WHO Guide for Inspection – Pharmaceutical Manufacturers

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 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


Appendix 1. Recommended publications and documents


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

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.

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 accepter 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-inspection

9.1 Short description of the self-inspection system.
Appendix 3
Guidance for inspection when pharmaceutical products are suspected to be counterfeit, spurious or substandard

Appendix 4
Sample receipt form

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
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**
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**
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.

**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
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
- 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.

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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.
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.

References


Selected further reading


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

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(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

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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


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
Footnotes


2 Extracted (with permission and minor changes) from an unpublished document (PH 6/91) prepared for the Pharmaceutical Inspection Convention, November 1991.


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