DECISION

No. 20/28.09.2007

on approval of Guideline on conduct of inspections of pharmaceutical manufacturers

The Scientific Council of the National Medicines Agency,
set up based on Minister of Public Health Order no. 485/09.05.2005, as amended, reunited on summons of the National Medicines Agency President in the ordinary meeting of 28.09.2007, in accord with Article 10 of Government Ordinance no. 125/1998 related to the set up, organisation and functioning of the National Medicines Agency, approved as amended through Law no. 594/2002, as further amended, agrees on the following

DECISION

Art. 1. – The Guideline on the conduct of inspections of pharmaceutical manufacturers is approved, according to the Annex which is integral part of this Decision.

Art. 2. – On the date of the coming into force of this Decision, on approval of Guideline on the conduct of Good Manufacturing Practice Inspections, approved through Minister of Public Health Order No. 1441/05.11.2004, Scientific Council Decision No. 28/01.10.2004 shall be repealed.

PRESIDENT
of the Scientific Council
of the National Medicines Agency

Acad. Prof. Dr. Victor Voicu

ANNEX

GUIDELINE
on conduct of inspections of pharmaceutical manufacturers

CHAPTER I
Introduction

Art. 1. – This Guideline is a translation into Romanian and an adaptation of Guideline EMEA/INS/GMP/313513/2006 on conduct of inspections of pharmaceutical manufacturers, issued by the European Medicines Agency (EMEA).

Art. 2. - The purpose of this document is to provide guidance on the conduct of inspection of a manufacturer of medicinal products holding or applying for an authorisation referred to in Article 748 of Directive 95/2006 on healthcare reform, Title XVII – The medicinal product, in order to harmonize inspection procedures, frequency of inspections and follow-up procedures, thus ensuring a consistent approach to assessment and decision-making by the National Medicines Agency (NMA).

CHAPTER II
Glossary of terms

Art. 3. - The definition of terms in the detailed guidelines published in Good Manufacturing Practice (GMP) for medicinal products for human use, approved through the NMA Scientific Council Decision No. 38/2006; in addition, the following apply:

- *inspection:* evaluation at the manufacturing site of compliance with GMP principles, carried out by NMA inspectors;

- *general GMP inspection:* - inspection which covers all general GMP-related aspects, carried out prior to the granting of the authorisation referred to in Art. 748 of Law No. 95/2006 and periodically, subsequently, if needed;

- *product/process-oriented inspection:* inspection focused on the manufacturer's compliance with the marketing authorisation (MA) of a medicinal product, of the manufacturing and dossier relating to that product or a specific manufacturing process;

- *quality control laboratory inspection*: inspection for the evaluation of the laboratory's Good Laboratory Practice (GLP) in view of the quality control of that medicinal product; normally, this is part of the GMP inspection.

Independent laboratories for the quality control of the medicinal product, authorised according to Art. 725 b) of Law No. 95/2006 are also inspected.

The laboratory inspection relating to the compliance with GLP principles shall be carried out in accordance with the guidelines mentioned in Decision No. 266/2006 for the change and completion of Government Decision No. 63/2002 on the approval of Good Laboratory Practice principles, as well as the inspection and verification of their compliance in case of tests carried out on chemical substances; the present guideline does not refer to this type of inspection.

- *inspection report:* Report prepared by the NMA stating whether the company inspected in general complies with the GMP principles.

CHAPTER III
General considerations

Art. 4. - The primary role of the inspector is the protection of public health in accordance with Community provisions.

Art. 5. - The function of the inspector is to ensure adherence by manufacturers to GMP principles and guidelines including licensing provisions.

Art. 6. - The primary goal for the inspector should be to determine whether the various elements within the quality assurance system are effective and suitable for achieving compliance with GMP principles; in addition to that, determining whether the medicinal product complies with the master formula approved by the NMA and thus with the licensing provisions for the standard product should be considered as one of the inspector's responsibilities.

Art. 7. - Inspectors should strive to create a positive atmosphere during the inspection.

Art. 8. - An inspector should be aware of his influence in decision making processes; he/she should answer questions but avoid entering the role of a consultant.

Art. 9. - (1) The task of an inspector is not limited to the disclosure of faults, deficiencies and discrepancies; the inspector should connect an observation with assistance in making the necessary improvements.

(2) An inspection should normally include educational and motivating elements.

Art. 10. - (1) Different types of inspection may be carried out according to the activities of the company.

(2) Conduct of inspections may vary according to their objectives and may focus for example on the general level of GMP, or on the manufacture of a specific medicinal product or on a specific manufacturing process.

Art. 11. - (1) General GMP inspections (also named regular, periodic, planned or routine) should be carried out before a manufacturing authorisation is granted.

(2) This kind of inspection may also be necessary for a significant variation of the manufacturing authorisation and if there is a history of GMP non-compliance.

Art. 12. - Re-inspections (also termed follow-up or reassessment) may be indicated to monitor the corrective actions required during the previous inspection.

Art. 13. - Product- or process-related inspections (also termed special or problem oriented) may be indicated to assess the adherence of the manufacturer to the marketing authorisation dossier and the way the batch documentation is kept; it is also indicated when complaints and recalls may concern one product or group of products or processing procedures (e.g.sterilization, labelling, etc).

Art. 14. - Due to the wide diversity of facilities (both in terms of physical lay-out and management structure) and the variety of products and production processes as well as analytical methods, the judgement by inspectors on-site of the degree of compliance with GMP is essential.

Art. 15. - A consistent approach to evaluation of the GMP standard of companies is essential.

Art. 16. - Inspections may disturb the normal work patterns within an inspected company, therefore, inspectors should carry out their work in a careful and planned way and take care not to put the medicinal product at risk.

Art. 17. - Inspectors will, while conducting the inspection, have access to confidential information and should handle it with integrity and great care.

CHAPTER IV
Inspection procedures

IV. 1. Planning of inspections:

Art. 18. - (1) The NMA should plan the succession of inspections in advance and elaborate a programme.

(2) This programme should ensure that the frequency of inspection of each manufacturers can be adhered to as planned.

(3) Sufficient resources must be made available by the NMA to ensure that the designated programme of inspections can be carried out in an appropriate manner.

IV. 2. Preparation of inspections:

Art. 19. - Prior to conducting an inspection, the inspector should familiarise himself with the company to be inspected.

Art. 20. – This may include:

- examination of a site master file (if available);
- a review of the medicinal products manufactured by the company;
- a review of the reports from previous inspections;
- a review of the follow-up actions (if any) arising from previous inspections;
- familiarisation with the relevant aspects of the manufacturing authorisation;
- a review of medicinal product recalls initiated since the previous inspection;
- an examination of relevant product defects notified since the previous inspection;
- a review of the analysis of all samples analysed by the NMA since the previous inspection, on samples taken from the manufacturer's medicinal products;
- a review of any special standards or special guidelines associated with the manufacturing site to be inspected;
- a review of relevant parts of the registration file of one or more selected medicinal products to be examined during the inspection.

Art. 21. - An aide-memoire may be prepared specifically for the inspection to be performed; the aide-memoire helps to avoid missing important aspects of GMP.

Art. 22. - It is recommended that inspectors prepare an inspection plan which may include:

- - the objectives and the scope of the inspection, in the light of previous inspections;
- identification of the persons who are directly responsible for manufacture and quality control/quality assurance. In cases where particular products and/or processes are to be inspected, the persons directly responsible for these products and/or processes;
- identification of the inspection team members and their respective roles, if more than one inspector is going to conduct the inspection;
- the date and place, where the inspection is to be conducted;
- identification of the organisational units to be inspected;
- the expected time and duration for each major inspection activity (premises, processes etc.)
- samples to be taken (if any);
- the hour when the final meeting shall take place;
- the approximate date for the transmission of the inspection report.

IV. 3. Announcement of inspection

Art. 23. - The NMA has the right to inspect at any time (including during shift work).

Art. 24. - Prior announcement of inspection may be given; by informing in advance the day/days for the inspection to take place and the length of time the inspector expects to

be at the premises, the objectives of the inspection will be known to the company and the relevant personnel and documentation can more easily be made available.

IV. 4. Opening meeting

Art. 24. - The inspector should normally meet the management and the key personnel of the company to introduce himself and any accompanying official or specialist and to discuss his inspection plan (of course subject to unannounced modifications).

Art. 25. – During the opening meeting the inspector should:

- outline the purpose of the inspection;
- review the management structure of the company (organisation chart);
- identify some of the documentation which may be required during the inspection.

Art. 26. - (1) During the opening meeting the company should:

- describe the Quality Management System;
- explain the company's quality policy;
- explain significant changes in facilities, equipment, products and personnel since the last inspection, as regards the facilities, equipment, products and staff;
- explain how deficiencies have been resolved if this information has not already been forwarded to the NMA;
- designate the people to accompany the inspector during the inspection;
- allocate a room for the inspector if needed.

(2) Immediate inspection after arrival on site may be of value in some cases.

IV. 5. Inspection of the plant

Art. 27. – (1) A rapid plant tour is often useful for familiarisation with the site and any major changes.

(2) This is followed by a detailed plant tour to determine whether the facilities and equipment are of suitable lay-out and design and whether the way in which they are used suits the intended operations.

(3) Normally, the inspector follows the logical flow of the starting materials, goods inwards warehouse, through the production areas, quality control areas to the warehouse for released finished products, taking into account the detailed guidelines of GMP.

Art. 28. - (1) Sometimes it is appropriate to concentrate effort in one department of the company if there are special problems or requirements, e.g. a department only producing sterile dosage forms or non sterile dosage forms.

(2) Relevant service areas should be included, e.g. water, steam and ventilation/dust extraction systems and engineering support.

Art. 29. - During the plant tour the inspector should always discuss observations as they arise with the key personnel, supervisors and operators in order to establish facts, indicate areas of concern and to assess the knowledge and competence of these personnel.

IV. 6. Review of documentation

Art. 30. - The whole system of documentation, based on specifications, manufacturing formulae, processing and packaging instructions, procedures and records covering the different production, QC and distribution operations should be checked by examining particular examples both during use and after compilation into complete batch records.

Art. 31. – A general GMP-orientated inspection will normally, in order to assess compliance with the terms and conditions of the manufacturing authorisation, include examination of the documentation relating to:

- job descriptions;
- standard operating procedures (SOPs);
- validation reports;
- manufacturing formulae, records and instructions;
- specifications;
- batch release procedure and the role of the Qualified Person(s) (QP(s)).

Art. 32. - A product-related inspection will normally, in order to assess compliance with the terms and conditions of the marketing authorisation, include examination of the specific documentation relating to one or several completed batches of a specified medicinal product including:

- SOP;
- manufacturing formulae, records and instructions;
- specifications, sampling and methods of analysis of components, starting materials, intermediates and finished products

Art. 33. - Contract manufacture and analysis: operations contracted out and the responsibilities of the different parties should be clearly identified; the contract between the contract giver and the contract acceptor should be examined for compliance with the detailed guidelines of GMP.

Art. 34. - Complaints and product recall: (1) The system for recording and reviewing complaints as well as the system for recalling batches of medicinal products from within and outside Romania should be examined during the inspection.

(2) The complaints file should be examined; defect reports and recalls should be discussed.

Art. 35. – Self-Inspection: the system for performing self-inspections in the company should be examined, although the reports themselves should not normally be read by the inspector.

IV. 7. Final meeting

Art. 36. - When the inspection has been completed, the inspector should summarize the findings in the final meeting with representatives of the company, normally the technical management including the key personnel and preferably some or all of the senior management, if these are different from the key personnel.

Art. 37. - The final meeting is a significant part of the inspection; the deficiencies observed during the inspection should be discussed, as well as their importance, so that deadlines for remedial actions may be fixed.

Art. 38. - Facts and objective evidence supporting the observations should preferably be agreed by the inspected company; the company may if they so wish discuss initial proposals for remedial action.

Art. 39. - As far as possible, all relevant observations should be reported at this meeting so that the company can initiate the necessary corrective actions as soon as possible.

Art. 40. - In case of serious deficiencies leading to possible serious risk for the patients, immediate action should be taken by the inspector.

CHAPTER V
Inspection report

Art. 41. - (1) Inspection reports should be based on notes taken during the inspection; these notes should be clear and legible.

(2) An inspection report should describe the purpose of the inspection and cover the observations arising from the inspection; deficiencies should be mentioned in the conclusion.

Art. 42. - The report should contain the general information on the company, a description of the inspection itself, the inspector's observations and conclusions.

Art. 43. - (1) The conclusions should clearly identify the critical deficiencies and contain a clear statement by the inspector whether or not the manufacturer complies with the Community GMP principles.

(2) It is recommended that a date be agreed by which the manufacturer should submit proposals and a time schedule for rectifying the deficiencies outlined in the report.

Art. 44. - The action taken by the NMA will depend upon the nature and the extent of non-compliance.

Art. 45. - A report prepared for communication to another Member State or a community body (e.g. CPMP) should include the general information of the company which may be based on the information contained in an up-to-date Site Master File prepared by the company and agreed by the inspector.

Art. 46. - The need for an early re-inspection to ensure that required changes have been carried out should be considered.

CHAPTER VI
Inspection frequency

Art. 47. - (1) Inspections should be carried out at least every two years; large companies may be inspected department by department, a full general GMP inspection being completed at least every five years.

(2) The interval between inspections should never exceed 3 years as lack of continuity may give rise to lower awareness of current GMP or allow significant deficiencies to develop.

Art. 48. - The activities of the individual company (products and dosage forms manufactured, units and substances handled, personnel, premises and equipment involved in the manufacture) and its past record of GMP compliance should be taken into consideration when planning the frequency, and duration of inspection.

CHAPTER VII
Quality management of the inspector’s activity

Art. 49. - (1) Most inspectors work alone or, at most, in pairs.

(2) The possibility of a specialist participating in the inspection should be taken into consideration.

(3) There should be a system to monitor and control the inspector's performance in order to ensure a correct and consistent approach on different occasions and between different inspectors.

Art. 50. - Monitoring of the inspector’s performance should be planned to assess at least:

- the extent and depth of the inspection;
- the ability to recognise deficiencies;

- the assessment of the seriousness of deficiencies;
- the action recommended;
- the effectiveness with which the determined action is carried out.

Art. 51. – This quality system should include periodic joint visits with senior or specialist inspectors, and follow-up of recommendations and subsequent action.

ANNEX 1

CONDUCT OF PRODUCT RELATED INSPECTIONS

CHAPTER I

Introduction

Art. 1. - The purpose of this Annex is to outline the extent to which the inspector may become involved in:

(a) the pre-marketing assessment of an application for a marketing authorisation and

(b) the assessment of compliance with the terms and conditions of a marketing authorisation granted in the European Community.

Art. 2. - (1) An application for a marketing authorisation is made in the format set out in Volume II of the Rules Governing Medicinal Products in the European Community.

(2) Information concerning the quality of a medicinal product is largely to be found in "Part II : Chemical, Pharmaceutical and Biological Documentation".

CHAPTER II

The role of inspectors in the pre-marketing assessment of an application for a marketing authorisation

Art. 3. - *Verification of authorisations:* There should be a systematic procedure whereby the person responsible for assessment of an application consults the inspectorate; the extent of such consultation will depend upon the nature of the product, the manufacturing and control operations involved and on the quality of the application.

Art. 4. - *Consultation should include the following*:

a) Verification that the proposed manufacturer holds the appropriate manufacturing authorisations for the product concerned (Article 748 of Law No. 95/2006).

b) Verification that the appropriate authorisation is held where third country importation is proposed;

c) Verification that any contract Quality Control laboratory has been inspected and approved (Article 725(b) of Law No. 95/2006).

CHAPTER III

The role of inspectors in assessing compliance with marketing authorisations

Art. 5. - (1) The inspector carries out an inspection of a manufacturer in order to assess the latter's compliance with GMP; GMP includes ensuring that all manufacturing operations are in accordance with the relevant marketing authorisation (Articles 8 and 9 of Law 95/2006); the inspector is also in a position to verify that the details relating to the

manufacture and control of a product which were provided in the marketing authorisation application for that product, as modified and/or agreed during the assessment, are being adhered to in the manufacture of batches of that product for sale.

(2) In certain circumstances, for example in relation to biological, biotechnological and other high technology products, it may be appropriate for the inspector to be accompanied by a relevant assessor. Alternatively, the inspector can be accompanied by a relevant expert on the particular type of product or by an independent expert nominated by the competent authority.

(3) The inspector should have all relevant sections from the marketing authorisation application to hand during the inspection for ready reference; this would be considerably facilitated by having an up to date summary of these sections readily available to the inspector.

CHAPTER IV
Carrying aut the inspection

IV. 1. Adherence to chemistry and pharmacy data supplied and approved in the Marketing Authorisation Application:

Art. 6.- The inspection should seek to verify, by means of examination of all relevant facilities, equipment and documents, that the information provided in the marketing authorisation application is being strictly adhered to; this examination might include:

a) composition of the medicinal product
b) primary package;
c) manufacturing formula;
d) manufacturing process including in-process controls;
e) source and nature of active substances;
f) other asubstances;
g) packaging materials;
h) control tests on intermediate products;
i) control tests on finished products;
j) labelling;
k) any other data requested by assessors, including ongoing stability investigations.

In addition to this verification the following specific points should also be borne in mind:

IV. 2. Samples:

Art. 7. - (1) Consideration should be given to taking the following samples:

a) active substance (if material from more than one source is available, take a sample of each);
b) excipients (samples may be taken of non-pharmacopoeial and unusual materials);
c) finished products (sufficient to carry out full duplicate analysis and to meet the legal provisions of Romania).
d) label;
e) printed carton;
f) primary data on paper.

(2) If finished product samples are to be taken directly from the market, the company should deliver relevant samples of:

a) active substances;

b) excipients to the NMA upon request;

c) any other samples requested by assessors.

(3) All samples should be submitted for testing/review and, if indicated by the results, necessary follow up action should be taken.

IV. 3. Copies of documents:

Art. 8. - (1) If necessary, copies of the finished product specification and method of analysis should be taken relating to the samples taken (if any) during the inspection.

(2) If necessary, copies of the batch manufacturing document and of the finished product specification and method of analysis should be delivered to the NMA upon request.

IV. 4. Complaints:

Art. 9. – Any complaint relating to the specified product should be reviewed.

IV. 5. Amendments and variations:

Art. 10. - (1) Following the granting of a marketing authorisation, the holder of a marketing authorisation may subsequently apply for amendments and variations to the original information to be approved by the NMA.

(2) Where such amendments and variations have been approved by the NMA, the inspector should check that any master document to which an amendment or variation related, was altered to include the amendment or variation shortly after this was approved by the competent authority.

IV. 6. Review of documentation relating to the product:

Art. 11. - (1) This should be carried out as set out in Chapter XII of the GMP Principles and Guidelines, approved through Minister of Public Health Order No. 905/200; documentation for a number of batches should be reviewed.

(2) Section 6.9. of the Guideline on the GMP of medicinal products for human use recommends that trend evaluation of analytical test results be carried out. If this has been done, it should also be reviewed.

ANNEX 2

CONDUCT OF INSPECTIONS FOR INVESTIGATIONAL MEDICINAL PRODUCTS FOR HUMAN USE

CHAPTER I
Introduction

Art. 1. - The purpose of this document is to fulfil the requirements of Article 57 of Minister of Public Health Order No. 904/2006 to provide guidance on the conduct of inspection of manufacturers (or importers) of investigational medicinal products holding or seeking the authorisation referred to in Article 48 (1) of Minister of Public Health Order No. 904/2006, in order to harmonise inspection procedures, frequency of inspections and

follow-up thus ensuring a consistent approach to assessment and decision-making by NMA.

CHAPTER II
Scope

Art. 2. - (1) Guideline applies to the inspection of manufacturers, importers or analytical laboratories authorised in accordance with Article 48 of Minister of Public Health Order No. 904/2006 by the NMA; it also applies to inspections of manufacturers based in third countries where these are inspected in accordance with Article 15.4 of Directive 2001/20/EC; in both cases the inspection is carried out on behalf of the European Community and the outcome is recognised by all Member States.

(2) Art. 55 of Minister of Public Health Order No. 904/2006 additionally refers to inspections carried aut at other sites associated with any clinical trial and, in certain cases, there will be a superposition between GMP and GCP, such as: release of investigational medicinal products, generating systems for expedited decodification of „blind" clinical trials, manufacturing of the investigational medicinal product at the investigational site, including labelling, complaints, adverse events and recalls.

(3) The NMA should ensure that overlap areas are identified, responsibilities understood and inspections performed by Inspectors with appropriate qualifications and training.

CHAPTER III
Glossary of terms

Art. 3. - The definition of terms in this guideline published in Guidelines on Good Manufacturing Practice for Medicinal Products, approved through the NMA Scientific Council Decision No. 38/2006, in particular those given in Annex 13; in addition, the following apply:

- *Inspection***:** on-site assessment of the compliance with the Community GMP principles performed by NMA officials.

a) A general GMP Inspection covering all general GMP aspects should be carried out before the authorisation referred to in Article 48 of Minister of Public Health Order No. 904/2006 is granted and periodically afterwards as required;

b) An inspection may be product- or process- related when it focuses on the adherence by the manufacturer to the dossier of an investigational medicinal product submitted to the NMA in order to obtain authorisation to conduct a clinical trial pursuant to Article 37 of Minister of Public Health Order No. 904/2006 and on the manufacture and documentation related to the product or to a specific manufacturing process.

- *Laboratory inspection for the Quality Control of the Medicinal Product*

a) On-Site assessment of the adherence to Good Quality Control Practice is normally part of a GMP Inspection;

b) Contract QC Laboratories authorised according to Article 48 of Minister of Public Health Order No. 904/2006 are also subject to these inspections;

c) Laboratory inspection for compliance with GLP Principles is performed in accordance with guidelines given in the annexes to Directive 63/2002 and is not part of this document; thus, inspections performed in laboratories analysing samples taken from trial subjects are likewise not included.

CHAPTER IV
General obligations

IV.1. **General obligations for Romania:**

Art. 4. – (1) The NMA should establish the legal and administrative framework within which Inspections relating to clinical trials including Good Manufacturing Practice (GMP) inspections as applied to investigational medicinal products operate.

(2) Inspectors should be issued with official means of identification, which include access to data and the collection of samples and documents for the purpose of inspection.

(3) The NMA should ensure that there are sufficient resources at all levels to effectively verify compliance with GMP for investigational medicinal products and that inspectors are competent and trained in order to carry out their tasks as referred to in the detailed guidelines for qualifications of GMP inspectors engaged in verifying GMP Compliance for Investigational Medicinal Products.

(4) The Inspectorate should adopt quality systems to ensure consistency of approach to inspection and evaluation of findings; within the quality system inspectorates should develop detailed procedures in line with this guideline to suit national requirements and practices but consistent with procedures agreed at Community level such as report formats for the exchange of information.

CHAPTER V
General Considerations on Inspections of Investigational Medicinal Products

Art. 5. - The primary goal for the inspector should be to determine whether the various elements within the quality assurance system are effective and suitable for achieving compliance with GMP principles. In addition, determining whether the investigational medicinal products comply with the dossiers submitted to the NMA in order to obtain authorisation to conduct a clinical trial, according to Article 37 of Minister of Public Health Order No. 904/2006.

Art. 6. – (1) Product- or process-related inspections (also termed special or problem oriented) may be indicated to assess the adherence of the manufacturer to the investigational medicinal product dossier and the way the batch documentation is kept; it is also indicated when complaints, recalls or adverse event patterns may concern one product or group of products or processing procedures (e.g.sterilisation, labelling, etc).

(2) These inspections may be triggered by an Assessor raising questions during the evaluation of an application for authorisation to conduct a clinical trial or marketing authorisation; they may also arise from questions raised during a GCP inspection.

CHAPTER VI
Inspection procedures

VI. 1 Preparation of inspections:

Art. 7. - Prior to conducting an inspection the inspector(s) should familiarize themselves with the organisation to be inspected.

Art. 8. – This may include:

a) Review of relevant parts of the investigational medicinal product dossier of one or more selected products to be examined during the inspection, including the History file;

b) For triggered inspections, a review of the questions raised by the Assessor or GCP Inspector (arising from a GCP inspection).

VI. 2 Review of documentation

Art. 9. - (1) The system of documentation, based on the Product Specification Files, procedures and records covering the various production operations, QC and distribution should be checked by examining particular examples both during use and after compilation into complete batch records.

(2) Change control and the traceability of changes should be examined.

Art. 10. - A general GMP-orientated inspection will normally, in order to assess compliance with the terms and conditions of the manufacturing authorisation, include examination of the documentation relating to:

a) medicinal product specifications;

b) Two-step batch release procedure and the role of the QP(s) including the assessment of products imported from third countries.

Art. 11. - A product-related inspection will normally, in order to assess compliance with the terms and conditions of the investigational medicinal product dossier, include examination of the specific documentation relating to one or several completed batches of a specified product including:

a) SOP;

b) product specification.

VI. 3 Complaints and recall of the medicinal product

Art. 12. - (1) The system for recording and reviewing complaints, interactions with the clinical research personnel as well as the system for recalling batches of investigational medicinal products from within and outside the Member States should be examined during the inspection; the system for retrieving recall information on comparator products should also be included.

(2) The complaints file should be examined; Defect Reports and recalls should be discussed.

VI. 4 Final Meeting

Art. 13. - In case of serious deficiencies leading to possible serious risk for trial subjects, the inspector should take immediate action.