside the EEA (Bosnia and Herzegovina, The Former Yugoslav Republic of Macedonia, Montenegro, Switzerland, Turkey, Canada, Ghana, Indonesia, Japan, Kenya, Republic of Korea, Nigeria, South Africa, United Republic of Tanzania, USA). The agenda of the course covered the following points:

- Data management and Data Safety Monitoring Boards,

- Computer systems and validation (eCRFs, e-patient diaries, e-medical records, e-TMF etc.),
- Inspections of technical facilities: IVRS system inspections, Clinical Laboratory and Clinical trials pharmacy inspections,
- Topic of Interest I:
  - Follow-up on inspections Inspection of emergency trials,
  - Adaptive design,
  - Inspection of clinical trials on advanced therapies,
  - Inspection of paediatric trials.
- Plenary session on case studies – special topics/experiences to be volunteered:
  - Misconduct at the Investigator's site: how to approach it,
  - Academic Trial Inspection,
  - Fraud and misconduct: how to manage detected cases?
- Break-out sessions every day with discussion points on the different topics covered in the agenda.
- During the GCP Inspector meetings held in 2010, the following topics have been addressed:
  - Develop peer review of case studies,
  - Develop and monitor opportunities for joint inspections.

5. Topics of interest

The GCP IWG has published the following documents focused on topics of interest:

- Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials **(final version)**
- Reflection paper on guidance for laboratories that perform the analysis or evaluation of clinical trial samples **(for consultation until 28/02/11)**

Members of the GCP IWG are also supporting the Pharmacokinetics Working Party in the review of the comments of the public consultation of the guideline on validation of bio-analytical method released for public consultation until 31 May 2010.

The GCP IWG has under preparation (UP) or pending preparation (PP) the following documents focused on topics of interest which will be included in the 2011 Workplan:

- Reflection paper on quality risk management in clinical trials (UP),
- Document with specific triggers for assessors in the context of the ethical conduct of clinical trials in countries outside the EU (PP),
- Revision of the document on triggers for GCP inspection (PP),
- Document for assessors in the context of the assessment of acceptability of clinical trials from 3rd countries (PP).

6. Collaboration with European Commission

6.1. Implementation of Directive 2001/20/EC and of Directive 2005/28/EC and related guidance documents

See section 4.1.

6.2. EudraCT database

The GCP IWG has agreed on the format of reports with information from EudraCT to assist in the prioritization of GCP inspections.

6.3. EU enlargement

- Bosnia and Herzegovina, Croatia, The Former Yugoslav Republic of Macedonia, Montenegro, Serbia and Turkey have been invited and in most of the cases attended, the GCP IWG meetings held in 2010 as observers.
- Delegates from these countries have also attended the 8th GCP IWG training workshop in London (see section 4.3).

6.4. Regulation on advanced therapies

The GCP IWG continues with the monitoring of the implementation of GCP guidelines on ATIMPs in clinical trials of advanced therapies.

7. Liaison with other groups

7.1. GMDP

The GMPD and GCP IWG, through the GCP/GMDP, contributed in 2009 to the revision of Annex 13 (Investigational Medicinal products) which the Commission has published this year in the EudraLex Volume 4 of the Rules Governing Medicinal Products in the European Union.

7.2. PhV IWG

The GCP IWG maintains a dialogue with the Pharmacovigilance Inspectors Working Group on areas of common interest and in particular concerning pharmacovigilance issues observed in relation to GCP inspections.

7.3. CTFG

Members of the CTFG are involved with members of the GCP IWG in the preparation of the Reflection paper on quality risk management in clinical trials which work is still ongoing.

7.4. CMD(h)

The GCP IWG and the CMD(h), mainly through the GCP/CMD(h) subgroup has contributed to:

- The preparation of a pilot 2010 risk based programme of routine GCP inspections of the Contract Research Organizations most often used in the conduct of the bioequivalence trials included in marketing authorization application in the mutual recognition and Decentralised procedure.

- The finalization of a document for assessors on triggers for inspections of Bioequivalence Trials.
- The discussion of processes for:
  - Exchange of information on BE trials/CRO inspections,
  - Communication of inspections findings,
  - Improve the exchange of information between inspectors and assessors,
  - Selection of trial/sites for inspection.

7.5. Heads of Medicines Agencies

See section 7.3.

7.6. Other regulatory agencies

- EMA FDA GCP initiative:
  - A Q&A document has been published this year in the EMA external web site to address some questions from the public about this initiative
  - A report of the outcome of the pilot phase of the EMA FDA GCP initiative with details on the exchanges of information and collaborative inspections is being prepared and will be published in 2011 in the EMA external website
- Delegates from the GCP IWG have contributed to the preparation of the "Draft reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted in countries outside EU and submitted in marketing-authorisation applications to the EMA" and have participated in the International workshop organized by EMA as part of the public consultation of this document on 6-7 September 2010
- An International Workshop involving the EU GCP IWG and inspectors from countries outside the EU took place on 8th September 2010. Delegates from Canada, China, Chinese Taipei, Ghana, Singapore, Thailand, US FDA, WHO, Bosnia and Herzegovina, Croatia, Montenegro, Russian Federation, Serbia, Singapore, Switzerland. The agenda of this workshop covered the following points:
  - Sharing of information on GCP activities
  - Overview of international cooperation initiatives
  - Joint Inspections
- Training Activities/ How to contribute to capacity building:
  - Communication network for inspection sharing.

7.7. Joint meeting with interested parties

A joint meeting of GCP IWG and interested parties did not take place as initially foreseen in the 2009 Workplan, but is scheduled for 2011.

For the details of the activities of the GCP IWG for next year see the Workplan for 2011.