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GENERAL ASPECTS OF PACKAGING

This text on "General aspects of packaging" is the result after review of comments received upon circulation and additional specialists' advice, as recommended by the WHO Expert Committee on Specifications for Pharmaceutical Preparations.

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I. INTRODUCTORY NOTE

This text is intended to give an overview of the various elements, essentially important when packaging a pharmaceutical product, to ensure that the medicines arrive safely in the hands of the patients.

Quality Assurance is the overall concept (1),

"1.1 *Principle*. ...the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use. ..."

This includes the provisions for the manufacture of pharmaceutical products (1) to ensure that

"1.2 (d) ...arrangements are made for the manufacture, supply, and use of the correct starting and packaging materials; "

Public opinion sometimes considers packaging as being superfluous. However, it needs to be emphasized that packaging permits preservation of stability and quality, and that it protects medicinal products against all spoilage mechanisms.

For this reason, all medicinal products need to be protected (2):

"1.6 ...They 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."

The existing complexity of packaging materials and high technology of medicinal products is such that manufacturers are confronted with significant problems. An enormous potential of interaction is possible due to the combination of a multiplicity of container components with the active pharmaceutical ingredients, excipients, and solvents used for a variety of dosage forms.

The quality of the packaging of pharmaceutical products plays a very important role in the quality of the pharmaceutical product.

It must

- protect against all adverse external influences that can alter the properties of the product, e.g. moisture, light, oxygen, temperature variations,
- protect against biological contamination,
- protect against physical damage, and
- 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, absorption), and
- the product does not have an adverse effect on the packaging, changing its properties or affecting its protective function.

The related requirements must be met over 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 guideline for Good Manufacturing practice (GMP) (1).

Requirements on pharmaceutical packaging and packaging materials as described in compendia (pharmacopoeias and standards e.g. International Standards Organisation, ISO) must be considered as general and can be interpreted as minimum requirements. The suitability of packaging or packaging material in function of the particular requirements and conditions can only be ascertained through detailed packaging development and stability studies on the product.

In this respect, a distinction must be made between primary and secondary packaging components. The primary packaging components (e.g. bottles, vials, closures, blisters) are in direct physical contact with the product, whereas the secondary components are not (e.g. aluminium cap, cardboard boxes).

The objectives of this document are mainly concerned to demonstrate the possibilities and efforts to control the problems mentioned, and to present different aspects of pharmaceutical packaging for use in Quality Assurance of pharmaceutical products.

II. GENERAL CONSIDERATIONS

The meaning of the term packaging is continually changing, and focus needs to be placed on packaging presentation including trends and issues. New packaging possibilities are steadily being developed, such as the use of plastic materials. Problems exist such as accidental wrong labels on the containers, persistent tampering, as well as competition between manufacturers concerning production costs. The real functions of packaging firstly need to be understood and its terms to be defined.

1. Definition of packaging

The concept of packaging encompasses a wide range of aspects including:

– *packaging development* (3)

- functions of packaging
- selection of packaging material
- tests for the properties of the material
- filling and assembling
- sterilization
- storage and stability

– *packaging materials:*

<i>types of raw materials</i>	<i>examples</i>
Board	carton display units
Paper	labels leaflets
Glass	ampoules bottles vials syringes
Plastic	closure bottles tubes laminates with paper or foil
Metal	collapsible tubes rigid cans foils

<i>types of container</i>
primary (immediate)/secondary
single dose container
multi-dose container

<i>types of closure</i>
well-closed
tightly closed
hermetically closed

– *packaging process:*

filling and assembling
sterilization in its final container
placing labels on the container
storage at the manufacturing and shipping sites
distribution and storage facilities at the wholesaler, hospital or pharmacy

– *packaging documentation:*

specification, quality assurance, quality control
labels, inks, adhesive materials (e.g. glue)
patient package inserts.

Packaging and its related terms have been defined in WHO publications as follows:

– *packaging (4)*

"All operations, including filling and labelling, that a bulk product has to undergo in order to become a finished product. Sterile filling would not normally be regarded as part of packaging, the bulk product being the filled, but not the finally packaged, primary container."

– *packaging material (4)*

"Any material, including printed material, employed in the packaging of a pharmaceutical product, excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product."

– *containers (5)*

" (a) The container and its closure must not interact physically or chemically with the substance within in any way that would alter its quality."

In the context of this document the terms have been used as follows:

Packaging

The collection of different components (e.g. bottle, vial, closure, cap, ampoule, blister) which surround the pharmaceutical product from the moment of production until its use.

Packaging component

Any material, including printed material, employed in the packaging of a pharmaceutical product, but excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are in direct contact with the product.

Packaging materials

The materials used for the manufacture of packaging components, e.g. glass, rubber, aluminium, plastic and cardboard.

Packaging process

The process a bulk material must undergo to become a finished product. The properties and attributes should be as specified by the manufacturer and required by the user.

2. Functions and general aspect of packaging

Packaging of medicinal products is an important issue and public opinion needs to be guided to recognize its functions.

The choice of containers in any type of material depends on the degree of protection required, its compatibility with its contents, the filling method, cost, but also the presentation (for OTC) and patient convenience (size, weight, opening, reclosing, legibility of printing).

2.1 Drug containment

Means to contain the product is the most fundamental function of medicinal products packaging. Quality packaging must incorporate in its design the needs of the product, the manufacturing and the distribution system. This requires the packaging:

- not to leak,
- to be strong enough to hold the contents with normal handling,
- not to be altered by the ingredients of the formulation in its final dosage form.

2.2 Protection of pharmaceuticals

The packaging must protect the product against:

- physical damage
- loss of contents or ingredients
- intrusion of unwanted components of the environment (e.g. water-vapour, oxygen, dirt, light, etc.)

The type of container is sometimes a matter of choice and can also depend on factors such as:

- degree of protection required
- compatibility with the active pharmaceutical ingredient

The second function is very important in order to maintain the standards of the active pharmaceutical ingredient.

2.2.1 Stability

Details on stability are described in the "Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms." (3)

For proper packaging it is necessary to know the real relation between container and content. Normally, product/component stability and compatibility must be confirmed during the primary research and development investigations.

Some interactions may be caused by the combination of the multiplicity of container components and the active pharmaceutical ingredients (*example*: adsorption: glass - proteins, release of particles).

Since these interactions can alter the stability of medicinal products, justification of the choice of container is essential. Choice should be given in relation to data on stability of the active pharmaceutical ingredient and the finished product. Scientific data collected during development such as information, uniformity of the material used for packaging and studies of interaction, should be evaluated to justify the choice of the container. Further considerations are:

- tightness of the closure,
- protection of the contents against external factors,
- container/contents interactions,
- influence of the manufacturing process on the container (i.e. sterilization conditions).

Packaging should not alter the formulation of the medicinal product. The specifications of the active pharmaceutical ingredients should remain over the shelf-life within the period established to ensure identity, quality and purity. Neither the packaging material nor the medicinal product should show signs of absorption or adsorption.

Physical aspect

Packaging must preserve the physical properties of solid dosage forms, such as tablets, and it must protect them against damage or breakage.

Identity

Packaging must remain unaltered.

Quality

Packaging must preserve the characteristic properties of the medicinal product, to comply with its specifications.

Purity

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

2.2.2 Storage

Packaging materials should be chosen in such a way as to maintain good storage conditions (6) (see Appendix 1). According to the characteristics of the active pharmaceutical ingredient, packaging will be different for medicinal products kept under refrigeration at 4 °C and for those intended for tropical countries (examples: a light-sensitive product needs a light-resistant container. If the contents are sterile, sterility must be maintained, including that of the unused remaining product).

Shelf-life is always determined in relation to storage conditions and stability of the active pharmaceutical ingredient.

Normal storage conditions are defined as (7)

"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."

2.3 Presentation and information

Packaging is a physical support to vehicle information of the medicinal product. The evolution of occurrence of diseases represents a larger consumption of medicinal products, which in turn brings more packaging into the hands of the consumers.

Two tools help to identify a medicinal product: labels and package inserts for patients.

Throughout manufacturing a succession of specific outer labels are applied to the container of the medicinal product. They distinguish the level of processing with the following texts:

- quarantine
- storage
- distribution

Specifications for labels (8) exclusively written on the packaging are defined in WHO GMP (*see Appendix 2*).

2.3.1 Labels

Written labels on the packaging:

- *permit individualization of the product* for each active ingredient by the International Nonproprietary Name (INN), the dosage form, and also the trade name. All information concerning the medicinal product as required by national regulation must be stated on the packaging;
- *preserve stability* in giving some advice on the storage of the medicinal product (9);

" 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)."

- *mask the real identity*. This function is extremely important for clinical trials for the determination of the real efficacy where it is recommended to work with blind tests. If the identity is masked by a code system, it must be possible to disclose the identity at any time in case of a medical urgency.
- *permit follow up a specific medicinal product* by the batch number on several labels. It must be possible to follow the route of distribution of a product from the manufacturing process to its administration to the patient. The aim is to avoid potential contamination if a potential risk is discovered (*examples*: blood products, blood-derived products).

2.3.2 Patient package inserts (leaflets)

Information to the patient. Product information must help patients and other users understand medication. The packaging can provide a way to dispense the contents, either into another container or for direct administration (e.g. oral, parenteral). Labels on the container together with the patient package inserts provide the patient with key information concerning adverse drug reaction, possible drug dependence, or potential interaction, and storage conditions.

Advice for the patient. It is to be noted that the package inserts together with the label may be the only pharmaceutical advice to the patient in OTC medicinal products.

2.4 Patient Compliance

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

A well-designed packaging which is relevant to the needs of endusers and patients is a prime requirement. Shape and form are important and the medicinal product should be easily accessible, using easy-to-open and reclose containers. If the patient is satisfied with the packaging and administration route, the design of the packaging becomes a key to increase compliance (*example:* in clinical trials, where compliance is extremely important).

2.5 Patient protection

Packaging must not only increase compliance through its design, but must also protect the patient. Packaging equipped with a tamper-resistant device protects the patient against poisoning and accidents. To protect children, several child resistant devices have been developed.

2.6 Packaging and counterfeit drugs

The Forty-first World Health Assembly recalled resolutions WHA37.33 and WHA39.27 on the rational use of drugs, and reviewed the report of the Executive Board on the implementation of WHO's revised drug strategy. It requests: (10)

"4.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."

Several documents (11, 12, 13, 14, 15) demonstrated that counterfeit pharmaceutical products are widely in circulation. In November 1985 during the WHO Conference of Experts on the Rational Use of Drugs in Nairobi, concern was expressed regarding the extent to which counterfeit pharmaceutical products were in circulation in developing countries. Realizing the importance of this issue, a preliminary text was drafted to provide model legislative provisions to deal with counterfeit drugs.

The design of the packaging must therefore contribute to prevention of tampering/counterfeiting of certain products. Such tamper-resistant containers can allow testing of the medicinal product by visual inspection before use.

2.7 Protection of environment

The protection of the environment has been more observed in many countries over the past years. The disposal and recycling of waste has been subject to more attention and legislative measures have been taken in many countries.

2.7.1 Packaging waste

Pharmaceutical packaging represent a very small percentage of waste, although their disposal can cause problems for the environment (16).

13.38 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.

13.39 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 originate to the practices used for the waste disposal. The issues are different in relation to the type of packaging waste, such as:

- non-contaminated waste (assimilated to domestic waste: paper, carton, glass, plastic)
- contaminated waste (paper, carton, glass, plastic) for example those in contact with:
 - blood, blood-derived products,
 - radioactive products,
 - cytotoxic products.

The type of elimination will by consequence be of different nature. In industrialized countries, contaminated packaging is mostly incinerated, but also discarded in dumps.

Non-contaminated packaging is usually eliminated in different ways in relation to type of waste.

	recycling	dump	incineration
paper, carton	+++	++	++
plastic	++	+	+++
glass	+++	++	+
foil, rubber	+	++	+++

(+++ best way of elimination ++ still recommendable + also possible)

2.7.2 Waste policies

The responsibility lies on the manufacturer to manage their packaging waste (16). Manufacturers have the obligation to avoid environmental pollution and contamination, such as AIDS or hepatitis (e.g. pricking by used syringes).

In certain countries, in which environmental issues are important, such as limitation of dump capacity, new political directives and new legislation are progressively being developed. Environmental concerns in the international community have led to the introduction of some changes to the licensing of medicines (*example: Directive of the European Community, Article 4.6, 65/65/EEC as amended by Article 1 (3) 93/39/EEC (27)*). The concept of safety is extended by requiring an Environmental Risk Assessment (ERA) to be carried out in some cases. The ERA is intended to identify

potential risks to the environment arising from storage, use and disposal of medicinal products. The medicinal product as a whole becomes the subject of the ERA as a result of this legislation, i.e. consideration has to be given not only to the active ingredient but also to the adjuvants/excipients in the formulation, the primary and secondary packaging.

Another major environmental issue which has an impact on certain types of pharmaceutical products concerns the chlorofluorocarbon (CFC) propellants, and the threat they represent to the ozone layer. A proposal for a European Council Directive on packaging and packaging waste has been published in the *Official Journal of the European Communities No. C.293 of 12.10.92 syn. 436* (see also *Medicines Control Agency - Euro Directive No. 5504/94 "Assessment of potential risk to the environment posed by medicinal products"*).

In several European countries, manufacturers must eliminate their waste, or must pay a specialized company to eliminate drug waste, and are encouraged to salvage packaging waste. Faced with this legislation, manufacturers and pharmacists have introduced new directives or new process policies, such as

reduce packaging. Packagers must pay attention to reduce the volume and weight of packaging materials, and eliminate packaging which are not essential to the protection of the contents.

salvage, recycle packaging. Packagers must be aware of the "green packaging" movement and anticipate in its growing importance. New packaging that integrates environmental precautions need to be considered, i.e. recyclable, or degradable packaging. (Valuable packaging materials, such as aluminium are extensively recycled since many years. Recently, paper, glass and plastic materials have joined the list of recyclable packaging materials.)

eliminate and incinerate packaging. Some plastic materials cannot be recycled and they are incinerated. The burning of polyvinyl chloride (PVC) is controversial since it causes, in case of insufficient combustion, a potential increase in the levels of dioxin. The technique can be recommended if the combustion heat produced from incineration can be further used. Developing countries are often short of incinerator. This method is still regarded as the best solution for the elimination of contaminated packaging.

3. Suited functions in relation to the use and administration routes

The evolution of technologies needs to be followed in relation to new trends: new innovative medicines, patients, and also the ageing of patients. Sophisticated packaging and containers for medicinal products are now appearing, which are more adapted to the patient, e.g. inhalers, nebulizers, transdermal delivery systems.

According to the use and administration, packaging materials for medicinal products, closures and containers vary a great deal and their requirements are extremely different. All routes used for systemic access have demanding requirements which often can only be fulfilled by complex structured and formulated medicinal products.

3.1 Packaging materials and containers for medicinal products

To ensure product efficacy during the total shelf-life of a product, pharmaceuticals must be considered as both the medicinal product and the packaging component. Extensive requirements are needed for them to ensure stability and compatibility. Large differences are noted in the approaches and requirements used to study the impact of packaging on the final product by pharmaceutical manufactures in Europe, Japan and the United States.

The present document describes below only the most commonly used material for packaging and several types of containers according to their use.

3.1.1 Type of material

a) Glass containers

- **Non-parenteral containers.** For a large number of pharmaceuticals, including medicinal products for oral and local administration, glass containers are usually the first choice (*example:* bottles for tablets, for unit- or multidose administration). Its characteristics and the intended use may require different types of glass.

Type of Glass: Classifications exist to describe with regard to the quality of glass containers. 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. Similar classifications are specified in the European Pharmacopoeia (Ph. Eur.) and in the United States Pharmacopoeia (USP), whereas no classification exists in the Pharmacopoeia of Japan (JP).

Tests: Two attributes are commonly tested for in JP, Ph. Eur. and USP¹ : light transmission and resistance. In JP, these tests are only performed for glass containers for injection, whereas in Ph. Eur. and USP they are performed for all glass containers.

- Parenteral containers

The three pharmacopoeias, JP, Ph. Eur. and USP have a common requirement of special labelling.

Tests in JP concern solely glass containers for injection. Normal glass containers and containers for injection are distinguished in Ph. Eur. and USP, and tests are generally more complex.

b) Plastic containers

- Non-parenteral containers

The dominant use of plastics in packaging results from several advantages:

Type of plastic: JP, Ph. Eur., and USP describe the same type of materials but the classification and presentation vary considerably.

¹ Monograph in preparation for *The International Pharmacopoeia*.

Tests: The three pharmacopoeias are extremely difficult to compare. Ph. Eur. is more detailed and adopts tests in relation to the use and routes of administration. Moreover, the same concept is extended to bulk containers for active ingredients.

- **Parenteral containers**

The type of containers found are ampoules, vials, bottles, cartridges, bags and prefilled syringes.

The tests in JP, Ph. Eur. and USP are again difficult to compare.

c) **Metal containers**

- **Non-parenteral containers**

Metal containers are solely used for medicinal products for non-parenteral administration, such as tubes, packs made from foil or blisters, cans, aerosol and also gas cylinders. Aluminium is the only metal used in primary packaging. As secondary packaging materials for medicinal products metals are less frequently used. It can present some advantages providing excellent tamper evidence for containers.

Neither pharmacopoeias nor GMP requirements give any descriptions and tests. References may be found in norms or standards established by manufacturers.

- **Pressurised containers**

The properties of metal being strong, impermeable to gases and shatter-proof, represent ideal qualities as packaging material for aerosol containers.

3.1.2 **Types of packaging**

Packaging trends for medicinal products are important to be understood, since they influence responsible persons producing the packaging material. In addition to basic requirements, issues need to be addressed, such as the protection of medicinal products. Major trends influencing packaging are as follows:

a) **"Normal" type**

Two kinds of packaging are distinguished, the most important being the primary packaging which is directly in contact with the product, and the secondary having no contact with the product.

b) **Unit-dose packaging**

This packaging guarantees a safer medication reducing medication errors and is more practical for the patient. It may become very useful to increase treatment adherence. For less stable products it may also serve as being very useful.

c) **Device packaging**

Packaging with the aid of an administration device is user-friendly and also improves compliance. This type of packaging permits easier administration using devices such as droppers, transdermal delivery system, or pump and aerosol sprays. Devices allow correct administration of the medicinal product and in the right amount.

3.2 **Closures¹**

Containers for medicinal products must be suitably closed after the filling procedure to avoid unacceptable alterations of the content during its storage before administration. Containers with one or more open ends should have closure(s) that are as inert as possible: it should avoid undesired interaction between the content and the outside environment (no noticeable desorption, absorption and permeation processes). Besides their protective functions, closures must also guarantee an easy and safe administration of the product in accordance with the functional characteristics, which are specific to the type of closure, selected for the intended application.

Various types of closures are currently in use, often manufactured from polyolefinic and elastomeric materials. Closures depend on the design of the container, the type of medicinal product, and the way of its predetermined administration. Closures are critical packaging elements and must be thoroughly selected; they are an essential component of the container and as such an integral part of the medicinal product. In the development and utilisation of a container type, preference is usually given by packaging technologists, to one not requiring a removable closure at the time of administration. The use of such a container/closure system would avoid, or at least minimize, the risk of biological recontamination and the generation of particulate matter.

For parenteral preparations, the combination of glass containers and elastomeric closures, mostly secured by an aluminium cap, is a widely used system (*typical examples*: infusion bottles, injection vials, prefilled syringes). The rubber sealing elements used within such a system must be carefully selected in accordance with the intended purpose. They require regular inspection for consistency of their dimensional, chemical and functional characteristics. This is an absolute prerequisite, because elastomeric materials may be composed of a number of different ingredients and vulcanised by various chemical methods. The composition of a given formulation is considered to be a valuable production know-how, and is usually not disclosed to the pharmaceutical user. Rubber closures must therefore not only meet the pertinent compendial requirements (e.g. JP, Ph. Eur., USP) but also the corresponding ISO standard (ISO 8871). Appropriate compatibility and stability tests must also be followed.

Three degrees of tightness for closures can be distinguished, i.e. well-closed, tightly closed and hermetically closed (see *Glossary*: Definition of containers). The closure will depend on the characteristics of the medicinal products, especially its degree of hygroscopicity.

Several types of closure are usually manufactured: caps, liners, inner seals, elastomers, and for aerosols, spray pumps, valves.

¹ Monograph in preparation for *The International Pharmacopoeia*.

3.3 Special packaging

Demographic trends cause new problems for packaging designers who need to find a compromise to produce adequate packaging, e.g. the creation of child resistant closures to safeguard children against drug intoxication. However, opening such packaging may prove difficult to elderly persons.

3.3.1 Tamper-resistant closure

Tampering includes three aspects: to alter, pilfer and falsify.

To prevent tragic incidents and principally malicious tampering, manufacturers try to create safe packaging and governments continue to update regulations for new tamper evident technology. The US regulation briefly illustrates this existing problem in *21.CFR.200.50*. In 1975, the US Food and Drug Administration (FDA) established a regulatory requirement for tamper-indicating packaging to be used for ophthalmic preparations, ensuring the sterility of ophthalmic products until their use.

The Regulation specifies that the container for an ophthalmic preparation "shall be so sealed that the contents cannot be used without destroying the seal."

The US Federal Register describes in the FDA regulations 1982, the standard for a tamper-resistant packaging as "one 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." (17)

USP gives the concept of tamper-resistant packaging in the "General Notice" and "Requirements". It stipulates that all OTC products must comply with tamper-resistant packaging and labelling requirement of the US-FDA, unless specifically exempted. Products covered by the regulation are:

- all OTC products, toothpaste and topical dermatological products
- oral cosmetic liquids
- contact lens solutions and tablets.

In May 1992, the US FDA (18) presented several technologies able to satisfy the definition of tamper-resistant packaging, twelve packaging technologies including one for sealed cartons. This still leaves the packagers free to create or innovate tamper-evident packaging. This list includes: film wrappers, blisters, 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.

3.3.2 Child resistant closure

New legislation has been developed after the incidence of tragic accidents involving drug intoxication of children. This new law hinders the opening of packaging for medicinal products by young children, but still allows adults possible access. Such packaging are designated as being child resistant.

For example, in 1966 in the USA, certain protocols for child resistant packaging were established. In 1970, the *Poison-Prevention Packaging Act* was passed under the jurisdiction of the FDA. This Act was transferred in 1973 to the Consumer Product Safety Commission, which is responsible for medicinal products and household substances (19). The application of child resistant packaging proved efficacious in reducing child mortality from intoxication of medicinal products or other substances for oral application. The protection of children against intoxication from such products has now received world-wide recognition.

ISO published an internationally agreed standard test procedure (ISO Standard 8317 for reclosable child resistant packaging) and in Europe norms were established (BS 6652 Child-resistant packaging, DIN 55559 Child Proof Packaging – Requirement tests, and EC Directive 91/40 as a compliment to the ISO Standard).

The European Committee for Standardisation (CEN) proposed a definition for child resistant packaging as "a package which is 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."

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

To determinate if a packaging is child resistant, it must pass the following test procedure: *ISO 8317, 1989*, Child-resistant packaging, and *European Protocol pr EN 862*.

As an example for testing whether a packaging is child resistant, manufacturers have established test panels composed of up to 200 children aged between 20 and 42 months old, and 100 normal adults between 18 and 65 years of age (70 female, 30 male). The children work two by two under a qualified supervisor. During five minutes, each child tries to open a packaging containing a placebo. If children are unsuccessful, they receive a visual demonstration without explanation, and then can try again during further five minutes.

Adults are asked to open the packaging individually using only the given printed directions. Then they are asked to reclose it properly, if it is a reclosable packaging, also carrying out these operations in five minutes.

Pass levels require that 80% of the children should fail to open the packaging after 10 minutes, and that 90% of the adults should succeed after five minutes.

Developments in newer packaging designs have lately been accomplished. Most designs that are child resistant require two hands to open the closure. These packaging can also cause problems for elderly people, and can even lead the customer to the voluntary purchase of medicinal products with packaging that are not child resistant, or to leave the child resistant closure off the container. Following up this problem, the *US Consumer Product Safety Commission* proposed to substitute its younger adult panel with a panel of adults aged between 60 to 75 years for the testing. The ISO Standard integrated this issue with the introduction of an optional "elderly adult test" also using adults aged between 60 and 75 years.

4. Quality assurance aspects of packaging to be observed by the pharmaceutical manufacturer

4.1 General aspect of quality assurance

The required quality of good packaging is obtained by the quality assurance system put in place by the pharmaceutical manufacturer. The following considerations need to be integrated:

- patient, other users
- national authorities' requirements and legislation
- product
- production
- manufacturers' internal policies (safety, marketing, etc.)

Quality in packaging cannot simply meet the normal manufacturers' in-house marketing policies or production efficiency, but has to satisfy the product standards relevant to national or international health organizations. Packaging is therefore placed in a complex situation, and only quality assurance can manage such quality indicators. Bad packaging due to a deficient quality assurance system for packaging can cause serious consequences for the pharmaceutical manufacturer.

Example:

- packaging problems such as breakage can be the source of return, resulting in destruction or repackaging of the medicinal product. In consequence, this represents a loss in confidence.
- problems relating to printing, inks or errors on labels and leaflets, can prevent release of the batch, representing additional production time. If the batch is released in spite of such an error, consequences can be serious, such as potential problems with patients. A drug recall could have political and economical consequences.
- batches released with errors on the packaging information can create problems with the national authority. Serious measures may have to be taken such as a drug recall.

Tools are needed to limit consequences due to bad packaging, such as GMP and quality control that represent barriers for the release of a medicinal product. Improvement can be achieved through quality control, audit and inspection.

4.2 Quality control

Pharmacopoeial specifications and standards available for quality control by national drug quality control laboratories, as already mentioned, may only be regarded as general and must be interpreted as minimum standards. The essential part of quality control is performed by the manufacturer during development, production, release and post-marketing surveillance of the entire medicinal product, i.e. the finished dosage form in its primary and secondary packaging. (20)

"3.1 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 the 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 (20):

"3.2 ...

(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.

(g) ...

(h) ..."

"3.3 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."

4.2.1 Sampling

Sampling is used to check the adequacy of the label, packaging material or container reference. Sampling may be required for different purposes such as: acceptance of consignments, clearance deterioration, adulteration, or obtaining a retention sample. The sampling procedure must take account of the homogeneity and uniformity of the material.

In a sampling procedure the sample should represent the entire batch. To obtain a representative sample, manufacturers need a sampling plan which should be chosen according to the specific situation.

The procedure for sampling should be described in a written protocol.

Further details are given in "Sampling procedure for industrially manufactured pharmaceuticals. (21)

4.2.2 Tests for packaging

The testing programme performed by quality control may vary from one manufacturer to another. Different tests are distinguished those used for development, and others for routine testing. Control tests are intended to:

- (a) check the identity of the material,
- (b) perform complete pharmacopoeial or analogous testing, or
- (c) perform special tests.

All written specifications for packaging material and containers should include the nature of the test, the extent and the frequency of routine tests. Routine tests vary according to The type of material and of its immediate packaging, the use of the product, or the route of administration. Nevertheless, several items for routine tests may be considered: (22)

- identification of material (especially plastic material)
- visual inspection
- dimensional tests
- physical tests
- microbiological tests

4.3 Inspection and audit

Reference is made to the WHO GMP text for self-inspection; (23) (*see Appendix 3*).

4.3.1 Rules

It is extremely important to control the security and quality of packaging. Pharmaceutical products require more stringent packaging than food products, although many similarities exist in their requirements. The size and quantities involved for pharmaceuticals are usually smaller than with food. The goal of inspection is to ascertain the quality, especially the quality of packaging. Items required for self-inspection are documentation, storage-quarantine, programme validation, in-process

control, equipment calibration of instruments, labels control, sanitation and hygiene, recall procedure, premises, maintenance of buildings and equipment.

An important part in the quality of packaging is the label on the container. Reports often document packaging and labelling errors within pharmaceutical manufacture. It was stated (24) that during the period 1988-1992, one third of all defects in pharmaceuticals were related to packaging, and of which 40% were due to errors on the label and/or in the product information.

4.3.2 Supplier audits

Pharmaceutical manufacturers are usually audited or inspected by national or international licensing authorities; the same is true for suppliers of starting materials. Awareness must be made that all suppliers of pharmaceuticals and packaging materials play an important role in the chain of quality assurance of the final medicinal product.

Further details are found in "Quality requirements for plastic containers" (25), and "Packaging materials"(26) and "General requirements for dosage forms" (27).

III. GLOSSARY

The definitions of the terms used in this document are as follows:

1. Definitions of terms and concepts

Packaging (4) – All operations, including filling and labelling, that a bulk product has to undergo in order to become a finished product. Sterile filling would not normally be regarded as part of packaging, the bulk product being the filled, but not the finally packaged, primary container.

Packaging material (4) – Any material, including printed material, employed in the packaging of a pharmaceutical product, excluding any other packaging used for transportation or shipment; packaging materials are referred to be in direct contact with the product.

Containers (5) 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:

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.

Protection from light. 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 the container is composed, or because a special coating has been applied to the container – 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.

Information on the label (5, 8) Official national labelling requirements should be met. The label should state whether an antimicrobial preservative has been added, its name and concentration, as well as those of other substances such as buffers and colouring agents.

Further indications should be given, such as special routes of administration of a dosage form and, whenever relevant, the shelf-life, as well as expiry date and storage conditions.

Additional information (5). Precautions, special routes of administration, and the usual strengths for dosage forms¹ are given.

Tests and assays (5). Alternative methods are given to be used in cases where the required instruments are not available.

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.

Bulk product (4). Any product that has completed all processing stages up to, but not including, final packaging.

Marketing authorization (product licence, registration certificate) (4). 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, that includes details on packaging, information given on the label, product information and shelf-life.

Materials (28). The main objective of a pharmaceutical plant is to produce finished products for patients' use from a combination of materials (active, auxiliary, packaging). Special attention should be given to the materials as such.

Production (4). All operations involved of all preparations including manufacturing of a pharmaceutical product, from receipt of materials, through processing and packaging, to completion of the finished product.

Quarantine (4). 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 *The use of essential drugs. Eighth report of the WHO Expert Committee. Geneva, World Health Organization, 1982 (WHO Technical Report Series, No.882).*

2. Definitions of containers used for pharmaceuticals

A list of standard terms was drawn up in response to a request from the European Commission to revise and replace the CPMP guideline (III/ 3593/ 91) Examples of terms as defined:

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

Blister. Multidose container consisting of two layers of which one is shaped to contain the individual doses. Strips are excluded.

Bottle. Container with a more or less pronounced neck and usually a flat bottom.

Child resistant closure. A closure which is difficult for young children to open but which is not difficult for adults to open properly.

Gas cylinder. Container usually cylindrical suited 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. Hollow needle with a locking device intended for the administration of liquid pharmaceutical forms.

Injection syringe. Administration device, cylindrical, with a cannula-like nozzle, with or without a fixed needle, and a movable piston with piston rod used for the administration, usually parenteral, of an accurately measured quantity of a liquid pharmaceutical form.

Pressurised container. Container suited for compressed, liquefied or dissolved gas fitted with a device to enable, after its actuation, a controlled spontaneous release of the contents at atmospheric pressure and room temperature.

Single-dose container. Container for single doses of solid, semi-solid and liquid preparations.

Tube. Container for multi-dose semi-solid pharmaceutical forms consisting of collapsible material intended to release the contents via a nozzle by squeezing the package.

Vial. Small container for parenteral medicinal products, with a stopper and overseal; the contents are removed after piercing the stopper. Single-dose and multi-dose uses are included.

IV. SPECIFICATIONS

1. Requirements in *The International Pharmacopoeia* (27)

1.1 Packaging materials

Monographs for glass containers and rubber closures are being prepared for inclusion into *The International Pharmacopoeia*.

1.2 Requirements for dosage form containers

1.2.1 Tablets

Packaging must be adequate to protect the tablets from light, moisture, and damage during packaging and transportation.

Every pharmaceutical preparation must comply with the labelling requirements established under Good Manufacturing Practice.

Tablets 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 packaging, storage, and transportation recommendations are specified in the individual monograph.

For effervescent tablets, the label should state: "Not to be swallowed directly".

1.2.2 Capsules

Capsules should be packaged and stored in a manner that protects them from microbial contamination.

Every pharmaceutical preparation must comply with the labelling requirements established under Good Manufacturing Practice.

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 packaging, storage, and transportation recommendations are specified in the individual monograph.

1.2.3 Parenteral preparations

Parenteral preparations 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 individual monographs, these containers should be made from 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 material of the container, or yield foreign substances into the preparation.

Closures for parenteral preparation containers should be equipped with a firm seal to prevent 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 components that react with the contents, nor should they allow foreign substances to diffuse into the preparation. Plastic materials or elastomers of which the closure is composed should be sufficiently firm and elastic to allow the passage of a needle with the least possible shedding of particles. Closures for multidose containers should be sufficiently elastic to allow the puncture to reseal when the needle is withdrawn and protect the contents from airborne contamination. A tamper-evident container is fitted with a device that reveals clearly whether it has ever been opened.

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

Every pharmaceutical preparation must comply with the labelling requirements established under Good Manufacturing Practice.

1.2.4 Topical semi-solid dosage forms

The container material should not adversely affect the quality of the preparation or allow diffusion of any kind into or across the material of the container into the preparation. The container should be fitted with a closure that minimizes microbial contamination and is equipped with a device that reveals whether the container has ever been opened.

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

Every pharmaceutical preparation must comply with the labelling requirements established under Good Manufacturing Practice.

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

2. Pharmacopoeial requirements in Europe, Japan and USA

2.1 Requirements for glass containers

Requirements for glass containers in Ph. Eur., JP and USP are quite similar. A classification of types of glass does not exist in Japan, whereas they are very similar in Ph. Eur. and USP.

Tests proposed are specifications for glass containers for injections. USP also gives a reference table in which the medicinal product is packaged, repackaged, and should be dispensed. Relevant specifications are given for all capsules and tablets with regard to light-resistant containers and tight, or well-closed closures.

Ph. Eur. gives a general description of the requirements for glass containers for pharmaceutical use. A specific part relates to glass containers for human blood and blood components.

2.2 Requirements for plastic containers

Materials used for plastic containers are numerous and their requirements differ greatly in the various pharmacopoeias. Tests described are very difficult to compare.

2.3 Requirements for rubber closures

Generally, closures are made from rubber. Comparison of requirements is as difficult as for plastic containers. Ph. Eur. and JP contain special requirements for rubber closures intended for containers of aqueous parenteral preparations. USP describes, more generally the use of closures made from elastomers for injections, with no details of the preparation they are to be applied.

Similarities exist in tests of Ph. Eur. JP and USP, others are quite different.

3. Packaging requirements of organizations for standardization – international standards

Many pharmaceutical components are designed in-house and are specific to individual manufacturers. A universally acceptable design can be standardized either by demand or in consent with supplier, customer or market regulations. National regional and international organizations for standardization exist. Reference is given below only to international standards.

International standards: The main standards for packaging by the International Standards Organization are the following:

- ISO 9001 1987: Packaging 4.15.4
- ISO 9002 1994: Packaging 4.15.4
- ISO 9003 1994: Packaging 4.15.4
- ISO 9004 1993: Packaging 16.1.4

Additional ISO standards are listed in numerical order (last update 10.10.98):

ISO 594-1:1986 Conical fittings with a 6% (Luer) taper for syringes, needles and certain other medical equipment -- Part 1: General requirements

ISO 594-2:1998 Conical fittings with 6% (Luer) taper for syringes, needles and certain other medical equipment -- Part 2: Lock fittings

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

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

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

ISO 1135-3:1986 Transfusion equipment for medical use -- Part 3: Blood-taking set

ISO 1135-4:1998 Transfusion equipment for medical use -- Part 4: Transfusion sets for single use

ISO 3826:1993 Plastics collapsible containers for human blood and blood components

ISO 6009:1992 Hypodermic needles for single use -- Colour coding for identification

ISO 6710:1995 Single-use containers for venous blood specimen collection

ISO 7864:1993 Sterile hypodermic needles for single use

ISO 7885:1996 Sterile, single-use dental injection needles

ISO 7886-1:1993 Sterile hypodermic syringes for single use -- Part 1: Syringes for manual use

ISO 7886-2:1996 Sterile hypodermic syringes for single use -- Part 2: Syringes for use with power-driven syringe pumps

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

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

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

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

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

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

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

ISO 8536-1:1991 Infusion equipment for medical use -- Part 1: Infusion glass bottles

ISO/DIS 8536-1 Infusion equipment for medical use -- Part 1: Infusion glass bottles
ISO 8536-2:1992 Infusion equipment for medical use -- Part 2: Closures for infusion bottles

ISO 8536-3:1992 Infusion equipment for medical use -- Part 3: Aluminium caps for infusion bottles

ISO/DIS 8536-3 Infusion equipment for medical use -- Part 3: Aluminium caps for infusion bottles

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

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

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

ISO 8536-7:1992 Infusion equipment for medical use -- Part 7: Caps made of aluminium-plastics combinations for infusion bottles
ISO 8537:1991 Sterile single-use syringes, with or without needle, for insulin

ISO 8871:1990 Elastomeric parts for aqueous parenteral preparations

ISO 8872:1988 Aluminium caps for transfusion, infusion and injection bottles -- General requirements and test methods

ISO 9187-1:1991 Injection equipment for medical use -- Part 1: Ampoules for injectables

ISO/DIS 9187-1 Injection equipment for medical use -- Part 1: Ampoules for injectables

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

ISO 9626:1991 Stainless steel needle tubing for the manufacture of medical devices

ISO 9997:1990 Dental cartridge syringes

ISO/DIS 9997 Dental cartridge syringes

ISO 10555-1:1995 Sterile, single-use intravascular catheters -- Part 1: General requirements

ISO 10555-2:1996 Sterile, single-use intravascular catheters -- Part 2: Angiographic catheters

ISO 10555-3:1996 Sterile, single-use intravascular catheters -- Part 3: Central venous catheters

ISO 10555-4:1996 Sterile, single-use intravascular catheters -- Part 4: Balloon dilatation catheters

ISO 10555-5:1996 Sterile, single-use intravascular catheters -- Part 5: Over-needle peripheral catheters

ISO 10985:1992 Caps made of aluminium-plastics combinations for infusion bottles and injection vials -- Requirements and test methods

ISO/DIS 10985 Caps made of aluminium-plastics combinations for infusion bottles and injection vials -- Requirements and test methods

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

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

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

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

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

ISO 11070:1998 Sterile, single-use intravascular catheter introducers

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

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

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

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

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

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

ISO/DIS 11608-1 Pen-injectors for medical use -- Part 1: Requirements and test methods

ISO/DIS 11608-2 Pen-injectors for medical use -- Part 2: Needles -- Requirements and test methods

ISO/DIS 11608-3 Pen-injectors for medical use -- Part 3: Finished cartridges -- Requirements and test methods

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

ISO/DIS 13926-2 Pen systems -- Part 2: Plungers and discs for pen-injectors for medical use

ISO/DIS 14972 Sterile obturators for single use with over-needle peripheral intravascular catheters

ISO 15010:1998 Disposable hanging devices for transfusion and infusion bottles -- Requirements and test methods

Appendix 1

Storage Areas

(Good manufacturing practices for pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-second Report. Geneva, World Health Organization, 1992 (WHO Technical Report Series, No. 823, Annex 1, p. 37).

11.11 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, released, rejected, returned or recalled products.

11.12 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.

11.13 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.

11.14 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.

11.15 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.

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

11.17 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.

11.18 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.

Labels

(Good manufacturing practices for pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-second Report. Geneva, World Health Organization, 1992 (WHO Technical Report Series, No. 823, Annex 1, p.45-46).

14.10 Labels applied to containers, equipment or premises should be clear, unambiguous, and in the company's agreed format. It is often helpful in addition to the wording on the labels to use colours to indicate status (for example: quarantined, accepted, rejected, clean).

14.11 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 undoded 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.

Appendix 3

Self-inspection and quality audits

(Good manufacturing practices for pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-second Report. Geneva, World Health Organization, 1992 (WHO Technical Report Series, No. 823, Annex 1, p.31-32).

9.1 *Principle* .The purpose of self-inspection is to evaluate the manufacturer's compliance with GMP on all aspects of production and quality control. The self-inspection program should be designed to detect any shortcoming towards 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 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

9.2 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 instruments or measurements systems
- (l) recall procedures
- (m) complaints management
- (n) labels controls
- (o) results of previous self-inspections and any corrective steps taken.

Self-inspection team

9.3 Management should appoint a self-inspection team from local staff who are experts 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

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

Self-inspection report

9.5 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

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

Quality audit

9.7 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 (*see section 8, "Contract production and analysis"*).

Suppliers' audits

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

9.9 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 (see section 18).

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