EUROPEAN MEDICINES AGENCY
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Compliance and Inspection

Annual report of the Good Clinical Practice Inspectors Working Group 2011

Adopted by the GCP IWG on 23 May 2012

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1. Introduction

This document is the fourth 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 2011 Workplan.

2. Meetings

The plenary GCP IWG meetings took place on: 01-02 Mar 2011, 14-15 June 2011, 13-14 Sep 2011 and 06-07 Dec 2011 (a joint meeting with CHMP clinical assessors took place on 6 Dec 2011)

During 2011, 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/CHMP Assessors (refer to section 4.1),
- CTFG[7] GCP (refer to section 7.3),
- GCP Clinical Laboratories (refer to section 5, 2nd bullet point),
- GCP Risk Based Quality Management (refer to section 5, 3rd bullet point),
- GCP IVRS (refer to section 5, 4th bullet point),
- GCP TMF (refer to section 5, 5th bullet point).

Delegates from this group are also involved in the Agency's multidisciplinary Working Group on 3rd country clinical trials (refer to section 7.6, 2nd bullet point).

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 64 GCP inspections in 2011 and the CVMP requested 1 GCP inspection. In total 46 GCP inspections were carried out by the inspectorates of the EU member states in the same year. The

[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
[7] Clinical Trials Facilitation Group

number of inspections requested and conducted is not consistent due to the fact that several inspections requested in the last 3 months of the year 2010 were conducted in 2011 and some inspections requested in the last 3 months of 2011 will be carried out in 2012. The data in this report relates to inspections carried out.

In figure 1, the number of inspections carried out in 2011 is shown by region and type of inspection. Most inspections were carried out in the EU/EEA[8] (37%) followed by inspections in North America (28%) and Middle East/Asia/Pacific (17%).

Figure 1. Inspections conducted per region and type of inspection

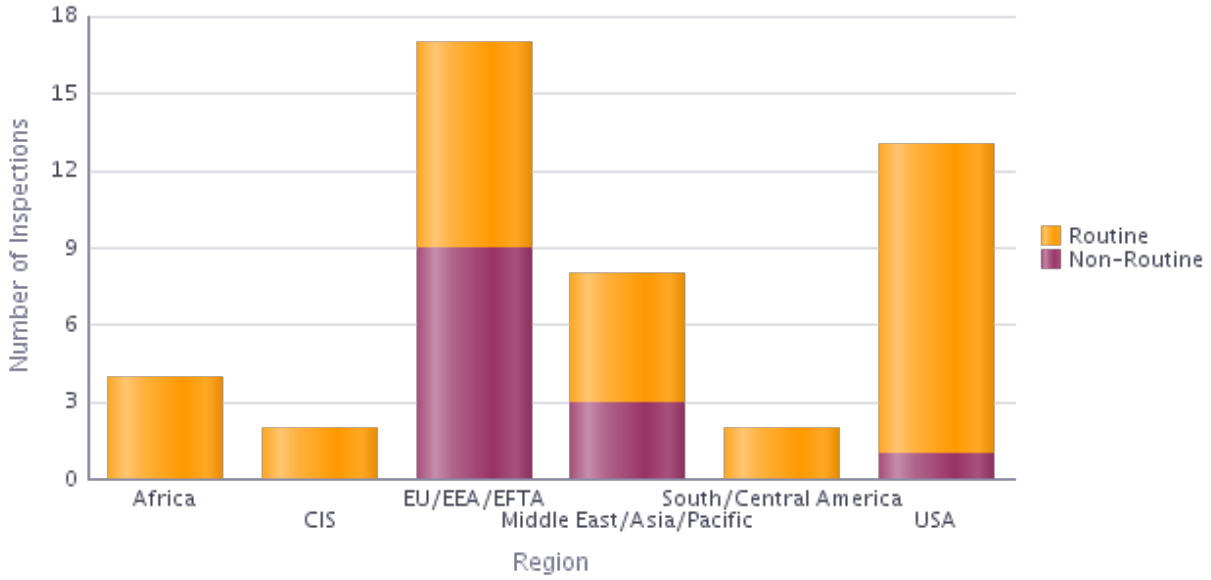


Table 1. Number of Inspections conducted per region and type of inspection.

Region	Non-Routine	Routine	Total
EU/EEA/EFTA	9	8	17
USA	1	12	13
Middle East/Asia/Pacific	3	5	8
Africa		4	4
South/Central America		2	2
CIS		2	2
Total in all regions	**13**	**33**	**46**

[8] European Union/European Economic Area/European Free Trade Association

Figure 2. Inspections conducted per type of site

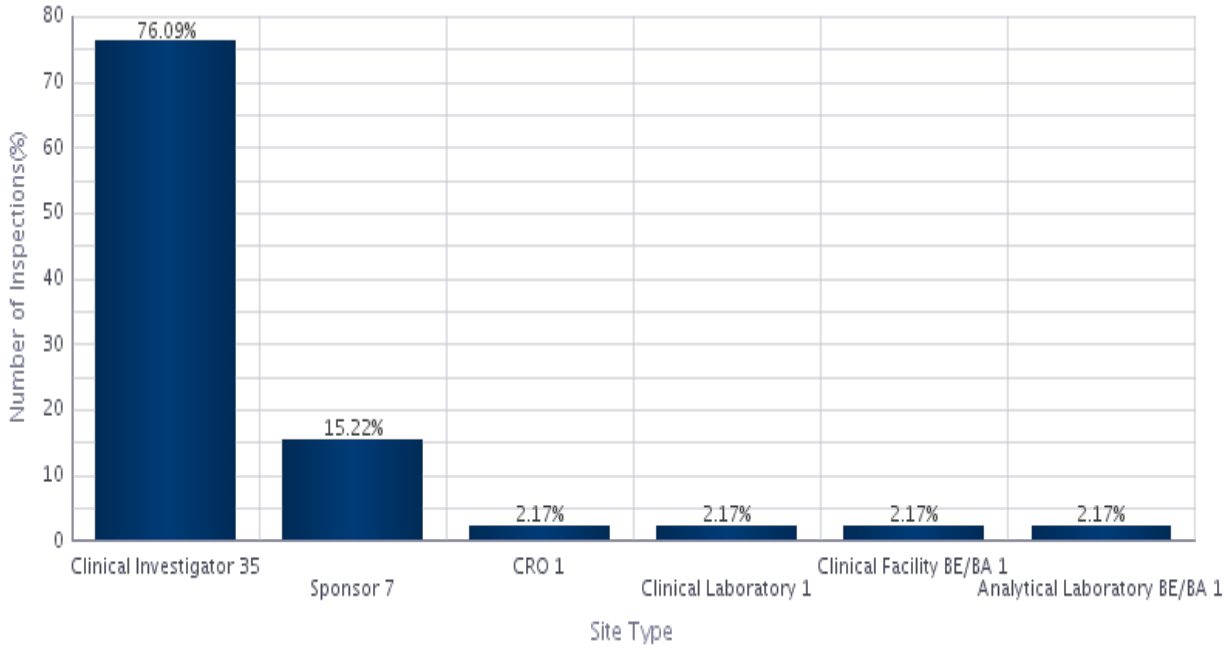


Figure 2 represents the number of inspections conducted in 2011 per type of site. Most inspections were conducted at clinical investigator sites (76%).

3.1.2. Categorization of findings

A total of 650 deficiencies, comprising 32 critical (5%), 254 major (39%) and 364 minor (56%) were recorded for the 45 CHMP requested inspections conducted in 2011 (the findings from the CVMP requested GCP inspection have not been categorised).

The main findings observed in the 2011 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

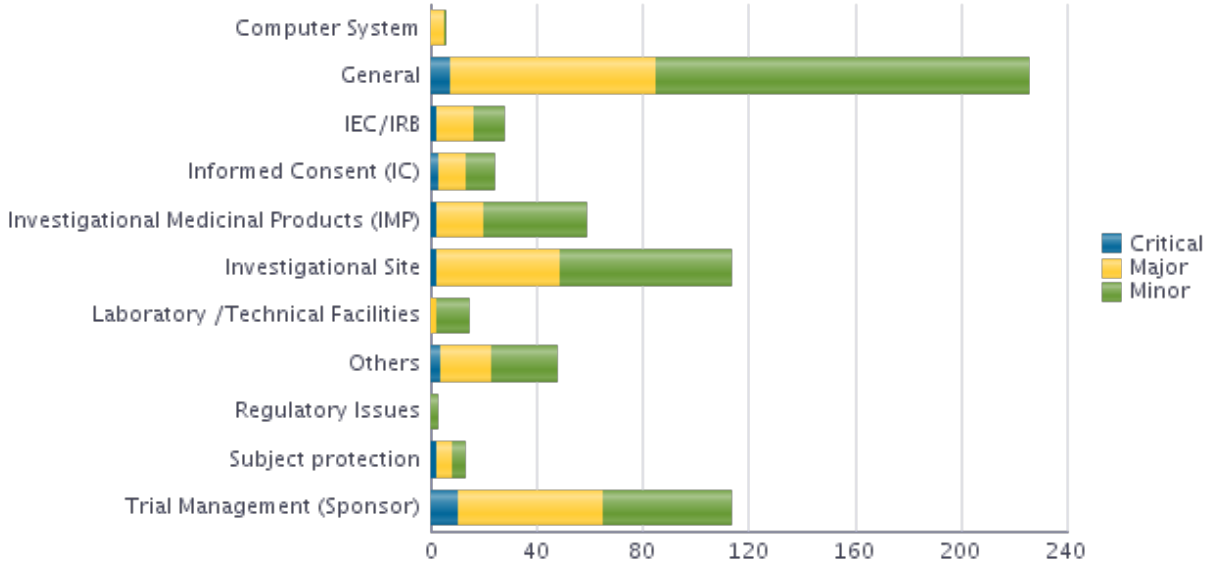


Table 2. Number of findings per sub-category of the top 3 main categories (general, investigational site and trial management) graded by critical, major and minor.

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	1	2	7	10
	Direct Access to Data		2		2
	Essential Documents	3	15	50	68
	Facilities and Equipment		5	6	11
	Organisation and Personnel		7	18	25
	Qualification/Training	2	10	20	32
	Randomization/Blinding/Codes IMP			1	1
	SOPs		19	21	40
	Source Documentation	1	18	18	37
General Total		**7**	**78**	**141**	**226**
Investigational Site	Protocol Compliance (Assessment of Efficacy)		4		4

Number of findings per sub-category of the top 3 main categories (general, investigational site and trial management) graded by critical, major and minor					
	Protocol Compliance (Others)	1	11	15	27
	Protocol Compliance (Safety Reporting)		8	9	17
	Protocol Compliance (Selection Criteria)		10	4	14
	Reporting in CRF/Diary	1	14	37	52
Investigational Site Total		**2**	**47**	**65**	**114**
Trial Management (Sponsor)	Audit			2	2
	CSR		3	2	5
	Data Management	7	24	13	44
	Document Control		7	12	19
	Monitoring	3	15	17	35
	Protocol/CRF/Diary/Questionnaires design		6	3	9
Trial Management (Sponsor) Total		**10**	**55**	**49**	**114**

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[9], DCP[10] or national procedures)

The following statistics are based on information obtained from EudraCT and include the CHMP requested inspections.

Table 3. Inspections conducted per Region

Region	Number of Inspections conducted in 2011
EU/EEA	455

[9] Mutual Recognition Procedure
[10] Decentralised Procedure

Region	Number of Inspections conducted in 2011
North America	13
Rest of the World	46
Total in all regions	**514**

Figure 4. Number of inspections conducted per type of site

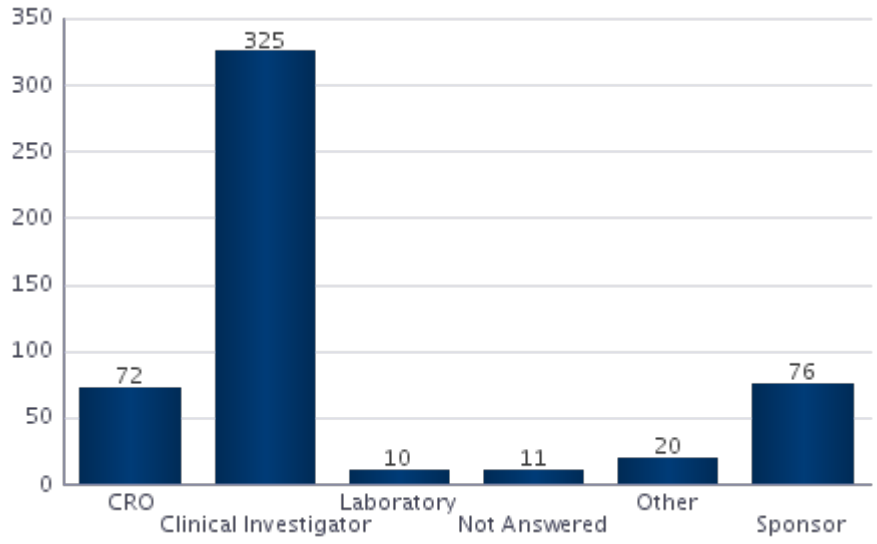
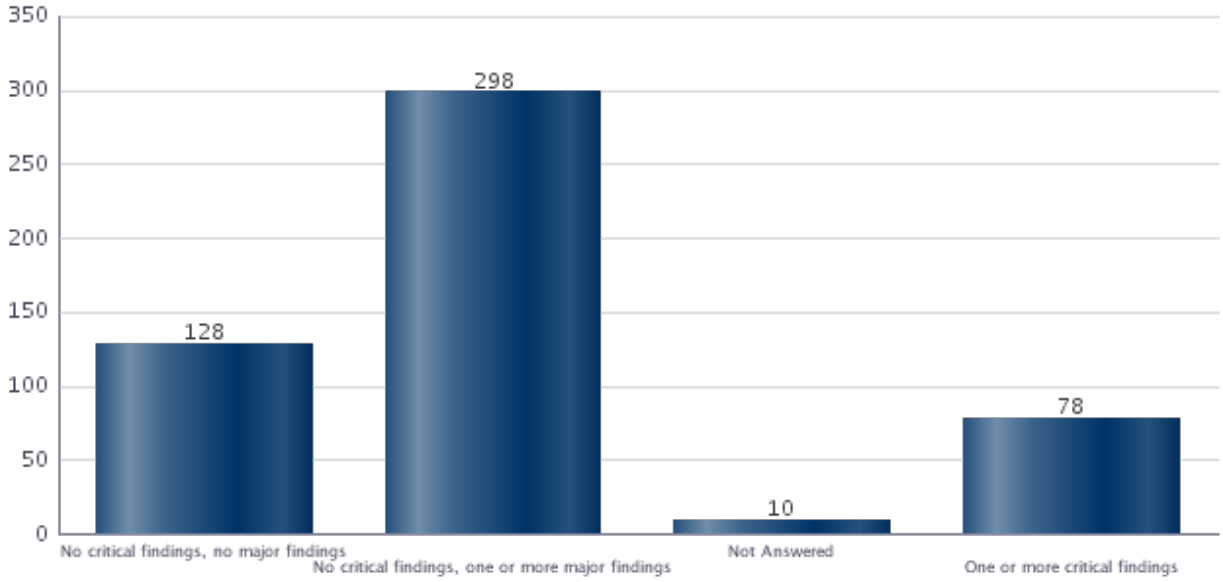


Table 4. Trial specific vs non-trial specific conducted inspections

Type of Inspections	Number of Inspections conducted in 2011
Trial Specific	257
Non trial specific	233
Not answered	24

Figure 5. Inspection outcome in relation to the number of critical and major 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 were not revised this year.
- As part of the CHMP Work Programme 2011-2013, a task has been introduced which will focus on the improvement of the inspection process with respect to the process of requesting inspections, reporting inspections, the interpretation and impact of inspection findings on the decision making process and the inspection follow up. A subgroup of GCP inspectors-CHMP assessors was formed in 2011 with the task of preparing the following documents:
  - Revised policy on the selection of routine inspections and their scope,
  - Points to consider document for assessors and inspectors on the identification of triggers for inspection, their investigation and scope,
  - Points to consider document for assessors and inspectors on the interpretation of inspection findings and their impact on risk benefit evaluation and the development of the CHMP opinion on an application,
  - Policy for follow-up of inspection findings, including those findings to be followed up as part of the opinion forming process and those to be followed up outside of that process for the future quality of the inspected entity.
- The guidance "Actions taken after completion of Good Clinical Practice inspection on GCP Inspections" required in accordance with article 29 of Directive 2005/28/EC and to be published in Chapter IV, Volume 10 of the Rules Governing Medicinal Products in the European Union is pending preparation.

4.2. Inspection cooperation

- Cooperation between the Member States:
  - In 2011 all the inspections requested by the CHMP were joint inspections involving inspectors from at least two Member States.
- Cooperation with 3rd countries (see also section 7.6):
  - Observers from countries outside EU have always been invited to observe the EU GCP inspections performed in those countries in the context of the centralized procedure. In 2011, observers from the FDA were involved in at least 6 inspections requested by the CHMP.

4.3. GCP training and development

The following activities took place during this year:

4.3.1. 2011 EU GCP Inspectors Working Group workshop

A 2011 EU GCP Inspectors Working Group workshop took place in London (EMA) on 03 – 05 October 2011. Participants included inspectors from the EEA (Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovenia, Spain, Sweden, United Kingdom) and from countries outside the EEA (Australia, Canada, Ghana, Indonesia, Japan, Kenya, Republic of Korea, Nigeria, Russian Federation, Switzerland, Chinese Taipei, USA).

The following topics were covered:

- Risk based approach to the management of clinical trials:
  - Reflection paper on the risk based quality management in clinical trials,
  - A current application, the Optimon Project in France,
  - MS experience, FDA[11] experience.
- Inspections of laboratories:
  - Reflection paper on laboratories that perform the analysis or evaluation of clinical trial samples,
  - Inspectors' experience.
- IVRS[12] and Inspection:
  - Reflection paper on IVRS,
  - Inspectors' experience,
  - Service provider's perspective.
- Trial Master File Inspection:
  - Inspectors' perspective paper record/e-TMF inspection,
  - Sponsor's perspective.

[11] Food and Drug Administration
[12] Interactive Response Technologies (Interactive Voice/Web Response Systems)

- Grading of findings.
- Data Management and Statistical Analysis:
  - Sponsor's perspective,
  - Assessor's perspective,
  - Inspector's perspective.
- Data Review: Tumour Response in Oncology Trials & ECG:
  - Oncology Trials,
  - ECGs Common Findings.

Break-out sessions were included every day with discussion points on the different topics covered in the agenda.

4.3.2. GCP Inspectors' basic training course

A GCP Inspectors' basic training course took place in London on 2-4 March 2011. Participants included inspectors from the EEA (Austria, Belgium, Bulgaria, Denmark, Finland, France, Germany, Italy, Latvia, Lithuania, Malta, Netherlands, Poland, Portugal, Romania, Slovenia, Spain, Sweden, United Kingdom) and from countries outside the EEA (Brazil, Croatia, Ghana, Indonesia, Japan, Kenya, The Former Yugoslav Republic of Macedonia, Malawi, Mexico, Montenegro, Nigeria, Russian Federation, Saudi Arabia, Serbia, Singapore, Switzerland, Chinese-Taipei , USA, Zambia) as well as representatives from the WHO.

During the first two days of the course, the following topics were covered:

- Soft skills (interview technique, opening/closing meeting),
- Criteria for selecting inspections (risk based, triggered),
- Types of inspections,
- Preparation for the various types of inspection,
- Conduct of inspections,
- Follow-up of findings.

The third day of the course focused on specific issues concerning inspections in 3rd countries. The topics covered included the following:

- Preparation and conduct of inspections at the Ethics Committees,
- Informed consent process- how do you ensure compliance in those situations where vulnerable or illiterate patients have to be included,
- Clinical trials in Anti-infective diseases,
- Common findings in inspections outside the EU.

Break-out sessions took place every day with discussion points on the different topics covered in the agenda.

4.3.3. GCP Inspector meetings

During the GCP Inspector meetings held in 2011, the following topics were addressed:

- Develop peer review of case studies,
- Develop and monitor opportunities for joint inspections.

5. Topics of interest

The GCP IWG published the following reflection paper for public consultation in 2010 and the comments were reviewed during 2011:

- Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU Regulatory Authorities.

The GCP IWG released the following reflection papers for public consultation in 2011:

- Reflection paper on guidance for laboratories that perform the analysis or evaluation of clinical trial samples,
- Reflection paper on the quality risk management in clinical trials (end of public consultation 15 Feb 2012)
- Reflection paper on the use of interactive response technologies (interactive voice/web response systems) in clinical trials(end of public consultation 15 Feb 2012)

The group has pending the preparation of the following document focused on topics of interest which will be included in the 2012 Workplan:

- Reflection paper on inspector's expectations on Trial Master File (TMF).

A new Question & Answer was published in the EMA external web site on the "Expectations of EU competent authorities concerning the use of electronic Trial Master Files (e-TMF)"

Members of the GCP IWG supported the Pharmacokinetics Working Party in the review of the comments of the public consultation of the guideline on validation of bio-analytical method which was published on 1 Aug 2011.

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 for an update of guidance on GCP Inspections required in accordance with Directive 2005/28/EC and prepared by the GCP IWG.
- The Commission was invited to the GCP IWG meeting on 13-14 September 2011. The Commission representative concentrated on the review of some ideas that emanated from the public consultations of the Clinical Trials Directive, especially the ones that affected the rules for IMPs[13]. The following topics were discussed with the possibility to review the rules in the future:
  - manufacturing including re-labelling,

[13] Investigational Medicinal Products

- manufacturing authorisation,
- content of labelling.

6.2. EudraCT Database

During the GCP IWG meetings, information that can be obtained from the EudraCT Data Warehouse such as pre defined reports (inspection report, inspection statistics, Bioequivalence inspection report) was presented to the group. Further training on the use of these reports will be provided to the inspectors in 2012.

6.3. EU enlargement

Albania, Bosnia and Herzegovina, Croatia, Kosovo, The Former Yugoslav Republic of Macedonia, Montenegro, Serbia and Turkey were invited and in most of the cases attended, the GCP IWG meetings held in 2011 as observers.

6.4. Regulation on advanced therapies

The GCP IWG continues with the monitoring of the implementation of GCP guidelines on ATIMPs[14] in clinical trials of advanced therapies.

7. Liaison with other groups

7.1. GMDP

This group has been consulted for the development of the reflection paper on the use of interactive response technologies (interactive voice/web response systems) in clinical trials (refer to section 5, 4th bullet point).

7.2. PhV IWG[15]

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 and GCP IWG are involved in:

- the preparation of the reflection paper on the quality risk management in clinical trials,
- the preparation of the GCP IWG-CTFG procedure on coordination of GCP inspections outside the context of MAA.

7.4. CMD(h)

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

[14] Advance Therapies Investigational Medicinal Products
[15] Pharmacovigilance Inspectors Working Group

- The revision of the Guidance for the coordination of GCP inspections and cooperation between GCP inspectors, the Reference and concerned Member States and CMD(h) in the context of the evaluation of GCP compliance of Clinical Trials submitted in support of a Marketing Authorization application (MAA) for the Mutual Recognition and Decentralised procedure.
- The adoption of the Mandate of the GCP/CMD(h) subgroup.
- The preparation of the 2011 risk based programme of routine GCP inspections of the CROs[16]most often used in the conduct of the bioequivalence trials included in a MAA in the Mutual Recognition and Decentralised procedure.
- The discussion of processes for:
  - CRO inspections coordination,
  - Exchange of information on BE trials/CRO inspections,
  - Communication of inspection findings,
  - Improving 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: the initiative began with a pilot phase that ran between September 2009 and March 2011. During the pilot, the EMA and the FDA exchanged more than 250 documents relating to 54 different medicines. They also organised joint inspections of clinical trials in conjunction with the GCP inspectors of the EU Member States.

  A report and question-and-answer document on the outcomes of the pilot are available, which detail the success of the information-sharing and collaboration on inspections relating to clinical trials:

  - Report of the EMA-FDA pilot GCP initiative
  - Questions and answers on the EMA-FDA GCP initiative

  The EMA and the FDA agreed to continue with the initiative, incorporating lessons learned during the pilot.
- Delegates from the GCP IWG contributed to the preparation of the “Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU Regulatory Authorities”.
- PMDA (Japan)[17]-MS initiative:
  - The exchange of information between EU-MS and PMDA inspectorate contact points for notification of GCP inspections, was agreed.
- The group is working on the creation of a platform for GCP inspections to be used by an international network.

[16] Contract Research Organisation
[17] Pharmaceuticals and Medical Devices Agency

7.7. Joint meeting with interested parties

A joint meeting of the GCP IWG and interested parties took place on 15 June 2011.

Delegates from ACRO[18], AESGP[19], BIA/EuropaBio[20], ECRIN[21], EFGCP[22], EFPIA[23], EGA[24], EORTC[25] and EUCROF[26] attended this meeting.

The following topics were covered:

- GCP IWG's Work programme 2011 and priorities
- Quality of Clinical Trials Data Across Regions: *ACRO Study: Preliminary Look at the Quality of Clinical Trials Data Across Regions*
- Computer Systems: *Storage of EDC data*
- Joint EMA/FDA GCP Inspection Programme: *Global CRO experiences under the joint EMA/FDA GCP Inspection Programme*
- Contracts: *Contracts between Sponsors and CROs and subsequent local sub-contracting – How does Sponsor keep oversight?*

For details of the activities of the GCP IWG for next year see the Workplan for 2012.

[18] Association of Clinical Research Organizations
[19] European Self-Medication Industry
[20] European Association for Bioindustries
[21] European Clinical Research Infrastructure Network
[22] European Forum for Good Clinical Practice
[23] European Federation of Pharmaceutical Industries and Associations
[24] European Generic medicines Association
[25] European Organisation for Research and Treatment of Cancer
[26] European CROs Federation