REVISED COMPILATION OF COMMUNITY PROCEDURES ON ADMINISTRATIVE COLLABORATION AND HARMONISATION OF INSPECTIONS

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PROCEDURE FOR HANDLING RAPID ALERTS AND RECALLS ARISING FROM QUALITY DEFECTS

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Notes:	Pharmacovigilance alerts are not included within the scope of this procedure. For information on procedures for pharmacovigilance rapid alerts, reference should be made to document reference CPMP/PhVWP/005/96, rev. 1 *Rapid Alert System (RAS) and Non-Urgent Information System (NUIS) in human pharmacovigilance* or subsequent updates.

Content:

PROCEDURE FOR HANDLING RAPID ALERTS AND RECALLS ARISING FROM QUALITY DEFECTS

1. Scope

This procedure covers the transmission of information by means of a rapid alert between the Competent Authorities of EU and EEA countries (the "Member States") and MRA partners relating to the recall of medicinal products which have quality defects, including counterfeit or tampered products, when urgent action is required to protect public health and animal health. The procedure may be used also for transmission of other information such as cautions-in-use or product withdrawals for safety reasons. This procedure covers both human and veterinary medicinal products and operates within the scope of the relevant Two Way Alert programmes established between Member States and MRA partners.

Pharmacovigilance alerts are not included within the scope of this procedure.

2. Introduction

2.1. In order to protect public health and animal health, it may become necessary to implement urgent measures such as the recall of one or more defective batch(es) of a medicinal product during its marketing period.

2.2. Each holder of an authorisation referred to in Article 16 of Directive 75/319/EEC or Article 24 of Directive 81/851/EEC (for veterinary products) is required by Article 13 of Directive 91/356/EEC or Article 13 of Directive 91/412/EEC (for veterinary products) to implement an effective procedure for the recall of defective products. The authorisation holder is required to notify the relevant Competent Authority of any defect that could result in a recall and indicate, as far as possible, the countries of destination of the defective product.

2.3. Each Competent Authority should have a written procedure which covers the receipt and handling of notifications of suspected defective products and batch recalls from companies or health professionals both during and outside normal working hours.

2.4. The Competent Authority of each Member State should assist the authorisation holder in the recall process, as appropriate, and monitor its effectiveness. The Competent Authority should ensure that information concerning the recall of medicinal products is notified rapidly to other Member States, if the nature of the defect presents a serious risk to public health. This information should be transmitted by means of the "Rapid Alert System".

2.5. Each Competent Authority should have a written procedure which covers the issue of rapid alerts both during and outside normal working hours (if the urgency of the situation warrants such action).

3. Criteria for Issuing a Rapid Alert

3.1. The aim of the Rapid Alert System is to transmit only those alerts whose urgency and seriousness cannot permit any delay in transmission. To ensure its effectiveness, the system must not be saturated by the transmission of less urgent information. In each case a professional assessment must be made of the seriousness of the defect, its potential for causing harm to the patient or (in the case of a veterinary product) harm to animals, consumers, operators and the environment, and the likely distribution of the affected batch(es). Appendix 1 provides guidance on the classification of the urgency of the recall of defective medicinal products.

3.2. Class I defects are potentially life threatening. A rapid alert notification must be sent to all Member States and MRA partners, irrespective of whether or not the batch was exported to that country.

3.3. Class II defects could cause illness or mistreatment, but are not Class I. A rapid alert notification should be sent only to those Member States and MRA partners to which it is known, or believed, that the batch has been distributed. In identifying those countries, due consideration should be given to parallel distribution and import arrangements and the free trade between wholesale distributors within the EEA. In the case of parallel imports where there is difficulty in establishing the traceability of batches, consideration should be given to notifying all Member States by the Rapid Alert System.

3.4. Class III defects may not pose a significant hazard to health, but withdrawal may be initiated for other reasons. These are not notified through the Rapid Alert System.

3.5. Where appropriate, the rapid alert system may be used for notification to Member States or MRA partners of the recall of products or an embargo on the distribution of products following suspension or withdrawal of a manufacturing authorisation.

4. Issue of a Rapid Alert Notification

4.1. Responsibility

4.1.1. For a batch manufactured in a Member State, or a batch manufactured in a third country and imported into the EEA, which is the subject of a national or mutually recognised (decentralised) marketing authorisation, the Competent Authority of the Member State in which the defect was first identified should issue the rapid alert. MRA partners identified by the manufacturer or importer as countries to which the defective batch was distributed should also be notified through the rapid alert system.

4.1.2. In the case of a centrally authorised product, and in the exceptional case of a product which has both a centralised and a national authorisation, the Competent Authority of the Member State in which the defect was first identified should issue a rapid alert. The alert should inform all recipients that EMEA will co-ordinate further action in co-operation with the relevant

Supervisory Authority and in accordance with EMEA's Crisis Management procedures.

4.1.3. In the case of parallel distribution of a centrally authorised product and where no repackaging is carried out, the procedure described under 4.1.2 applies. This procedure also applies if the defect resulted from a repackaging operation. Where repackaging is carried out but the defect results from the original manufacturing process, the procedure described under 4.1.2 still applies, but the rapid alert should include descriptions of the different packaging in which the product might appear (for example different language versions and pack sizes) where this information is available from EMEA.

4.1.4. In the case of a parallel import, the Competent Authority of the Member State in which the defect was first identified should issue the rapid alert, which should include MRA partners as appropriate. The Competent Authority should also notify the Supervisory Authority of the Member State in which the batch was manufactured or repackaged depending on the nature of the defect.

4.2. Format of the rapid alert and its transmission

4.2.1. A suitable format for the notification of quality defects by the Rapid Alert System is given in Appendix 2. The form should be completed clearly and (preferably) in English. It should be attached to a distribution list and the documents sent by fax or electronic mail where relevant, to the persons nominated in the EMEA rapid alert list, which includes working hours and out-of-hours contact names and numbers. Changes to contact names and/or numbers must be notified to EMEA so that the list can be updated as necessary.

In the case of a Class I defect which must be notified out of hours, it may be necessary to use the out-of-hours contact telephone numbers in addition to the rapid alert fax.

4.2.2. Transmission of a Class I rapid alert must be concurrent with the national action. Whenever feasible, transmission of a Class II rapid alert should be concurrent with the national action but in all cases should be within 24 hours of the national notification.

4.3. Action on receiving a notification under the Rapid Alert System.

Each Competent Authority should have a written procedure for the receipt and handling of rapid alerts from other authorities during and outside working hours. Unless it can be established unequivocally that the defective batch in question has not been distributed in the Member State (including parallel imports) the Competent Authority should apply its national procedure for ensuring recipients of the batch are alerted. The class and urgency of the alert should correspond to those of the initial rapid alert.

5. Fraud and Counterfeit Products

The Rapid Alert System should be used to notify EEA Member States and MRA partners of the possible presence in the distribution network of counterfeit products or those resulting from fraud in manufacture, packaging, distribution or promotion and products containing counterfeit starting materials.

The Competent Authority of the Member State or MRA partner in which the fraud or counterfeit was first detected should issue the notification. The format for a rapid alert notification may be used, but the heading on the document should make clear that the notification relates to fraud or to a counterfeit product and sufficient information should be provided under "details of defect" to enable it to be identified. Notification should be sent concurrently to EMEA.

6. Follow-Up Action

Each Competent Authority should have a written procedure to describe follow-up action to a rapid alert notification.

The Competent Authority of each Member State and MRA partner to which a recalled product was exported should monitor the conduct and effectiveness of any national recall which it instituted as a result of the rapid alert notification.

The relevant Supervisory Authority should investigate the circumstances which led to the distribution of the defective product and ensure that any necessary corrective action is taken by the manufacturer and marketing authorisation holder as appropriate.

EMEA should co-ordinate follow-up action for recalls of centrally authorised products.

7. Appendices

7.1. Appendix 1 : Classification of Rapid Alerts

7.2. Appendix 2 : Format for Rapid Alert Notification of a Quality Defect

Appendix 1

Rapid Alert System : Classification of Urgency of Defective Medicinal Product Alerts

CLASS I

Class I defects are potentially life-threatening or could cause a serious risk to health. These must be notified through the Rapid Alert System in all cases.

Examples:

- Wrong product (label and contents are different products)
- Correct product but wrong strength, with serious medical consequences
- Microbial contamination of sterile injectable or ophthalmic product
- Chemical contamination with serious medical consequences
- Mix-up of some products (rogues) with more than one container involved
- Wrong active ingredient in a multi-component product, with serious medical consequences.

CLASS II

Class II defects could cause illness or mistreatment, but are not Class I. These should be notified through the Rapid Alert System only to Member States and MRA partners to which it is likely or known that the batch has been distributed (including parallel import/distribution).

Examples:

- Mislabelling, e.g. wrong or missing text or figures
- Missing or incorrect information (leaflets or inserts)
- Microbial contamination of non-injectable, non-ophthalmic sterile product with medical consequences
- Chemical/physical contamination (significant impurities, cross-contamination, particulates)
- Mix up of products in containers (rogues)
- Non-compliance with specification (e.g. assay, stability, fill/weight)
- Insecure closure with serious medical consequences (e.g. cytotoxics, child- resistant containers, potent products).

CLASS III

Class III defects may not pose a significant hazard to health, but withdrawal may have been initiated for other reasons.

Examples:

- Faulty packaging, e.g. wrong or missing batch number or expiry date
- Faulty closure
- Contamination, e.g. microbial spoilage, dirt or detritus, particulate matter

Appendix 2

IMPORTANT - DELIVER IMMEDIATELY

Rapid Alert Notification of a Quality Defect / Recall

<table>
<tr><td colspan="3">[add title in national language if necessary]
[add letter head of sender]
[turn into bilingual model as required].</td></tr>
<tr><td colspan="3">1. To:
(see list attached, if more than one)</td></tr>
<tr><td colspan="2">2. Product Recall Class of Defect: I II
(circle one)</td><td>3. Counterfeit / Fraud (specify)*</td></tr>
<tr><td>4. Product:</td><td colspan="2">5. Marketing Authorisation Number:*
For use in humans/animals (delete as required)</td></tr>
<tr><td>6. Brand/Trade Name:</td><td colspan="2">7. INN or Generic Name:</td></tr>
<tr><td>8. Dosage Form:</td><td colspan="2">9. Strength:</td></tr>
<tr><td>10. Batch/Lot Number:</td><td colspan="2">11. Expiry Date:</td></tr>
<tr><td>12. Pack size and Presentation:</td><td colspan="2">13. Date Manufactured:*</td></tr>
<tr><td colspan="3">14. Marketing Authorisation Holder:*</td></tr>
<tr><td>15. Manufacturer†:

Contact Person:

Telephone:</td><td colspan="2">16. Recalling Firm (if different):

Contact Person:

Telephone:</td></tr>
<tr><td colspan="3">17. Recall Number Assigned (if available)÷</td></tr>
<tr><td colspan="3">18. Details of Defect/Reason for Recall:</td></tr>
<tr><td colspan="3">19. Information on distribution including exports (type of customer, e.g. hospitals):*</td></tr>
<tr><td colspan="3">20. Action taken by Issuing Authority:</td></tr>
<tr><td colspan="3">21. Proposed Action:</td></tr>
</table>

22. From (Issuing Authority):		23. Contact Person: Telephone:
24. Signed:	25. Date:	26. Time:*

* Information not required, when notified from outside EU.

† The holder of an authorisation referred to under Article 16 of Directive 75/319/EEC or Article 24 of Directive 81/851/EEC and the holder of the authorisation on behalf of whom the Qualified Person has released the batch in accordance with Article 22 of Directive 75/319/EEC or Article 30 of Directive 81/851/EEC if different.

This is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us by telephone immediately and return it to us at the above address by mail. Thank you.

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CONDUCT OF INSPECTIONS OF PHARMACEUTICAL MANUFACTURERS

Guideline Title:	Conduct of Inspections of Pharmaceutical Manufacturers
Publisher:	European Commission Directorate-General III
Date of publishing:	1995
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Date of entry into force:	Immediate

Content:

CONDUCT OF INSPECTIONS OF PHARMECEUTICAL MANUFACTURERS

Introduction

The purpose of this document is to provide guidance on the conduct of inspection of a manufacturer of medicinal products holding or seeking an authorization referred to in Article 16 of Directive 75/319/EEC and Article 24 of Directive 81/851/EEC 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.

Glossary of Terms

The definition of terms in the detailed guidelines published in Good Manufacturing Practice for Medicinal Products in the European Community, Volume IV are applicable to this document. In addition, the following apply:

Inspection:

On-Site assessment of the compliance with the Community GMP principles performed by officials of Community Competent Authorities.

A **general GMP Inspection** covering general GMP aspects should be carried out before the authorization referred to in Article 16 of Directive 75/319/EEC and Article 24 of Directive 81/851/EEC respectively, is granted and periodically afterwards as required.

An inspection may be more **product- or process- related** when it focuses on the adherence by the manufacturer to the marketing authorization of a medicinal product and on the manufacture and documentation related to the product or to a specific manufacturing process.

QC Laboratory Inspection:

On-Site assessment of the adherence to Good Quality Control Laboratory Practice is normally part of the GMP Inspection.

Contract QC Laboratories authorized according to Article 5(b) of Directive 75/319/EEC or Article 10.2 of Directive 81/851/EEC are also subject to these inspections.

Laboratory Inspection for compliance with GLP Principles is performed in accordance with guidelines given in the annexes to the Directive 90/18/EEC and is not part of this document.

Inspection Report:

Report prepared by the official representing the Competent Authority stating whether the company inspected in general complies with the Community GMP principles.

General Considerations on Inspections

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

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

3. 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 licensing authority and thus with the licensing provisions for the standard product should be considered as one of the inspectors responsibilities.

4. Inspectors should strive to create a positive atmosphere during the inspection.

5. An inspector should be aware of his influence in decision making processes. The inspector should answer questions but avoid entering the role of a consultant.

6. 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. An inspection should normally include educational and motivating elements.

7. Different types of inspection may be carried out according to the activities of the company.

   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.

   General GMP inspections (also termed regular, periodic, planned or routine) should be carried out before a manufacturing authorization is granted. This kind of inspection may also be necessary for a significant variation of the manufacturing authorization and if there is a history of non-compliance.

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

Product- or process-related inspections (also termed special or problem oriented) may be indicated to assess the adherence of the manufacturer to the marketing authorization 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).

8. The wide diversity of facilities (both in terms of physical lay-out and management structure) together with the variety of products and production processes as well as analytical methods means that judgement by inspectors on-site of the degree of compliance with GMP is essential.

9. A consistent approach to evaluation of the GMP standard of companies is essential.

10. Inspections may disturb the normal work patterns within a company. Therefore, inspectors should take care not to put the product at risk, and should carry out their work in a careful and planned way.

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

Inspection Procedures

12. Planning of inspections: 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.

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

    This may include:

    - examination of a site master file (if available)
    - a review of the 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 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 the Competent Authority 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 registration file of one or more selected products to be examined during the inspection

An aide-memoire may be prepared specifically for the inspection to be performed. The aide memoire helps 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 etc.)
- samples (if any) to be taken
- the schedule for the final meeting
- the approximate schedule for the transmission of the inspection report

14. Announcement of inspection: Competent Authorities have the right to inspect at any time (including during shift work). 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.

15. 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 special-

ist(s) and to discuss his inspection plan (of course subject to unannounced modifications).

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 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
- explain how deficiencies have been resolved if this information has not already been forwarded to the competent authority
- designate the people to accompany the inspector during the inspection
- allocate a room for the inspector if needed

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

16. Inspection of the plant facilities: a rapid plant tour is often useful for familiarisation with the site and any major changes. 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. 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 goods, taking into account the detailed guidelines of GMP.

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

    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.

17. 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-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:

- job descriptions
- standard operating procedures (SOP's)
- validation reports
- manufacturing formulae, records and instructions
- specifications
- batch release procedure and the role of the QP(s)

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

- standard operating procedures (SOP's)
- manufacturing formulae, records and instructions
- specifications, sampling and methods of analysis of components, starting materials, intermediates and finished products

18. 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.

19. 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.

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

20. 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.

Final Meeting

21. 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.

22. 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.

23. Facts and objective evidence supporting the observations should preferably be agreed by the company. The company may if they so wish discuss initial proposals for remedial action.

24. 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.

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

Notes

26. Inspection reports should be based on notes taken during the inspection. These notes should be clear and legible.

Inspection Report

27. An inspection report should describe the scope of the inspection and cover the observations arising from the inspection. Deficiencies should be mentioned in the conclusion.

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

29. 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. 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.

30. The action taken by the Competent Authority will depend upon the nature and the extent of non-compliance.

31. 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.

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

Inspection Frequency

33. 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. 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.

34. It should be stressed that the activities of the individual company (products and dosage forms manufactured, units and substances handled and 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.

Quality Management of the Inspector's Activity

35. Most inspectors work alone or, at most, in pairs. The possibility of a specialist participating in the inspection should be taken into consideration. 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 recognise deficiencies
- the assessment of the seriousness of deficiencies
- the action recommended
- the effectiveness with which the determined action is carried out

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

ANNEX ON CONDUCT OF PRODUCT RELATED INSPECTIONS

Introduction

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.

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***.

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

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

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.

Consultation should include the following:

i. Verification that the proposed manufacturer holds the appropriate manufacturing authorisations for the product concerned (Article 16 of Directive 75/319/EEC and Article 24 of Directive 81/851/EEC).

ii. Verification that the appropriate authorisation is held where third country importation is proposed (Article 16 of Directive 75/319/EEC and Article 24 of Directive 81/851/EEC).

iii. Verification that any contract Quality Control laboratory has been inspected and approved (Article 5 (b) of Directive 75/319/EEC and Article 10.2 of Directive 81/851/EEC).

The role of inspectors in assessing compliance with marketing authorisations

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 (Article 5 of Directive 91/356 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

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.

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 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.

Carrying out the inspection

Adherence to chemistry and pharmacy data supplied and approved in the marketing authorisation 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 authorisation application is being strictly adhered to. This examination might include:

(a) composition of the medicinal product

(b) container

(c) manufacturing formula

(d) manufacturing process including in-process controls

(e) source and nature of active ingredients

(f) other ingredients

(g) packaging materials

(h) control tests on intermediate products

(i) control tests on the finished product

(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:

Samples

Consideration should be given to taking the following samples:

(a) active ingredient (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 product (sufficient to carry out full duplicate analysis and to meet the legal provisions of the Member State).

(d) label

(e) printed carton

(f) data sheet

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

(a) active ingredients, and

(b) excipients to the competent authority upon request.

(c) 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.

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.

Complaints

Review any complaints relating to the product.

Amendments and variations

Following the granting of an marketing authorisation, the holder of an marketing authorisation 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.

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 IV, recommends that trend evaluation of analytical test results be carried out. If this has been done the evaluation should be reviewed.

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OUTLINE OF A PROCEDURE FOR CO-ORDINATING THE VERIFICATION OF THE GMP STATUS OF MANUFACTURERS IN THIRD COUNTRIES

Guideline Title:	Outline of a Procedure for Co-ordinating the Verification of the GMP Status of Manufacturers in Third Countries
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Responsible authority:	Technical Co-ordination Unit

Content:

OUTLINE OF A PROCEDURE FOR CO-ORDINATING THE VERIFICATION OF THE GMP STATUS OF MANUFACTURERS IN THIRD COUNTRIES

1 Verification of the GMP Compliance Status of Third Country Manufacturers of Medicinal Products.

1.1 The Supervisory Member State for the manufacturing authorisation holder who is responsible for importation of a product should verify the GMP compliance status of any third country manufacturer(s) mentioned in the application in accordance with their own policies and procedures. This may be based on the following:-

a) A report of an inspection for the product or product category concerned carried out by the Supervisory Member State in accordance with the procedure contained in the Compilation of Community Procedures on Administrative Collaboration and Harmonisation of Inspections , III/5698/94-EN.

or

b) Information supplied by another EU/EEA Competent Authority in accordance with the procedure contained in the Compilation of Community Procedures on Administrative Collaboration and Harmonisation of Inspections , III/5698/94-EN.

or

c) A report of an inspection for the product or product category concerned carried out by another EU/EEA competent authority in accordance with the procedure contained in the Compilation of Community Procedures on Administrative Collaboration and Harmonisation of Inspections , III/5698/94-EN.

or

d) Either an inspection report or a statement of GMP compliance obtained under a finalised Mutual Recognition Agreement between the European Community and the Competent Authorities of the third country in which the manufacturer is located.

1.2 Where the Supervisory Member State is unable to verify the GMP status of any third country manufacturer(s) on the above basis they may request another EU/EEA Competent Authority to carry out an inspection in accordance with the procedure contained in the Compilation of Community Procedures on Administrative Collaboration and Harmonisation of Inspections, III/5698/94-EN and to provide confirmation of the manufacturer's GMP compliance status. This arrangement should be subject to obtaining the written consent of any other Supervisory Member States involved. This should also take account of the

readiness of the Member States involved to carry out third country inspections, their workloads, their experience in the type of inspections required, language capability for the inspection and overall economics of travel etc.

1.3 Where the Supervisory Member State and the competent authorities of another EU Member State are unable to agree on the acceptability of an inspection report for a manufacturer in a third country they should utilise the arrangements described for human products in Article 17 of Council Regulations 2309/93 or where appropriate the arbitration procedure provided by Article 10 of Council Directive 75/319/EEC and for veterinary products Article 39 of Council Regulations 2309/93 or where appropriate the arbitration procedure provided by Article 18 of Council Directive 81/851/EEC.

2 Exchange of Information on Third Country Manufacturers.

2.1 On the basis of a "reasoned request" from the competent authorities of another Member State or from the EMEA the Supervisory Member State should provide a summary of the most recent verification of the GMP status of a third country manufacturer for a particular product or product category.

2.2 Where the Member State requested to supply the information is unable to do so the requesting authorities may carry out a GMP inspection of the third country manufacturer, in which case they will provide the other authorities with a copy of their inspection report or a statement of GMP compliance.

3 Organisation and Records of Inspections and Composition of Inspection Teams.

3.1 The EMEA will maintain a rolling plan of all the third country inspections that are planned by the Competent Authorities of the EU/EEA and will make this available on a regular basis.

3.2 The EMEA will maintain a record of the third country inspections that have been carried out by the competent authorities of the EU/EEA and will make this available on a regular basis.

3.3 The co-ordination of planned third country inspections will be discussed and agreed at the Working Party on the Control of Medicinal Products and Inspections and the meetings of inspectors organised by the EMEA.

3.4 The competent authorities planning inspections of manufacturers in third countries may invite the participation of the other Member States who have a shared "Supervisory" responsibilities for the product(s).This should take into account planned applications for marketing authorisations, problems encountered with the products from the manufacturer, their workloads, their experience in the type of inspections required, language capability for the inspection and overall economics of travel etc.

4. The "Supervisory Authorities"

4.1 The "Supervisory Authorities" for a medicinal product and their responsibilities are defined for products for human use in Articles 16 and 17 of Council Regulations (EEC) No 2309/93 and for products for veterinary use in Articles 38 and 39 of the same Regulations. They are the Competent Authorities which have granted the manufacturing authorisation either for the manufacturing site if it is in the EU or for the importer if the product is manufactured in a third country.

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TRAINING OF INSPECTORS

Guideline Title:	Training of Inspectors
Publisher:	European Commission Directorate-General III
Date of publishing:	1995
Responsible authority:	Working Party on Control of Medicines and Inspections
Date of adoption:	3. December 1996

Content:

- Basic training
- In-service training
- Continuous training
- Time spent in training

TRAINING OF INSPECTORS

Taking into account the paramount importance of the management of inspection services, this guideline establishes some requirements concerning qualifications, experience and training of pharmaceutical inspectors.

Objectivity and professional integrity, competence in technical matters (GMP) and auditing skills should be the main features of inspectors. They should also be able to maintain a positive atmosphere during inspections.

Although it is the main task of inspectors to identify deficiencies, an acknowledgment of adequate GMP attitudes or "solutions" may also help in creating an open atmosphere. Inspectors should be aware of their influence on the Company's decision making process, they should answer questions but avoid entering into the role of a consultant.

Inspectors should be very well trained in all the relevant topics concerning Quality Assurance management, manufacturing processes, control and distribution of medicinal products and in the way of conducting an inspection.

Basic training

Inspectors have to be officials of the Competent Authorities. They should preferably have the same level of qualification as the "Qualified Person" as defined in art. 23 of the directive 75/319/EEC and therefore be eligible as a Qualified Person.

Moreover, in order to be appointed pharmaceutical inspectors, the candidates should demonstrate their knowledge of the relevant matters in the pharmaceutical field, including:

- Community Good Manufacturing Practice
- Community and national legislations
- organisation of the national regulatory authority
- structure and principles of operation of commercial organisations
- marketing and manufacturing authorizations systems and their relationships
- microbiology, process and ventilation engineering, analytical instrumentation, computer systems, process validation
- interrelation of inspection, sampling and analysis, licencing
- distribution of medicinal products
- pharmaceutical technology
- auditing techniques
- principle of quality standards (at least awareness of CEN 29000)
- communication skills, oral and written.

Previous experience in the pharmaceutical industry is desirable.

In-service training

After recruitment and in addition to their basic training, new inspectors should be trained by senior inspectors. The theory of inspection should be explained and the practice should be shown in the field, so that concrete examples of the meaning and of the goals of inspections are given and can be discussed. New inspectors should participate, but only as observers, in on the spot inspections carried out during their initial training.

Beside this and where needed, training courses in auditing techniques and communications, reporting, languages, legal matters and management should be organised by national inspectorates.

Continuous training

Considering the rapid implementation of the manufacturing technologies, the ever more frequent utilization of automatic and computerized systems both in production and quality control of medicinal products, inspectors should also receive continuous training.

This could be reached through their participation in courses, seminars, scientific meetings and conferences organized either by the national inspectorates or by national or international scientific organizations.

When appropriate, joint inspections or training visits with other inspectors of the same Member State or of other Member States may be a useful training method.

Time spent in training

Ten days of training (e.g. courses, symposiums, conferences, etc.) per year should be considered as a reasonable average

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GMP INSPECTION REPORT - COMMUNITY FORMAT

Title of Form: GMP Inspection report - Community format

Publisher: -

Date of publishing: 1999

Content:

- GMP Inspection report - Community format
- Definition of Significant Deficiencies

GMP Inspection report - Community format

Inspected site(s):	*Name and full address of the Inspected site*
Activities Carried out by company	*Manufacture of Active Ingredient* ☐ *Manufacture of Finished Medicinal Product* ☐ *Manufacture of Intermediate or bulk* ☐ *Packaging* ☐ *Importing* ☐ *Laboratory Testing* ☐ *Batch Control and Batch Release* ☐ *Other* _____ ☐
Inspection date(s):	*Date(s), month, year*
Inspector(s):	*Name of the inspector(s),* *Name of expert / assessor (if applicable)* *Name of the Competent Authority(ies).*
References:	*Reference Number of Marketing and / or Manufacturing Authorisations* *EMEA reference number(s).(If the inspection is an EMEA inspection)*
Introduction:	*Short description of the company and the activities of the company.* *<u>For inspections in non-EC/EEA countries</u> it should be stated whether the Competent Authority of the country, where the inspection took place, was informed of the inspection and whether the Competent Authority took part in the inspection.* *Date of previous inspection* *Names of Inspectors involved in previous inspection* *Major changes since the previous inspections*
Brief report of the inspection activities undertaken:	
Scope of Inspection:	*Short description of the inspection (Product related inspection and/or General GMP inspection). The reason for the inspection should be specified (e.g. new marketing application, routine, investiagion of product defect)*
Inspected area(s):	*Each inspected area should be specified.*
Personnel met during the inspection:	*The names and titles of key personnel met, should be specified,(listed in annex)*

Inspectors Team's findings and observations relevant to the inspection; and deficiencies:	*Relevant headings from The Rules Governing Medicinal Products in the European Community, Good Manufacturing Practice for Medicinal Products Vol. IV. (Guide to GMP, Basic Requirements, relevant for scope of inspection)* *New headings may be introduced as relevant.* *This section can link the findings to the deficiencies and used to explain classification*
Headings to be used	Quality Management Personnel Premises and Equipment Documentation Production Quality Control Contract Manufacture and Analysis Complaints and Product Recall Self Inspection
Distribution and Shipment	e.g. Compliance with Good Distribution Practice
Questions raised relating to the assessment of a marketing application	e.g. Pre- authorisation Inspections
Other specific issues identified	e.g. Relevant future changes announced by company
Site Master File	Assessment of SMF if any; date of SMF
Miscellaneous: Samples taken Distribution of Report	
Annexes attached:	*List of any annexes attached*

List of Deficiencies classsified into critical, major and others:	*All deficiencies should be listed and the relevant reference to the EU GMP Guide and other relevant EU Guidelines should be mentioned.* *All deficiencies found should be listed even if corrective action has taken place straight away.* *If the deficiencies are related to the assessment of the marketing application this should be clearly stated.* *The company should be asked to inform the Inspectorate about the progress of the corrected actions and a proposed time schedule for corrections.*
Recommendations	*To the Committee requesting the Inspection or to the Competent / Enforcement Authority for the site inspected*
Summary and conclusions:	*The Inspection Team should state if the Company operates in accordance with the EU GMP Rules and mention any other item to alert requesting authority.*
Name(s) **Signatures(s)** **Organisation(s)** **Date:**	*The Inspection Report should be signed and dated by the Inspector(s)/Assessors who participated in the Inspection.*

Definition of Deficiencies to be used in Community Inspection Report

1. **CRITICAL DEFICIENCY**:
   A deficiency which has produced, or leads to a significant risk of producing either a product which is harmful to the human or veterinary patient or a product which could result in a harmful residue in a food producing animal.

2. **MAJOR DEFICIENCY:**
   A non-critical deficiency:

   which has produced or may produce a product, which does not comply with its marketing authorisation;

or

   which indicates a major deviation from EU Good Manufacturing Practice;

or

   within EU) which indicates a major deviation from the terms of the manufacturing authorisation;

or

   which indicates a failure to carry out satisfactory procedures for release of batches or (within EU) a failure of the Qualified Person to fulfil his legal duties;

or

   a combination of several "other" deficiencies, none of which on their own may be major, but which may together represent a major deficiency and should be explained and reported as such.

3. **OTHER DEFICIENCY**

   A deficiency which cannot be classified as either critical or major, but which indicates a departure from good manufacturing practice.

   (A deficiency may be "other" either because it is judged as minor, or because there is insufficient information to classify it as major or critical)

COMMUNITY BASIC FORMAT FOR MANUFACTURERS AUTHORISATION

Title of Form:	Community Basic Format for Manufacturers Authorisation
Publisher:	European Commission Directorate-General III Industry
Date of publishing:	1999
Legislative basis:	The attached provides the basic format and content for manufacturers authorisation granted by the Competent Authorities of Community Member States in accordance with Article 16 of Council Directive 75/319/EC and Article 24 of Council Directive 81/851/EC.
Status:	It has been agreed (at the Control of Medicinal Products and Inspections Working Party on 18/12/98) that this model format will be introduced for all new and renewed manufacturing authorisations issued by the Competent Authorities of the EU Member States from July 1st 1999 onwards.
Additional Notes:	**Use by Competent Authorities in the EU** This document describes the order in which information will appear in manufacturers' authorisations and the basic content of each section. Otherwise manufacturers authorisations will reflect the individual requirements of the Competent Authorities and National Legislation. **Content of the Manufacturing Authorisation** Manufacturers authorisations should contain, as a minimum, the information included in pages 1 - 3 in the attached model document, with the exception of sections 1 and 3 of Annex I which are optional (indicated as such in the text). The remaining pages consist of Annexes (2 to 7) which are optional and are to be used at the discretion of the Competent Authorities concerned.

Content:

- ANNEX 5 (Optional) - Name of person responsible for quality control / production
- ANNEX 6 (Optional) - Date of Inspection / Scope of last Inspection
- ANNEX 7 (Optional) - Products authorised to be manufactured

COMMUNITY BASIC FORMAT FOR MANUFACTURERS AUTHORISATION

1	Authorisation Number	.....
2	Name of Manufacturer	
3	Address of manufacturing site	....
4	Legally registered address of authorisation holder	....
5	Scope of Authorisation (Manufacturing operations* / Production Activities)	See Annex 1
6	Dosage forms produced*	See Annex 1
7	Legal Basis of Authorisation *(Reference to Directives and National legislation implementing them)*	
8	Name of Responsible officer of the competent authority of the member state granting the manufacturing authorisation	.....
9	Signature	.....
10	Date	Day / month / year

Annexes attached

Annex I

Annexes 2*, 3*,4*,5*,6*, 7* (as required)

* Optional

ANNEX 1

SCOPE OF AUTHORISATION:

(Please delete the areas which do not apply)

Human Medicinal Product
Veterinary Medicinal Product

1	**MANUFACTURING OPERATIONS (Categorised as per GMP Guideline) ***
1.1	Purchase of Materials
1.2	Purchase of Products
1.3	Production
1.4	Release Quality Control
1.5	Storage
1.6	Distribution
1.7	Related Controls for these operations

* Optional section

2	**PRODUCTION ACTIVITIES**
2.1	**Sterile products**
	2.1.1 Liquid dosage forms (Large Volume Parenterals) - aseptically prepared - terminally sterilised
	2.1.2 Liquid dosage forms (Small Volume Parenterals) - aseptically prepared - terminally sterilised - eye drops
	2.1.3 Semi-solid dosage forms
	2.1.4 Solid dosage forms - solid fill - freeze-dried
2.2	**Non-sterile products** 2.2.1 Liquid dosage forms 2.2.2 Semi-solid dosage forms 2.2.3 Solid dosage forms - unit dose form (tablets, capsules, suppositories, pessaries) - multi dose form (powders, granules)
2.3	**Biological products** 2.3.1 Vaccines 2.3.2 Sera 2.3.3 Blood products

	2.3.4 Other (describe: e.g. hormones, enzymes of human or animal origin, genetically engineered products)
2.4	**Packaging only** 2.4.1 Liquid dosage form 2.4.2 Semi-solid dosage form 2.4.3 Solid dosage form

3	**LIST OF PRODUCT DOSAGE FORMS ***
3.1	Oral Preparation – liquid and semi solid
3.2	Oral Preparations – solid forms
3.3	Oromucosal and gingival preparations
3.4	Preparations for dental use
3.5	Cutaneous and transdermal preparations
3.6	Eye preparations
3.7	Ear preparations
3.8	Nasal Preparations
3.9	Vaginal Preparations
3.10	Rectal Preparations
3.11	Preparations for inhalation
3.12	Parenteral preparations
3.13	Implants
3.14	Preparations for dialysis
3.15	Preparations for intravesical and urethral use
3.16	Tracheopulmonary preparations
3.17	Endocervical preparations
3.18	Intramammary preparations
3.19	Intrauterin preparations
3.20	Environmental preparations
3.21	Miscellaneous

* Optional

ANNEX 2 (Optional)

Address(es) of Contract Manufacturing Sites .....

.....

.....

ANNEX 3 (Optional)

Address(es) of Contract Laboratories .....

.....

.....

ANNEX 4 (Optional)

Name of Qualified Person .....

ANNEX 5 (Optional)

Name of person responsible for quality control .....

Name of person responsible for production .....

ANNEX 6 (Optional)

Date of Inspection on which Manufacturers Authorisation was granted / / 19

Scope of last Inspection .....

ANNEX 7 (Optional)

Products authorised to be manufactured (in accordance with Article 17 of Council Directive 75/319/EEC

.....

.....

.....

.....

EXCHANGE OF INFORMATION ON MANUFACTURING AND WHOLESALE DISTRIBUTION AUTHORIZATIONS IN THE FRAMEWORK OF ADMINISTRATIVE COLLABORATION BETWEEN COMPETENT AUTHORITIES IN THE EUROPEAN ECONOMIC AREA

Title of form:	Exchange of information on manufacturing and wholesale distribution authorizations in the framework of administrative collaboration between Competent Authorities in the European Economic Area
Publisher:	European Commission Directorate-General III
Date of publishing:	1995
Responsible authority:	Working Party on Control of Medicines and Inspections
Date of adoption:	2.-3. December 1996
Date of entry into force:	December 1996

Content:

EXCHANGE OF INFORMATION ON MANUFACTURING AND WHOLESALE DISTRIBUTION AUTHORIZATIONS IN THE FRAMEWORK OF ADMINISTRATIVE COLLABORATION BETWEEN COMPETENT AUTHORITIES IN THE EUROPEAN ECONOMIC AREA

Introduction

Effective control of medicinal products circulating within the Community requires a high level of administrative collaboration and consequently a good system of exchange of information between competent authorities.

Either within the context of a normal routine check or sampling programme of medicinal products distributed in a Member State, or in the event of suspicion concerning the origin of a medicinal product coming from another Member State, it may be necessary for a competent authority to seek confirmation of the manufacturer's authorization from another competent authority.

In most cases, the transmission of inspection reports as provided for in article 30 of Directive 75/319/EEC, as modified, for medicinal products for use in man and in Directive 81/851/EEC, Article 39, as modified, for veterinary medicinal products would not be justified and would create a needless administrative workload. In addition, should exchange of information on individual authorizations concerning wholesale distributors as provided for in article 3, 4 of Directive 92/25/EEC on the wholesale distribution of medicinal products for human use be needed, generally a simple confirmation of the existence of an appropriate authorization would suffice.

Therefore, following data could be exchanged:

- a reference to the legal basis of the authorization (Community and national provisions);
- reference number, if any, of the current valid authorization;
- legally registered address of the holder of the authorization;
- address(es) of the manufacturing and/or wholesale distribution site(s) covered by the authorization, including contract Quality Control laboratories;
- scope of the authorization:
    1. manufacture of medicinal products for use in man or animals
    2. import from third countries;
    3. manufacturing operations which are authorized: total or partial manufacture and for what dosage forms (pharmaceutical form).
    4. wholesale distribution of medicinal products for use in man or animals.

The request form should be used by competent authorities looking for confirmation on the manufacturer's legal status. The reply form should be used by competent authorities replying to a request.

EXCHANGE OF INFORMATION ON MANUFACTURING AND WHOLESALE DISTRIBUTION AUTHORIZATIONS IN THE FRAMEWORK OF THE ADMINISTRATIVE COLLABORATION BETWEEN COMPETENT AUTHORITIES IN THE EEA

Request Form

The competent authority of.....

requests the competent authority of..... to confirm that:

The company .....,
Address:.....

.....

.....

has been authorized, in accordance to Directive 75/319/EEC, Article 16, and /or Directive 81/851/EEC, Article 24, or Directive 92/25/EEC article 3, to carry out the following operations:

+ manufacture of medicinal products for use in man (*) / animals (*)
+ import of medicinal products from third countries (*);
+ total/partial manufacture of the following medicinal products:

.....

.....

.....

the following dosage forms: (see overleaf).

+ wholesale distribution of medicinal products for use in man(*) / animals(*)

Reason for the request:.....

.....

Date: Name and Signature of a responsible officer of the competent authority

.....

(*): delete that which does not apply

EXCHANGE OF INFORMATION ON MANUFACTURING AND WHOLESALE DISTRIBUTION AUTHORIZATIONS IN THE FRAMEWORK OF THE ADMINISTRATIVE COLLABORATION BETWEEN COMPETENT AUTHORITIES IN THE EEA

Reply Form

As requested by the competent authority of.....

on ...../...../199..., the competent authority of.....

confirms the following:

The company ....., whose legally registered address is:

.....

.....

has been authorized, in accordance to Directive 75/319/EEC, Article 16, and /or Directive 81/851/EEC, Article 24, or Directive 92/25/EEC article 3, transposed in the following national legislation: .

.....

under the authorization reference number ....., covering the following sites of manufacture and/or wholesale distribution:

1.....

2.....

3.....

to carry out the following operations:

+ manufacture of medicinal products for use in man (*) / animals (*)
+ import of medicinal products from third countries (*);
+ total/partial manufacture of the following medicinal products:

.....
.....

the following dosage forms: (see overleaf).
+ wholesale distribution of medicinal products for use in man(*) / animals(*)

Date:

Name and Signature of a responsible officer of the competent authority

.....

(*): delete that which does not apply

Dosage forms of which manufacture is authorized (*):

Sterile products:

Liquid dosage forms (Large Volume Parenterals)
- aseptically prepared
- terminally sterilized

Liquid dosage forms (Small Volume Parenterals)
- aseptically prepared
- terminally sterilized
- eye drops

Semi-solid dosage forms

Solid dosage forms
- solid fill
- freeze-dried

Non-sterile products:

Liquid dosage forms

Semi-solid dosage forms

Solid dosage forms
- unit dose form (tablets, capsules, suppositories, pessaries)
- multi dose form (powders,granules)

Biological products:

Vaccines

Sera

Blood products

Allergens

Other (describe: e.g. hormones, enzymes of human or animal origin, genetically engineered products)

Packaging only:

Liquid dosage form

Semi-solid dosage form

Solid dosage form

(*: delete that which does not apply).

(Rev. December 1996)

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REPLY FORM FOR INFORMATION ON A MANUFACTURER

Title of form:	Reply Form for Information on a Manufacturer
Publisher:	The European Agency for the Evaluation of Medicinal Products
Date of publishing:	2000
Responsible authority:	Inspectors Group

Content:

- Reply Form for Information on a Manufacturer

REPLY FORM FOR INFORMATION ON A MANUFACTURER

As requested by the competent authority of .....

on (date of request) ...../...../.....

The competent authority of .....

confirms the following:

The address of the manufacturing site inspected:

.....

.....

.....

has been inspected on ...../...../..... and found ☐ to be: ☐ not to be in compliance with Good Manufacturing Practice (GMP) for the following operations: (please tick the relevant).

☐ total ☐ partial manufacture of medicinal products for use ☐ in man ☐ animals of the following medicinal products:

.....

.....

.....

in the following dosage forms[1]

The signing competent authority undertakes to inform the requesting competent authority of any subsequent change in this GMP compliance. Responsible officer of the competent authority:

Name (please type) .....

Signature .....

Date ...../...../.....

[1] Use separate form for dosage forms and enclose.

CONTENT OF THE FABRICATOR'S/MANUFACTURER'S BATCH CERTIFICATE FOR DRUG/MEDICINAL PRODUCTS EXPORTED TO COUNTRIES UNDER THE SCOPE OF A MUTUAL RECOGNITION AGREEMENT (MRA)

Title of form:	Content of the Fabricator's/Manufacturer's Batch Certificate for Drug/Medicinal Products Exported to Countries under the Scope of a Mutual Recognition Agreement (MRA)
Publisher:	-
Date of publishing:	1. February 2001
Explanatory Note:	In the framework of Mutual Recognition Agreements, the Sectoral Annex on Good Manufacturing Practices (GMP) requires a batch certification scheme for drug/medicinal products covered by the pharmaceutical Annex. The internationally harmonised requirements for the content of the batch certificate of a drug/medicinal product is attached. The importer of the batch is to receive and maintain the batch certificate issued by the fabricator/manufacturer. Upon request, it has to be readily available to the staff of the Regulatory Authority of the importing country. This certification by the manufacturer on the conformity of each batch is essential to exempt the importer from re-control (re-analysis). Each batch transferred between countries having an MRA in force, must be accompanied by a batch certificate issued by the fabricator/manufacturer in the exporting country. This certificate will be issued further to a full qualitative and quantitative analysis of all active and other relevant constituents to ensure that the quality of the products complies with the requirements of the Marketing Authorisation of the importing country. This certificate will attest that the batch meets the specifications and has been manufactured in accordance with the Marketing Authorisation of the importing country, detailing the specifications of the product, the analytical methods referenced, the analytical results obtained, and containing a statement that the batch processing and packaging quality control records were reviewed and found in conformity with GMP. The batch certificate will be

signed by the person responsible for releasing the batch for sale or supply/export at the fabrication/manufacturing site.

These harmonised requirements have been agreed by the Regulatory Authorities of the following parties/countries: Australia, Canada, European Community, New Zealand and Switzerland.

Content:

- Content of the Fabricator's/Manufacturer's Batch Certificate for Drug/Medicinal Products Exported to Countries under the Scope of a Mutual Recognition Agreement (MRA)

CONTENT OF THE FABRICATOR'S/MANUFACTURER'S BATCH CERTIFICATE FOR DRUG/MEDICINAL PRODUCTS EXPORTED TO COUNTRIES UNDER THE SCOPE OF A MUTUAL RECOGNITION AGREEMENT (MRA)

[LETTER HEAD OF EXPORTING MANUFACTURER]

1. Name of product.

Proprietary, brand or trade name in the importing country.

2. Importing Country.

3. Marketing Authorization Number.

The marketing authorisation number of the product in the importing country should be provided.

4. Strength/Potency.
Identity (name) and amount per unit dose required for all active ingredients/constituents.

5. Dosage form (pharmaceutical form).

6. Package size (contents of container) and **type** (e.g. vials, bottles, blisters).

7. Lot/batch number.

As related to the product.

8. Date of fabrication/manufacture.

In accordance with national (local) requirements.

9. Expiry date.

10. Name and address of fabricator(s)/manufacturer(s) - manufacturing site(s).

All sites involved in the manufacture including packaging and quality control of the batch should be listed with name and address. The name and address must correspond to the information provided on the Manufacturing Authorisation/Establishment Licence.

11. Number of Manufacturing Authorisation / Licence or Certificate of GMP Compliance of a manufacturer/fabricator.

Number should be given for each site listed under item 10.

12. Results of analysis.

Should include the authorized specifications, all results obtained and refer to the methods used (may refer to a separate certificate of analysis which must be dated, signed and attached).

13. Comments/remarks.

Any additional information that can be of value to the importer and/or inspector verifying the compliance of the batch certificate (e.g. specific storage or transportation conditions).

14. Certification statement.

This statement should cover the fabrication/manufacturing, including packaging and quality control. The following text should be used: "I hereby certify that the above information is authentic and accurate. This batch of product has been fabricated/manufactured, including packaging and quality control at the above mentioned site(s) in full compliance with the GMP requirements of the local Regulatory Authority and with the specifications in the Marketing Authorisation of the importing country. The batch processing, packaging and analysis records were reviewed and found to be in compliance with GMP".

15. Name and position/title of person authorizing the batch release.

Including its company/site name and address, if more than one company is mentioned under item 10.

16. Signature of person authorizing the batch release.

17. Date of signature.

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PROCEDURE FOR CO-ORDINATING FOREIGN AND COMMUNITY PRE-AUTHORISATION INSPECTIONS DURING THE ASSESSMENT OF APPLICATIONS

Guideline Title:	Procedure for Co-ordinating Foreign and Community Pre-Authorisation Inspections during the Assessment of Applications
Publisher:	European Commission Enterprise Directorate-General
Date of publishing:	January 2001
Note:	This Procedure is included in The Rules Governing Medicinal Products in the European Community The Notice to Applicants, Volume 2A, Procedures for marketing authorisation as Chapter 4.

Content:

- Pre-authorisation inspections (GMP inspections)
- Pre-submission notification by the applicant for a marketing authorisation
- Designation of an inspection team and preparation for the inspection
- Contacts with the applicant and the manufacturer(s) to be inspected
- Inspection and transmission of the report and check on the importer
- Submission of the final report to the Rapporteur and the EMEA

PROCEDURE FOR CO-ORDINATING FOREIGN AND COMMUNITY PRE-AUTHORISATION INSPECTIONS DURING THE ASSESSMENT OF APPLICATIONS (GMP INSPECTIONS)

Pre-authorisation inspections (GMP inspections)

The legal basis for pre-authorisation inspections of manufacturers of medicinal products in connection with the granting of a marketing authorisation by the Community is laid down in Article 8.2 of the Regulation, which provides that:

"Where it considers it necessary in order to complete its examination of an application the Committee may require the applicant to submit to a specific inspection of the manufacturing site of the medicinal product concerned. The inspection, which shall be completed within the time limit referred to in Article 6, shall be undertaken by inspectors from the Member State who possess the appropriate qualifications and who may, if need be, be accompanied by a Rapporteur or expert appointed by the Committee".

The EMEA has a coordinating role for these inspections whilst the responsibility for carrying them out rests with the Supervisory Authority which is defined by legislation as the Competent Authority of the Member State in which the product is either manufactured or imported, controlled and released for sale within the European Economic Area (EEA).

Member countries of the EEA, i.e. Norway, Iceland and Liechtenstein participate in the system of mutual recognition of inspections and quality controls of the European Union.

For applications where the manufacturer of the product is outside the EEA and where there is an operational Mutual Recognition Agreement ([2]) between the country in which the manufacturer is located and the EEA, the EMEA will inform the Rapporteur for the application and the relevant Supervisory Authority of the nature of the agreement and whether or not it covers pre-authorisation inspections.

Importation and batch release should be carried out in accordance with the guidelines in force. Where a product is to be manufactured outside the EEA and the applicant wishes to import and batch release it through more than one Member State (and hence there will be more than one Supervisory Authority), the EMEA will consult the CPMP and the applicant to identify a preference for one of the Supervisory Authorities to take on the responsibility for the inspection of the manufacturer. Taking account of this request, the EMEA will agree the responsibility for inspection with the Supervisory Authorities involved.

([2]) The European Commission has negotiated Mutual Recognition Agreements with New Zealand, Australia, Canada, and the USA. Negotiations are on-going with Switzerland and Japan.

1 Pre-submission notification by the applicant for a marketing authorisation

In their notification of intention to submit (see section 3.1), applicants should mention the name (including contact point) and the address of the proposed manufacturer of the active substance(s) and finished product together with the proposed name and address of the site(s) in the EEA responsible for batch release of the medicinal product. In the case of a medicinal product imported from a third country the notification must also include the name and address of the proposed importer responsible for batch release (including the Member State in which it is located) and site(s) responsible for sampling and testing. Final manufacturing and batch release arrangements will have to be provided when submitting the application. The sequence of all different sites involved should be clearly described.

2 Designation of an inspection team and preparation for the inspection

Once the application is received, the EMEA determines whether or not the manufacturing, control, batch release and importation site(s) concerned have already been inspected, by whom, and if satisfactory inspection reports are available. Where a satisfactory report is not available the EMEA contacts the Rapporteur and Co-Rapporteur, and a decision is made whether or not to ask the CPMP to make a request for an inspection in connection with specific aspects of the application or, in the case of manufacturers in third countries, for general GMP compliance. Such request is adopted by the CPMP at day 90 or at the latest by day 120. For an inspection covering specific aspects of the application, issues to be checked during the inspection will be detailed in an attachment to the day 70 assessment report(s).

When the Supervisory Authority is not able to inspect in a third country, the Rapporteur and the Supervisory Authority together designate another Competent Authority as the "Leading Inspection Service" for the inspection (this is the only difference between EU and foreign inspections).

Each request for inspection must be adopted by the CPMP. It should be pointed out that the inspections, where requested by the CPMP, should be carried out within the 210 days set out in the legislation for the scientific evaluation of the application and that companies therefore, should be required to be ready for inspection from the time of submission of the application and be in compliance with EU Good Manufacturing Practice (GMP). The EU Guidelines on Good Manufacturing Practise are contained in Volume IV of the Rules Governing Medicinal Products in the European Union. Manufacturers located in third countries must comply with these guidelines. Manufacturers located in third countries where there is an Operational Mutual Recognition Agreement between the EU and the third country involved need to comply with the GMP guidelines as contained in the Mutual Recognition Agreement.

3 Contacts with the applicant and the manufacturer(s) to be inspected

Once the CPMP has requested an inspection and the inspection team has been agreed, the EMEA notifies the applicant that an inspection will take place, gives details of the inspection team and asks for the inspection fees to be paid.

Payments for inspections are made in accordance with the decision on a scale of fees adopted by the Management Board under Article 53 (3) of the Regulation. For inspections outside the EU, travel costs are paid directly by the company in accordance with Article 5 (4) of Council Regulation (EEC) 297/95, as amended. However, one fee will be charged, at the rate mentioned in Council Regulation (EC) No 297/95, as amended, for each site inspected provided that only one manufacturing operation is carried out. Additional fees may be charged for activities on the same site that require a separate inspection and also for each contract manufacturing site and contract testing laboratory that requires to be inspected in connection with an application.

The inspectors make the arrangements with the manufacturer and fix an inspection date. In preparation of the inspection, the manufacturer(s) or the applicant may be asked to provide information about the site and operations to be inspected (the most convenient format for this information is a “Site Master File” in the format currently adopted by the European Community). The applicant may be requested to supply a copy of Part II of the application to the members of the inspection team.

Prior to the inspection, the Part II assessor liases with the inspection team on any points for special consideration during the inspection and whether or not any aspect of the manufacture of the starting material(s) is critical to ensure the quality of the finished product, in which case an inspection of the starting material(s) will be considered.

4 Inspection and transmission of the report and check on the importer

At the end of the inspection, the inspectors make a report of the main findings to the management of the site or company inspected.

A single inspection report is promptly drafted for each site or operation inspected by the inspection team.

The draft inspection report is sent by the inspectors to the management of the site or company with a request for comments on major factual errors, points of disagreement or remedial actions to be provided within 15 (calendar) days of receipt. The timing of any discussions or the provision of additional information will be agreed and communicated to the Rapporteur and the EMEA.

For imported products the relevant Supervisory Authority verifies the importer’s ability to store, distribute, release and, unless there is an operational Mutual Recognition Agreement between the EU and the country where the product is manufactured, to carry out the controls mentioned in Article 22.1.b of Council Directive 75/319/EEC.

5 Submission of the final report to the Rapporteur and the EMEA

One month after transmission of the inspection report to the manufacturer, the inspection team send their report to the Rapporteur and the EMEA indicating whether or

not the report has been agreed by the company inspected and, if not, the reason. A copy of the comments from the manufacturer is included. In all cases the inspection team will include their final conclusions.

This must be completed by day 180 of the assessment procedure.

Any further pre-authorisation inspections that are needed are coordinated by the EMEA.

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GUIDELINE ON THE PREPARATION OF REPORTS ON GMP INSPECTIONS REQUESTED BY EITHER THE CPMP OR CVMP IN CONNECTION WITH APPLICATIONS FOR MARKETING AUTHORISATIONS AND WITH PRODUCTS AUTHORISED UNDER THE CENTRALISED SYSTEM

Guideline Title:	Guideline on the Preparation of Reports on GMP Inspections Requested by Either the CPMP or CVMP in Connection with Applications for Marketing Authorisations and with Products Authorised under the Centralised System
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GUIDELINE ON THE PREPARATION OF REPORTS ON GMP INSPECTIONS REQUESTED BY EITHER THE CPMP OR CVMP IN CONNECTION WITH APPLICATIONS FOR MARKETING AUTHORISATIONS AND WITH PRODUCTS AUTHORISED UNDER THE CENTRALISED SYSTEM

A Background

1 In order to complete the assessment of applications for marketing authorisations under the centralised system the Committee on Proprietary Medicinal products or the Committee on Veterinary Medicinal products may request that an inspection is carried out of the manufacturing site for a medicinal product in accordance with Articles 8 (2) and 30 (2) of Council Regulation 2309/93 respectively.

2 Inspections may also be requested according to the provisions of Articles 17(3) and 39(3) of the same Regulation.

3 The results of these inspections should be reported to the EMEA and the CPMP and CVMP in accordance with the highest scientific standards.

4 In order to assure these standards the Board of Management of the EMEA and the representatives of the Member States of the European Union have agreed that inspection reports will be prepared in accordance with guidelines that have been agreed by European Commission at the Working Party on the Control of Medicinal Products and Inspections.

5 This guideline has been prepared in accordance with this agreement and was discussed and finalised at the Ad Hoc Meeting of Inspection Services on September 3rd 1997 and implemented from November 13th 1997. It has been subsequently modified following discussion at the Ad-hoc meeting of GMP Inspection Services on February 18th and 19th 1999 and at the meeting of the Control of Medicinal Products and Inspections Working Party on March 25th 1999. This guideline should be read in conjunction with the terms of the standard contract between the EMEA and the Competent Authorities of the EU Member States.

6 This guideline does not apply to routine GMP inspections carried out by Member States of the European Union under Article 26 of Council Directive 75/319/EEC and Article 34 of Council Directive 81/851/EEC.

B Procedure for Preparing Inspection Reports

1 Inspection reports will be prepared by the inspectors of the Supervisory Member State for all inspections requested by either the CPMP or CVMP under the obligations of Articles 8(2) or 30(2) of Council Regulation (EEC) No 2309/93.

(Note: Should a Supervisory Member state not be able to inspect in a third country, another Competent Authority may be requested to carry out the inspection)

2 The Inspectors of the Supervisory Member State may be assisted in the preparation of the report by either experts (for quality, inspections or other) or a Rapporteur appointed by either the CPMP or CVMP to take part in the inspection.

3 The EMEA requires the Inspection report to be in English. If the preliminary report is in another language, translation into English should be arranged by either the manufacturer or the applicant. In any case the inspectors will be responsible for ensuring that the report is completed in the agreed format. Translations should also be completed in the agreed format and should contain a cautionary statement as follows: "This report is a translation of the original text. For confirmation and clarification of the content, reference should be made to the original report".

4 The content and format of the report should be that described in Appendix 1.

5 The scope of the inspection should include a short description of the inspection (product-related inspection and/or General GMP Inspection). The reason for the inspection should be specified.

6 The report should record the evaluation of the manufacturing facilities/operations/systems, the quality control system and other aspects of the manufacturing activities in accordance with the agreed scope of the inspection making reference to the following:

- the site master file (if available) for the site/facilities inspected
- the European Community GMP Principles and Guidelines (Rules Governing Medicinal Products in the European Community Volume IV)
- questions raised by the Rapporteur / Co-Rapporteur relating to the assessment of the manufacturing activities and/or control procedures
- any other specific issues identified by the CPMP or the CVMP and/or the EMEA (e.g. reported problems, quality defects).

7 The inspection report should include a section giving a summary of the GMP deficiencies and other relevant observations (e.g. response to the Rapporteur's or Assessor's questions). All defects which will or may affect the safety of the product should be clearly stated. Deficiencies should be referred to in accordance with the chapter numbers and headings given in the European Community GMP

Principles and Guidelines (Rules Governing Medicinal Products in the European Community Volume IV)

8 Additional appendices (e.g. Site Master File) may be added to the Inspections report, if considered necessary.

9 The draft inspection report (or at least the list of deficiencies) should be prepared as outlined above within 15 days of the completion of the inspection and sent to the manufacturer. The manufacturer should be asked to comment within a further 15 days. If a response is not received within this time the inspectors should record the absence of a reply and that the manufacturer did not choose to comment.

10 On receipt of comments on the draft report (within the allowed time) from the manufacturer the report should be finalised by the author(s) taking account, as necessary, the comments received.

11 When the report is complete the author(s) should prepare a summary of the inspection report for circulation to the scientific committee or other body that requested the inspection. This summary will follow the format given in Appendix II and should contain an overall conclusion as to whether or not the manufacturer is acceptable for either the proposed activities and/or the activities already carried out.

12 The inspection report should be finalised and sent to the EMEA and in the case of pre-authorisation inspections the Rapporteur and Co-Rapporteur within 40 days of the inspection.

13 In the case of a marketing application that is given an "accelerated" assessment the time allowed for reporting and finalising the inspection may need to be reduced significantly. In these circumstances the timetable for reporting the inspection will be agreed for each application with the Rapporteur/Co-Rapporteur, the EMEA, the inspection team, the applicant and the manufacturer.

14 The EMEA will check inspection reports received for adherence to this guideline and for their scientific content and overall quality. Reports that are found to be deficient, incomplete or below the required scientific standard will be returned to the authorities who were responsible for their preparation with a written explanation of the reasons for non-acceptance and proposed deadline for revision, for a re-inspection or other remedial action. This deadline for re-submission of the report will be set by the EMEA taking account of the overall timetable adopted for completion of the assessment of the application

Appendix 1

Format for the preparation of GMP inspection reports requested by either the CPMP or CVMP in connection with applications for marketing authorisations and with products already authorised under the centralised system.

1 The Community format for GMP Inspection Reports should be used.

Appendix 2

Format of the CPMP/CVMP summary report on GMP inspections carried out under the centralised system.

1. Name of the product and pharmaceutical form.
2. EMEA reference number.
3. Name of the manufacturer/manufacturing authorisation holder.
4. Address and exact location/designation of the sites and production facilities inspected.
5. Name(s) of the Inspector(s) or/and "experts" participating in the inspection.
6. Date(s) of inspection.
7. Scope of the inspection.
8. Summary of the main steps/history of the inspection.
9. List of deficiencies and observations, which will or may affect the safety of the product
10. Inspectors comments on the manufacturer's response to the inspection findings (i.e. is the company's response acceptable?).
11. Conclusions on the acceptability of the manufacturer (are the manufacturing operations for the product in compliance with European Community GMP Principles and Guidelines?) for the product mentioned in the application.
12. Recommendations for further actions (if any).

Name(s) of Inspectors responsible for preparing the report

Organisations

Signatures:

Date .....

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ACTIVITY / DECISION DIAGRAM FOR INSPECTION FINDINGS FOR APPLICATIONS UNDER THE CENTRALISED SYSTEM

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