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Compliance and Inspection

Annual report of the Good Clinical Practice Inspectors Working Group 2012

Adopted by the GCP IWG on 21 May 2013

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1. Introduction

This document is the fifth 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 Work plan 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], PRAC[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 2012 Workplan.

2. Meetings

The plenary GCP IWG meetings took place on:

- 28-29 Feb 2012
- 22-23 May 2012
- 12-13 Sep 2012
- 11-12 Dec 2012

During 2012, 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),
- GCP Clinical Laboratories (refer to section 5, 1st bullet point),
- GCP-CTFG Risk based quality management in clinical trials subgroup (refer to section 5, 2nd bullet point),
- GCP IRT[7] (refer to section 5, 3rd bullet point),
- GCP TMF[8] (refer to section 5, 4th bullet point).

[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 Risk Assessment Committee
[5] Co-ordination Group for Mutual Recognition and Decentralised Procedures
[6] Good Manufacturing Distribution Practice Inspectors Working Group
[7] Interactive Response Technologies
[8] Trial Master File

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 72 GCP inspections in 2012. In total 71 GCP inspections were carried out by the inspectorates of the EU member states in the same year. The 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 2011 were conducted in 2012 and some inspections requested in the last 3 months of 2012 will be carried out in 2013. The data in this report relates to inspections carried out.

In figure 1, the number of inspections carried out in 2012 is shown by region and type of inspection. Most inspections were carried out in the EU/EEA[9] (37%) followed by inspections in the Middle East/Asia/Pacific (15.5%) and the USA (14%).

Figure 1. Inspections conducted per region and type of inspection

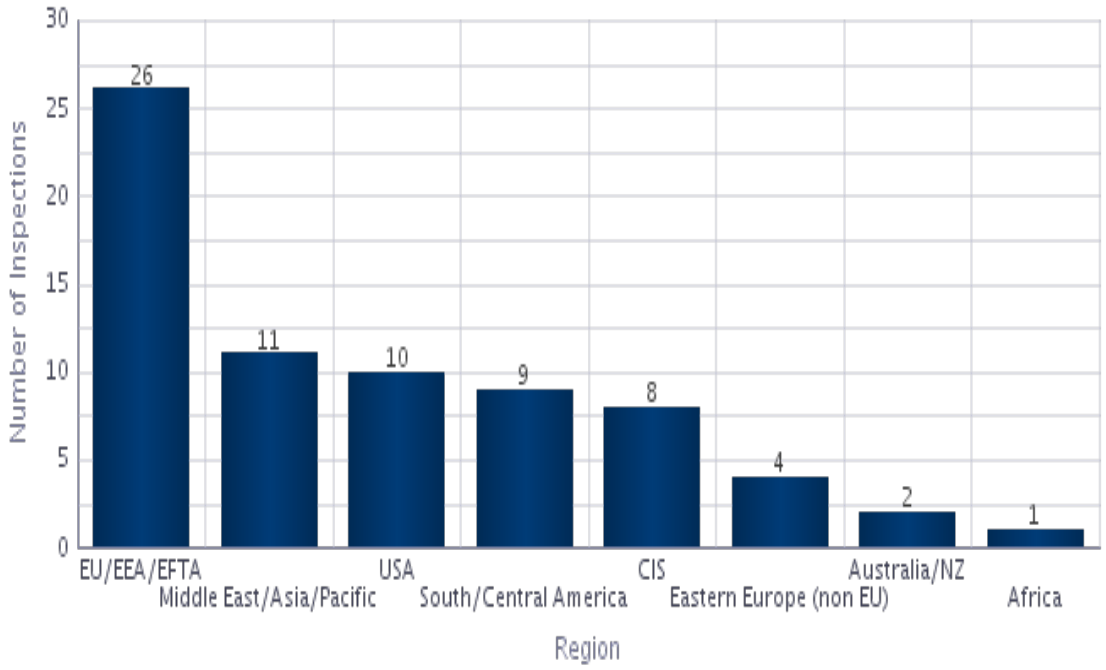


Table 1. Number of Inspections conducted per region and type of inspection.

Region	Non-Routine	Routine	Total
EU/EEA/EFTA	14	12	26
Middle East/Asia/Pacific	2	9	11
USA	4	6	10
South/Central America	-	9	9

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

Region	Non-Routine	Routine	Total
CIS	1	7	8
Eastern Europe (non EU)	1	3	4
Africa	-	1	1
Australia/NZ	-	2	2
Total in all regions	**22**	**49**	**71**

Figure 2. Inspections conducted per type of site

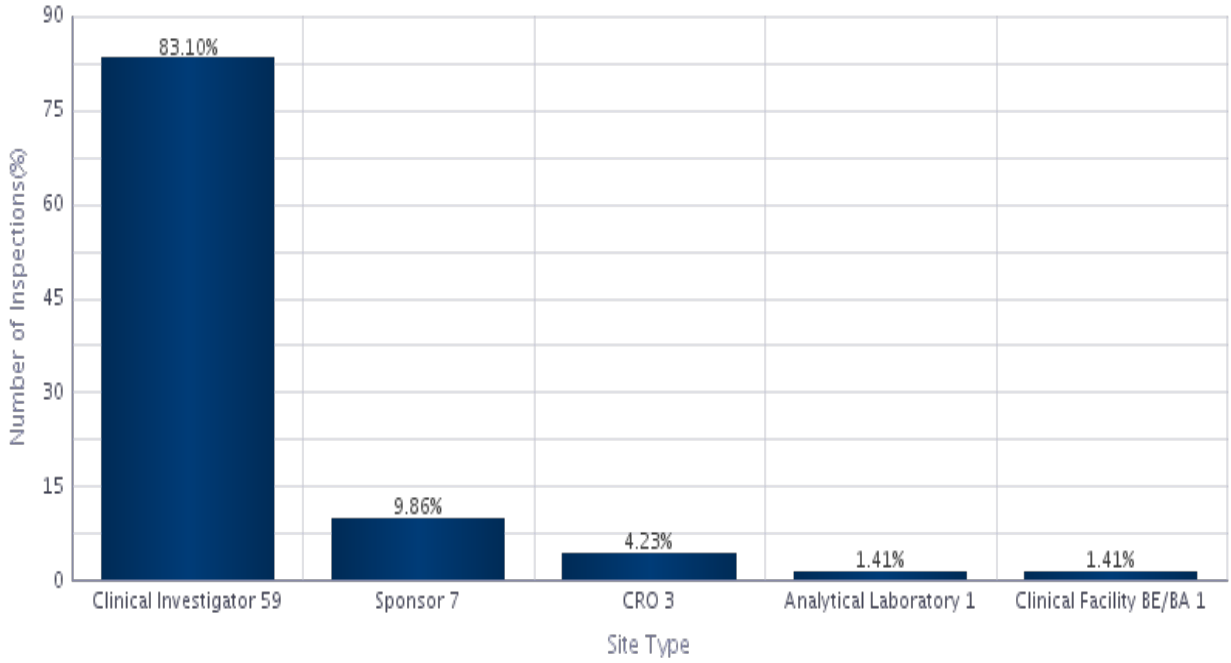


Figure 2 represents the number of inspections conducted in 2012 per type of site. Most inspections were conducted at clinical investigator sites (83%).

3.1.2. Categorization of findings

A total of 918 deficiencies, comprising 37 critical (4%), 392 major (43%) and 498 minor (53%) were recorded for the 71 CHMP requested inspections conducted in 2012.

The main findings observed in the 2012 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

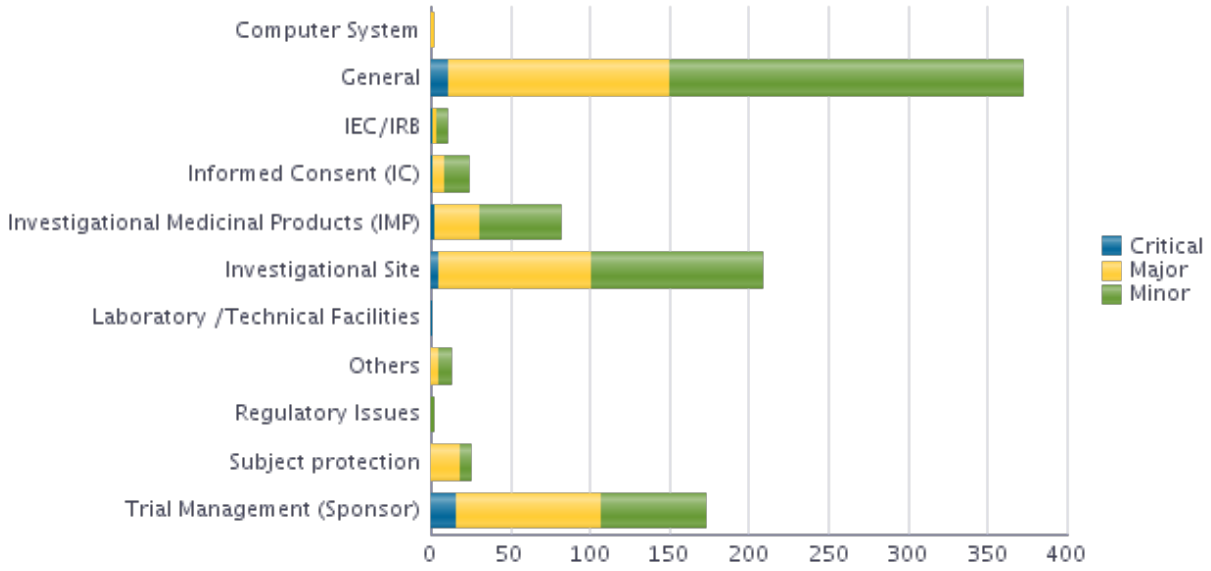


Table 2. Number of findings per sub-category of the top 3 main categories (general, investigational site and trial management) graded by critical, major and minor.

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	9	18
	Direct Access to Data	-	1	-	1
	Essential Documents	1	38	93	132
	Facilities and Equipment	-	4	4	8
	Organisation and Personnel	-	7	26	33
	Qualification/Training	-	16	24	40
	Randomization/Blinding/Codes IMP	-	1	1	2
	SOPs	2	33	23	58
	Source Documentation	8	29	45	82
General Total		**11**	**138**	**225**	**374**
Investigational Site	Protocol Compliance (Assessment of Efficacy)	1	7	9	17
	Protocol Compliance (Others)	-	32	27	59

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 (Safety Reporting)	1	14	7	22
	Protocol Compliance (Selection Criteria)	3	23	9	35
	Reporting in CRF/Diary	-	21	58	79
Investigational Site Total		**5**	**97**	**110**	**212**
Trial Management (Sponsor)	Audit	-	2	1	3
	CSR	2	1	-	3
	Data Management	4	29	16	49
	Document Control	-	8	30	38
	Monitoring	4	32	20	56
	Protocol/CRF/Diary/Questionnaires design	6	19	3	28
Trial Management (Sponsor) Total		**16**	**91**	**70**	**177**

Examples of cross section (critical, major, minor) findings in the top sub-categories of the main three categories “general”, “investigation site” and “trial management” are listed below:

General:

Essential documents

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

Source documentation

- discrepancies between source data and data reported in the Clinical Study Report (CSR)
- corrections on source documents not explained, dated and signed
- lack of document specifying location of source data

Standard Operating Procedures (SOPs)

- lack of evidence that sponsor SOPs had been followed and used
- pharmacy SOPs overdue
- sponsor failure to implement an efficient quality management system

Qualification training

- incomplete training documentation
- lack of GCP training of study personnel

Organisation and Personnel

- incomplete site personnel signature log
- tasks performed by staff not authorised to do so
- no calibration records for the equipment used for the study

Investigational Site:

Reporting in CRF/Diary

- several discrepancies between source data such as medical history, concomitant medication… etc. and the CRF for a sample of subjects
- the patient's diary used in the study as a source document to capture crucial information about adverse events and IMP usage not filled in, in a timely manner
- data not reported to the sponsor in a timely manner

Protocol Compliance (Others)

- the administered IMP dose was in several cases not in compliance with the dose adjustment guidelines of the protocol
- protocol visits were not performed within the visit windows specified in the protocol
- no physical examination was performed at screening as required by the protocol
- the sponsor established and used a system of prospectively accepting deviations from the protocol
- laboratory tests were repeated in case of values outside the ranges stipulated in the protocol

Protocol Compliance (Selection Criteria)

- violation of a number of inclusion criteria for some patients
- final decision about eligibility not always documented in hospital records
- pregnancy tests not performed before randomisation of a number of patients

Protocol Compliance (Safety Reporting)

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

Protocol Compliance (Assessment of Efficacy)

- site did not strictly follow the protocol criteria that had to be used to assess the disease status
- based on documentation review, primary end point assessment for patients was mainly performed by different clinical fellows and not the principal investigator as required by the clinical protocol

Trial management:

Monitoring

- monitor not following monitoring plan

- monitor has not identified number of deficiencies on site
- lack of escalation process to resolve issues identified by monitor
- insufficient quality control and reconciliation of data between source data, CRF and laboratory database both at trial and sponsor site

Data management

- inappropriate system for reporting protocol violations
- erroneous queries reported by sponsor

Document Control

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

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[10], DCP[11] or national procedures)

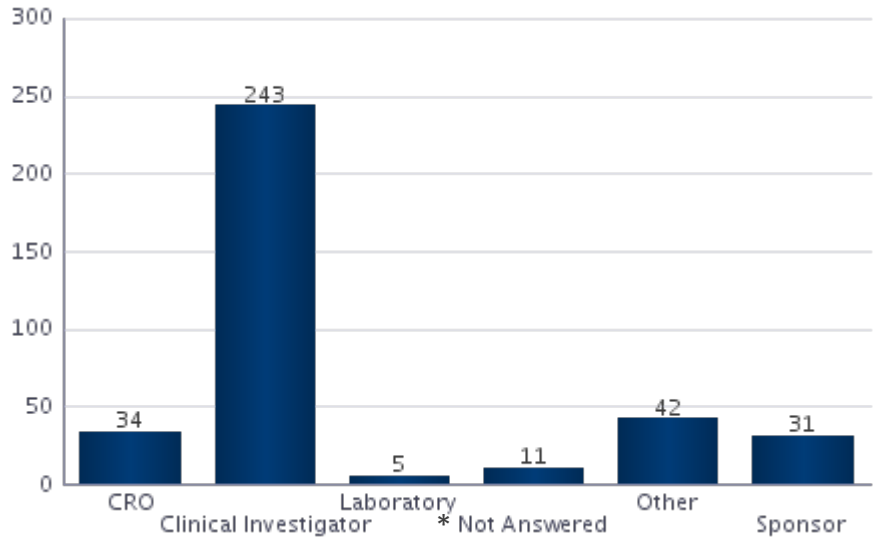
The following statistics are based on information obtained from EudraCT and include the CHMP requested inspections.

Table 3. Inspections conducted per Region

Region	Number of Inspections conducted in 2012
EU/EEA	295
North America	12
Rest of the World	59
Total in all regions	**366**

Figure 4. Number of inspections conducted per type of site

[10] Mutual Recognition Procedure
[11] Decentralised Procedure

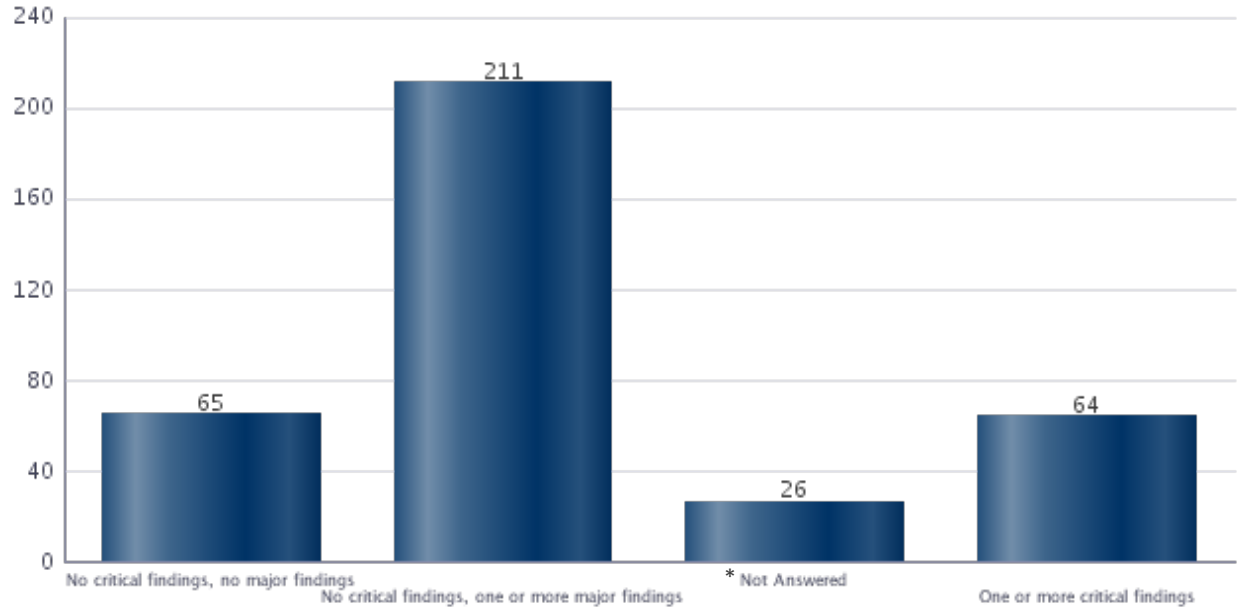


* The information has not been provided in EudraCT.

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

Type of Inspections	Number of Inspections conducted in 2011
Trial Specific	241
Non trial specific	118
Not answered (information not provided in EudraCT)	7

Figure 5. Inspection outcome in relation to the number of critical and major findings



* The information has not been provided in EudraCT.

4. Harmonisation topics

4.1. Procedures and guidance documents

- As part of the CHMP Work Programme 2011-2013, a task was introduced with a 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 clinical assessors was formed in 2011 with the task to prepare a set of documents in relation to the above objectives. The subgroup developed the following documents in 2012:
  - "Points to consider document on GCP inspection findings and the benefit-risk balance". This document was finalised in 2012 and published in January 2013.
  - A "Discussion paper on the follow-up actions from inspection findings" which formed the basis for the revision of the "Procedure for Reporting GCP inspections conducted in the context of the Centralised Procedure".
  - "Procedure for Reporting GCP inspections conducted in the context of the Centralised Procedure" including a revision of the inspection report(IR) and integrated inspection report (IIR) templates . This document was prepared in 2012 and is pending publication . It will be used in a 12month pilot phase after which the procedure and the IR/IIR templates are to be revised.
  - "Points to consider document for assessors and inspectors on the identification of triggers for the selection of applications for "routine" and/or "for cause" inspections, their investigation and scope of such inspections". This document was prepared in 2012. Its finalisation and publication are still pending.

4.2. Inspection cooperation

- Cooperation between the Member States:
  - In 2012 all the inspections requested by the CHMP were joint inspections involving inspectors from at least two Member States.
- Cooperation with 3rd countries:
  - 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 2012, out of the 45 inspections performed outside the EEA, at least 7 EU GCP inspections were observed i.e. Serbia observed 3 inspections, Russia 1 inspection, India 1 and the FDA observed 2 inspections. In addition, 3 joint GCP inspections were carried out between EU inspectors and the US-FDA and 1 joint inspection between EU inspectors, the US-FDA and the WHO.
- The "Procedure on the coordination of GCP inspections of EU interest, outside the context of the marketing authorization procedure, and to be performed under national programmes" was finalised by the GCP IWG and the CTFG (refer to section 7.3).

4.3. GCP training and development

The following activities took place during this year:

4.3.1. 2012 EU GCP Inspectors Working Group workshop

A 2012 EU GCP Inspectors Working Group workshop took place in London (EMA) on 12 – 14 November 2012. Participants included inspectors from the EEA (Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovenia, Spain, Sweden, United Kingdom) and from countries outside the EEA (Bosnia and Herzegovina, Brazil, Canada, Croatia, Ethiopia, Ghana, Indonesia, Japan, Kenya, Republic of Korea, Kosovo, The Former Yugoslav Republic of Macedonia, Malawi, Malaysia, Montenegro, Russian Federation, Serbia, Switzerland, Chinese Taipei, Tanzania, USA).

The following topics were covered:

- Reporting EMA inspections-revised procedure:
  - CHMP evaluation process - where /when do the inspections fit in,
  - The revised procedure on Reporting EMA requested inspections-what are the new expectations
- Inspections of Oncology trials-inspectors' and assessors' perspective
- Inspections of Cardiovascular clinical trials- inspectors' and assessors' perspective
- Inspection findings- Grading and Impact
- GCP and ethical standards in non EU/EEA Countries
- International cooperation on GCP inspections
- Data Management and Statistical Analysis:
  - Inspecting Clinical Data Management and Statistical Analysis –common issues for inspectors to watch out for, Assessor's perspective,
  - Computer validation-practical steps for inspectors.
- Inspections of BE trials:
  - Specificities of BE trials- most common findings and how to identify them; practical examples,
  - Short presentation on inspection findings identified in BE trials.

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

4.3.2. GCP Inspector meetings

During the GCP Inspector meetings held in 2012, the following topics were addressed:

- Develop and monitor opportunities for joint inspections,
- Discuss and respond to queries received from stakeholders,
- Discuss GCP compliance interpretation and ethical issues identified during inspections,
- Discuss and develop peer review of product/company inspection related issues (Bioequivalence and non-bioequivalence studies),
- Update on EudraCT development and training on how to retrieve reports of interest from EudraCT data warehouse (DWH).

5. Topics of interest

The GCP IWG published the following reflection paper in 2012:

- "Reflection paper on guidance for laboratories that perform the analysis or evaluation of clinical trial samples".

The GCP IWG published the following reflection papers for public consultation in 2011 and the comments were reviewed during 2012:

- "Reflection paper on risk based quality management in clinical trials",
- "Reflection paper on the use of interactive response technologies (interactive voice/web response systems) in clinical trials".

The group prepared the following reflection paper in 2012, which will be released for public consultation in 2013:

- "Reflection paper on trial master files (paper and electronic) for GCP compliance and inspection".

In April 2012, the EMA Working Group on clinical trials on medicinal products for human use conducted outside the EU/EEA which included representatives from the GCP IWG, published in the EMA external website the following reflection paper:

- "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 following Question & Answer was published in the EMA external web site:

- "How can proper documentation of eligibility be ensured?"

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 29 February and 12 December 2012. The Commission representative updated the group regarding the progress of the draft proposal of the Clinical Trials Regulation and invited the inspectors to send the Commission comments in relation to GCP aspects that are not reflected well enough in the current legislation. The Commission representative highlighted the main changes of interest to the GCP IWG, proposed in the draft Regulation.

6.2. EudraCT Database

During the GCP IWG meeting on 28- 29 February 2012 the GCP inspectors were trained on how to retrieve predefined reports available on the EudraCT Data Warehouse (EudraCT DWH) Dashboard. These reports could be considered for use by the NCAs when preparing for their national GCP inspection programmes or for retrieving national/European statistics on clinical trials/inspections. Inspectors' queries regarding reports retrieved from EudraCT DWH were answered during the plenary meetings.

6.3. EU enlargement

Bosnia and Herzegovina, Croatia, Kosovo, The Former Yugoslav Republic of Macedonia, Montenegro and Serbia were invited and in most of the cases attended, the GCP IWG meetings held in 2012 as observers.

6.4. Regulation on advanced therapies

The GCP IWG continues with the monitoring of the implementation of GCP guidelines on ATIMPs[12] in clinical trials of advanced therapies.

7. Liaison with other EU groups

7.1. GMDP IWG

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, 3rd bullet point).

7.2. PhV IWG[13]

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. A presentation on the requirements of the new PhV legislation was given during the September GCP IWG meeting.

7.3. CTFG

Members of the CTFG and GCP IWG were involved in the finalisation of the following document:

- "Procedure on the coordination of GCP inspections of EU interest, outside the context of the marketing authorization procedure, and to be performed under national programmes".

Members of the CTFG and GCP IWG are currently involved in the finalisation of the following:

- "Reflection paper on the risk based quality management in clinical trials".

7.4. CMD(h)

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

- The adoption of the Workplan of the GCP/CMD(h) subgroup.
- The preparation of the 2012 risk based programme of routine GCP inspections of the CROs most often used in the conduct of bioequivalence trials included in a MAA in the Mutual Recognition and Decentralised procedures.
- The discussion of processes for:
  - CRO inspections coordination,
  - Exchange of information on BE trials/CRO inspections,

[12] Advance Therapies Investigational Medicinal Products
[13] Pharmacovigilance Inspectors Working Group

- 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. Joint meeting with interested parties

A joint meeting of the GCP IWG and interested parties on the reflection paper on risk based quality management in clinical trials, took place on 22 May 2012.

Delegates from ACRO[14], AESGP[15], BIA/EuropaBio[16], EFGCP[17], EFPIA[18], EGA[19], ACRP[20], BPI[21], Cancer Research UK, University of Oxford, DGGF e.V.[22], DMB[23], EQAC[24], Faculty of Pharmaceutical medicine, IFAPP[25], KKS-Network[26], University of Liverpool and EUCROF[27] attended this meeting.

The following topics were covered:

- Quality by design in clinical trials [expectations, concerns, examples];
- Establishing priorities [What matters more in clinical trials, which are the main priorities, concerns, expectations, examples, points for discussions];
- Quality Tolerance Limits [What tolerance limits mean, who will set up those limits, when, where, types (per protocol vs per GCP);
- Adaptations to monitoring [types and definitions (central, on site, others), descriptions of situations/activities when these different types can be used];
- Measuring and Reporting Quality [What and how to measure, what to report, where in the CSR, what is acceptable when tolerance limits are exceeded, is it acceptable to implement corrective actions and still report that the study was conducted on an acceptable level of quality?];
- The annex in the Reflection paper [Advantages, disadvantages, points missing and to be included etc];
- Three case studies were presented including:
  - Neonatal Antibiotic Study,
  - QA in Clinical Development: a case study of a positive interaction,
  - Risk Based Quality Management in Clinical Trials.

[14] Association of Clinical Research Organizations
[15] European Self-Medication Industry
[16] European Association for Bioindustries
[17] European Forum for Good Clinical Practice
[18] European Federation of Pharmaceutical Industries and Associations
[19] European Generic medicines Association
[20] association of Clinical Research Professionals
[21] Bundesverband der Pharmazeutischen Industrie
[22] Deutsche Gesellschaft für Gute Forschungspraxis e.V. (German Society for Good Research Practice)
[23] Biomedical Data Management association
[24] European Quality Assurance Confederation
[25] International Federation of Associations of Pharmaceutical Physicians
[26] Netzwerk der Koordinierungszentren für Klinische Studien
[27] European CROs Federation

8. Liaison with international partners

8.1. Regulatory agencies from outside the EEA

- 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.

The initial steps for the implementation of a similar pilot programme for generics were taken at the end of 2012. The full implementation of this initiative is expected to take place in 2013.

- PMDA (Japan)[28]-MS initiative:
  - The exchange of information between EU-MS and PMDA inspectorate contact points for notification of GCP inspections, was agreed,
  - EU inspectors observed GCP inspections carried out by PMDA in their MS

The MHLW/PMDA representative at the EMA joined the GCP IWG meeting in February 2012 to present the MHLW/PMDA SOP for providing the GCP inspection schedule from MHLW/PMDA to the EU NCAs & the EMA for inspections conducted in Europe.

8.2. International Initiatives

- The initiative of the Pharmaceutical Inspection Co-operation Scheme (PIC/S) to expand its activities to include training in the field of GCP inspections (e.g. joint inspections), was welcomed by the GCP IWG. In this context the EU GCP inspectors proposed some topics of interests that could be organised by PIC/S including the arrangement of joint GCP inspections with a specific pre-determined focus.
- In 2012, the EMA (along with ASEAN and the WHO) endorsed and supported the "Roadmap to Promote Good Clinical Practice Inspection", a Thai-FDA proposed and APEC supported project, with the goal to further promote regulatory convergence in the area of GCP inspection. The APEC initiative is in line with the EMA “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” (see section 5, 5th bullet point) which emphasises the need to create a robust framework for oversight and conduct of clinical trials through international collaboration of regulators to share best practices, to share information and experiences and to link networks to support all these activities, including GCP inspections.

  The Roadmap outlines a series of stepwise activities over the years 2012-2015, the first of which is a questionnaire. This questionnaire was finalised in September 2012 through the cooperation of

[28] Pharmaceuticals and Medical Devices Agency

APEC, ASEAN, EMA, and WHO and distributed in October 2012 to all the EU/EEA member states through the GCP IWG members.

For details of the activities of the GCP IWG for next year see the Work plan for 2013.