



European Medicines Agency
Inspections

London, 20 September 2007
EMEA/INS/GCP/197226/2005

Procedure no: INS/GCP/4

<p style="text-align: center;">PROCEDURE FOR REPORTING OF GCP INSPECTIONS REQUESTED BY THE EMEA</p>
--

<p style="text-align: center;">GCP Inspectors Working Group</p>
--

Applies to: EMEA, EU/EEA Inspectorates

Summary of scope: This procedure describes the content of GCP inspection reports and the process of their approval and the distribution to the EMEA and CHMP

Keywords: GCP Inspection, Reporting, IR, IIR

Public

Supersedes: N/A

Finalisation	Date
Adoption by GCP Inspectors Working Group	5 September 2007
Adoption by CHMP	20 September 2007

1	INTRODUCTION	3
2	PREPARING INSPECTION REPORTS	3
2.1	RESPONSIBILITIES OF THE LEAD INSPECTOR	3
2.1.1	The Inspection Report (IR)	3
2.1.2	Language of IR	4
2.1.3	Content and format of IR	4
2.2	RESPONSIBILITIES OF THE REPORTING INSPECTOR	4
2.2.1	The Integrated Inspection Report (IIR)	5
3	SUBMISSION AND ACCEPTANCE OF THE INSPECTION REPORTS	5
3.1	REVIEW OF THE FORMAT OF THE IIR	5
3.2	COMMUNICATION BETWEEN INSPECTORS, (Co)-RAPPORTEUR AND ASSESSORS	5
3.3	FORWARDING THE IIR TO RAPPORTEUR/CO-RAPPORTEUR AND CHMP	6
3.4	FOLLOW-UP TO THE INTEGRATED INSPECTION REPORT	6
	APPENDIX 1A. TENTATIVE FORMAT FOR AN INSPECTION REPORT (IR) - INVESTIGATOR SITE	7
	APPENDIX 1B. TENTATIVE FORMAT FOR AN INSPECTION REPORT (IR) – SPONSOR SITE	10
	APPENDIX 1C COVER PAGE TO THE INSPECTION REPORTS:	14
	APPENDIX 2. INTEGRATED INSPECTION REPORT (IIR).	15
	APPENDIX 3: GRADINGS OF FINDINGS	17
	APPENDIX 4: REFERENCES AND LIST OF DOCUMENTS USED IN THE PREPARATION OF THIS PROCEDURE	18

1 INTRODUCTION

Only GCP Inspection Reports relating to inspections requested by the EMEA are detailed in this procedure.

The duties of the involved parties (Reporting Inspector, Lead Inspector etc.) are provided in the “Procedure for co-ordinating GCP Inspections requested by the EMEA” INS/GCP/1, the legal basis of which is to be found in article 57(i) of Regulation (EC) No. 726/2004. When a GCP inspection has been performed, the GCP Inspection Reports should be part of the documentation used for the assessment of the application.

This document allows for incorporation of modules pertaining to a particular type or focus of the inspection. The module presented provides procedure for reports of inspections at the investigator site. Inspections are co-ordinated by the EMEA Inspection Sector and in general conducted by the EU/EEA national inspectors. The request for an inspection is made by CHMP in a document stating the grounds for the inspection, the scope and suggested sites as well as any other information relevant to the inspectors.

2 PREPARING INSPECTION REPORTS

For each site inspected an Inspection Report (IR) is prepared.

In some circumstances it may be appropriate to generate 1 report for two or more sites, even though these represent separate inspections (e.g. where a particular process at a sponsor/MAH is inspected at two or more sites globally, but it makes more sense to combine the findings as they address elements of the same process). If this is to apply it will be indicated in the CHMP adopted Inspection Request, that a single report is requested combining the results for a group of specified sites. These remain separate site inspections nonetheless.

For multiple site inspections on a given application, the individual Inspection Reports are integrated into one report, the Integrated Inspection Report (IIR), addressing the major and critical findings recorded and providing an evaluation of the quality and usefulness of the data inspected.

The Definition of Terms in the procedure INS/GCP/1 provides definitions for the IR and IIR. Section 3.4 of procedure INS/GCP/1 should also be referred to concerning provision of relevant inspection findings in advance of the circulation of the inspection reports.

See sections 2.2.4 and 2.2.5 of the procedure for co-ordinating GCP inspections requested by the EMEA (INS/GCP/1) regarding signatures and availability of inspectors to sign reports.

Where only one site is inspected an IR can fulfil the requirement for IIR provided the objectives and content of both are addressed.

The target dates for the availability of the inspection reports are agreed and stated in the Inspection Request adopted by CHMP.

2.1 Responsibilities of the Lead Inspector

2.1.1 *The Inspection Report (IR)*

The Lead Inspector(s) appointed by the Inspectorate(s) concerned prepares an Inspection Report for each site inspected. This Inspection Report (IR) is prepared according to a common standard and in cooperation with all participating inspectors, and will be ready within [15]* days of the end of the inspection. Where multiple sites are inspected in sequence the IR may be prepared [15]* days from the last day of inspection, at the last site inspected.

* The times shown in square brackets should be considered as indications and can be modified if necessary (see appendix 2 of procedure INS/GCP/1).

The IR should be sent to the inspectee and/or the sponsor responsible with a request for comments on major factual errors, points of disagreement or remedial actions to be provided, to the Lead Inspector, within [15] days of receipt of the report. If a response is not received within the stipulated time frame, the absence of a reply should be recorded in the IR. On receipt of comments, these should be included in the final version of the IR as an appendix. The inspectors will consider the responses of the inspectee and will indicate, as an additional appendix, whether or not these are acceptable and what impact, if any, they have on the original inspection findings. A copy of the assessment of the comments will be sent to the the inspectee and/or the sponsor.

The final version of the IR should be prepared and sent by the Lead Inspector to the Reporting Inspectorate within [40] days after the completion of the inspection.

2.1.2 Language of IR

The Inspection Report will be written in English, unless required by local regulations to be in local language. In the latter case the Inspection Report will be translated / modified to English under the responsibility of the Lead Inspector prior to signature by all involved inspectors. The timelines for the finalisation of the IR will be extended as needed.

2.1.3 Content and format of IR

The IR should reflect the inspection procedures as described in “Procedure for conducting GCP inspections requested by the EMEA (INS/GCP/3)”. There should be an evaluation of the compliance with EU and local regulations, the principles and guidelines of Good Clinical Practice and applicable ethical and scientific standards. The validity and reliability of the data submitted should be evaluated in accordance with the scope of the inspection and issues identified in the request for the inspection. Also any other major or critical findings may be addressed. The IR should be printed on the paper with the Lead Inspectorate/Reporting Inspectorate (as applicable) national authority headed paper or on plain A4 paper. A common format has been developed for the IR. Appendix 1a gives an example of the table of contents for an IR of an investigator site and Appendix 1b for a sponsor site, other examples (e.g. for clinical laboratories) are given in the procedure on the inspection of that type of site. The table of contents will be amended in accordance with the scope of the individual inspection.

Items inspected will be extensively described in the IR (for structure and content see appendices 1a and 1b) and the findings classified as minor, major and critical deviations (see appendix 3 for definitions). Each finding should refer to the requirement for which it is non-compliant.

An evaluation of the significance of the deviations should be presented. An overall conclusion should be presented on whether the conduct, recording and reporting of the trial is acceptable/non-acceptable according to the principles of GCP. A recommendation should be given on whether the quality of the reported data allows use their for the assessment by the CHMP.

2.2 Responsibilities of the Reporting Inspector

The Reporting Inspector is nominated by the Reporting Inspectorate.

It is the duty of the Reporting Inspector to monitor the timely production of the IRs. The Reporting Inspector is also responsible for the integration of the IRs into the IIR and the communication with the EMEA Inspection Sector.

Any questions related to the reports are handled by the Reporting Inspector, who is responsible for the necessary communication with the Lead Inspectors, EMEA, CHMP Members, (Co)-Rapporteur and the assessors.

2.2.1 The Integrated Inspection Report (IIR)

The Reporting Inspector compiles an **Integrated Inspection Report (IIR)** in English based on the IRs. The format of the IIR will be as outlined in Appendix 2. The IIR will summarise the major and critical findings and contain an evaluation of the quality of the data submitted and compliance with the principles of GCP based on the findings at all inspected sites. Any finding that is process related and not site specific will also be highlighted in the IIR. The IIR will also contain a conclusion on whether the quality of the data inspected as a whole or in parts may be used for the evaluation by the assessors regarding acceptance/non-acceptance of the trial data. The IIR conclusions should recommend any follow-up to be requested from the applicant or a further inspection if considered necessary.

The IIR will be approved and signed by all the Lead Inspectors who have contributed with IRs.

This should be done within [50] days after the completion of the inspection. The Reporting Inspectorate sends the signed IIR to the EMEA Inspection Sector. This refers to a electronic copy by secured email and a paper copy with the original signature page by post.

3 SUBMISSION AND ACCEPTANCE OF THE INSPECTION REPORTS

3.1 Review of the format of the IIR

3.1.a

A review of the reports is conducted on behalf of the CHMP by the EMEA Inspection Sector. The EMEA will check the IIR (with the appended IRs) for adherence to:

- the procedures established by the GCP Inspectors Working Group (GCP IWG),
- the Inspection request adopted by the CHMP,
- the citation of applicable regulations and guidelines.

Acceptance of the IIR will be notified to the Reporting Inspectorate without delay.

Any difficulties encountered by this review will be notified to the Reporting Inspectorate in writing, with a deadline for revision or other remedial action.

If the Reporting Inspectorate does not agree with the EMEA the reasons should be explained. If the EMEA still considers there is a problem with the report, the Rapporteur/Co-Rapporteur and CHMP will be sent the report and a document describing the point(s) of disagreement.

3.1.b

In the event of outstanding disagreement, the report and problems identified are circulated to the GCP IWG, for peer review, by written procedure. Fifteen calendar days will be allowed for response, after which the responses will be collated and appended to a final recommendation made by EMEA Inspection sector which will be communicated to the Rapporteur/Co-Rapporteur, CHMP and the Reporting Inspectorate.

3.1.c

The IIRs and IRs will be managed in accordance with the “Statements of Principles governing the Partnership between the National Competent Authorities and the European Agency for the Evaluation of Medicinal Products”.

3.2 Communication between inspectors, (Co)-Rapporteur and assessors

Direct communication is encouraged between the Reporting Inspector, the Lead Inspectors, (Co)-Rapporteur and assessors and EMEA Inspection Sector as early as possible in the process of preparing reports. After the reports are finalised and signed the discussion on matters such as implication of findings described in the report may continue.

3.3 Forwarding the IIR to Rapporteur/Co-Rapporteur and CHMP

The EMEA Inspection Sector forwards the IIR to the Rapporteur/Co-Rapporteur and CHMP according to the EMEA internal procedures. The Rapporteur/Co-Rapporteur and CHMP consider the content and findings of the IIR and may ask for clarification or additional information from the inspection team.

The EMEA inspection sector will forward the IIR to the applicant after obtaining a corresponding authorisation from the sponsor or other owner of the data if it is a different organization, and after agreement with the CHMP while safeguarding confidential aspects.

3.4 Follow-up to the Integrated Inspection Report

Some inspection reports will require follow-up due to the critical or major findings. Depending on the authorisation status of the product and the nature of the findings this may be pre or post authorisation. The inspection team should be involved in the formulation of the List of Questions and/or List of Outstanding Issues, to the extent possible, if one is presented to the applicant as part of the follow-up, and in any event copied to the inspection team once adopted. Where there are follow-up documents to be reviewed this review should be led by the Rapporteur/Co-Rapporteur in conjunction with the Reporting inspector, EMEA, GCP inspection coordinator and EMEA product team leader.

In order to achieve this in an effective way the following steps are taken for each inspection, or follow-up:

- The Inspection Request will make clear the status of the evaluation timeline at the time of adoption of the request,
- The letter announcing the inspection to the applicant, from EMEA, will make clear that any responses to the issues raised by the inspection must be addressed by the applicant to each member of the inspection team, in addition to Rapporteur/Co-Rapporteur, CHMP, and EMEA PTL (Product Team Leader) and Inspection Coordinator. This in particular means any responses submitted as part of a response to a LoQ or LOI, and/or any written comments related to the inspection, GCP compliance and/or validity of the data.
- The Rapporteur and Co-Rapporteur may request a review of the applicant's responses by the inspection team; this has to be done in writing to the Reporting Inspector (cc EMEA Inspection sector and PTL)
- Where an evaluation of the responses by the inspection team is required, the points and the timelines for such review will need to be agreed on a case-by-case basis with the Rapporteur/Co-Rapporteur, the Reporting Inspector and the EMEA (GCP coordinator and Product Team Leader).
- The inspection team, through the Reporting Inspector, may decide in any event to make a written comment to the responses. In this case he should inform the Rapporteur/Co-Rapporteur and the EMEA (GCP coordinator and Product Team Leader) and agree on the timelines.
- The written evaluation will be provided by the Reporting Inspector to the Rapporteur/Co-Rapporteur and the EMEA (GCP coordinator and Product Team Leader) in parallel.
- The Rapporteur/Co-Rapporteur integrates the inspectors' assessment/comment into the relevant assessment report.
- Other inspectorates wishing to comment may do so via their CHMP member.

The reporting inspector and lead inspectors should ensure, to the extent possible, that deputies are nominated to provide input where they are not themselves available. In some cases the Reporting inspector may need to provide the evaluation alone if the Lead inspector(s) are not available in the timeframe required.

APPENDIX 1a. Tentative format for an INSPECTION REPORT (IR) - Investigator site

A. Administrative Information.

Investigational Medicinal Products:

Test product: Name, active ingredient,

Reference product: Name, active ingredient,

Trial protocol: Protocol title

Sponsor: Name and full address

Inspection Reference: The CHMP/EMA inspection reference number(s)

Inspected site: Name and full address

Principal Investigator: Name, position

Inspection date(s): Date(s), month, year

Inspector(s): Name of the Lead and other inspector(s) and name of the competent authority/ies

B. Background and general information

1. Reasons/cause for the inspection.
2. Reference texts
List of the main legal references applicable within the context of this inspection
3. List of persons involved in the trial and contacted during the inspection:
 - Investigators, nurses and other key persons involved in the trial:
 - At the pharmacy
 - At the laboratory (ies), technical departments etc.
 - From the sponsor, i.e. monitor, auditor, QA responsible person.

C. Administrative aspects of the trial.

1. Application/notification to competent authority.
 - Protocol, amendments and patient information and consent.
 - Contacts during the trial, i.e. adverse event reporting, change of expiry date(s), reports.
2. Contacts with the independent ethics committee
 - Approval of protocol, amendment(s) and patient information and consent.
 - List of IEC members and members present at the meeting.
 - Contacts during the trial,
3. Contacts with other committees, any other validation or authorisation.

- Authorisation by local ethics committee of the hospital
- Authorisation by local authorities for particular studies or subjects included.

D. Trial documents

- Protocol, version, date of signatures.
- Amendments, dates, signatures.
- Patient information and consent
- Secrecy statement/agreement
- Randomisation list, code envelopes
- Investigator's Brochure
- Laboratories, technical departments, reference values
- Investigators file
- Quality management at the site
- Archiving of trial documents, including archiving of hospital files
- Other essential documents of the trial.

E. Conduct of trial.

- Interview with principal investigator and key members of the trial team
- Trial co-ordination
- Trial subjects: examination, inclusion and follow up
- Assessment and follow up of safety parameters

F. Documentation and reporting of data

- Procedures, data and files examined
- Informed consent
- Inclusion, exclusion criteria and efficacy parameters
- Recording and reporting of adverse events/reactions
- Treatment discontinuation
- Compliance, protocol and treatment.

G. Accountability of medicinal products

1. At the pharmacy / investigators site
 - Documentation
 - Receipt and storage
 - (Randomisation, decoding)
 - Dispensing
 - Returns from clinic / trial subjects
 - Destruction/recovery by the sponsor
2. Administration to trial subjects
 - Documentation
 - Compliance
 - Returns

H. Laboratories, technical departments.

- Certification or accreditation
- Established quality control (external/internal) or other validation
- Methods used
- Reference data
- Labelling and storage of samples
- Transportation and samples examined
- Documentation and archiving

I. Monitoring and auditing

1. Monitoring

- Monitoring visits and procedures used
- Actions taken by the monitor
- Monitor visit log

2. Auditing

- Audit and audit certificate
- Actions taken subsequent to the audit(s)

J. Summary, discussion and conclusions.

- Closing meeting
- List of observations made during the inspection with a reference to the GCP requirement not met and grading.
- Summary and evaluation of observations
- GCP compliance

K. Dates and signature(s) of Lead inspector and other inspector(s)

L. Response from the sponsor and investigator

An evaluation by the inspectors of the response

Other appendices as required

Appendix 1b. Tentative format for an INSPECTION REPORT (IR) – Sponsor site

A. Administrative information

Investigational Medicinal Product

Test Product:: Name, active ingredient,

Reference Product: Name of the active Ingredient (INN),

Clinical trial protocol: *Protocol title*

Sponsor: Name and full address

Other administrative information

- Total number of investigational sites involved in the trial:
- Total number of patients involved:
- Total number of investigational sites for which the inspected sponsor site is responsible:
- Reference to other inspection reports related:

Inspection Reference:

The CHMP/EMEA inspection reference number(s)

Inspected site: Name and address of the site inspected

Inspection date(s) Date(s), month, year

Inspector(s): Name of the Lead Inspector and inspector (s) and name of the competent authority/ies

B. Background and general information

1. Reason/cause for the inspection

2. Reference texts

List of the main legal references applicable within the context of this inspection

3. List of persons involved in the trial and contacted during the inspection

C. Sponsor system inspection

1. Organisation and personnel

- Organisation at the sponsor site.
- Contracting out of trial related duties.
- Personnel involved in clinical research at the sponsor.
- Job descriptions, qualifications and training of personnel involved.
- Relationships between monitoring personnel and the sponsor staff.
- Existence of an independent quality assurance unit
- Training procedures

.2. Facilities and equipment

- Measures taken to assure a safe storage of the clinical trials documentation.
- Characteristics of facilities used for:
 - Archiving the clinical trial documents.
 - The storage of investigational medicinal products.
 - Review of the electronic equipment regarding clinical trials (planning, monitoring, Randomisation/IVRS system, management of AE/SAE.
 - Issues related to validation of computerised systems used in clinical research

3. Standard Operating Procedures

- Procedures for approval, implementation and review SOP
- Availability of procedures related to different clinical trial activities:
 - Development and protocol approval,
 - Monitoring
 - Management of investigational medicinal products,
 - Safety and adverse drug events management and reporting
 - Writing and approval of the clinical trial report
 - Data management,
 - Auditing, etc.

D. Specific aspects of the clinical trial inspected

1. Application/Notification to the competent authorities

- Details of the submission of the original version and amendments of the protocol, if any, to competent authorities for review and approval (date of the submission, date of the approval, etc).
- Periodical study reports (annual) submission.
- Communications related to the finalisation of the clinical trial

2. Independent Ethics Committees (IEC) approvals

- Protocol approval and their amendments, if any, by the IEC for the different centres involved in the clinical trial (date of the approval, correspondence between sponsor and IEC, etc)
- Availability of information about the composition of IECs (list of members and their positions) and confirmation that they are organised and operate according to GCP.

3. Agreements between the sponsor and the head of investigator centres

- Review of the agreements and dates when they were signed.

4. Trial documents

- Information about the approval of the protocol and amendments, if any, by the sponsor and investigators in every centre involved in the trial.
- Review of the CRF(s) used and the system in place to assure their correct distribution among investigator site.
- Identification of the investigator brochure (IB) used and how it was reviewed and updated.
- Informed consent form, available versions and review of their contents
- Availability of an insurance covering the clinical trial, dates of the last update.
- Accurate archiving of the essential clinical trial documents.
- Other trial documents as: randomisation list

5. Conduct of trial

- Distribution of sponsor's duties and functions
- Investigator's Selection and training
- Critical dates
- Patient recruitment versus planned
- Closing of participating centres

6. Monitoring

- Identification and training of the monitors.
- Monitoring plan for the clinical trial: existence and follow up
- Review of the content of the monitoring reports.
- Reporting system and actions taken by the sponsor

7. Investigational Medicinal Product

- Manufacturing authorisation and GMP certificate compliance
- Documentation on manufacturing and control.
- Release of batches
- Records of receipt and distribution.
- Returns from the investigator sites.
- Destruction.
- Randomisation/blinding

8. Laboratories and technical departments

- Certification and accreditation.
- External/internal quality control programme.
- Analytical methods used.
- Reference data.
- Labelling, transportation and storage of samples.
- Results reporting and communication.
- Documentation and archiving.

9. Data Management

- Validation of the computerised systems used.
- CRF validation and correction.
- Quality control of the database.
- Statistical analysis: existence and follow up of the protocol and the statistical analysis plan.
- Clinical trial report generation and approval.

10. Safety and adverse events reporting

- Clinical trial drug adverse events registration.

- Notification of the drug adverse reactions to competent authorities, IEC and investigators.
- Updating of the safety information and the Investigator Brochure.
- Independent Drug Safety Monitoring Board Mandate and competence

11. Auditing

- Identification and training of the auditors involved.
- Number and dates of the audits performed.
- Follow up of the audit reports.
- Actions taken subsequent to the audit(s)
- Audit certificate(s).

E. Summary and conclusions

- List of observations made during the inspection with a reference to the GCP requirement not met and grading.
Summary and evaluation of observations
- GCP compliance.

F. Date and signature of Lead Inspector and inspectors

G. Response from sponsor

An evaluation by the inspectors of the response
Other appendices as required.

Appendix 1c Cover page to the Inspection Reports:

ON BEHALF OF THE EUROPEAN MEDICINES AGENCY

Inspectors in charge of this inspection report: <full name>

Phone number: <number>

Fax number: <number>

E-mail: <e-mail>

INSPECTION REPORT

<Protocol number>

<Protocol Title>

Protocol version: *<version>*

Protocol date: *<xx-xxx-yy>*

Amendment No./Date of protocol amendments: No. 1: *<xx-xxx-yy>*

No. 2: *<xx-xxx-yy>*

No. 3 *<number>*: *<xx-xxx-yy>*

Centralized Procedure Reference: EMEA/H/C/xxxxx

Inspected site:

<Name>

<Address>

<Country>

Inspection dates: *<day-day month year>*

Date of Inspection Report *<day month year>*

Date of comments from the inspectee *<day month year>*

Date of the inspector's response to comments from the inspectee *<day month year>*

APPENDIX 2. INTEGRATED INSPECTION REPORT (IIR).

A. Administrative Information.

Investigational medicinal products:

Test product: Name, active ingredient,

Reference product: Name, active ingredient,
Manufacturer

Application: Name of the applicant

Trial protocol: Protocol, title, and version, date.
Protocol amendment(s), date(s)

Sponsor: Name and full address

Total number of investigator sites in the trial:

Total number of investigational sites in the study report to which the inspection is related:

Total number of investigator sites inspected in the context of this inspection request:

Number of patients recruited, in the study report to which the inspection is related:

Number of patients recruited by this investigator site (in the context of the study report to which this inspection is related):

Inspection:

Reference: The CHMP/EMA inspection reference number(s)

Inspected sites: Name and full address
(Indicate type of site – Investigator (name Principal Investigator),
Sponsor, CRO, Laboratory (state main tests), other specify:

Inspector(s) and Inspectorate(s)

and experts if applicable,
and observers from the national
authority of 3rd countries,
if applicable:

Name of the Reporting, Lead and other inspector(s) and name of the
competent authority(ies)

Inspection date(s): Date(s), month(s), year:
for each site and country

B. Background and general information

1. Reasons/cause for the inspection

- as requested by the CHMP

2. Scope of the inspection.

- Compliance with required documents.
- Documents and data concerning the subjects, primary end points and safety parameters.
- Investigational medicinal product(s) administration and accountability.

- Investigational medicinal product(s) manufacturing (GMP-Inspection Report/summary or reference number)
- 3. Documentation requested for the inspection from investigator/sponsor
- 4. Reference texts

C. Description of findings (in particular Critical and Major findings)

1. Foreword
2. Regulatory aspects
3. Ethical aspects
 - Informed consent
 - Other ethical aspects
4. Trial documentation
5. Trial management
6. Site management
7. Quality of data
 - Inclusion and exclusion criteria
 - Efficacy data
 - Safety data
8. Investigational Medicinal Products
 - Manufacturing, delivery, receipt, storage
 - Prescription, dispensing, accountability and compliance
9. Other major findings not directly related to the scope of the inspection
10. An evaluation by the inspectors of the response from the investigator/sponsor

D. Summary and evaluation of findings

- Evaluation of the Quality of the data and GCP compliance
- Assessment of the relevance of the findings for the full study
- Recommendation for the use of the inspected data and procedures as a basis for acceptance/non-acceptance of the submitted trial.

E. Dates and signature(s) of the Reporting Inspector and all Lead Inspectors concerned.

F. Appendices

- Inspection Reports
- Other appendices as required

APPENDIX 3: GRADINGS OF FINDINGS

Grading of inspection findings.

1. **Critical:** Conditions, practices or processes that **adversely affect** the rights, safety or well being of the subjects and/or the quality and integrity of data.
Critical observations are considered totally unacceptable.

Possible consequences: rejection of data and/or legal action required

Remark: Observations classified as critical may include a pattern of deviations classified as major, bad quality of the data and/or absence of source documents. Fraud belongs to this group.

2. **Major:** Conditions, practices or processes that might adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data.
Major observations are serious deficiencies and are direct violations of GCP principles.

Possible consequences: data may be rejected and/or legal action required

Remark: Observations classified as major, may include a pattern of deviations and/or numerous minor observations.

3. **Minor:** Conditions, practices or processes that would not be expected to adversely affect the rights, safety or well being of the subjects and/or the quality and integrity of data.

Possible consequences: Observations classified as minor, indicate the need for improvement of conditions, practises and processes.

Remark: Many minor observations might indicate a bad quality and the sum might be equal to a major finding with its consequences.

4. **Comments:** The observations might lead to suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.

Appendix 4: References and list of documents used in the preparation of this procedure

- See “Principal documents taken into account for the preparation of procedures for inspections requested by the EMEA”.

- “Statement of principles governing the partnership between the national competent authorities and the European Agency for the Evaluation of Medicinal Products” (Doc. Ref: EMEA/MB/013/97.final)