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PACKAGING MATERIALS, TECHNOLOGIES AND INFRASTRUCTURE FOR PHARMACEUTICALS*

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* The views expressed in this paper are the author's and do not necessarily reflect the views of the Secretariat of UNIDO. Mention of firm names and commercial products does not imply the endorsement of UNIDO. This document has not been edited.

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ANNEXES

1. INTRODUCTION

A/ The packaging of pharmaceuticals implies all operations, inclusive of filling, labelling, cartoning by means of which the products in bulk can be transformed into marketable finished products.

B/ The packaging of dosage forms defined in Annex No 1 is discussed in details by this study, concentrating on the packaging of tablets, coated tablets, capsules, medicated syrups, injection and infusion fluids.

C/ Pharmaceuticals being not neutral products have direct influence on the human health. Therefore the product/packaging interaction, including absorption and chemical reaction must be very carefully investigated and eliminated .

D/ Packing materials having a direct contact with the drug can be made from

glass
metal
plastic
paper /lamination/ based material.

Besides the widely used glass packaging being the least reactive, plastic packaging materials and their laminations are gaining ground. Plastics create new possibilities for the reliable, tamper-resistant, and at the same time transparent, tasteful packaging of pharmaceuticals.

E/ A considerable part of developing countries are situated in the tropical /dry or humid/ climatic division, which raises special requirements for the packaging of drugs.

Only those with high barrier capabilities, mainly laminated packaging materials can resist to the intensive humidity and very high temperatures.

F/ For the sake of the economic packaging of pharmaceuticals, taking into account their high prices and the great transport costs, it seems to be expedient if at least a part of the packaging materials needed by a developing country could be derived from local sources.

In the developing countries having adequate petrochemical industry, there are possibilities for the manufacture of some plastic intermediers and for the production of packaging materials from them using relatively simple processing technologies indicated in this study.

G/ In consequence of the special protective function of the packaging of pharmaceuticals, a considerable regulation system has been built in this field. This regulates the packaging requirements and their observance through laws, rules, regulations, standards and by the national pharmacopeias. The function of the highly important quality control is ensured by the Good Manufacturing Practice which is prescribed and recommended also by the national pharmacopeias.

H/ In the developing countries the research and development of pharmaceuticals packaging should be ensured by the R+D centres integrated with the national packaging centres or research institutes.

2. CURRENT SITUATION AND BASIC REQUIREMENTS

2.1. Outlining the main kinds of pharmaceutical products reviewed from packaging aspects

Pharmaceutical production includes the whole process of drug preparation beginning with the supply of basic substances through manufacturing operations and packaging to the release and delivery of the end-products.

Every drug for human use falling under control measures according to the public health law of the producing or importing country is qualified as a pharmaceutical product. Every substance has to be considered as a drug that can be used therapeutically for influencing living organism or can be introduced into the body for diagnostic purposes.

Pharmaceutical preparations imply the drugs shaped in specific forms, consisting of several constituents /active ingredients and additives/. They are manufactured from substances and therapeutical additives of chemical, plant, animal or another biological origin and are prepared in serviceable /selective/ pharmacological forms.

The adequate quality of the preparations can be guaranteed simultaneously by the observence of the directives of the Good Manufacturing Practice /GMP/ and by the quality and production conditions of the processed ingredients and additives.

The packaging of pharmaceuticals implies all operations, inclusive of filling, labelling, cartoning by means of which the products in bulk can be transformed

into marketable finished products.

The tasks of the packaging of pharmaceuticals are:

- protection of the pharmaceuticals from harmful outside effects,
- forwarding of the pharmaceuticals to the sick in the most convenient way,
- providing the necessary information for the physicians, pharmacists and the sick. /As an information medium/.

Packaging material:

Every material available for the packaging of preparations and suitable for the proper use as well as for the preservation of the nature, quality and stability of the drug in question within the expiry date can be considered as packaging material for medicine.

Materials applied to the packaging of pharmaceuticals can be divided into two groups: the packing materials having a direct contact with the drug, on the other hand those having indirect or no contact with the medicines.

The packaging materials coming into direct contact with the drug may especially influence the use of the drug according to prescription, characteristics and quality but they may also influence the stability of the pharmaceuticals. Thus, first and foremost, the packaging materials having a direct contact with the drug are dealth with here.

The choice of the aforesaid packaging materials must be

taken in the product development phase, considering the form, the physical and chemical constants as well as the stability of the preparation to be packed. Similarly, attention has to be paid to the technical and technological potential of the factory in question, furtheron to the climatic conditions of the place of manufacturing, packing and cartoning and to those of the transport route and country of destination. The qualification of the management and personnel as well as the technological potential and hygienic conditions of the packing workshop must also be taken into account.

Packing materials having a direct contact with the drug can be based on

- glass,
- metals,
- plastics,
- paper /mainly in the form of laminations/

and may be specified or unspecified depending on the nature of the individual preparations. The unspecified group includes the packaging types utilizable for several preparations.

In the present study the packaging of the drug forms defined in Annex No 1 is dealt with full particulars, concentrating on the packaging of tablets, coated tablets, capsules as well as of medicated syrups, injection and infusion fluids /liquiform preparations/.

2.2. Requirements for pharmaceutical packaging

The pharmaceutical products due to their special medical application need reliable, safe, hygienic and well controlable packaging.

For this reason the primary packaging materials and media used for pharmaceutical packaging should protect against the risk of damage or deterioration associated with the hazards as follows

- mechanical or physical
- biological, microbiological
- climatic and environmental
- chemical including compatibility between product and pack.

These hazards usually constitute not only a major risk to the product but also the most complex part of the packaging function. As a result, the stage prior to deciding the type of pack must involve the knowledge on the product. This includes finding out how a product may deteriorate or degrade under various challenges such as moisture, oxygen, carbon dioxide, light, temperature, microbiological attack, vibration, etc. or combinations of these effects.

At the pharmaceuticals the product/pack interaction /including absorption and chemical reaction/ must be very carefully investigated using analytical tests as well as visual observations. Product/pack exchanges may occur in either direction /product ingredient into the pack and pack ingredient into the product/, sometimes in indirect and unexpected ways.

The secondary pack of pharmaceuticals consists of those materials aimed to assist warehousing, trans-

./.

portation and distribution, which can involve a combination of physical and climate hazards.

Physical hazards include compression, usually associated with stacking pressures, vibration /which may occur over a range of amplitudes and frequencies/ drops or impacts /shock/ and puncture.

Beyond the above mentioned general hazards and requirements, pharmaceutical packaging should also meet very special requirements, as following:

2.21 Requirements of regulation

The pharmaceuticals, being not neutral products, have direct influence on the human health. Consequently the unprofessional application and distribution of drugs can be highly dangerous. Taking it into consideration most of the regulations in the field of public health deal with the packaging of pharmaceuticals in different ways.

The most general regulation is carried out through the national and international pharmacopoeias /e.g. the U.S. Pharmacopoeia USP, The British Pharmaceutical Codex BPC, The International Pharmacopoeia by WHO etc/ The instructions of pharmacopoeias have legal force in the practice.

In a number of countries there are other regulations to specify and support the instructions of pharmacopoeias. E.g. there is in force the Poison Prevention Packaging Act since 1970 in

accordance with the Federal Food, drug and Cosmetic Act of the United States. There exist Poison Prevention Packaigng Standards, Pharmaceutical Labelling Standards etc. In consequence all the drugs manufactured, exported and imported should comply with the existing packaging regulations of the country in question.

2.22 Identity and information

The shape, colour-composition and labelling of packaging should promote to recognize and identify the certain pharmaceutical product in the home country and abroad as well. According to the experiences of export promotion actions it is necessary to keep the main features of a drug-package composition /colour, shape, label/ for the easy identification in accordance with the special habits of the importer country.

The content and composition of the instructions of a label have special significance in the identification of the drug.

The "labelling" of pharmaceuticals in this study designates all labels and other written, pointed or graphic matter upon an immediate container of an article or upon or in, any package or wrapper in which it is enclosed /exept any shipping container/. The term "label" designates that part of the labeling upon the immediate container.

The minimal, compulsory and recommended content of a drug-label will be discussed in other chap-

ters of this study.

There is a special kind or information used in the form of bar-code during the manufacturing, storing and packaging process of drugs. This "Pharmacode" has been applied mainly for safety reasons. The Pharmacode should be indicated on each pieces of the same packaging /material, label, leaflet of instructions/ to avoid the chance of muddle. By the help of pharmacode the mistaken indentity of drugs can be eliminated. It is essential to consult a professional pharmacode advisory service on designing the specific code.

2.23 Tamper resistance

In the recent decade some serious accidents of poisoning occured in connection with the unsafe or insatisfactory accumplishment of pharmaceutical packaging. There are also examples of malicious substitution of /expensive/ original drugs with fake copies of medicines.

To avoid the dangerous aftermathes in more and more countries new regulations have been introduced prescribing or advicing the use of "tamper resistant" packaging at specific pharmaceuticals.

The generally accepted terminology of tamper-resistant packaging:

"A tamper resistant package is 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 occured." /Food and Drug Administration, USA/

The tamper-resistant packages may involve also immediate-container or closure system, secondary-container or carton system or any combination of systems intended to provide a visual indication of package integrity. The tamper-resistant feature shall be designed to and shall remain intact when handled in a reasonable manner during manufacture, distribution and retail display. There is a list of typical tamper-resistant packagings in Annex No 2.

2.24 Child-resistant packaging

For the safety of children and preventing any poisoning accident there is a number of regulations advicing or prescribing the use of "Child resistant" packaging - special closure system - for specific pharmaceuticals.

The closing unit of the packaging is considered as "child resistant" in the international practice, if:

a/ the power needed to open the packaging is greater than the pulling and pressing force could be exerted by the hand of a child.

b/ the size /diameter/ of the closing unit is larger than the size of the hand of a child to seize and open the packaging.

c/ the use of the aid-device is too complicated for the children to open the packaging.

A test-panel of children under the age of 5 years and a contra-panel of older adults should be chosen to control the safety of packaging. The closing unit should not be opened by the children in a certain period of the test. On the other hand, the packaging should not be difficult for normal adults to open. /For the various pharmaceuticals different test-panels could be set up depending on the age, sex, type of illness of adults etc/.

The list of pharmaceuticals to be put in child-safe or tamper resistant packaging is usually published in the national pharmacopoeias.

2.25 Requirements of tropical conditions

The majority of developing countries is situated in the dry or humid tropical climatic zones. A great number of pharmaceuticals are very sensitive to extreme climatic conditions like the tropical ones. /The characteristics of Technical Climate Divisions are shown in Annex No 3./

The hazards are as follows

a/ dry tropical climate:
- steadily high temperature during the day
- high fluctuation of temperature between day and night
- massive atmospheric pollution

b/ humid tropical climate
- steady high temperature
- extremely high relative humidity

- steady rainfalls in the rainy season
- biological danger in a greater extent /pestiferous, microorganism, fungoid etc/

To protect the sensitive pharmaceuticals from the above mentioned hazards it is necessary to accomplish the following steps:

1/ To use high barrier packaging materials /multilayers, laminates, coextrusions/ and waterproof, tight closure system

2/ To apply special vapour absorbing materials /silicagel, bluegel, active coal etc./

3/ To ensure the required climatic conditions during the manufacturing, storing and transport processes.

These preventing methods are outlined in detail in the chapters of packaging materials and technologies.

3. ANTICIPATED TRENDS AND REQUIREMENTS IN PACKAGING MATERIALS, CONTAINERS AND TECHNOLOGIES

In this chapter the main characteristics and requirements of the pharmaceutical packaging materials, containers and technologies are presented in connection with the trends of development. The product / packaging interaction and compatibility - as a prime aspect of medicaments - are carefully analysed at the most important glass, metal, plastic, paper /lamination/ packagings.

The specifications and suppliers of the major intermediate materials for manufacturing packaging materials are introduced particularly in the subchapter of plastics. There are also indications for infrastructure needed for the production of selected packaging materials for pharmaceuticals.

The special quality and technological requirements of tropical climate regions - where a great number of developing countries are situated - are systematically examined and submitted.

3.1. Glass containers

3.11 Material of containers

Glass is not fully indifferent packaging material. Its soluble alkali content may cause difficulties chiefly in case of solutions because water induces hydrolysis of some silicates resulting alkali or alkaline earth hydroxides. Every new glass packaging must be tested from the aspect of compatibility with the given pharmaceutical preparation and of the stability of the preparation.

The standards range glasses among hydrolytic classes according to their alkali emission. Only those glasses can be used for the packaging of pharmaceuticals, the water-soluble alkali content of which - depending on their destination - complies with the following hydrolytic classes:

Hydrolytic class No I - infusion bottles
- injection powder ampoules
- injection ampoules
- ophtalmic solutions

" " No II - glasses for pharmaceutical liquids

" " No III - glasses for preparations

Glass has been used for the packaging of pharmaceuticals for centuries and is still being used. Glass packaging is in immediate contact with the product.

3.12 Types of containers for medicaments

A/ Packaging of tablets, coated tablets and capsules

In case of solid pharmacutical products /tablets, granules, capsules etc./ alkali emission degree of glass packaging does not influence product quality, therefore the so-called medicine bottles marufactured from glasses of the hydrolytic classes No III-IV can be used for this purpose.

Medicine bottles serve for the direct drug supply to the sick - through pharmacies - as well as for hospital pharmacies, mostly in major doses. The gauge of the bottles varies between 5 g and 1000 g.

Several medicine bottles have a flange /projecting edge/ and are closed mostly by plastic or metal caps. In the first variation, tropics-resistancy can be realized by damp-proof capsules, and in the second variation, by vacuum caps and hermetic seals. Screw caps can also be made in pilfer and/or child resistant forms.

Hospital supplies are carried out in bottles containing 100 to 1000 pieces of tablets etc. outfitted with plastic screw caps or twist-of cap closures. Damp-proof capsules may also be used for rendering these bottles tropics-resistant as well as their safety can be ensured by application of pilfer resistant caps.

B/ Packaging of medicinal syrups

Medicinal syrups have to be filled into medicine bottles suited for fluids. These bottles must be fabricated from glasses of the second hydrolytic class because the degree of alkali emission influences the quality of the medicinal fluids.

Syrups are sold in units of 50 to 200 ml, thus the calibers of the used bottles should comply with these doses.

Their closure should be leak-and pilferproof, child resistant, and well, possibly hermetically sealed.

The closures can be made

1. from plastics /PE, PP/ with child and pilfer resistant caps
2. from metal /Al/ with pilferproof caps.

C/ Injection containers

The ampoules for injection solutions have to be fabricated from glasses of the second hydrolytic class, using a special tubular process with calibers of 1 to to 20 ml.

Filling of the ampoules with the injection solution is a part of the injection manufacturing. Injections should be produced in a building suitable for this purpose using a special equipment under aseptic, sterile conditions.

The injection manufacturing process:

- preparation of the solution,
- ampoule washing,
- ampoule drying,
- ampoule filling /with the solution/,
- ampoule welding,
- ampoule marking,
- sterilization of the injection by heat, in autoclave,
- ampoule supervision,
- ampoule signing completes the production process of the semi-finished preparation. This latter has to be packed in its traditional sense, chiefly into blister or carton.

Therefore, glass ampoule is a packaging material used in the manufacturing process of injections, more correctly said, it is a part of the injection. The glass material of the ampoule directly influences the quality of the injection solution.

Powder ampoules

Powder preparations are made for injection purposes under sterile conditions /processed by lyophilization and sterile crystallization/, and are filled into so-called powder ampoules /flanged injection containers/. Powder filling constitutes a part of the production.

The manufacturing process:

- sterile powder production,
- powder ampoule washing and drying
  closure sterilization

- sterile ampoule filling
  closure /sealing/
  covering by metal cap
  marking.

The whole process must be performed under sterile conditions, in a building constructed especially for this purpose.

The sterilized injection powder filled into the powder ampoule must be packed together with the dissolvent because the preparation can be used for injection not earlier than having dissolved it.

Packaging form: 1 ampoule powder ingredient + + dissolvent /5 ml/. The actual packing operation consists of making carton packages for both items.

D/ Infusion containers

The preparation /manufacture/ of infusion solutions requires a laboratory and workshop planned and built especially for this purpose.

Filling of the solution is a part of the fabrication. According to the regulations laid down in the pharmacopeias the infusion solutions must be filled into containers made from glass of the first hydrolytic class.

The process of infusion production:

- preparation of the solution under sterile conditions

container washing
container drying
closure sterilization
cap sterilization
- filling of the infusion solution
sealing
closure, covering by metal cap
sterilization
labelling

The infusion container is a part of the infusion product. For shipping, protective packaging is needed; in general carton covers are used for this purpose.

Packaging technologies

The technological process begins with the washing and drying of the container followed by the filling, closing, labelling and cartoning operations.

In the course of the filling operation the dosage may be carried out by counting the number of pieces as in the case of tablets, coated tablets, capsules. The dosage of syrups can be effected by use of the volumetric dosage method.

The packaging operation itself may be processed by man-power, by partial or full automatization. Within the whole process, single operation phases can also be mechanized. A list of the manufacturers of equipment suitable for automatizing technologies can be found in Annex No 4

The packaging technology of injection and infusion containers, together with the preparation of the solutions as a constituent part of this production, are dealt with in chapter No 3.12.

3.2. Metal based packagings

The metal packaging materials mostly used for packages of pharmaceuticals are:

Aluminium packaging materials

- hard and soft aluminium foils
- aluminium tubes
- aluminium aerosol containers
- aluminium thin foils

Other metal packaging materials are only seldom used for the packaging of pharmaceuticals and only in small quantities. Aerosol containers as well as metal boxes for large dosages can also be made from tinplate. Metal drums can be used for semi-finished products in bulk /e.g. tablets, ointments/.

A/ Tablets, coated tablets, capsules to be packed in metal based packaging materials.

Aluminium

Aluminium containers are widely used for certain solid preparations /tablets/. Aluminium containers and tubes are tropics- resistant if their closure come up to the tropical conditions by an adequate moisture barrier system. The absorbent medium can be made in capsule form placed at the top of the preparation or built into the cap.
Aluminium foil packages may contain tablets, coated tablets and capsules.

Strip packagings can be manufactured from soft aluminium foil in combination with one or more kinds of plastics or paper.

For blister packagings

Hard aluminium cover foils are used the inner side of which is coated with thermoweld lacquers, while the outer side is lacquered and printed. In combination with different plastics /e.g. PA/AL/PVC/ or AL/PP blister can also be used under tropical conditions.

B/ Syrup packages

For the closure of syrup glass containers aluminium caps, together with plastic barriers are often used. For the selection of the cap, the compatibility of the plastic barrier and the syrup has to be examined. Aluminium pilferproof caps are manufactured in standard size, equipped with different barriers.

C/ Packaging of injection and infusion solutions

Injection powder ampoules are closed by aluminium caps, the size and form of which should be adjusted to the powder ampoule to be fabricated. This cap can be

- formed from aluminium plate having been exposed to an electrolytic oxidation process
- a flanged cap shaped from aluminium plate with a plastic closure.

Infusion glass containers have to be closed by so called aluminium, infusion caps the sizes and forms of which are standardized /E.g. DIN standards/

D/ Metal based packaging materials for other pharmaceuticals

Aluminium tubes

Aluminium collapsible tubes are used for the packaging of ointments and creams.
Aluminium tubes are manufactured by an impact extrusion process with internal lacquering external coloured and printed coating. The inside surface of the tube has direct contact with the medicinal ointment, therefore the interaction between lacquer and ointment has to be examined.

The nozzle of the tube may be blind /diaphragm sealed/ or open, its mantle may be pointed or cone-shaped. In order to render the closure safer, the end of the tube may carry an anti-seepage band made from rubber or plastic.

Aluminium has good barrier properties against the permeation of moisture and gases.

E/ Aerosol containers

Medicinal sprays are packaged mainly in metal containers outfitted with a valve /cup/. The containers can be fabricated from aluminium or tinplate. The aerosol valves have several components. Aerosol production is a special branch within the pharmaceutical technology and requires a specially trained personnel.

3.3. Plastic based packagings

3.31 Packaging materials and containers

Plastic based packaging materials were widely introduced to the pharmaceutical industry some ten years ago only. The most frequently used basic materials are the Polyethylenes, PE /LDPE, MDPE, HDPE/; Polypropylenes, PP; Polyvinylchloride, PVC; Polyvinylidene chloride, PVdC; Polyamides, PA; Polystyrene, PS and their combinations. It is a primary condition for their use that plastic in question should be odorousless and should not involve any danger for human health. It must not be toxic, neither contain or emit toxic substances.

Plastic packaging should ensure the stability of the preserved preparations within the expiration date. The compatibility of the active substances and additives of the dosage forms /tablets, coated tablets, capsule syrup, injection/ with the packaging material must be examined in each case separately. The national pharmacopeias as well as USP, BPC or the regulations of FDA, for example, contain rules for compatibility tests.

The plastic based materials manufactured for the packaging of pharmaceuticals have to be processed, packed, transported and stored in such a manner that the product should remain fully clean and sterile.

Plastic products used for the packaging and keeping of pharmaceuticals can:

- have direct and permanent contact with the preparation,
- have a direct but only occasional contact with the preparation,

- have an indirect contact with the preparation.

Thus, plastic packaging materials have contact to a certain extent with any forms of the pharmaceutical preparations. Therefore, it is very important to ensure the cleanliness of the packaging material. After the production, it is difficult to clean /wash or dry/ the packaging material but the simultaneous post-sterilization of the plastic packaging and the preparation filled into the container can be realized. /autoclave or radiation sterilization/

A/ Packaging materials and containers for tablets, coated tablets and capsules

1/ Plastic packaging materials

Plastic packaging materials do not influence the stability of solid pharmaceutical preparations within the Cold and Temperate Climatic regions. But in the Tropical Climate divisions they exert a significant effect on their stability. Therefore, special measures must be taken at the choice of the packaging forms when manufacturing is carried out in a dry or humid tropical country or a preparation is exported there. Both compatibility and stability tests should be performed particularly for tropical conditions.

a/ Containers /bottles, flacons, ampoules, boxes etc/
The main plastic containers used for bulk packaging are as follows:

Polystyrene containers
Volume: 5 to 100 g, ampoulelike or rased-edge forms
Closure: PE wadless caps, possibly with moisture-absorbent facing

Polypropylene containers

- ampoulelike, raised-edge neck, volume: 5 to 100 g
- closure: PE wadless cap, possibly with moisture absorbent facing
- safeguard closure gauge: 5 to 2000 g
- closure: PE, tear-off, tamper resistant cover, or the same, with moisture -absorbent facing.

Safely closed, tamper resistant boxes, like "Securitainer" box can be adapted for tropical packagings when a moisture-absorbent material is put at the top of the tablets. The tropics-resistance can be increased through filling the preparation into a PE bag, on the top is the necessary quantity of moisture-absorbent material /e.g. silica gel/, then the PE bag is closed by welding and put into the PP container, finally the container is closed as well.

- screwed neck, volume: 5 to 2000 g
  closure: PE or PP cap. According to need, with moisture-absorbent facing or tear-off closure. Screw cap can also be made in child resistant form. Screw closure is the most reliable packaging because of its tamper resistance.
- the cap can be rendered child resistant as well. The permeability of the container has to be measured, the quantity of the needed moisture-absorbents should be specified according to the result of the measurement.

b/ Strip packaging

To be applied to the strip packaging of tablets, coated tablets and capsules:

- Viscose-foil
- Biaxial orientated Polypropylene, BOPP foil
  These materials should not be used in tropical climatic regions unless combined with other ma-

terials, as follows.

2/ Combined packaging materials

a/ Strip packaging

For this purpose paper can be combined with polyethylene, PVC and/or PVdC. Another alternatives: plastic /BOPP-PVdC/ or aluminium foil, with polyethylene, and/or PVdC.

b/ Blister packaging

It is in wide use for tablets, coated tablets and capsules, because of its efficient protection against environmental and climatic effects. Blisterpacks can be manufactured by heavyduty machinery, the finished preparations can easily and quickly be removed from the pack.

Blister packaging system raises complex requirements against the packaging materials to be processed. They should be

- chemically neutral,
- moisture and gas resistant to a high degree,
- qualified for thermoforming and welding,
- mechanically properly solid.

Blister packaging consists of a lower, so called mouldable foil and a cover foil. The most employed plastic thermoforming foils are made from hard PVC and its combinations. When childresistant packs are wanted, the cover film is coated for hiding the content. The individual bubbles are separated by perforation in order to make easier the detachment of the tablets from the carrier.

Basic films

	permeability of moisture g/m²/24 hours 20C° 85% relative humidity
PVC 250μ	1,1
PVC 200μ/PVdC 40 g/m²	0,22
PVC 250μ/PVdV 40 g/m²	0,17
PVC 200μ/PVdC 60 g/m²	0,14
PVC 250μ/PVdC 40 g/m²	0,08
PA 25μ/Al soft 40μ/PVC 60μ	0

For tropical use only PVC/PVdC combinations are convenient. The PVC/PVdC/PVC combination has a significant advantage:

The cover foil of the packaging can be used in all four climatic divisions.

The combination PA/Al/PVC, the so called Alublister-pack, can be cold-moulded. This kind of packaging is moisture, gas, light and tropics-resistant.

B/ Containers and closures for medicated syrups

After a successful stability and compatibility test medicated syrups can be filled into plastic /PE or PP/ flacons. Their closure must not allow any egress or ingress.

The closure of medicated syrups is similar to that of glass bottles. It is also possible to shape child resistant closures where opening can be done by a simultanous combined movement /e.g. by pushing and screwing/. Caps can be manufactured from plastics /PE,PP/ as well if the stability of the given preparation is not influenced.

C/ Packaging for injections and infusion fluids

The manufacture of injections and infusions requires

aseptic conditions. The injection ampoules and infusion fluid containers are not packagings in their traditional sense but rather parts of a pharmaceutical form.

Injections and infusion solutions can be filled into plastic containers as well. These containers are made from thermoplastic PE or PP granules or powder. After filling the sterile solutions into the containers they are sealed: the containers /ampoules, infusion bottles, bags/ can simultaneously be manufactured and filled by the Bottle-Pack system. The conversion process of thermoplastics within this system is:

- tubing extrusion,
- blow moulding /by compressed, sterilized air/,
- filling with sterile solution,
- sealing /neck forming/
- finished product output.

The Bottle-pack system in used mainly for packing sterile solutions for injection or infusion prepared by steril filtration.

The solutions are marked in the course of the manufacturing process by engraving or by immediate labelling of the finished product.

Infusion solutions can also be filled into plastic bags when the bags are not manufactured at the same place. In this method the sterilized PE or PP infusion bags are forwarded to the place of the infusion manufacturing in order to integrate them with the solution-manufacturing process.

Infusion bags are closed in such a manner that after the removal of the cover foil the filling needle should be introduced through the sterilized part of

the film reaching the inner surface of the bag. In this way sterile filtered solutions can be filled into the infusion containers. If sterile conditions cannot be ensured during the process of transport and opening of the container, the infusion solution has to be post-sterilized. /At 120 C^0, for 20 minutes at least/. The conditions of sterilization should be regulated according to the characteristics of each preparation.

If plastics are processed for manufacturing of such containers, their climate-resistance must be tested according to the rules laid down in USP, BPC or in the International Pharmacopoeia of WHO. In connection with the given climatic division compatibility and stability tests must be performed.

It seems to be advisable to adapt a complete technology of injection and infusion solution production. The know-how or licence may be bought from factories well functioning under similar conditions. Nevertheless it is not sufficient to buy e.g. the whole Bottle-pack system because the aseptic equipment must be integrated in a complex manner with the packaging unit.

Closures used for injection and infusion containers

For the closure of injection powder ampoules - multiple-dose vials - as well as of infusion solutions rubber stoppers should be applied the quality of which is strictly prescribed in the pharmacopeias. The quality of the stopper must be chosen very carefully in order to avoid any interaction with the preparation. Furtheron, stopper should prevent fragmentation upon puncturing the closures and also should ensure the vacuum reclosure of the container after pulling out the injection needle.

Plastics utilizable for injection packaging

For the /collective/ packing of the filled injection ampoules plastics can be used as well.
E.g. the packaging materials applied to the blister packaging or to the blister nest of injections are plastic packagings of this kind.

The gauge of the ampoules /1 ml, 2 ml, 5 ml, 10 or 20 ml/ and the applied packaging unit /5 or 10 each/ may influence the thickness of the foil to be used/.

Plastic closure elements for the packaging of pharmaceuticals:

The closures of glass containers for tablets, coated tablets, capsules and syrups, first of all the stoppers and caps are manufactured more and more from plastics. According to their function they may be snap-on caps, screw caps, seal caps etc.

3.32 Plastic packaging technologies

a/ Plastic containers

Packaging technology includes filling, closure and labelling of the processed /clean, germfree/ container. Depending on the characteristics of the product, tablets, coated tablets, capsules are filled according to the number of the pieces, syrups according to the volume of the container. These operations can be performed by handwork, by auxiliary devices /e.g. measuring-feeders/, semi- or full automatic machines. As to some manufacturers of these equipment see Annex No 4.

Plastic container packaging is generally protected by an outer carton packaging. This can also be mechanized in case of a continuous production on a large scale.

b/ Strip packaging

Small articles, such as capsules or tablets are packaged in a continuous plastic strip. The manufacturing technology consists of strip slitting, of putting in the preparations and of closure. This kind of packaging can only be manufactured by a machinery. Some well-known machine factories are to be found in the Annex No 4.

Strip packaging is mostly completed by carton box outer packaging. This operation can be performed both by handwork, and by machines.

c/ Blister packaging

The technology includes heating and thermoforming of the lower foil, putting in the preparations and setting the cover foil. The blister process requires a full-automatic equipment.

Some manufacturers are listed in the Annex No 4. Blisterpacks are forwarded in distribution packagings i.e. in carton boxes. Packaging operation can be performed both by hand and machines.

3.33 Specifications of some major intermediates for selected plastic packaging materials

A/ For blister packaging

Rigid /unplasticized/ PVC films are used for blister packaging of pharmaceuticals. These films are manufactured from PVC powder with the following characteristics:

Type Orgrovil S-100, suspension PVC powders /manufacturer: BORSOD INTEGRATED CHEMICAL WORKS, Kazincbarcika/

	S-155	S-160	S-165
K-value	55 ± 1	60 ± 1	65 ± 1
Volume mass g/l	610 ± 35	600 ± 35	590 ± 35
Granulation size partition %:			
over 250 μ	max.1	max.1	max.1
under 90 μ	max.90	max.90	max.90
under 60 μ	-	-	-
Softener absorption %	10-20	10-20	10-20

Vinoflex S type suspension PVC powders

/manufacturer: BASF, FRG/

	S-5715	S-6015	S-6115
K-value	57	60	60
Volume mass g/l	570	580	560
Granulation size	max.300	max.300	max.300

B/ For strip packaging

For strip packaging the heatsealable BOPP films can be used. The films produced in Hungary have the following characteristics: BOPPK, KK - On one side or both sides coextruded, POPP heatsealable film. BOPP B- PVdC coated, heatsealable BOPP film

	BOPP K,KK	BOPP B
Density g/cm^3	0,91	0,91
Thickness /μ/	20-40	20-40
	Plastics	
Tear-strength N/mm^2	MD 110	MD 100
	TD 210	TD 180
Tensile-strength %	MD 200	MD 200
	TD 80	TD 85

O_2 permeability $cm^3/m^2/24$ h	850-1000	10-50
Water vapor permeability $g/m^2/24$ h	6-8	max.6

Other types of BOPP films:

- Oppalyte MB 747 /manufactured by Mobil Plastics Europe/ one side PVdC coated heatsealable thickness 50 u
  Oxigen permeability 10-50 $cm^3/m^2/24$ h
  Water vapor permeability 6-10 $g/m^2/24$ h.
- Shorko SCF type can also be mentioned /manufactured by British Cellophane Ltd./

B/ Containers, flacons, closure elements

Containers, flacons, jars, closure elements are manufactured from:

Polyethylene of low density /manufactured under high pressure/	LDPE
" of high " " " low " /	HDPE
Linear polyethylene	LPE
Polypropylene	PP
Polystyrene	PS

LDPE types used for blow molding:

	Tipolen PB 2212	Fertene ZB 2000	Alkathene WING 14
Density g/cm^3	0,922	0,920	0,917
MFI g/10 min*	0,7	0,25	7

Manufacturer: e.g. TVK-TISZA Integrated Chemical Works

HDPE types used for blow molding:

	Hostalen GM 5050	Lupolen 4261 AX	Eltex C 4003 SP
Density g/cm^3	0,95	0,94	0,95
MFI g/10 min*	0,4	5,4-6,8	0,4

Manufacturers: e.g. HOECHST and BASF

HDPE types used for injection moulding

	Hostalen GD 6250	Lupolen 3010 S	Eltex A 1050 SD
Density g/cm^3	0,95	0,93	0,96
MFI g/10 min*	1,2	17,0-22,0	3,7

Manufactured e.g. by HOECHESR and BASF

Main characteristics and application of LPE produced in Hungary

Type	Application	Density g/cm^3	MFI g/10 min
BB 640-16	blow moulded flacons	0,964	0,75
MG 670-06	injection moulded containers	0,967	30,0

PP types used for injection moulding

	Hostalen PPH	Moplen S 30 G	Tipplen K 623
Density g/cm^3	0,905	0,90	0,89
MFI** g/10 min	1,3	1,4	2

Manufactured e.g. by HOECHST and Montedison

Polystyrene is frequently used for the injection moulding of minor plastic vials.
The characteristics of some types:

Please note:

* Melt-index /MFI/ measured at 190 ^{o}C/2,16 kg
** " " " at 230 ^{o}C/2,16 kg

	BASF PS 427 M	Hostyren N 4000	Lustrex HF 55
Density g/cm^3	1,05	1,05	1,05
MFI^{xxx} 10 min	1,5	-	18

/First item manufactured by BASF, the others by HOECHST/

3.34 Specific infrastructure and technology to produce selected plastic packaging materials for pharmaceuticals

The main plastic packaging materials used for pharmaceuticals are manufactured by means of the following conversion processes:

Rigid PVC films

Calendering is one of the conversion technologies of rigid PVC films. Essentially it consists in passing the intermixed, homogenized and softened plastic material through heated, coupled rolls facing each other. The maximal width of the fabricated film is determined by the roll width, its thickness by the roll throat size.

Calendering is a technology of high productivity. The complete production line consists of several units to be installed on different levels /thus it requires a lot of space/:

- measuring system,
- mixer,
- explorer unit,
- calender,
- cooling rolls, winder.

Calender technology has the advantage that - with a well-chosen equipment - both rigid and soft /plas-

Please note:
xxx Melt-index /MFI/ measured at 200 ^{o}C/5 kg

ticized/ PVC films can be manufactured and these films can also be used for packaging of other products that the packaging of pharmaceuticals.

Indicative manufacturers: Kleinewefers, FRG and Buzuluk, Czechoslovakia.

Calendrette technology is another conversion method for the manufacture of rigid PVC films. The intermixed and homogenized plastic material is poured by a special pulley-shaped extruder, then the poured plastic bulk is passed through a slanting, three roll calender, the so-called calendrette.

The advantages of such a machine line are:

- minor lots can be manufactured economically as well,
- the waste-material can fully be utilized,
- energy is utilized at a degree of high efficiency,
- modest space is required only,
- relatively low investment cost.

BOPP film

This film is manufactured through streching technology. The film leaving the wide aperture extruder is stretched in a reciprocating manner: at the first stage in longitudinal, at the second stage in transversal direction. In the course of the longitudinal stretching the film is streched by doubled coupled rolls rotating at high-speed. Streching can even be fivefold to tenfold. In the course of the transversal process the edge of the film is grasped by pincers; the film is passed through a widening-line which performs the transversal stretching. Stretching can be effected under the condition of maintaining the required film temperature.
Manufacturer: e.g. E. Kampf, RFG.

The above-mentioned technology is characterized by

- high productivity /4000 t/year/
- increased space requirements
- high energy intensity.

BOPP films can be easier processed when the base film is coated by different layers. Heatsealability is ensured by the outer ethylenepropylene copolymer layer resulting from coextrusion and solvent coating technology.

BOPP films with PVdC coating is the optimal material for the packaging of pharmaceuticals which is the primary factor to be taken into account when chosing the production technology.

Plastic jars, flacons, containers, closures

LDPE, HDPE, LPE /linear PE/, polystyrene and PP base materials can be used for the manufacture of the above-mentioned packaging.

Blow moulding is one of the methods for flacon fabrication. In the course of the extrusion blowing process the required base materials /LDPE, HDPE, LPE or PP/ are melted in the extruder, then, after the extruding it into the air, a tube is formed which is cooled down by the ambient air to a moulded, elastic state. This moulded tube is forced through a die of the desired shape and is pressed by compressed air against th inner side of the die. After further cooling, the finished packaging can be pulled out from the die.

Blowing is a relatively simple technology, the processing machines represent a large scale of automatization. Blowing machines require comparatively small space. Within a given size range several

kinds of flacons can be produced with a single machine by changing the tools.

Minor flacons, vials are manufactured through injection moulding from the base materials HDPE, PP, PS. In the course of the injection moulding process the material melted by pulley is forced through a blow-tube into the mould and cooled down under pressure. Thereafter the product can be taken out. The injection moulding process brings about a steady wall-thickness.

For the manufacture of various products particular tools are needed the design and fabrication of which requires a special knowledge.

Well-known injection moulding machine types are: Knasy, Battenfeld, Corpoplast. Stoppers, caps and other closure elements can also be fabricated by injection moulding, first of all from LDPE and HDPE base materials.

3.4. Paper based packagings

A/ Some kinds of paper used for the packaging of pharmaceuticals:

- printing papers: India paper, weight 50 g/m^2 /prospectuses/
  printing paper of 50-70 g/m^2 weight /labels/
- paperboard: weight: 180-400 g/m^2 /cartons, printed boxes/
- containerboard: weight: over 400 g/m^2 /shipping containers/
- corrugated board: shipping containers, made in four flute sizes and several thicknesses depending on the shipped products
- shelf-adhesive labels: for identification of the products on all levels, from the single bottle to the shipping container.

B/ Paper as packaging material may have a direct contact with the pharmaceutical preparation as a paper bag or sachet. In general, paper is used for the packaging of pharmaceuticals in combination with plastics /e.g. PE-PVC-coated/. The paper based packages play the role of information vehicles. Therefore in every package of pharmaceuticals, paper appears as a subsidiary printed material.

Paper based packaging materials without imprints having no direct contact with the pharmaceutical preparations:

- shipping containers /printed containerboard/
  shipping containers /microwave corrugated board/

may have 3 layers,
5 "
7 "

Freight and ocean shipping containers are made from boards containing 5 or 7 layers.

C/ Outer paper packagings having no direct contact with the pharmaceutical products are: paperboard box, containerboard box, corrugated and solid fibre box as well as fibre drum for large distribution packages.

In humid tropical climatic zones - except impregnated paperboard - aforementioned packagings must not be used for shipping and processing unless climatized conditions could be created.

3.5. Techno-economic evaluation of packaging materials for pharmaceuticals

Concerning the different packaging materials analysed in this chapter the following result can be summarized:

Glass packaging is the oldest and widely used packaging for pharmaceuticals. The main advantages of glass are the very limited interaction between product and packaging as well as the excellent protective characteristics. Glass packaging is particularly advantageous from the point of view of tropics -resistance /realized by a hermetic metal cap closure/. Moreover it is very well cleanable and sterilizable. A disadvantage of the glass is the relatively high volume-weight and large unit-dimension in empty form. If the glass should be transported or imported from a long distance it needs a relatively high transport cost. According to the experiences 150-200 km is the maximum distance from where it

is reasonable to collect glass containers for the filling process. Above that the cost of distribution on the one hand and the amount of breaking of glass containers on the other hand become very high which jeopardizes the profitability of the application.

Plastic packaging materials - above the significant technological benefits - has a major advantage of easy and low-cost transportablity in the form of film or granulate /intermediate/ to be processed on the spot. The specific weight of the packaging itself being considerably less than that of the glass container. Consequently the small weight of the filled plastic packaging can result a significant saving in transportation costs.

The simultaneous processing of the plastic packaging material in the pharmaceutical production unit has an additional advantage: the plastic granulate needed for the production requires substantially less storing and inventory costs than in the case of glass packaging stocks./ The storing space needed for plastic granulate is one twentieth of that of glass containers/.

Plastic packaging implies far more possibilities of application than glass containers, and offers a large scale of packaging products including flexible and laminated packagings but also rigid containers.

The processing technologies of injection moulded and blow moulded products can be built up as "bricks" and linked with each other in an adaptable way. By means of these methods different alternatives of quantity and assortment can be developed.

After all, the choice of plastic packagings is practically unlimited and satisfies the most particular requirements of utilization, taking into consideration

especially the packaging material combinations.

As a further advantage can also be regarded that the production capacity of plastic packagings can be established in an easier and quicker way, and at much lower investment costs /machinery, energy etc./ than required by the production of any other packaging media.

Rigid plastic containers has the same disadvantage like glasses from the point of the transport of large container dimensions. Moreover it is difficult to ensure the prescripted cleanness and sterility of plastic packaging media.

It is worth mentioning that plastic packagings are more sensitive to certain environmental effects /e.g. climatic factors/ than glass containers.

Paper-pack materials have good properties from the point of transportation /light, flexible/. At the same time paper is very sensitive to vapour and humidity, sunshine, fungi etc. So they should be used in risky climatic conditions only in the form of laminations with plastic/s/ and/or aluminium foil for pharmaceutical packaging.

For outer packaging the paper - with special coatings or improved properties for tropical use - has significant advantages and it is a highly economic media.

Metal based packaging has good protective characteristics and used for pharmaceuticals, mainly for ointments. Significant disadvantage is the limited space utilization originated from the dimensions of metal containers.

Metal closures have still high importance in pharma-

ceutical industry being the most important, economic devices for tamper-resistant packaging.

The Annex No 5 contains an indicative list of manufacturers and suppliers of different packaging materials, containers and closures for pharmaceuticals.

4. REGULATIONS FOR THE CONTEMPORARY PACKAGING OF PHARMACEUTICALS AND THEIR DEVELOPMENTAL BACKGROUND

4.1. Questions arisen in connection with the regulations

Pharmaceutical preparations influence health in a direct way, being correlated with the environment. Thus, drugs cannot be considered as neutral products, and they require specific regulations in the field of packaging as well. The regulations in question are mostly of legal character and should include the following issues:

- basic requirements related to the packaging of pharmaceuticals,
- authorized and accepted packaging methods divided into groups according to different aspects /e.g. product category as a given kind of injection fluids or packaging form as blister packaging etc./
- the scheme of the requirements in relation to the use of packaging materials and equipment for the packaging of pharmaceuticals as well as the methods and procedures of the tests, qualifications, acceptance and control.
- the specific requirements laid down for the shaping of pharmaceutical packaging /dosage, information contents, how to open and handle the unit package/.
- sales rules /e.g. drugs freely distributed /OTC drugs/ or only through pharmacies by medical prescription /ethical drugs/.

The above mentioned regulations appear in different forms, depending on their importance and character. These regulations can mostly be regarded as sources of law and, at the same time, they represent hierarchical correlations. The usual and also internationally well-proved forms of the regulations

are as follows:

- law,
- government and ministry-decrees,
- regulations issued by authorized bodies,
- standards and technical guidelines,
- contracts, specifications,
- self-regulation.

It is purposeful that the general requirements in this domain as well as the specific requirements affecting the shaping of pharmaceutical packagings should be regulated by law or decree. The establishment of the rules concerning the range of the approved packaging methods, the continuous maintenance and registration of this regulation as well as the regulatory function in the field of distribution and sales can be referred to authorized bodies. Standardization, technical guidelines, self-regulations, or contractual stipulations can be applied to the requirements connected with the packaging materials and equipment and to such special fields as qualification, tests and quality control.

In order to perform these tasks of regulation and recommendation the international experiences initiate the utilization of the following indicative sources:

- ISO standards,
- GATT notifications,
- The International Pharmacopeia,
- The U.S.Pharmacopeia,
- The British Pharmaceutical Codex,
- WHO recommendations,
- Publications of the International Federation of Pharmaceutical Manufacturers Associations /IFPMA/

It is necessary to follow with attention the changes in the enumerated exemplary international or national standards as well. As an example, the Annex No 6 summarizes some important changes in the ISO regulations and GATT notifications effected within the period January 1, 1986 to September 30, 1989.

The rules relating to the labelling of the preparations must be considered as a question of high priority because it plays an important role in the identification and control, in the handling and use of the pharmaceuticals. The requirements prevalent in the different countries were published in the collection "Legal and Practical Requirements for the Regustration of Drugs /Medicinal Products/ for Human Use", IFPMA.

In general labels should give the following information both on outer and inner packagings:

- Official /registered/ denomination of the pharmaceutical preparation,
- Quantity of the preparation put or filled into the packaging,
- Active ingredients, their quantity,
- Exact quantity of the additives the mass of which is not indifferent from the viewpoint of medical effects,
- Manufacturer's name and address,
- Official licence /register/ number,
- Instruction for application, dosage and use,
- Indication and counterindication,
- Whether the preparation is subject to prescription,
- Expiration date,
- Storage instructions if needed,
- Other necessary data /e.g. importer, retail price/.

4.2. Requirements of control by the Good Manufacturing Practice

Chapter 4.1. has presented the possible ways of the regulation of pharmaceutical packaging. The quality control of the packaging materials is a good example for this. Owing to the importance of quality control, national Pharmacopoeias prescribe its general aspects and methods in the frame of Good Manufacturing Practice. On the other hand, each manufacturer and distributor of pharmaceuticals, keeping the general regulations of the GMP, must elaborate and operate the quality control regulation of the inner packaging materials/media adapted to its own functioning conditions /factory GMP/.

The following items serve as examples for the general GMP packaging quality control regulations, published in national pharmacopoeias /as in the USP/. Annex No 7. presents the GMP packaging directives in a pharmaceutical factory, as an example.

Indicative list of general GMP reqirements:

a/ There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, examination, and/or testing of labelling and packaging materials including drug product containers and closures; such written procedures shall be followed. Labelling and packaging materials shall be representatively sampled, and examined or tested upon receipt and before use in packaging or labelling of a drug product.

b/ Any labelling or packaging materials meeting appropriate written specifications may be approved and released for use. Any labelling or packaging materials that do not meet such

specifications shall be rejected to prevent their use in operations for which they are unsuitable.

c/ Records shall be maintained for each shipment received of each different labelling and packaging material indicating receipt, examination or testing and whether accepted or rejected.

d/ Drug product packaging materials, containers and closures shall not be reactive, additive or absorptive so as to alter the safety, identity, strength, quality or purity of the drug beyond the official or established requirements.

e/ Standards or specifications, methods of testing and where indicated, methods of cleaning, sterilizing and processing to remove pyrogenic properties shall be written and followed for drug product-pack materials, containers and closures.

4.3. Formation of the developmental background

In the developing countries, the development of packaging constitutes one of the chief backgrounds of the establishment of a pharmaceutical industry and a supply of satisfactory level. This development is based on three factors:

- foundation of technical and material bases
- creation of an intellectual background
- raising of the logistic infrastructure to a convenient level.

The first topic is dealt with in the chapter No 3. while the logistic questions are discussed in the subchapter No 4.4. In this part, some problems of the intellectual background are analyzed.

The packaging operations of pharmaceuticals require a lot of knowledge, information and professional training,

furtheron they imply at the same time:

- the organization of an information centre,
- the professional training of specialists of various levels,
- the establishment of profiled capacities for research and development.

The information centre should be based on a collection of special literature comprising the standard regulations being in force in the given country, in international or in the important foreign relations and, in the most developed countries, respectively. Besides, the library of the information centre should acquire the basic technical books, trade periodicals and other documents.

It is purposeful to build up a computerized processing system for the whole information material which can be operated by mini and personal computer respectively.

The information base may be established in the sphere of interest of the manufacturer as well but preference should be given to locate it in an institutional centre covering the whole domain of packaging. In this way the collection of standards and reference books for professional training can satisfy without any difficulty the requirements of the pharmaceutical industry as well.

Professional training is one of the important preconditions of a substantial progress. Depending on the tasks to be performed, training courses of basic secondary or higher level have to be organized. The completion of basic courses is needed for the proper packaging workers, machine operators and mechanics as well as for the servicemen charged with the handling of packaging materials and equipments or of the finished packagings /storemen and market-men/. Training courses of secondary and higher level can be organized in a postgraduate

form for those technicians being in command of a basic qualification who want to be appointed planning, development and management duties. The programme of the training courses to be adapted to various degrees is outlined in the Annex No 8.

The research and development activity of pharmaceuticals has to be carried out on an adequate experimental base. It is indispensable that the laboratories to be established should be adapted for basic physical, chemical, mechanical and interaction tests. The instrumentation of the laboratories can be completed gradually according to the prevailing development trends. The specialized R+D centre can possibly be brought into action within the frame of a national packaging research and/or development institute in order to exploit the equipment and knowledge of the specialists in the optimal manner.

Considering the present conditions and potentials, it is worth having in view the following tasks:

a/ Evaluation of the suitability of the domestic basic materials as well as of the finished packaging materials,

b/ Quality control of packaging machines, equipment and systems manufactured or imported in a country including the conditions of operation.

c/ Adaptation of pack materials, media and machines of well-proved results obtained in the developed countries.

These R+D centres may be charged with the task to elaborate the methods of the acceptance, qualification, quality insurance of the usable packaging materials, equipment and finished packagings as well as to precondition and train the personnel.

4.4. Development of a logistic background

The building up of the logistic process comprising the product and information flow beginning from the pharmaceutical factory to the user depends on the questions whether

- hospitals or other institutions should be supplied,
- the products are distributed through the network, of the pharmacies,
- OTC or a wholesale distribution system is adopted.

The supply in big units or in bulk can be based on the various kinds of unit loads /pallets, containers/. It is a necessary precondition that adequate materials, handling machines and equipment /forklift truck, crane/ should be at disposal on each loading and unloading, handling points. Where complete transport chain cannot be set up, a throw-away system has to be built for making unit loads.

The sale through the pharmacy network requires the implementation of consumer collective and transport packaging as well. Transport packaging is applied during the transport route to the distribution centre. From there collective package is used to the point of sale.

The well designed transport and collective packaging is the most important mean in the distribution chain during the transportation, handling, storing processes to protect the medicines from the mechanical hazards. At the same time it is necessary to protect the transport and collective packagings /corrugated boxes etc/ from the most dangerous climatic hazards. In difficult , e.g. tropical, conditions it needs a special "distribution background" of climatized warehouses and transport devices for pharmaceuticals.

Annex No 1.

Pharmaceutical dosage forms*
examined in the study from packaging aspect
/Definitions/

1./ TABLETS

Tablets are solid dosage forms containing medicinal substances with or without suitable diluents. They may be classed, according to the method of manufacture, as molded tablets or compressed tablets.

The preparation of compressed tablets is almost exclusively a large-scale production process, although small hand-operated or mechanically driven single-punch machines are available for small-scale operations. The vast majority of all tablets manufactured are made by compression. Compressed tablets can be produced in a wide variety of sizes, shapes, and surface markings, depending upon the design of the punches and dies.

Molded tablets are prepared by forcing dampened powders under low pressure into die cavities. Solidification depends upon crystal bridges built up during the subsequent drying process, and not upon the compaction force.

2./ COATED TABLETS

Tablets may be coated for a variety of reasons, including protection of the ingredients from air, moisture, or light, masking of unpleasant tastes and odors, improvement of appearance, and control of the site of drug release in the gastrointestinal tract.

Classically, tablets have been coated with sugar applied from aqueous suspensions containing insoluble

* Compiled from the U.S. Pharmacopeia, 1985.

powders such as starch, calcium carbonate, talc, or titanium dioxide, suspended by means of acacia or gelatin. For purposes of identification and esthetic value, the outside coatings may be colored. The finished coated tablets are polished by application of dilute solutions of wax in solvents such as chloroform or powdered mix.

3./ CAPSULES

Capsules are solid dosage forms in which the drug is enclosed in either a hard of a soft, soluble container or "shell" of a suitbale form of gelatin. Hard gelatin capsule sizes range from No. 5, the smallest, to No. 000, which is the largest, except for the veterinary sizes. Factory-filled hard capsules are often of distinctive color and shape or are otherwise marked to identify them with the manufacturer.

Hard gelatin capsules are made from special blends of bone and pork skin gelatins of relatively high gel strength.

Soft gelatin capsules generally require large-scale production methods. The gelatin shell is somewhat thicker than that of hard capsules and is plasticized by the addition of some polyol, such as glycerin or sorbitol.

4./ SYRUPS

Syrups traditionally are solutions of concentrated sugar, usually sucrose, intended for oral administration, often containing additional flavoring agents,

and into which medicaments are incorporated. A near-saturated sucrose solution in purified water is known as syrup or "simple syrup".

Syrups may contain a small concentration of alcohol as a preservative or as a solvent to incorporate flavors. Antimicrobial agents may be present to prevent the growth of bacteria, yeasts, and molds. When the syrup contains a medicament, the product is described as a medicated syrup. Syrups require storage in tight containers.

5./ INJECTIONS AND INFUSIONS

In this study the sterile preparations for parenteral use are grouped into three classes, defined as follows:

a./ medicaments or solutions or emulsions thereof suitable for injection, bearing titles of the form, - Injection;

b./ dry solids or liquid concentrates containing no buffers, diluents, or other added substances, and which, upon the addition of suitable solvents, yield solutions conforming in all respects to the requirements for Injections, and which are distinguished by titles of the of the form, Sterile;

c./ preparations the same as those described under /b./ except that they contain one or more buffers, diluents, or other added substances, and which are distinguished by titles of the form, for Injection.

The designation Large-volume intravenous solution - infusion - applies to an Injection that is intended for intravenous use and is packaged in containers holding 100 mL

Containers, including the closures, for preparations for injection do not interact physically or chemically with the preparations in any manner to alter the strength, quality, or purity beyond the official requirements under the ordinary or customary conditions of handling, shipment, storage, sale, and use. The container is made of a material that permits inspection of the contents.

Annex No 2.

EXAMPLES OF TAMPER-RESISTANT PACKAGING

PACKAGE TYPE	TAMPER PROTECTION
1. Film Wrappers	A transparent film with distinctive design is wrapped securely around a product or product container. The film must be cut or torn to open the container and remove the product.
2. Blister or Strip Packs	Dosage units /for example, capsules or tablets/ are individually sealed in clear plastic or foil. The individual compartment must be torn or broken to obtain the product.
3. Bubble Packs	The product and container are sealed in plastic and mounted in or on a display card. The plastic must be torn or broken to remove the product.
4. Shrink Seals and Bands	Bands or wrappers with distinctive design are shrunk by heat or drying to seal the union of the cap and container, The seal must be cut or torn to open the container and remove the product.
5. Foil, Paper, or Plastic Pouches	The product is enclosed in an individual pouch that must be torn or broken to obtain the product.
6. Bottle Seals	Paper or foil with a distinctive design is sealed to the mouth of a container under the cap. The seal must be torn or broken to open the container and remove the product.
7. Tape Seals	Paper or foil with a distinctive design is sealed over all carton flaps or a bottle cap. The seal must be torn or broken to open the container and remove the product.
8. Breakable Caps	The container is sealed by a plastic or metal cap that either breaks away completely when removed from the container or leaves part of the cap attached to the container. The cap must be broken to open the container and remove the product.

9. Sealed Tubes	The mouth of a tube is sealed and the seal must be punctured to obtain the product.
10. Sealed Carton	All flaps of a carton are securely sealed and the carton must be visibly damaged when opened to remove the product.
11. Aerosol Containers	Aerosol containers are inherently tamper resistant.

ENVIRONMENTS AND THEIR FACTORS
Characteristics of the technical climate-divisions

/From the Hungarian national standard of MSZ 8882/1-69/

Climate region	Features /characteristics/
1./ Cold climate division	In the coldest month the monthly average temperature is below -15 ^{o}C. A temperature below -40 ^{o}C is to be expected every year. In the extremly cold climate region temperature may fall below -55 ^{o}C and what is more in the Antarctic below - 80 ^{o}C. The absolute steam-pressure is very low, so the high relative humidity has no significant effect. Additional characteristics: white-frost, formation of rime, ice accretion, heavy snow-storms.
2./ Temperate climate divison	The monthly average temperature fluctuates largely between -15 ^{o}C and +25 ^{o}C. In winter temperature rarely goes down below -30 ^{o}C, and in summer it rarely rises above +37 ^{o}C. A $\geq$20 ^{o}C temperature with a simaltenous $\geq$80% relative humidity rarely occurs. It is the occurence of a temperature below -25 ^{o}C which is characteristic of the difference between the warm temperate and the cold temperate climate. A temperate below -25 ^{o}C occurs in the cold temperate climate. Additional characteristics: there is rainfall every month, in winter largely in form of snow.

Climate region	Features /characteristics/
3./ Dry tropical climate division	The monthly average temperature is above + 22 °C at least in one amonth with no simultenous high relative humidity /in the extremely dry tropical climate region above +25 °C/. Besides the very high temperature /the yearly average value up to +45 °C/ low temperature is also typical /up to -10 °C, in the Gobi-desert even below -25 °C/. In the extremely dry tropical climate region the yearly maximum normal value may rise above +45 °C. The highest temperature up till now has been registrated in North Sahara. Its value is +57,8 °C. Additional characteristics: high global radiation, low humidity, great daily fluctuation in temperature, high sand and dust concentration of the air.
4./ Humid tropical climate division	A ≥20 °C temperature and a simultenous ≥80% relative humidity continuously exists for 12 hours every day and for a period of 2 month at least. The normal value of the monthly average temperature is above +20 °C for at least a month. An extremely high temperature above +40 °C is rare. The normal value of the monthly rainfall is often above 200 mm. The alternating humid warm /hot/ climate region can be characterized by the alternation of humid and dry seasons.

Climate region	Features /characteristics/
	There are regions where humid seasons are followed by seasons corresponding to the temperate climate /e.g. South China/. In the coastal strip of the Arab-Persian Bay /extremely humid-hot climate region/ occur temperatures above + 35 ^{o}C with simultenous relative humidity above 80%.

Annex No 4.

INDICATIVE LIST OF MANUFACTURERS OF SKINPACK, BLISTERPACK AND CONTAINER /FILLING, CLOSING, CARTONING/ PACKAGING MACHINES

Company	Sphere of activity
1./ Uhlmann Pac Systeme D-7958 Laupheim Uhlmannstrasse 14-18 GFR	Thermoforming, filling and closing machines
2./ Waldinger GmbH Maschinen und Apparatebau Fockesstr. 33. D-7958 Laupheim GFR	Thermoforming, filling and closing machines blister machines for ampoules
3./ Hassia Verpackungs-maschinen GmbH D-6479 Ranstadt 1 / Hessen Postfach 1120 GFR	Forming, filling and closing machines for flexible packages /Infusion bags/
4./ Honing AG packaging / Tobacco Division Witikonerstr. 173. CH-8053 Zürich Switzerland	Filling and closing machines
5./ Soteco GmbH "IMA GROUP" Heiligenstädterstrasse 32 A-1190 Wien Austria Agent: IMA S.p.A. I-40064 Ozzano Emillia Bologna Via Emillia 394 Italy	Tube feeding, filling and closing machines Thermoforming, filling and closing machines, blister packs, infusion bags etc.

6./ Harro - Höfliger Verpackungsmaschinen GmbH Laudhausstr. 8. D-7151 Allmersbach im Tal GFR	Thermoforming, filling and closing machines, blister packages, flexible packages Folding box erecting, filling on closing machines
7./ Robert Bosch GmbH Geschäftsbereich Verpackungsmaschinen D-7050 Waiblingen Stuttgarter str. 130. Postfach 1127 GFR	Filling and closing machines for rigid packages, ampoules, glasses Thermoforming, filling and closing machines, blister machines, flexible packages Folding box erecting, filling and closing machines Labelling and marking machines Machines for cleaning, drying and protecting from microorganisms of packaging materials and packages Aseptic and vacuum packaging machines
8./ IWK verpackungstechnik GmbH D-7513 Stutensee, Lorenzstrasse 6. Postfach 1151 GFR	Thermoforming, filling and closing machines, blister machines Inspections and testing equipment for packaging processes, checking scales
9./ C.E. King Ltd 41 London Street GB-Chertsey/Surrey England	Filling and closing machines for riding packages, bottles, glasses
10./ Bausch + Ströbel Maschinenfabrik GmbH. & Co. D-7174 Ilshofen Postfach 20	Filling and closing machines for rigid packages, ampoules Packaging machines and packaging lines with special product protection devices

11./ Otto Hänsel GmbH Produktbereich Klöckner - Wolkogon Industriestr. 57. D-4800 Bielefels 11. Postfach 119353 GFR	Thermoforming, filling and closing machines, blister packages etc.
12./ Somatak H-7622 Pécs Szalai A. u. 15. Postfach 201 Hungary	Labelling and cartoning machines

INDICATIVE LIST OF MANUFACTURERS OF PACKAGING MATERIALS AND CONTAINERS FOR PHARMACEUTICALS

Company	Sphere of activity
1./ Alcan Aluminiumfolienwerk GmbH & Co. D-1000 Berlin 27 Hobzhauzer Strasse 96. GFR	Laminated aluminium foils Aluminium foils
2./ Aluminiumwerk Tscheulin GmbH D-7835 Teningen 1. Fr.-Meyer Strasse 23. Postfach 1160 GFR	Laminated aluminium foils Aluminium foils Closures, closing means Climatic packaging /tropicalized protective packaging/
3./ Alcan Aluminiumwerke GmbH Werk Göttingen D-3400 Göttingen Hannoversche Strasse 1. Postfach 1241 GFR	see in No 2.
4./ Pharma - Metal GmbH D-5190 Stalberg-Vicht Eifelstrasse 63. Postfach 810 GFR	closures, closing means
5./ Alusingen, Aluminium - Walzwerke Singen GmbH Alusingen Plaz 1. D-7700 Singen / Hohentwiel GFR	Aluminium foils, laminated aluminium foils Climatic packaging /tropicalized protective packaging/ Blister packages Closures, closing means

6./ Franz Pohl Metall und Kunststoffwaren-fabrik GmbH Hertz str. 12. D-7500 Karlsruhe 21. GFR	cap closures, closing elements
8./ Helvod Pharma N.V. Industriepark B-3820 Alken Belgium	see in No 7.
9./ Adriaplast S.p.A. Via Lorenzini 12. I-20139 Milano Italy	PVC-, and PVdC foils
10./ Mazzucchelli Celluloide s.p.a. Castiglione Olona /Varese/ Italy	Blister packaging, PVC, PVdC foils
11./ TVK-Tisza Integrated Chemical Works Postfach 20. H-3581 Leninváros Hungary	PE, PP, BOPP foils bags, containers
12./ Borsodi Vegyi Kombinát Borsod Integrated Chemical Works Postfach 208. H-3702 Kazincbarcika Hungary	PVC foils for blister packaging
13./ Papíripari Vállalat Kiskunhalas H-6400 Kiskunhalas Hungary	Fiber - drums

14./ Ampullenfabrick De Nederlandse De N.A.F.B.V. NL-6541 RP Nijmegen Postfach 1274 Netherlands	ampoules
15./ Pharma - glas Volgelwerder str. 65a A-5020 Salzburg Austria	Flacons, glasses
16./ Continental Fiber - drum 21 Harbor Plaza Box 10303 England	Fiber - Drums
17./ Gunter Gotz GmbH Huttengasse 53 A-1160 Wien Austria	EAN - cod systems Pharma - cod process-Controling machines /in-process-control/
18./ bicke Wolf GesmbH 1231 Wien Breitenfurter str. 260 Austria	different packaging materials
19./ MCG Closures Limited PO. Box 32 Bromford Lane West Bromwich West Midlands B70 7HY England	Metal and plastic closures
20./ Johnsen & Jorgensen /Plastics/ Ltd Parkside House, Grinstead Road London SE8 5AB England	Plastic containers and closures /SECURITAINER/

21./ Bormioli Rocco /UK/ Ltd.
I-20094 Assago, Milano
Fiori, Edificio E/3
Italy

ampoules

Annex No 6.

GATT NOTIFICATIONS AND ISO STANDARDS - IN CONNECTION WITH PHARMACEUTICAL PACKAGING - PUBLISHED BETWEEN 1 JANUARY AND 30. SEPTEMBER 1989.

Number and place of issue	Title of Notifications and standards
ISO TC76 1135/1	Transfusion equipment for medical use; glass transfusion bottles, closures and caps
ISO TC76 88-72	Aluminiumcaps for transfusion, infusion and injection bottles
ISO TC76 8362/2	Injection containers for injectables and accessories; Pf.2. Closures for injection vials
88.85 USA	Tamper-resistant packaging requirements for certain over-the-counter /OTC/ human drug products
88.141 CANADA	Food and drug regulations - Amendment
88.169 USA	Cold, cough, allergy, bronchodilator and antiasthmatic drug products for over-the-counter human use
88.180 USA	External analgetic drug products for over-the-counter human use
88.213 EK	Proposals for a Cornail Directive Concerning 88/c 36/01-05 and C 308/01-10 /packaging regulations/
86.14 JAPAN	The 11th edition of the Pharmacopoeia of Japan /established as follows (1).....(5)

Number and place of issue	Title of Notifications and standards
87.89 CANADA	Food and drug regulations, amendment /the definition of "Child resistant package"/
87.133 SWEDEN	Legislation on drugs /packaging aspects/ /the agreements between the state and Apoteksbolaget AB/ /National Corporation of Swedish Pharmacies/
87.164 CANADA	Cosmetic regulations - Amendment /schedule No.643/ Regulatory/Impact analysis statement
88.29 USA	Oral health care drug products for over-the-counter human use
89.106 CANADA	Food and drug regulation - amendment /schedule No. 612./ Revision to the limits of variations for package content
89.185 USA	Current good manufacturing practice in Manufacture, Processing, Packing or Holding /proposed revision of certain labelling controls/

Annex No 7.

PACKAGING DIRECTIVES OF PHARMACEUTICAL PRODUCTS IN CONFORMITY WITH THE GOOD MANUFACTURING PRACTICE

Introduction

The present directives will contribute to the accomplishment of all practical tasks in the field of packaging of pharmaceutical products pointing out the main aspects as well as the requirements laid down for manufacturers by the different professional control organizations. The directives in question are not of legal force but they establish a regulation enabling the pharmaceutical market to "realize the principle of good manufacturing practice" /GMP/.
Other methods and measures equivalent to the described ones can be accepted in the same way.

Definitions

Packaging

All operations, filling and labelling included in the course of which the bulk product is fully processed for distribution.

Packaging material

Any material to be utilized throughout the package process of pharmaceutical products.

Primary packaging material

The packaging material having direct contact with the drug and possibly influencing in this way the quality of the preparation.

Printed packaging material

The packaging material printed by any printing or similar

method carrying the information pertaining to the preparation.

1. Personnel

1.1. The person responsible for the management of the packaging workshop must be in command of the necessary professional knowledge and practice.

1.2. Great care should be taken of the professional training of the personnel of the packaging workshop according to the statutes of Controlled Pharmaceutical Production.

2. Premises and equipment

2.1. The rooms serving for the package of pharmaceutical preparations must be projected in such a manner that they should comply with the operations to be performed there and at the same time, any mixing and contamination could be avoided.

2.2. Special attention must be paid to the areas where the pharmaceutical preparations are exposed to environmental effects. In this case the same quality level has to be ensured as prescribed for the production process of the preparation in question.

2.3. In the packaging workshop, sufficient room must be reserved for the separation of materials not needed for the current operation.

2.4. In the rooms a satisfactory lighting has to be guaranteed, especially at the machine control points.

3. Packaging materials

3.1. Manufacturers of pharmaceuticals must select carefully the suppliers of packaging materials that might influence the quality of the preparations. The decision in this respect can only be made after

the matter has been discussed with the quality control department and other competent sections.

3.2. Manufacturers of pharmaceuticals have to ensure that the suppliers should pack the ordered packaging material in a way that the shipment should be protected against damages, contamination and confusion. In order to avoid any mixing, these materials should be handled by the suppliers with special care.

3.3. In a case the packaging material must satisfy certain microbiological requirements, the manufacturer has to make certain whether the hygienic measures taken by the supplier are sufficient.

3.4. The packaging material should be qualified for the requested purpose without damaging the preparation in question. The primary package should provide sufficient protection against external effects and possible contaminations, furtheron, it should resist any necessary antimicrobial handling.

3.5. Printed packagings have to be designed according to the accepted regulations and have to be approved by the quality control authority. The exteriors of packagings have to be distinguished from each other in order to avoid any misuse or confusion. If possible the identification code numbers or markings should be indicated on the packaging.

3.6. The technical descriptions of the packaging materials are approved by the quality control authority. As far as printed or primary packages are concerned, these descriptions should contain at least the following data:

a/ individual internal denomination of the material and/or its code number,

b/ description of the material, i.e. exhaustive characterization, dimensions, composition and quality requirements,

c/ particular data of the quality control tests, in accordance with the description /specification/,

d/ storing conditions,

e/ code date if necessary.

3.7. For comparison purposes, a collection of samples of all printing materials has to be maintained in a way that no item of the collection should be used up.

3.8. The receipt, registration, sampling and examination of printed and primary packaging materials should be effected according to written instructions.

3.9. Printed and primary packaging materials have to be marked with code number or identification label referring to the shipment or the product lot in question.

3.10. Printed and primary packaging materials must be set apart until the quality control authority approves of the use of them. The release for use should explicitly be marked on the packaging material.

3.11. Printed packaging materials should be stored under safe conditions lest unauthorized persons may get at them. Cut labels and other printed packaging materials in bulk should be stored in a closed room, separated, in order to avoid mixing with other materials.

3.12. Packaging materials must not be delivered for processing without written and controlled permission or to unauthorized persons. The delivery instruction has to include the results of the identification and feasibility tests prescribed in the packaging provisions and, as far as possible, also the control system of the stock.

3.13. Obsolete or out-of-date primary and printed packaging materials and the respective printing blocks should be destroyed and this operation should be recorded.

4. Packaging provisions

4.1. Packaging provisions constitute a part of the general regulation that has to be drafted for each packaging workshop and for each preparation.

4.2. In general, packaging provisions contain the following issues or refer to them:

a/ Denomination of the pharmaceutical preparation

b/ Description of the form of the preparation and, if necessary, its power

c/ Numerical data about the dimensions of the package quantity, mass or cubical contents of the product packed in the end-container

d/ Specification of the needed packaging materials, including quantity, size and type

e/ Reference or code number of each packaging material in accordance with the technical description

f/ On occasion, a sample or copy of the given printed packaging material. The samples have to show the place where the production number and code date should be indicated

g/ Description of the packaging process inclusive of the essential elements of the used main equipment .

h/ Any preparatory operations needed for the packaging material

i/ Special safety measures

j/ The intermediary test instructions furtheron the limit values of control sampling.

5. Packaging process

5.1. In the course of the packaging design, attention should be paid to eliminating the danger of cross-contamination and confusion. Therefore, it has to be avoided that preparations of about the same exterior should be packed close to each other.

5.2. Duties before the commencement of the packaging process:

a/ It should be controlled whether every product, material or printed matter previously used but not needed for the subsequent working process, is removed from the benches, packaging lines, printing machines, stamps and other equipment. It is also advisable that this cleanliness examination should be carried out on the base of a control specification.

b/ Attention has to be given to the microbiological cleaning on the filling machine which is particularly important if the equipment has not previously been used for a space of time and/or it has been stored in humid atmosphere.

c/ Every product and packaging material conveyed into the packaging room has to be controlled before utilization with a view to their identity and conformity with the package provisions. Similarly, it should be checked whether the junction of the conduits and other conveyer elements are in accordance with the technical requirements.

d/ The exactness of all printing operations /as code number, code date/ performed during the packaging process has to be checked and documented. Hand-stamping should be checked from time to time regularly.

5.3. The containers to be filled must be cleaned. Before filling it should be taken care that such filths as glass or metal fragments should be removed from the container.

5.4. The denomination and production registry number of the preparation being packaged has to be indicated at every packaging machine and line.

5.5. If the packaging process has been interrupted for any extraordinary reason or the packaging material has been changed, the operation must not be resumed unless under the supervision of an authorized person.

5.6. Labelling should follow the filling as promptly as possible. When the containers are not labeled right after filling, the filling operation has to be organized in such a way that the products might not be got mixed up or mislabeled.

5.7. Particular attention should be paid to the use of cut labels, espesially if they receive an original stamp outside the machine line.

5.8. The proper function of every code reader, label counter and other similar devices has to be controlled and ensured.

5.9. The control performed within the machine line should include at least the following inspections:

a/ appearance of the unit package,
b/ completeness of the unit package,
c/ Whether the proper preparation or packaging material has been processed,
d/ whether the impressed data are correct.

5.10. Relabelling should not be effected unless on the base of written instructions and under particularly safe conditions.

5.11. Printed packaging materials should not overprinted with another denomination, mark of effectiveness or other pharmaceutical form.

5.12. Measures for dust prevention have to be taken in case of the packaging of solid products as well as the environmental pollution has to be controlled in the course of every packaging process.

5.13. Any printed or engraved information on the package surface should be well legible, as well as fading and detachment resistant.

5.14. As soon as the packaging operations have been done, all packaging materials having a registration number but left over should be destroyed. Packaging materials without any code mark should be conveyed to the store-room and, at the same time, this action should be documented.

5.15. The quantity of a pharmaceutical product in bulk, the packaging material used up and the number of the finished unit packages have to be verified and documented by registration. Any essential or unusual deviation should be checked up and settled in a satisfactory way before releasing the item in question.

5.16. If an unusual event occurs during the production process, the packaging operation can be continued only after a careful supervision and control effected by a responsible person.

6. Documentation

6.1. The packaging progress report is based on the packaging provisions. By completing the progress report clerical errors should be avoided.

6.2. The packaging report includes the following data which have to be registered at each processing phase:

a/ Denomination, product registration number and quantity of the finished products,

b/ Denomination, registration number and the quantity of the product in bulk to be packaged,

c/ Delivered, used packaging material, furtheron

packaging material returned to the store-room or destroyed indicating their quantity if necessary. Also the reference or code numbers /marks/ should be shown.

d/ Any other data needed for accounting the production item /see 5.15/.

e/ Confirmation of the cleanness of the packaging line before the beginning of the packaging operation.

f/ Results of the tests prescribed in the identification and packaging provisions, inclusive of those of the intermediary check inspections.

g/ Main data of the performed packaging operation, inclusive of the time spent in and the identification number of the equipment and packaging lines.

h/ Possibly a sample of the used printed packaging material as well as a code sample.

i/ Particular observations and remarks.

j/ Signature of the persons responsible for the packaging operation.

6.3. The packaging report constitutes a part of the production progress report and is subject to the supervision of the quality control authority before the given product can be released for distribution. If a single production item of a product in bulk constitutes a part of different packaging operations, this fact must be documented in order to make possible the release of any partial items.

6.4. The manufacturer of pharmaceuticals should introduce an information retrieval system that renders a survey of all production items possible when, owing to a defective packaging material, a sub-standard preparation has been manufactured.

Annex No 8.

PROGRAMME OUTLINES OF A TRAINING COURSE FOR PACKAGING OF PHARMACEUTICALS

1. Genral subjects

1.1. Fundamentals of packaging
1.2. Tasks of packaging
1.3. Specific reqirements of the pharmaceutical industry
1.4. Main forms of the packagings of pahrmaceuticals

2. Packaging materials and media

2.1. Glass packagings
- 2.11 Glass types, their characteristics and classification
- 2.12 Vials and ampoules
- 2.13 Bottles
- 2.14 Ballcon-flasks

2.2. Metal packagings
- 2.21 General characteristics of steel and aluminium
- 2.22 Foils
- 2.23 Tubes
- 2.24 Vials and bottles
- 2.25 Boxes and cases
- 2.26 Cans, pails, drums

2.3. Plastic packagings
- 2.31 Plastic materials and their classification
- 2.32 Foils
- 2.33 Tubes
- 2.34 Vials and bottles
- 2.35 Boxes and cases
- 2.36 Cans and drums

2.4. Paper packagings

2.41 Paper, paperboard, boxboard, their classification

2.42 Satchels, bags, sacks

2.43 Boxes and cases

2.44 Drums and barrels

2.5. Combined packaging materials and packagings

2.51 Characteristics and classification of combined packaging materials and packagings

2.52 Paper metal, paper plastic laminations

2.53 Plastic-plastic and plastic-metal laminations

2.54 Consisting of three or more compounds

2.6. Ancillary packaging materials

2.61 Ancillary materials, their tasks and classification

2.62 Labels

2.63 Closures

2.64 Adhesives

2.65 Adhesives and self-adhesive strips, metal strapping

2.66 Pads, vibration damper and resistant materials

2.67 Vapor barrier materials

2.68 Paints

3. Packaging technology

3.1. General knowledge

3.11 Packaging technology with regard to the specific problems of the pharmaceutical industry

3.12 Elements of packaging technology

3.13 Principles for the development of packaging technology

3.2. Preparatory tasks

3.21 Initial phases of packaging materials ha ...y and of the packaging process

3.22 Training of the personnel
3.23 Preparatory process of the product
3.24 Precursory measures to be taken at the working site and around the machines

3.3. Filling of containers with products
3.31 Dosage and filling
3.32 Wrapping and banding
3.33 Filling of containers with products

3.4. Packaging closures
3.41 Closure by use of a component of the packaging itself
3.42 Closure by a subsidiary component
3.43 Closure with an individual closure element

3.5. Joint production of packaging materials and packagings
3.51 Joint shaping and filling
3.52 Integrated shaping, filling and closing process

3.6. Marking of packagings
3.61 Marking, its tasks and types
3.62 Imprints
3.63 Labelling
3.64 Marking joined with packaging
3.65 Specific marking, identification and coding regulations of the pharmaceutical industry

3.7. Additional elements of packaging technology
3.71 Sterilization
3.72 Unit load forming
3.73 In-house packaging manufacture
3.74 Control

4. Fields joined with the packaging industry

4.1. Packaging regulations
4.11 Laws, decrees, official regulations

4.12 International regulations
4.13 Standards, technical directives
4.14 Forwarding regulations
4.15 Purchase contracts
4.16 Internal, enterprise regulations

4.2. Technological linkages
4.21 Acceptance and storage of pharmaceuticals, packaging materials and packages
4.22 Inside materials handling in packaging workshops
4.23 Storage of finished products
4.24 Dispatching and shipping

4.3. Packaging and hygiene
4.31 Basic reqirements and objectives
4.32 Environmental hygiene
4.33 Cleaning of machines and equipment
4.34 Personal hygiene
4.35 Importance of observance of hygienic regulations

4.4. Packaging and quality control
4.41 Competence of the Quality Control Authority
4.42 Control of supplied materials
4.43 Intermediary and final control during the packaging process
4.44 Examination of complaints
4.45 Organization and function of the Quality Control Authority

4.5. Organizational contact points of packaging with other branches
4.51 The rank of the packaging workshop in the production process
4.52 Organization of the packaging workshop
4.53 Interlinkage of packaging, material supply, production, marketing and distribution, research and development and quality control.