



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 May 2014
EMA/INS/GCP/123295/2013
Compliance and Inspection

Annual report of the Good Clinical Practice Inspectors Working Group 2013

Adopted by the GCP IWG 28 April 2014

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom

Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8594

E-mail info@ema.europa.eu **Website** www.ema.europa.eu

An agency of the European Union



Table of contents

1. Introduction	3
2. Meetings	3
3. Inspections conducted in support of the centralised procedure and under national programmes	3
3.1. CHMP requested inspections	3
3.1.1. General overview	3
3.1.2. Categorisation of findings	5
3.2. GCP inspections performed under national programmes	9
4. Harmonisation topics	10
4.1. Procedures and guidance documents	10
4.2. Inspection cooperation	11
4.3. GCP training and development	11
4.3.1. 2013 EU GCP Inspectors Working Group workshop	11
4.3.2. On-line GCP inspectors' basic training course	12
4.3.3. GCP IWG meetings	12
5. Topics of interest	13
6. Collaboration with European Commission	13
6.1. Implementation of Directive 2001/20/EC and of Directive 2005/28/EC and related guidance documents	13
6.2. EudraCT Database	13
6.3. EU enlargement	13
6.4. Regulation on advanced therapies	14
7. Liaison with other EU groups	14
7.1. GMP/GDP IWG	14
7.2. PhV IWG	14
7.3. CTFG	14
7.4. CMDh	14
7.5. Heads of Medicines Agencies	15
7.6. PDCO	15
7.7. Joint meetings with interested parties	15
8. Liaison with international partners	16
8.1. Regulatory agencies from outside the EEA	16
8.2. International Initiatives	16

1. Introduction

This document is the sixth Annual Report of the GCP IWG. 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](#), which was revised in 2013, [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, CVMP, CMDh, PhV IWG, GMP/GDP 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 2013 [workplan](#).

2. Meetings

The plenary GCP IWG meetings took place on:

- 05-06 March 2013
- 11-12 June 2013
- 11-12 September 2013
- 03-04 December 2013

During 2013, the following GCP inspectors' subgroups were involved in the discussion of specific topics and drafting documents:

- GCP/CMDh (refer to section 7.4),
- GCP/CHMP assessors (refer to section 4.1),
- GCP-CTFG risk based quality management in clinical trials subgroup (refer to section 5, 1st bullet point),
- GCP IRT¹ (refer to section 5, 2nd bullet point),
- GCP TMF² (refer to section 5, 3rd 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 72 GCP inspections in 2013. In total 83 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 2012 were conducted in 2013 and some inspections requested in the last 3 months of 2013 will be carried out in 2014. The data in this report relates to inspections carried out.

¹ Interactive Response Technologies

² Trial Master File

In figure 1, the number of inspections carried out in 2013 is shown by region and type of inspection. Most inspections were carried out in the EU/EEA/EFTA³ (37%) followed by inspections in the USA (25%) and the Middle East/Asia/Pacific (12%).

Figure 1. Inspections conducted per region and type of inspection

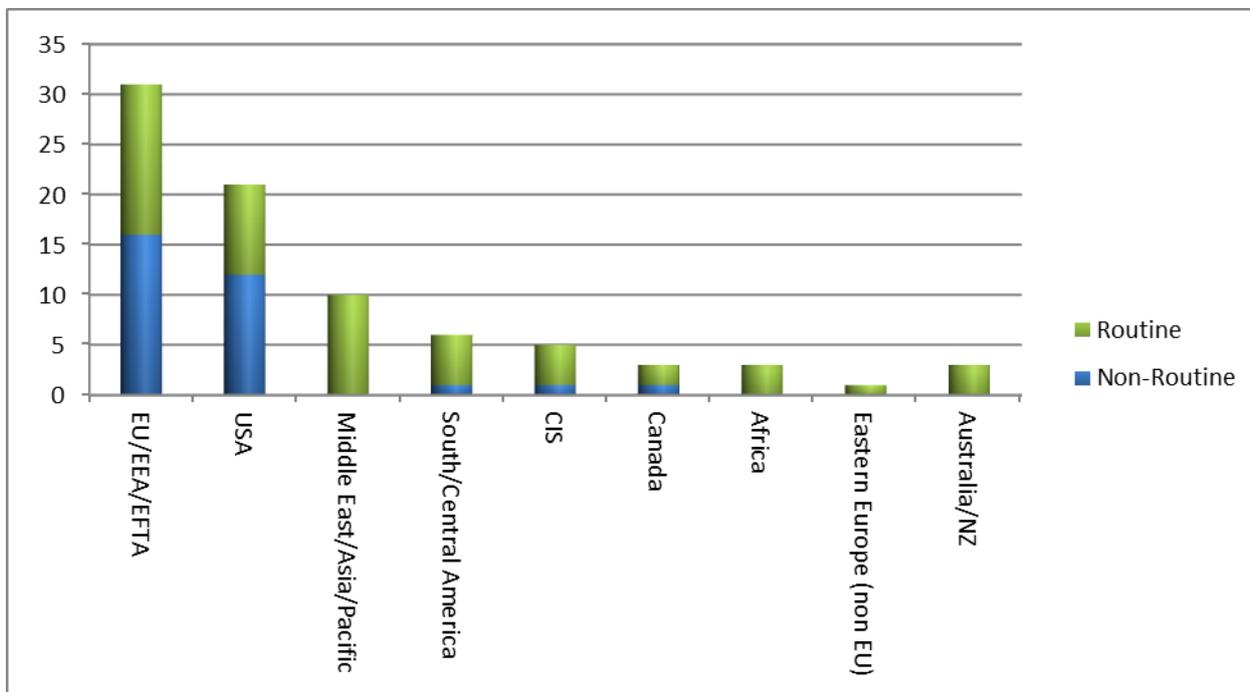


Table 1. Number of Inspections conducted per region and type of inspection.

Region	Non-Routine	Routine	Total
EU/EEA/EFTA	16	15	31
USA	12	9	21
Middle East/Asia/Pacific	-	10	10
South/Central America	1	5	6
CIS	1	4	5
Canada	1	2	3
Africa	-	3	3
Eastern Europe (non EU)	-	1	1
Australia/New Zealand	-	3	3
Total in all regions	31	52	83

³ European Union/European Economic Area/European Free Trade Association

Figure 2. Inspections conducted per type of site

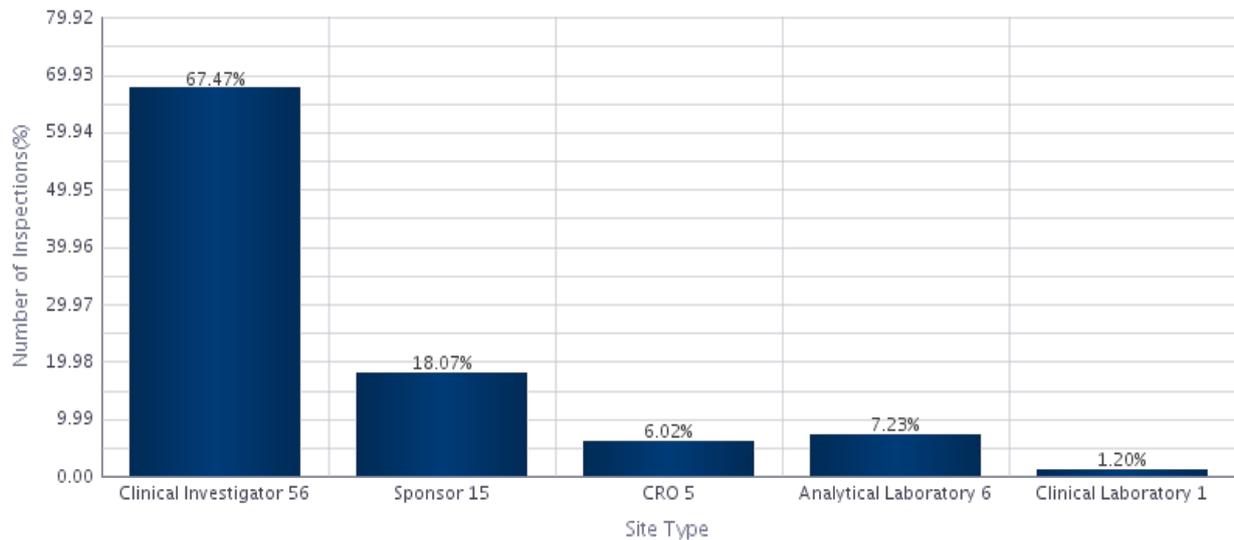


Figure 2 represents the number of inspections conducted in 2013 per type of site. Most inspections were conducted at clinical investigator sites.

3.1.2. Categorisation of findings

A total of 1052 deficiencies, comprising 64 critical (6%), 429 major (41%) and 559 minor (53%) were recorded for the 83 CHMP requested inspections conducted in 2013.

The main findings observed in the 2013 inspections are detailed below in accordance with the GCP organisation of findings agreed by the GCP IWG.

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

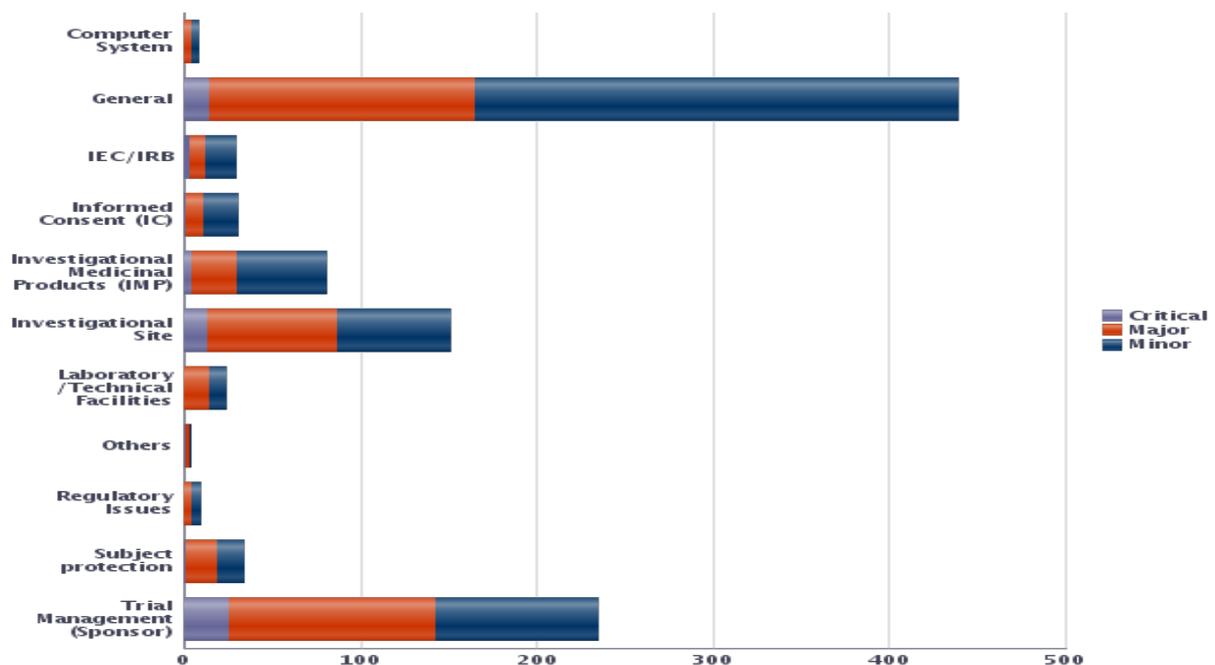


Table 2. Number of findings per sub-category of the top 3 main categories (general, trial management and investigational site) graded by critical, major and minor.

Number of findings per sub-category of the top 3 main categories (general, trial management and investigational site) graded by critical, major and minor					
Deficiency Category Name	Deficiency Sub Category Name	# Inspected Deficiencies			# Inspected Deficiencies Total
		Critical	Major	Minor	
General	Contracts/Agreements	1	5	20	26
	Direct Access to Data	2	2	2	6
	Essential Documents	4	32	112	148
	Facilities and Equipment	-	7	2	9
	Organisation and Personnel	-	14	18	32
	Qualification/Training	2	19	33	54
	Randomisation/Blinding/Codes IMP	-	3	1	4
	SOPs	4	48	43	95
	Source Documentation	2	20	44	66
General Total		15	150	275	440
Trial Management (Sponsor)	Audit	-	2	9	11
	CSR	5	14	5	24
	Data Management	9	36	28	73
	Document Control	2	10	21	33
	Monitoring	8	40	24	72
	Protocol/CRF/Diary/Questionnaires design	2	12	5	19
	Statistical Analysis	-	3	-	3
Trial Management (Sponsor) Total		26	117	92	235
Investigational Site	Protocol Compliance (Assessment of Efficacy)	1	6	4	11
	Protocol Compliance (Others)	3	20	12	35
	Protocol Compliance (Safety Reporting)	4	16	9	29

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

	Protocol Compliance (Selection Criteria)	3	16	20	39
	Reporting in CRF/Diary	2	16	20	38
Investigational Site Total		13	74	65	152

Examples of cross section (critical, major, minor) findings in the top sub-categories of the main three categories "general", "trial management" and "investigation site" 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

Standard Operating Procedures (SOPs):

- lack of evidence that sponsor SOPs have been followed and used
- SOPs not update as required
- sponsor failure to implement an efficient quality management system

Source documentation:

- discrepancies between source data and data reported in the Clinical Study Report (CSR)
- missing source documents
- lack of document specifying location of source data

Qualification/training:

- incomplete training documentation
- lack of training of study personnel on trial related procedures

Organisation and personnel:

- incomplete site personnel signature log
- tasks performed by staff not authorised to do so

Trial management

Data management:

- inappropriate system for reporting protocol violations
- laboratory reports were submitted late to the site
- data management activities were only undertaken after the clinical conduct of the trial was completed

- the decisions made by the DMSB were not communicated to the site

Monitoring:

- monitor has not identified number of deficiencies on site
- lack of escalation process to resolve issues identified by monitor
- monitor not following monitoring plan
- investigator's training was done over the phone

Document control:

- lack of version/date on the document

late introduction of amendments in the study

Investigational Site

Protocol compliance (selection criteria):

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

Reporting in CRF/Diary:

- several discrepancies between source data such as medical history, concomitant medication etc. and the CRF for a sample of subjects
- corrections on CRF not signed and dated
- data not reported in CRF in a timely manner

Protocol Compliance (others):

- IMP and concomitant medication protocol deviations
- protocol visits were not performed within the visit windows specified in the protocol
- the sponsor established and used a system of prospectively accepting deviations from the protocol
- insufficient maintenance of blinding of IMP

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
- the procedures for the primary end point assessment for patients were not always strictly followed as required by the clinical protocol

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 Authorisation Applications (MRP⁴, DCP⁵ 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 2013
EU/EEA	268
North America	17
Rest of the World	54
Total in all regions	339

Figure 4. Number of inspections conducted per type of site



* The information has not been provided in EudraCT

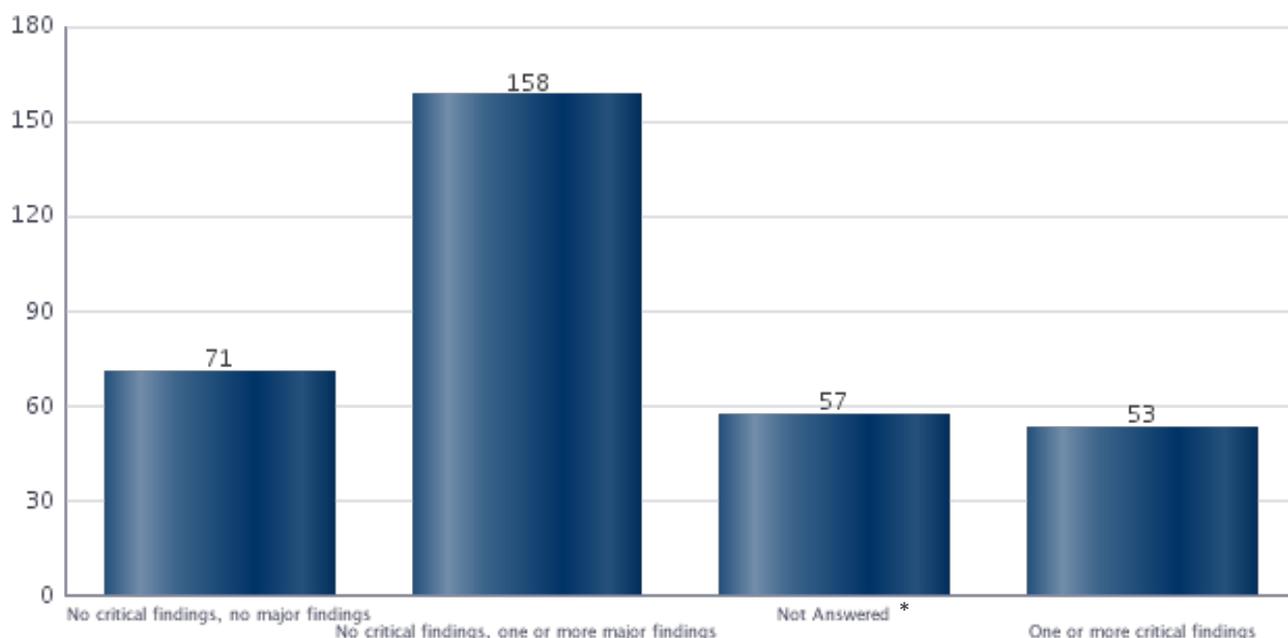
⁴ Mutual Recognition Procedure

⁵ Decentralised Procedure

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

Type of Inspections	Number of Inspections conducted in 2013
Trial Specific	158
Non trial specific	175
Not answered (information not provided in EudraCT)	6

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 following documents were published in 2013:
 - [“Points to consider document on GCP inspection findings and the benefit-risk balance”](#).
 - [“Points to consider for assessors, inspectors and EMA inspection coordinators on the identification of triggers for the selection of applications for “routine” and/or “for cause” inspections, their investigation and scope of such inspections”](#).

- [“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. It is to be used in a 12month pilot phase after which the procedure and the IR/IIR templates are to be revised.](#)

The “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” was finalised in 2013 and agreed by the GCP IWG and the CHMP.

- The GCP IWG/CMDh published a revised version of the [‘Guidance on triggers for inspections on bioequivalence trials’](#).
- The GCP IWG adopted a new version of the [‘Procedure for coordinating GCP inspections requested by the CHMP’](#).

4.2. Inspection cooperation

- Cooperation between the Member States:
 - In 2013 the majority of 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 centralised procedure. In 2013, out of the 52 inspections performed outside the EEA, at least 19 GCP inspections requested by the CHMP were observed by 3rd country regulatory authorities including Belarus, South Africa, Brazil, Canada, Switzerland, Turkey, Australia, Japan, China, Mexico, USA, Ukraine, Russia and India. In addition, 1 joint GCP inspection between EU inspectors and the US-FDA took place in 2013.

4.3. GCP training and development

4.3.1. 2013 EU GCP Inspectors Working Group workshop

A 2013 EU GCP Inspectors’ Working Group workshop took place at the Agency on 14 – 16 October 2013. Participants included inspectors from the EEA (Austria, Belgium, Bulgaria, Croatia, Denmark, Estonia, Finland, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovenia, Spain, Sweden, United Kingdom), from countries outside the EEA (Belarus, Brazil, Canada, Ghana, Japan, Republic of Korea, Kosovo, The Former Yugoslav Republic of Macedonia, Montenegro, Russian Federation, Kingdom of Saudi Arabia, Serbia, Swaziland, Singapore, South Africa, Switzerland, Chinese Taipei, Tanzania, USA) and from the WHO.

The following topics were covered:

- Risk-based approach to inspection planning:
 - How to develop a risk-based inspection programme,
 - What should trigger an inspection-clinical assessor’s perspective.
- Risk based approach to GCP inspection preparation:
 - General considerations,

- Review of data listings.
- Inspection of eTMF and eSource Data
 - Industry’s perspective,
 - Inspectors’ expectations and common findings,
 - Inspection of eTMF and eSource data.
- Categorisation and impact of inspection findings
- Safety Reporting in the context of a GCP inspection
 - Overview of the EU guidance requirements on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use (‘CT-3’),
 - Overview of PhV aspects to be reviewed during a GCP inspection.
- International cooperation on GCP inspections
 - Overview of international collaboration initiatives,
 - The EAMI and APEC initiatives,
 - Particularities of the informed consent process.
- Inspection of Statistical Aspects of a Marketing Authorisation Application (MAA):
 - Assessors’ review of the statistical aspects of a marketing authorisation (MAA) application,
 - How to look at practical aspects of statistical analysis whilst on inspection.

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

4.3.2. On-line GCP inspectors’ basic training course

In 2013, the GCP IWG began working on the design of an on-line GCP inspectors’ basic training course. There are three modules planned for this course covering a broad range of topics:

- Module 1: General background and preparation of GCP inspections,
- Module 2: Conduct of GCP inspections,
- Module 3: Reporting of GCP inspections.

A number of senior GCP inspectors will introduce the topics outlined above and the presentations will be posted on EudraPortal. Participants will be asked to complete some exercises which are to be discussed during webinars organised by the Agency in collaboration with the senior inspectors. This course is expected to be launched in 2014, initially, for a one year pilot phase.

4.3.3. GCP IWG meetings

During the GCP IWG meetings held in 2013, the following topics were addressed:

- develop and monitor opportunities for joint inspections,
- information and discussions on new pharmaceutical legislation, procedures and guidance,

- the GCP IWG contributed to the Agency comments provided to the World Medical Association on the 2013 version of the Declaration of Helsinki,
- discuss and respond to queries received from stakeholders,
- discuss how risk based monitoring is evaluated during inspections,
- 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.

5. Topics of interest

The GCP IWG reviewed the comments received during the public consultations of the following reflection papers which were subsequently finalised and published in 2013:

- [“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 GCP IWG published the following reflection papers for public consultation in 2013 and the comments received were reviewed:

- [“Reflection paper on good-clinical-practice compliance in relation to trial master files \(paper and / or electronic\) for management, audit and inspection of clinical trials”](#).

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 group was regularly updated by its chair on the progress of the draft Clinical Trials Regulation.

6.2. EudraCT Database

The group was updated regarding the development of the EudraCT database on a regular basis. During the March GCP IWG meeting a presentation was given on the data quality in EudraCT regarding data on inspections. During the December GCP IWG meeting the group was informed about the new features of EudraCT version 9.0 and the upgrade of EU CTR. A demo was also provided to the inspectors.

6.3. EU enlargement

Albania, Bosnia and Herzegovina, 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 2013 as observers.

6.4. Regulation on advanced therapies

The GCP IWG continues with the monitoring of the implementation of GCP guidelines on ATIMPs⁶ in clinical trials of advanced therapies.

7. Liaison with other EU groups

7.1. GMP/GDP 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, 2nd bullet point).

7.2. PhV IWG⁷

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 were involved in the finalisation of the following document:

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

7.4. CMDh

The GCP IWG and the CMDh, mainly through the GCP/CMDh subgroup, have contributed to:

- The preparation of the 2013 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 revision and publication of the guidance on triggers for inspections on bioequivalence trials (refer to section 4.1, 2nd bullet point).
- 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.

⁶ Advance Therapies Investigational Medicinal Products

⁷ Pharmacovigilance Inspectors Working Group

7.5. Heads of Medicines Agencies

See section 7.3

7.6. PDCO

A representative of the scientific secretariat of the PDCO attended the GCP IWG meeting in June 2013 in order to present a discussion paper on GCP inspections of paediatric clinical trials agreed in Paediatric Investigation Plans. The GCP IWG endorsed this document and it was agreed that the Agency would prepare an internal document (SOP or WIN) which will describe the steps taken to increase communication between the Agency, the PDCO and the GCP IWG. It is anticipated that the Agency will inform the PDCO of GCP inspections requested involving paediatric clinical trials and will share the IIR with the committee. Also, it is foreseen that the PDCO will identify paediatric clinical trials with particular points of interest and inform the Agency about clinical trial results provided as part of a marketing authorisation application under the centralised procedure and the member states for on-going clinical trials.

7.7. Joint meetings with interested parties

- On 10 June 2013 the Novartis eSource Team, in collaboration with Clinical Ink and Cmed, met with representatives of the GCP Inspectors' Working Group including delegates who were responsible for drafting the "Reflection Paper on Expectations for Electronic Source Data and Data Transcribed to Electronic Data Collection tools in Clinical Trials", to have an open dialogue on the use of eSource in Novartis sponsored clinical trials. The intent of the meeting was to present Novartis' experiences with eSource to date and share metrics from its pilots, to show how data flow changes in an eSource setting and to review other implications for monitoring and data management.
- A joint meeting between the GCP IWG and eClinical Forum (eCF) representatives took place on 11 June 2013 in order to discuss current electronic data capture systems and clarify the requirements expressed by the GCP IWG. The document on investigator site eSource readiness developed by the eCF was also discussed. For further details please refer to the [minutes](#) of the meeting.
- A risk based quality management in clinical trials workshop organised by the Agency in conjunction with the Clinical Trial Transformation Initiative (CTTI) and one of its members, the US Food and Drug Administration (FDA), took place within the margins of the December GCP IWG meeting. Delegates from AKU Society, Apotex Europe BV, B. Braun Melsungen AG, Bio Industry Association, Boehringer Ingelheim Limited, Bristol-Myers Squibb, German Medicines Manufacturers' Association, Bundesverband der Pharmazeutischen Industrie, ACRP⁸, Cancer Research UK, Clinical Trials Transformation Initiative, Covance Late Stage Development Services, Cystic Fibrosis Trust, Duke Clinical Research Institute, Eli Lilly & Co., EUPATI⁹, INSERM-DRCT¹⁰, EORTC¹¹, Ferring Pharmaceuticals Inc, Fight Colorectal Cancer, Genova Ltd, GlaxoSmithKline Research & Development Ltd, Hoffmann-La Roche Ltd, IST GmbH, Institut de Sante Publique, International Drug Development Institute, King's College London, Merck KGaA, National Breast Cancer Coalition, Inspectie voor de Gezondheidszorg, Parexel, Pharmaceuticals and Medical Devices Agency, Quintiles Transnational Corp., Reckitt Benckiser, Sandoz International GmbH, Sanofi-Aventis, ,

⁸ Association of Clinical Research Professionals

⁹ European Patients' Academy on Therapeutic Innovation

¹⁰ European Clinical Research Infrastructure Network

¹¹ European Organisation for Research and Treatment of Cancer

Statens legemiddelverk Target Health Inc., Tecnimede Sociedade Tecnico Medicinal, The Medicines Company, University of Oxford, U.S. Food and Drug Administration, University of Leipzig, Universitaetsklinikum Freiburg, Universitaetsklinikum Leipzig, Arnoult.Org, attended this workshop.

The topics covered, in the form of presentations and breakout sessions, included:

- The Reflection paper 'Risk based quality management in clinical trials' and summary of the main changes introduced during the revision;
- Study design and planning for quality;
- How to review the risks and report on quality;
- Risk based approach to monitoring;
- Identifying ways to foster innovative approaches.

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 Agency 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.

A similar pilot programme for generics was fully implemented in 2013.

- PMDA (Japan): a representative of the PMDA from the Office of Conformity Audit joined the December GCP IWG meeting by T-con in order to discuss common topics of interest with the EU GCP inspectors.

8.2. International Initiatives

- The GCP IWG was updated regarding the initiative of the Pharmaceutical Inspection Co-operation Scheme (PIC/S) to expand its activities to include training in the field of GCP inspections. The group was informed that the topics of interest it proposed to PIC/S in 2012 were taken on board. Two groups consisting of three GCP inspectors have performed joint GCP inspections in 2013 under the PIC/S.
- In 2012, the Agency (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 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 APEC, ASEAN, EMA, and WHO and distributed in October 2012 to all the EU/EEA member states

through the GCP IWG members. The results of this questionnaire were presented by the Agency, on behalf of APEC, at the 2013 EU GCP IWG workshop.

- During the 2013 EU GCP IWG workshop a session was devoted to international cooperation in GCP inspections (refer to section 4.3.1, 6th bullet point). During this session various possibilities offered by the EU GCP IWG to the international network of GCP inspectors were presented.

For details of the activities of the GCP IWG for next year see the [workplan](#) for 2014.