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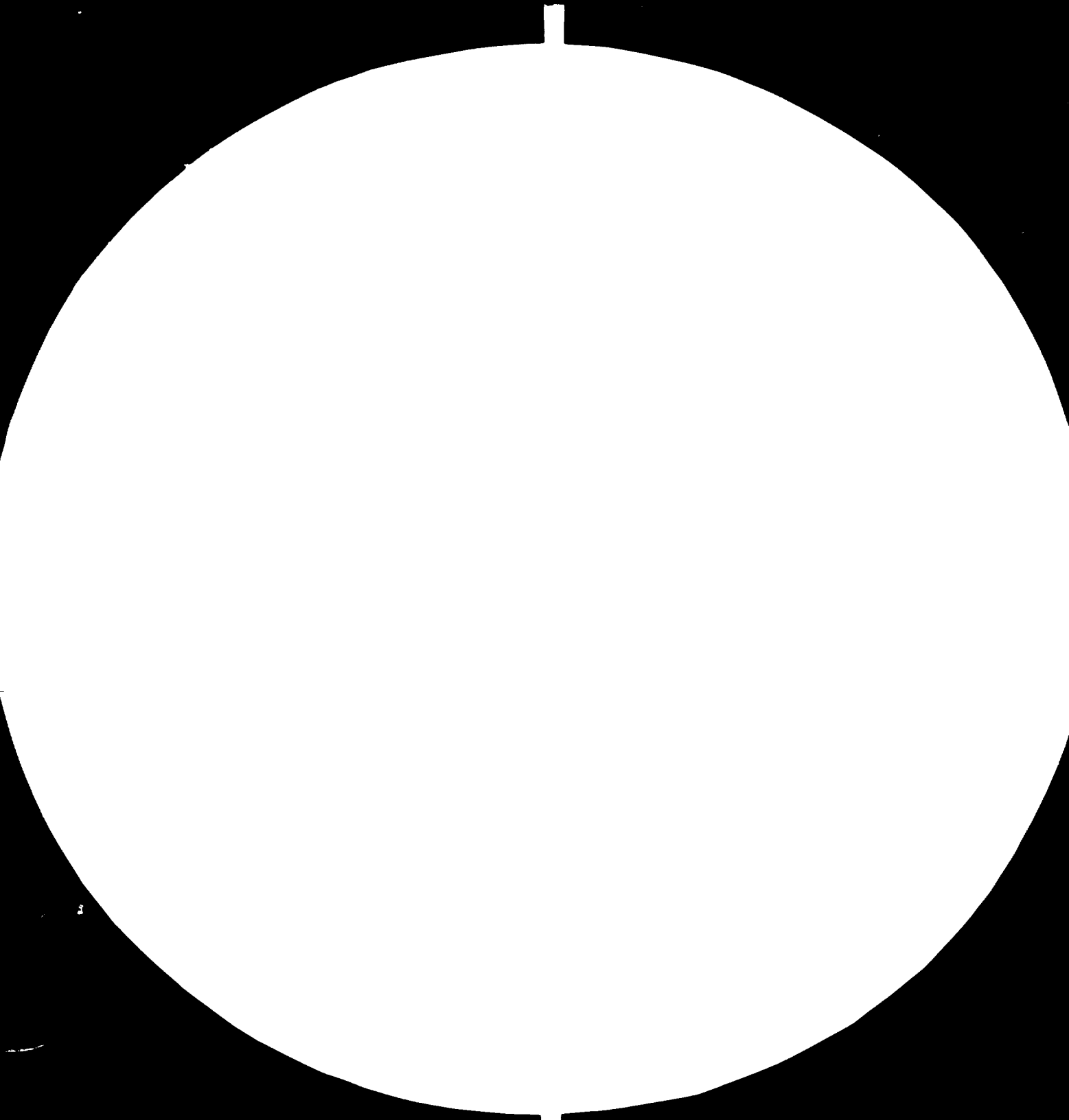

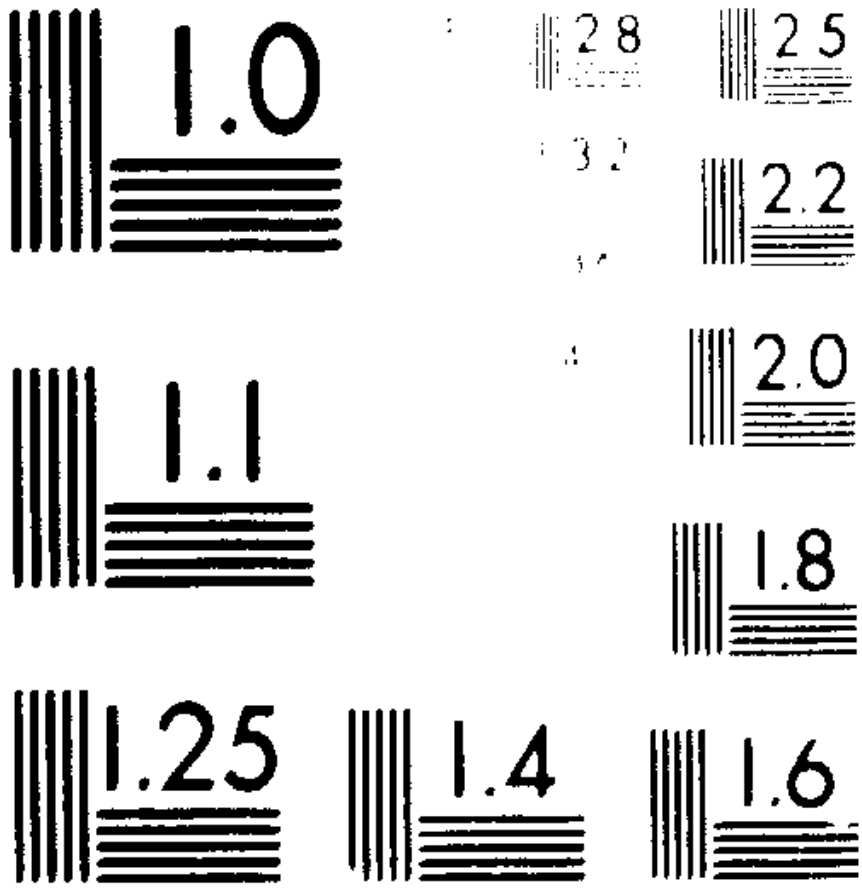
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16 April 1981
English

ADVISER ON PRODUCTION OF INTRA-UTERIN DEVICES

SI/CUB/75/804

CUBA

Terminal Report*

Prepared for the Government of Cuba by the
United Nations Industrial Development Organization,
executive Agency for the United Nations Development Programme

Based on the work of Sven A. Eriksson, pharmaceutical adviser

United Nations Industrial Development Organization
Vienna

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SUMMARY

The intra-uterine device (IUD) has a prominent position among the methods of family planning. The effectiveness is high and the duration is long. In 1977 there were 15 million users of IUD:s versus 55 million users of oral contraceptives in the world.

A preliminary lay-out of a production unit complying with the regulations for good manufacturing practice of sterile plastic products is presented. All stages involved in the manufacture, assembly and quality control of the IUD is described.

A cost calculation has been made for a batch size of 100 000 units, with a labor cost of 1 dollar/hour and investment cost of 100 000 dollar and a production first year of 300 000 units. With a calculated payback time one year of production equipment the cost for one package is about one dollar.

INTRODUCTION

The government of many development countries have drawn up populations programs as part of their National Development Programs. In this way they receive the support of various United Nations Organizations, such as World Health Organization and United Nations Development Programs.

Among the methods of family planning, the intra-uterine device (IUD) has now come to occupy a prominent position. The great advantage of these devices is that they only act locally and do not interfere with the extremely subtle natural mechanism that regulates a woman's reproductive function.

The effectiveness is high and the duration is long and no continuous supply is required. Between 5 - 15% of women will have to discontinue with intrauterine contraception during the first year after insertion. The most common side-effects associated with the use of any intrauterine device (IUD) is the occurence of heavy and prolonged menses. Bacterial infection of the genital tract is a serious complication in women wearing an IUD. The organisms responsible may ascend from vagina along the cervical tail of the device. The tails of the IUD interferes with the protective mechanisms of the cervix. To minimize this complication, the tail must be monifilamentous and only one tail is recommended. The design and consistence of the IUD, share responsability in the risk for perforation, which also depends upon the technique of insertion. A good instruction must follow each IUD.

Although the design and the bioactive material released are important, the training and eduction around the IUD technique may be more important than the IUD itself.

The most common IUD in Sweden is copper T - 95% of the market. This device is made in Finland by Autocompe and sold in Sweden by KABI AB. The plastic compound, as well as the molding is made in USA. The inserter is made in Denmark. The producer of the monofilament tie containing titanium oxide is unknown for the expert. In the near future we may be able to deliver those parts which on economical base are not decided to be produced in Cuba.

Manufacture of Device

Building facilites

The existing plastic factory in Havanna producing spectacle frames was located in an old building, without air-condition and equipment for filtering the air, which of course was not needed for the production of frames. For production of sterile products as IUD:s the production premise must have a high hygienic standard with electrostatic air purification and HEPA-filtered air. The amount of bacteria must be very low and test for bacterial contamination in the production area has to be done.

Storage rooms with quarantine areas and lockable rooms for approved raw materials and separate lockable storage rooms for the finished product and a special area for rejected materials is necessary.

Machinery

The existing available plastic extruders was from Negro Bossi, Milano, Italy. The extruders had no electronic control system. With an electronic control system and a winding device an automatic and aseptic production of the IUD is possible. With a hot runner system in the molds for skeleton and solid rod it is no rinse of inguts.

Production

The compound of polyethylene and the actual active ingredient may be imported as a granulate. After molding the IUD the copper wire is mechanically wound on the shaft of the IUD skeleton. After cutting the wire end is tightly pressed against the end of the shaft. The skeleton with tie is manually placed into the insertion tube on which the flange is mounted. The insertion tube with the IUD is packed together with the solid rod into the pouch. The pouches are sealed and labelled (Annex 2).

Control samples are drawn for visual inspection.

Sterilization

The welded pouches are sterilized by Ethylene oxide. A detailed description of the sterilization process and the control measures should be provided. Ethylene oxide sterilization cycles should be controlled by biological indicators of known sensitivity. Suitable indicators may be prepared. It may be necessary to monitor the residues of ethylene oxide exposure.

Quality control

A complete account of the tests which will be carried out routinely on each batch of the intrauterine device and its constituents is given in annex 6. Imported constituents have to be bought to a purchase specification with a certificate of analysis, or tested in Cuba for compliance with the specifications.

PLANNING

1. Basic information

A flow-sheet of the IUD production has been made (see annex 1 + 2).
Preliminary lay-out of production unit (see annex 3).

2. Equipment to be imported and to be constructed locally in Cuba (annex 4 + 5).

3. Proposed procurement procedure

For procurement the following procedure is proposed: The expert contacts possible suppliers and discuss with them the best technical solution. For the equipments which can be made in Cuba, specifications will be prepared.

4. Working program

Factory lay-out: A drawing of the factory building taking into account that the factory can be used for other medical plastic products such as disposable syringes, infusion sets etc.

5. Time schedule

1. Consultations by expert with equipment suppliers and preparation of precise specifications
2. Purchase of equipment
3. Preparation of final drawings
4. Building of prod. plant
5. Installation of equipment
6. Presence of IUD expert to start up the factory
7. Presence of Quality Control expert

Time schedule about 18 months from start.

Cost calculation

A preliminary cost calculation is presented in annex 7.
Exchange rate 1 pesos = 1,5 US$. With an efficiency of 70% is the calculated production capacity in one shift about 400.000 units per year, which will be the quantities of IUD need in Cuba.

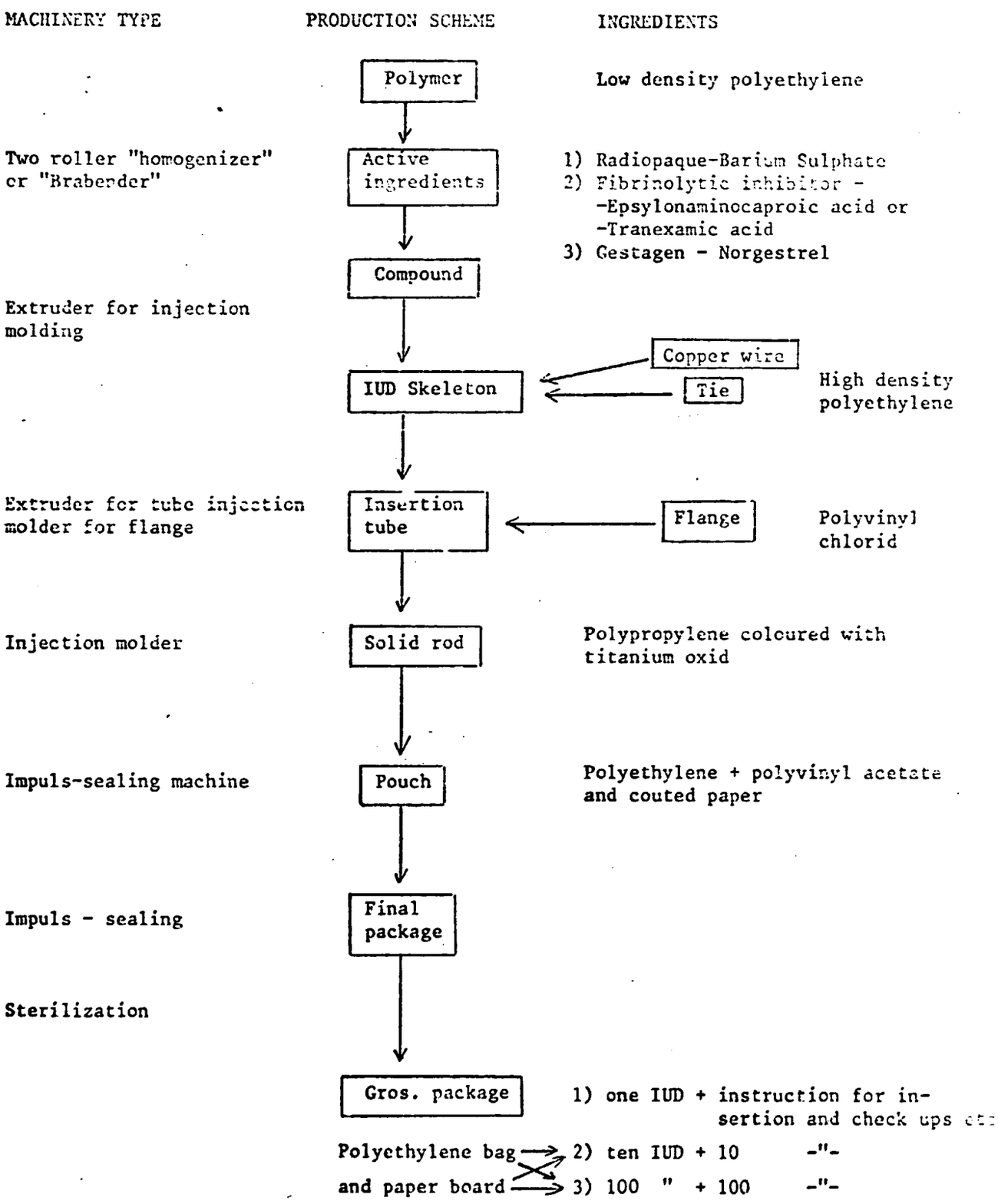
Recommendations

To evaluate the existing plastic factory in Havanna to a standard according the regulations for good manufacturing practice of sterile plastic products will be very expensive. The devices should be manufactured and assembled under conditions which minimise particulate and microbial contamination. Since the authorities have not issued specific regulations for the production of intrauterine devices it will be recommended to use good manufacturing practices. It is important that all personnel engaged in production and control of IUD:s that even with today's sophisticated analytical procedures inspecting, sampling and testing do not alone ensure the quality of final products. Only by strict adherence to a well-defined set of good manufacturing practices, which become the basis for written standard operating procedures, it is possible to consistantly manufacture, process, package and distribute IUD:s that are both safe and effective. The employees should be taught in carefully developed, continuing training programs.

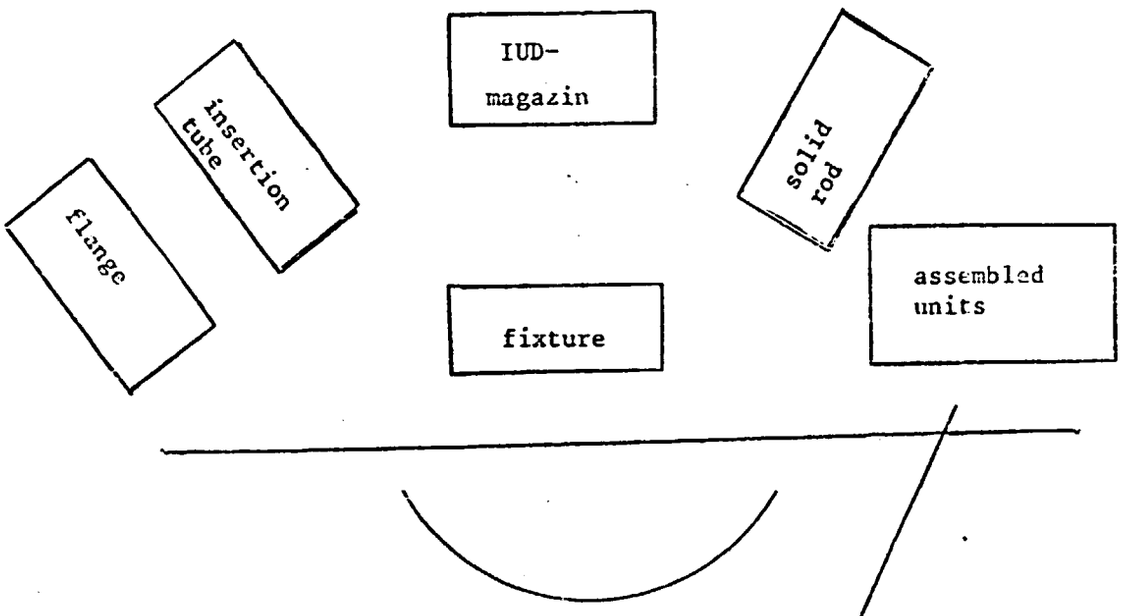
The production may be separated from non sterile plastic products.

Since there is a project being studied by the Ministry of Health for the production infusion equipments it is recommended that the production of IUD will be included in this project, rather than rebuild the existing factory for frames.

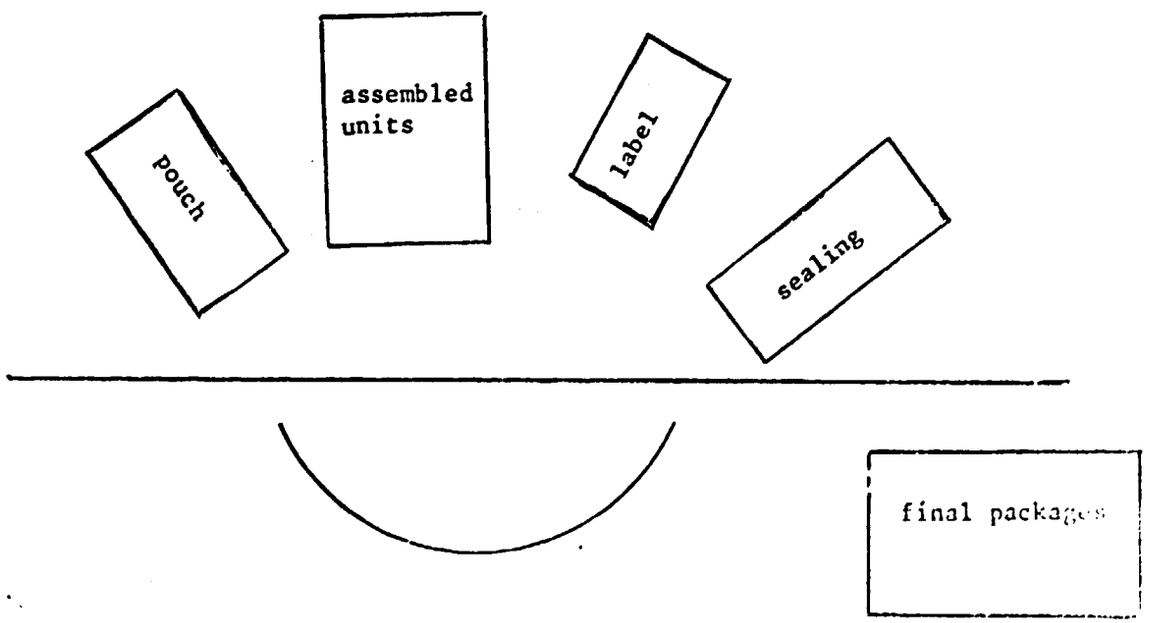
Annex 1


MACHINERY TYPE
PRODUCTION SCHEME
INGREDIENTS
Polymer
Low density polyethylene
Two roller "homogenizer" or "Braberder"
Active ingredients
1) Radiopaque-Barium Sulphate
2) Fibrinolytic inhibitor - -Epsylonaminocaproic acid or -Tranexamic acid
3) Gestagen - Norgestrel
Compound
Extruder for injection molding
Copper wire
Tie
IUD Skeleton
High density polyethylene
Extruder for tube injection molder for flange
Insertion tube
Flange
Polyvinyl chlorid
Injection molder
Solid rod
Polypropylene coloured with titanium oxid
Impuls-sealing machine
Pouch
Polyethylene + polyvinyl acetate and couted paper
Impuls - sealing
Final package
Sterilization
Gros. package
1) one IUD + instruction for insertion and check ups etc
Polyethylene bag and paper board
2) ten IUD + 10 -"-
3) 100 " + 100 -"-

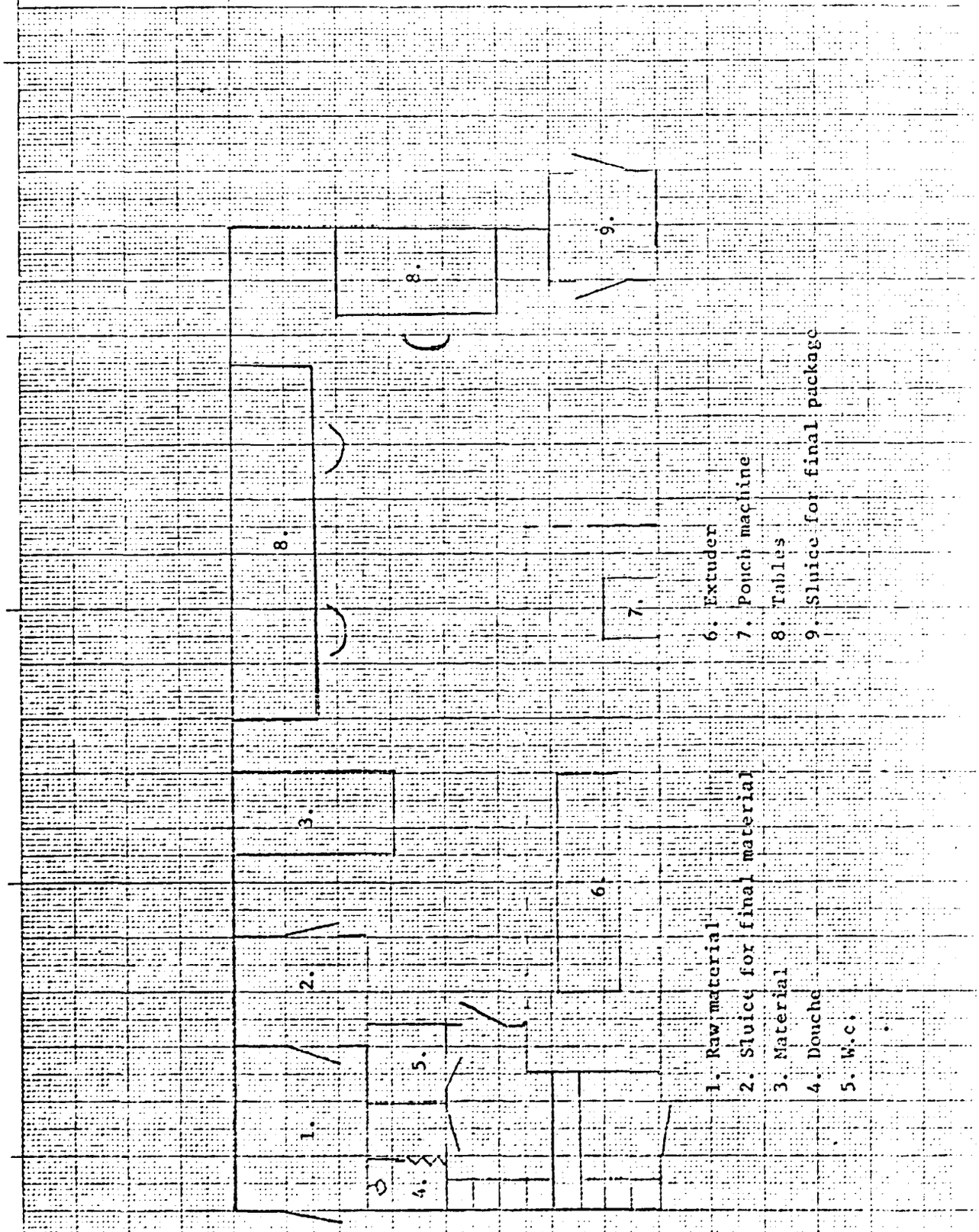
Operatorś position 1 + 2



Operaterś position 3



Production unit lay-out



Annex 4

IUD production unit in Cuba

Equipment to be imported

Code	Equipment	Units	Capacity	Supplier	Estimated price US$
01	Extruder	1	Clumping pressure 20 tons	Arburg, West Germany	36.000
02	Electronic control system	1		Hunkar or Sikab, West Germany	5.000
03	Winding device	1		Moderna Verktyg, Söderköping, Sweden	5.000
04	Skeleton mold	1	4 cavities	-"-	10.000
05	Hot runner system	1		-"-	7.000
06	Flange mold	1	8 cavities	-"-	6.000
07	Solid rod mold	1	4 "	-"-	8.000
08	Hot runner system	1		-"-	7.000
09	Pouch machine	1	1200/hour	Cloab AB, Stockholm, Sweden	13.000
10	Pouch tool	1		-"-	300
11	Heat sealing machine	1			400
				s:a	97.700

Annex 5

Equipment to be constructed locally in Cuba

Code	Equipment	Price, US$
12	x) Inserter tube moli	300

x) For molding the inserter tube, the existing extruder for production of insemination tubes can be used.

QUALITY CONTROL OF INTRAUTERINE DEVICE (IUD)

I. Quality of materials

IUD skeleton made of low density polyethylene.
Density, 23°C (after one hour heating at 100°C) is 0,917 - 0,919.
Test method DIN 53479.
Melt Index MFI 190/2,15: 1,2 - 1,7 g per 10 minutes.
Extraction test for classic II plastics according to the USP XIX.
Quality of molding powder after compounding content of active ingredients.

II. Quality of molded IUD

1) Molded IUD must not cause unacceptable tissue reaction. This test is run on the first batch of molded IUD made with a new lot of the compound: Implant 1 cm length of each of eight IUD intramuscularly in two rabbit using 4 test sections and two negative control sections in each animal. The materials is sterilized before implantation. Sacriface the animals after fourteen days and observe for gross and histologic evidence of tissue reaction.

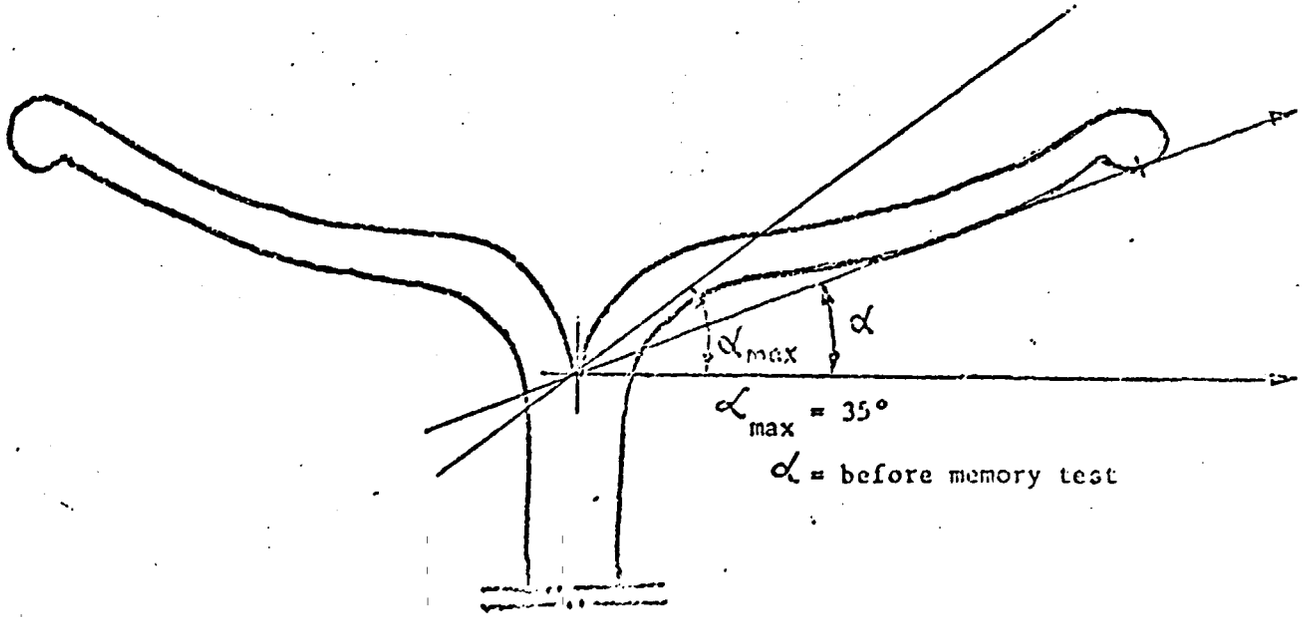
   Reaction to not more than one of four pieces can be greater than the strips of USP Negative Control Plastic Standard.

2) Dimensions of IUD is measured in a projection microscope and compared with a special transparent drawing. Acceptable Quality Level (AQone) is applied with measures with tolerances.

3) Memory test of IUD is measured in terms of recovery after acute flexation.

   a) Apparatus: Stop-watch, Fixture with hole diameter = IUD handle and profite projector with magnification 5X.

   b) Procedure = The horizontal arms are folded and inserted in the fixture. They are allowed to remain in this folded position for five minutes and then removed and allowed to recover their shape under zero load for ten minutes. Measure the angle α as shown in figure in a profile projector with magnification 5X. The recovery of the arms must be such that the displacement does not exceed 35°.



III. Quality of tie

The tie is made of high density polyethylene containing 1% of titanium oxid.

a) The length shall be about 300 mm from the end of IUD, diameter 0,25 mm.

b) Tanacity = About 300 mm of the tie from each spool is subjected to pull test in an Alwetron pull-tester. If any breaks at pull less than 12 N take three samples at the distance of 10 meter from the first sampling place. If another of these breaks at pull less than 12 N reject the spool. (N=Newton).

IV. Quality of cooper wire in a copper IUD

a) Dimensions of the wire = Diameter 0,30 mm length 220 mm.

b) Surface area of the wire 195-220 mm^2.

c) The winding must be uniform and the ends must not protrude.

d) Quality of copper = 99,9 % pure (ASTM 101 OFE). Analyses are obtained by Quantro-metric.

Analyzing Equipment except Se and P which are determined by Quanto-VAC-Analyzer.

V. Insertion tube

Is made of low density of high density polyethylene.

a) Dimensions = Length 197 - 201 mm
Inner diameter 2,89 - 2,91 mm
Outer " 3,64 - 3,66 mm

b) Must pass extraction test performed according to USP XIX class II plastics.

VI. Flange

Is made of polyvinyl chloride or polyethylene containing a certified colour. The resistance to movement when pulled at the rate of 20 mm/sec. Shall be within 2 - 7 Newton.

VII. Solid rod

Is made of polypropylene containing 0,5 % titanium oxide. Dimensions: Length from handle brace to top 200 mm - Diameter 2,0 - 2,3 mm.

VIII. Pouch

The pouch is made of polyethylene and polyvinyl acetate on the clear side and for sterilization with ethylen oxide the other side is made of coated paper with controlled pore size.

IX. Final package

Is sterilized by ethylene oxide at a temperature of 50-55°C during 24 hours.

a) All components IUD, insertion tube, flange plunger and label must be present.

b) The IUD must be present in the insertion tube.

c) The IUD must be approximately 9 cm from end of insertion tube containing the IUD.

d) The pouch must be undamaged and sealed and shall give a complete closure.

e) Printing and the lot number must be clear and legible.

f) Sterility test according to USP XIX.

COST CALCULATION FOR IUD

Batch size: 100 000 units

	Dollar
1. Direct material cost	1650,5
2. Captial cost for material	55,0
3. Direct labour	1790,0
4. Control cost	350,0
5. Service cost	187,5
6. Production Overhead	450,0
7. Cost for production equipment	33500,0
8. Research cost	40000,0
Calculated cost/batch	77983,0
Calculated cost/unit	0,78
Calculated cost excluding production equipment and research	
per batch	4483
per unit	0,05

Calculated cost for one package

Package 1 x 1 IUD

Cost for IUD	0,78
Package cost	0,30
	1,08 dollar/package

Package 1 x 10 IUD

Cost for IUD 10 x 0,78	7,80
Package cost	0,40
	8,20 dollar/package

Package 1 x 100 IUD

Cost for IUD 100 x 0,78	78,0
Package cost	3,5
	81,5 dollar/package

1. Direct material cost for IUD

Batchsize: 100 000 units

Material cost for polyethylene and polypropylene used for manufacturing:

	weight	cost/kg	cost/batch
IUD skeleton	15 kg	2,5 dollar	37,5 dollar
Inserter	70 kg	2,5 "	175,0 "
Solid rod	80 kg	2,5 "	200,0 "
Flange	60 kg	2,5 "	150,0 "
Tie	1,4 kg	2,5 "	3,5 "
Bariumsulfat	3,0 kg	4,0 "	12,0 "
Copper Wire	14,5 kg	5,0 "	72,5 "
Direct material cost excl. pouch			650,5 "
Material cost for pouch and paper			1000,0 "
Direct material cost			1650,5 "

2. Capital cost for raw materials and goods in process

Calculated months in stock/year: 4

Rate of interest = 10%

$$\frac{4 \times 10 \times 1650,5}{12 \times 100} = 55 \text{ dollar}$$

3. Direct labour

Batch size: 100 000 units

Operation	Labour time	Machinery time	Cost/hour	Cost/batch
Assembling for IUD in final package	1100 hours		1 dollar	1100 dollar
		490 hours	1 "	490 "
Assembling copper wire	200 hours		1 "	200 "
				1790 "

4. Control cost

Raw material quality control/batch	300 dollar
Direct quality control in operation/batch	50 "
	350 "

5. Service cost for mold

Cost/batch IUD skeletons	75 dollar
" " solid rods	75 "
" " flanges	37,5 "
	187,5 "

6. Production overhead

25 % of direct labour and machinery

$$\frac{25 \times 1790}{100} = 447{,}50 \approx 450 \text{ dollar}$$

7. Cost for production equipment

Calculated payback time one year

Irvestment cost: 100000 dollar

Production first year: 300 000 units

Cost/batch ≈335000 dollar

8. Research cost

Development cost for EACA	60000 dollar
Cost for clinical test	60000 "
	120000 "

Payback time one year

Cost/batch 40000 "

Cost for Crospackage

A. Package 1 x 1 IUD Batch size: 1 package

Material cost for label and filing box:	0,25 dollar
Direct labour	0,02 "
	≈ 0,30 " /package

B. Package 1 x 10 IUD Batch size: 1 package

Material cost for label and box:	0,30 dollar
Direct labour	0,10 "
	≈ 0,40 " /package

C. Package: 1 x 100 IUD Batch size: 1 package

Material cost for label and box:	3,0 dollar
Direct labour	0,5 "
	3,5 " /package

UNITED NATIONS

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION

UNIDO 30 January 1976

Request from the Government of the Republic of Cuba

for Special Industrial Services

JOB DESCRIPTION
IS/CUB/75/004/11-01/04

POST TITLE	Adviser on Production of Intrauterine Devices.
DURATION	One month
DATE REQUIRED	June 1976
DUTY STATION	Havana
DUTIES	The expert will co-operate with the Ministry of Health and will be expected to:

1. Evaluate the existing plastic factory in Havana producing spectacle frames and vials for the pharmaceutical industry;
2. S tudy the quality and quantity of intrauterine devices used in and imported to the country.
3. Evaluate the existing available machines in the factory and their utilization for the production of intrauterine divices.
4. Prepare a list of equipment and additional machines and moulds for such a production.
5. Work out a programme within the existing factory for the production of intrauterine devices.

The expert will also be expected to prepare a final report setting out the findings of his mission and his recommendations to the Government ,on further actions which might be taken.

QUALIFICATIONS	Chemical Engineer with experience in the production of intrauterine devices.
LANGUAGE	Spanish; English an asset.

..../..

BACKGROUND INFORMATION

The Government of Cuba imports every year considerable quantities of intrauterine devices in order to cover the country's needs.

Since there is a well established plastic factory, producing different kinds of articles for the pharmaceutical and optical industries, the Government wishes to utilize fully the capacity of available machinery for the local production of intrauterine devices in order to save hard currency, which is presently spent on importing these articles.

CANDIDATES REQUESTED BY 26 MARCH 1976