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Conduct of Inspections for Pharmaceutical Manufactures or Importers as Per EU Guidelines

K. Vaishnavi, N. Vishal Gupta*, Shanawaz Anis, M. P. Venkatesh, T. M. Pramod Kumar and K. Pranitha

Department of Pharmaceutics, JSS College of Pharmacy, JSS University, Sri Shivarathreeshwara Nagar, Mysore, Karnataka, India

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ABSTRACT

Inspections have become a standard assessment tool deployed by regulatory authorities and standard bodies when monitoring external organizations under their remit. The objective of the present study was to document the requirements for the condition of inspection of pharmaceutical manufacturers or importers as per European Union (EU) guidelines. These guidelines provided by EU gives a general guidance on conducting inspections. 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 compliances with GMP principles. In addition the goal is to determine that medicinal products comply with their marketing authorization. The task of an inspector is not limited to the disclosure of faults deficiencies and discrepancies. An inspection should normally include educational and motivating elements.

Key words: EU, inspection, GMP.

INTRODUCTION

Audit and inspection are the most important functions of a manufacturing facility. The international standards organization (ISO) has defined quality audit as a "systematic and independent examination to determine whether quality activities and related results comply with planned arrangements, and whether these arrangements are implemented effectively and are suitable to achieve objectives." Self inspections should be conducted in order to monitor the

implementation and the respect of good manufacturing practice (GMP) principles and to propose necessary corrective measures. The reasons for quality audit are:

1. Determine the level of compliance.
2. Build confidence in GMP and QA system.
3. Determine measures necessary to improve, e.g.,
a. Premises, equipment, environment
b. Operations, actions, procedures
c. Personnel/training
4. Provide a stimulus for improvement
5. Recommend corrective action
6. Monitor improvement

The purpose of this study was to provide guidance on the conduct of inspections to harmonize inspection procedures, frequency of inspections and follow-up procedures thus ensuring a consistent approach to assessment and decision-making by competent authorities.

Inspection planning and preparation
The competent authority should plan the succession of inspections in advance and elaborate a programme. This programme should ensure that the frequency of inspection of individual manufacturers can be adhered to as planned. Sufficient resources must be determined and made available to ensure that the designated programme of inspections can be carried out in an appropriate manner. The planning of inspections should be performed according to the Community Procedure "A model for risk based planning for inspections of pharmaceutical manufacturers".

Preparation of inspections: Prior to conducting an inspection the inspector(s) should familiarize themselves with the company to be inspected.

This may include:
- Assessment of a site master file
- A review of the products manufactured/imported by the company
- A review of the reports from previous inspections
- A review of the follow-up actions (if any) arising from previous inspection
- Familiarization with the relevant aspects of the manufacturing authorization including variations
- A review of any variations to the manufacturing authorization
- A review of product recalls initiated since the previous inspection
- An examination of relevant product defects notified since the previous inspection
- A review of the analysis of any samples analyzed by an OMCL since the previous inspection
- A review of any special standards or guidelines associated with the site to be inspected
- A review of relevant parts of the marketing authorization of one or more selected products to be examined during the inspection
- A review of variations to marketing authorizations, applied for, granted and refused
- A review of information available on regulatory databases (EudraGMP, FDA warning letters)
- A review of significant changes to equipment, processes and key personal

- A review (or preparation) of aide-memoires for the specific inspection to be performed to avoid missing important aspects of GMP
- 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 people who are directly responsible for production and quality control / quality assurance. In cases where particular products and/or processes are to be inspected, the people 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 organizational units to be inspected
- The expected time and duration for each major inspection activity (premises, processes)
- Samples (if any) to be taken
- The schedule for the final meeting
- The approximate schedule for the transmission of the inspection report

Inspection steps

Announcement of inspection: Competent Authorities have the right to inspect at any time. Prior announcement of inspection may be given. By informing in advance the day/days for the inspection to take place, the objectives of the inspection will be known to the company and the relevant personnel and documentation can more easily be made available.

Opening meeting: The inspector should normally meet the management and the key personnel of the company to introduce himself and any accompanying official(s) or specialist(s) and to discuss his inspection plan.

During the opening meeting the inspector should:

- Outline the purpose and scope of the inspection
- Review the management structure of the company (organization chart)
- Identify some of the documentation which may be required during the inspection
- During the opening meeting, which normally should take no more than 30 minutes, the company should:
- Describe the Quality Management System, when requested
- Explain significant changes in facilities, equipment, products and personnel since the last Inspection
- Explain significant changes in facilities, equipment, products and personnel since the last Inspection

Inspection of the plant facilities: Inspectors may follow the logical flow of the starting materials, goods inwards warehouse, through the production areas, quality control areas to the warehouse for released finished goods, taking into account the detailed guidelines of GMP. This could be followed by a detailed plant tour to determine whether the facilities and equipment are of suitable lay-out and design. In some cases immediate inspection after arrival on site may be of value.

A risk based approach to conducting the inspection would be to look for signals during the rapid plant tour or review of documents, which might indicate a problem with a product, processes or system and they focus the inspection on these areas.

Likewise any identification of a high risk during the inspection could lead to change in the inspection plan to go into more depth in the identified area. During the inspection 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.

Review of documentation: The whole system of documentation, based on specifications, manufacturing formulae and 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.

A general GMP inspection will normally, include examination of the following:
- Conformity with good manufacturing practice
- Compliance with marketing authorization
- Quality Management
- Personnel
- Premises and equipment
- Documentation
- Production
- Quality control
- Contract manufacture and analysis
- Complaints and product recall
- Self-inspection

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.

Complaints and product recall: The system for recording and reviewing complaints as well as the system for recalling batches of medicinal products from within and outside the Member States should be examined during the inspection. Defect reports and recalls should be discussed.
Self-Inspection: The system for performing self-inspections in the company should be examined, A product-related inspection will normally, include examination of the specific documentation relating to one or several completed batches of a specified product including:

- Standard operating procedures (SOPs)
- Product quality review
- Manufacturing formulae, records and instructions
- Specifications, sampling and methods of analysis of components, starting materials, intermediates and finished products

For active substances used as starting materials: A check should also be made to ensure that the manufacturing authorization holder is complying with the requirements of Article 46 (f) of Directive 2001/83/EC and Article 50 (f) of Directive 2001/82/EC as amended

Final meeting

- When the inspection has been completed, the inspector should summarize the findings in the final meeting with representatives of the company, if these are different from the key personnel.
- The final meeting is a significant part of the inspection. The deficiencies observed during the inspection should be discussed. Their importance should also be discussed so that deadlines for remedial actions may be fixed.
- Facts and objective evidence supporting the observations should preferably be agreed by the company.
- As far as possible all relevant observations should be reported at this meeting so that the company can initiate the necessary corrective actions at the earliest possible date.
- In case of serious deficiencies leading to possible serious risk for the patients, immediate action should be taken by the inspector.

Inspection report

- Inspection reports should be based on notes taken during the inspection. These notes should be clear and legible.
- The inspection report should give a short description of the company and its activities, description of the inspection itself and the inspector's findings, observations and deficiencies.
- The report should be in line with the Community format of the GMP inspection report.
- The contents of the initial inspection report should be sent to the company for its comments to enable the report to be finalized within the relevant timeframe of the inspection request and to enable, if applicable, the issue of a GMP certificate within the statutory 90-day timeframe.

Inspection frequency

The frequency of inspections may be based on the Community procedure "A model for risk based planning for inspections of pharmaceutical manufacturers".

Quality management of the inspector's activity

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. Monitoring should be planned to assess at least:

- The extent and depth of the inspection
- The ability to recognize deficiencies
- The assessment of the seriousness of deficiencies
- The action recommended
- The effectiveness with which the determined action is carried out
- This quality system should include periodic joint visits with senior or specialist inspectors, and follow-up of recommendations and subsequent action.

Conduct of product related inspections

The purpose of this is to outline the extent to which the inspector may become involved in:

i. The pre-marketing assessment of an application for a marketing authorization and,
ii. The assessment of compliance with the terms and conditions of a marketing authorization granted in the European Community and in connection with Art. 58 of EC/726/2004.

A. The role of inspectors in the pre-marketing assessment of an application for a marketing authorization

1. Verification of authorizations
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.

2. Consultation should include the following
1. Verification that the proposed manufacturer holds the appropriate manufacturing authorizations for the product concerned (Article 40 of Directive 2001/83/EC and Article 44 of Directive 2001/82/EC).
2. Verification that the appropriate authorization is held where third country importation is proposed (Article 40 of Directive 2001/83/EC and Article 44 of Directive 2001/82/EC).
3. Verification that any Quality Control laboratory has been inspected and approved (Article 20(b) of Directive 2001/83/EC or Article 24(b) of Directive 2001/82/EC), including third country inspections.

B. The role of inspectors in assessing compliance with marketing authorizations
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 authorization (Art. 5 of Directive 2003/94/EC and 91/412/EEC). 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 authorization 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. 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 the competent authority's expert on the particular type of product or by an independent expert nominated by the competent authority.

The inspector should have all relevant sections from the marketing authorization 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.

C. Carrying out the inspection
1. Adherence to chemistry and pharmacy data supplied and approved in the marketing authorization application
The inspection should seek to verify, by means of examination of all relevant facilities, equipment and documents, that the information provided in the marketing authorization application is being strictly adhered to. This examination might include:

- Composition of the medicinal product
- Container
- Manufacturing formula
- Manufacturing process including in-process controls
- Source and nature of active ingredients
- Other ingredients
- Packaging materials
- Control tests on intermediate products
- Control tests on the finished product
- Labeling
- 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:

2. Samples

Consideration should be given to taking the following samples:

- Active ingredient (if material from more than one source is available, take a sample of each).
- Excipients (samples may be taken of non-pharmacopoeial and unusual materials).
- Finished product (sufficient to carry out full duplicate analysis and to meet the legal provisions of the Member State).
- Label
- Printed carton
- Data sheet

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

- Active ingredients, and
- Excipients to the competent authority upon request.
- Any other samples requested by assessors.
- All samples should be submitted for testing/review and, if indicated by the results, necessary follow up action should be taken.

3. Copies of documents

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.

If necessary, copies of the batch manufacturing document and of the finished product specification and method of analysis should be delivered to the competent authority upon request.

4. Complaints

Review any complaints relating to the product.

5. Amendments and variations

Following the granting of a marketing authorization, the holder of a marketing authorization may subsequently apply for amendments and variations to the original information to be approved by the competent authority. Where such amendments and variations have been approved by the

competent authority, 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.

6. Review of documentation relating to the product

This should be carried out as set out in Section 12 of the main guideline. Documentation for a number of batches should be reviewed. Section 6.9 of the Rules Governing Medicinal Products in the European Community, Volume 4, recommends that trend evaluation of analytical test results be carried out. If this has been done the evaluation should be reviewed.

Conduct of inspections for investigational medicinal products for human use

General Considerations on Inspections of Investigational Medicinal Products

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 Competent Authority in order to obtain authorization to conduct a clinical trial pursuant to Article 9.2 of Directive 2001/20/EC. 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. sterilization, labeling, etc). These inspections may be triggered by an Assessor raising questions during the evaluation of an application for authorization to conduct a clinical trial or marketing authorization.

Inspection Procedures

Preparation of inspections:

Prior to conducting an inspection the inspector(s) should familiarize themselves with the organization to be inspected. This may include:

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

Review of documentation:

The system of documentation, based on the Product Specification Files, 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. Change control and the traceability of changes should be examined. A general GMP-orientated inspection will normally, in order to assess compliance with the terms and conditions of the manufacturing authorization, include examination of the documentation relating to:

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

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:

- Standard operating procedures (SOP's)
- The Product Specification File

Complaints and product recall

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. The complaints file should be examined. Defect Reports and recalls should be discussed.

Final Meeting

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

Conduct of inspections of active substance manufacturers

The purpose of this is to provide guidance on the conduct of inspection of a manufacturer of active substances as referred to in Article 111 of Directive 2001/83/EC and Article 80 of Directive 2001/82/EC in order to harmonize inspection procedures, frequency of inspections and follow-up procedures thus ensuring a consistent approach to assessment and decision-making by Competent Authorities.

General Considerations on Inspections of Active Substances

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 and pharmacopoeial requirements. In addition, when the inspection has been requested, for example, by the EDQM for the purpose of verifying whether the data submitted in order to obtain a conformity certificate comply with the monographs of the European Pharmacopoeia, this must also be assessed. Manufacture of active substances is defined in Article 46 of Directive 2001/83/EC and Article 50 of Directive 2001/82/EC as including both

- Total and partial manufacture or import of an active substance used as a starting material and,
- The various processes of dividing up, packaging or presentation prior to its incorporation into a medicinal product, including repackaging or re-labeling, such as are carried out by a distributor of starting materials.

Inspections will therefore be performed of sites producing active substances and also those where active substances are being imported, repackaged or relabeled. However the scope of the guidance given in Volume 4, EU Guidelines to Good manufacturing Practice, Medicinal Products for Human and Veterinary Use Part II, Basic Requirements for Active Substances used as Starting Materials should be noted as these apply to the manufacture of active substances for medicinal products for both human and veterinary use, but only apply to the manufacture of sterile active substances up to the point immediately prior to the active substance being rendered sterile. The sterilization and aseptic processing of sterile active substances are not covered, but

should be performed in accordance with the principles and guidelines of GMP as laid down in Directive 2003/94/EC and interpreted in the GMP Guide including its Annex 1. Whole blood and plasma are excluded, as Directive 2002/98/EC and the technical requirements supporting that directive lay down the detailed requirements for the collection and testing of blood, however, active substances that are produced using blood or plasma as raw materials are included. In the case of ectoparasiticides for veterinary use, other standards than the guidelines, that ensure that the material is of appropriate quality, may be used. It should also be noted that Section 19 of the guidance covers the manufacture of new active substances used in the production of investigational medicinal products and although recommended its application in this case, is not required by Community legislation.

Inspection Procedures

Preparation of inspections

Prior to conducting an inspection the inspector(s) should familiarize themselves with the organization to be inspected. This may include:

- Review of relevant parts of the active substance drug master file in addition to the items outlined in the main procedure or CTD for one or more selected products to be examined during the inspection.
- For triggered inspections, a review of the questions raised by the assessor or GMP inspector (arising from a GMP inspection of a manufacturing authorization holder).
- Site Master File or other equivalent document.

Review of documentation: An inspection will normally include examination of the documentation for one or several completed batches of a specified product relating to:

- Job descriptions and training of staff
- Standard operating procedures (SOPs)
- Qualification reports
- Validation reports
- Manufacturing formulae, records and instructions
- Reprocessing, reworking and solvent recovery SOPs
- Specifications, sampling and methods of analysis of components, starting materials, intermediates and finished product.
- Product quality review
- Batch release
- Complaints
- Recalls

For sites that are importing, repackaging or relabeling active substances some of the above will not apply. Sites at which these activities are being performed should be assessed for compliance with the relevant sections of Part 2 of the GMP Guide including the requirements set out in chapter 17.

Inspection Frequency

Following Article 111 of Directive 2001/83/EC and Article 80 of 2001/82/EC a competent authorities should perform an inspections of active substance manufacturers whenever it

considers that there are grounds for suspecting non-compliance with the principles and guidelines of GMP. The European Directorate for the Quality of Medicines and HealthCare (EDQM) may request an inspection of the starting material manufacturer for the verification whether the data submitted in order to obtain a conformity certificate complies with the monographs of the European Pharmacopoeia. In line with these legal provisions the Guidance on the occasions when it is appropriate for Competent Authorities to conduct inspections at the premises of Manufacturers of Active Substances used as starting materials details triggers for inspections. These principles do not imply a systematic approach for inspections of all active substance manufacturers [1-5].

CONCLUSION

From the above review, it can be concluded that the guidelines for audit and inspection according to the various regulatory agencies gives information about almost the similar requirements and instruct to follow same procedure. Except for guidelines provided by USFDA, none of the other guidelines specifically discuss about inspection of tablet manufacturing facility but still the information provided by the guidelines are useful for inspection of the tablet manufacturing facility.

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