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Annex 9
Guidelines on packaging for pharmaceutical products

Introductory note

This review of the various elements of the packaging of a pharmaceutical product is aimed at ensuring that medicines arrive safely in the hands of the patients for whom they are prescribed.

In the manufacture of pharmaceutical products, quality assurance is defined as "the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use" (*1*).

In addition, the system of quality assurance for the manufacture of pharmaceutical products should ensure that "arrangements are made for the manufacture, supply and use of the correct starting and packaging materials" (*1*).

Public opinion sometimes considers packaging to be superfluous. However, it must be emphasized that packaging preserves the stability and quality of medicinal products and protects them against all forms of spoilage and tampering.

All medicinal products need to be protected and "consequently need to be packaged in containers that conform to prescribed standards, particularly with respect to the exclusion of moisture and light and the prevention of leaching of extractable substances into the contents and of chemical interaction with the contents. . . . However, the limits of acceptability in these various respects depend, at least in part, on climatic variables. Recommendations in *The international pharmacopoeia* can only be advisory; precise quantitative standards will have to be locally determined" (*2*).

The complexity of packaging materials and the highly technological nature of medicinal products is such that manufacturers are confronted with significant problems. Interaction between packaging and such products is possible due to the combination of a multiplicity of container components and active pharmaceutical ingredients, excipients and solvents used in a variety of dosage forms.

The quality of the packaging of pharmaceutical products plays a very important role in the quality of such products. It must:

— protect against all adverse external influences that can alter the properties of the product, e.g. moisture, light, oxygen and temperature variations;
— protect against biological contamination;
— protect against physical damage;
— carry the correct information and identification of the product.

The kind of packaging and the materials used must be chosen in such a way that:

— the packaging itself does not have an adverse effect on the product (e.g. through chemical reactions, leaching of packaging materials or absorption);
— the product does not have an adverse effect on the packaging, changing its properties or affecting its protective function.

The resulting requirements must be met throughout the whole of the intended shelf-life of the product. Given the link between the quality of a pharmaceutical product and the quality of its packaging, pharmaceutical packaging materials and systems must be subject, in principle, to the same quality assurance requirements as pharmaceutical products.

The appropriate system of quality assurance for the manufacture of pharmaceutical products should therefore follow the WHO guidelines for good manufacturing practices (GMP) (*1*).

The requirements to be met by pharmaceutical packaging and packaging materials as described in compendia (pharmacopoeias) and standards (e.g. those of the International Organization for Standardization (ISO)) must be considered only as general in character. The suitability of packaging or packaging material for any particular requirements and conditions can only be ascertained through detailed packaging and stability studies on the product concerned.

Glossary

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

General

bulk product

Any product that has completed all the processing stages up to, but not including, final packaging (*1*).

containers

A container for pharmaceutical use is an article which holds or is intended to contain and protect a drug and is or may be in direct contact with it. The closure is a part of the container. The container and its closure must not interact physically or chemically with the substance within in any way that would alter its quality. The following terms include general requirements for the permeability of containers (*3*):

- *Well-closed containers* must protect the contents from extraneous matter or from loss of the substance under normal conditions of handling, shipment or storage.
- *Tightly closed containers* must protect the contents from extraneous matter, from loss of the substance, and from efflorescence, deliquescence or evaporation under normal conditions of handling, shipment or storage. If the container is intended to be opened on several occasions, it must be designed to be airtight after reclosure.
- *Hermetically closed containers* must protect the contents from extraneous matter and from loss of the substance, and be impervious to air or any other gas under normal conditions of handling, shipment or storage.

Substances and dosage forms requiring protection from light should be maintained in a *light-resistant container* that — either by reason of the inherent properties of the material of which it is composed, or because a special coating has been applied to it — shields the contents from the effects of light. Alternatively, the container may be placed inside a suitable light-resistant (opaque) covering and/or stored in a dark place (*3*).

labels

All finished drug products should be identified by labelling, as required by the national legislation, bearing at least the following information:

(a) the name of the drug product;

(b) a list of the active ingredients (if applicable, with the International Nonproprietary Names (INNs)), showing the amount of

each present, and a statement of the net contents, e.g. number of dosage units, mass or volume;

(c) the batch number assigned by the manufacturer;

(d) the expiry date in an uncoded form;

(e) any special storage conditions or handling precautions that may be necessary;

(f) the directions for use, and any warnings and precautions that may be necessary;

(g) the name and address of the manufacturer or the company or person responsible for placing the product on the market.

marketing authorization (product licence, registration certificate)
A legal document issued by the competent drug regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, information given on the label, product information and shelf-life (*1*).

materials
A term used to denote starting materials, process aids, intermediates, active pharmaceutical ingredients, packaging and labelling materials.

packaging material
Any material, including printed material, employed in the packaging of a pharmaceutical product, excluding any outer packaging used for transportation or shipment. Primary packaging materials are those that are in direct contact with the product (*1*).

packaging process
All operations, including filling and labelling, that a bulk product has to undergo in order to become a finished product (*1*).

production
All operations involved in the preparation of a pharmaceutical product, from receipt of the starting materials, through processing and packaging, to completion of the finished product (*1*).

quarantine
The status of starting or packaging materials, intermediates, or bulk or finished products isolated physically or by other effective means while a decision is awaited on their release, rejection or reprocessing (*1*).

Containers for pharmaceuticals[1]

ampoule
A container sealed by fusion and to be opened exclusively by breaking. The contents are intended for use on one occasion only.

bag
A container consisting of surfaces, whether or not with a flat bottom, made of flexible material, closed at the bottom and at the sides by sealing; the top may be closed by fusion of the material, depending on the intended use.

blister
A multi-dose container consisting of two layers, of which one is shaped to contain the individual doses. Strips are excluded.

bottle
A container with a more or less pronounced neck and usually a flat bottom.

cartridge
A container, usually cylindrical, suitable for liquid or solid pharmaceutical dosage forms; generally for use in a specially designed apparatus (e.g. a prefilled syringe).

gas cylinder
A container, usually cylindrical, suitable for compressed, liquefied or dissolved gas, fitted with a device to regulate the spontaneous outflow of gas at atmospheric pressure and room temperature.

injection needle
A hollow needle with a locking device intended for the administration of liquid pharmaceutical dosage forms.

injection syringe
A cylindrical device with a cannula-like nozzle, with or without a fixed needle and a movable piston, used for the administration, usually parenteral, of an accurately measured quantity of a liquid pharmaceutical form. The syringe may be prefilled, and can be for single-dose or multi-dose use.

[1] Based on a list of terms drawn up in response to a request from the European Commission to revise and replace the guidelines of the Committee for Proprietary Medicinal Preparations (III/3593/91).

pressurized container
A container suitable for compressed, liquefied or dissolved gas fitted with a device that, after its actuation, produces a controlled spontaneous release of the contents at atmospheric pressure and room temperature.

single-dose container
A container for single doses of solid, semi-solid or liquid preparations.

strip
A multi-dose container consisting of two layers, usually provided with perforations, suitable for containing single doses of solid or semi-solid preparations. Blisters are excluded.

tube
A container for multi-dose semi-solid pharmaceutical forms consisting of collapsible material; the contents are released via a nozzle by squeezing the package.

vial
A small container for parenteral medicinal products, with a stopper and overseal; the contents are removed after piercing the stopper. Both single-dose and multi-dose types exist.

1. Aspects of packaging

1.1 *General considerations*

Packaging may be defined as the collection of different components (e.g. bottle, vial, closure, cap, ampoule, blister) which surround the pharmaceutical product from the time of production until its use.

The aspects of packaging to be considered (*4*) include:

— the functions of packaging;
— the selection of a packaging material;
— the testing of the material selected;
— filling and assembling;
— sterilization;
— storage and stability.

Packaging materials (see section 2) include printed material employed in the packaging of a pharmaceutical product, but not any outer packaging used for transportation or shipment. Examples of the types of materials used are shown in Table 1.

A distinction must be made between primary and secondary packaging components. The primary packaging components (e.g. bottles,

Table 1
Types of raw materials used in packaging

Types of materials	Uses
Cardboard	Boxes Display units
Paper	Labels Leaflets
Glass	Ampoules Bottles Vials Syringes Cartridges
Plastic	Closures Bottles Bags Tubes Laminates with paper or foil
Metal, e.g. aluminium	Collapsible tubes Rigid cans Foils Needles Gas cylinders Pressurized containers
Rubber	Closures, including plungers

vials, closures, blisters) are in direct physical contact with the product, whereas the secondary components are not (e.g. aluminium caps, cardboard boxes). The choice of primary and/or secondary packaging materials will depend on the degree of protection required, compatibility with the contents, the filling method and cost, but also the presentation for over-the-counter (OTC) drugs and the convenience of the packaging for the user (e.g. size, weight, method of opening/reclosing (if appropriate), legibility of printing).

Containers may be referred to as primary or secondary, depending on whether they are for immediate use after production of the finished product or not. Both single-dose and multi-dose containers exist. Containers may be well-closed, tightly closed, hermetically closed or light-resistant, as defined in the glossary (*3*).

The packaging process, as defined in the glossary, is the process that a bulk material must undergo to become a finished product. The properties and attributes of the product should be as specified by the manufacturer and required by the user. The packaging process consists of the following stages:

— filling and assembling;
— sterilization in the final container, if applicable;
— placing labels on the container;
— storage at the manufacturing and shipping sites.

Packaging documentation (*1*) includes aspects related to:

— specifications and quality control, including batch records;
— labels, inks and adhesive materials (e.g. glue);
— package inserts for patients.

Apart from primary and secondary packaging, two types of special packaging are currently in use, as follows:

- *Unit-dose packaging*. This packaging guarantees safer medication by reducing medication errors; it is also more practical for the patient. It may be very useful in improving compliance with treatment and may also be useful for less stable products.
- *"Device" packaging*. Packaging with the aid of an administration device is user-friendly and also improves compliance. This type of packaging permits easier administration by means of devices such as prefilled syringes, droppers, transdermal delivery systems, pumps and aerosol sprays. Such devices ensure that the medicinal product is administered correctly and in the right amount.

1.2 *Functions of packaging*

1.2.1 *Containment*

The containment of the product is the most fundamental function of packaging for medicinal products. The design of high-quality packaging must take into account both the needs of the product and of the manufacturing and distribution system. This requires the packaging:

— not to leak, nor allow diffusion and permeation of the product;
— to be strong enough to hold the contents when subjected to normal handling;
— not to be altered by the ingredients of the formulation in its final dosage form.

1.2.2 *Protection*

The packaging must protect the product against all adverse external influences that may affect its quality or potency, such as:

— light
— moisture
— oxygen
— biological contamination
— mechanical damage.

The compatibility of the packaging with the active pharmaceutical ingredients is very important in maintaining the integrity of the product.

Stability. Information on stability is given in the guidelines for stability testing of pharmaceutical products containing well-established drug substances in conventional dosage forms (*4*).

For primary packaging, it is necessary to know the possible interactions between the container and the contents. Normally, product/component stability and compatibility are confirmed during the primary research and development stage.

While excluding the effect of external factors on the product, the packaging itself should not interact with it so as to introduce unacceptable changes. There are numerous possibilities of interactions between (primary) packaging materials and pharmaceutical products, such as:

— the release of chemicals from components of the packaging materials;
— the release of visible and/or subvisible particles;
— the absorption or adsorption of pharmaceutical components by the packaging materials;
— chemical reactions between the pharmaceutical product and the packaging materials;
— the degradation of packaging components in contact with the pharmaceutical products;
— the influence of the manufacturing process (e.g. sterilization) on the container.

The active pharmaceutical ingredients should remain within their specification limits over the shelf-life of the pharmaceutical product. The question of whether a packaging will provide the required protection for the pharmaceutical product and the required stability over a certain time period can only be answered by means of real-time stability studies. Such studies must evaluate the changes in the quality of the product, in contact with its packaging, during a period equivalent to its intended shelf-life.

In addition, packaging must meet the following requirements:

— it must preserve the physical properties of all dosage forms and protect them against damage or breakage;
— it must not alter the identity of the product;
— it must preserve the characteristic properties of the product, so that the latter complies with its specifications;

— it must protect the product against undesirable or adulterating chemical, biological or physical entities.

Storage. Packaging materials should be stored in accordance with GMP for storage areas (*1*; see Appendix 1). The characteristics of the active pharmaceutical ingredients will determine whether different packaging will be needed. For example, the packaging requirements of medicinal products kept at temperatures between 2 and 8 °C may differ from those of products intended for tropical countries or light-sensitive products. If the contents are sterile, sterility must be maintained, including that of any unused remaining product.

The shelf-life and utilization period are always determined in relation to storage conditions and the stability of the active pharmaceutical ingredient.

Normal storage conditions are defined as "storage in dry, well-ventilated premises at temperatures of 15–25 °C or, depending on climatic conditions, up to 30 °C. Extraneous odours, other indications of contamination, and intense light have to be excluded" (*5*).

1.3 *Presentation and information*

Packaging is also an essential source of information on medicinal products. Such information is provided by labels and package inserts for patients.

The information provided to the patient may include the following:

— the name of the patient;
— the identification number for dispensing records;
— the name, strength, quantity and physical description or identification of the medicinal product;
— directions for use and cautionary statements, if applicable;
— the storage instructions;
— the date of dispensing and period of use (related to the expiry date);
— the name and address of the dispenser.

1.3.1 *Labels*

Throughout manufacturing, a succession of specific outer labels are applied to the container of the medicinal product. The level of processing is indicated by the following words:

— quarantine
— storage
— distribution.

Specifications for labels for finished drug products are defined in the WHO guidelines on GMP for pharmaceutical products (*1*; see Appendix 2).

Written labels on the packaging:

- Permit the identification of each active ingredient by means of its INN, and also give the dosage form and the trade name/trademark. All information concerning the medicinal product, as required by national legislation, must be stated on the packaging.
- Preserve the stability of the medicinal product by giving advice on its storage (*4*):

  > After the stability of the product has been evaluated, one of the following recommendations as to storage conditions can be prominently indicated on the label:
  >
  > — store under normal storage conditions;
  > — store between 2 and 8 °C (under refrigeration, no freezing);
  > — store below 8 °C (under refrigeration);
  > — store between –5 and –20 °C (in a freezer);
  > — store below –18 °C (in a deep freezer).

- Permit the follow-up of a specific medicinal product by means of the batch number on the labels. It must be possible to follow the route of distribution of a product from the manufacturing process to its administration to the patient with the aim of locating and identifying products that are of potential risk (e.g. blood products, blood-derived products).
- Mask the real identity of the medicinal product in clinical studies. This is extremely important in clinical trials in determining the real efficacy of a medicinal product in blinded studies. If the identity is masked by a code, it must be possible to disclose it at any time in a medical emergency.

National legislation must be followed with regard to the information provided to the patient, as well as the record-keeping and packaging instructions.

1.3.2 *Repacking, relabelling and dispensing*

In some countries, it is common practice not to dispense drugs in the original packaging, but rather in a personalized manner to each patient. This applies especially to solid oral dosage forms, and involves the "repacking" and "relabelling" of drugs in small quantities. Different drugs may even be included in "customized" medication packages, also referred to as "patient med packs". The quantities of drugs supplied in this way are usually enough only for a short period of time,

i.e. to provide drugs for immediate use. It should be remembered, however, that data obtained in stability studies undertaken by the manufacturer are no longer valid for drugs removed from the original package.

Where repacking and relabelling are necessary, the WHO guidelines on GMP for pharmaceutical products (*1*) should be followed to avoid any mix-up or contamination of the product, which could place the patients' safety at risk.

1.3.3 *Package inserts for patients (patient information leaflets)*

Product information must help patients and other users to understand the medication. The patient package insert, together with the label, provides the patient with key information concerning the proper use of the product, potential adverse drug reactions and interactions, storage conditions and the expiry date.

In OTC medicinal products, the package insert, together with the label, may constitute the only pharmaceutical advice that the patient receives.

1.4 ***Compliance***

Packaging and labelling may help to reinforce the instructions given by the physician or the pharmacist, and improve compliance with drug therapy. In this respect, packaging becomes a compliance aid.

The design of pharmaceutical packaging should be such that the product can easily be administered in a safe manner to the patient. If the patient feels at ease with the packaging and route of administration, the design of the packaging may become a key factor in increasing compliance. This is also an important factor in clinical trials.

1.5 ***Protection of patients***

Packaging must not only increase compliance through its design, but must also protect the patient and indicate the integrity of the product. Packaging equipped with a tamper-evident device protects against incidental and accidental poisoning. To protect children, several child-resistant closures have been developed (see section 2.2.3).

1.6 ***Detection of counterfeiting***

The Forty-first World Health Assembly, after reviewing the report of the Executive Board on the implementation of WHO's revised drug strategy, requested: ". . . governments and pharmaceutical manufacturers to cooperate in the detection and prevention of the increasing

incidence of the export or smuggling of falsely labelled, spurious, counterfeited or substandard pharmaceutical preparations" (*6*).

Several documents (*2*, *6–9*) show that counterfeit pharmaceutical products are in wide circulation. In November 1985, during the WHO Conference of Experts on the Rational Use of Drugs in Nairobi, Kenya, concern was expressed regarding the extent to which counterfeit pharmaceutical products were in circulation in developing countries (*10*). In view of the importance of this issue, a text has been drafted to provide model provisions to deal with counterfeit drugs (*11*).

The design of the packaging must therefore contribute to preventing tampering with, or the counterfeiting of, certain medicinal products. Such tamper-evident containers can allow the visual inspection of the medicinal product before use, and this may serve as a first stage in detecting counterfeit drugs.

2. Packaging materials and closures

In accordance with the methods of use and administration of medicinal products, packaging materials, closures and containers vary a great deal and have to meet a wide variety of different requirements. All the routes used for systemic access have demanding requirements, which often can only be met by complex structured and formulated medicinal products. This is particularly true of the new medicinal products that are now appearing, such as those administered via transdermal delivery systems.

To ensure the efficacy of a product during its total shelf-life, pharmaceuticals must be regarded as a combination of the medicinal product itself and the packaging.

2.1 *Types of material*

Only the most commonly used packaging materials and containers are described here.

2.1.1 *Glass*

For a large number of pharmaceuticals, including medicinal products for oral and local administration, glass containers are usually the first choice (e.g. bottles for tablets, injection syringes for unit- or multi-dose administration). Different types of glass may be necessary, depending on the characteristics and the intended use of the medicinal products concerned.

Manufacturers should arrange with their suppliers to obtain the appropriate type of glass container for the intended use. Suppliers

should provide the raw and packaging materials in conformity with industrial norms. Classifications of types of glass are given in the European and United States pharmacopoeias, whereas no such classification exists in the Japanese pharmacopoeia.

Glass can be tested for light transmission and hydrolytic resistance. In the Japanese pharmacopoeia, such tests are described only for glass containers for injection, whereas in the European and United States pharmacopoeias they are given for all types of glass containers.

2.1.2 *Plastics*

Some containers are now being made of plastics; the main use is for bags for parenteral solutions. Plastic containers have several advantages compared with glass containers:

— they are unbreakable
— they are collapsible
— they are light.

The European, Japanese and United States pharmacopoeias all describe materials of the same type, but there are considerable differences in the classification and presentation.

As far as tests are concerned, the three pharmacopoeias are extremely difficult to compare. The European pharmacopoeia is the most detailed and requires tests in relation to the use and routes of administration of the medicinal product. Moreover, the same concept is extended to bulk containers for active ingredients.

2.1.3 *Metal*

Metal containers are used solely for medicinal products for non-parenteral administration. They include tubes, packs made from foil or blisters, cans, and aerosol and gas cylinders. Aluminium and stainless steel are the metals of choice for both primary and secondary packaging for medicinal products. They have certain advantages and provide excellent tamper-evident containers.

Since metal is strong, impermeable to gases and shatterproof, it is the ideal packaging material for pressurized containers.

Descriptions and tests can be found in the norms and standards of the ISO; these have been established in collaboration with manufacturers. Requirements are not given in pharmacopoeias; the suitability of a particular material for a container is normally established by conducting stability studies in which the material is in contact with the drug in question.

2.2 *Closures*

Closures used for the purpose of covering drug containers after the filling process should be as inert as possible. They should not give rise to undesired interactions between the contents and the outside environment, and should provide a complete seal. Besides their protective function, closures must also allow the easy and safe administration of the drug.

Depending on the application, closures may have to be pierced with a needle for intravenous sets. Such closures are made from elastomeric materials (rubbers), while those that cannot be pierced are generally made from plastics such as polyethylene or polypropylene.

Depending on the type of container, closures may have different shapes and sizes, e.g. stoppers for infusion or injection bottles or plungers for prefilled syringes. A special design of stopper may also be required for some pharmaceutical production processes such as lyophilization.

Closures, as primary packaging components, are of critical importance and must be carefully selected. They are an essential component of the container and, as such, an integral part of the drug preparation.

A container type which does not require a removable closure at the time of administration is usually preferred since such a container/closure system avoids, or at least minimizes, the risk of biological and other contamination as well as tampering.

For parenteral preparations, the combination of glass containers and elastomeric closures, usually secured by an aluminium cap, is widely used. Typical examples are infusion bottles, injection vials and prefilled syringes. The rubber closures used within such a system must be carefully selected in accordance with the intended purpose. Most often, improper rubber closures are the cause of incompatibility between the packaging and the drug.

2.2.1 *Rubber closures*

Rubber consists of several ingredients, one of which is elastomer. Modern rubber compounds used in packaging pharmaceuticals contain only a limited number of ingredients, which are very difficult to extract. Closures made from such materials generally do not pose any problems, and can be used in contact with a large number of drug preparations.

Rubber closures for pharmaceutical use must meet the relevant requirements of the most important pharmacopoeias (the European,

Japanese and United States pharmacopoeias). International standards have also been established (ISO 8871). It should be emphasized that the requirements of pharmacopoeias and standards must be seen as minimal requirements. The suitability of a rubber closure for a given application can only be established by means of stability studies.

2.2.2 *Caps or overseals*

Caps or overseals are used to secure the rubber closure to the container in order to maintain the integrity of the seal under normal conditions of transport, handling and storage during the intended shelf-life of the product. Such caps are usually made of aluminium and can be equipped with a plastic top to facilitate opening. Caps also provide evidence of tampering: once opened or removed they cannot be repositioned. This is especially true for caps with a plastic top.

2.2.3 *Special types of closure*

Demographic trends are causing new problems for packaging designers. Thus while child-resistant closures safeguard children against drug intoxication, opening such packaging may prove difficult for the increasing number of elderly persons in the population.

Tamper-evident closures. Tampering includes three aspects, namely altering, pilfering and falsifying the pharmaceutical product.

To prevent tragic accidents and especially malicious tampering, manufacturers try to create safe packaging and governments continue to update regulations to include new tamper-evident technology. In 1975, the United States Food and Drug Administration issued a regulatory requirement for tamper-evident packaging to be used for ophthalmic preparations, thus ensuring that such preparations remained sterile until their use (*12*). This regulation specifies that the closures must be sealed in such a manner that the contents cannot be used without destroying the seal. In 1982, a further regulation (*13*) on tamper-evident packaging for OTC human drug products described such packaging as "having an indicator or barrier to entry which, if breached or missing, can reasonably be expected to provide visible evidence to consumers that tampering has occurred".

The concept of tamper-evident packaging is also found in the "General Notice" and "Requirements" of the United States pharmacopoeia, which stipulate that all OTC drugs must comply with the tamper-evident packaging and labelling requirements of the Food and Drug Administration, unless specifically exempted. Products covered by the regulation include all OTC drugs, toothpaste and topical

dermatological products, oral cosmetic liquids, contact lens solutions and tablets.

In May 1992, the Food and Drug Administration (*14*) listed 11 technologies capable of satisfying the definition of tamper-evident packaging, while a twelfth was added for sealed cartons. The list includes film wrappers, blister packs, bubble packs, heat-shrunk bands or wrappers, paper foil or plastic packs, bottles with inner mouth seals, tape seals, breakable cap-ring systems, sealed tubes or plastic blind-end heat-sealed tubes, sealed cartons, aerosol containers and all metal and composite cans.

Child-resistant closures. Tragic accidents involving the drug intoxication of children has led to new legislation making it difficult for drug packaging to be opened by young children, while allowing adults easy access. Such packaging is designated as child-resistant.

Certain protocols for child-resistant packaging were established in the USA in 1966. In 1970, the Poison-Prevention Packaging Act was passed and placed under the jurisdiction of the Food and Drug Administration. This Act was transferred in 1973 to the Consumer Product Safety Commission, which is responsible for drugs and household substances (*15*). The use of child-resistant packaging has proved effective in reducing child mortality from intoxication by oral prescription drugs, and it is now recognized worldwide that children must be protected against such intoxication.

The ISO has published an internationally agreed standard test procedure for reclosable child-resistant packaging (*16*). In Europe several norms have been introduced, which complement the ISO standard (*17*, *18*).

The European Committee for Standardization (CEN) has defined a child-resistant package as one "which makes it difficult for young children to gain access to the contents, but which is not too difficult for adults to use properly in accordance with the requirement of this European standard" (*19*).

The three most common reclosable child-resistant types of closure are the "press–turn", the "squeeze–turn" and a combination lock.

To determine whether a packaging is child-resistant, it must be subjected to the ISO test procedure for reclosable child-resistant packaging (*14*).

Most designs that are child-resistant require two hands to open the closure. Such packaging can cause problems for elderly people, and can even lead to the deliberate purchase of drugs with packaging that

is not child-resistant; alternatively, the child-resistant closure may not be replaced on the container. An optional "elderly adult test" has been inserted in the ISO standard to deal with this problem.

3. Quality assurance aspects of packaging

3.1 *General considerations*

To ensure that patients and consumers receive high-quality drugs, the quality management system must take the following considerations into account if the required quality of packaging is to be obtained:

— the requirements of the national authorities and the relevant legislation
— the product
— the production process
— the manufacturers' internal policies (safety, marketing, etc.).

Bad packaging which is the result of deficiencies in the quality assurance system for packaging can have serious consequences, and packaging defects can create problems that may result in drug recalls. Such defects may include breakage, and problems relating to printing or inks, or errors on labels and package inserts (patient information leaflets). The use of GMP and quality control will prevent the release of a defective medicinal product.

Packaging processes and equipment need validation/qualification in the same way as any other part of processing within a pharmaceutical facility.

3.2 *Quality control*

Pharmacopoeial specifications and standards for quality control established by national drug quality control laboratories, as already mentioned, can only be regarded as general in character and must be interpreted as minimum standards. The essential part of quality control is performed by the manufacturer during the development, production, release and post-marketing surveillance of the entire medicinal product, i.e. the finished dosage form in its primary and secondary packaging. As pointed out by the WHO Expert Committee on Specifications for Pharmaceutical Preparations at its thirty-second meeting (*1*):

> Quality control is the part of GMP concerned with sampling, specifications and testing, and with the organization, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory. Quality control is not confined to laboratory operations but must be involved in all decisions concerning the quality of the product.

In the production chain, quality control for packaging contains several critical points. The basic requirements for quality control are as follows (*1*):

(a) Adequate facilities, trained personnel and approved procedures must be available for sampling, inspecting and testing starting materials, packaging materials, and intermediate, bulk and finished products, and where appropriate for monitoring environmental conditions for GMP purposes.

(b) Samples of starting materials, packaging materials, intermediate products, bulk products and finished products must be taken by methods and personnel approved of by the quality control department.

(c) Test methods must be validated.

(d) Records must be made (manually and/or by recording instruments) demonstrating that all the required sampling, inspecting and testing procedures have actually been carried out and that any deviations have been fully recorded and investigated.

(e) The finished products must contain ingredients complying with the qualitative and quantitative composition of the product described in the marketing authorization; the ingredients must be of the required purity, in their proper container, and correctly labelled.

(f) Records must be made of the results of inspecting and testing materials and intermediate, bulk and finished products against specifications; product assessment must include a review and evaluation of the relevant production documentation and an assessment of deviations from specified procedures.

. . . The quality control department as a whole will also have other duties, such as to establish, validate and implement all quality control procedures, to evaluate, maintain and store the reference standards for substances, to ensure the correct labelling of containers of materials and products, to ensure that the stability of the active pharmaceutical ingredients and products is monitored, to participate in the investigation of complaints related to the quality of the product, and to participate in the environmental monitoring. All these operations should be carried out in accordance with written procedures and, where necessary, recorded.

Tests and assays are normally carried out at room temperature (between 15 and 25°C, or up to 30°C in some climatic zones), unless otherwise indicated. *The international pharmacopoeia* gives alternative methods to be used if certain instruments are not available.

3.2.1 *Sampling*

Sampling is used to check the correctness of the label, packaging material or container reference, as well as in the acceptance of consignments, detecting adulteration of the medicinal product, obtaining a sample for retention, etc.

The sampling procedure must take into account the homogeneity and uniformity of the material so as to ensure that the sample is representative of the entire batch.

The sampling procedure should be described in a written protocol. Further details are given in "Sampling procedure for industrially manufactured pharmaceuticals" (*20*).

3.2.2 *Testing programme*

The testing programme for quality control purposes may vary from one manufacturer to another. Quality control tests are intended to check the identity of the material concerned. Complete pharmacopoeial or analogous testing may also be carried out, as may special tests, where necessary.

All written specifications for packaging materials and containers should include the nature, extent and frequency of routine tests. Routine tests vary according to the type of material and its immediate packaging, the use of the product, and the route of administration. Nevertheless, such tests usually include the following (*21*):

— visual inspection (cleanliness, defects)
— tests to identify the material
— dimensional tests
— physical tests
— chemical tests
— microbiological tests.

3.3 ***Inspection and audit***

Self-inspection is covered in Appendix 3, which is taken from Annex 1 of the thirty-second report of the Committee (*1*).

3.3.1 *Rules*

It is extremely important to control the security and quality of packaging. The requirements to be met by packaging for pharmaceutical products are more stringent than those for the packaging of food products, although many similarities exist. The goal of inspection is to ascertain the quality of the products, and especially the quality of the packaging. Items for self-inspection include documentation, storage of starting materials and finished products, validation of programmes, production and in-process controls, calibration of instruments or measurement systems, control of labels, sanitation and hygiene, recall procedures, premises (including personnel facilities), and maintenance of buildings and equipment.

Labels play an important part in the quality of packaging. Packaging and labelling errors in the manufacture of pharmaceutical products are often reported.

3.3.2 *Audits of suppliers*

Pharmaceutical manufacturers are usually audited or inspected by national or international licensing authorities; the same applies to suppliers of starting materials, active pharmaceutical ingredients, excipients and packaging materials. All suppliers of pharmaceuticals and packaging materials play an important role in the chain of quality assurance of the final medicinal product.

Further details can be found in the twenty-fifth and thirtieth reports of the Committee (*2*, *22*), and "General requirements for dosage forms" in *The international pharmacopoeia* (*3*).

4. Protection of the environment

The protection of the environment has become increasingly important in many countries in recent years. Greater attention has been paid to the disposal and recycling of waste, and legislation has been introduced in many countries.

4.1 ***Packaging waste***

Pharmaceutical packaging represents a very small percentage of waste, but its disposal can cause problems for the environment. For this reason, the Committee, at its thirty-second meeting (*1*), decided that:

> . . . Provisions should be made for the proper and safe storage of waste materials awaiting disposal. Toxic substances and flammable materials should be stored in suitably designed, separated, enclosed cupboards, as required by national legislation.
>
> . . . Waste material should not be allowed to accumulate. It should be collected in suitable receptacles for removal to collection points outside the buildings and disposed of safely and in a sanitary manner at regular and frequent intervals.

Environmental problems result from the methods used for waste disposal, and will depend on the type of packaging waste concerned. Such waste may include:

— uncontaminated waste (assimilated to domestic waste: paper, cardboard, glass, plastic);
— contaminated waste (paper, cardboard, glass, plastic), e.g. waste that has been in contact with blood, blood-derived products, radioactive products or cytotoxic products.

The method of disposal will therefore vary but should always be in accordance with national legislation. Contaminated packaging is often incinerated. The methods of disposal of uncontaminated packaging are shown in Table 2.

Table 2
Methods of disposal of uncontaminated packaging

Material	Recycling	Landfill	Incineration
Paper, cardboard	+++	++	++
Plastics	++	+	+++
Glass	+++	++	NA
Rubber	+	++	+++
Metal	+++	+	NA

+++: Highly recommended; ++: recommended; +: acceptable; NA: not applicable.

4.2 *Waste policies*

Waste is created at all stages in the production, supply and use of a pharmaceutical product. At each step, care therefore needs to be taken, either by the manufacturer or the end-user, to protect the environment.

Environmental concerns in the international community have led to certain changes in the conditions for the licensing of medicines (*23*). Thus an environmental risk assessment may have to be carried out in some cases in order to identify potential risks to the environment arising from the storage, use and disposal of medicinal products. The medicinal product as a whole may become the subject of the environmental risk assessment so that consideration has to be given not only to the active ingredient but also to the adjuvants/excipients in the formulation, and the primary and secondary packaging.

Another major environmental issue affecting certain types of pharmaceutical products concerns the chlorofluorocarbon (CFC) propellants, and the threat that they represent to the ozone layer (*24*). A European directive has been published on this subject (*25*).

In several European countries, manufacturers must dispose of their drug waste, or must pay a specialized company to do so for them, and are encouraged to salvage packaging waste. Faced with this problem, manufacturers and pharmacists have, respectively, introduced new directives and new process policies aimed at:

- *Reducing packaging.* Efforts should be made to reduce the volume and weight of packaging materials, and to eliminate packaging which is not essential for the protection of the contents of medicinal products.
- *Salvaging and recycling packaging.* The use of environmental-friendly packaging needs to be considered, i.e. recyclable or degradable packaging. (Valuable packaging materials, such as

aluminium, have been extensively recycled for many years. Recently, paper, glass and plastic materials have joined the list of recyclable packaging materials.) However, materials that have been in contact with toxic or highly potent drugs require special consideration.

- *Eliminating and incinerating packaging.* Some plastic materials cannot be recycled and are therefore incinerated. The burning of polyvinyl chloride (PVC) is controversial since, if combustion is not complete, it causes a potential increase in the levels of dioxin in the environment. Incineration can be recommended if the combustion heat produced by it can also be used for other purposes. Developing countries are often short of incinerators. This method is nevertheless regarded as the best available for the elimination of contaminated packaging.

5. Quality specifications

5.1 *Requirements in The international pharmacopoeia*

5.1.1 *Packaging materials*

Monographs for inclusion in Volume 6 of *The international pharmacopoeia* (*3*) have been proposed for glass containers and rubber closures.

5.1.2 *Requirements for dosage form containers*

Every pharmaceutical preparation must comply with the labelling requirements laid down in the WHO guidelines on GMP for pharmaceutical products (*1*).

Tablets. These should be kept in well-closed containers and protected from light, moisture, crushing and mechanical shock. Any special storage conditions should be stated on the label. Tablets should be able to withstand handling, including packaging and transportation, without losing their integrity. Moisture-sensitive forms, such as effervescent tablets, should be stored in tightly closed containers or moisture-proof packs, and may require the use of separate packages containing water-adsorbent agents, such as silica gel.

Additional special recommendations for packaging, storage and transportation are specified in the relevant individual monographs.

For effervescent tablets, the label should state “Not to be swallowed directly”.

Capsules. These should be packaged and stored in a manner that protects them from microbial contamination. Capsules should be kept in well-closed containers. They should be protected from light, excessive moisture, or dryness, and should not be subjected to temperatures above 30 °C.

Additional special recommendations for packaging, storage and transportation are specified in the relevant individual monographs.

Parenteral preparations. These are usually supplied in glass ampoules, bottles or vials, plastic bottles or bags, and prefilled syringes, which are coloured in the case of light-sensitive substances.

Except where otherwise indicated in the relevant individual monographs, the containers for parenteral preparations should be made from a material that is sufficiently transparent to permit the visual inspection of the contents. They should not adversely affect the quality of the preparation, allow diffusion of any kind into or across the container, or release foreign substances into the preparation.

Closures for containers for parenteral preparations should be equipped with a firm seal to prevent the entry of microorganisms and other contaminants while permitting the withdrawal of a part or the whole of the contents without removal of the closure. They should not be made of materials that react with the contents, nor should they allow foreign substances to diffuse into the preparation. The elastomers of which the closure is made should be sufficiently firm to allow the passage of a needle with the least possible shedding of particles. Closures for multi-dose containers should be sufficiently elastic to allow the puncture to reseal when the needle is withdrawn and thus protect the contents from airborne contamination. A tamper-evident container is fitted with a device that reveals clearly whether it has ever been opened.

On visual inspection, solutions, reconstituted solutions and intravenous infusions (except dispersions) should be clear and free from visible particulate matter.

Topical semi-solid dosage forms. Containers for these dosage forms should be made from a material that does not adversely affect the quality of the preparation or allow diffusion of any kind into or across the container into the preparation. Closures for these containers should be of a design that minimizes microbial contamination and be equipped with a device that reveals whether the container has ever been opened.

Containers for topical semi-solid dosage forms should protect the preparation from light, moisture, and damage during handling and transportation. The use of suitable metal or plastic flexible tubes is preferred. Preparations for nasal, aural, vaginal or rectal use should be supplied in containers adapted for the appropriate delivery of the product to the site of application, or should be supplied with a suitable applicator.

Topical semi-solid dosage forms should be kept in well-closed containers. The preparation should maintain its pharmaceutical integrity throughout the shelf-life when stored at the temperature indicated on the label; this should normally not exceed 25 °C. Special storage recommendations or limitations are indicated in the relevant individual monographs.

5.2 *Pharmacopoeial requirements for containers in Europe, Japan and the USA*

5.2.1 *Glass containers*

As previously mentioned in section 2.1.1, a classification of types of glass for containers for pharmaceutical products does not exist in the Japanese pharmacopoeia, while those given in the European and United States pharmacopoeias are very similar.

Both the European and United States pharmacopoeias provide specifications for glass containers for injections. The latter publication also gives specific guidance for the packaging, repackaging and dispensing of medicinal products. Both the European and United States pharmacopoeias also provide specifications for light-resistant containers and tightly or well-closed closures for capsules and tablets.

The European pharmacopoeia gives a general account of the requirements for glass containers for pharmaceutical use, together with those specifically applicable to glass containers for human blood and blood products.

5.2.2 *Plastic containers*

Many different plastics are used for containers for medicinal products and the requirements applicable to them differ greatly in the various pharmacopoeias. It is very difficult to compare the tests described. Other and possibly different requirements may be found in international standards.

5.2.3 *Rubber closures*

A comparison of the requirements for rubber closures is as difficult as that for plastic containers. The European and Japanese pharmacopoeias contain special requirements for rubber closures intended for containers of aqueous parenteral preparations. The United States pharmacopoeia describes more generally the use of closures made from elastomers for injection bottles, but does not specify the preparations for which they can be used.

Similarities exist between the tests given in the European, Japanese and United States pharmacopoeias, but international standards also exist which differ considerably from one another.

5.3 *International Standards*

A list of recent International Standards on packaging is given in Appendix 4.

References

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).
2. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirtieth report.* Geneva, World Health Organization, 1987 (WHO Technical Report Series, No. 748).
3. *The international pharmacopoeia*, 3rd ed. *Vol. 4. Tests, methods, and general requirements. Quality specifications for pharmaceutical substances, excipients, and dosage forms.* Geneva, World Health Organization, 1994.
4. Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report.* Geneva, World Health Organization, 1996, Annex 5 (WHO Technical Report Series, No. 863).
5. Stability of drug dosage forms. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-first report.* Geneva, World Health Organization, 1990, Annex 1 (WHO Technical Report Series, No. 790).
6. WHA41.16. In: *Handbook of resolutions and decisions of the World Health Assembly and the Executive Board, Volume III*, 3rd ed. (1985–1992). Geneva, World Health Organization, 1993:89.
7. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-first report.* Geneva, World Health Organization, 1990 (WHO Technical Report Series, No. 790).
8. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report.* Geneva, World Health Organization, 1996 (WHO Technical Report Series, No. 863).
9. *Report of the international workshop on counterfeit drugs, Geneva, 26–28 November 1997*. Geneva, World Health Organization, 1998 (unpublished document WHO/DRS/CFD/98.1; available from Essential Drugs and Medicines Policy, World Health Organization, 1211 Geneva 27, Switzerland).
10. *The rational use of drugs: report of the Conference of Experts, Nairobi, 25–29 November 1985*. Geneva, World Health Organization, 1987.
11. *Counterfeit drugs: guidelines for the development of measures to combat counterfeit drugs*. Geneva, World Health Organization, 1999 (unpublished document WHO/EDM/QSM/99.1; available from Essential Drugs and Medicines Policy, World Health Organization, 1211 Geneva 27, Switzerland).
12. Department of Health and Human Services, Food and Drug Administration. Section 200.50. Ophthalmic preparations and dispensers. In: *U.S. Code of*

Federal Regulations. Title 21. Food and drugs. Vol. 4. Parts 200 to 299. Washington, DC, United States Government Printing Office, 2000:6–7.

13. Department of Health and Human Services, Food and Drug Administration. Section 211.132. Tamper-evident packaging requirements for over-the-counter (OTC) human drug products. In: *U.S. Code of Federal Regulations. Title 21. Food and drugs. Vol. 4. Parts 200 to 299*. Washington, DC, United States Government Printing Office, 2000:125–126.
14. Department of Health and Human Services, Food and Drug Administration. *Tamper-resistant packaging requirements for certain over-the-counter (OTC) human drug products*. Washington, DC, United States Government Printing Office, 1992 (FDA Compliance Policy Guide, 7132a.17).
15. Department of Health and Human Services, Food and Drug Administration. Part 1700. Poison-Prevention Act of 1970 Regulations. In: *U.S. Code of Federal Regulations. Title 16. Commercial practices. Chapter 2. Consumer Product Safety Commission*. Washington, DC, United States Government Printing Office, 1999:690–705.
16. *Child-resistant packaging — requirements and testing procedures for reclosable packages. International Standard ISO 8317*. Geneva, International Organization for Standardization, 1989.
17. *Specifications for packagings resistant to opening by children. British Standard BS 6652*. London, British Standards Institution, 1985.
18. *Packaging — child-resistant packages — requirements, testing procedures, non-reclosable packages for pharmaceutical products. DIN 55559*. Berlin, German Standardization Institute, 1998.
19. *Packaging — child-resistant packaging — requirements and testing procedures for non-reclosable packages for pharmaceutical products. European Protocol prEN862*. Brussels, European Committee for Standardization, 2000.
20. Sampling procedure for industrially manufactured pharmaceuticals. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-first report*. Geneva, World Health Organization, 1990, Annex 2 (WHO Technical Report Series, No. 790).
21. Plastic primary packaging materials. In: *The rules governing medicinal products in the European Union. Vol. 3. Guidelines on the quality, safety and efficacy of medicinal products for human use*. Brussels, European Commission, 1998:75–82.
22. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Twenty-fifth report*. Geneva, World Health Organization, 1975 (WHO Technical Report Series, No. 567).
23. Council Directive 93/39/EEC of 14 June 1993 amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC in respect of medicinal products. *Official Journal of the European Communities*, 1993, 214:22–30.
24. Matters relating to the replacement of CFCs in medicinal products (3BR2a). In: *The rules governing medicinal products in the European Union. Vol. 3B. Safety, environment and information*. Brussels, European Commission, 1998.
25. *Assessment of potential risk to the environment posed by medicinal products. European Directive No. 5504/94*. London, Medicines Control Agency, 1994.

Bibliography

Good manufacturing practices

Department of Health and Human Services, Food and Drug Administration. Part 210. Current good manufacturing practice in manufacturing, processing, packing, or holding of drugs; general. In: *U.S. Code of Federal Regulations. Title* 21. *Food and drugs. Vol. 4. Parts 200 to 299*. Washington, DC, United States Government Printing Office, 2000:113.

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).

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).

Guidelines for good clinical practice (GCP) for trials on pharmaceutical products. In: *WHO Expert Committee on the Use of Essential Drugs. Sixth report*. Geneva, World Health Organization, 1995, Annex 3 (WHO Technical Report Series, No. 850).

Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Vol. 1. Geneva, World Health Organization, 1997.

Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Vol. 2. Good manufacturing practices and inspection. Geneva, World Health Organization, 1999.

The rules governing medicinal products in the European Union. Vol. IV. Good manufacturing practices: medicinal products for human and veterinary use. Brussels, European Commission, 1998.

Regulations for buildings and facilities of pharmacies and manufacturing plants of drugs, medical devices, quasi-drugs and cosmetics. (MHW Ordinance No. 2, dated 1 February 1961; amended by MHW Ordinance No. 54, dated 28 March 2001.) Tokyo, Ministry of Health, Labour and Welfare, 2001.

Regulations for manufacturing control and quality control of drugs and quasi-drugs. (MHW Ordinance No. 3, dated 27 January 1994; amended by MHW Ordinance No. 16, dated 12 March 1999.) Tokyo, Ministry of Health and Welfare, 1999.

Pharmacopoeias

European pharmacopoeia, 3rd ed. Strasbourg, Council of Europe, 1997; Supplements 1998, 1999.

The international pharmacopoeia, 3rd ed. *Vol. 4. Tests, methods and general requirements. Quality specifications for pharmaceutical substances, excipients, and dosage forms*. Geneva, World Health Organization, 1994.

The Japanese pharmacopoeia, 13th ed. Tokyo, Ministry of Health and Welfare, 1996; Supplement 1, 1998.

The United States pharmacopeia, 23rd ed. Rockville, MD, The United States Pharmacopeial Convention, 1995; Supplements 1–9, 1995–1998.

Guidelines and documents

Guideline for submitting documentation for packaging for human drugs and biologics. Washington, DC, Center for Drug Evaluation and Research, Food and Drug Administration, 1987.

WHO Expert Committee on Specifications for Pharmaceutical Preparations. Twenty-sixth report. Geneva, World Health Organization, 1977 (WHO Technical Report Series, No. 614).

WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirtieth report. Geneva, World Health Organization, 1987 (WHO Technical Report Series, No. 748).

WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-first report. Geneva, World Health Organization, 1990 (WHO Technical Report Series, No. 790).

WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report. Geneva, World Health Organization, 1992 (WHO Technical Report Series, No. 823).

WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report. Geneva, World Health Organization, 1996 (WHO Technical Report Series, No. 863).

Books

Banker GS, Rhodes CT, eds. *Modern pharmaceutics*, 3rd ed. *Vol. 40. Drugs and the pharmaceutical sciences*. New York, NY, Dekker, 1996.

Cooper J. *Plastic containers for pharmaceuticals: testing and control*. Geneva, World Health Organization, 1974 (WHO Offset Publication, No. 4).

Gennaro AR, ed. *Remington's pharmaceutical sciences*, 18th ed. Easton, PA, Mack, 1990.

[Guide to packaging.] Guide de l'emballage. Paris, Usine Nouvelle (annual).

Jenkins WA, Osborn KR. *Packaging drugs and pharmaceuticals*. Buffalo, NY, Technomic, 1993.

Leonard EA. *Packaging: specifications, purchasing, and quality control*, 4th ed. New York, NY, Dekker, 1996.

Lockhart H, Paine FA. *Packaging of pharmaceuticals and healthcare products*, 1st ed. Glasgow, Blackie Academic & Professional, 1996.

Reinhardt PA, Gordon JG. *Infectious and medical waste management*. Chelsea, MI, Lewis Publishers, 1991.

Ross CF. *Packaging of pharmaceuticals*. Melton Mowbray, Institute of Packaging, 1975.

Snyder D, ed. *FDA-Speak. The Interpharm glossary of FDA acronyms and regulatory terms*. Buffalo, NY, Interpharm, 1992.

Snyder DE. *Interpharm international dictionary of biotechnology and pharmaceutical manufacturing*. Buffalo, NY, Interpharm, 1992.

Reviews and articles

Casola AR. FDA's guidelines for pharmaceutical packaging. *Pharmaceutical Engineering*, 1989, **9**:15–19.

Child-resistant containers. *Pharmaceutical Journal*, 1988, **241**:219.

Choppen DF. Packaging and labelling for patient and site compliance. *Clinical Research and Regulatory Affairs*, 1994, **11**(1):61–65.

Department of Health and Human Services, Food and Drug Administration. Section 211.132. Tamper-evident packaging requirements for over-the-counter (OTC) human drug products. In: *U.S. Code of Federal Regulations. Title 21. Food and drugs. Vol. 4. Parts 200 to 299.* Washington, DC, United States Government Printing Office, 2000:125–126.

Rodgers GB. The safety effects of child-resistant packaging for oral prescription drugs: two decades of experience. *Journal of the American Medical Association*, 1996, **275**:1661–1665.

Tighter standards for blister packs wanted. *Pharmaceutical Journal*, 1995, **255**:232.

USP Subcommittee on Packaging, Storage, and Distribution. Survey on the practice of repackaging solid oral dosage forms in blister packs. *Pharmacopeial Forum*, 1996, **22**(6):3265–3267.

Appendix 1
Storage areas[1]

1. Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products: starting and packaging materials, intermediates, bulk and finished products, products in quarantine, and released, rejected, returned or recalled products.

2. Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these should be provided, checked and monitored.

3. Receiving and dispatch bays should protect materials and products from the weather. Reception areas should be designed and equipped to allow containers of incoming materials to be cleaned if necessary before storage.

4. Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorized personnel. Any system replacing the physical quarantine should give equivalent security.

5. There should normally be a separate sampling area for starting materials. If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination.

6. Segregation should be provided for the storage of rejected, recalled or returned materials or products.

7. Highly active materials, narcotics, other dangerous drugs, and substances presenting special risks of abuse, fire or explosion should be stored in safe and secure areas.

8. Printed packaging materials are considered critical to the conformity of the pharmaceutical product to its labelling, and special attention should be paid to the safe and secure storage of these materials.

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[1] Previously published in "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).

Appendix 2

Labels[1]

1. All finished drug products should be identified by labelling, as required by the national legislation, bearing at least the following information:

(a) the name of the drug product;

(b) a list of the active ingredients (if applicable, with the International Nonproprietary Names), showing the amount of each present, and a statement of the net contents, e.g. number of dosage units, weight or volume;

(c) the batch number assigned by the manufacturer;

(d) the expiry date in an uncoded form;

(e) any special storage conditions or handling precautions that may be necessary;

(f) directions for use, and warnings and precautions that may be necessary; and

(g) the name and address of the manufacturer or the company or the person responsible for placing the product on the market.

[1] Previously published in "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).

Appendix 3
Self-inspection and quality audits[1]

1. *Principle.* The purpose of self-inspection is to evaluate the manufacturer's compliance with GMP in all aspects of production and quality control. The self-inspection programme should be designed to detect any shortcomings in the implementation of GMP and to recommend the necessary corrective actions. Self-inspections should be performed routinely, and may be, in addition, performed on special occasions, e.g. in the case of product recalls or repeated rejections, or when an inspection by the health authorities is announced. The team responsible for self-inspection should consist of personnel who can evaluate the implementation of GMP objectively; all recommendations for corrective action should be implemented. The procedure for self-inspection should be documented, and there should be an effective follow-up programme.

Items for self-inspection

2. Written instructions for self-inspection should be established to provide a minimum and uniform standard of requirements. These may include questionnaires on GMP requirements covering at least the following items:

(a) personnel
(b) premises including personnel facilities
(c) maintenance of buildings and equipment
(d) storage of starting materials and finished products
(e) equipment
(f) production and in-process controls
(g) quality control
(h) documentation
(i) sanitation and hygiene
(j) validation and revalidation programmes
(k) calibration of instruments or measurements systems
(l) recall procedures
(m) complaints management
(n) labels control
(o) results of previous self-inspections and any corrective steps taken.

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[1] Previously published in "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).

Self-inspection team

3. Management should appoint a self-inspection team from local staff who are expert in their own fields and familiar with GMP. The members of the team may be appointed from inside or outside the company.

Frequency of self-inspection

4. The frequency at which self-inspections are conducted may depend on company requirements.

Self-inspection report

5. A report should be made at the completion of a self-inspection. The report should include:

(a) self-inspection results
(b) evaluation and conclusions
(c) recommended corrective actions.

Follow-up action

6. The company management should evaluate both the self-inspection report and the corrective actions as necessary.

Quality audit

7. It may be useful to supplement self-inspections with a quality audit. A quality audit consists of 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.

Suppliers' audits

8. The quality control department should have responsibility together with other relevant departments for approving suppliers who can reliably supply starting and packaging materials that meet established specifications.

9. Before suppliers are approved and included in the specifications they should be evaluated. The evaluation should take into account a supplier's history and the nature of the materials to be supplied. If the audit is required, it should determine the supplier's ability to conform with GMP standards for active pharmaceutical ingredients.

Appendix 4
International standards on packaging

A list is given below of the standards on packaging issued by the International Organization for Standardization (ISO), as of 10 October 1998, starting with the four main standards, after which they are listed in numerical order.

Quality systems — model for quality assurance in design, development, production, installation and servicing. International Standard ISO 9001. 1994.

Quality systems — model for quality assurance in production, installation and servicing. International Standard ISO 9002. 1994.

Quality systems — model for quality assurance in final inspection and test. International Standard ISO 9003. 1994.

Quality management and quality systems elements. Part 1: *Guidelines. International Standard ISO 9004-1*. 1994.

Quality management and quality systems elements. Part 2: *Guidelines for service. International Standard ISO 9004-2*. 1994.

Quality management and quality systems elements. Part 3: *Guidelines for processed materials. International Standard ISO 9004-3*. 1994.

Quality management and quality systems elements. Part 4: *Guidelines for quality improvement. International Standard ISO 9004-4*. 1994.

Reusable all-glass or metal-and-glass syringes for medical use. Part 1: Dimensions. International Standard ISO 595-1. 1986.

Reusable all-glass or metal-and-glass syringes for medical use. Part 2: Design, performance requirements and tests. International Standard ISO 595-2. 1987.

Transfusion equipment for medical use. Part 1: Glass transfusion bottles, closures and caps. International Standard ISO 1135-1. 1987.

Plastics collapsible containers for human blood and blood components. International Standard ISO 3826. 1993.

Injection containers for injectables and accessories. Part 1: Injection vials made of glass tubing. International Standard ISO 8362-1. 1989.

Injection containers for injectables and accessories. Part 2: Closures for injection vials. International Standard ISO 8362-2. 1988.

Injection containers for injectables and accessories. Part 3: Aluminium caps for injection vials. International Standard ISO 8362-3. 1989.

Injection containers for injectables and accessories. Part 4: Injection vials made of moulded glass. International Standard ISO 8362-4. 1989.

Injection containers for injectables and accessories. Part 5: Freeze–drying closures for injection vials. International Standard ISO 8362-5. 1995.

Injection containers for injectables and accessories. Part 6: Caps made of aluminium–plastics combinations for injection vials. International Standard ISO 8362-6. 1992.

Injection containers for injectables and accessories. Part 7: Injection caps made of aluminium–plastics combinations without overlapping plastics part. International Standard ISO 8362-7. 1995.

Infusion equipment for medical use. Part 4: Infusion sets for single use, gravity feed. International Standard ISO 8536-4. 1998.

Infusion equipment for medical use. Part 5: Burette-type infusion sets. International Standard ISO 8536-5. 1992.

Infusion equipment for medical use. Part 6: Freeze–drying closures for infusion bottles. International Standard ISO 8536-6. 1995.

Infusion equipment for medical use. Part 7: Caps made of aluminium–plastics combinations for infusion bottles. International Standard ISO 8536-7. 1992.

Sterile single-use syringes, with or without needle, for insulin. International Standard ISO 8537. 1991.

Elastomeric parts for aqueous parenteral preparations. International Standard ISO 8871. 1990.

Aluminium caps for transfusion, infusion and injection bottles — general requirements and test methods. International Standard ISO 8872. 1988.

Injection equipment for medical use. Part 1: Ampoules for injectables. International Standard ISO 9187-1. 2000.

Injection equipment for medical use. Part 2: One-point-cut (OPC) ampoules. International Standard ISO 9187-2. 1993.

Dental cartridge syringes. International Standard ISO 9997. 1999.

Caps made of aluminium–plastics combinations for infusion bottles and injection vials — requirements and test methods. International Standard ISO 10985. 1999.

Prefilled syringes. Part 1: Glass cylinders for dental local anaesthetic cartridges. International Standard ISO 11040-1. 1992.

Prefilled syringes. Part 2: Plungers and discs for dental local anaesthetic cartridges. International Standard ISO 11040-2. 1994.

Prefilled syringes. Part 3: Aluminium caps for dental local anaesthetic cartridges. International Standard ISO 11040-3. 1993.

Prefilled syringes. Part 4: Glass barrels for injectables. International Standard ISO 11040-4. 1996.

Prefilled syringes. Part 5: Plungers for injectables. International Standard ISO 11040-5. 1996.

Containers and accessories for pharmaceutical preparations. Part 1: Drop-dispensing bottles. International Standard ISO 11418-1. 1996.

Containers and accessories for pharmaceutical preparations. Part 2: Screw-neck bottles for syrups. International Standard ISO 11418-2. 1996.

Containers and accessories for pharmaceutical preparations. Part 3: Screw-neck bottles (vials) for solid and liquid dosage forms. International Standard ISO 11418-3. 1996.

Containers and accessories for pharmaceutical preparations. Part 4: Tablet bottles. International Standard ISO 11418-4. 1996.

Containers and accessories for pharmaceutical preparations. Part 5: Dropper assemblies. International Standard ISO 11418-5. 1997.

Containers and accessories for pharmaceutical preparations. Part 7: Screw-neck vials made of glass tubing for liquid dosage forms. International Standard ISO 11418-7. 1998.

Pen-injectors for medical use. Part 1: Requirements and test methods. International Standard ISO 11608-1. 2000.

Pen-injectors for medical use. Part 2: Needles — requirements and test methods. International Standard ISO 11608-2. 2000.

Pen-injectors for medical use. Part 3: Finished cartridges — requirements and test methods. International Standard ISO 11608-3. 2000.

Pen systems. Part 1: Glass cylinders for pen-injectors for medical use. International Standard ISO 13926-1. 1998.

Pen systems. Part 2: Plungers and discs for pen-injectors for medical use. International Standard ISO 13926-2. 1999.

Disposable hanging devices for transfusion and infusion bottles — requirements and test methods. International Standard ISO 15010. 1998.