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SCIENCE MEDICINES HEALTH

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Inspections Office
Quality and Safety of Medicines Department

Annual Report of the Good Clinical Practice (GCP) Inspectors' Working Group (IWG) 2022

Adopted by the GCP IWG on 10 October 2023

List of Abbreviations

BE	BioEquivalence
CHMP	Committee for Medicinal Products for Human Use
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures - Human
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical/Contract Research Organisation
CSR	Clinical Study Report
CTCG	Clinical Trials Coordination Group
CTIS	Clinical Trials Information System
CVMP	Committee for Medicinal Products for Veterinary Use
DG SANTE	Directorate-General for Health and Food Safety
eCRF	electronic Case Report Form
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDP	Good Distribution Practice
GMP	Good Manufacturing Practice
HMA	Heads of Medicines Agencies
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMRA	International Coalition of Medicines Regulatory Authorities
IEC	Independent Ethics Committee
IIR	Integrated Inspection Report
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IWG	Inspectors Working Group
MS	Member State
PDCO	Paediatric Committee
PhV	Pharmacovigilance
PMDA	Pharmaceuticals and Medical Devices Agency (Japanese competent authority)
Q&A	Question & Answer
ROW	Rest of the World
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
UK	United Kingdom
UNSC	United Nations Security Council
US(A)	United States (of America)
WHO	World Health Organisation

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1. Introduction

This document is the fifteenth Annual Report of the GCP IWG. This group was established in 1997 under the scope of Article 51(e) of Council Regulation (EEC) No. 2309/93, subsequently amended as Article 57(1)(i) of Regulation (EC) No. 726/2004.

The GCP IWG focuses on harmonisation and coordination of GCP related activities at European Union (EU)/European Economic Area (EEA) level. The group's role and activities are described in more detail in its mandate, which was revised in 2013, its current Work Plan and also in Volume 10, chapter IV of the publication "The rules governing medicinal products in the European Union".

The group supports the coordination of the provision of GCP advice and maintains a dialogue with other groups, such as the Committee for Medicinal Products for Human Use (CHMP), the Committee for Medicinal Products for Veterinary Use (CVMP), the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh), the Pharmacovigilance (PhV) IWG, the Good Manufacturing Practice/Good Distribution Practice (GMDP) IWG and other groups, as needed, in areas of common interest.

This Annual Report has been drawn up in line with the format and objectives of the 2021-2023 Work Plan.

2. Meetings

Four regular GCP IWG meetings took place in 2022:

- 8-9 March 2022 (virtual);
- 21-22 June 2022 (virtual);
- 13-14 September 2022 (virtual);
- 29-30 November 2022 (hybrid).

During 2022, the following GCP inspectors' subgroups/working parties were involved in the discussion of specific topics and drafting documents:

- GCP IWG/CMDh working party (refer to section 6.5);
- GCP IWG subgroup on drafting guidance on electronic systems used in clinical trials (refer to section 4.1);
- GCP IWG subgroup on decentralised clinical trials (refer to section 4.1);
- GCP IWG subgroup on Integrated Inspection Report (IIR) Peer Review process;
- GCP IWG subgroup on serious breaches submitted and assessed according to the new Clinical Trials Regulation (CTR);
- GCP IWG subgroup on embedding the outcome of GCP inspections into the benefit-risk assessment and modernisation of the GCP inspection process;
- GCP IWG subgroup on drafting a Q&A about the considerations when direct remote access of identifiable personal and health data is required in a clinical trial (former Subgroup on remote source data verification);
- GCP IWG subgroup on selection of procedures and site exploiting the individual patient data listings (raw data pilot);

- GCP IWG subgroup on revising the reporting procedure;
- GCP IWG subgroup on revising the Annex V on inspection of phase I units (refer to section 4.1);
- GCP IWG subgroup on recommendations for the management of clinical trials impacted by major disruptions (refer to section 4.1);
- GCP IWG subgroup on the redaction of inspection reports for publication in the Clinical Trials Information System (CTIS).

3. Inspections conducted in support of the centralised procedure

3.1. CHMP requested inspections

3.1.1. General overview

a) Foreword

The data in this report relates to inspections carried out in 2022.

In April 2022, a new system for the management of GCP inspections was deployed: IRIS. This report compiles data from IRIS and from the previously used (internal) system.

In total, 36 GCP inspections including 26 routine and 10 triggered were requested by CHMP and carried out by the inspectorates of the EU/EEA Member States (MSs) in 2022. It should be noted that several inspections requested in 2021 were conducted in 2022, which are therefore included in this report. In addition, several inspections requested in 2022 were carried out in 2023, which are therefore not included in this report.

The figures cited above reflect the number of inspections performed at a given site. If a site was inspected for several clinical trials, it was counted once for the purpose of this report. It should be noted that different methods for counting inspections coordinated by the European Medicines Agency (EMA) can be used in other reports, for instance when the indicator is the number of fees invoiced for distinct inspections, as defined in the Rules for the implementation of Council Regulation (EC) No 297/95 on fees payable to the European Medicines Agency and other measures.

At the start of the year 2022, due to the COVID-19 pandemic and associated restrictions (similarly to 2020 and 2021), some site inspections were conducted remotely or in a hybrid setting. Please refer to section 4.2 for more information.

b) Geographical distribution

Similarly to the 2021 annual report, this report distinguishes the following regions:

- EU/EEA;
- North America:
  - United States of America (USA);
  - Canada.
- Rest of the World (ROW):
  - Africa;
  - Asia;

- Eastern Europe, non-EU (Belarus, Bosnia, the Republic of North Macedonia, Moldova, Russia, Serbia, Ukraine);
- Western Europe, non-EU (Switzerland, United Kingdom [UK]);
- Latin America and the Caribbean;
- Oceania.

c) Inspection figures

In Figure 1 and Table 1, the number of inspections conducted in 2022 is shown by region and type of inspection. Most inspections were carried out in the North America region (44.4%) followed by the EU/EEA (36.1%) and Western Europe, non-EU (8.3%).

Table 1: Number of inspections conducted per region and type of inspection.

Region	Non-Routine	Routine	Total
EU/EEA	12	1	**13**
North America	9	7	**16**
Africa	0	0	**0**
Asia	1	1	**2**
Eastern Europe, non-EU	0	0	**0**
Western Europe, non-EU	2	1	**3**
Latin America and the Caribbean	2	0	**2**
Oceania	0	0	**0**
Total in all regions	**26**	**10**	**36**

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

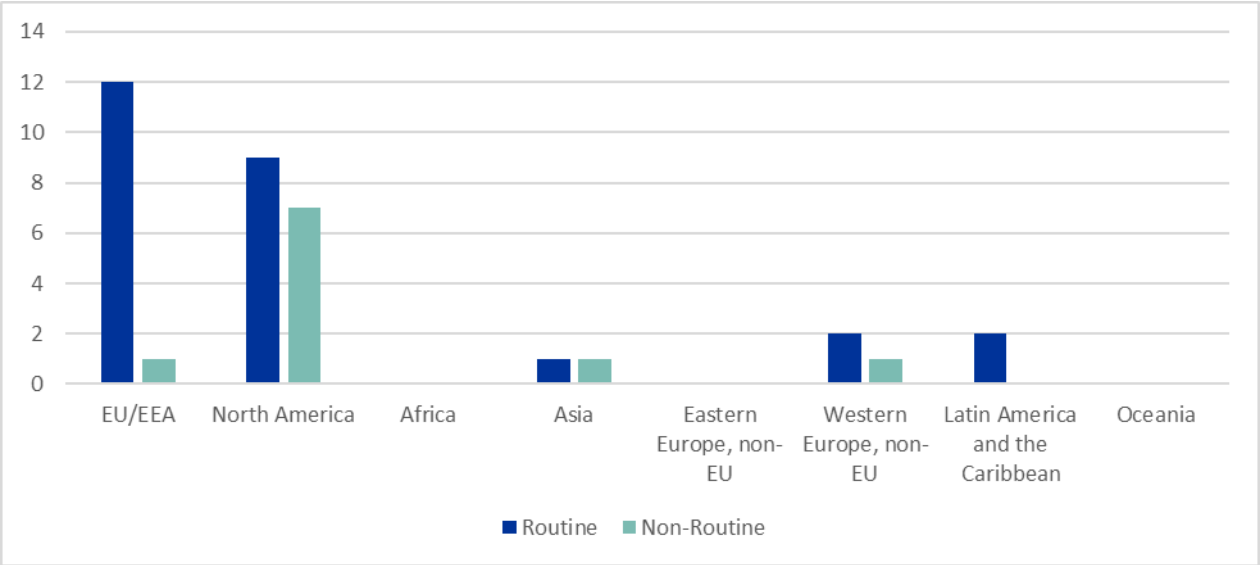
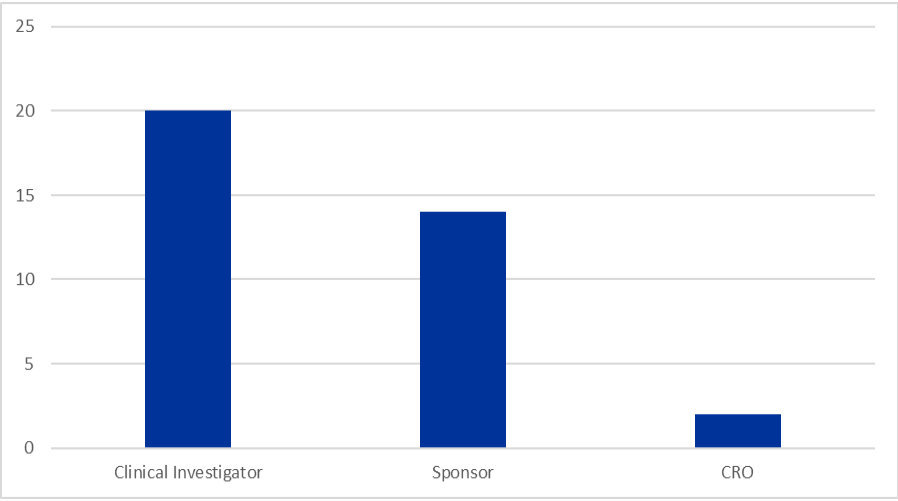


Table 2 and Figure 2 represent the number of inspections conducted in 2022 per type of site. Most of the inspections were conducted at clinical investigator sites, followed by sponsors and Clinical/Contract Research Organisations (CROs).

Table 2: Inspections conducted per type of site.

Site	No. of inspections conducted
Clinical investigator	20
Sponsor	14
CRO	2
Total in all sites	**36**

Figure 2: Inspections conducted per type of site.



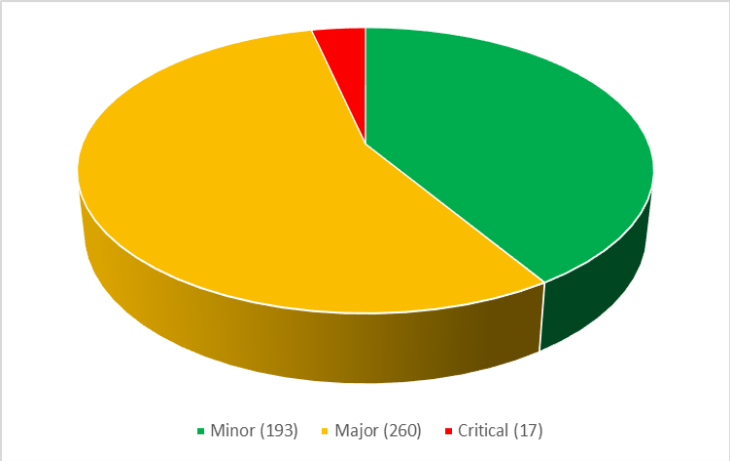
3.1.2. Categorisation of findings

a) General overview

A total of 470 deficiencies, comprising 17 critical (3.6%), 260 major (55.3%) and 193 minor (41.1%) findings were recorded for the 36 CHMP requested inspections conducted in 2022. This represents an average of 13 findings per site inspected.

The main findings observed in the 2022 inspections are detailed below in accordance with the GCP categorisation of findings agreed by the GCP IWG.

Figure 3: Number of findings by grading categories: critical, major, and minor.

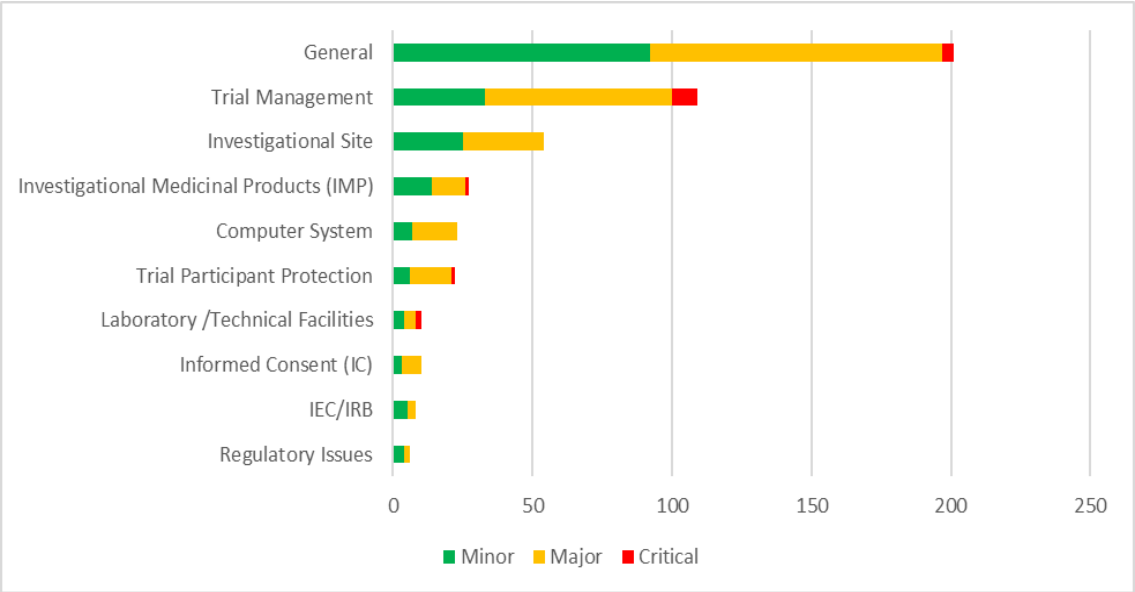


b) Distribution by categories and sub-categories

Table 3: Number of findings by main category and grading categories: critical, major, and minor.

Main category	Minor	Major	Critical	Total
General	92	105	4	**201**
Trial Management	33	67	9	**109**
Investigational Site	25	29	0	**54**
Investigational Medicinal Products (IMPs)	14	12	1	**27**
Computer System	7	16	0	**23**
Trial Participant Protection	6	15	1	**22**
Laboratory/ Technical Facilities	4	4	2	**10**
Informed Consent	3	7	0	**10**
Independent Ethics Committee (IEC)/Institutional Review Board (IRB)	5	3	0	**8**
Regulatory Issues	4	2	0	**6**
Total	**193**	**260**	**17**	**470**

Figure 4: Number of findings by main category and grading categories: critical, major, and minor.



Findings are detailed below for the top three categories: General, Trial Management, and Investigational Site.

Table 4: Number of findings per sub-category of the top 3 main categories (General, Trial Management and Computer System) graded as critical, major, and minor.

		# Inspected deficiencies			Total
Deficiency category name	**Deficiency sub-category name**	**Minor**	**Major**	**Critical**	
General	Contracts/Agreements	4	11	0	**15**
	Direct Access to Data	1	2	1	**4**
	Essential Documents	24	33	1	**58**
	Facilities and Equipment	13	10	0	**23**
	Organisation and Personnel	14	9	0	**23**
	Qualification/Training	15	9	0	**24**
	Randomisation/Blinding/Codes IMP	1	5	0	**6**
	Quality System	12	18	2	**32**
	Source Documentation	8	8	0	**16**
General Total		**92**	**105**	**4**	**201**
Trial Management	Audit	3	6	0	**9**
	Clinical Study Report (CSR)	3	7	1	**11**
	Data Management	9	236	3	**35**
	Document Control	9	6	3	**16**
	Monitoring	5	11	1	**17**
	Protocol/ Case Report Form (CRF)/ Diary/ Questionnaires design	6	8	1	**15**
	Statistical Analysis	0	6	0	**6**
Trial Management Total		**33**	**67**	**9**	**109**
Investigational Site	Protocol Compliance (Others)	5	5	0	**10**
	Protocol Compliance (Assessment of Efficacy)	1	0	0	**1**
	Protocol Compliance (Safety	9	13	0	**22**
	Protocol Compliance (Selection Criteria)	5	6	0	**11**
	Reporting in CRF/Diary	5	5	0	**10**
Investigational Site Total		**25**	**29**	**0**	**54**

Examples of critical and major findings in the sub-categories of the three main categories "General", "Trial Management", and "Investigational Site" are listed below.

General

- Misleading, inaccurate, and incomplete information prior to and during inspection in addition to a lack of inspection readiness and deficient document request management during inspection have impacted the preparation and conduct of the inspection.

Contracts/Agreements:

- The contracts and/or master service agreements with third party vendors and/or service providers that were inspected in detail did not (or not adequately) address the legal right for representatives of regulatory agencies (inspectors) to inspect those third parties, their activities, and systems on site.
- The contract for long term archiving of the site documents including the investigator site file did not adequately address specific GCP requirements for these documents (e.g. period for archiving conditions, etc.).
- There were no separate written agreements with three hospital departments that provided study specific services for the principal investigator.

Direct Access to Data:

- Relevant access to source data was not in compliance with GCP for a number of clinical sites. This impacted both source data verification by clinical research associates (CRAs) and conduct of the inspection by the inspectors. In addition, at the site inspected, an unvalidated process was used to generate certified copies. There was no robust process for CRAs or inspectors to verify the completeness and correctness of the printouts of electronic systems/repositories.
- Issues in accessing data systems (electronic CRF [eCRF], Interactive Web Response Systems) prior to and during the inspection due to decommissioning.
- Incomplete information provided to inspectors prior to inspection regarding data management and computerized systems.

Essential Documents:

- The investigator site file (regulatory binder) and a third of the trial participant binders could not be located by the site during the inspection making it difficult for inspectors to reconstruct and validate the data from the study for these trial participants and recreate the study. Without the knowledge of the staff at the site, the investigator site file, and the missing trial participant source documents, inspectors could not validate the data of these trial participants.
- The hybrid Trial Master File (TMF), as presented to the inspectors, was incomplete with respect to relevant and crucial trial-related documentation including, but not limited to miscellaneous communication (e.g. emails), relevant decisions or important events (e.g. migration of the TMF, Database unlock) and electronic systems (selection, qualification, and validation). In addition, many documents in the electronic part of the hybrid system proved to have been uploaded with significant delay.
- The sponsor did not identify and have a clear understanding of the content of the TMF(s).The eTMF was not properly maintained during the conduct of the trials and/or the audit trails were not complete.

Facilities and Equipment:

- Electronic long-term storage/archiving arrangements for the essential documents were not adequate.
- Equipment standardisation and documentation of certification was insufficient. This indicates a lack of risk assessment given the relevance for the primary endpoint.
- During the pharmacy visit, the inspectors observed that the available space is globally insufficient to store the IMP of ongoing studies and does not allow to allocate specific areas for product quarantine or expired products, which increases the risk of human error.

Organisation and Personnel:

- Delegation of trial specific tasks had not been done and/or documented properly.
- Insufficient resources available to perform the trial duties, including timely entry of source data in the eCRF and performance of assessments in real time.
- The trial supervision was insufficient to ensure the timely resolution of several significant observations identified during the trial monitoring.

Qualification/Training:

- Lack of training of CRAs on sponsor Standard Operating Procedures (SOPs)/ guidance documents and GCP.
- Missing CVs for a substantial part of the personnel involved in the study; CVs not signed.
- The periodic eye examinations specified in the study protocol were performed by an independent ophthalmologist. Although the contracted ophthalmologist had been involved in other clinical trials according to the explanation provided, no GCP training was available in the trial master file.

Randomisation/Blinding/Codes IMP:

- Accidental Suspected Unexpected Serious Adverse Reaction (SUSAR) unmasking: there were three cases where unblinding information was included in SUSAR queries / acknowledgement reports that were sent to blinded sponsor personnel and in two cases the unblinding information was subsequently forwarded to investigator sites.
- Deficiencies in maintaining the integrity of the blind.
- An issue in the Interactive Response Technology (IRT) system was not solved during the study. No possibility of changes in the IRT system were planned at least in the agreement with the vendor in case of issues. Only a simple communication to investigators was undertaken.

Quality System:

- The sponsor had no formal organisation or systems to support planning, conduct, oversight, and reporting of clinical trials.
- Late implementation of SOPs, management plans, process flowcharts, guidelines, and meetings as a consequence of an immature quality management system at the beginning of the trial.
- Lack of controlled procedures and documentation in relation to protocol development.

Source Documentation:

- The source documentation did not detail the reason for the trial participant's early termination from the trial or whether it was the trial participant's or the doctor's decision.

- Diaries were not available for several trial participants.
- In the trial specific binders with source data, all names of trial participants had been redacted.

Trial management

Audit:

- For a number of vendors and partner organisations that provided trial-related services according to their own SOPs, the sponsor did not conduct audits or alternative qualification activities prior to the start of the trials or evidence of such could not be provided.
- Audit reports were not delivered at all or delivered with significant delay to the auditees.
- There was no documentation of the planned audit schedule which was provided for in the audit SOP. In addition, internal audits were not outlined within the audit SOP.

CSR:

- The clinical study report is misleading in the presentation and interpretation of clinical trial results.
- The CSRs should have included more information about the trial quality assurance in order to allow the possibility to evaluate whether the sponsor had appropriately maintained trial oversight and assessed the reasons and impact of protocol deviations.
- The CSR, by not mentioning serious privacy data/personal information issues that occurred during the conduct of the trial, did not fulfil all requirements set out by GCP for this document.

Data Management:

- The management of protocol deviations in particular positive urine drug screens and restricted concomitant medication use was not consistent across the study, and there were similar deficiencies in the reporting of protocol deviations.
- Deficient decision-making process to prevent biased decisions from unblinded sponsor key personnel and key committees including the data and safety management board.
- There was insufficient evidence of how reconciliations were conducted for several data transfers.

Document Control:

- Late creation and implementation of key management documents.
- Shortcomings in the formal aspects of documents: no formal approvals, missing signatures, missing or substandard change controls on study relevant document.
- Study documents were not harmonised with regard to visit names. The document review process was not robust enough to maintain harmonisation between e.g. the protocol, the statistical analysis plan, the CSR, and the trial participant information sheet.

Monitoring:

- The process in place to allow for remote monitoring visits to be performed by the CRA was not GCP compliant as the protection of the privacy of the trial participants was insufficiently ensured.
- Lack of a monitoring plan.
- There was no evidence provided to inspectors that the monitoring issues identified at the sites were escalated in a timely manner. There was no evidence for continuous and effective medical monitoring activities.

Protocol/ CRF/ Diary/ Questionnaires design:

- The paper diary was scored using a 1-10 scale instead of the correct 0-10 scale, which was the scale used in the electronic diaries and the widely used validated questionnaire.
- The clinical trial protocol (and amendments) lacks a clear description of how bias between treatment arms is minimised or avoided.
- The design of the eCRF did not enable investigators to confirm correctness of data reported to the sponsor before trial completion. Safety information was reported in the eCRF by study coordinators without providing the investigator with an option to document endorsement of the information forwarded.

Statistical Analysis:

- A series of post hoc analyses were initiated following completion of the SAP derived tables, listings, and figures. There was no clear rationale or documentation by the sponsor as to why the additional ad hoc analyses were conducted at the time and why some of these analyses were not included in the original SAP.
- The quality control applied on the listings of reported major protocol deviations for the determination of the per-protocol population and the quality control on the data processing and statistical programming were insufficient, leading to inclusion of trial participants into the per-protocol population that should not have been included.
- Due to an oversight (and quality) issue, a final package of (6) adjudicated events had not been uploaded/updated in the database before final database lock. As a consequence, a defreeze action was required and conducted. Documentation on this very extraordinary event was very limited.

Investigational Site

Protocol Compliance (Others)

- Appropriate measures were not taken to keep the investigator personnel blinded to trial participant treatment assignment.
- Not all investigations/trial visits for trial participants were performed as specified in the trial protocol.
- Treatment of a trial participant with prohibited medication.

Protocol Compliance (Safety Reporting)

- Reporting of serious adverse events not done within the 24-hour timeline.
- Classification of "life threatening" adverse event as non-serious.
- Several potential adverse events collected by the clinical nurses or by oncologist residents in the electronic medical records were not collected, assessed or reported in the trial eCRF.

Protocol Compliance (Selection Criteria)

- Inclusion of trial participants not meeting eligibility criteria.
- A patient was considered eligible while failing one exclusion criterion. Although the examination performed on randomisation day met the acceptance criteria, the patient should have been considered a screen failure considering that rescreening was not allowed in this trial.

Reporting in CRF/Diary

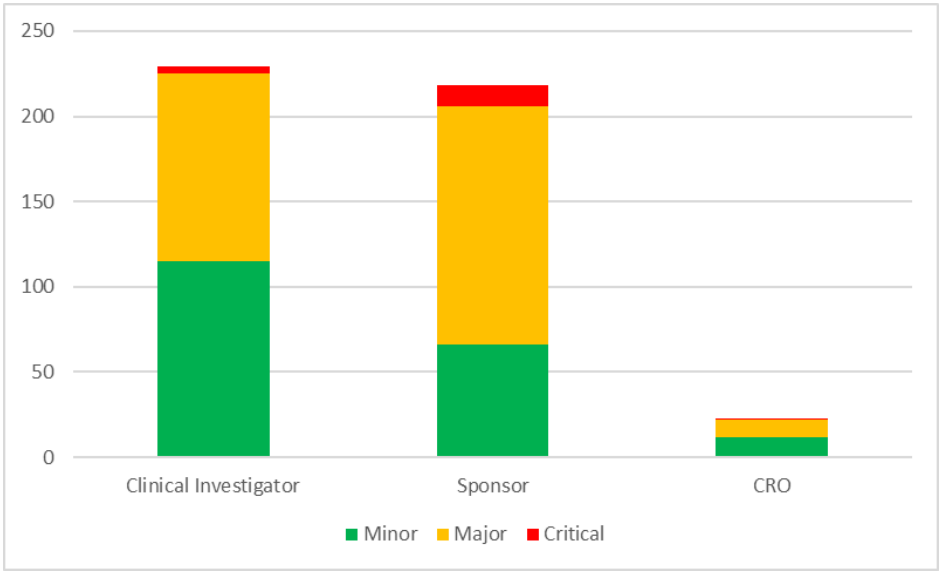
- Based on the eCRF verifications performed ahead of the inspection, it was noted that the site data entries had been performed with significant delays during the trial.
- For the patients that were reviewed regarding adverse event reporting, events were described in the medical record that had not been reported on the adverse event log or in the eCRF.

c) Distribution by type of site inspected

Table 5. Findings graded as critical, major, and minor per site type.

Inspection Site Type	Minor %, #		Major %, #		Critical %, #		Total %, #	
Clinical Investigator	24.5%	115	23.4%	110	0.8%	4	48.7%	229
Sponsor	14.0%	66	29.8%	140	2.6%	12	46.4%	218
CRO	2.6%	12	2.1%	10	0.2%	1	4.9%	23
Grand Total	**41.1%**	**193**	**55.3%**	**271**	**3.6%**	**17**	**100%**	**470**

Figure 5: Findings graded as critical, major, and minor per site type.



The figures below present the categories of findings at the three types of sites: clinical investigators, sponsors, and CROs.

Table 6. Number and categorisation of findings at clinical investigator sites.

Main category	Minor	Major	Critical	Total
General	63	45	1	**109**
Investigational Site	21	23	0	**44**
Trial Management	7	11	1	**19**
IMPs	10	7	1	**18**
Trial Participant Protection	4	6	0	**10**
Informed Consent	2	7	0	**9**
Computer System	1	6	0	**7**
Laboratory/ Technical Facilities	3	2	2	**7**
IEC/IRB	4	2	0	**6**
Total	**115**	**109**	**5**	**229**

Figure 6: Number and categorisation of findings at clinical investigator sites.

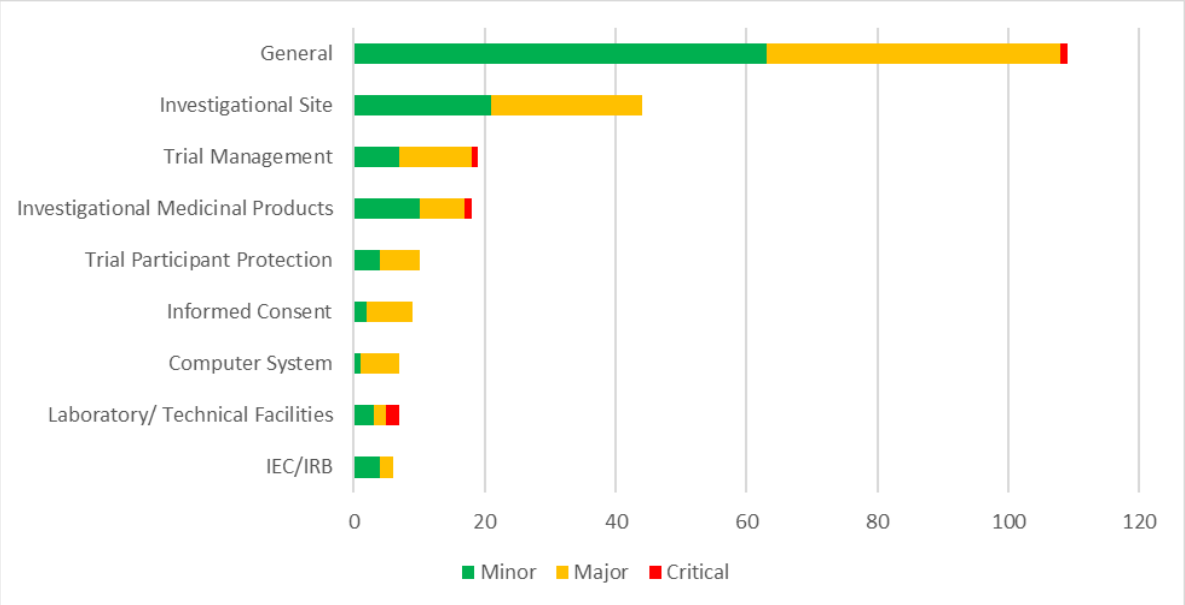


Table 7. Number and categorisation of findings at sponsor sites.

Main category	Minor	Major	Critical	Total
General	26	56	2	**84**
Trial Management	23	50	9	**82**
Investigational Site	3	6	0	**9**
Computer System	3	9	0	**12**

Main category	Minor	Major	Critical	Total
Trial Participant Protection	1	9	1	**11**
IMPs	4	5	0	**9**
Regulatory Issues	3	2	0	**5**
Laboratory/Technical Facilities	1	2	0	**3**
IEC/IRB	1	1	0	**2**
Informed Consent	1	0	0	**1**
Total	**66**	**140**	**12**	**218**

Figure 7: Number and categorisation of findings at sponsor sites.

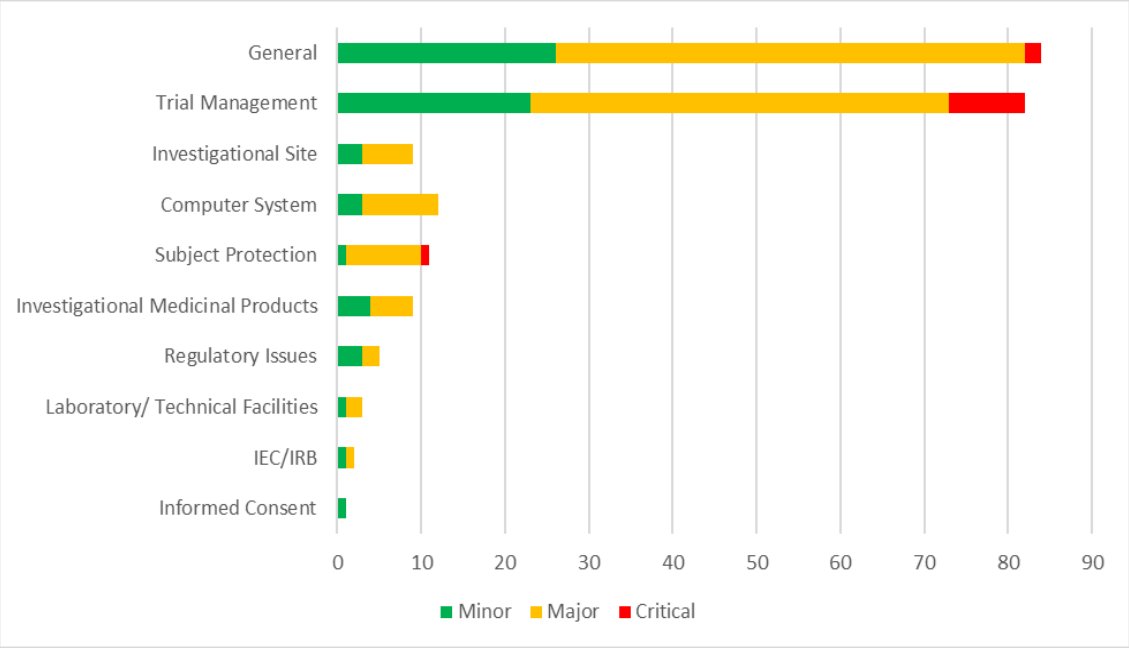
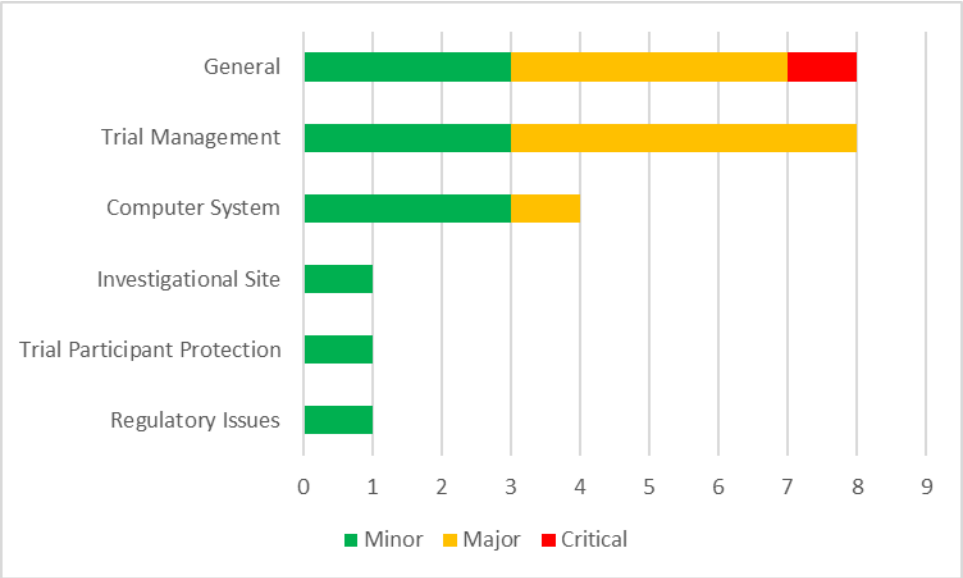


Table 8. Number and categorisation of findings at CRO sites.

Main category	Minor	Major	Critical	Total
General	3	4	1	**8**
Trial Management	3	5	0	**8**
Computer System	3	1	0	**4**
Investigational Site	1	0	0	**1**
Trial Participant Protection	1	0	0	**1**
Regulatory Issues	1	0	0	**1**
Total	**12**	**10**	**1**	**23**

Figure 8: Number and categorisation of findings at CRO sites.



d) Distribution by responsible party

Finally, Table 9 shows the distribution of responsibilities for each grading of finding.

Table 9. Responsibility of findings from each type of site.

Responsibility	Minor findings		Major findings		Critical findings		Total #	Total %
	#	%	#	%	#	%		
Clinical Investigator	71	36.8%	58	22.3%	0	0%	**129**	**27.4%**
Sponsor	58	30.1%	122	46.9%	11	64.7%	**191**	**40.6%**
CRO	3	1.6%	3	1.2%	2	11.8%	**8**	**1.7%**
IEC/IRB	0	0%	1	0.4%	0	0%	**1**	**0.2%**
Multiple Responsibility	61	31.6%	76	29.2%	4	23.5%	**141**	**30.0%**
Grand Total	**193**	**100%**	**260**	**100%**	**17**	**100%**	**470**	**100%**

4. Harmonisation topics

4.1. Procedures and guidance documents

The GCP inspectors contributed to and/or adopted the following documents in 2022:

- Guideline on computerised systems and electronic data in clinical trials, which replaces the replaces the Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-computerised-systems-electronic-data-clinical-trials_en.pdf
- Recommendation paper on decentralised elements in clinical trials: https://health.ec.europa.eu/system/files/2023-03/mp_decentralised-elements_clinical-trials_rec_en.pdf

- Annex V – to guidance for the conduct of good clinical practice inspections – Phase I units: https://health.ec.europa.eu/system/files/2022-12/mp_annex5_phase1_units_en.pdf
- EMA GCP IWG points to consider regarding the management of ongoing clinical trials impacted by political conflicts, natural disasters or other major disruptions: https://www.ema.europa.eu/en/documents/other/ema-gcp-iwg-points-consider-regarding-management-ongoing-clinical-trials-impacted-political_en.pdf
- Guidance document on how to approach the protection of personal data and commercially confidential information while using the Clinical Trials Information System (CTIS) (this document was worked on in 2021-2022 and published in 2023).

The Guideline on the responsibilities of the sponsor with regard to handling and shipping of investigational medicinal products for human use in accordance with Good Clinical Practice and Good Manufacturing Practice, which was adopted at the end of 2021 by the GCP IWG, was also published in 2022.

In addition, the Principal Documents taken into account for the preparation of procedures for GCP inspections requested by the CHMP document and the annexes I, II, IV, VI, and VII to the Procedure for conducting GCP inspections requested by the CHMP, published on the EMA website, were updated to reflect the new clinical trials legislation.

Two new GCP Q&As were published on the EMA website (https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp):

- B.16: Is the monitoring of bioequivalence clinical trials mandatory?
- B.17: How can sponsors demonstrate oversight for those activities that are delegated by written contract?

In addition, the following Q&A published on the EMA website were revised in 2022:

- A.3: How should the containers be labelled?
- B.1: Can a sponsor prospectively approve deviations (so-called "protocol waivers") from the inclusion/exclusion criteria of the approved protocol without additional approval of the ethics committee and competent regulatory authority?
- B.2: GCP sets out responsibilities for the sponsor and the investigator, but tasks are increasingly undertaken by a range of contractors – how should this situation be addressed?
- B.3: How and where should source data be defined?
- B.8: What are the pitfalls to be aware of regarding contractual arrangements with vendors for electronic systems in connection with clinical trials?
- B.11: According to the ICH-GCP and applicable EU laws, is it allowed that the sponsor contracts third parties to conduct trial-related duties and functions that are clearly responsibility of the investigator?
- B.14: Does the sponsor of a clinical trial have the right to audit the manufacturer of the IMP even if the manufacturer has been subcontracted by a CRO involved in the clinical trial?
- B.15: Do GCP inspectors from regulatory authorities of an EU/EEA Member State have the authority to inspect trial participants' medical records and other data, even if there is no statement in the ICF establishing that trial participants consent to the review of their medical records and other personal data by EU inspectors?

- D.2: What should be considered when transferring copies of medical records to clinical trial sponsors or their service providers?

The contribution of the GCP IWG in the third revision of the ICH GCP guideline (E6 R3) is described in section 5.1.

4.2. Remote/ hybrid inspections

Remote and hybrid inspections are defined as follows in the Reflections on the regulatory experience of remote approaches to GCP and GMP regulatory oversight during the COVID-19 Pandemic document published by the International Coalition of Medicines Regulatory Authorities (ICMRA):

- Remote inspection: *the process of conducting inspections (…) at a distance/virtually, supported by technology for communicating, sharing, reviewing, accessing systems, without the inspectors being physically present at the sites where the activities subject to an inspection have taken place/where the inspection would routinely be hosted.*
- Hybrid inspection: *an inspection (…) performed using a combination of on-site and remote means.*

As already outlined in the 2020 and 2021 Annual Reports, the COVID-19 pandemic — still ongoing at the start of 2022 — made some on-site inspections challenging due to multiple factors, such as difficulties and restrictions related to travelling between and within the borders of countries (including travel warnings/restrictions, border controls, transportation difficulties), restrictions on accessing facilities justified by health hazards and local authorities' recommendations/orders, as well as additional health risks for inspectors and inspected entities.

Therefore, to enable the continuity of GCP inspections requested by the CHMP, remote and hybrid inspections were sometimes conducted in lieu of on-site inspections, where considered appropriate and feasible.

In 2020, the GCP inspectors developed a Guidance on remote GCP inspections during the COVID-19 pandemic to outline the requirements and specificities of such inspections identifying the points to be considered during the preparation, conduct, and reporting phase, which continued to be applied in 2021.

In 2022, 4 CHMP requested GCP inspections were conducted entirely remotely, and 1 inspection was conducted in a hybrid setting (partly on-site and partly remotely).

4.3. Inspection cooperation

- Cooperation between the EU/EEA MSs:

Nearly all the inspections conducted in 2022 were joint inspections involving inspectors from at least two MSs. Only two inspections were carried out by one MS only: in both cases, these were triggered inspections with a narrow scope, where one Member State was deemed enough for the purpose.

- Cooperation with third countries:

Observers from countries outside the EU/EEA are systematically invited to observe the EU/EEA GCP inspections performed in those countries in the context of the centralised procedure. In 2022, inspectors from Argentina, China, Turkey, Switzerland, UK, and USA observed GCP inspections requested by the CHMP. In addition, one inspection was conducted jointly with the US FDA.

4.4. GCP training and development

4.4.1. EMA hosted training

- 2022 virtual EU GCP inspectors training

A virtual GCP IWG training on EMA inspection findings and their impact was organised by the EMA Inspections Office and took place online on 20 June 2022. The topics covered were derived from the outcome of the GCP IWG subgroup on Integrated Inspection Report (IIR) Peer Review process and included considerations on the writing of GCP inspection report findings with practical examples, and EMA inspections and the EMA IIRs with a focus on the IIR summary and conclusion.

4.4.2. MS hosted training

- 2022 on-site GCP IWG workshop

An on-site GCP IWG workshop was organised and hosted by the Danish Medicines Agency on 10 and 11 October 2022. The training focused on the onboarding of new GCP inspectors and the inspection of specific areas including data management, statistical analysis, computerised systems and complex trials and adaptive designs.

- 2022 hybrid GCP Bioequivalence (BE) inspections forum

A BE forum took place in a hybrid setting on 12 October 2022, and was hosted by the Danish Medicines Agency. GCP inspectors from the EU/EEA, US FDA, and the World Health Organisation (WHO) were present. Topics covered included the ICH M10 guideline on bioanalytical method validation, potential risks for data integrity associated with computerised systems used in GxP environment, recent findings with data integrity tools, and remote data review.

4.5. GCP IWG meetings and topics of interest

- During the plenary meetings of the GCP IWG held on 8-9 March 2022, 21-22 June 2022, 13-14 September 2022 and 29-30 November 2022, the following topics were discussed:
  - Update on the new system for the management of GCP inspections: IRIS
  - Regulation (EU) No 536/2014 (Clinical Trials Regulation) implementation, CTIS and Union controls
  - European Commission revision of the pharmaceutical legislation
  - Accelerating Clinical Trials in the EU (ACT EU) initiative and relevant priority actions
  - Decentralised clinical trials initiative
  - Ongoing guidelines, Q&As, and procedures
  - Renovation of ICH E8 and E6, and new ICH E19 and M11
  - COVID-19 and impact on GCP inspections, including remote inspections
  - EMA Emergency Task Force (ETF) and GCP IWG representation
  - Update on ongoing inspections of interest
  - Update from subgroups on their activities
  - Updated inspection templates

- GCP compliance interpretation matters and ethical issues; response to queries received from third parties
- Coordination and observation of EMA inspections, and GCP inspection programme
- National inspection processes
- Training activities and BE forum.

5. Collaboration with European Commission

A representative from the Directorate F – Health and food audits and analysis, of the Directorate-General for Health and Food Safety (DG SANTE) of the European Commission attended two out of four 2022 GCP IWG plenary meetings.

5.1. Clinical trial legislation and related guidance documents

- The GCP IWG, EMA Inspections Office and the European Commission collaborated on the Recommendation paper on decentralised elements in clinical trials (see section 4.1) and on the redaction of inspection reports for publication in CTIS.
- Representatives of the GCP IWG have been appointed by the European Commission as ICH E6 (R3) Expert Working Group (EWG) members. The EWG is chaired by the Head of Inspections Office at EMA. These representatives and the EMA Inspections Office have worked closely on the draft ICH E6 (R3) document and the organisation and planning of an ACT EU workshop dedicated to the revision and associated public consultation. The outcome of these activities will be described in the 2023 Annual Report.
- EMA Inspections Office also collaborated with the European Commission for publication of the relevant documents adopted by the GCP IWG on the Eudralex Volume X website.

5.2. EU portal and database

The Clinical Trials Regulation became applicable on 31 January 2022, and the CTIS went live on the same day. GCP IWG members were updated on the CTIS, including the inspections module, during all GCP IWG plenary meetings in 2022. The topic of the redaction of inspection reports for upload in the CTIS, as provided for in Article 78(6) of the Clinical Trials Regulation for clinical trials submitted under the Regulation, was also extensively discussed in the meetings of the GCP IWG and the related sub-group.

5.3. EU enlargement

The EU (potential) candidate countries, Bosnia and Herzegovina, Kosovo under United Nations Security Council (UNSC) Resolution 1244/99, Albania, Republic of North Macedonia, Montenegro, Serbia, and Turkey, were not invited to the GCP IWG meetings held in 2022 due to the Agency's Business Continuity Plan and prioritisation of activities for the COVID-19 pandemic.

6. Liaison with other EU groups

6.1. GMDP IWG

The GCP IWG maintains a dialogue with the GMDP IWG on areas of common interest. In 2022, the two IWGs collaborated in particular on the revised Reflection paper on the use of interactive response

technologies (interactive voice/web response systems) in clinical trials, with particular emphasis on the handling of expiry dates and on the interpretation of Article 61.5 (a) of the Clinical Trials Regulation.

6.2. PhV IWG

The GCP IWG maintains a dialogue with the PhV IWG on areas of common interest and in particular concerning PhV issues observed in relation to GCP inspections.

6.3. HMA/ CTCG

The GCP IWG maintains a collaboration with the Heads of Medicines Agencies (HMA) and the Clinical Trials Coordination Group (CTCG) on areas of mutual concern in the supervision of clinical trials conducted in the EU/EEA. In 2022, the GCP IWG and the CTCG collaborated on the decentralised clinical trials initiative, the implementation of the Clinical Trials Regulation, and the interpretation of Article 61.5 (a) of the Clinical Trials Regulation in addition to ad hoc issues and meetings.

6.4. CHMP

The GCP IWG maintains a dialogue with the CHMP on areas of common interest and in particular on matters related to GCP inspections. In 2022, topics included the collaboration between GCP inspectors and assessors by means of the GCP IWG subgroup on embedding the outcome of GCP inspections into the benefit-risk assessment and modernisation of the GCP inspection process, the triggers for GCP inspection, and the ICH E6 (R3) revision.

6.5. CMDh

The GCP IWG and the CMDh, mainly through the GCP/CMDh Working Party, which met 5 times in 2022, have contributed to the following topics:

- CROs of interest and CRO inspection programme;
- CRO inspection outcomes and subsequent actions;
- Development of the ICH M10 document — Bioanalytical Method Validation of Assays for Chemical and Biological Drugs;
- Tracking of data manipulation at the sponsor level;
- International collaboration, working group, and clusters;
- Workshops and the BE forum;
- BE inspection resources and training needs;
- Q&A on the monitoring of BE trials.

6.6. Joint meetings with interested parties

There were no joint meetings organised between the GCP IWG and interested parties in 2022.

6.7. Paediatric Committee (PDCO)

Communication on inspection issues with the PDCO continued in 2022 with the exchange of information on inspections of clinical trials with a paediatric population and the decentralised clinical trials initiative.

7. Liaison with international partners

7.1. Regulatory agencies from outside the EEA

- The EMA and the FDA have had a collaboration initiative in place since 2009 in the area of GCP[1]. This collaboration was extended in 2013 to BE, together with some of the EU/EEA MSs[2].
  - During 2022 there were 5 regular teleconferences of the EMA-FDA GCP collaboration and 4 teleconferences as part of the EMA-FDA-WHO-MSs BE collaboration. There was also one ad-hoc meeting focused on the EMA raw data pilot.
  - In addition, the EMA Inspections Office attended the EMA - FDA – MHRA – Health Canada – Swissmedic – Israeli MoH generics cluster when data integrity issues were discussed.
  - As part of the EMA-FDA GCP initiative the FDA observed two EMA inspections, and there was a joint EMA/FDA inspection. In addition, in 2022, the Danish, Greek and Swedish inspectorates observed one FDA inspection on their territory, while the Italian and Latvian inspectorates observed two FDA inspections on their territory.
  - Several FDA representatives also attended the BE Forum.
- Pharmaceuticals and Medical Devices Agency (PMDA, Japan):
  - PMDA joined the FDA-EMA initiative as an observer in June 2017 for an 18-month pilot phase. Based on the outcomes of this pilot initiative, EMA and FDA agreed to add PMDA as an official member of the GCP initiative and to continue the activity.
  - Regular exchanges of information have occurred during EMA and PMDA meetings.
  - PMDA participated in all regular teleconferences with EMA and FDA as part of the GCP collaboration.
- WHO:
  - Since 2018, WHO has been an observer of the GCP IWG under the EMA, European Commission and WHO confidentiality arrangement.
  - WHO participated in all regular teleconferences with EMA and FDA as part of the BE collaboration.
  - EMA, WHO and the EU/EEA MSs that perform the highest number of BE inspections had 4 teleconferences to pursue the existing collaboration and exchange BE inspection information.
- Swissmedic:
  - The Swiss Agency for Therapeutic Products (Swissmedic) is an observer of the GCP IWG under the European Commission, EMA, Swiss Federal Department of Home Affairs and Swissmedic confidentiality arrangement, in place since 2015.
  - In 2022, Swissmedic observed one inspection requested by the CHMP.
- Other regulatory agencies:
  - As noted in section 4.3, Argentina, China, Turkey, and UK also observed GCP inspections requested by the CHMP.

[1] Announcement of the EMA-FDA GCP Initiative
[2] Announcement of the generic medicines application inspections initiative

- Collaboration is being strengthened with additional regulatory agencies. Regular exchange of information occurs with the regulatory authorities with which EMA has confidentiality arrangements in place.

7.2. International initiatives

- Inspection information was exchanged with the regulatory authorities in Canada, Serbia, and Singapore.

For details on the activities of the GCP IWG for the period 2024-2026 please see the Work Plan for 2024-2026.