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EVALUATION OF THE PACKAGING PROBLEMS OF BIOCHEMICAL REAGENTS IN THE FINLAY INSTITUTE

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CUBA

Technical report: Findings and recommendations *

Prepared for the Government of Cuba
by the United Nations Industrial Development Organization
acting as executing agency for the United Nations Development Programme

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Vienna

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ABSTRACT

Objective: To improve the design and the quality of packaging materials used in the pharmaceutical industry

I. The first part of the report describes the types, quantity, components, specifications and defects of the packages used in the Finlay Institute; the quality control of the packages; the procedure for the selection of a new package; the Good Manufacturing Practices to be applied; the control Laboratories in Finlay Institute; the visits in the pharmaceutical group and in the suppliers factories; the contacts established in Embassies of the countries capable to cooperate with the Cuban pharmaceutical industry in the packaging field.

II. The second part contains the various recommendations suggested to the Finlay Institute, the pharmaceutical group and their package suppliers, the Cuban Administration, the bilateral cooperation between Finlay and UNIDO.

III. In the third part, annexes supplement the report and one of them contains complete reports on the visited factories.

Contents

PART I

FACTS FINDING

I. THE PACKAGES IN FINLAY INSTITUTE

A. TYPES OF PACKAGES

Six types of packages are used in Finlay Institute:

1. For the primary packages

a) Glass bottles and vials

i) Bottles: mainly in ambered glass ordinary used for the pharmaceutical industry (class III glass), imported by MediCuba (from Saint-Gobain Desjonquères, France);

ii) small vials: for some reagents (all made with class I glass). All are made by blow-molding except one series (made in La Lisa plant of Union de Vidrio, with glass I road imported from Mexico).

Some of the vials are sold with a closure including a dropping pipet in glass.

b) Plastic products

i) Plastic bottles
in high density polyethylene (HDPE), imported from Germany (Pohli factory).

c) Plastic closures
in Bakelite phenolic resin (black closures), PP and probably for some in HDPE sold by the same supplier than the glass and plastic bottles.

d) Rubber stoppers
Made in Butyl (bromo- and chloro-) rubber, supplied mainly by the German company Pharma-Gummi and for a part by the French company Verneret.

2. Secondary packages

Carton boxes manufactures and printed in Cuba

3. Shipment boxes

Corrugated boxes made in Cuba

B. QUANTITIES OF PACKAGES

The quantity of each packages, used in all the Cuban pharmaceutical industry, have been determined by family:

1. Ampoules

17.5 Millions equivalent to about 140 T/glass roads

2. Glass vials

22.176 Mx 347 t
(in which ambered 0.721 = 24 t)

0.39 Mx 31.8 T
(in which ambered glass 0.620 = 15.2 T)

3. Glass bottles

11.7 Mx 2626 t
(in which ambered glass : 1,6 Mx = 173 t)

0,82 Mx 252 t
(in which ambered glass : 0,429 = 220 t)

27.851 Mx 1147 t
(in which ambered glass : 26 Mx = 603 t).

4. Plastic bottles

0.11 Mx 2.3 t

0.03 Mx 90 t.

5. Closures

33.5 Mx 30 t

6.16 Mx 16 t

16.355 Mx 33 t

(for memory, Cuba having no cork-tree)

6. Aluminum containers

4.732 Mx (=400-500 t)

7. Blister components

8. Secondary carton boxes

9. Corrugated boxes

REMARK

Few investments made in the packaging industry could be profitable for the Cuban industry.

1. Glass industry

A new small ampoules unit implementation has been studied in order to double the production of a rather new Italian line and to close the two old Hungarian lines; for such investment, it will be necessary to standardize as much as possible the glass (class I for instance) and the various sizes. On the other hand very few factories are selling the machines for the glass rods and ampoules manufacturing.

A new modern glass unit for the drug industry could be studied only for the ambered 60 to 150 ml class III bottles, because the same glass could be used for the food industry. At present, a pharmaceutical production of about 500 tonnes a year will never be amortized. A white class III glass line could be examined, should the exportation in large quantities of some products (rum, fruit juices) permit the development of such packages.

2. Plastic industry

Small lines could be implemented for the production of very standardized HDPE bottles and PP or HDPE closures. Such implementation, if possible in a GMP (or clean) area, could permit the development of plastic industry, mainly for the local market and some sub-regional exportations.

The production of PVC bags for blood collecting and perfusion is examined hereafter. Should a local unit be implemented, it will be advisable to implement, in the same place, a HDPE bottle production and closures, in order to take advantage of the GMP conditions.

3. Aluminum Industry

The local needs can be considered only for the collapsible tube productions. An agreement with an international aluminum manufacturer is necessary to find the equipment and a good locker producer; the use of aluminum cylindric tubes could be examined for the enzymes impregnated paper bands.

4. Special closures

Only a twist-off production could be studied. But three problems have to be solved:

- The supply of a production line (probably very few producers);
- The supply of a good plastisol (main world producer : W.R. Grace-Cryovac, USA);
- The eventual patents (opposed if the finished goods are exported).

C. COMPONENTS OF THE PRIMARY PACKAGES

As all the materials used in the packages must be conformed to a national or international pharmacopeia, it seems interesting to know (for an eventual checking) the nature of the materials. At present, Finlay Institute knows very little about their chemical composition.

1. Glass vials and bottles

   a) ambered glass
      Generally class III (ordinary glass):

   b) small vials
      Similar to antibiotic vials (Class I glass).

2. Plastic bottles

   High density polyethylene: no information on the nature of plastic additives (such as antioxidants and lubricants).

3. Plastic closures

4. Rubber stoppers

   Butyl rubber: no information concerning the vulcanizing agents and the other antioxidants.

D. SPECIFICATIONS

The specifications will be described in the following chapter.

E. DEFECTS OCCURRING ON AND PROBLEMS DUE TO THE PACKAGES

1. Glass vials and bottles

On the imported ambered glass bottles and transparent vials,

- some minor defects were noted: generally less than 5 air bubbles in the imported ambered glass wall;
- more bubbles in the Cuban bottles;
- on some of them the partition line is too important that can abrade the plastic closure, generating the contamination of the content by foreign particles and a leakage and/or evaporation of the solvent;
- one critical defect has been noted on one 50 ml vial: a crack of the bottleneck; this defects could be damageable after closing (glass scale, leakages, etc.).

2. Plastic bottles

Two defects were noted on the imported and cuban made bottles :

- on imported bottles (HDPE) lack of capacity: 115-118 ml instead of 120 ml:

- on Cuban bottles (HDPE) poor finishing of the bottleneck causing leakages and air introduction.

Another problem is occurring:

- a ready-to-use "biuret reagent" (similar to Fehling reagent [alkaline copper tartrate] is reacting with the HDPE, with a precipitation of copper sulfide and a thin black layer of the same product on the PE wall. It seems that a reducing product (anti-oxidants of the polymer?) could be the cause of this accident several solutions have been suggested:

Some tests had been conducted to determine the simplest and cheapest solution.

At present and for an accelerated test at 60°C.

- the treatment of the HDPE bottles has no (or a small) effect on the biuret reagent:

- the Finlay biuret reagent presents the same stability defect when it is packed in a glass or HDPE bottle:

- the Canadian reagent, used for the reference test, is slightly more stable in the two types of containers.

In conclusion, this last reagent may contains, (in small quantity), a special additive, used like stabilizer. It seems evident that the testing procedure for ageing (60°C) is far more severe.

II. QUALITY CONTROL OF THE PACKAGES BATCHES

The quality control department employs 18 graduate persons and 14 technicians; it works both to control the raw materials including some packages and the finished products. The four sections of the department are: microbiological, biological, chemical and animal testing; the microbiological and the chemical ones is concerned with the package testing.

a. Performed tests

The following tests are done on:

1. Rubber stoppers

All the tests described in the pharmacopoeias; the most important being the reducing substances and the UV spectrum of the migrate.

2. Glass vials and bottles

a. Vials

- alkalinity along the pharmacopoeia method;
- processability (acceptability on the filling line);
- diameter and weight;
- for class I glass (neutral glass) an analysis is made in the Technical and Pharmaceutical Laboratory (La Habana)

No other tests are done except a visual inspection in order to eliminate (and sometime complaint about) the broken vials.

b. Bottles

For the class III bottles (ordinary glass) only a dimensional control is performed for the bottle height and its screw diameters. A visual examination is done in order to eliminate the broken items. (The batches are sent on palettes with a shrinkable films; all the palettes are sent by containers).

Finlay received the specification of the French manufacturers (Saint-Gobain Desjonquères).

3. Plastic closures

Two controls are done:

a. dimensions
Diameters and height

b. nature of the liner or of the insert
In principle, if the liner is in carton, it must be eliminated.

4. Plastic bottles
More tests are performed:

a. Dimensions (diameters and height);
b. Resistance to concentrated alkaline and acid solutions followed by a visual control:

c. leakage test on bottles filled with a 15% coloured water;

d. Permeability and leakages by weighing before and after the former test of the filled bottles (1 week);

e. Capacity
Controlled by filling with a pipette.

No visual inspection is performed, except to eliminate the broken packages.

5. Pipettes

Tests are done to select an appropriate pipette (dropper), in order to obtain the same weight for each drop. According to the type of dropper, the material and the nature of the product, the weight of each drop can vary from 20 to 60 ug.

6. Carton boxes
Few tests are done:

a. dimensions
b. a printing control

7. Corrugated boxes
Only a dimensional control is performed.

8. Printing of Labels and boxes

A double check is made before printing the labels and boxes. A visit in the print shop is done in order to control the printing plate.

B. SPECIFICATIONS

The specifications, applied or to be adopted, will be described in the following chapter.

C. PROBLEMS OCCURRING ON PACKAGES

1. Plastic closures

By accident, two qualities of phenolic black closures were mixed in a German shipment; one of the colour reacted with an alkaline solution and was dissolved. The only solution was to change the closure.

2. Plastic bottles

a. The capacity of the 120 ml bottle, imported from Germany, is inferior to the nominal one in 1 or 2 ml. It may be caused by the mould design. A complaint has to be sent to the supplier.

b. Another problem is occurring during the plastic storage of the "Biuret" reagent (a reagent similar to the Fehling's); after an accelerated test a reduced copper sulfide appears, probably due to a reduction reaction.

Several tests (see above) have been proposed.

3. Glass and plastic pipettes

At present, it seems difficult to obtain pipettes distributing very constant drops, except with a model made with PE; generally, the last drop has a different size (and weight) due to capillarity on the glass rod.

4. Carton boxes
Three main defects are occurring:

a. <u>Cutting defect and poor assembly</u>
This is caused by the cutting board. A better cutting (with a laser preparation of the plywood board) could improve this operation.

b. <u>Lightness of the cardboard</u>
Caused by an inappropriate supply of the factory.

c. <u>Poor water resistance of the cardboard</u>
During summer the relative humidity is very high. A waxed carton could improve the boxes resistance to moisture, especially for those stored in a refrigerated area.

d. <u>Bad sticking of some boxes</u>
Dextrine or starch adhesive is generally used; it is suggested to be replaced by a polyvinyl acetate dispersion adhesive or dope the starch adhesive with such plastic dispersion.

5. Corrugated cartons

The same sticking problem is occurring for the same reasons as the small boxes.

III. SPECIFICATIONS FOR THE QUALITY CONTROL OF THE PACKAGES BATCHES

A. PROPOSED METHOD FOR CONTROL

The following specifications are used or could be used in the quality control laboratory to determine the conformity of the package to a pharmacopoeia:

1. Glass

A European pharmacopoeia (edited January 1983) indicates how to control the various glasses used for parenteral and injectable solutions:

For both the vials and bottles

At present, some controls are made, such as dimensional characteristics, weight, capacity. Some complementary tests are recommended to determine the type of glass (alkalinity), (for the first determination, a written guaranty of a well-known supplier could be sufficient), visual control (mainly to determine the number and importance of bubbles), glass particles in liquid after conditioning at 37°C during a week, leakages occurring after storage of a closed bottle filled with a coloured solution (eosine or methylene blue) after storage at 37°C during a week, evaporation of the content (determined by weighing after 1, 2 and 3 weeks at 37°C).

Specifications, guarantees and quality level will be required from the supplier concerning:

i) the bottles and vials (from Saint-Gobain Desjonquères);

ii) the pipettes (class I if the vial is also in class I glass)

For some special reagents, a special control has to be made in order to control the extraction of iron salts (for the chromazul reagent used for iron determination) and metallic cations (Al, Ca and Fe in the case of the solutions of colours).

2. Plastic

Several tests are described in European and French pharmacopoeias, such as:

- High density polyethylene.
- Polypropylene.
- Low density polyethylene.

No test is done at present. It seems important to do an extraction test with water and solvents (ethanol and heptane) and a UV spectrum of the migrate. Such spectrum made on each batch could be used like an identity card of the material permitting to know the changes occurring in the components and to pay attention, in this case, to the stability of the packaged reagents. It permits also to identify some of the stabilizers used in the polymer.

3. Rubber

The main tests described in the standards (DIN 58 367, ISO 8871 and European Pharmacopoeia [elastomers for parenteral solutions]) are done.

Some of them are more important such as extraction test with control of opalescence, reducing substances, heavy metals, ammonium salts, chlorides, zinc, pH and UV spectrum. The fragmentation test can be also done if the stopper is punctured by a needle. It will be necessary for some preparations to control after storage the content of some reagents in order to determine if some absorption, adsorption or desorption could occur.

B. COMPLEMENTARY SUGGESTED TESTS

1. Stoppers

a. absorption test with the product, if it contains some aromatic substances (phenol and derivatives), organic solvent (aliphatic and aromatic), fatty product (olive oil or other) or some organo-metallic components (organo-mercuric derivatives).

b. after a week (or 4 weeks) absorption test, control analytically the content of the component in the finished product.

c. If necessary, saturate the stopper (one day immersion) with the component to avoid (or limit) more important absorption.

d. In this case, control the desorption (mainly for phenol and derivatives).

2. Glass vials and bottles

a. Visual inspection to determine mainly the critical defects:

b. capacity control by weighing filled containers.

c. for some reagents (iron determination kit), use only transparent II or I glass of HDPE; if the ambered glass is used, control the iron migration in an alkaline and/or acid solution.

3. Plastic closures

a. For the coloured closures control the migration of the color in 15% ethanol solution (can be tested with spectrometer), alkaline and acid solutions (5 N for example).

b. For all the closures
- eliminate the carton liners and replace by a PE foamed liner or a PE insert;

- during a long term (3 months) leakage testing, control the apparition of stress cracking along the closure. If it appears, consult the supplier and change of reference of PE or PS.

  An accelerated test can be made by immersion of the filled bottles + closure in a 55°C hot water-bath containing 1% of a standard surfactant, during a maximum of 2 months.

4. Plastic containers

   a. Visual inspection, mainly to control the bottleneck;

   b. for the national production, control of both the diameters and of the thickness of the wall;

   c. for both the imported and national productions:
      - UV spectrum on the migrate in alcohol and hexene (or heptane);
      - ask for a guarantee to the health regulation (pharmacopoeia and/or food packaging regulation),
      - if possible ask for the qualitative indication of the stabilizers (antioxidants).

   d. capacity control by weighing filled containers.

5. Printing

   a. Control of the printing plates: they must never contain 2 or more different models (labels or boxes).

   b. Foresee, for each label, a small coloured printing (about 2x2 mm) at a specific place of the edge for each type of label, in order to facilitate the batch control.

6. Pipettes

   If they are in glass, specify a class I glass.

IV. SELECTION OF A NEW PACKAGE

A. THE PROCEDURE

In order to select a new material and a new type of packages, several steps must be followed:

1. Determination of the number of packages

Before deciding such a study, implying several months of works, an economical study is necessary: has the product a sufficient market? If not, can the product be assimilated to another similar reagent? For example, another alkaline reagent.

2. Disponibility of the packages on the Cuban market

One important point to examine is the possibility to find a local producer or to import the tested package; for example, is it possible to import PP or PET bottles without problems or is it customs regulation to limit such imports?

3. Tests to programme

a. General tests

Some tests have to be made on all the materials in order to know the level of the material inertial (glass and plastic):

- resistance in alkaline and acid solutions;
- extraction with a fresh distilled water;
- for plastics, a solvent extraction (ethanol and hexane or heptane) will permit to know the total extractable components by solvents; it will permit also to realize a UV spectrum on the migrate;
- UV spectrum who can be considered like an identification card of the material and used like a specification for the following orders.

Such UV spectrum will be made for plastics bottles, plastic closures including plastic liners and inserts inside the closure and rubber stoppers.

The conditions of such extractions are generally described in pharmacopoeias (USP, European Pharmacopoeias, etc.) for the temperature, the reagents and the time of extraction.

For alkaline and acid test, the room temperature (+20-25°C) and a week contact could be used; for the ethanol and hexane (or heptane) extraction, a reflux boiling temperature during 1 hour could be chosen.

b. Specific tests

Before selecting a material for a particular reagent, it will be

necessary to operate a long term storage test and to determine how the components (vial, bottle, closure, pipette) are changed by or change the reagent composition.

i. Operating conditions

They have to be standardized and it seems reasonable to adopt the same ageing conditions as those used to control the reagents:

- temperature	room temperature, 37 and 60°C
- time of contact	1 week, 1, 2 and 3 months A contact of 6 months could be added.

A special attention will be paid to some products :

- migration of phenolic derivatives and fungicides in the rubber stoppers or in the plastic container or closure;
- presence of iron in the package material of a reagent used for the iron determination;
- incompatibility of some products with the reagent (such as too important alkalinity for a buffer, volatile solvent in a low density PE...).

ii. Chemical determination
Two methods can be applied:

- either the chemical analysis of the reagent (sometimes it may be difficult, especially for natural products (albumen, proteins, etc.);
- or an indirect method, using the reagent in order to control the biological analysis performing normally.

In each time, the storage in the glass and/or plastic packages will be compared with a blank test.

4. Absorption and adsorption tests

These tests are very important for some specific products, such as some fungicides, aromatic derivatives, solvents who can be absorbed by the rubber stopper of some PE materials (LDPE for instance). A curious case of interaction between the reagent was noted for the "biuret" reagent (a variety of alkaline cupric sulfate and tartrate solution): after an accelerated test (60°C) a reaction occurs with the reduction of copper sulfate in copper sulfide and precipitation including the HDPE walls of the bottle and inside the bottle.

The absorption of organic fungicides, used in some preparations (albumen, vaccines, etc.) could decrease very rapidly the stability and the chemical composition of the reagent. A careful study is always useful.

5. Leakages of the containers

Such test is done for some products, with a 10-15% alcoholic solution, colored with an organic color.

Two tests have to be standardized and can be conducted at the same time as the ageing test:

a. a leakage test of the association bottle (or vial) and closure, with an aqueous solution of a colour (methylene blue or eosine);

b. an evaporation test of the same solution (or better of the reagent, controlled by weighing the filled container.

The testing conditions has to be standardized:

- temperature : 37 or 60°C
- time : 1 or 2 weeks for the leakages; 1, 2 and 3 months for the evaporation.

A longer period does not seem necessary, the 3 points obtained permitting to foresee the evolution in time.

This last result is in fact the total result of evaporation + permeation through a component of the package (bottle wall, liner or insert of the closure, closure itself). A limited decrease of the quantity ($\leq$1%) can be accepted if the precision of the clinical analytical method ($\pm$ 10% for instance) permits it.

5. Visual Inspection

Essentially to determine the main defects able to alter the ageing of the reagent:

a. defects of the bottleneck (such as screw);
b. bubbles inside the wall, etc.

6. Processability

It is always important to determine the processability on the filling machines : are the tested packages able to be used without a prohibitive cost? External diameter? Inside bottleneck diameter? Tolerances on the diameter? Good finishing and correlation between the bottleneck, insert, stopper and plastic closure?

7. Economical study

a. Such as comparison of the prices, disponibility on the local market, easy importation, custom duty?

b. Sometimes a new package can simplify the secondary package used for the reagent or the pharmaceutical product. What is the total economy ?

B. RESPONSIBILITY FOR THE SELECTION

As most of the stability tests on new products are done under the control of the research department, it could be interesting to operate the packaging study in the same department and with the same team.

As a matter of fact,

1. a part of the study is mainly technological,

2. the production department having the responsibility of the quality control of raw material (including packages), is directly concerned by the change of a material or a package, and is already performing some tests and has the equipment for it.

It seems that the responsibility for selecting a package or a new package could be assumed by the production department with the scientific and technical support of the research department well equipped with some devices (UV spectrometer, chromatography, etc.).

C. SELECTION IN SITU OF PACKAGES

A selection of the most appropriate packages was made with 5 responsible persons engaged in research or production in Finlay Institute, each of them being capable of formulating some objections for a choice. 202 reagents were examined. The results, for the 113 reagents being manufactured and the 89 in project, are the following:

- 2 need to be packed in class I vials (urease, thrombin + NaCl);
- 24 can be packed in glass class III;
- 40 need a glass II (eventually III after chemical testing);
- 117 can be packed either in glass (I or III) or in plastic (HDPE), opening a choice for a more economical solution;
- 16 can always be packed in HDPE bottles;
- 3 can be packed in glass III or HDPE;
- for one product (alumina) the reaction tube (4000 a year) used to pack alumina could be cheaply chosen in the catalogue of a specialized equipment producer.

An internal Finlay report notes the conclusions of this panel study.

The following remarks can be made for the packaging of:

1. The reference solutions

   a. All solutions have to be packaged in glass II (or I if it is more economical);

   b. for some products, HPPE bottles can be used: potassium phosphate, reference solutions for calcium, sodium + potassium, urea, sodium carbonate;

2. The buffer solutions

In order to preserve the pH of these solutions, only glass II (eventually I) or HDPE can be used;

3. The acids and alkaline solutions

They must be preferably packaged only in HDPE;

4. Specific problems

a. oxalates
Use preferably HDPE (or glass II after control of calcium ions migration);

b. iron sensible reagents and iron determination kits
Use preferably HDPE (or white glass II, eventually I); do not use ambered glass without testing the Fe ion migration; this remark is available for Dabkin, phenantroline and ferrocyanide;

c. alkaline sensible reagents
Use preferably HDPE (or glass II) for bilirubin test (containing caffeine), phenolic Folin Ciocalteu test, phosphato-tungsto-molybdic reagent; class III could be used but after testing the effect of alkalinity on the reagent;

This rule must always be applied for the buffers (see above);

d. light sensitive reagents
Some products (bilirubin) are sensitive to light; for a better preservation of the reference product, an amber glass will always be used; it is the same for the pipes reagent;

e. volatile products
Before using HDPE, an evaporation control of some components, such as acetic acid and hydrochloric acid, through the wall of the plastic containers;

f. preservatives
Some reagents, and vaccines, contains a conservator in order to preserve the biological integrity of the solution, such as: phenol, phenol derivatives, sodium azide, etc.;

Some of these organic compounds can be absorbed by some rubbers; a preliminary absorption test has to be made before using such stoppers;

g. Glass I and II
Most of the time, glass II can replace glass I; for a question of supply (vials made by the ampoule technique or produced by molding), the choice depends only on the supply possibility;

h. Glass II or III
In some cases, glass III can replace glass II probably without

problems. A preliminary migration test of alkaline products in the reagents is necessary before the change is decided;

i. HDPE

The same remark concerns the HDPE bottles; in more than 50% of reagents, they probably be used without problems; a preliminary test of ageing (37°C) is always necessary except for well known reagents (alkaline and acid solutions).

V. THE GOOD MANUFACTURING PRACTICES APPLIED TO THE PACKAGES

Like for the other pharmaceutical industries, some rules have to be observed in order to assume a permanent quality control of the vaccines and reagents kits. Such rules are generally applied within the so called Good Manufacturing Practices.

They permit, from the early part of the process (raw material controls) to the very last step (shipment or delivering) a continuous control of the quality and a guarantee of such quality.

The GMP do not concern only the raw material and the product at each step of the process, but also the packages, considered as another raw material.

The following rules have to be applied:

A. Definitions of the functions and products

1. Responsible Persons

In each factory, it is important to define the role of the most important people responsible for the GMP rules application, for instance at each step of the process especially when a quality control manager does not exist with a full responsibility of the decisions:

a. **The Production manager**

i. is responsible for the quality control of all raw materials including the packages;

ii. he refers directly to the General manager and he is assisted by the quality control laboratory and the responsible persons in charge of the reception of packages, printed boxes and labels;

iii. when necessary he can require the assistance of the Research Department Manager, especially in order to define or apply some determination methods of analysis.

REMARKS

In all the occidental pharmaceutical and agro-food factories, the quality control manager is independent of the production or the commercial managers directly reports to the General Manager.

b. The **quality control laboratory and inspectors** and the responsible persons in charge of the reception of packages and printed boxes and label should perform:

i. the main normalized methods of pharmacopeias to control the primary packages (containers, closures);

ii. the visual inspection and control
- of bottles
- of the printed labels, folding boxes and corrugated boxes

In case of non-conformity of the products to some specifications, the responsible person can take the decision to refuse a batch or to use it.

The above concerns to all the packages including:

a) the primary containers (ampoules, vials, bottles, in glass and plastic, and their closures);

b) the secondary packages (individual boxes, printed information);

c) the printed labels;

d) the shipment boxes (corrugated boxes, if necessary the shrinkable films).

B. SPECIFICATIONS

For both the control and inspection, the responsible persons in charge of GMP appliance will use:

a. <u>for the chemical and physico-chemical controls</u>
the monographies of pharmacopeias (European and if not US pharmacopoeias),

b. <u>for the physical determinations</u>
such as dimensions, capacities and mechanical resistances, the ISO standards or, if not available, the ASTM or other standards.

c. <u>for the visual inspection</u>
determining the main defects and damages occurring during a shipment, the usual control applied in pharmaceutical industry and specified in the packaging producers literatures.

Such specifications are listed in Annex IV.

The main tests to apply are listed further in "the reception of a batch".

C. PREMISES

The storage of packages has to :

- be done in premises well organized and clean,
- never directly on the floor, but on shelves or palettes,
- permit a clear identification of batches.

These storage rules will avoid a close contact, in the same warehouse, with any dangerous product capable of contaminating the packages;

All shipments of packages will be registered on a warehouse book, with the clear identification of the batches (chronological number of the batch).

D. RECEPTION OF A PACKAGE BATCH

1. Reception of the product

a. **Identification of the product**

Control the identity of the labelled boxes and of the product specified on the order; create an identification sheet, with the reception date, the name of the product, the number of units and a specific number;

b. **Aspect of the batch boxes or palettes**

Note, if necessary, on the identification sheet the defects, with an appreciation of the number of defectuous items and refer to the buying department for a further request; take some samples of the defectuous items and store with the same identification number. **Apply a red label on the batch during the quarantine period.**

c. **Sampling**

For the various packages, take a random sample of the packages:

- 10 for vials, ampoules and bottles;
- 20 for closures and stoppers;
- 10 for small cardboard boxes;
- 10 for the labels;
- 3 for the corrugated boxes.

Identify and label the sample with the same number as the batch; pack either in a clean plastic bag (bottles, vials, ampoules, closures, stopper and folding boxes); bind the 3 corrugated boxes.

d. **Destination of the samples**

Send the following samples:

- vials, ampoules, bottles, closures, stoppers to the quality control department;

- folding boxes, labels and corrugated boxes to the inspection;

with a copy of the identification sheet, registered with the number of samples.

e. **Testing and inspecting**

Apply the minimum following tests and controls:

i. in the quality control laboratory

- physical tests

  weight, height, dimensions, outside and inside diameters of the bottleneck, inside diameter of the closures, outside diameters of the stoppers,

- physico-chemical tests

  after a solvent extraction (ethanol and hexane or heptane) on plastic and rubber, do an UV spectrum,

- chemical test

  extraction test with distilled water and reducing substances according to pharmacopoeias,

  resistance to acid and alkaline solutions (for plastic bottles and closures),

  alkalinity (glass and pipettes),

- visual inspection

  aspect of the bottles with critical defects (bubbles, finish of the bottleneck, cracks, importance of the parting-line, etc.), internal aspect of the closure, etc.

- microbiological control

  only for the steriles packaging, control of aseptic (pyrogens).

ii. for the printed matters and boxes inspection

- dimensions
- weight if necessary
- printing (colour, quality, etc.)
- visual defects (sticking, poor cutting, etc.)
- conformity of the printed product to the referenced product.

f. **Reports**

Even if the packages are conform, prepare a short report and send:

- one copy of the technical dept (or to the purchase department)

- one to the warehouse

After the report reception, the warehouse stops the quarantine period and **labels the batch with a green label.**

E. PACKAGE FILLING IN THE PROCESSING LINE

1. Issuing of a packaging order by the production department for supplying the production line, including:

   - Types of the packages (bottles, closures, labels, folding boxes),
   - Nature of packages (glass, plastic, stopper, etc.)
   - Number of each package units,
   - Date and destination (workshop):

2. Forwarding of the requested packages by the warehouse to the production department

   - Prior to the forwarding, detect with a visual inspection and eliminate the dirty and visible defectuous packages;

   - For the sterile products or products sensible to germs (albumen, sera, etc.), repack the primary packages in a new plastic bag (bottles and closures) or in a plastic or metal (aluminum) tray;

3. Never introduce in the workshop a corrugated box or a wooden palette; they could contaminate the product (fibers, germs, ...):

4. Verify in the production department, that the packages conform to the order

5. Inspect the line

   - in order to detect any foreign package (container, closure, label and folding box) on the packaging line, action the line (if possible with a known number of empty containers and not-printed labels and boxes);

   - count the number of empty packages coming out.

   After this operation:

6. Pack the product

   - supply with the normal and counted packages;
   - action the line;
   - at the end of the operation, indicate on the working form the number of packages entering and used; sign the production order form;
   - sample the normal number of packages (between, 3 and 5) and forward them, with a sampling form, to the quality control department.

7. Forward to and store in the warehouse

   - prepare a form before forwarding the product;
   - forward it to the warehouse;
   - in the warehouse, **apply a red label on the boxes and/or palettes**;
   - store during the quarantine

8. Operate normally the quality control

- If it is normal, prepare a small form giving the appreciation:
- Send two copies, one for the production department, the second one for the responsible warehouse:

9. After reception of the quality control report, the responsible warehouse **applies a green label and stops the quarantine**.

VI. LABORATORIES

Two groups of laboratories are under operation in Finlay Institute:

1. The first group, depending on the research management and located on the first floor, is devoted to the research and formulation of new vaccines, kits and reagents. It includes:

   - one physico-chemical laboratory equipped with modern devices : 1 UV Phillips spectrometer (1987), 2 liquid high performance chromatographies (1989), 1 pH-meter, 1 electrophoretic equipment (19900, 1 X-rays fluorescent equipment (1993);

   - one small laboratory with 2 ovens for ageing tests (two other ovens are on the same floor, one of them being out of order);

   - one small laboratory of enzymology mainly specialized in the preparation of tests;

   - one small laboratory devoted to the antibodies studies, working mainly for the products preparations.

   On the same floor, a small laboratory is devoted to the preparation of dried products and may be considered as a small workshop.

2. The second group, on the third floor, is devoted to the raw material and production control. Two laboratories are devoted to chemistry; the third one to microbiological activities.

   A small activity concerns the control of rubber stoppers for vaccines.

A. PREMISES

The building of the research department is rather old but the laboratories have been implemented and renewed about 20 years ago. They begin to be old and needed a normal rehabilitation (plumbing, some wall ceramic tiles, flooring and painting).

The plastic flooring has to be renewed in some laboratories and needs its replacement by ceramic ones and a finish with an epoxy varnish in order to limit to a minimum the dust up in the air.

B. EQUIPMENT

1. In the research laboratories

   Except the conventional material in glass and the ovens, the equipment is new and well adapted to the research. Depending on the laboratories' specialization, no special equipment has to be foreseen to test the packages components.

If some controls may be made, they may concern the identification of the plastic additives in the material (mainly antioxidants) and the solvent residues (and occasionally of monomers [styrene and vinyl chloride]) with the following equipment:

- one gas chromatograph for the determination of solvents and monomer (vinyl chloride, styrene) residues in some packages; estimated cost: US$ 25 to 30,000.

- one thin-layer chromatograph for identification of plastic and rubber additives in the packages; estimated cost with the complementary equipment : US$ 2000 to 3000.

2. In the production department

Some equipment is old and has to be replaced in the:

a. Conventional chemical laboratory
Mainly glass materials, as the scales are renewed from time to time.

b. Physico-chemical laboratory

With normal apparatus but limited to 1 UV spectrometer, one pH-meter, one electrophoretic equipment, 2 scales ; except the scales, the other apparatus have to be renewed in the next five years; estimated cost for one UV spectrometer and one pH-meter : US$ 20 000

Some equipment would be useful in order to control the compatibility between the packaging material and the product to determine the water vapor permeability and to conduct long term shell-life tests on the finish products : US$ 10 000

The implementation of such ageing-test ovens (requiring a complementary area, mainly of about 15 m^2 or more) could be made either in the research laboratories, in the quality control laboratories or in any place having a sufficient area.

The overall equipment cost will be approximately

US$ 150 000.

3. Documentation

A broad information will be needed in order to succeed in the determination, for instance the additives used in plastic materials. A collection of UV spectra of the main additives could be obtained from the plastic suppliers or from the additives manufacturers (Ciba-Geigy, Switzerland, for instance). Another source of information will be the European Pharmacopoeia, Strassbourg, France (c/o the EEC delegation in La Habana) and from the French Pharmacopoeia, (c/o The French Embassy, Scientific Attaché, La Habana). A first technical participation to the information was given within the form of a scientific book written by the expert concerning polymers for packaging.

A complementary information could be assumed within the form of small reference samples (5 to 10 g) of each additive prescribed in the European Pharmacopoeias for the following plastics: HDPE, LDPE, PP, PS. Such partition could be obtained by means of the bi-lateral cooperation with EEC or a European country, or through some representation of an additive manufacturer, even by the actual supplier of the plastics containers.

4. Control in production area

At present, few tests (except some on the rubber stoppers) are done to control the batches of packages. Some small equipment will be needed in order to operate the best selection of material and to assume a statistical quality control of the raw materials, such as:

- four series of gauges for each bottle and vial type in order to control the internal and external diameters and the height of the body and bottleneck;

- a series of gauges to control the internal diameters of the plastic closures;

- a series of gauges to control the external diameter of the rubber stoppers;

- a light-box (such as those used to examine the photo films) to facilitate the statistical visual control of the glass vials and bottles;

- a stainless steel hot-water bath, with a thermostatic temperature control (55°C), will be necessary to determine the stress-cracking sensitivity of the polyolefin (PE and PP) containers and polyolefin or polystyrene closures.

Such equipment can be made in Cuba. A limited cost of US$2000 is expected.

5. Methods

The principles and the standard references are given in the chapter 2 and in annex V. More information was given concerning the (glass and plastic) bottles and vial controls (in chapter 2 and 3).

6. Personnel

About 3 persons are in charge of the raw material quality control, two of them doing generally some routine tests and quality controls on the packages.

7. Training

In order to succeed with the selection of the convenient packages and to release a well conducted quality control on the batches, a one-month training would be useful in order to examine:

- the organization of similar control laboratories in Western industrial countries;

- the most useful controls and necessary methods;
- the main defects occurring for each type of packaging;
- the actual studies made in international and national organizations, such as the European pharmacopoeia.

A one-day contact with each of the main suppliers will be highly profitable.

The profile of the candidate for such training is described in Annex VI.

VII. VISITS IN THE PHARMACEUTICAL GROUP

A. VISITED COMPANIES

Several visits were made in the Cuban pharmaceutical group, to the factories supplying packages and in the Cuban Packaging Institute. The main facts are described hereafter and the detailed reports concerning each of the visits are in Annex VI.

1. Departamento de Envase - Industria Medico-Farmaceutica
   Dirección de Desarrollo

2. MediCuba
   Packaging buying department

3. Litograficas de la Habana

4. Union de Vidrio
   Plant La Lisa

5. Flascos Plasticos FrasPlast

6. Union Plasticos
   Plant of Habana

7. Cuban Packaging Institute

B. FACTS RELATED TO THE PACKAGES

1. Most of the time, Cuban pharmaceutical industry meets problems concerning the quality of the locally manufactured packages : glass, plastic bottles, aluminum collapsible tubes, printed folding boxes; to avoid these problems and for the more important products such as injectable and pomades, the packages are imported from Europe.

2. However, an effort is done at present in the glass La Lisa Plant which produces rather good ampoules and vials with imported glass rods.

C. FACTS RELATED TO PACKAGING FACTORIES

Two types of factories are existing:

1. Two visited plants (Union de Vidrio la Lisa and Union de Plasticos Habana) are old factories rebuilt about 30 years ago.

2. In some cases - especially for plastic - a lack of maintenance is visible in the premises (oily and dusty ground) and consequently cannot comply with the GMP pharmaceutical industry working conditions.

3. The machines are generally old, with few exception:

   - one still working line in La Lisa (Belgium-British machine I.S.).

- two or three 10-year old German (ex RDA) plastic machines in Union de Plasticos.

All the other machines are about 20 years old (or more) and now suffers lack of maintenance, partly due to the fact that some lines (glass) were supplied by the ex-RDA.

A real effort has to be made to rehabilitate these two units.

4. A lack of technology was also noted in both companies, but mainly in the glass one; any kind of technical and scientific assistance could be helpful and would improve the factory performance.

5. Except few methodological controls, no chemical and physico-chemical control (very important in pharmacy) are made; only some visual inspections are made for glass vials and bottles.

6. A totally new and well conceived factory (Frascos Plasticos FrasPlast) can work within GMP conditions: pressurized workshop, new building, new machines and new staff. Such factory, directly linked to the pharmaceutical pole has to be technically supported, mainly to increase the personnel training (plastic engineering and plastic controls) and to supply the technical information (technical publications and books, foreign catalogues, etc.).

D. DIVERSIFICATION

To permit a local supply of packages some projects were discussed:

1. Production of flexible bags

   - for injectable solutions (transfusion),
   - for blood collecting and storage of blood components.

A contact with the Paris' Pharmacie Centrale des Hopitaux was suggested in order to know if they could accept to help the pharmaceutical group in this new manufacture.

A provisional budget to begin the economical and technological study is proposed:

a. Economical study

supported by UNIDO to determine the Caribbean market; a 2-3 m/m mission could be necessary to examine all the opportunities for the bags, injectable solutions and disposable for transfusions. Such production unit could produce about 4 millions bags/year for the Cuban market, prepacked by 3 or 6 in 0.6 or 1.3 millions LDPE bags (for over-packaging) meaning about 40-50 tons of imported PVC compound and 3-4 tons of LDPE. **Cost: approximately US$5,060,000**

b. Technological study

supported partly or totally by the French-Cuban bi-lateral cooperation fund or both bilateral fund and an international organization (UNIDO, EEC,

WHO) conducted in two steps:

i. a preliminary report describing shortly the working process, the production controls and the total cost of investment, in order to facilitate a decision;

ii. a detailed study, made after the decision, describing in details all the process, equipment and controls.

It would require 4 to 6 months work, not including the translation time. Cost: approximately US$ 80-100.000

2. Collapsible aluminum tubes

Cuban pharmaceutical group do not find on the local market good quality varnished tubes for pomade and must import them. It was proposed:

a. to contact some of the main occidental companies (Alcan, Canada; Alusuisse, Switzerland; Pchiney, France) in order to be informed of their interest in the sub-regional market and in a joint-venture; or to find out the availability of some second hand equipment sold at a reasonable prices; and the possibility of a technical agreement with one of them, mainly for the varnishing and testing operations.

Such contacts could be established by Industria Medico-Farmaceutica through the Commercial Attachés of the concerned countries.

Another procedure could consist in looking for a second hand equipment towards the big international pharmaceutical groups in order to find out if they have such available equipment or towards other plants by means of the UNIDO monthly newsletter.

3. Shipment of heat-sensible products

A solution could be to insert, inside good corrugated boxes, 2 to 4 cm insulating foamed PS boards (made in Cuba), stocked with a polyvinyl acetate dispersion, using a glycol or brine deep-frozen bag, or dry ice; such package is enough per format and partly realized with a national production. Cost of insulation: difficult to evaluate, probably 1/2 US$ per box.

4. Syringes

The actual international market is saturated and the prices offered late 1992 was about 10 US cent per unit. An investment for a such production would be difficult to amortize on the local market. A tentative operation could be made for two specific markets (with 1 to 2 ml syringes): the anesthetics for dentistry; the vaccines.

Such production like the blood bags manufacture - in a sterile area - could be located in a new building of FrasPlast area.

5. Packaging consumption

(See above, chapter II)

6. Miscellaneous

a. Regarding the inks, it was suggested to contact one of the biggest international groups of manufacturers (French Petroleum TOTAL Group) in order to find out their interest for a free-zone warehouse located in one Litografica factory.

b. For the plywood boards used to cut the folding boxes, it was suggested to contact the Centro Nacional des Embalagem, Sra M-A. Ramos, Rua Telhal, Matinha, 1900-Lisboa, Portugal, in order to know the current Portuguese prices for the laser cutting.

VIII. OTHER CONTACTS

Other contacts were made with the commercial attachés of the British and French Embassies; the technical director of Finlay Institute and the responsible officer of Cooperation in the Pharmaceutical group joined for these visits.

A general aspect of the mission was described and some specific points, which could be solved by means of the bi-lateral cooperation, have been considered.

A. BRITISH EMBASSY

(Visited person: the Commercial Attaché)

1. Information

One main conclusion of the various visits to the factories was their lack of technical information as well as in the Center of Packaging. It would be most useful for Finlay, MediCuba, Union de Vidrio and the Center of Packaging, to receive:

- some packaging technical publications, such as British Packaging and the PIRA abstracts (concerning packaging) monthly publication;
- one plastic publication, such as British Plastic;
- one glass publication (if it does exist in England);
- one paper and cardboard publication.

Such publications would be a good support not only for their technical work but also a source of reference for addresses.

2. Specific bio-medical information

A contact between Finlay and a medical organization would be useful to get on clinical tests. Two addresses were given:

- The British Medical Association
- The Saint-Mary Hospital (two addresses) in London

Contact will be established by Finlay.

3. Formation

A general problem concerns the technical training of qualified plastic engineers. There is only one Austrian technical school giving a 6 weeks training (Vienna) with the support of UNIDO and a German technical school giving a 2-3 years training (Sarbruck).

The problem will be submitted to the British Cultural Attaché as it does not concern only Cuba but most of ex-British colonies.
A semester formation, with training periods (two months for instance), in factories was suggested.

At the present time, the budget for training sessions is already allocated but candidatures could be examined for 1994-1995.

It was suggested to Cuban Authorities to facilitate such a training for the FrasPlast factory, in order to give the maximum chances to their outstanding unit.

It was also suggested to the Commercial Attaché to visit in La Habana the Frasplast new plant and the Cuban Packaging Center in order to have an idea of the status of the actual research and technology in the country. The Cooperation Service of the Pharmaceutical group would arrange such visit.

Conclusion:

The British administration seems open to some cooperation. It will take care of the request for publications and will also forward it to professional organizations so that technical documents be sent to Cuba.

It was decided that the further contacts would be maintained by the Cooperation Service of the Pharmaceutical group.

Note

The training of a qualifie specialist in the laboratory of a well-known hospital such as Saint-Mary hospital would be highly profitable.

B. **French Embassy**

(Visited persons: Mr Bernard Paulien, Economical and Commercial Counselor; Ms Jocelyne Preciado, assistant to the Commercial Counselor)

1. Technical cooperation with the French factories

The following points have been examined:

a. **Implementation of a sterile bags for blood**

The project of implementation of a 4 M units in Cuba was discussed, reporting the difficulty of finding a licensor for such a manufacturing process. A contact will be taken by the expert with the General Management of the Paris Pharmacie Centrale des Hopitaux; an evaluation of the budget for the study and of the expenses share between UNIDO and French Cooperation was given.

b. **Implementation of a free-zoned warehouse for inks**

The project was discussed and a contact with the General Management of the French Petroleum Company TOTAL will be arranged by the expert. It is

interesting to note that a project concerning solvents is currently discussed between the Cuban administration and TOTAL.

2. Information

As mentioned in the paragraph concerning the British Embassy, the factories needs badly all kinds of technical information. The Center of Packaging as well as Finlay, MediCuba, Union de Vidrio and the Center of Packaging should receive or have access to:

- some packaging technical monthly publications such as Emballage Magazine and Emballage Digest (concerning packaging);
- one plastic publication, such as Plastiques Modernes et Elastomères (concerning plastics);
- one glass publication (if it still does exist in France), such as L'Industrie du Verre;
- one paper and cardboard publication;
- eventually some technical catalogues published for the pharmaceutical and the packaging industries.

Again, such publications would be precious for both the technical information and for the references.

3. Formation

One main problem concerns the technical training for a qualified engineer specialized in the plastic quality control applied in the pharmaceutical industry. Only two opportunities are offered:

- one in the Paris XII University (Faculty of Pharmacy of Chatenay-Malabry), Pr Bellocq, speciallized in the plastic containers controls;
- the second one in the Pharmacie Centrale des Hopitaux (Paris), Pr. Michel Hamon and Pr. Eric Postaire.

A one-month training, sponsored by UNIDO with the assistance of French ACTIM administration would be highly profitable, especially if the project of blood plastic bags is realized.

It is suggested to Cuban Authorities to facilitate such a training for the FrasPlast factory, in order to give the maximum chances to its outstanding unit.

It was also suggested to the Commercial Counselor to visit in Havana the Frasplast new plant and the Cuban Packaging Center in order to have an idea of the actual status of research and technology in the country. The Cooperation Service of the Pharmaceutical group will arrange such visits.

It was decided that the further contacts would be maintained by the Cooperation Service of the Pharmaceutical group.

The expert will prepare a list of the publications which would be appropriate for the above mentioned needs and forward to the Embassies Commercial Attaché as well as to UNIDO.

RECOMMENDATIONS

I. FOR FINLAY INSTITUTE

A. PACKAGING

1. Approximately 50% of the 202 reagents which were examined can be packaged in HDPE bottles in lieu of glass. Such change must be made after:

   - a careful chemical study in order to control with ageing tests that such replacement is feasible;

   - an economical study, especially to determine the interest for Finlay and for the new Frasco Plastico.

2. Some new products, such as enzymes testing papers, could be packaged either in aluminum tubes or in PP tubes; prior to the decision to look for a second hand aluminum stamping machine, a market study is necessary; if the market is limited, the PP tubes will be the most appropriate choice.

3. For such containers and whatever the result of the above decision, a good plastic closure is necessary; addresses could be found in the catalogues to be provided by the bi-lateral cooperation.

4. The quality of packages used for reagents and drugs depends most of the time of the chemical composition of the packaging material, on its inertia and of the leak-proofing of the couple package + closure. Some technical information should be required from the suppliers:

   - a guarantee of conformity to the world known pharmacopoeias (European, USP, etc.)

   - for the glass, the specification and the quality control procedure guaranteed by the glass manufacturer;

   - for the plastic containers and for the rubber stoppers, if possible the qualitative composition of the material (including additives) and/or the UV spectrum of the solution obtained by extraction according to the pharmacopoeias monographies.

B. CHOICE AND CONTROLS OF THE PACKAGES

5. Some controls have to be standardized and applied in order to respect the GMP rules:

   - for the packaging materials, the most important tests requested in the pharmacopoeias (extraction, reducing agent, UV test);

   - for the couple container + closure, the capacity, leakage and evaporation tests.

6. Prior to the selection of a new packaging material (including the

closures), an absorption test must be always applied in order to control the chemical composition of the reagent and/or of the drug is not significantly changed. A special attention must be given when some aromatic substances (phenols, etc.) or organo-metallic derivatives (mercury derivatives) are included in the product. The decision has to be taken by a responsible person formally designated:

- the research manager, if it concerns a reagent not yet commercialized,
- the production manager, if it concerns a product already commercialized.

The selection procedure must be standardized:

- temperature and time for ageing;
- the conditions specified in the report concerning the new reagents can be applied.

7. The liners included in the closures have to be considered as a part of the primary package. For the liquids, the cardboard or cork liners have to be avoided and replaced by a plastic liner (PE for instance).

8. A visual and a methodological inspections, using small equipment (light box, gauges) will permit to eliminate most of the defectuous bottles and vials.

9. A careful control of all the printed packages has to be implemented (labels, inserted notices, folding boxes):

- to avoid mistakes and to help with the control it is suggested, for each important product, to print a specific and coloured mark on a place specified for each model;
- for the labels and inserts, the off-set plates should never hold two different labels or notices;
- prior to the printing operations, Finlay must check and approve the plates;

C. GOOD MANUFACTURING PRACTICES

10. For the manufacturing and the control process, the packages must be considered like one of the raw materials. The Good Manufacturing Practices have to be applied in order to permit a high quality production;

D. LABORATORY EQUIPMENTS

11. The laboratory equipment, permitting an improved control of the packaging raw materials, has to be reinforced or replaced by a few physico-chemical equipments such as:

gas chromatograph, thin-layer chromatograph, UV spectrometer, pH-meter, 3 hot-cold ovens (for ageing),

for a total budget of about US$ 65 000;

E. INFORMATION

12. A lack of technical and scientific information was noted; Finlay and Pharmaceutical Group shculd contact the Commercial Attaché and Counselor, as well as the most important reagents manufacturing company (Pasteur-Sanofi and Pasteur Mérieux) in order to receive the literature published for the clinical laboratories;

The same request concerns the packaging material and machines, mainly those used in pharmaceutical industry;

A contact has to be taken by the Cuban authorities (Minister of Health) with the European Pharmacopoeia (Council of Europe) in order to receive (as observer) each new version of the monographies;

F. TRAINING

13. A one-month training (two would even be better) for a pharmacist or a biochemist in a good pharmaceutical laboratory of a world known hospital would be very profitable to deepen his/her knowledge in new methods. Contact have to be kept with the British Embassy and to be established with the Saint-Mary Hospital and with the British Medical Association in order to obtain the fellowships in their laboratories.

II. FOR THE PHARMACEUTICAL GROUP

A. PACKAGING

1. Probably many solutions or powders could be packaged in HDPE bottle in lieu of glass; such change must be made after:

   - a careful chemical study in order to control by ageing test to verify that such replacement is feasible;

   - an economical study, especially to determine the interest for the pharmaceutical group and for the new Frasco Plastico.

2. In order to facilitate the choice of pharmaceutical packages and/or machines, a repertory of addresses is necessary; addresses could be found in the catalogues to be sent by the bi-lateral cooperation;

3. For such containers and whatever the chosen solution, a good plastic closure is necessary; addresses could be found in said catalogues.

4. The quality of packages used for reagents and drugs depends most of the time of the chemical composition of the packaging material, on its inertia and on the leak-proofing of the couple package + closure. Some technical information should be required from the suppliers:

   - a guarantee of conformity to the world known pharmacopoeias (European, USP, etc.)

   - for the glass, the specification and the quality control procedure guaranteed by the glass manufacturer;

   - for the plastic containers and for the rubber stoppers, if possible the qualitative composition of the material (including additives) and/or the UV spectrum of the solution obtained by extraction according to the pharmacopoeias monographies.

B. CONTROLS AND CHOICE OF PACKAGES

5. Some controls have to be standardized and applied in order to respect the GMP rules:

   - for the package materials, the most important tests requested in the pharmacopoeias (extraction, reducing agents, UV test);

   - for the couple container + closure, the capacity, leakage and evaporation tests.

6. Prior to the selection of a new packaging material (including the closures), an absorption test must always be applied in order that the chemical composition of the reagent and/or of the drug is not significantly changed. A special attention must be given when some aromatic substances (phenols, etc.) or organo-metallic derivatives (mercury derivatives) are included in the product. The decision has to be

taken by a responsible person formally designated:

- the research manager, if it concerns a reagent not yet commercialized.
- the production manager, it it concerns a product already commercialized.

The selection procedure must be standardized:

- the temperature and time for ageing;
- the conditions specified in the report concerning the new reagents can be applied.

7. The liners included in the closures have to be considered as a part of the primary package. For the liquids, the cardboard or cork liners have to be avoided and replaced by a plastic liner (PE for instance).

8. Visual and a methodological inspections, using small equipment (light box, gauges) will permit to eliminate most of the defectuous bottles and vials.

9. For the pipettes, it is necessary to specify a Class I glass or HDPE (or LDPE), in order to limit to a minimum the modification of the reagents.

10. A careful control of all the printed packages has to be implemented (labels, inserted notices, folding boxes); to avoid any mistake and to facilitate the control, it is suggested, for each important product, to print a specific mark located on a specified spot of the label edge: for the labels and inserts, the off-set plates must never show two different labels or notices; the packaging department of Medicuba must control the plates before the printing operation.

11. For the manufacturing and the control process, the packages must be considered like one of the raw materials and the good manufacturing practices have to be applied in order to permit a high quality production.

12. The Finlay laboratory equipment (permit an improved control of the packaging raw materials), has to be reinforced; in addition, it is necessary to purchase few physico-chemical equipments:

    gas chromatograph, thin-layer chromatograph, UV spectrometer, pH-meter, 3 hot-cold ovens (for ageing),

    for a total budget of about US$ 65 000; if might be necessary that such budget be approved by the pharmaceutical group;

C. INFORMATION

13. A lack of technical and scientific information was noted; Finlay and Pharmaceutical Group should contact the Commercial Attaché and Counselor, as well as the most important reagents manufacturing company (Pasteur-Sanofi and Pasteur Mérieux) in order to receive the literature published for the clinical laboratories.

The same request concerns the packaging material and machines, mainly those used in pharmaceutical industry;

A contact has to be taken by the Cuban authorities (Ministry of Health) with the European Pharmacopoeia (Council of Europe) in order to receive (as observer) each new version of the monographies;

D. DIVERSIFICATION

14. PVC Blood bags

The implementation of such production has been examined with the pharmaceutical group; it appears that in a not too distant future, Cuba will need PVC bags for the blood collecting. An economical study of the subregional market is recommended before starting a technical approach.

The workshop has to be implemented as closely as possible to a GMP unit in order to take advantage of the technical assistance of such unit (controls, management, etc.)

III. FOR THE BILATERAL COOPERATION

A. INFORMATION

1. A lack of technical and scientific information was noted; Finlay and Pharmaceutical Group should contact the Commercial Attaché and Counselor, as well as the most important reagents manufacturing company (Pasteur-Sanofi and Pasteur Mérieux) in order o receive the literature published for the clinical laboratories;

   The same request concerns the packaging material and machines, mainly those used in the pharmaceutical industry;

   A recent edition of the professional catalogues published for the pharmaceutical industry as it is for the packaging industry would be highly profitable to provide the addresses of the main European producers of packaging products and machines;

   A contact has also to be taken by the Cuban authorities (Ministry of Health) with the European Pharmacopoeia (Council of Europe) in order to receive (as observer) each new version of the monographies.

B. FORMATION

2. For Frasco Plasticos, a one-month training would be very profitable for the plastic control of the pharmaceutical packages in France, partly in the University Paris XII (Chatenay-Malabry, Pr. Bellocq) and in the laboratories of the Pharmacie Centrale des Hopitaux (Paris); this training concerns a pharmacist, biochemist or chemist in charge of the quality control. Its purpose is to apply the European pharmacopoeia methods and to determine the needed material to be implemented in Frasco Plasticos; the training period could be supported partly by UNIDO and partly by the French Embassy.

3. Still for Frasco Plasticos, a longer training in plastic processing would be highly profitable to permit the knowledge actualization of the responsible technician; such training should not be organized for less than three or four months in an engineering technical school and for two or three months in various supplying companies (materials, additives, machines, factories, laboratories, etc.); the training could be supported and partly financed by UNIDO and the bilateral cooperation, contacts have to be maintained with the British Embassy.

D. DIVERSIFICATION

4. PVC Blood bags

   This project is examined hereafter (6) and seems important enough to be carefully studied.

   If the actual project of cooperation between France and Cuba concerning the blood collecting and blood derivatives materializes, it is recommended

to assist the Cuban pharmaceutical group as much as possible for finding a know-how licensor for the needed bag production. The Paris Pharmacie Centrale des Hopitaux could be contacted for the project.

E. TECHNICAL COOPERATION

5. Pharmaceutical plastic control

The actual monographies of European Pharmacopoeia described the methods used for the control of the various packages and their plastic components. Such controls will be necessary in the future, mainly for the PVC blood bags or other transfusion disposable items.

A one-month training for a quality control technician in a specialized laboratory (Faculty of Pharmacy of Chatenay-Malabry and Paris Pharmacie Centrale des Hopitaux) is recommended both to UNIDO and French cooperation.

6. PVC blood bags

The implementation of such production has been examined with the pharmaceutical group; it appears that in a not too distant future, Cuba will need PVC bags for the blood collecting. An economical study of the subregional market is recommended before starting the technical approach.

The technical study could be divided in two parts:

First, supported by the French cooperation, to determine the project and to evaluate a broad budget for investments;

Second, supported by UNIDO for the full know-how writing.

7. Union de Vidrio

At present, this group of factories has few contacts with the international glass groups, except for a limited technical assistance. All possible contacts have to be facilitated, including invitations to seminars and congresses.

IV. FOR FRASCOS PLASTICOS

A. PACKAGING

1. Visual and a methodological inspections, using small equipment (light box, gauges) would permit the elimination of most of the defectuous bottles.

2. For the manufacturing and the control process, the packages used in pharmaceutical industry, must be considered as one of the raw materials and the good manufacturing practices have to be applied in order to permit an high quality production.

B. INFORMATION

3. Lack of technical and pharmaceutical information was noted; contacts have to be established through the Pharmaceutical group with the British Commercial Attaché and Counselor, in order to receive the literature published in their respective countries on the packaging material and machines, mainly those of the pharmaceutical industry.

   A similar contact has to be taken through the Cuban authorities (Ministry of Health) with the European Pharmacopoeia (Council of Europe) in order to receive (as observer) each new version of the monographies concerning the plastic packaging.

C. FORMATION

4. A one-month training for the person in-charge of the quality control, on the plastic control of the pharmaceutical packages in France would be very profitable, partly in the University of Paris XII (Chatenay-Malabry, Pr. Bellocq) and in the laboratories of the Pharmacie Centrale des Hopitaux (Paris); its purpose is to apply the European pharmacopoeia methods and to determine the needed material to be implemented in Fiasco Plasticos; the training period could be supported by UNIDO and by the French cooperation;

5. Due to the fact that the new unit presents a real interest for the development of a high quality packaging for the pharmaceutical industry, it is recommended to plan three training periods.

6. A 2-3 weeks period, for one of the two persons responsible of the unit, in a similar foreign unit; the purpose would be to examine directly in the factory all the working conditions especially the GMP conditions; this training could be organized and supported by UNIDO in the Jordanian Arab Medical Containers (Amman, Jordan).

5. A longer training in plastic processing would be very profitable to permit the knowledge actualization of the responsible technicians, such training should not be organized for less than three to four months in an engineering technical school and for two to three months in various supplying companies (materials, additives, machines, factories, laboratories, etc.); the training could be supported and partly financed by UNIDO and the bilateral cooperation; contacts have to be maintained

with the British Embassy.

D. DIVERSIFICATION

6. PVC Blood bags

The implementation of such production has been examined and it appears that in a not too distant future, Cuba will need PVC bags for blood collecting. An economical study of the subregional market is recommended before starting a technical approach.

The workshop has to be implemented as closely as possible to a GMP unit in order to take advantage of the technical assistance of such unit (controls, management, etc.).

V. FOR UNION DE PLASTICO

A. PACKAGING

1. Two defects are noted:

   - the insufficient finishing of the bottleneck, cause for leakage and alteration of the reagents and/or drug; an appropriate method to separate the bottle and the parisian (hot electrical resistance for instance) is suggested;

   - the packaging of the empty bottles as well as the packing of closures is done in poor quality cardboard boxes; some of them are spoiled by oil (storage on the ground); due to the intended purpose of the packages (drugs and pure reagents) a careful attention must be given to avoid any further spoilage in these plants.

B. TECHNICAL AUDITS

2. To determine a schedule and the cost of the plant rehabilitation, it is recommended to request a one-month technical audit (premises, machines, production) supported by an international organization (UNIDO, ITC/UNCTAD, etc.)

VI. FOR UNION DE VIDRIO - LA LISA

A. TECHNICAL AUDITS

1. Due to the ageing of the production lines, a technical unit is recommended in order to determine a schedule and the cost of the plant rehabilitation (premises, machines, production); the management of Union de Vidrio, through the Ministry of Industry, has to apply to UNIDO for a one-month technical mission.

B. DOCUMENTATION

2. Lack of technical information has been observed, through the Ministry of Industry, Union de Vibrio would find an interest in maintaining contacts with the Commercial Attachés of the Occidental countries embassies, in order to receive some technical information (publications, catalogues) related to packaging. This assistance could be supported by the bilateral cooperation budget of the concerned countries.

VII. FOR LITOGRAFICA

A. PACKAGING

1. A careful control of all the printed packages has to be implemented (labels, inserted notices, folding boxes); to avoid any mistake and to facilitate the control it is suggested, for each important product, to print for each model a specific mark located on a specified spot of the label edge.

   For the labels and inserts, the off-set plates should never have two different labels or notices.

   Finlay or Medicuba should control all the plates before printing.

B. RAW MATERIALS

2. At present, the cardboard is imported from Scandinavian countries; a special attention must be paid in order to assure, for both the pharmaceutical folding boxes and the food packaging, a normal quality because most of the European governments have regulations which impose now the recycling of used packages.

   The imported cardboard for pharmaceutical uses must be specified "virgin" and if necessary "food and pharmaceutical grade".

3. In order to facilitate the inks supply, it is suggested to come into an agreement with an international group and to create for a free-zone warehouse for the sub-region; a contact could be established with the international group Lhorilleux-Coates-Sicpa, affiliated to the French Petroleum Holding TOTAL; for Litografica, such warehouse may limit to one or two months the storage of inks;

C. TECHNICAL AUDITS

4. Due to the plant and machines ageing, it is recommended to apply, through the Ministry of Light Industries, for a technical audit in order to determine a schedule and evaluate the cost of the plant rehabilitation; a one-month mission of a specialist in off-set printing would permit to plan a modernization programme, such a mission could be supported by an international organization (UNIDO, ITC/UNCTAD, etc.).

VIII. FOR UNIDO

A. EQUIPMENT

1. The Finlay laboratory equipment, allowing an improved control of the packaging raw materials, has to be reinforced or replaced by a few physico-chemical equipments:

   gas chromatograph, thin-layer chromatograph, UV spectrometer, pH-meter, 3 hot-cold ovens (for ageing), for a total budget of about US$ 65,000.

B. TRAINING

2. A one-month training (two months would even be better) for a Finlay pharmacist or a biochemist in a specialized pharmaceutical laboratory of a world known hospital would highly profitable to deepen his/her knowledge in new methods and reagents; contacts have to be established with the British Embassy in order to facilitate such training in the London Saint-Mary Hospital of London and/or with the assistance of the British Medical Association; the participation of UNIDO could be limited to the payment of the travel.

3. A one-month training in the plastic control of pharmaceutical packages is suggested in France, partly in University Paris XII (Chatenay-Malabry, Pr. Bellocq) and in the laboratories of the Pharmacie Centrale des Hopitaux (Paris); this training concerns a pharmacist, biochemist or chemist in-charge of the quality control in Fiasco Plasticos. Its purpose is to apply the European Pharmacopoeia methods for the bottles (and eventually for the PVC bags) and to determine the needed control equipment to be implemented; the training could be supported partly by UNIDO (it could be limited to the travel expenses) and by the French bilateral cooperation.

4. Still for Fiasco Plasticos, a longer training in the plastic processing would be highly profitable to permit the knowledge actualization of the responsible technician; such training should not be organized for less than three or four months in an engineering technical school and for two or three months in various supplying companies (materials, additives, machines factories, laboratories, etc.); such training could be supported and partly financed by UNIDO (it could be limited to the travel expenses) and the British bilateral cooperation; contacts have to be maintained with the British Embassy.

C. DIVERSIFICATION

5. PVC Blood bags

   The development of the blood collecting and treatment requires a number of PVC bags, eventually made in Cuba; it is recommended that UNIDO facilitates and supports the subregional market study, first step in the procedure necessary for the implementation of such production.

D. TECHNICAL AUDITS

6. Three visited aged factories need a technical audit in order to determine the steps and the cost of the plants rehabilitation and to prepare an eventual schedule; it concerns:

- Union de Plastico
- Union de Vidrio (la Lisa plant)
- Litografica

A one-month mission of a qualified specialist in each factory is recommended.

IX. FOR THE CUBAN AUTHORITIES

A. INFORMATION

1. A lack of technical and scientific information was noted: Finlay and Pharmaceutical Group should contact the Commercial Attaché and Counselor, as well as the most important reagents manufacturing company (Pasteur-Sanofi and Pasteur Mérieux) in order o receive the literature published for the clinical laboratories;

   The same request concerns the packaging material and machines, mainly those used in the pharmaceutical industry;

   A recent edition of the professional catalogues published for the pharmaceutical industry as it is for the packaging industry would be highly profitable to provide the addresses of the main European producers of packaging products and machines;

   A contact has also to be taken by the Cuban authorities (Ministry of Health) with the European Pharmacopoeia (Council of Europe) in order to receive (as observer) each new version of the monographies.

B. TRAINING

2. A one-month training (two months would even be better) for a Finlay's pharmacist or a biochemist in a specialized pharmaceutical laboratory of a world known hospital would be highly profitable to deepen his/her knowledge in new methods and reagents; contacts have to be carried on with the British Embassy and to be established with the London Saint-Mary Hospital and with the British Medical Association in order facilitate such training; the expenses could be supported by UNIDO and eventually by the British Embassy.

3. For Fiasco Plasticos, a one-month training in France, in the plastic control for pharmaceutical packages, partly in University Paris XII (Chatenay-Malabry, Pr. Bellocq) and in the laboratories of the Pharmacie Centrale des Hopitaux (Paris); this training concerns a pharmacist, biochemist or chemist in charge of the quality control; its purpose is to apply the European pharmacopoeia methods and to determine the needed material to be implemented in Fiasco Plasticos; the training could be supported partly by UNIDO and the French Embassy.

4. Still for Fiasco Plasticos, a longer training in plastic processing would permit a knowledge actualization of the technical aspects of the manager; such training, in order to be profitable, could be organized for three or four months in an engineering technical school and for two or three months in various supplying companies (materials, additives, machines factories, laboratories, etc.); it could be supported and partly financed by UNIDO and the British bilateral cooperation; contacts have to be maintained with the concerned embassy.

C. **BUDGET**

5. The Finlay laboratory equipment has to be reinforced or replaced by a few physico-chemical equipments:

gas chromatograph, thin-layer chromatograph, UV spectro-meter, pH-meter, 3 hot-cold ovens (for ageing), for a total budget of about US$ 65 000.

Such investment needs to be approved in order to assure an improved control of the quality.

D. **RAW MATERIALS**

6. In order to facilitate the inks supply, it is suggested to come into an agreement with an international group and to create a free-zone warehouse for the sub-region; the international group Lhorilleux-Coates-Sicpa, affiliated to the French Petroleum Holding TOTAL, could be contacted; for Litografica, the above mentioned warehouse would limit the inks storage to one or two months instead of the current six to twelve months. Such free-zone warehouse could be a tentative experience for occidental companies to initiate a re-exportation in the subregion. It will also permit a close contact with an important international holding.

E. **TECHNICAL AUDITS**

7. Three visited old factories need a technical audit in order to determine the steps and the cost of the rehabilitation of the plants and to prepare an eventual schedule. It concerns:

- Union de Plastico
- Union de Vidrio (la Lisa plant)
- Litografica

A one-month mission of a qualified specialist in each factory is recommended.

It is also recommended to apply for a one-month technical audit (premises, machines, production) supported by an international organization (UNIDO, ITC/UNCTAD, etc.)

8. A one-month mission in MediCuba, similar to the mission done in Finlay Institute is recommended to go further with the points brought up during this first mission and to determine more precisely with the drug factories the possible improvements or changes to adopt (GMP, etc.)

F. **DIVERSIFICATION**

9. The development of the blood collecting and treatment requires a number of PVC bags, eventually made in Cuba; it is recommended to concerned authorities (Ministry of Health) to contact UNIDO and later on the French Cooperation Attaché to start the preliminary studies necessary to decide the implementation of such production.

ANNEXE I

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION

SI/CUB/90/801/ 11-54

JOB DESCRIPTION

Post title

Expert in design and production of packaging materials used in the Pharmaceutical Industry

Duration

1 month

Date required

ASAP

Duty station

Havana, Cuba

Purpose of project

To assist the Government in improving design and quality of packaging material used in the Pharmaceutical Industry.

Duties

The expert will be assigned to the Institute Carlos J. Finlay to perform the following activities:

1) To study and assess the present design/arrangements for the packaging of clinical reagents and diagnostic kits involving mainly control seras, enzymes andprotease inhibitors. The physical shape/dimensions, appearance, functionality, quality and compatibility of the employed materials and the clinical reagents within should be checked: glass and plastic bottles, plastic caps, rubber stoppers, means of mesuring and dosing, labelling, assembling.

2) To propose alternative designs, carefully considering the functionality, fitness/appropriateness, attractiveness, compatibility, possibility of local production, costs and storage/transport requirements.

3) To assist the national counterpart and cooperate with them to prepare/improve the design of a selected group of clinical reagents and diagnostic kits as for example:

- colorants for microbiology and hematology tests
- reference solutions (such as glucose, creatinine, Na, K, Ca)
- diagnostic kits for glucose, creatinine, urea, urates, cholesterol, iron, triglycerides, phosphatases, amylases, bilirubin, etc.
- control seras for same above parameters and for lipids and enzymes
- auxiliary solutions like bases, oxalates and other anti-coagulants

4) The expert should prepare a final report with his findings and recommendations for the future course of action on the above subjects.

Industrial Engineer or Industrial Pharmacist with extensive experience in production and design of packaging material for pharmaceuticals and reagents.

English, Spanish desirable

The Institute of C.J. Finlay in Havana has developed a group of clinical reagents, diagnostic kits and reference substances that are mainly consumed by the national health system. The Institute should support the production of some of these items in other laboratories within the country and should be ready to incorporate new developments in the field, based on the on-going genetic engineering research as those based in monoclonal antibodies, strip tests, etc. into its production. The improvement of packaging design and quality will also allow the possibility of future exports.

ANNEXE II

ABREVIATIONS

ABS	Acrylonitrile-Butadiene-Styrene copolymer
ACTIM	Agence pour la Coopération Technique, Industrielle et Economique
ASTM	American Society for Testing Materials
GMP	Good manufacturing practices
HDPE	High density polyethylene
ISO	International Standards Organization
LDPE	Low density polyethylene
LLDPE	Linear low density polyethylene
PA	Polyamide
PC	Polycarbonate
PE	Polyethylene
PET	Polyethylene terephtalate
PMMA	Polymethyl methacrylate
PP	Polypropylene
PUR	Polyurethane
PVC	Polyviny chloride

ANNEXE III

VISITED FACTORIES, ORGANIZATIONS, ADMINISTRATIONS AND PERSONS

BRITISH EMBASSY
. The Commercial Attaché

CENTRO NACIONAL DE ENVASES Y EMBALAJES
. Ing. Roberto Perez Jimenez, General Manager

FINLAY INSTITUTE
. Sra Marta Carreeliro, General Manager
. Lic. Lillian Valdes Diez, Technical Manager and collaborators

FRASCO PLASTICOS FrasPlast
. Ing. Lucrecia Cuon Chong, Director
. Julio Torres, technical manager

FRENCH EMBASSY
. Mr Bernard Paulien, Economical and Commercial Conseiller
. Ms Jocelyne Preciado, assistant near the Commercial Conseiller

LITOGRAFICA
. Mr Carlos Martinez, General Manager and Techical director + assistant

MEDICUBA
. Lic. Maria Critina Ylizastigui, Technical adviser, Buying Dept

PHARMACEUTICAL GROUP
. Sra Maria Julia Cuesta, Cooperation Manager
. Mrs Daysi Campoanes Casado and collaborators
. Ing. Lucia Preito, head of Packaging dept and
Lic. Mrs Alina Souzales Bravo
both in the Departamente Envase, Industria Medico-Farmaceutica, Direccion de Dessarolo
. Ing. Xiomara Martinez Grulla, Dept Development IMEFA-MINSAP
. Lic. Antonio Padillo Rubiera, Quality Control Mgr, Insulin Plant and
Lic. Luis Martinez Gonzales, Quality Assurance

UNION DE PLASTICO

. Mr Ramon Gonzales, Head of the technical dept + the responsible of quality control

UNION DE VIDRIO - LA LISA

. Ing. Reinaldo Hernandez, Head of the technical dept

ANNEXE IV

MOST IMPORTANT APPLICABLE SPECIFICATIONS

EUROPEAN PHARMACOPOEIA MONOGRAPHIES

- Empty and sterile plastified poly(vinyl chloride) containers for human blood and blood derivatives (Edition: Jan. 1983),

- Glass containers for injectable preparations (Edition: Jan. 1983),

- High density polyethylene for parenteral injection solutions (Edition: Jan. 1991),

- Low density polyethylene for parenteral injection solutions (Edition: Jan. 1993),

- Poly-ethylene terephtalate (Editions: Jan. 1987),

- Polypropylene for parenteral injection solutions (Edition: Jan. 1991),

- Plastic containers containing aquous solutions for intravenous transfusion (Edition: Jan. 1991),

- Plastic containers and closures (Edition: Jan. 1992),

- Plastic containers for aquous eye-drops (Edition: Jan. 1990),

- Plastified poly (vinyl chloride) containers for injectable solutions for transfusion (Edition: Jan. 1990),

- Rubber stoppers of containers for parenteral injection solutions (Edited: Jan. 1993)

- Sterile plastic containers for human blood and blood derivatives (Edition: Jan. 1983),

- Sterile plastified poly (vinyl chloride) containers for human blood containing an anti-coagulation solution (Edition: Jan. 1991),

ISO STANDARDS

- ISO 1133-1981 Plastics; melt-index,

- ISO 1265-1979 Plastics; PVC resin, determination of foreign particles,

- ISO 4608-1978 Plastics; PVC resin for general uses; determination of the plasticizer content,

- ISO RT 4616 Plastics; Determination of thermal stability of PVC by conductimetric method.

ANNEXE V

OTHER VISITS IN THE PHARMACEUTICAL GROUP

I. DEPARTAMENTE ENVASE - INDUSTRIA MEDICO-FARMACEUTICA

Direccion de Dessarolo

(Mrs. Lucia Preito, Mrs. Daysi Campoanes Casado, Mrs. Alina Souzales Bravo and Mrs. Xiomaara Martinez Grulla)

Several points have been discussed regarding the pharmaceutical group:

1. Production of flexible bags
for two purposes:

. For injectable solutions (transfusion),
. for blood collecting and storage of blood componants.

They could be made in medical grade plastified PVC. A few companies or production factories exist at the present time (Travenol, USA; Aguettant and Pharmacie Centrale des Hopitaux, France; Solvay, Belgium). Right now, the French Pharmacie Centrale des Hopitaux (branch of the parisian public hospitals subsidized partly by the French health system) is probably the only factory capable of offering a full know-how. The French Cooperation Attaché in La Habana has been informed of the contact to be established with the top management of this semi-public group inorder to discuss the possibility of subsidizing the preliminary technical study.

Such production unit could produce for the Cuban market some 4 millions bags/year, prepacked in 3 or 6 in 0.6 or 1.3 millions LDPE bags, resulting some 40-50 tons of imported PVC compound and 3-4 tons of LDPE.

The preliminary study could be divided in two parts:

a. Economical study
supported by UNIDO to determine the Caraibs market; a 2-3 m/m mission would be necessary to examine all opportunities for the bags, injectable solutions and disposables for transfusions. Cost:

approximately US$ 5,060,000

b. Technical study
supported partly or totally by the bi-lateral cooperation fund or by both the bilateral fund and an international organization (UNIDO, EEC, WHO) would be carried out in two steps:

i. a preliminary report describing shortly the working process, the production controls and the total cost of investment, in order to facilitate the decision;

ii. a detailed study, done after the decision, describing in depth all the process, equipment and controls.

This plan means a 4 to 6 months work for a well informed specialist, not including the translation time. Cost:

approximately US$ 80-100 OOO.

2. Collapsible aluminium tubes

Cuba had in the past a unit to produce tooth paste tubes and cigar aluminium tubes. At the present time, the production (or the imported tubes) are not sufficient for the pharmaceutical needs, mainly due to the quality of the aluminium profiles (probably second fusion aluminium).

After discussion, it was proposed:

a. to contact some of the main occidental companies (Alcan, Canada; Alusuisse, Switzerland; Péchiney, France) in order to know:

i. their interest for the Caribbean or center-American market eventually by the means of a joint-venture;

ii. if not, the disponibility of some second hand equipment sold at a reasonable price;

iii. and the possibility of a technical agreement with one of these companies, mainly for the varnishing and testing operations.

Industria Medico-Farmaceutica could establish such contacts through the Commercial Attachés of the concerned countries.

Another approach could be made for a second hand equipement towards the big international pharmaceutical groups in order to know if they have still such available equipment.

The last research could be made through the UNIDO monthly letter, with an announcement in order to detect a possible partner. The chances of success with such methods are unpredictable.

3. Shipment of heat-sensible products

Except for small distances, the problem of maintaining a low temperature is difficult for some products, such as vaccines. Shipments are generally made in refrigerated cars. But for exportation and rather long distances (including air shipment), it is insufficient.

Two packages can be used:

a. a moulded foamed polystyrene box inside a corrugated carboard box, with a glycol or brine deep-frozen bag, or dry ice; it is the most common method used, but it requires a maintenance to produce the box and its top; the package cannot be returned (cost and fragility); price: approximately ½ US$/box.

b. a HDPE or PP box, with an injection between the two walls of a PUR foam, with a glycol or brine deep-frozen bag, or dry ice; such package, which does not require any corrugated box, is very efficient and can be used for the normal supply of hospitals; it is reusable; but must be imported. Cost 5 to 10 US$/container.

c. an intermediate solution could be to insert, inside good corrugated boxes, 2 to 4 cm of insulating foamed PS boards (made in Cuba), sticked with a polyvinyl acetate dispersion, using the same glycol or brine deep-frozen bag, or dry ice; such package is enough performant and partly realized with a national production.
Cost of insulation: difficult to establish, may be ½ US$/box.

4. Closures for vaccine and injectable products

In Europe, it appears that aluminium caps and flip-off aluminium caps are used in equal quantities. Advantages for the latter is the opening easiness and the protection of the stopper during the storage. Unfortunately, this closure does not permit a protection for the multi-uses products (insulin for instance).

5. Disposables

a. Plastics bags for blood and solution (see above);

b. Syringes

The international market is actually saturated and the prices offered end-1992 was approximately 10 US cents/unit. An investment for such a production would be difficult to amortize on the local market.

A tentative operation could be done for two specific markets (with 1 - 2 ml syringes).

. the anesthesics for dentistry;
. the vaccines.

Such production of one model syringes needs a GMP (Good Manufacturing Pratices) workshop, if possible in a large GMP factory. The seringes have to be filled, if possible, in the same area after the quarantine time.

II. MEDICUBA

Packaging buying department

(Mr. Felipe Guttierrez, Division Farmaceutica, and Mrs. Maria Cristina Ylizastigui, technical adviser)

The most important part of the visit concerns the current problems of the pharmaceutical factories.

Four types of packages are bought:

1. Glass
Mainly imported from France (St Gobain Desjonquères); no specific problems, except sometimes some fragility which is reported to the supplier.

Cuba is studying a project for a local production of pharmaceutical bottles. At the present time, the total production for MediCuba and Finlay is:

53 M° Millions of units/year,
which means approximately 4400 T/year
of the 3 classes of glass.

Such production is not big enough to permit a local high quality production of pharmaceutical bottles.

In order to be more performent, it would be necessary to acquire the know-how of the pressed-blown bottles (good regularity and lightness) and of the line automatic control thus eliminating the defectives bottles.

It will never be possible to manufacture blown glass I vials, as the quantity used is limited.

A possible way would be to modernize the production with glass I rods; such production needs to buy the forming equipment and to import the glass rods (with all the shipment problems.)

In terms of environment, it was suggested to always compare the real energetic cost (in US $) between the glass and the HDPE bottles; for a similar result (dry products, sirups, alcaline solutions, alcohol, etc.), the glass (or the plastic) is not necessarily the cheapest solution, when the packages recovery prices for recycling has to be included.

2. Plastic containers

A solution to some packaging importation was found with the implementation of a special GMP blow-moulding plastic bottles unit.

Prior to a normal production of the Frasco Plasticos unit, it seems useful to contact good regional suppliers; the names of performing Venezuelian and Columbian companies were suggested :

. CIPLAST C.A.
Ing. Bernardo J. Raaijen, General Manager
Caraacas (Venezuela)

. Corporacion Plastica
Sr Amaury Benedetti Lecompte, General Manager
Carthagena (Columbia)

III. Packaging suppliers

A. LITOGRAFICAS DE LA HABANA

(Mr. Carlos Martinez, Director, and his two technical assistants).

The factory, more than 50 years old, is specialized in off-set printing. Three shops were visited:

. a memorial workshop, nearby the head office, still printing labels and rings for cigars;
. a large although old workshop, equipped for 50% with old machines (more than 40 years old) and 50% rather new machines (about 10 years old) includes the board cutting plate shop, still working manually;
. a last shop, with few machines, works only on small printing series.

Some problems have been discussed with the team:

a. The printing plates

For pharmaceutical industry, the GMP rules require to have on each printing plate, a single model of box, label and notice. It avoids the mixing of printed items and reduces the working time in both the printing shop and the pharmaceutical factory for controls.

b. The cutting board

A test of engraving with laser was successfully done with an Italian factory. It was suggested to contact the Portuguese Packaging Center(*) in order to experiment a similar test with another factory and to compare prices and results.

The expert will inquire about the current price of a laser encarving machine and forward it to the Director.

b. The inks

All inks are imported but sometimes, from one supplier to the next and even from one factory to another, one observes variations inside the same colours.

It was suggested to try to come to an agreement with an international supplier wishing to be commercially implemented in Caraibes so that a free-zone warehouse be installed in La Habana in order to supply the regional factories without delays.

(*) Centro Nacional des Embalagem
Sra M-A. Ramos
Rua Telhal
Matinha, 1900-Lisboa, Portugal

Such warehouse could be located inside the Litograficas de La Habana, requesting only for this international group a small office and a telephone.

It was also suggested to contact the French petroleum company TOTAL, owner of the three ink manufacturers: Lorilleux-Lefranc (France), Coates (Great-Britain) and Sicpa (Switzerland and France). Should an agreement be reached with TOTAL, it would generate the advantage of providing in the first instance its technical assistance and to pay the product only after the official importation.

B. UNION DE PLASTICO, LA HABANA

La Habana Plant

(Ing. Ramon Gonzalez, Head of Technical dept)

This factory is one of the 10 factories of the holding (8 for plastics, 1 for toys, 1 for brushes); it was created about 30 years ago in order to have within the same premices all the machines until then installed in several small private units. It explains why the machines do not constitute a really homogeneous group, with various models and ages. Some 400 persons work in the factory.

A. PREMISES

1. The premices are very large, with a very important workshop containing most of the conventional machines and some smaller ones speciallized in special productions, warehouses, etc.;

2. The maintenance
Due to the leakages of most of the machines, the ground is everywhere oily. It is most difficult to work under such conditions for the drug and food containers production; a complete rehabilitation of the building will be necessary in a not too distant future;

3. Warehouses
The warehouses are cleaner and rather well managed; all the raw material (about 6 months of plastic supplies) are stored on pallettes;
the cardboards and folding boxes are also stored on pallettes (2-3 meters high) which is not really steady. The implementation of some shelves would permit a flat and improved storage preserving the quality of the cardboard boxes.

The storage of some finish products (feeling bottles) is done correctly in corrugated boxes; however, these boxes have visible defects and are polluted because of their filling is done directly on the oily grounds.

4. Quality control laboratory
A very small place (about 20 m^2) is devoted to the PE melt index and to some metrological controls; in such conditions, a permanent and efficient quality control is difficult.

5. Mechanical workshop
A small workshop is devoted to the maintenance of the maintenances; in another factory, more than 90% of the new maintenances are manufactured.

6. Maintenance warehouse
A rather big warehouse (about 100m²), well equipped with shelves, allows a good storage of the maintenances.

B. Machines

In the packaging workshop, two types of machines are installed:

1. Injection machines
Mainly from Italy and Germany (RFA) such as Battenfeld;

2. Blow-moulding equipment
Mainly from Italy; some of them from Germany (ex-RDA).

3. Some other machines are American or Japanese (Nissei).

4. Three German Engel machines (with a computerized regulation) are rather new.

The origin of the machines forms an heterogeneous park, generating a lot of problems for the maintenance (numerous spare pieces). Most of them are in rather poor conditions (numerous water and oil leakages, due to defects in the hydraulic circuit).

A general check-up of all these machines is highly recommended, before deciding if most of them have to be replaced or could be repaired.

At the present time, it may be cautious to evaluate the budget necessary to the replacement of all 20-year old machines.

4. Maintenances
Maintenances are manufactured in one Union de Plastico plant; depending of the models, their price varies between 4000 and 40 000 pesos (conversion rate: 1 peso = 1 US$).

Now ,the La Habana plant has officially 130 maintenances but uses only 70 (for injection, blow moulding and compression).

Steel maintenances are not used for small series but a cheaper one (with a shorter production life) made of Zamac (zinc-magnesium alloy).

C. PRODUCTION

The factory manufactures closures, bottles, crates, pipes, PE blown film and some toys; it also produces vacuum formed high impact PS sheets for meat packaging.

B. RAW MATERIALS

1. Imported materials

The group works with most of the plastic materials; in La Habana factory, they use mainly:

LD, HD and LLD PE; PP; PS (cristal and impact modified); ABS; probably PC and injectable PUR.

In another factory: PVC resin, unsaturated polyester, sheets of PMMA and sheets of plastified PVC are used.

All the raw materials are imported, at the beginning from Europe, and now partly from the regional producers (Brazil, Venezuela, Mexico, Nicaragua and Canada).

2. Specifications

a. The products are examined in order to control their specifications; in fact, for PE it means only that the melt index is correct:
b. no control is done about the identification of the added components; a written guarantee of conformity to a foreign regulation for food or drug packaging is asked;
c. the additives imported to prepare the PVC compounds are not controlled; PVC and additives are bought to expected serious companies (what about PVC control in Venezuela?).

3. Incidents

Few incidents are occuring:

a. Melt index

In the same batch, the melt-index of an Italian-French LDPE was decreasing from one bag to one another; two reasons were supposed to be the cause:

. a lack of control during the process,

. a mixture in the same silo or in the filling machine of a residue of a former batch with a new one.

It seems that the last hypothesis is the most evident.

A request, with the right identification of the batch and the number of bags defectuous, must be sent to the the supplier; a sample (few hundreds grams) of the defectuous product must be put aside for a further control by the supplier.

b. Wetting
A batch of melamine resin, imported from Mexico, was wetted during the shipment.

A request, with a right identification of the batch and the number of defectuous bags, must be sent to the supplier (or the ship-handler if Cuba took the responsibility of choosing the shipping company).

c. Defectuous bags
Some bags sometimes arrive damaged. The same procedure of control and request as above must be followed.

NOTE
For all the incidents occuring during the shipment or for the defectuous quality of the imported products, two methods could be applied:

i. Pre-control before shipment, by an expert company, such as the Swiss company:

Compagnie Générale de Surveillance (SGS)
16, Rue du Louvre, Paris, France

which can inspect in most of the industrialized countries;

ii. A post-control, when the shipment arrives in the port and/or in the factory; a local expert in shipment damages is generally required to examine the batch, estimate the importance of the damages and take a sample for an eventual laboratory expertise.

C. PACKAGING DEFECTS

Two main defects are noted for the bottles:

1. Poor hermeticity
due to a defectuous finish of the bottleneck; after blowing, the bottle is generally manually separated (with a knife) from the parison; an automatic cutting (heated resistance for instance) would improve the quality;

2. Defects of the bottleneck
also due to the evident partition line on both the body and the bottleneck of the containers; two reasons can be responsible of this defect:
. a wear of the maintenance,
. and/or an unsufficient hydraulic pressure to close the maintenance.

The latter seems the most evident, (numerous oil and water leakages on the machines). A general check-up of the machines is ncessary.

D. INFORMATION AND TECHNICAL ASSISTANCE

1. Information

The factory gets no plastic and packaging publications; it would be very useful for all the engineers to be informed about the new technologies, materials and controls;
another helpful information would be some catalogues containing the main names and addresses for the raw material and machines suppliers.

Such information could be supplied by the means of the bi-lateral cooperations (with the assistance of Embassies in Cuba).

2. Training

a. Technical training on the site

Two main subjects are highly requested by Union de Plastico:

. Extrusion blowing technology,
. Mould manufacturing and maintenance.

Such trainings could be provided by a former plastic engineer, having a sound knowledge on the subject and teaching skills.

b. Technical training in control

A few years ago, three engineers of Union de Plastico had the benefit of a six-week training in LKT, Vienna (Austrian & Unido program). At the present time, a similar training would be profitable in order to specialize one engineer in quality control and to permit the implementation of a valuable quality control laboratory.

C. FRASCOS DE PLASTICO FRASPLAST

(Ing. Lucrecia Cuon Chong, Director, Julio Torres, technical manager and the persons responsible of the quality control and mechanical maintenance)

This factory, bound to the pharmaceutical group, was recently built on a large site of the Scientific Pharmaceutical Pole, with an Italian credit and at the present time, only some manufacturing trials were done on the machines but no real production. About 45 persons are working in the factory.

A. PREMISES

1. The premices, designed by the two managers, are large, with a medium-size workshop containing the manufacturing machines, a separate shop for the plastic preparation, a small regulation room, and, separately, two storage warehouses for the raw materials and the finish products. The workshop is pressurized in order to avoid any external contamination and to guarantee a production within GMP conditions.

2. The maintenance: due to the fact that the plant is new, the maintenance is correct; in order to facilitate this operation, the floor of the production hall should soon be varnished with an an epoxy.

3. Warehouses
The warehouses, not yet built, are expected to be separate from the production area.

4. Quality control laboratory
A small place (about $30m^2$) is devoted to the quality control of the raw materials: PE melt-index and to some metrological controls; leakage control (in vacuum-oven); eventually some chemical controls.

5. Mechanical workshop
A small workshop is devoted to the maintenance of the machines and maintenance; the material is limited.

6. Maintenance warehouse
The mechanical workshop is used at the same time for the storage of maintenances.

B. Machines

In the packaging workshop, two types of machines are installed:

1. Production machines

a. Injection machines
From Italy (Presital);

b. Blow-moulding equipment
From Italy (Gramma).

c. Two grinders
Implemented in the plastic preparation shop, one for the PE scrap, the second for the PVC scrap. No one has a magnetic separator in order to eliminate the iron particles.

No printing machine has been bought but, in view of a cosmetic containers production, a silk-screen printing machine (Machine Dubuit for instance) could be implemented. A complete information concerning the machines (including the flame or corona treatment equipment) and the inks used for polyolefins (PE and PP) and PVC will be provided by the expert.

2. Maintenance equipment

The equipment is limited to a lathe and a movable bench with the normal hand-tools.

Half a day was devoted to check the list of the spare pieces which are necessary. It was also suggested to contact the other factories which work with the same equipment from the same supplier in order to create a pool of spare pieces permitting fast repairements.

4. Maintenances
The maintenances are manufactured in Italy; some quality problems have been noted. It was suggested :

. to contact, in Ecuador, the company IEPESA (Quito), one of the best maintenances manufacturers in So.th-America;

. in Europe, through the Commercial Arttachés of some countries (France, Germany, Portugal), to collect the addresses of the main manufacturers;

. and, for the small series of blow-moulded bottles, to produce in Cuba the aluminium maintenances; their price is about 4000 pesos (conversion rate: 1 peso = 1 US$).

For new or second hand imported maintenances, it was suggested to commission a specialist, for instance, the Swiss expert company:

Société Générale de Surveillance,
16 Rue du Louvre, Paris, France

for the inspection of the material before shipment.

5. Laboratory equipment

Some conventional equipment:

. scale,
. some small glass outfits,
. vacuum oven,
. spectrometer.

It was suggested to buy a gas chromatographic equipment in order to control the vinyl chloride residues in the imported PVC resin.

C. UTILITIES

1. Chilling unit
One unit, imported from Italy; with the spare pieces, one motor was supplied for emergency repair;

2. Compressed air
One unit, imported from Germany (Siemens); only some spare pieces were supplied, as Siemens has an agency in La Habana.

3. Electrical power
The power is expected to be supplied by two lines connected to two different areas of La Habana; there is no generator to supply the workshop during a general energy breakout. It was suggested to have at least a small unit permitting to purge the PVC machines, avoiding corrosion.

D. PRODUCTION

The factory expects to produce a full line of bottles and jars for pharmacy but also for cosmetics and perhaps food industry.
These products will be made in rigid amber PVC and HDPE; it should also be possible to produce some PP containers.

The installed capacity is 35 M° units in three shifts.

E. RAW MATERIALS

1. Imported materials

The group imports the LDPE and HDPE from Italy (Enichem) and the PVC from France (Atochem) and Italy.

It was suggested to import two stabilizers necessary to:
restabilize the ground scraps (about O.1-O.2%)

- 100 to 500 kgs of calcium stearate (PVC stabilizer and PVBC and PE lubricant),
- 100 to 500 kgs of BHT (PE anti-oxydant).

2. Specifications

a. The products are imported with a garantee for the pharmaceutical packaging;

b. except a visual inspection, no control is done on the batches of resins.

It was suggeted:

. to ask the PVC supplier to provide an analytical certificate for the residual vinyl chloride content;

. to record, on each batch, an UV spectrum of the substances extracted from the resins with two solvents (ethanol and heptane or hexane);

. it seems evident that the most important control of the European Pharmacopoeia should be carried out rather soon, in order to be conform to the GMP rules.

3. Incidents

An incident concerning leakages has been noted and a complaint sent to the Italian maintenance manufacturer.

F. INFORMATION AND TECHNICAL ASSISTANCE

1. Information

The factory does not receive any plastic and packaging publications; it would be very useful for all the engineers to be aware of new technologies, materials and controls;
another valuable information would be some catalogues containing the main names and adresses for the raw material and machines suppliers.

Such information could be supplied by the means of the bi-lateral cooperations (with the assistance of Embassies in Cuba).

The pharmaceutical group should send the European Pharmacopoeia new monographies to facilitate the adaptation of the laboratory to the specified controls.

2. Training

Considering that Frascos Plasticos is a new unit and due to its very specialized character, some training might be useful to permit a satisfactory development; some subjects might be considered:

a. the GMP management of a plastic container factory:
for a technician, a two-week study of the procedure applied inside the Jordanian "Arab Medical Containers Ltd" (Amman, Jordan) which stands the comparison with Frascos Plasticos for the investment, should be devoted to the implementation and the production;
profile of the candidate: the person who takes the responsability in the general or the technical managements;

b. the quality control management:
a one-month training in one specialized laboratory (French faculty of Pharmacy of Paris XII University [Pr. Bellocq] and in the laboratory of the Paris Pharmacie Centrale des Hopitaux [Pr. Hamon and Pr. Postaire] would be highly profitable;
profile of the candidate: the person capable of managing a Quality Insurance laboratory and of applying technically the methods specified in the monographies;

c. the plastic processing:
At the present time, there is no plastic training in Cuba; it would be interesting to organize a six-month training in one European (or Canadian?) engineering school or university; the training would be more profitable if, during two or three months, some visits and contacts with suppliers were scheduled;
profile of the candidate: the person in charge of either the technical management or the production.

These last two trainings could be supported partly by UNIDO and the bi-lateral cooperations. The three projects were discussed with the British and French Commercial Attachés.

G. DIVERSIFICATION

The large surface permits the implementation of a new building; the fact that the factory was GMP planned will allow a diversification in bio-medical disposable products.

The PVC blood-bags production project of the Pharmaceutical Group should find within two or three years an ideal site in this Pharmaceutical Pole, both for the material and for the human facilities (GMP oppotunities and good technical training). A study of the workability of such a project should take into account this possibility of implementation.

D. UNION DE VIDRIO - LA LISA

Union de Vidrio has three glass factories; La Lisa plant (la Lisa, near La Habana) was formerly a Owens-Illinois factory.

A. PREMISES

1. Buildings

The visited plant was rebuilt some 30 years ago with an Hungarian engineering assistance. The production halls are very large with a good layout of the lines. Unfortunately, a large part of the production has to be stored directly in the same halls.

A new building on the same site and formerly devoted to the electric tubes, has been partly converted to the production of ampoules and glass I ampoules and vials made with imported glass rods. The production of these rods is planned.

2. Maintenance

A better maintenance would facilitate the production (floor repairs). The fact that the sheds are open gives access to insects and birds in the production and storage areas. A net would limit the intrusion (such as bird-nesting).

B. EQUIPMENT

1. Production machines

a. Bottles

10 lines (imported from Germany-ex-RDA [Kaiseer] and Belgium [I.S. company]) are installed; right now, only five are working, one of them for the bottles production. The German lines are more than 25 years old and the IS machines about 13 years.

This last line capacity is 10 000 tons/[illegible]

Some information and tarifs concerning the silk-screen printing machines and UV polymerizable inks have to be sent (Machines Dubuit, France).

b. Ampoules and vials

Two lines, imported from Hungary, are still producing ampoules; a second line, imported from Italy, produces within better conditions, vials for injectable drugs.

The implementation of a new Italian unit would permit both to double the production and to stop the two old Hungarian lines; it seems also important to standardize and to limit the various sizes of ampoules and vials produced by the pharmaceutical factories.

c. Spare pieces
The spare pieces supply for the German lines is a problem; for this reason, about 95% of the needed pieces are made in Cuba.

A similar problem occurs with the Belgium I.S. pieces for which the delay is a minimum of three months but sometimes can go up to one year.

For the furnaces, the pieces are imported from the French Saint-Gobain group.

d. Moulds
The maintenance is done in Cuba; however, during the visits, it was observed that a defectuous mould-clamping results in a visible partition line both on the bottle and the bottle-neck.

2. Laboratory

The laboratory equipment is limited (scales, gauges and conventional chemical material for some raw material controls).

C. PRODUCTION

1. Bottles
During the visit, the factory was producing ambered 150 ml bottles for pharmacy;

2. Ampoules and vials
The production is limited to some models of ampoules (2 capacities) and vials (25 ml), made with imported glass I.

D. RAW MATERIALS

With the exception of the silica and calcite, all other raw materials are imported (dolomite, felspath and sodium carbonate). One of the problems is the iron content in the sand used for the white bottles.

E. QUALITY CONTROL

1. Raw material

The controls seem to be limited to the sand granulometry and iron content.

2. Finish products

a. Present controls

With the exception of a few metrological controls (calibration, capacities and weight) and a visual inspection of the vials and bottles, there are no chemical and physico-chemical controls done although very important in pharmacy.

It was suggested:

. to control once or twice a day the scraps container in order to determine the main occuring defects and to operate the fitting of the moulds;

. to mark the number of each mould to assure the fitting location;

. to create a collection of the defectuous bottles for the training of the people in charge of the production control.

b. Controls to foresee

. Vials and ampoules

. A control of the class I quality has to be made on each batch by a specialized laboratory (the Technical and Pharmaceutical Laboratory, (La Habana);

. an alcalinity control along the pharmacopoeia method should be programmed;

. diameter, weight and visual inspections have to be done carefully for the pharmaceutical containers.

. Bottles

A visual and a metrological inspections, using small equipment (light box, gauges) would permit to eliminate most of the defectuous bottles and vials.

c. Defects

Most of the time, the Cuban pharmaceutical industry has quality problems with the locally manufactured packages; to eliminate them, but only for the most important products (injectable and pommades, etc.), the packages are imported from Europe.

However, an effort is done now in the La lisa glass plant which produces ampoules and vials of a better quality.

Some defects are nevertheless observed:

- more bubbles in the Cuban bottles;
- an important partition line, which results in leakages and/or evaporation.

d. Methods

The actual controls are made along the conventional methods.

For ampoules and vials
It would be useful to apply the international pharmacopoeias, such as the European pharmacopoeia (last edition of the monography: January 1983) for the chemical controls of class I glass and alcalinity.

For both the vials and bottles
Some complementary tests are recommended such as a visual control (mainly to determine the number and importance of bubbles), glass particules, after storing at 37°C during a week, leackages and evaporation of the liquid content.

e. Guarantees

A guarantee, concerning the class I quality, has to be given by the glass rods supplier;
a garantee, concerning the quality level of the containers (critical defects) must be given by the La Lisa plant.

F. INFORMATION AND TECHNICAL ASSISTANCE

1. Information

A lack of technical information has been observed and the technical responsible persons would appreciate all updated information concerning the glass technology and especially the energy economies. Some information would be very useful such as:

. some packaging publications, such as British Packaging (in English) or Emballage Magazine and Emballage Digest (in French) monthly publications;
. one glass publication (if it still exists in England or in France)***.

Such publications would also be appreciated as references for the suppliers addresses.

2. Technical assistance

A lack of technology was observed mainly due to the limited contacts with international glass groups and organizations. It is to be noted that the world glass industry is very concentrated within a few holdings; a recent visit of a technician of the French Saint-Gobain group allowed some new contacts; any kind of technical and scientific assistance and contacts would be helpful and would impove the factory performance.

However, a real effort has to be made to rehabilitate this unit (See recommendations).

CONCLUSIONS

1. A new modern glass line for both the drug and food industries should be studied for the ambered 60 to 330ml class III bottles. A white class III glass line should be implemented for a wide exportation of some products (rum, fruit juices). It would facilitate the development of similar bottles for pharmaceutical products. However, the glass color problem has to be solved.

2. It is recommended:

a. to apply for a technical audit in the factory, in order to determine the most important modernizations to realize, the schedule for such programme, the total investments to consider;

b. to establish inside the factory, especially in the workshop and on the line, a careful control similar to those used in the pharmaceutical industry;

c. to train, at each level, the people in order to improve the quality of the production.

3. Documentation

Subscriptions to technical publications, mainly through the channels of the bi-lateral cooperation, would maintain the technical level of this industry and allow further contacts with the main international glass holdings and equipment suppliers.

E. CENTRO NACIONAL DE ENVASES Y EMBALAJES

(Ing. Roberto Pérez Jimenéz, General Manager)

This center, located in a residencial part of La Habana, employs at the present time 88 persons and plans an extension.

A. FUNCTIONS

The various functions concern:

1. the economical evaluation of any new package,
2. the laboratory evaluation of raw materials (mainly paper and cardboard) and packages,
3. the design creation: structural and graphic,
4. training and information,
5. pilot production of new models.

B. ECONOMICAL EVALUATION

The study concerns the materials to be used and is always conducted with the close participation of the laboratories.

C. LABORATORY WORK

The laboratories have two main activities:

1. Paper and cardboard controls

   Especially for the raw materials but also for the half-finished products (corrugated paper); the equipment is conventional, the air conditioning normal (but the laboratory does not benefit of all the new technologies in the matter of insulation);

2. Shipment packages

   with the normal equipment of testing laboratories (conditionning chambers, vibration table, dynamic compression material).

3. Other tests

   Some small other tests are done (or could be done if requested) on plastic, metal and glass (mainly mechanical tests).

D. DESIGN

A team of four persons works on both the structural and the graphic designs. The work is partly done with the assistance of a computer.

E. INFORMATION

A small library (about 50-60m^2) receive 45 specialized publications; but it seems that some of the suscriptions were not renewed.

It was suggested to the foreign Commercial Attachés, contacted during the mission, to send to Cuba (through the Cooperation service of the pharmaceutical group) some of the most representative publications and professionnal catalogues in order to provide a certain number of addresses which could be useful in the country.

F. TRAINING

The Packaging Center organizes on a regular basis training periods for the Cuban technicians; the last one concerned the metal packages; the next one will be devoted to plastics.

G. PILOT PRODUCTION

A small quantity of packages is produced with pilot machines, including the preparation of cardboard boxes, the printing, etc..

A new building is erected and all the pilot machines (including some new ones: off-set printing machine, blow-moulding plastic equipment, etc.) will be centralised on two floors.

The pilot plant has not for objective to become a producing enterprise but to supply small series of new packages; it was suggested, during the visit, to limit the production for instance to 10 000 packages of a model and, if necessary in the future, to transfer the production to one industrial factory. An accurate cost evaluation would also be useful (including the real amortization of the production equipment and premices) in order to avoid some surprises for the factory after the manufacturing transfer.

H. FINANCING

1. Creation of the center
The center was financially assisted (and probably still is for the equipment) by the Swedish government;

2. Operating budget
At the present time, the operating budget is supported by Cuba; in the future, when the pilot production is sufficient, the center should be able to partly self-finance his budget.

I. MISCELLANEOUS

1. Material
Although the laboratory equipment is sufficient, in the future it could be interested to consider the new generation of laboratory machines; most of them are actually computerized and some manufacturers propose the interfaces to connect all equipments of various origin to a central computer;

2. Congress
A congress of the International Association of Packaging Research Institutes (IAPRI) is scheduled next autumn in Brazil. Some information will be sent to the center.

ANNEXE VI

PROFILES OF THE CANDIDATES

FOR TRAINING PROGRAMMES

A. FRASCOS PLASTICOS

1. GMP management of a plastic container factory
   . A two-week study of the procedure applied inside the Jordanian "Arab Medical Containers Ltd" (Amman, Jordan),
   . profile of the candidate:
   the person responsible for the general or the technical managements;
   . serious knowledge of English is necessary.

2. Quality control management
   . A one-month training in one specialized laboratory (French faculty of Pharmacy of Paris XII University [Pr. Bellocq] and in the laboratory of the Paris Pharmacie Centrale des Hopitaux [Pr. Hamon and Pr. Postaire];
   . profile of the candidate:
   the person capable of managing a Quality Insurance laboratory and applying technically the monographies method;
   . good knowledge of French if not English is necessary.

3. Plastic processing
   . A six-month training in one European (or Canadian?) engineering school or university including, during two or three months, some visits and contacts with suppliers;
   . profile of the candidate:
   the person in charge of the technical management or of the production;
   . sound (if not good) knowledge of English is necessary.

B. UNION DE PLASTICO

Plastic quality control training
. A six week-training in LKT (Vienna) (Austrian & Unido program);
. profile of the candidate:
engineer specialized in quality control (objective: the implementation of a valuable quality control laboratory);
. good knowledge of German if not English is necessary.

C. FINLAY

. Technical training in bio-chemical analysis
. A two month-training in a outstanding hospital pharmacy, such as the London Saint-Mary Hospital;
. profile of the candidate;
pharmacist, bio-chemist of chemist;
. good knowledge of English is necessary.

ANNEX VII

UNIDO comments on expert's mission report

During his short visit to the producers of reagents (Finlay Institute) and to the different manufacturers of glass and plastic containers, as well as other packaging materials in Havana, Mr. Botrel has been able to identify the most critical problems that the producers and users are facing and have given concrete recommendations for short, medium and long term solutions.

Among the aspects which could be improved and could contribute to the amelioration of the quality of delivered reagents, special emphasis must be done to the performance of quality control tests for materials which should also include the determination of the compatibility of the chemical composition of the packaging material with the packed products in it. The composition of the utilized packaging material for pharmaceutical products should correspond to the requirements established in the international pharmacopoeias.

It is advisable to receive from the suppliers the exact information about the material composition of glass and plastic bottles, rubber stoppers and plastic closures. Before taking the decision on the type of container to be selected for a specific reagent, it is important to study the compatibility of materials as a measure of assurance in the quality and stability of the end product.

The consultant has given some valuable recommendations on the type of analysis to be undertaken for specific kind of packaging materials. For optimal utilization of available resources, it is recommended to study and select the optimal design for the specific reagents. The study must be done based on the physico-chemical characteristics of the product to be packed. Once the design has been decided, appropriate manufacturing techniques must be followed to guarantee the quality of the packaging products and to avoid leakages and contamination of the products.

From the findings of the consultant's activities and recommendations, it is advisable to introduce on an urgent basis some improvements in the production facilities of Union de Vidrio de La Lisa and Union de Plasticos de La Habana to achieve the required qualify for products, and also to ameliorate the organization of the whole production process and hygiene of production from reception of raw materials to the delivery of products and to assure the observance of G.M.P. regulations during all the production phases.

The organization of several training programmes for the above are strongly recommended. Scope of diversification of the production mainly for such products directly utilized by the health services could be studied in details considering the present and future potential markets (both national and international) for the products and availability of raw materials, equipment, infrastructure, personnel, etc. Taking into consideration the increased demand for disposable syringes and condoms, it would be advisable to study the feasibility and convenience of establishing the production facility for the local production of the indicated items.

The recovery and reprocessing of utilized materials should be studied as a way to save hard currency and as a contribution to the protection of the environment. Solutions for collection on hospitals, clinics, housings, etc. must be studied as well as application of modern techniques for the reutilization of the products.

It is also advisable to coordinate technical assistance services for the improvement of the design of the packaging materials for the most important group of reagents and for training of the personnel on the performance of that type of work.