

4.

Inspection

Pre-approval inspections¹

1. General	139
2. Glossary	139
3. Objectives	140
4. Priorities	141
5. Preparation for the inspection	141
6. Carrying out the inspection	142
7. Sample collection and testing	143
8. Follow-up regulatory/administrative decisions	144
References	145

1. General

The advice provided here extends that given in the “Provisional guidelines on the inspection of pharmaceutical manufacturers” (1). The objectives of an inspection, as given in the introduction to the guidelines, are:

- to control and enforce compliance with general good manufacturing practices (GMP) (2); and
- to authorize the manufacture of specific pharmaceutical products, normally in response to a licensing application.

These guidelines are applicable mainly to inspections of the first type, whether performed as a condition for the issue of a manufacturing licence/authorization, or on a periodic, routine basis. They are essentially concerned with inspections of manufacturing and quality-control facilities conducted before a marketing authorization (product licence or registration) for a pharmaceutical product is granted.

2. Glossary

The definitions given below apply to the terms used in this guide. They may have different meanings in other contexts.

¹ Guidelines on pre-approval inspections. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report*. Geneva, World Health Organization, 2002, Annex 7 (WHO Technical Report Series, No. 902).

application

A marketing authorization for a new drug application.

manufacture

All operations concerned with the purchase of materials and products, production (including packaging), quality control, release, storage, the distribution of pharmaceutical products, and the related controls (2).

manufacturer

A company that carries out at least one step of manufacture (2).

method validation/verification

Method validation is conducted where non-compendial analytical methods are included in the application to confirm that the applicants' proposed analytical methods are suitable for regulatory purposes. A side-by-side comparison with a compendial method, if available, should be included. Method verification is conducted where the methods are compendial, to confirm whether the product as compounded can be analysed satisfactorily by the official method.

pre-approval batches

Pilot or laboratory-scale batches, upon which the application is based, e.g. batches used for pivotal clinical trials and/or those used for bioavailability, bioequivalence and stability studies, and scale-up batches.

3. Objectives

Before any application is approved, it is necessary to determine whether all establishments participating in the manufacture of the finished dosage form are in compliance with GMP and the application commitments. Pre-approval inspections have the following specific objectives:

- Evaluation of the establishment's compliance with GMP requirements, particularly regarding proper environment, quality management, personnel, facilities and equipment.
- Evaluation of the procedures and controls implemented in the manufacture of the product (pre-approval batches), to determine whether they are in conformity with the application commitments.
- Audit of the completeness and accuracy of the manufacturing and testing information submitted with the application, and of the conformity of pre-approval batches with planned commercial batches (process validation protocol).
- The collection of samples for the validation or verification of the analytical methods included in the application.

4. Priorities

Pre-approval inspections are considered to be an important part of the application review and approval process. However, since this represents a considerable workload, inspections are not normally carried out routinely, but rather only in specific cases where non-compliance is possible. Thus inspections may be required for:

- new chemical entities;
- drugs of narrow therapeutic range, and drugs for serious conditions requiring an assured therapeutic response;
- products previously associated with serious adverse effects, complaints, recalls, etc.;
- products that are difficult to manufacture or test, or that are of doubtful stability (and therefore associated with the risk of defects);
- new applicants or manufacturers; and
- applications from manufacturers who have previously failed to comply with GMP or official quality specifications.

For other applications, the drug regulatory authority will rely on the results of recent inspections of the applicant's or manufacturer's facilities for the production of dosage forms similar to that of the proposed product.

5. Preparation for the inspection

An inspection team should, where possible, include analysts and other specialists, e.g. in pharmaceutical technology, or if available, persons with expertise in these fields, when needed. Team members may be assigned to inspect new operations or manufacturing sites associated with product failures. When possible, the analyst involved in the laboratory evaluation of the product under review should participate in the inspection. Pre-approval inspection is often carried out by a single inspector.

It is necessary to verify that the applicant holds an appropriate manufacturing authorization and that manufacturing is carried out in conformity with that authorization (licence).

An essential step in the review of applications is determining whether the commitments made by the manufacturer are reflected in actual practice. A review of the application information is also important in preparing for inspections of firms or processes with which the inspector is unfamiliar. The drug regulatory authority should provide inspectors with relevant information on the application. (Some countries request an additional copy of this information from applicants which is forwarded to the inspection team.) The information provided should include a copy of the manufacturing and controls section of the application, together with information relating to pre-approval batches.

Reasonable efforts should be made to conduct pre-approval inspections at the earliest possible opportunity, since unnecessary delays will prevent the timely review of applications. However, in some facilities the development or the manufacturing processes may not have been completed. In addition, changes may have occurred in the status of the application, e.g. major deficiencies in the application or the closure of an ancillary facility may affect the need for an inspection. In any case, the timing of the inspection should be coordinated between the inspectorate and the applicant.

For the inspection of major new facilities involving many applications, special coordination efforts are often beneficial.

When desirable, pre-approval inspections should be coordinated with the laboratory scheduled for method validation so as to enable it to participate in the inspection and in the collection of samples.

6. Carrying out the inspection

Emphasis should be placed on the evaluation of the manufacturing process, including data verification and the assessment of compliance with GMP. The production and control procedures described in the application must be compared with those used for the manufacture of pre-approval batches. If warranted by records of past label mix-ups, packaging and labelling control procedures should be evaluated. A programme of ongoing stability testing needs to be addressed.

The inspection team will determine whether the application provides the scientific data justifying full-scale production procedures and controls. The validation of pertinent manufacturing procedures, including equipment qualification, will also be evaluated.¹ However, inspectors should not recommend withholding approval of applications based on a lack of complete full-scale, multiple-batch validation of sterile and non-sterile processes, unless the data submitted in the application are found to be of questionable validity or completeness. It should be understood that full-scale validation may be completed after approval of the application, but before shipment of the first commercial batches. Nevertheless, certain data must be included in the application to demonstrate that the sterilization or aseptic fill process has been qualified. The inspection team is expected to audit the data to determine their authenticity, accuracy and completeness.

Investigational products are often produced in facilities other than those used for full-scale production (4). These facilities and the associated manufacturing and control procedures are not routinely inspected unless validation of the transfer of the methods from the “investigational” facilities to the full-scale facilities is lacking or questionable. The facilities may be periodically inspected when this is required by national legislation/regulation.

¹ For details of recommended validation programmes, see reference 3.

All suppliers and manufacturers of starting materials used in the formulation of pre-approval batches should be identified. The physical characteristics and specifications of the drug substance should be reviewed. This is particularly important for solid oral dosage forms where the physical characteristics of the drug substance often affect uniformity, dissolution and absorption of the dose.

When a pharmaceutical manufacturer replaces the supplier or manufacturer of the drug substance used for the manufacture of the pre-approval batches by another supplier or manufacturer, the application should include data demonstrating that the dosage forms formulated with the drug substance from the two different sources are equivalent in terms of conformity with established specifications, including those given in the application. Specifications should also cover the physical characteristics of the drug substances.

The addition of any new drug substance and/or dosage form to a production environment must be carefully evaluated in terms of its impact on other products already under production. Any changes that may be necessary in the building and facility must be assessed for their effect on overall compliance with GMP requirements. For example, a new toxic, potent or highly sensitizing product may require additional measures against cross-contamination, and facilities already operating at full capacity may not have adequate space for additional products. The evaluation should also include an assessment of whether any change in the manufacturing authorization is necessary.

Laboratory equipment and procedures must be qualified and validated. Every pre-approval inspection should include an evaluation of laboratory controls and procedures, and a review of some of the raw data used to generate results. The authenticity and accuracy of the data used in the development of a test method should be reviewed.

The inspection team should pay special attention to any newly established facilities, newly installed equipment and/or new raw material suppliers. If unapproved facilities are in use, this should be reported immediately. Inspections of these facilities are not normally required.

7. Sample collection and testing

The pre-approval inspection may include the collection of samples for validation of the analytical methods. Normally the sample size should be sufficient for three full analyses. Unless otherwise indicated by the laboratory, samples of the following sizes may be taken, depending on the dosage form of the product:

- tablets and capsules: 300 units of production;
- injections (single component): 100 units of production;
- injections (combination): 100 units of production plus 10 samples of each component;
- oral powders for reconstitution: 10 units of production;
- oral liquids: 1 litre.

It is important to collect, with the samples, the relevant manufacturer's analytical documentation, namely a copy of the analytical methods used by the inspected laboratory and the report of the analyses performed by the applicant on the batch sampled. A method validation report may be of some use in better understanding and reproducing the analytical methods. Problems encountered in the performance of the analyses may be resolved by an exchange of information between the applicant and the government laboratory.

Samples are tested in accordance with methods described in the application. If there are problems with the methods that require additional information from the applicant, the laboratory director must review the situation and decide whether the applicant should be contacted. The written request should be included in the documentation submitted to the review analyst.

Each method validation/verification report should contain the following:

- The identification of the test samples received, a description of the product tested, and confirmation of conformity with the product described in the application.
- The original analytical worksheets with calculations, the results of all tests performed, comments by the analyst(s), associated spectra, chromatograms, etc., and a comparison of the results obtained with the applicant's data and with the applicable specifications.
- An evaluation of each test performed by the applicant and the laboratory.
- A recommendation as to whether the methods are acceptable, acceptable only after specified changes have been made, or unacceptable.

If samples have not been collected in the course of a pre-approval inspection, the results of the analytical examination of the samples submitted by the applicant may nevertheless be used as supporting information.

The reserve samples, associated documentation and copies of laboratory reports should be stored in an orderly and retrievable way for a time period specified by national regulations. It is usually recommended that all material should be kept for a minimum of 3 years or for 1 year after the expiry date of the finished product.

8. Follow-up regulatory/administrative decisions

The inspectorate (inspection group of the drug regulatory authority) should recommend withholding approval when significant deviations from GMP requirements and other application commitments have occurred having an adverse effect on the product covered by the application. Examples of significant problems are:

- Misrepresentation of data or conditions relating to pre-approval batches.
- Pre-approval batches not manufactured in accordance with GMP.

- Inconsistencies and/or discrepancies raising significant questions concerning the validity of the records.

If applications are refused because of significant non-compliance with GMP, action must be taken to ensure that the necessary corrective measures are taken.

The drug regulatory authority is expected to advise the applicant that the inspectorate has recommended withholding approval of the application and give the reasons for this recommendation.

References

1. Provisional guidelines on the inspection of pharmaceutical manufacturers. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report*. Geneva, World Health Organization, 1992, Annex 2 (WHO Technical Report Series, No. 823).
2. *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Vol. 2. Good manufacturing practices and inspection*. Geneva, World Health Organization, 1999.
3. Good manufacturing practices: guidelines on the validation of manufacturing processes. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report*. Geneva, World Health Organization, 1996, Annex 6 (WHO Technical Report Series, No. 863).
4. Good manufacturing practices: supplementary guidelines for the manufacture of investigational pharmaceutical products for clinical trials in humans. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report*. Geneva, World Health Organization, 1996, Annex 7 (WHO Technical Report Series, No. 863).

Inspection of pharmaceutical manufacturers¹

These guidelines are intended to promote harmonization of pharmaceutical inspection practices among WHO Member States. They are directed to government inspectors—particularly those operating within small national regulatory authorities (1)—to assist them in assessing manufacturers' compliance with good manufacturing practices (GMP) (2). They will also be of value to manufacturers themselves when engaged in self-inspection or audit.

They cover inspection of the production and control of final dosage forms of pharmaceutical products destined for human and veterinary use and of drug substances (active pharmaceutical ingredients or bulk drug substances) employed in their manufacture. Within the national context their scope may need to be

¹ Provisional guidelines on the inspection of pharmaceutical manufacturers. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report*. Geneva, World Health Organization, 1992, Annex 2 (WHO Technical Report Series, No. 823).

extended since similar regulations are often enforced to control pharmaceutical and biological products, medical devices, diagnostic products, foods, and food additives. In all cases the same fundamental principles apply.

Inspection and licensing of pharmaceutical manufacturing facilities on the basis of compliance with GMP are a vital element of drug control. They are also pivotal to the operation of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (3), which requires an attestation by the competent regulatory authority in the exporting country that a given product is manufactured in premises and using operating practices that conform with GMP.

The guidelines also have relevance in various other contexts, including:

- self-inspection or internal audit of a factory or a part of it carried out by personnel of the company;
- inspection by an independent person or group of persons as a review of the quality system of a company in compliance with the standards issued by the International Organization for Standardization (ISO 9000–9004 (4)) or the British Standards Institution (BS 5750 (5)) or with other equivalent national standards;
- audit of a manufacturer or supplier by authorized agents of the customer.

The government inspectorate represents the enforcement arm of the national drug regulatory authority. Its function is to ensure adherence by manufacturers to all licensing provisions and specifically to GMP. The objectives are to control and enforce general standards of production and to provide authorization for the manufacture of specific pharmaceutical products. The first objective involves a sequential examination of production and control activities on the basis of the GMP guidelines issued by WHO or of nationally determined requirements. The second requires verification that production and quality control procedures employed in the manufacture of specific products are performed correctly and that they accord with data supplied in the relevant licensing applications.

Inspection will, of course, depend on national legislation and regulations and/or the resources available.

The role of the inspector

Inspectors should have previous training and practical experience in the manufacture and/or quality control of pharmaceutical products. Graduate pharmacists, chemists, or scientists with an industrial background in pharmaceutical production would qualify for consideration.

In-post training should include an element of apprenticeship gained by accompanying experienced inspectors on site visits as well as participation in courses and seminars on relevant subjects including modern pharmaceutical technology, microbiology, and the statistical aspects of quality control.

The primary responsibility of an inspector is to present a detailed factual report on standards of manufacture and control applied to specific products. However, inspection should not be limited to compilation of an inventory of faults, irregularities, and discrepancies. Provided it is in keeping with national policy and does not breach understandings regarding confidentiality of information having commercial value, advice may be offered on how production and control procedures can be usefully upgraded. An inspector should always be expected, for example, to offer advice on how to improve an in-process test procedure or to offer other assistance which, in his or her opinion, serves the public interest. An inspection should be regarded as an opportunity to assist and motivate a manufacturer to comply with GMP and to correct any specific deficiencies.

The inspection process

The planning, organization, method of work, and format of the resultant report should always be determined by the precise objective of the inspection. Inspections vary in nature according to the objective:

Routine inspection

This is a full inspection of all applicable components of GMP and licensing provisions. It may be indicated when the manufacturer:

- is newly established;
- requests renewal of a licence to operate;
- has introduced new product lines or new products, or has made significant modifications to manufacturing methods or processes, or has made changes in key personnel, premises, equipment, etc.;
- has a history of non-compliance with GMP;
- has not been inspected during the last 3–5 years.

Concise inspection

Manufacturers with a consistent record of compliance with GMP through previous routine inspections are eligible for concise inspection. The focus of a concise inspection is on a limited number of GMP requirements selected as indicators of overall GMP performance, plus the identification of any significant changes that could have been introduced since the last inspection. Collectively, the information obtained will indicate the overall attitude of the firm towards GMP. Evidence of unsatisfactory GMP performance observed during a concise inspection should trigger a more comprehensive inspection.

Follow-up inspection (reassessment or reinspection)

Follow-up visits are made to monitor the result of corrective actions. They are normally carried out from 6 weeks to 6 months after the initial inspection, depending on the nature of the defects and the work to be undertaken. They are limited to specific GMP requirements that have not been observed or that have been inadequately implemented.

Special inspection

Special visits may be necessary to undertake spot checks following complaints or recalls related to suspected quality defects in products. Reports of adverse drug reactions may also indicate that all is not well. Such inspections may be focused on one product, a group of related products, or specific operations such as mixing, sterilization, or labelling.

Special visits may also be made to establish how a specific product is manufactured as a prerequisite for marketing approval or issuance of an export certificate.

A further reason for special visits is to gather specific information on—or to investigate—specific operations and to advise the manufacturer of regulatory requirements.

Quality systems review

A quality systems review is a relatively new concept. Its purpose is to describe a quality assurance system that has been shown to operate satisfactorily. It entails a description of the quality system and the standards to be observed, normally in a manual containing a statement of the manufacturer's policy on quality assurance. It should also define the management structure needed to implement the policy, along with the procedures in each management area needed to ensure that adequate quality standards are set for the product, manufacturing processes are correctly defined, records are kept, and quality control and other quality assurance activities are carried out.

Frequency and duration of inspections

The frequency and duration of visits should be determined by the type of inspection required as well as by the workload and number of inspectors. New manufacturing establishments must be inspected before they are licensed, and new facilities must be inspected before production is started.

For all companies, inspections should be carried out on a regular schedule, ideally annually.

For large companies marketing a wide range of products, the inspection of the site may be split up into several visits over a longer period, e.g., 5 years

where this is the period of validity of the manufacturing licence or the GMP certificates.

The length of a given inspection is determined by the size of the company and the purpose of the visit. It can extend from a few days to 2 weeks or more. The time taken also depends on the number of inspectors assigned to the visit. In many countries, visits are made by one (or more) inspectors, sometimes accompanied by a specialist when production of biologicals, sterile production areas, or other special facilities are to be examined.

Preparing for the inspection

Drug inspection begins at the desk of the inspector. A review should be made of the documents relating to the company to be visited, available from the drug regulatory authority. These may include the manufacturing licence, the marketing authorization dossiers for leading products, reports of adverse drug reactions, complaints and recall records, the results of regulatory (surveillance) testing, and the previous inspection reports.

Company documents, including the annual report for the shareholders, the complaints file, and self-inspection/internal audit reports, are valuable sources of information. The last of these, depending on national legislation, may be withheld from the inspector. In some countries, a compromise is reached, the company presenting the internal audit reports to the inspector for general information after the latter's own report has been finalized. In any case, it should be possible to verify the frequency of self-inspections, and to which parts of the plant they have been applied.

Conduct

Announced inspections cover regular visits to evaluate new plants and new production lines and to decide on the renewal of a licence.

Unannounced inspections are necessary for concise, follow-up, and special visits.

In certain countries regular inspections are unannounced as a matter of policy.

The visit usually begins with a meeting between the inspector(s), representatives of the company or plant management, and those responsible for the products or areas to be inspected. Credentials should be presented, letters of authority inspected, and an explanation given of why the inspection is being carried out.

It is advantageous for the company to appoint at least one "escort" who is directly involved in the preparation of the products that are the object of the inspection. Escorts should be chosen who are generally familiar with the quality systems of the company and who are involved in the self-inspection programme.

The meeting may be followed by a perusal of the company's documents by the inspector or by a walk-through visit, or both. This will permit the inspector to finalize the plan for the inspection. It is recommended that the inspector both develops and follows this plan independently, rather than accepting guidance from company management. Some basic rules for conducting the inspection are as follows:

- Inspection should follow the original plan as far as possible; items that are specific to certain areas of the facility, such as in-process testing and working documents, may need to be checked at the point of operation. Care should be taken to cover activities such as water production, sample storage, and validation.
- It is advisable to follow production flow from reception of the starting materials to the shipment of the finished products. The frequency of recalls and return of goods should be carefully noted.
- Documents such as master formulae, test specifications, standard operating procedures, and batch records (including protocols of analyses, etc. and documents relating to the control of printed materials and labelling operations) require close verification.

Without prejudice to the need to verify documentation, it is essential that the inspection be based largely on observation and cover the total working hours of the manufacturer. It is recommended that the inspector start the plant tour as soon as possible after arrival.

Inspectors can profitably use a short checklist to ensure that all areas of operations have been investigated. A very detailed checklist developed from GMP guidelines is of use specifically for the training of inspectors. Experience has shown that rigid adherence to a too-detailed checklist can lead to possible overlooking of vulnerable areas of a quality assurance system specific to the company/plant under investigation. For an experienced inspector, knowledge of the manufacturer's weak points allied with intuition may serve better than a checklist. Different checklists may be found in the recommended publications and documents listed in Appendix 1.

Stability-testing programme. The inspector should be satisfied that there exists a documented ongoing programme specifying the regular withdrawal of samples of all products from the production line for stability testing. The testing schedule for stored samples should employ appropriate conditions of temperature and light stress, and suitable stability-indicating analytical methods that yield conclusions consistent with claimed shelf-life. The systems should permit re-evaluation of product stability following any changes in the manufacturing process or formula.

Significant changes in facilities, equipment, products, and senior personnel since the last inspection should be noted. The principle here is that changes represent possible areas of weakness or causes of non-compliance with GMP. For example, new equipment may require changes to be made in procedures; new

product lines may require new product master files; and departures of senior personnel such as the quality control manager may result in behavioural or procedural changes.

Occasionally, an inspector may require access to other premises, documents, or information on the company. Ideally, the inspector's authority should be determined by legislation, but in the absence of clear legal or regulatory provisions, it is suggested that the GMP code is used as a guide and the inspector should have the right to verify compliance with every requirement listed in the code.

The inspector should not be concerned about information not covered by GMP—e.g., finance and personnel—where this does not infringe on the company's responsibilities or staff education and training.

Photographs or videos taken during the visit may be excellent illustrative material for the report. National legislation should stipulate that the inspector has the right to take visual records during the inspection to document the production premises or laboratories.

In many cases, an aerial photograph of the manufacturing site, possibly with surrounding grounds, may be obtained from the company together with other relevant materials for inclusion in the report.

Collecting samples. It is normal practice during the visit for the inspector to take samples for testing by the official quality control laboratory. Samples are usually taken from released products (e.g., from the finished-goods warehouse) but may also be taken from stocks of raw materials or in-process material. In order to protect sample integrity, any protocol meant for enforcement or legal purposes should set out the procedures for sample collection, analysis, and documentation. The following should be stated:

- name(s) of the sampled product(s), batch number(s), date, source, number of samples, and remarks on type of packaging and storage conditions;
- circumstances of sampling, e.g., suspected quality defects, routine surveillance, verification of compliance with GMP;
- instructions for the placing of seals on containers of sample materials;
- written confirmation of the receipt of the samples by the inspector (possibly together with the manufacturer's certificates of analysis and any other supporting documents).

The manufacturer, represented by the company escort, should be encouraged to take duplicate samples from the same batch(es), for "in-house" testing if a problem is later identified.

Before the inspector leaves the premises after the inspection, a final discussion with company management is recommended. If possible, the inspector should list any unsatisfactory findings and outline any irregularities or other observations to which management may wish to respond.

Report

It is recommended that reports be divided into four parts: general information on the company or manufacturing facility, description of the inspection, observations, and conclusions. Annexes may contain supporting information (a list of products manufactured, an organization chart, the annual company report, photographs, etc.). The third and fourth parts may be combined. Appendix 2, which is an extract from a document prepared for the Pharmaceutical Inspection Convention, provides an example of the form and content of the inspector's report.

In order to save the inspector's time, the first part of the report containing basic data may be supplied by the company beforehand, provided that this fact is clearly stated in the report and the information supplied is verified by the inspector during the visit. An example of items that should be considered for inclusion is given in Appendix 2, section C, "Site master file".

The second part should describe the complete progress of the inspection step by step, documenting which parts of the factory, warehouses, laboratories, records, documents, etc. were inspected.

The third part is devoted to observations. Changes, improvements, and examples of deterioration since the previous inspection should be noted by the inspector.

Positive observations should take the form of a description of the processes that the firm is carrying out particularly well and that may be considered examples of particularly good manufacturing practice.

Negative observations (non-compliance with GMP requirements) should distinguish between whether the defect lies in the system itself or in a failure to comply with the system. For instance, when cleaning is found to be suboptimal, it is important to know whether the standard operating procedures are inadequate or lacking, or whether adequate written procedures exist but are not being followed by personnel.

In the final part of the report, the inspector should summarize deficiencies, unsatisfactory practices, etc. (listed in decreasing order of importance), suggest corrective actions, and make recommendations. This part, together with the third part, should be discussed with the company management and responsible authorized persons at the end of the inspection.

A copy of the complete written report, after supervisory approval, should be provided to the company management with a covering letter. The corrective actions to be taken, together with a time limit for their execution, should also be presented to the management of the company.

Inspection reports may be treated as confidential documents depending on national legislation. Under certain international agreements, reports may be exchanged between drug regulatory authorities.

Regulatory actions

Depending on national legislation, regulatory authorities may take action to correct unsatisfactory practices and prevent the distribution of products with suspected quality defects or manufactured under conditions that do not comply with GMP requirements. In extreme cases, the closing down of operations may be required. In practice, these measures are used only in exceptional cases constituting a hazard to health.

In many countries, the drug regulatory authority has the legal power to suspend or revoke the marketing authorization for a product when the manufacturer does not comply with GMP. In addition, manufacturing or marketing authorizations (licences), the reregistration of products, and the issue of a variation licence or a GMP certificate may be delayed until appropriate measures have been taken by the company, and possibly have been confirmed by reinspection. As a rule, the manufacturer concerned has the right to appeal.

References

1. Guiding principles for small national drug regulatory authorities. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-first report*. Geneva, World Health Organization, 1990: 64–79 (WHO Technical Report Series, No. 790).
2. Good manufacturing practices for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report*. Geneva, World Health Organization, 1992: 14–79 (WHO Technical Report Series, No. 823).
3. WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-first report*. Geneva, World Health Organization, 1990: 57–63 (WHO Technical Report Series, No. 790).
4. *International Standards: Quality management and quality assurance standards—Guidelines for selection and use (ISO 9000), Quality systems—Model for quality assurance in design/development, production, installation and servicing (ISO 9001); Quality systems—Model for quality assurance in production and installation (ISO 9002); Quality systems—Model for quality assurance in final inspection and test (ISO 9003); Quality management and quality system elements—Guidelines (ISO 9004)*. Geneva, International Organization for Standardization, 1987 (rev. 1990).
5. *Quality systems. Part 2. Specification for manufacture and installation (BS 5750: Part 2)*. London, British Standards Institution, 1979.

Appendix 1. Recommended publications and documents

ASEAN manual for inspection of GMP. Association of South East Asian Nations, 1988.

Drug manufacturer's self-inspection manual as to conformity with GMP requirements. In: *GMP regulations of Japan*, 3rd ed. Tokyo, Ministry of Health and Welfare, 1988: 101–195.

Good drug manufacturing practices (GMP), audit check-list. Government of Brazil, Ministry of Health, 1983.

Grundregeln für die Herstellung von Wirkstoffen und die Sicherung ihrer Qualität; Fragebogen zu den Grundregeln für die Herstellung von Wirkstoffen und die Sicherung ihrer Qualität [Basic rules for the production of active ingredients and their quality assurance; audit checklist to the basic rules for the production of active ingredients and their quality assurance]. *Pharmazeutische Industrie*, 1981, **43**: 537–542 (republished in: **Oeser W, Sander A**. *Pharma-Betriebsverordnung, Kommentar [GMP comments]*. Stuttgart, Wissenschaftliche Verlagsgesellschaft, 1988).

Guide to inspection of bulk pharmaceutical chemical manufacturing. Food and Drug Administration, US Department of Health and Human Services, Public Health Service, 1987.

Steinborn L. *Quality assurance manual for the pharmaceutical and medical device industries*. Buffalo Grove, IL, Interpharm Press, 1986.

Appendix 2. Form and content of the inspector's report¹

A. Inspector's information

1. Date of inspection(s) on which the information is based and name(s) of inspector(s).
2. Brief report of inspection activities undertaken.
3. Samples taken and results obtained.
4. Assessment of the site master file (see section C).
5. GMP-related recalls from the market of any product in the last two years.

B. Summary and conclusions

1. The inspector's general impression of the firm and his or her assessment of the acceptability of its GMP status for the range of products concerned.

¹ Extracted (with permission and minor changes) from an unpublished document (PH 6/91) prepared for the Pharmaceutical Inspection Convention (PIC), November 1991.

2. Failures to comply with the PIC Guide to Good Manufacturing Practice (in order of importance) and with the time limits set for them to be corrected by the manufacturer.

C. Site master file

A site master file is a document prepared by the manufacturer containing specific and factual GMP information about the production and/or control of pharmaceutical manufacturing operations carried out at the named site and any closely integrated operations at adjacent and nearby buildings. If only part of a pharmaceutical operation is carried out on the site, the site master file need describe only those operations, e.g., analysis, packaging.

A site master file should be succinct and, as far as possible, not exceed 25 A4 pages.

1. General information

- 1.1 Brief information on the firm (including name and address), relation to other sites, and, in particular, any information relevant to understanding the manufacturing operations.
- 1.2 Pharmaceutical manufacturing activities as licensed by the national authority.
- 1.3 Any other manufacturing activities carried out on the site.
- 1.4 Name and exact address of the site, including telephone, fax, and 24-hour telephone numbers.
- 1.5 Type of products manufactured on the site, and information about any specifically toxic or hazardous substances handled, mentioning the way they are manufactured (in dedicated facilities or on a campaign basis).
- 1.6 Short description of the site (size, location, and immediate environment and other manufacturing activities on the site).
- 1.7 Number of employees engaged in production, quality control, storage, and distribution.
- 1.8 Use of outside scientific, analytical, or other technical assistance in relation to manufacture and analysis.
- 1.9 Short description of the quality management system of the firm responsible for manufacture.

2. Personnel

- 2.1 Organization chart showing the arrangements for quality assurance, including production and quality control.

- 2.2 Qualifications, experience, and responsibilities of key personnel.
- 2.3 Outline of arrangements for basic and in-service training and how records are maintained.
- 2.4 Health requirements for personnel engaged in production.
- 2.5 Personnel hygiene requirements, including clothing.

3. Premises and equipment

Premises

- 3.1 Simple plan or description of manufacturing areas with indication of scale (architectural or engineering drawings not required).
- 3.2 Nature of construction and finishes.
- 3.3 Brief description of ventilation systems. More details should be given for critical areas with potential risks of airborne contamination (schematic drawings of the systems are desirable). Classification of the rooms used for the manufacture of sterile products should be mentioned.
- 3.4 Special areas for the handling of highly toxic, hazardous, and sensitizing materials.
- 3.5 Brief description of water systems (schematic drawings of the systems are desirable), including sanitation.
- 3.6 Description of planned preventive maintenance programmes for premises and of the recording system.

Equipment

- 3.7 Brief description of major equipment used in production and control laboratories (a list of equipment is not required).
- 3.8 Description of planned preventive maintenance programmes for equipment and of the recording system.
- 3.9 Qualification and calibration, including the recording system. Arrangements for computerized systems validation.

Sanitation

- 3.10 Availability of written specifications and procedures for cleaning manufacturing areas and equipment.

4. Documentation

4.1 Arrangements for the preparation, revision, and distribution of necessary documentation for manufacture.

4.2 Any other documentation related to product quality that is not mentioned elsewhere (e.g., microbiological controls on air and water).

5. Production

5.1 Brief description of production operations using, wherever possible, flow sheets and charts specifying important parameters.

5.2 Arrangements for the handling of starting materials, packaging materials, and bulk and finished products, including sampling, quarantine, release, and storage.

5.3 Arrangements for the handling of rejected materials and products.

5.4 Brief description of general policy for process validation.

6. Quality control

6.1 Description of the quality control system and of the activities of the quality control department. Procedures for the release of finished products.

7. Contract manufacture and analysis

7.1 Description of the way in which the GMP compliance of the contract acceptor is assessed.

8. Distribution, complaints, and product recall

8.1 Arrangements and recording system for distribution.

8.2 Arrangements for the handling of complaints and product recalls.

9. Self-inspections

9.1 Short description of the self-inspection system.

Inspection of drug distribution channels¹

Introductory note	158
General considerations	159

¹ Guidelines for inspection of drug distribution channels. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fifth report*. Geneva, World Health Organization, 1999, Annex 6 (WHO Technical Report Series, No. 885).

Glossary	160
1. Drug inspectors	163
1.1 Qualifications	163
1.2 Organizational aspects	164
1.3 Methods of inspection	165
1.4 Reference/information sources	166
2. Inspection of establishments in the drug distribution chain	167
2.1 Broad objectives	167
2.2 Establishments	167
2.3 Inspections	167
2.4 Special categories of drugs	167
References	168
Selected further reading	168
Appendix 1	
Checklist for inspection and the preparation of a report	169
Appendix 2	
Guidance on sampling	173
Appendix 3	
Guidance for inspection when pharmaceutical products are suspected to be counterfeit, spurious or substandard	174
Appendix 4	
Sample receipt form	175

Introductory note

The quality assurance of drugs at the level of the manufacturer is outlined in the guidelines on good manufacturing practices for pharmaceutical products (GMP) published by WHO (1). Compliance with these guidelines will ensure that products released for distribution are of the appropriate quality. However, if this is to be realized in practice, it is essential that an established drug regulatory authority exists in a Member State, which complies at least with the “Guiding principles for small national drug regulatory authorities” (2).

In addition, the holder of a marketing authorization for a pharmaceutical product, or alternatively the (legal) person responsible for the initial marketing of a product, who ideally should be a pharmacist or a pharmaceutical company authorized to practise in the Member State, should ensure that the product is only released for distribution after it has been established that it conforms with the product specification lodged with the drug regulatory authority.

This level of quality should be maintained throughout the pharmaceutical supply system or distribution network. Basic principles of GMP are applicable to wholesale operations and (to some extent) to retail outlets. These principles may be summarized as follows:

- only authorized products are distributed;
- a quality system is in place which includes quality policy, quality management, appropriate analytical controls, self-inspection;
- personnel are quality-conscious, adequately trained and motivated;
- premises and equipment are suitable for their intended use, and kept in a good sanitary condition;
- all products are received, stored and handled appropriately (protected against contamination, cross-contamination, mix-ups, environmental factors such as heat, severe cold, moisture, light);
- all drug-related operations are performed in accordance with written procedures, are properly supervised and adequately documented; documentation ensures complete traceability of receipt of all materials, quality testing processes (if any) and shipping;
- adequate provisions exist to handle complaints, recalls, and returned goods.

At the same time, many provisions of the GMP guidelines published by WHO are clearly not addressed to wholesalers and retail pharmacies where specific rules and requirements apply. These rules are determined partly by pharmaceutical science and common sense, and partly by national (regional) regulations and standards. In this context reference is made particularly to the guidelines entitled “Good pharmacy practice in community and hospital pharmacy settings” (3). It follows then that the “Provisional guidelines on the inspection of pharmaceutical manufacturers” (4), which are directed to government GMP inspectors, are not adequate to cover inspection in the distribution system. The present document addresses this specific issue.

These guidelines are intended for use by pharmaceutical inspectors in national drug regulatory authorities. They are therefore presented in a format that will allow for easy reference in the field. They should, however, be adapted by national drug regulatory authorities to suit their national legal requirements and available resources.

This document discusses the “simplified” situation when there is a single authority, the drug regulatory authority, where all kinds of drug inspections are located, ranging from those of drug manufacture to the inspections of pharmacies. In reality, these tasks, requiring different inspection skills, are usually distributed among different (national and local) authorities.

General considerations

A comprehensive system to assure the safety, efficacy and quality of pharmaceutical products at a national level has the following elements:

- Legal: drug legislation
- Administrative:
 - drug regulatory authority with functions of product registration, licensing of manufacturers, importers and distributors (wholesale, retail

- and for institutional supply), inspection and independent testing of samples
 - enforcement
- Technical:
 - regulations
 - standards and norms
 - guidelines
 - independent quality control laboratory(ies)

This document focuses on one element—inspection—and in particular on inspection in the pharmaceutical supply system.

The usefulness of drugs in the treatment of ailments, diseases and disorders is well recognized and appreciated. It is also recognized that the inappropriate use of drugs can produce severe toxic effects, some of which may be fatal. National drug laws have therefore been introduced to reduce risks associated with the use, misuse and abuse of pharmaceutical preparations.

Drugs differ in the severity of their side-effects and toxicity and these differences are taken into consideration in the classification of drugs in national drug laws. Drugs may be classified into four types as follows: over-the-counter drugs, pharmacy-only drugs, prescription-only drugs and prohibited drugs.

The distribution, supply, import, export, sale, storage, advertisement and dispensing of drugs are normally regulated by national drug laws, which provide for a system of licences to be issued by a drug regulatory authority for such drug-related activities. The drug laws may identify a ministry/department/agency that would function as the drug regulatory authority as well as provide for the enforcement of the drug laws, using a system of inspections organized through an inspectorate(s).

The inspectorate advises on whether applicants and premises should be issued licences to engage in drug-related activities. The inspectorate ensures that counterfeit, spurious and substandard pharmaceutical products are not found in the national pharmaceutical supply system or outside it, and that licensed premises and authorized persons adhere to existing laws and regulations. To do this, the inspectorate gathers information on the working of the drug laws by liaising with other law enforcement agencies and health institutions, including health-care professional associations.

Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

batch

A defined quantity of any drug product processed in a single process or series of processes such that it can reasonably be expected to be uniform in character and quality.

*batch number*¹

A distinctive combination of numbers and/or letters which specifically identifies a batch on the labels, the batch records, the certificate of analysis, etc.

controlled drugs

Narcotic drugs and psychotropic substances regulated by provisions of national drug laws.

counterfeit pharmaceutical product

A pharmaceutical product which is deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients, with the wrong ingredients, without active ingredients, with an insufficient quantity of active ingredient or with fake packaging.

drug (pharmaceutical product)

Any substance or mixture of substances that is manufactured for sale or distribution, sold, supplied, offered for sale or presented for use in:

- (i) the treatment, mitigation, cure, prevention or diagnosis of disease, an abnormal physical state or the symptoms thereof and abnormal physiological conditions in human or animal; or
- (ii) the restoration, correction or modification of organic functions in human or animal.

finished pharmaceutical product

A pharmaceutical product that has undergone all stages of production and quality control, including being packaged in its final container and labelled.

*good manufacturing practice*¹

Good manufacturing practice is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.

good pharmacy practice

The practice of pharmacy aimed at providing and promoting the best use of drugs and other health care services and products, by patients and members of the public. It requires that the welfare of the patient is the pharmacist's prime concern at all times.

¹ As defined in "Good manufacturing practices for pharmaceutical products" (1).

over-the-counter drugs

These are drugs that can be sold from licensed dealers without professional supervision and without prescriptions. These drugs are suitable for self-medication for minor diseases and symptoms.

pharmacist

A pharmacist is a holder of a degree or diploma in pharmacy from a recognized higher institution of learning and is registered or licensed to practise pharmacy.

pharmacy-only drugs

These are drugs authorized to be sold only in licensed pharmacies under the supervision of licensed and registered pharmacists; they may be sold without a prescription.

poison

A preparation or substance defined by a national drug law as a poison.

prescription-only drugs

These are drugs supplied only in licensed pharmacies on the presentation of signed prescriptions issued by a licensed and registered medical practitioner, licensed and/or registered dentist (for dental treatment only), and/or licensed and/or registered veterinarian (for animal treatment only), and the supply and dispensing of these drugs must be carried out by a pharmacist or under the supervision of a pharmacist. Prescription drugs are further subdivided into controlled drugs (narcotic drugs and psychotropic substances) and non-controlled drugs.

product recall

Product recall is a process for withdrawing or removing a pharmaceutical product from the pharmaceutical distribution chain because of defects in the product or complaints of serious adverse reactions to the product. The recall might be initiated by the manufacturer/importer/distributor or a responsible agency.

prohibited drugs

These are drugs with toxicity or side-effects that outweigh their therapeutic usefulness, so that public health and welfare are protected by prohibiting their production, manufacture, export, import, trade, distribution, supply, possession or use, except in amounts required for medical and scientific research. Prohibited drugs are normally determined by the national or supranational registration/licensing authority.

*quality assurance*¹

Quality assurance is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use.

quality control

Quality control covers all measures taken, including the setting of specifications, sampling, testing and analytical clearance, to ensure that raw materials, intermediates, packaging materials and finished pharmaceutical products conform with established specifications for identity, strength, purity and other characteristics.

unauthorized market (in some countries called parallel market)

The unauthorized market consists of wholesale establishments and retail outlets distributing or selling drugs without authorization from a competent authority.

1. Drug inspectors

1.1 Qualifications

Inspectors should normally be pharmacists who have working experience in community and/or hospital pharmacy. Where persons other than pharmacists are employed as drug inspectors, they should be adequately experienced in drug control affairs and suitably trained in inspectorate functions. The possibility of having part-time inspectors with specialist knowledge as part of inspection teams should also be considered.

The inspector should possess the following attributes:

- good knowledge of pharmacy, drugs, and poisons
- good knowledge of the laws and regulations to be enforced
- good command of technical terms and excellent communication skills
- awareness of the probable methods of using forged or false documents for transactions in pharmaceutical preparations and skill in determining the genuineness of documents presented for examination
- maturity, honesty and integrity
- responsible conduct which commands respect
- willingness to accept challenges
- ability to organize their own work with minimum supervision
- ability to assess facts quickly and take rational and sound decisions without delay

¹ As defined in "Good manufacturing practices for pharmaceutical products" (1).

- ability to assess character and honesty of persons being interviewed
- good public relations image with key personnel/pharmacists in charge of premises while remaining firm, fair and resolute
- ability to hold discussions with company management at the completion of inspection
- ability to motivate others
- commitment to hard work and long hours
- ethical approach to any potential conflict of interest.

1.2 Organizational aspects

Inspectors should be embedded in an organization, usually called an inspectorate, which ensures the following aspects:

- A job description which describes the duties of the inspector.
- Proper reporting: inspectors should report either to the drug regulatory authority or to the pharmaceutical department (chief pharmacist) of the ministry of health.
- Uniformity of approach:
 - (a) Regular meetings of inspectors, in which experiences on the job are exchanged, will help promote a uniform approach to inspection as well as enhance the performance of the inspectors.
 - (b) Inspectors should work according to a work plan and to standard operating procedures (SOPs).
 - (c) Inspection reports should preferably be in three or four parts:
 - (i) date of inspection and general information on the establishment inspected,
 - (ii) description of the inspection activities undertaken, including analytical data of samples taken,
 - (iii) observations and recommendations,
 - (iv) conclusions.
 - (d) Inspectors should be encouraged to submit weekly reports of work to headquarters.
- Total coverage of the country. This can be achieved by:
 - (a) dividing the country into defined areas for the purpose of inspection and placing an inspector in charge of a defined area for the purpose of inspecting wholesale, community and hospital pharmacies, and clinics,
 - (b) inspection of ports and border posts in a defined area.
- Total coverage of the field. The inspector will be expected to inspect establishments such as:
 - (a) pharmaceutical manufacturers in respect of drug distribution,
 - (b) pharmaceutical importers/exporters,
 - (c) pharmaceutical wholesalers and retailers,

- (d) hospital pharmacies/clinics,
- (e) ports and international border posts,
- (f) drug warehouses, stores and unauthorized markets.

(Note: The existence of unauthorized markets for the distribution of drugs poses considerable health hazards. The inspectors should, with the assistance of task forces if necessary, investigate the extent of the unauthorized market, the types of drugs distributed and supplied, and the sources of the drugs. Where possible, unauthorized markets for drugs should be prohibited through effective inspectorate activities. Inspectors should also investigate the sources of supply of suspect counterfeit or substandard pharmaceutical products.)

- Cooperation with other agencies. The inspector will be expected to interact and cooperate with other interested parties such as:
 - (a) industrial, community and hospital pharmacists,
 - (b) management and supervisory staff of pharmaceutical establishments and hospitals,
 - (c) medical practitioners, dentists, veterinarians, nurses and midwives and other health workers,
 - (d) public analysts,
 - (e) ministry of justice officials and court officials,
 - (f) drug law enforcement officers including the police and customs,
 - (g) officers of port authorities, clearing agents at the ports, importers and exporters,
 - (h) members of the public,
 - (i) staff of faculties of medicine/pharmacy,
 - (j) foreign drug regulatory authorities.
- Independence. Inspectors should, for example, have the use of official vehicles.
- Adherence to a code of inspection.

1.3 Methods of inspection

The inspector uses different methods to check compliance with the national, supranational or international drug laws and regulations. Among these methods are:

- *Comprehensive/routine inspection.* This form of inspection is generally reserved for a new pharmaceutical establishment, when an establishment is applying for permit to extend its scope of operations beyond that for which it was originally licensed, has made important changes in key personnel or is changing premises, has not been inspected for a long time (3–5 years), or when there is information (even of an informal nature) of serious lapses. Where the inspection is for a new establishment or for extension of scope of operation or because of changes in key personnel, the inspection should be announced.

- *Concise inspection.* This is reserved for establishments that have previously been inspected with a view to assessing standards of good pharmacy practice. The outcome of the inspection will help in the proper assessment of the establishment. The inspection may be unannounced.
- *Follow-up inspection.* This is normally carried out to ensure that corrective measures have been undertaken following advice and notice given during a previous inspection. Where a time limit was given for applying the corrective measures, the inspection may be unannounced.
- *Special inspection.* This is undertaken to deal with specific complaints received about lapses or non-compliance with standards of professional practice. The inspection should preferably be unannounced.
- *Investigative inspection.* This type of inspection is used to assess the performance of a new establishment whose scope of operation was previously unknown.

Any of these methods may be applied with or without prior announcement. Normally inspections should be announced but it serves a useful purpose to undertake some unannounced inspections. Follow-up, special and investigative inspections should preferably be unannounced.

Inspections should be held regularly. Premises should be inspected at least once every 12–18 months. Where contravention is often noticed, the inspection should be more frequent (e.g. every six months). For premises with a good record, less frequent inspections may be needed.

1.4 Reference/information sources

The reference/information sources of an inspector should include:

- Existing national and international drug laws and regulations, covering such aspects as:
 - licensing
 - GMP
 - good distribution practice
 - good pharmacy practice
 - promotion of pharmaceutical products
 - controlled drugs
 - counterfeit, spurious or substandard pharmaceutical products.
- Codes of inspection (national and regional), where in existence.
- Codes of professional ethics.
- Health consequences of drug abuse and misuse.
- Available data on imports/exports/prohibited drugs.

2. Inspection of establishments in the drug distribution chain

2.1 Broad objectives

The welfare of patients and other members of the public is of prime concern in the distribution chain of drugs, either manufactured within the country or imported. Inspections of establishments are therefore undertaken to ensure:

- Protection of patients and members of the public from malpractice by distributors and suppliers of drugs.
- Adherence to the drug laws and regulations governing compounding, distribution, importation, export and storage of drugs.
- High ethical and professional standards of pharmaceutical practice.

2.2 Establishments

In the drug distribution chain several kinds of establishments can be distinguished:

- production sites
- storage or warehouse facilities
- establishments for the supply, sale, dispensing and distribution of drugs, such as pharmacies, hospitals, clinics, ports and stores.

2.3 Inspections

When inspecting these establishments the inspector uses the appropriate references. The method of inspection should be laid down in a SOP which also contains the requirements for a specific type of establishment. The inspection SOP may be in the format of a checklist (see Appendix 1 for an example applicable to most drug distribution establishments). When sampling is part of the inspection procedure, the SOP should contain detailed guidance for the inspector; an example of this guidance is to be found in Appendix 2.

2.4 Special categories of drugs

When special categories of drugs are present the inspector may require a modified SOP. This situation is likely to occur with controlled drugs, pharmaceutical products moving in international commerce, or with counterfeit, spurious or substandard pharmaceutical products. For this last category, an example of extra guidance is given in Appendix 3.

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1. Good manufacturing practices for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report*. Geneva, World Health Organization, 1992, Annex 1 (WHO Technical Report Series, No. 823).
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Appendix 1

Checklist for inspection and the preparation of a report

Inspection applicable to all drug distribution establishments

1. General information

- (a) name of establishment inspected
- (b) date of inspection
- (c) name(s) of the inspector(s)
- (d) date of last inspection.

2. Type of inspection

Comprehensive, concise, follow-up, special, investigative, announced, unannounced.

3. Licensing

- (a) licensing of premises
- (b) person with supervisory role in establishments handling prescriptions and pharmacy sale-only drugs (is normally a registered pharmacist or a person so prescribed by national legislation)
- (c) personnel authorized to sell only over-the-counter drugs (licensed, where such licensing is required)
- (d) adherence to licensing provisions.

4. Activities undertaken on premises

Manufacturing, wholesale, importation, export, retail, hospital pharmacy, clinic, nursing and maternity homes.

5. Adequacy and suitability of premises

- (a) premises clean, tidy and in good state of repair
- (b) premises secure
- (c) floor durable and easily cleaned
- (d) premises constructed to prevent infestation by vermin and pests
- (e) clean shelves in retail pharmacy and premises for sale of over-the-counter drugs
- (f) changing rooms and toilet available
- (g) adequacy of lighting and ventilation
- (h) appropriate layout of premises.

6. Warehouse/store

- (a) adequacy and suitability of warehouse/store
- (b) warehouse/store clean and uncluttered
- (c) warehouse/store inaccessible to unauthorized persons
- (d) temperature and humidity control
- (e) enforcement of stock rotation
- (f) adequacy of shelving
- (g) existence of areas for returned drugs, recalled drugs, expired drugs, and drugs in quarantine
- (h) warehouse/store free from vermin and insects.

7. Special storage

- (a) availability of cold room storage or refrigerator for vaccines and biological products
- (b) suitability of the cold storage facilities
- (c) standard written procedure prepared by an appropriate national regulatory agency for the maintenance of cold chain
- (d) special storage area for controlled drugs and other prescription drugs
- (e) suitable and secure storage facility for controlled drugs and poisons.

8. Record-keeping

- (a) name and address of supplier of each drug product with date
- (b) name and address of purchaser of each drug product with date
- (c) supplier or purchaser licensed

- (d) retention of order forms, copy of delivery notes, stores receipt, and issue vouchers, and book of records (controlled drugs book/prescription drugs book) on the premises as provided for in the drug laws
- (e) accuracy of records kept.

9. Conditions for sale and supply

- (a) sale and supply of prescription and pharmacy sale-only drugs under the control of a registered pharmacist
- (b) sale and supply of prescription and pharmacy sale-only drugs effected from registered/licensed premises
- (c) sale of prescription drugs on the basis of valid prescription
- (d) sale and supply of over-the-counter drugs undertaken in registered premises under the supervision of a pharmacist or premises licensed for the purpose of sale and supply of over-the-counter drugs only, where such registration or licence is required by law.

10. Diversion of controlled drugs

Diversion of controlled drugs prevented by examining the records and by physical examination of stock.

11. Returned and expired drugs

Procedures in place for handling returned and time-expired drugs.

12. Product recall

Procedures in place for recall of drugs and handling recalled drugs.

13. Product complaints

Procedures in place for dealing with complaints about drugs.

14. Promotional activities

Assess promotional materials for compliance with drug laws.

15. Personnel

- (a) person responsible for supervising sale in a wholesale/retail pharmacy is a registered/licensed pharmacist
- (b) name of the pharmacist in continuous personal control noted
- (c) personnel wear clean protective clothing.

16. Labelling of drug products and package inserts

Check adequacy of labelling of drug and information on package inserts.

17. Physical examination and sampling of drugs

Conduct physical examination of drugs in stock and take samples of drugs for quality assessment.

18. Reference books

Check existence of reference books on premises, where they are required.

Specific inspection applicable to individual establishments

19. Importer

- (a) all drugs accompanied by import documents such as bill of lading, export authorization, product licence and batch certificate
- (b) controlled drugs also accompanied by export authorization certificate or export declaration, whichever is applicable
- (c) imported drugs are in original packs, except for drugs imported in bulk for repackaging and/or manufacturing drug formulations.

20. Retail and hospital pharmacy

- (a) compounding of drugs carried out by or under the supervision of a pharmacist
- (b) quality of raw materials used in compounding complies with pharmacopoeial specifications
- (c) dispensing of prescription drugs carried out by or under the supervision of a pharmacist
- (d) entries of dispensed prescription drugs made in prescription book and for controlled drugs in controlled drugs book
- (e) prescriptions for prescription drugs retained on premises for periods provided in the drug laws
- (f) dispensed drugs labelled appropriately with name of drug, name of patient, name and address of pharmacy, clinic or hospital, instructions for using the drugs and, where appropriate, warning labels
- (g) counselling of patients on use of dispensed drugs
- (h) adequacy of containers for dispensed drugs
- (i) personnel observe high standard of personal hygiene and wear clean protective clothing
- (j) dispensing area clean, adequate and has necessary equipment
- (k) walls in dispensing area easily cleaned

- (l) quality of extemporaneous preparations
- (m) sources of drugs sold and supplied from the pharmacy
- (n) suitable cabinets for storage of controlled drugs and poisons.

21. Clinics, nursing and maternity homes

- (a) sources of drugs used, supplied and administered
- (b) records of controlled drugs used, supplied and administered
- (c) storage facilities and security for controlled drugs.

22. Unauthorized markets

- (a) investigate sources of drugs in the unauthorized market
- (b) sample drugs for quality assessment
- (c) seize drugs in the unauthorized market.

Appendix 2 Guidance on sampling

This guidance is applicable to collecting samples of drugs to be tested by the official quality control laboratory. The collection may be aimed either at assessing the quality of products on the market, in which case adequate sampling plans should apply (see, for example, “Sampling procedures for industrially manufactured pharmaceuticals” (1, 2)), or at detecting substandard, spurious and counterfeit pharmaceutical products. In this case sampling shall be based on information and may involve confiscation of entire stocks to prevent further distribution. Compliance with legal procedures for sample collection, analysis and documentation is obligatory.

- (a) Check that the sample is properly labelled with the following:
 - (i) name of sampled pharmaceutical preparation
 - (ii) batch number
 - (iii) date and source of sample; the original manufacturer’s label may be helpful.
- (b) Check that the records contain the following:
 - (i) number of samples
 - (ii) types of packaging and storage conditions
 - (iii) circumstances of sampling that may include suspected quality defects.
- (c) Place seals on containers of the samples.
- (d) Hand over one-third of the samples to the representative of the inspected establishment.
- (e) Confirm in writing that samples were taken from the premises and have the confirmation countersigned by an appropriate official of the inspected establishment (see, for example, the sample receipt form in Appendix 4).

References

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Appendix 3

Guidance for inspection when pharmaceutical products are suspected to be counterfeit, spurious or substandard

This section addresses specifically the situation in which the inspector suspects counterfeit, spurious or substandard pharmaceutical products to be present during an inspection. This may be during either a regular inspection or an investigation aimed at detecting such products.

1. Broad objective

The presence of counterfeit, substandard and spurious pharmaceutical products in the drug distribution channels may present a danger to public health, and it is imperative that suspect products are effectively and rapidly taken out of the distribution channels and quarantined. In order to facilitate the work of the inspector, the help of capable and experienced persons involved in the distribution of products should be obtained on a proactive basis to help identify such products.

2. Standard operating procedures

- (a) A written SOP for inspectors should be drawn up and made available to them.

This SOP should include at least the following information:

- (i) how the suspect product should be isolated to prevent its further distribution
- (ii) the size of the samples required for testing purposes
- (iii) the manner in which the samples should be taken
- (iv) the record-keeping procedure to be followed in recording the details of the action taken
- (v) the details which should be recorded on the receipt issued for the embargoed product and/or samples taken
- (vi) the type of materials which should be used for sealing samples or for embargoing or confiscating suspect products

- (vii) the names, addresses and telephone numbers of persons who should be contacted to report on the action taken
 - (viii) special precautions to be noted by the person initiating the sampling or seizure procedure, with particular reference to correct legal procedures to be followed
 - (ix) where appropriate, the manner in which the suspect product should be destroyed.
- (b) Where other persons are involved in the detection of counterfeit pharmaceutical products they shall operate on the basis of a suitable SOP. In any case of suspicion of counterfeit pharmaceutical products an inspector shall be notified immediately.

3. Counterfeit products

The following applies specifically to counterfeit products:

- (a) When examining a possible counterfeit pharmaceutical product the inspector shall first screen the product by looking, smelling, touching and listening to the sound of the packing and its contents. The inspector shall look for anything, in particular its labelling and packing, that makes the product look different from an original reference sample. A SOP may assist in examining the product in this way.
- (b) When the organoleptic examination does not give conclusive evidence the inspector shall have a sample tested using appropriate simple screening methods, such as the basic tests recommended by WHO or a suitable thin-layer chromatography method.
- (c) In addition to any full analytical testing, the drug regulatory authority of the country of origin stated on the label of the product may be asked to establish whether the product is counterfeit.
- (d) Proven cases of counterfeit pharmaceutical products shall be fully documented and communicated to all other inspectors, to increase their level of expertise. Information on counterfeit products shall also immediately be made available to drug regulatory authorities of other countries concerned and to WHO.

Appendix 4 Sample receipt form

Institution/company (under inspection)

Address

Date of inspection

Name of representative of the inspected establishment

Name of inspector

Name of the drug and description of sample

.....

Dosage form

Batch no.

Place sampled (warehouse, production line, packaging section, etc.)
.....

No. of samples taken (tins, packets, etc.)

.....

Signature	Signature
Inspector	Representative of the inspected establishment

Quality systems requirements for national good manufacturing practice inspectorates¹

Background	177
1. Introduction	177
2. Glossary	177
3. Administrative structure	178
4. Terms of reference	179
5. Organizational structure	179
6. Inspection personnel	181
7. Documentation	182
8. Records	183
9. Inspection procedures	184
10. Inspection facilities required	186
11. Quality manual	187
12. Confidentiality	188
13. Publications	189
14. Appeals	189
15. Internal audit and periodic review	190
16. Complaints	191
17. Recalls	191
References	192

¹ Quality systems requirements for national good manufacturing practice inspectorates. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report*. Geneva, World Health Organization, 2002, Annex 8 (WHO Technical Report Series, No. 902).

Background

Following the provisional guidelines on the inspection of pharmaceutical manufacturers (1), the WHO Expert Committee on Specifications for Pharmaceutical Preparations acknowledged that additional guidelines concerning national inspectorates would be of value in strengthening the implementation of good manufacturing practices (GMP) (2) and enhancing mutual recognition among inspectorates.

A trend has recently become apparent in WHO Member States for non-commercial institutions, such as certification bodies, testing laboratories, etc., to introduce quality systems principles in their internal operations. The same principles are also being applied by governmental pharmaceutical inspectorates and drug control laboratories.

The Pharmaceutical Inspection Convention (PIC) has published a document (3), with the objective of adapting the standards of the International Organization for Standardization (ISO) of the 9000 series and related norms (4–8) to the activities of the GMP inspectorates of Member States. It is based on European Standard EN 45012, *General criteria for certification bodies operating quality systems certification* (9), but has been modified for this particular purpose.

1. Introduction

These requirements are applicable to quality systems for the operation of inspection services within competent authorities concerned with GMP inspections. It is intended that each inspection service should use these requirements as the basis for developing its own quality system.

The establishment and operation of a quality system is an essential element in the mutual recognition of national GMP inspections. The willingness to accept national inspections is significantly enhanced when it is known that the GMP inspectorate of the competent authority follows uniform procedures incorporating quality system principles. The quality system should include all the activities involved in the inspection.

2. Glossary

authorized person

A person (among key personnel of a manufacturing establishment) responsible for the release of batches of finished products for sale (10).

quality audit

An examination and assessment of all or part of a quality system with the specific purpose of improving it. A quality audit is usually conducted by outside or independent specialists or a team designated by the management for this purpose. Such audits may also be extended to suppliers and contractors (2).

quality manual

A handbook that describes the various elements of the system for assuring the quality of the test results generated by a laboratory (see section 11).

quality system

An appropriate infrastructure, encompassing the organizational structure, procedures, processes and resources necessary to ensure adequate confidence that a product (or service) will satisfy given requirements for quality (2).

standard operating procedure (SOP)

An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material but of a more general nature (e.g. equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation (2).

3. Administrative structure

3.1 The structure, membership and operation of the GMP inspectorate should be such that impartiality is safeguarded.

3.2 The national inspection services are responsible for ensuring that the requirements of the relevant national legislation are satisfied.

3.3 All personnel employed or used by the GMP inspectorate, including outside inspectors or subcontracted personnel, should not be subject to any commercial, financial or other pressures which might affect their judgement. They should not be under the control of pharmaceutical manufacturers, and must be assessed and licensed.

3.4 The system for obtaining fees should not improperly influence the inspection procedure.

Recommended procedure

The administrative structure, membership, operation and legal status of the GMP inspectorate should be described in the quality manual (see section 11).

The quality manual should show how all personnel working for the GMP inspectorate, including subcontracted staff or advisers, and persons serving on committees providing advice, can maintain their impartiality. The GMP inspectorate should ensure that such persons:

- (a) are not subject to any commercial, financial or other pressures which might influence their judgement;

- (b) are not improperly influenced in their inspection of pharmaceutical manufacturers or persons assessed;
- (c) have not been involved in the design or maintenance of inspected facilities by way of any consultancy service or commercial arrangement.

The remuneration of GMP inspectorate personnel engaged in inspection activities should not depend on the result of such activities or on the granting of a marketing authorization.

Only in exceptional cases may GMP inspectorates provide advisory or consultancy services. Where the GMP inspectorate does provide such services, it should develop a code of conduct or defined policy which clearly distinguishes between the process of inspection and that of providing an advisory or consultancy service to clients. This service should be of benefit to all of industry, and not solely to individual manufacturers.

4. Terms of reference

4.1 The functions of the GMP inspectorate should be clearly defined and should cover:

- (a) legal responsibilities;
- (b) the formulation of policies;
- (c) an overview of the implementation of its policies;
- (d) an overview of its finances;
- (e) as required, the setting up of committees to which defined activities are delegated.

Recommended procedure

The terms of reference, legal responsibilities and functions of the GMP inspectorate and the way in which policy guidelines are established should be documented in the quality manual.

For any committee established to advise the GMP inspectorate or the chief inspector, the following details should be included:

- (a) its role and function;
- (b) the procedure for selecting and appointing the members (the names of the chairperson, secretary and members, their current appointments and the interests, if any, which they represent on the committee, should be available);
- (c) the rules of procedure.

5. Organizational structure

5.1 The GMP inspectorate should have an organization that enables it to maintain the capability to perform its technical functions satisfactorily.

5.2 The GMP inspectorate should have:

- (a) documentation clearly identifying its legal status;
- (b) an organizational chart showing clearly the responsibility and reporting structure of the inspectorate and, in particular, the relationship between its inspection and authorization (licensing) functions;
- (c) a description of the means by which the inspectorate obtains financial support;
- (d) a description of the relationship between the GMP inspectorate and other departments within the drug regulatory authority and other government agencies, where they operate as separate bodies.

5.3 The GMP inspectorate should have and make available a formal statement explaining how the results of inspections are taken into account in granting and maintaining authorizations (licences).

5.4 The senior management of the GMP inspectorate should make a formal commitment to the recommended principles by ensuring that the quality policy of the inspectorate is documented, relevant to the objectives, and implemented.

5.5 The responsibility, authority and reporting structure of the GMP inspectorate should be clearly defined and documented (see above) and should be supported by written job descriptions for each member of staff.

5.6 An appropriately experienced, responsible and qualified person (2) should be nominated to carry out the quality assurance function, including implementing and maintaining the quality system. This person should have direct access to senior management. If necessary, this task may be assigned to more than one person.

5.7 The GMP inspectorate should have sufficient resources at all levels to enable it to attain its objectives effectively and efficiently. Senior management should ensure that all personnel are competent to carry out their assigned duties. They should receive appropriate training that should be documented and its effectiveness assessed.

5.8 Periodic management reviews of the quality system should be conducted and documented; records of these reviews should be retained for a specified period of time.

Recommended procedure

The above-mentioned recommendations are intended to ensure a reasonable level of transparency, both nationally and internationally.

The organizational chart, source(s) of finance, legal status of the GMP inspectorate and its relationship with the drug regulatory authority and other

government agencies should be documented in the quality manual, together with a description of the quality system.

6. Inspection personnel

6.1 The personnel of the GMP inspectorate should be competent to perform the functions that they undertake.

6.2 The GMP inspectorate should maintain information on the relevant qualifications, training and experience of each inspector. Records of training and experience should be kept up to date.

6.3 Personnel should have clear, documented instructions specifying their duties and responsibilities. These instructions should be kept up to date.

6.4 When work is subcontracted to an external body or use is made of experts, the inspectorate should ensure that the personnel employed meet the relevant requirements of the quality system. The liability of third party inspectors should be clearly defined in the contract or agreement.

6.5 The GMP inspectorate should possess the required personnel, expertise and other resources to perform inspections of manufacturers and wholesale distributors to determine whether they comply with the principles and guidelines of current good practices and with the relevant legislation.

6.6 The staff responsible for inspections should have appropriate qualifications, training, experience and knowledge of the inspection process. They should have the ability to make professional judgements as to the conformity of the inspected party with the requirements of good practices and the relevant legislation and be able to make an appropriate risk assessment. Knowledge of current technology is essential, including computerized systems and information technology.

6.7 The GMP inspectorate should establish a documented system for recruiting and training its personnel. The training received and the training needs of each member of staff should be regularly reviewed, and individual training records should be maintained.

Recommended procedure

The credibility of the GMP inspection process will depend to a large degree on the technical competence and integrity of the inspectors. The quality manual should provide up-to-date details of the names, qualifications, experience and terms of reference (job description and duties to be performed) of each member of staff engaged in the GMP inspection process (see also section 10).

Formal arrangements should exist for personnel training, and details of these arrangements should be documented. Training undertaken by each member of

staff engaged in GMP inspections should be documented (see also “Recommended procedure” in section 10).

A documented procedure for selecting the members of an inspection team and deciding on its size should be available. The inspection team may include a person or persons with specialist knowledge and/or experience of a particular area of technology.

If an inspection is carried out on behalf of the GMP inspectorate by an external body or person, the GMP inspectorate should ensure that the external personnel satisfy the relevant requirements contained in these recommendations.

GMP inspectors working with or advising the GMP inspectorate should:

- (a) be academically qualified in a recognized scientific/technological discipline related to pharmaceuticals (normally pharmacy, chemistry or microbiology); direct personal experience of pharmaceutical manufacture or control is not a requirement but would be considered as a valuable asset for an inspector;
- (b) have satisfactorily completed a recognized training course on auditing quality management systems;
- (c) undergo at least 10 days of training per year (e.g. courses, symposia, conferences, etc.);
- (d) have a competent working knowledge of the WHO guidelines on GMP for pharmaceutical products (2) and/or the GMP inspection procedures of the relevant national regulatory authority;
- (e) have undergone appropriate training in the current procedures and techniques of GMP inspections before conducting an inspection alone;
- (f) have the necessary personal qualities of integrity, tact and character to perform the duties of a GMP inspector.

7. Documentation

7.1 The GMP inspectorate should maintain a system for the control of all documentation relating to GMP inspections of manufacturers and recommendations relating to authorization holders, and should ensure that:

- (a) the current versions of the appropriate documentation are available at all relevant locations;
- (b) all revised documents or amendments to documents are correctly authorized and processed in a manner which ensures that they are introduced without delay;
- (c) superseded documents are removed from use throughout the GMP inspectorate and elsewhere in the organization and its agencies, but are retained for a defined period of time.

7.2 The GMP inspectorate should ensure that all of its activities are described in SOPs that clearly describe the responsibilities, policy and actions. These should

include, but not be limited to, training (introduction, GMP and task-related), inspections, reporting after inspections, handling of complaints, licensing (issue, suspension, revocation), certification, documentation control, planning and handling of appeals.

7.3 Proper and accessible records should be maintained of the activities carried out, including training, as well as the assessment of inspectors after training, the preparation of inspection reports, the handling of complaints, and the drawing up of authorized checklists (where in use) and other related documents.

7.4 Reports should be prepared on all inspections performed. They should be prepared in the approved format, and signed and dated by the relevant inspector.

7.5 The documentation system should ensure that any changes to documents are made in a controlled manner and are properly authorized. There should be a means of identifying changes in individual documents.

Recommended procedure

The following information should be included or referred to in the quality manual:

- (a) a list of all the documents used;
- (b) for each document, the name(s) or position(s) of the person(s) responsible for authorizing its issue and any subsequent amendments or changes;
- (c) a description of the system whereby relevant documents and subsequent amendments are made available at the appropriate location from the point of view of the functioning of the inspection process;
- (d) the method by which amendments and changes are made, so that documents are speedily updated, changes recorded and superseded documents promptly withdrawn and archived.

8. Records

8.1 The GMP inspectorate should maintain a system of records to suit its particular method of operation and circumstances. It must comply with the relevant obligations under national legislation and demonstrate that the quality system is operating satisfactorily.

8.2 Records should be available which demonstrate that all the relevant procedures have been followed in the performance of each GMP inspection, including the initial inspection, the recommendation for issue of a marketing authorization, routine inspections and corrective action.

8.3 All records should be safely stored for an adequate period, and held under conditions that guarantee their security and confidentiality, unless otherwise required by the national legislation.

Recommended procedure

The quality manual should describe or refer to separate SOPs which describe the system adopted by the GMP inspectorate for maintaining its records. The manual should include blank specimen copies of the various checklists, certificates and reports used during the inspection process and describe the way in which these are processed, stored and archived, and/or disposed of.

The procedures for recommending to the authorization holder the issue, suspension or revocation of marketing authorizations should be described.

Documented staff instructions on security and on the use and handling of inspection reports should be identified and described in accordance with the confidentiality requirements specified in national legislation. Information as to who should have access to confidential information should be given and such access should be controlled.

Records associated with inspection activities should be retained for a minimum period of three full inspection cycles or for 6 years, whichever is the longer.

9. Inspection procedures

9.1 The GMP inspectorate should have the required resources (financial, human, facilities and others) and documented procedures to enable the inspection of manufacturing operations to be carried out in accordance with the requirements of the WHO guidelines on GMP (2) and/or the national GMP guidelines.

9.2 The GMP inspectorate should require the manufacturer to have documented procedures in accordance with a quality management system, and complying with the WHO guidelines on GMP (2) and/or the national GMP guidelines.

9.3 The GMP inspectorate should perform regular inspections of the manufacturing premises, procedures and quality systems of authorization holders at least once every 2 years in accordance with a written inspection programme. Written inspection reports should be prepared and sent to the national regulatory authority to keep it informed of the outcome of such inspections.

9.4 The planning of inspections of manufacturers and the assessment of compliance with the planning regarding the performance of the different types of inspections should be documented. The types of inspections should include as a minimum routine inspections, specific inspections, follow-up inspections and concise inspections.

9.5 The activity of the GMP inspectorate should be described, indicating how it relates to the system(s) for granting manufacturers' and product authorizations.

9.6 The activities relating to post-marketing surveillance and product testing should be described. The description should also cover the process of handling non-conforming products (e.g. substandard or counterfeit products).

9.7 The procedure for operations in support of a surveillance sampling programme should be documented.

9.8 The GMP inspectorate should have the documented procedures and resources to enable the inspection of manufacturing and wholesale distribution operations to be carried out in accordance with the official guidelines and national legislation. A formal inspection plan should be followed. All instructions, standards or written procedures, worksheets, checklists and reference data relevant to the work of the GMP inspectorate should be kept up to date and be readily available to staff.

9.9 A chief inspector should be appointed to coordinate inspection activities if more than one inspector is involved in an inspection. The lead inspector, who should be selected by all the participating inspectors, should normally prepare the inspection report.

9.10 Observations and/or data obtained in the course of inspections should be recorded in a timely manner to prevent loss of relevant information.

9.11 Completed inspections should be reviewed to ensure that the requirements have been met.

Recommended procedure

The procedures covering initial inspections of new applicants for marketing authorizations and ongoing inspections of authorization holders should be documented.

Manufacturers should be inspected at least every 1 or 2 years, although new authorization holders should be inspected more frequently until inspectors are confident that the manufacturers are complying with the WHO guidelines on GMP and/or the national GMP guidelines. The frequency of inspection should not normally fall below once every 2 years as lack of continuity may give rise to a reduced awareness of current GMP or allow significant deficiencies to develop.

The time available for undertaking inspections should be adequate to enable sufficient investigations and enquiries to be made to give confidence in the findings of the inspection.

The report to the authorization holders following GMP inspections should include as a minimum:

- (a) the name and location of the manufacturing site(s);
- (b) the date(s) of the inspection(s);

- (c) the reason for the inspection and the product categories and manufacturing areas inspected;
- (d) the suitability of key personnel, including the authorized person;
- (e) observations, failures to comply with the WHO guidelines on GMP and/or the national GMP guidelines, and the recommended frequency of reinspection;
- (f) a recommendation on the issue/continuation, suspension or revocation of the marketing authorization.

The GMP inspectorate should have the power, under the national or regional legislation or other arrangements, to require reinspection of a manufacturer's premises if there are changes in personnel, facilities, internal organization or scope of activity, or if analysis of a complaint or any other information indicates that the manufacturer is failing to comply with the requirements of the WHO guidelines on GMP and/or the national GMP guidelines, or with the conditions imposed by the marketing authorization.

10. Inspection facilities required

10.1 The inspection service should have the required facilities in terms of staff, expertise, equipment and other resources to perform inspections of manufacturers to determine compliance with the requirements of the WHO guidelines on GMP and/or the national GMP guidelines. This does not preclude the use of external resources, when necessary, provided that the requirements as described for "subcontracting" are met (see section 3.3).

10.2 If inspections are carried out on behalf of the GMP inspectorate by an external body or person, the GMP inspectorate should ensure that this body or person satisfies the requirements specified in section 3.3. A properly documented agreement covering these arrangements, including confidentiality aspects and the declaration of any conflict of interests, should be drawn up.

Recommended procedure

A sufficient number of competent personnel should support the GMP inspectorate, whether employed or contracted for the functions that they undertake.

The quality manual should describe the procedures for the management of the GMP inspectors and of the necessary records. A record should be kept for each individual employed to carry out GMP inspections (whether an employee or under contract), which should include the following information:

- (a) the name;
- (b) the designated area of responsibility within the declared scope of the GMP inspectorate;

- (c) the educational qualifications;
- (d) the professional qualifications, where relevant to the activities of the GMP inspectorate;
- (e) the work experience;
- (f) details of the GMP inspector training received, supported by documentary evidence of course attendance and assessment results.

Where an external body or person carries out a GMP inspection, the quality manual should describe the process adopted by the GMP inspectorate to comply with the above-mentioned requirements.

Whenever an external body or person is used to carry out any function on behalf of a GMP inspectorate, the GMP inspectorate should have documented evidence to demonstrate that the external body or person concerned is competent to do so.

Staff members authorized to carry out audits of external bodies or persons should be identified.

Documented agreements with all external bodies or persons should be available for scrutiny.

A register of all external bodies or persons employed by the GMP inspectorate should be maintained. The register should include:

- (a) the name of the external body or person;
- (b) the legal status of the external body and details of any relationship with a parent company, group of companies or any other organization of which the external body or person is part, with specific reference to possible conflicts of interest;
- (c) the names and qualifications of all personnel engaged in GMP inspection work for the GMP inspectorate.

11. Quality manual

11.1 The GMP inspectorate should define and document its policy and objectives for, and commitment to, quality in a quality manual. It should ensure that this policy is understood, implemented and maintained at all levels in the organization.

11.2 The information contained in the quality manual and procedures should include at least:

- (a) a quality policy statement;
- (b) a brief description of the legal status of the GMP inspectorate (see section 4.1(a));
- (c) a code of ethics and conduct relating to GMP inspection activities;
- (d) a description of the organization of the GMP inspectorate, including details of any governing board, its constitution, terms of reference and rules of procedure (see section 5.2(b));

- (e) the names, qualifications, experience and terms of reference of the senior staff and other GMP inspection personnel, both internal and external (see sections 6 and 10);
- (f) details of training arrangements for inspection personnel (see sections 6 and 10);
- (g) an organizational chart showing the responsibility and reporting structure of the inspectorate and the allocation of functions stemming from the person in charge of the GMP inspectorate (see section 5.2(b));
- (h) details of the documented procedures for inspecting manufacturers under the WHO guidelines on GMP and/or the national GMP guidelines (see section 8);
- (i) details of the documented procedures for recommendations to the authorization holder for the issue, suspension or revocation of marketing authorizations (see sections 7.2 and 8.1);
- (j) a list of any subcontractors used for GMP inspections and details of the documented procedures for assessing and monitoring their competence (see section 6);
- (k) details of appeals procedures (see section 14);
- (l) a procedure for ensuring that complaints made to the GMP inspectorate are investigated so that any shortcomings of the authorization holders are revealed (see section 16);
- (m) a list of those staff members responsible for investigating complaints and those with the authority to take remedial action (see section 16);
- (n) details of internal quality audits (see section 15);
- (o) details of testing of samples (see sections 9.6–9.8);
- (p) the control of non-conforming products (see section 9.6).

Recommended procedure

In order to keep the quality manual brief, reference may be made to other documents and/or procedures contained in other manuals.

12. Confidentiality

12.1 The GMP inspectorate should have adequate arrangements to ensure confidentiality of the information obtained in the course of its inspection activities at all levels of its organization, including committees.

12.2 The exchange of inspection reports between countries should be described. The format and content of reports should be specified.

Recommended procedure

The quality manual should describe how the GMP inspectorate discharges its responsibility for ensuring that all communications between itself and the companies inspected are kept confidential. The following are necessary:

- (a) instructions to personnel on confidentiality;
- (b) a written undertaking by all personnel not to divulge to third parties any information gained about any business affairs of clients;
- (c) the inclusion of provisions in all subcontracts to maintain confidentiality;
- (d) provisions to ensure the physical security of all documents and records relating to inspection activities.

13. Publications

13.1 The GMP inspectorate should produce and update, as necessary, a list of authorization holders, together with an outline of the scope of the marketing authorization issued to each manufacturer. The extent to which this list will be distributed should be specified.

13.2 An outline of the inspection and marketing authorization system should be available in published form.

13.3 Other publications, such as GMP guidelines and other guidelines and information brochures, should be available to industry and other interested parties, as appropriate.

Recommended procedure

The quality manual should list the publications issued by the authorization holder and GMP inspectorate. The following information should also be provided:

- (a) the name of the person responsible for compiling and updating each publication;
- (b) the frequency with which each publication is updated;
- (c) how the publications are distributed and to whom;
- (d) the procedure for issuing amendments.

14. Appeals

14.1 The GMP inspectorate should have procedures for the consideration of appeals against its decisions.

Recommended procedure

Appeals procedures should be established by the GMP inspectorate and should include:

- (a) the method by which an appeal may be lodged;
- (b) the method by which an impartial appeals panel, independent of the activity under review, is selected;
- (c) the names and positions of the members of the GMP inspectorate to whom appeals are referred, and the procedure for handling them;
- (d) a register of all appeals and their outcome.

15. Internal audit and periodic review

15.1 The GMP inspectorate should implement a system of planned and documented internal audits and periodic reviews of its compliance with the criteria of these guidelines.

15.2 There should be procedures for corrective and preventive action whenever faults are detected in the quality system, or in the performance of inspections and the general performance of the inspection service.

15.3 The management of the inspectorate should periodically review the quality system for its continuing suitability and effectiveness.

15.4 Inspectors should be evaluated before being allowed to perform inspections. Periodic reviews should also be undertaken to examine the performance of individual inspectors in order to ensure consistency among them, and in the operations and procedures of the GMP inspectorate.

15.5 A record of all audits and reviews should be kept and should include the findings, conclusions, recommendations and follow-up action. These records should be retained for a specified period of time.

Recommended procedure

Internal periodic review procedures should be documented. The review procedure should include internal audits by staff competent to ensure that all formulated procedures are adhered to. Based on the results of these audits, management must ensure that the GMP inspection system remains effective and that inspections conducted by different inspectors arrive at similar conclusions when the same operation is inspected under the same conditions.

Internal audit procedures should state:

- (a) the names or positions of staff members authorized to conduct internal audits;

- (b) what is to be examined and how often (a schedule for the examination of the whole organization over a given period should be drawn up);
- (c) how the audit will be conducted;
- (d) to whom the results will be reported;
- (e) who will initiate any corrective action.

Management reviews should take account of the results of internal audits and should include:

- (a) consideration of the overall operation of the GMP inspectorate;
- (b) uncovering defects or irregularities in the operation of the GMP inspection system;
- (c) ensuring that action has been taken to effectively correct defects revealed in previous reviews and audits.

Periodic audit by an experienced person or persons from another national regulatory authority is a useful means of providing an independent review of the GMP inspectorate's operations and procedures.

16. Complaints

16.1 The GMP inspectorate should have documented procedures for dealing with complaints arising from its activities.

16.2 A record should be maintained of all complaints received and the actions taken by the GMP inspectorate. These records should be retained for a specified period of time.

Recommended procedure

The GMP inspectorate should require each authorization holder to keep a record of all complaints received, as well as remedial actions relating to the manufacturing activities and products covered by the marketing authorization.

The GMP inspectorate should have a procedure for recording and investigating complaints received about its inspection activities. The procedure should include a list of those staff members responsible for investigating complaints and those with the authority to take remedial action.

17. Recalls

17.1 The GMP inspectorate should have a documented procedure for dealing with recalls and withdrawals of products from the market.

17.2 Records should be maintained of all recalls and withdrawals registered and dealt with by the inspectorate.

References

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3. *Recommendations on quality system requirements for GMP inspectorates of PIC Contracting States*. Geneva, Pharmaceutical Inspection Convention, 1994 (unpublished document PH 7/94; this document forms the basis of the publication *Recommendations on quality system requirements for pharmaceutical inspectorates*. Geneva, Pharmaceutical Inspection Convention, Pharmaceutical Inspection Co-operation Scheme (PIC/S, 2000 (PI 002-1); available from PIC/S Secretariat, 9–11 rue de Varembé, 1211 Geneva 20, Switzerland).
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6. *Quality systems — model for quality assurance in production, installation and servicing. International Standard ISO 9002*. Geneva, International Organization for Standardization, 1994.
7. *Quality systems — model for quality assurance in final inspection and test. International Standard ISO 9003*. Geneva, International Organization for Standardization, 1994.
8. *Quality management and quality system elements — guidelines. International Standard ISO 9004*. Geneva, International Organization for Standardization, 1990.
9. *General criteria for certification bodies operating quality systems certification. European Standard EN 45012*. Brussels, European Committee for Standardization, 1989 (available from CEN Central Secretariat, 36 rue de Stassart, B-1050 Brussels, Belgium).
10. Good manufacturing practices: authorized person — role, functions and training. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fifth report*. Geneva, World Health Organization, 1999, Annex 4 (WHO Technical Report Series, No. 885).

Guidance on good manufacturing practices: inspection report¹

When a site at which pharmaceutical products are manufactured is inspected, the inspector(s) responsible must draw up a report containing the items listed below. Where relevant, the appropriate section of the WHO GMP (Annex 4) is indicated.

A. Manufacturer

- (a) Name of inspected manufacturer.
- (b) Address of inspected manufacturer (including telephone, fax, email and 24-hour telephone numbers).
- (c) Address of manufacturing site if different from that given above.
- (d) Site number (e.g. site master file or number allocated by the responsible authority).
- (e) Manufacturing licence number, if applicable.
- (f) Activities.
- (g) Pharmaceutical products manufactured.
- (h) Key personnel.
- (i) Key persons met.

B. Inspection details

- (a) Date(s) of inspection(s).
- (b) Previous inspection date.
- (c) Type of inspection.
- (d) Scope of inspection.
- (e) The regulatory authority.
- (f) GMP guidelines used for assessing compliance.
- (g) For foreign inspections, state whether the national regulatory authority (NRA) of the country where the inspection took place was informed and whether it took part in the inspection.
- (h) Brief report of inspection activities undertaken.
- (i) Samples taken and results obtained.
- (j) Assessment of the site master file.
- (k) GMP-related recalls from the market of any product in the last 2 years.

C. Inspector(s)

- (a) Name(s) of inspector(s) and accompanying experts.

¹ Guidance on good manufacturing practices (GMP): inspection report. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report*. Geneva, World Health Organization, 2002, Annex 6 (WHO Technical Report Series, No. 908).

D. Introduction

- (a) Brief summary of the manufacturing activities.
- (b) Other manufacturing activities carried out on the site (e.g. manufacture of cosmetics, research and development).
- (c) Use of outside scientific, analytical, or other technical assistance in manufacture and quality control.
- (d) Brief description of the quality management system of the firm responsible for manufacture. Reference can be made to a site master file if one is available.

E. Observations

The observations made during the inspection that are considered to be non-compliant with GMP should be listed. Where positive observations are included in the report, clear distinction should be made between “positive” and “non-compliant”. Non-compliant observations can be classified, e.g. as “critical”, “major” and “minor” if the Member State concerned has defined these terms. The date by which corrective action and completion are requested in accordance with the policy of the national regulatory authority should be given.

E.1 Quality assurance (see WHO GMP, section 1)

- (a) Quality system and documented quality policy of the manufacturer, e.g. as described in the quality manual.

E.2 Organization and personnel (see WHO GMP, section 9)

- (a) Organizational chart showing the arrangements for quality assurance, including production and quality control.
- (b) Qualifications, experience and responsibilities of key personnel.
- (c) Outline of arrangements for basic and in-service training and method of keeping records.
- (d) Health requirements for personnel engaged in production.
- (e) Personnel hygiene requirements, including clothing.

E.3 Premises (see WHO GMP, section 12)

- (a) Manufacturing areas (design, location, etc.) used, e.g. for storage and manufacturing (e.g. weighing, production, packaging) and flow of personnel and material.
- (b) Special areas for the handling of highly toxic, hazardous and sensitizing materials.
- (c) Nature of construction and finishes.

- (d) Systems such as drainage, ventilation, air conditioning, and supply of steam and gas. Detailed description of critical areas with potential risks of contamination and cross-contamination.
- (e) Classification of the rooms used for the manufacture of products, including clean rooms.
- (f) Water systems.
- (g) Planned preventative maintenance programme.
- (h) Qualification of premises and systems as appropriate.

E.4 Equipment (see WHO GMP, section 13)

- (a) Design, location and adaptation of equipment used in production and control laboratories.
- (b) Planned preventative maintenance programmes for equipment and records.
- (c) Qualification and calibration, including records.

E.5 Materials (see WHO GMP, section 14)

- (a) Sourcing of materials.
- (b) Control, storage and handling of materials, including:
 - starting materials;
 - packaging materials;
 - intermediate and bulk products;
 - finished products;
 - returned and rejected materials;
 - reagents and culture media;
 - reference standards;
 - waste material.

E.6 Good practices in production (see WHO GMP, section 16)

- (a) Transport, handling and use of starting materials, packaging materials, and bulk and finished products.
- (b) Production operations and important parameters (e.g. sampling, quarantine, weighing, process operations and conditions, acceptance limits).
- (c) Validation (e.g. process).
- (d) Change control and deviation reporting.

E.7 Quality control (see WHO GMP, section 17)

- (a) Activities of quality control (including quarantine control, sampling, chemical and microbial analysis).
- (b) Organization and personnel.
- (c) Premises.

- (d) Equipment and instrumentation.
- (e) Materials.
- (f) Documentation (e.g. specifications, procedures, reports, records).

E.8 Sanitation and hygiene (see WHO GMP, section 3)

- (a) Procedures for sanitation and/or cleaning (e.g. of premises and equipment) and records.
- (b) Personal hygiene.

E.9 Validation (see WHO GMP, section 4)

- (a) Validation master plan.
- (b) Validation and qualification protocols and reports for qualification and validation (e.g. of premises, systems, equipment, process, computer, cleaning, analytical methods).
- (c) Stages of validation.
- (d) Types of validation.

E.10 Documentation (see WHO GMP, section 15)

- (a) Documentation (e.g. specifications, procedures, records, protocols, reports).
- (b) Preparation, revision and distribution of documentation.
- (c) Reports on production, quality control (including environmental control), engineering and other relevant areas.

E.11 Complaints (see WHO GMP, section 5)

- (a) Procedure, records and investigation.

E.12 Product recalls (see WHO GMP, section 6)

- (a) Procedure, records and investigation.

E.13 Contract production and analysis (see WHO GMP, section 7)

- (a) Responsibilities of contract giver.
- (b) Responsibilities of contract acceptor.
- (c) Contract (containing clearly defined responsibilities).
- (d) GMP compliance of the contract acceptor (initial assessment and continued compliance audited at regular intervals).

E.14 Self-inspection and quality audits (see WHO GMP, section 8)

- (a) Procedure, programme and compliance.
- (b) Items for self-inspection.
- (c) Self-inspection team.
- (d) Frequency of self-inspection.
- (e) Self-inspection report.
- (f) Follow-up action.
- (g) Quality audit.
- (h) Suppliers' audits.

F. Summary

Brief summary of the findings, and recommendations (where applicable).

G. Conclusions

A statement regarding the GMP status.

Name: _____ Signature: _____ Date: _____

Model certificate of good manufacturing practices¹

A model certificate of Good Manufacturing Practices (GMP) for a manufacturing site is suggested (see below). This is not part of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce but is intended to serve in situations where a specific GMP certificate is requested by importers, exporters, procurement agencies and regulatory authorities. It is suggested that the certificate should remain valid for a period of 2 years from the date of issue, but not exceeding 3 years after the inspection was carried out.

It is recommended that, where possible, GMP certificates should have, e.g. security seals, watermarks or holograms, to help prevent counterfeiting, tampering and other fraudulent activities.

Letterhead of regulatory authority

Model Certificate of Good Manufacturing Practices

This one-page certificate conforms to the format recommended by the World Health Organization (general instructions and explanatory notes attached).²

¹ Model certificate of good manufacturing practices. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report*. Geneva, World Health Organization, 2003, Annex 5 (WHO Technical Report Series, No. 908).

² This model certificate of GMP is not part of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce.

Certificate No: _____

On the basis of the inspection carried out on ____ [date] ____ we certify that the site indicated on this certificate complies with Good Manufacturing Practices for the dosage forms, categories and activities listed in Table 1.

1. Name and address of site:

2. Manufacturer's licence number:

3. Table 1:

Dosage form(s)	Category(ies)	Activity(ies)

The responsibility for the quality of the individual batches of the pharmaceutical products manufactured through this process lies with the manufacturer.

This certificate remains valid until ____ [date] ____ It becomes invalid if the activities and/or categories certified herewith are changed or if the site is no longer considered to be in compliance with GMP.

Address of certifying authority:

Name and function of responsible person:

Email: _____ Telephone no.: _____ Fax no.: _____

Signature:

Stamp and date:

Explanatory notes

- (1) This certificate, which is in the format recommended by WHO, certifies the status of the site listed in point 1 of the certificate.
- (2) The certification number should be traceable within the regulatory authority issuing the certificate.

- (3) Where the regulatory authority issues a licence for the site, this number should be specified. Record “not applicable” in cases where there is no legal framework for the issuing of a licence.
- (4) Table 1

List the dosage forms, starting materials, categories and activities. Examples are given below.

Example 1

<i>Pharmaceutical Product(s)</i> ¹	<i>Category(ies)</i>	<i>Activity(ies)</i>
<i>Dosage form(s):</i>		
Tablets	Cytotoxic	Packaging
	Hormone	Production, packaging, quality control
	Penicillin	Repackaging and labelling
Injectables	Cefalosporin	Aseptic preparation, packaging, labelling

Example 2

<i>Pharmaceutical Product(s)</i> ¹	<i>Category(ies)</i>	<i>Activity(ies)</i>
<i>Starting material(s):</i> ²		
Paracetamol	Analgesic	Synthesis, purification, packing, labelling

¹ Pharmaceutical Products: Any medicine intended for human use or veterinary product administered to food-producing animals, presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in both the exporting state and the importing state.

² Starting Materials: Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.