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UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION
Vienna International Centre, P.O. Box 300, 1400 Vienna, Austria
Tel: (+43-1) 26026-0 · www.unido.org · unido@unido.org

15035

Distr.
RESTRICTED

UNIDO/IO/R. 182
16 September 1985

UNITED NATIONS
INDUSTRIAL DEVELOPMENT ORGANIZATION

ENGLISH

ESTABLISHMENT OF A DEVELOPMENT PLAN
FOR THE PHARMACEUTICAL INDUSTRY

UC/ALG/85/062

ALGERIA

Technical report: Opportunities for
production of intrauterine devices (IUDs) *

Prepared for the Government of the Democratic
and People's Republic of Algeria by the
United Nations Industrial Development Organization

Based on the work of Mr S.A. Eriksson, expert
in the production of intrauterine devices

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V.85-30906 (EX)

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I. RECOMMENDATION

The annual use of intrauterine devices in Algeria is nowadays too low to start a production of IUDs. When the consumption reaches about 100,000 IUDs per year, the production ought to be started to get a good benefit.

The capacity of the production unit in this report will be one million IUDs/year in one working shift, which should be sufficient until the year 2010. To make better use of the capacity of the production unit in the beginning it is excellent for moulding of parts to infusion sets and plastic syringes.

II. BACKGROUND INFORMATION

Birth control is becoming increasingly accepted at both the national and the family level, and has been greatly facilitated by the widespread use of "the pill". However, as the years go by, the disadvantages of this approach to contraception are becoming ever more clear. Apart from the still as yet unknown possibility of a long-term carcinogenic effect, "the pill" is responsible for:

- diminution of physical and/or mental well-being
- venous thromboembolism
- persistent amenorrhoea during and/or after use

Many women (and their medical attendants) are increasingly concerned about these problems with "the pill" and would welcome a simple alternative. The intrauterine device (IUD) has the following conceptual advantages over other forms of contraception:

- it requires only the initial motivation for insertion, not a day-by-day or occasion-to-occasion decision;
- its efficacy almost matches that of "the pill" and is much greater than with all other methods;
- it does not involve a general interference with body metabolism and hormone balance.

However, the acceptability of the IUD has remained rather low because its use has been associated with an often troublesome increase in menstrual blood loss, intermenstrual spotting, pain and expulsion. Surveys have shown that the number of women who would select the IUD for birth control would increase two- to four-fold, where a device is available which did not have these attendant problems.

These devices with copper represents a new principle in intrauterine contraception.

Whereas any foreign body of sufficient size has some antifertility action when placed in the uterus, it has been shown that metallic copper has a specific anticonception effect. This in comparison with other IUDs, these can be designed to minimize damage to the uterine endometrium due to physical shape, since its antifertility effect is not primarily dependent on mechanical interference with implantation.

The "T" shape has been developed and tested to provide good confirmation to the endometrial cavity with minimal endometrial compression and myometrial distension as compared with conventional IUDs. Clinical tests have confirmed that this shape is associated with a lower incidence of pain and bleeding than with other IUDs. The high efficacy of the copper IUDs is due to the slow release of copper from the fine wire which is wound round the vertical arm of the "T". Many trials of various thicknesses of wire already have been made to secure the greatest antifertility effect with the longest life of the device.

General experience with copper has indicated tolerance for a broad dosage range in the diet. The quantity of copper in the device is less than 125 mg and measurements have shown that the slow release of copper would contribute less than 10 per cent of the daily intake, were it absorbed. Blood analyses have shown no evidence for absorption, and probably a substantial part of the copper released from the device is lost eventually in uterine secretions. Various studies of any local effect of copper have been favourable.

The selection of patients for the IUD and insertion of the device present no problems. In fact, most patients who have discontinued using other IUDs because of bleeding and/or pain also are considered suitable subjects. The device contains barium sulphate to allow for location by X-ray examination, should this be necessary. If ultrasonography is available the barium sulphate can be excluded.

Dr. Malika Dadjali gave the following data from the family planning program: In 1984 the total number of consultations was 834,?54 females. 150,494 of these were newcomers. The first insertion of IUD was on 16,903

females and together with the reinsertions 30,000 IUDs were used in 1984. The types of IUD in use are C u T 200, Multi load and Lippes Loop.

Quality control of imported IUDs is not performed in Algeria. From ENEMEDI I got the price $0.93 when they buy 16,000 units from WHO-organization for Copper-T. This subsidized price is not comparable with commercial prices, e.g. for:

Multiloads - 6.10 HFl each in 16,000 units
Gyn T 200 - 48.23 FF each in 20,000 units

Registration

The need for registration of IUDs varies from one country to another. The requirement for safety can better be maintained when registered and controlled according to given specifications of the authority.

"Life-time" of IUD

The life-time in situ of Copper-T is three years as recommended by Population Counsel.

With a three-year usage or life of each inserted Copper IUD and the first insertion to a newcomer at the age of 16 until first child at 19; one insertion before second child at 22; one insertion before third child at 26 and only three children and a child-bearing life then of 21 years, will be an estimated need of 10 IUDs per woman. These IUDs will be spread over a thirty years period.

Assuming that 5% of the child-bearing population eventually accept this form of contraception, the annual usage would be 2.33% of that population.

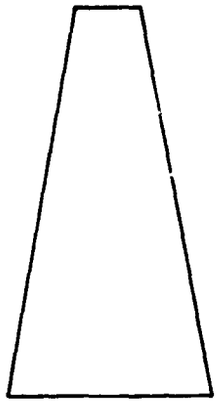
The child-bearing population in Algeria, 1985 = 4,330,000 and annual use of IUDs 101,000
The child-bearing population in Algeria, 2010 = 9,196,000 and annual use of IUDs 214,000

The real figures from 1985 are lower but when an active family planning organization now exists the consumption soon will reach this number.

Further, the life-time in situ of Copper-T will be prolonged to 4 years as in Sweden now.

The cost-effectiveness of population control

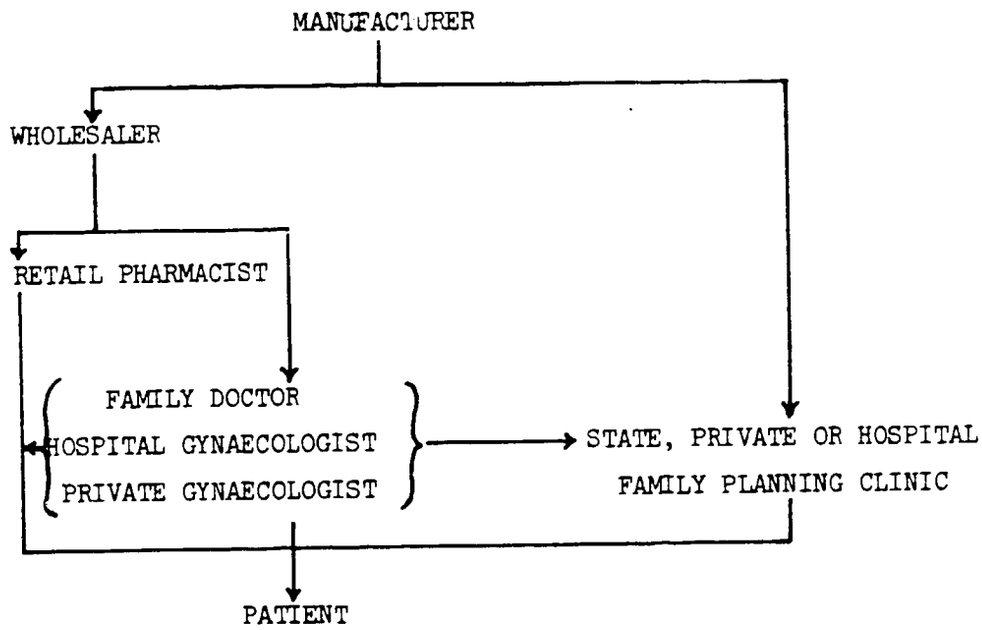
Of the available methods of contraception only the use of condoms, the IUCD or the pill can be considered as usefully effective, and the failure rate with the condom is comparably high. A consideration of cost over a three-year period shows that the Copper-T IUD is the least expensive, most efficient, reversible means of contraception.

METHOD	EFFICIENCY	COST RATIO /3 years/	REVERSIBILITY
Safe period		0	+
Withdrawal		0	+
Caps etc.		± 0,5	+
Spermicides		± 1,0	+
Condoms		10,0	+
IUCD		1,0	+
"Pill"		6-12	+
Abortion		15,0+	±
Sterilization /♀/		20,0+	-

The cost effectiveness of population control

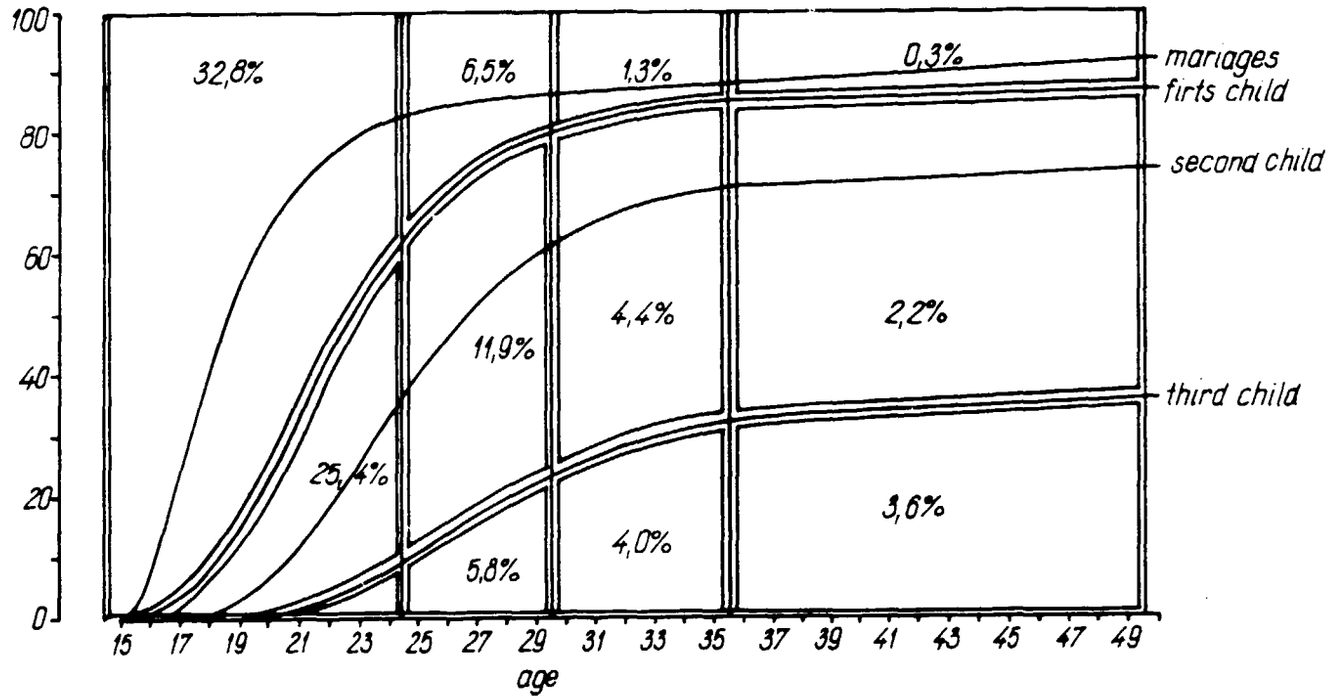
The Marketing plan for the COPPER-T

The channels of distribution are common to all geographic outlets and comprise the wholesaler, the retail pharmacist, the gynaecologist (who may be a dispenser) and the patient. The sales force distribution is not uniform among the outlets, and access may be gained only to gynaecologists and family planning clinics. Company expertise in family planning matters is lacking, except in Sweden.



Lines for the IUCD

Percentage of COPPER-T users according to age-group and parity. - U.S. study, Aug. 1973, 12901 women



Comparison between IUDs for pregnancy, bleeding/pain and total closure rates per 100 users, with more than 5000 women-month of experience

Device	Pregnancy	Expulsions	Bleeding/Pain	Total Closures	Woman-months
Loop D	2.4	4.8	10.4	22.6	72,046
COPPER-T	1.8	5.6	4.5	16.8	7,662
Loop D	2.1	10.3	7.6	26.6	5,760
Saf-T coil	2.8	16.3	?	30.5	7,636
Large spiral	1.3	7.9	9.6	27.0	18,744
Large bow	3.9	1.0	8.8	19.3	24,637
Double coil	2.2	7.8	12.8	27.3	12,015
Antigon F	1.8	8.8	?	28.2	8,093
Lippes shell	1.7	2.1	?	18.2	10,886
Dalkon shield	3.8	3.9	4.6	19.3	6,669

This table confirms the efficacy, good tolerance and high continuation rate of the copper-T.

III. FACILITIES FOR PRODUCTION OF IUD

A. Building facilities

My recommendation is to have a unit for IUD production in the new building for injectibles having premises for production control and storage, furthermore office, dressing and rest-room.

The production unit must have a high hygienic standard and be cleaned easily. Wall and floor covering will be in PVC plastic and the ceiling painted with alkyd-paint. It should have electrostatic air purification and HEPA-filtered air in room no. 10 and sluices. The production premises shall be cleaned every day according to written instructions. Before entering the production unit the personnel must change to special working clothes, put on overalls and wash their hands.

Storage rooms

Raw materials while under quality control shall be stored in quarantine areas, and transferred into a lockable storage room when approved.

The finished products shall be stored separately in a lockable storage room. A separate area shall be provided for rejected materials.

Personnel

Head of manufacturing, one engineer or pharmacist, 3 workers.

Production

The skeleton will be made by injection moulding according to written instructions. The copper wire will be mechanically wound on the moulded skeleton. After cutting the wire end is tightly pressed against the skeleton (T) body. The ties are tied on the T which is manually placed

into the insertion tube on which the flange is sitting.

The inserting tube with the T is packed together with the solid rod and the label insert into the pouch.

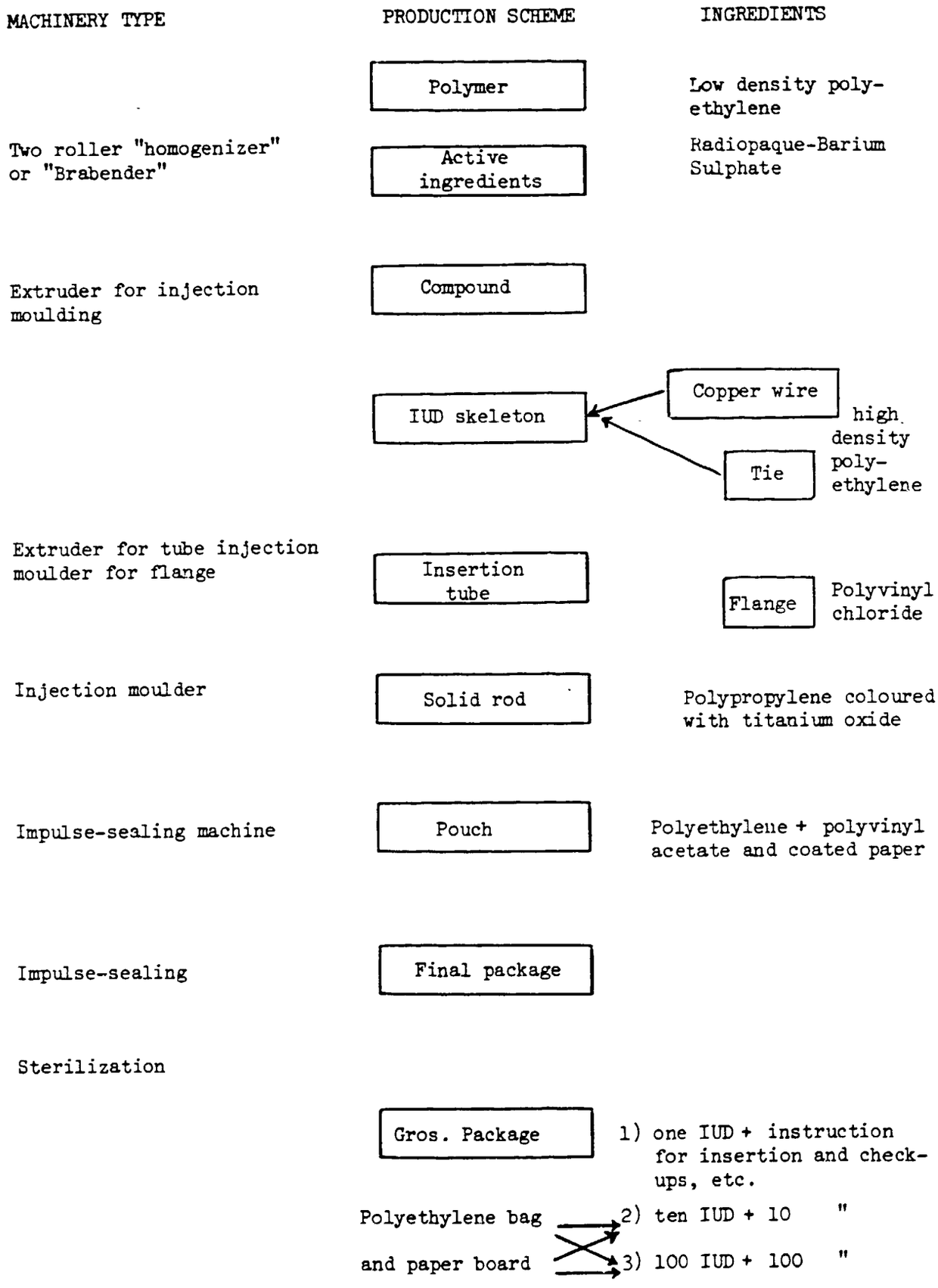
During the final packaging, control samples are drawn for visual inspection.

Sterilization

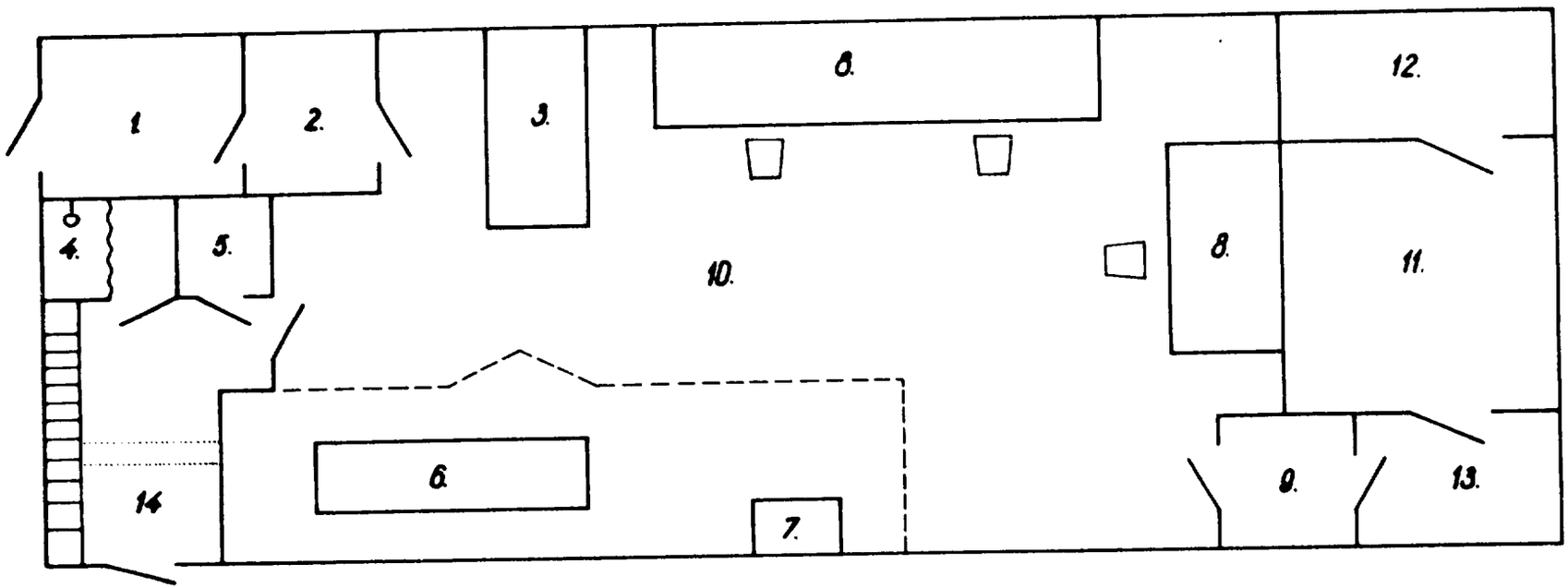
The best method for sterilization is using B-radiation. This method is not available in Algeria. We have to use gas sterilization (50% of ethylene oxide and 50% of methyl formate or 90% of ethylene oxide and 10% of carbon dioxide).

The containers with IUDs are supplied with biological indicators (spore samples) for sterility control.

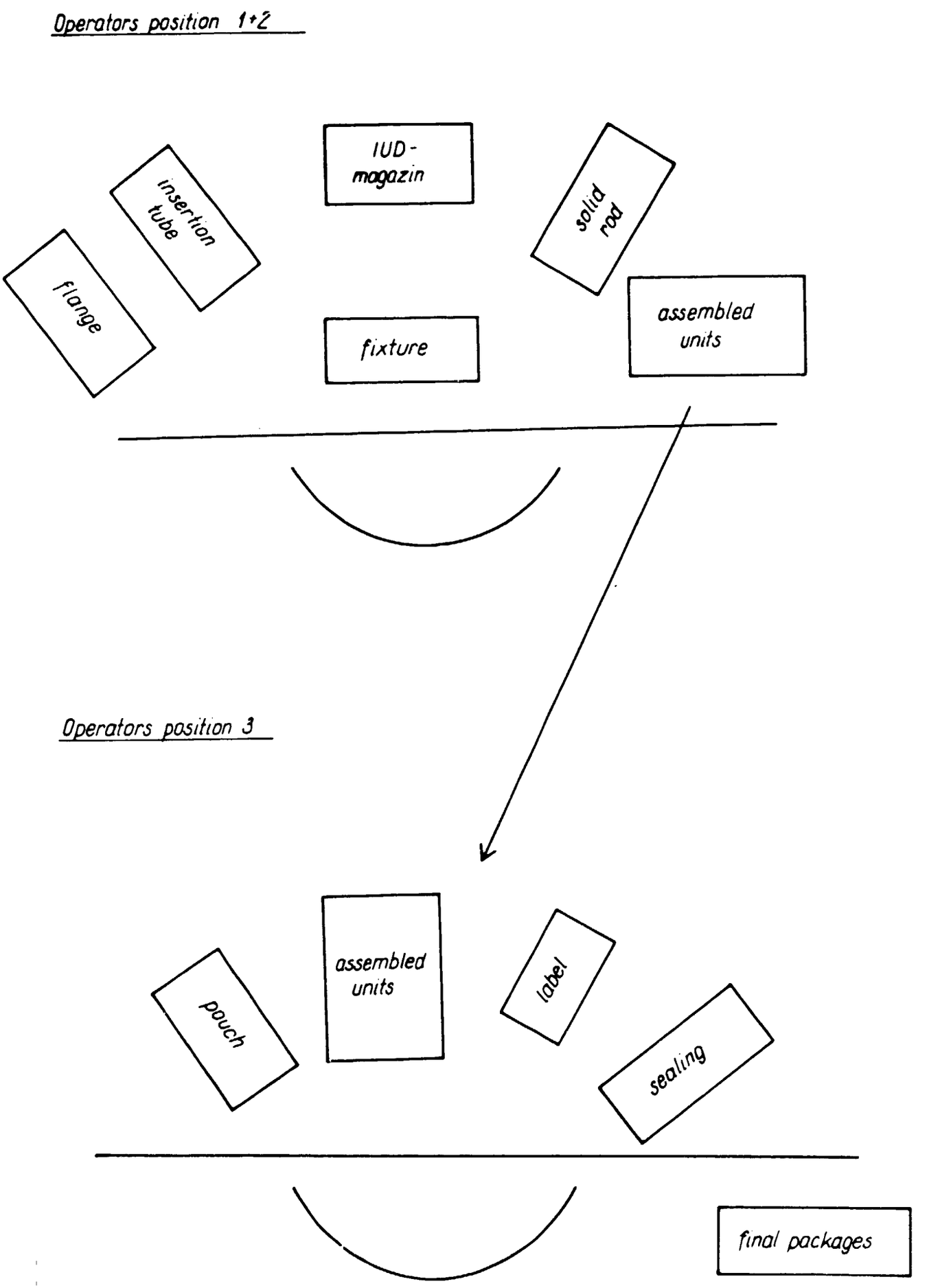
Follow written instructions.


MACHINERY TYPE
PRODUCTION SCHEME
INGREDIENTS
Polymer
Low density poly-ethylene
Two roller "homogenizer" or "Brabender"
Active ingredients
Radiopaque-Barium Sulphate
Extruder for injection moulding
Compound
IUD skeleton
Copper wire
Tie
high density poly-ethylene
Extruder for tube injection moulder for flange
Insertion tube
Flange
Polyvinyl chloride
Injection moulder
Solid rod
Polypropylene coloured with titanium oxide
Impulse-sealing machine
Pouch
Polyethylene + polyvinyl acetate and coated paper
Impulse-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 IUD + 100 "

PRODUCTION UNIT FOR IUD
SURFACE AREA 200 m²



1. Raw material
2. Sluice for final material
3. Material
4. Douche
5. W.C.
6. Extruder
7. Pouch machine
8. Tables
9. Sluice for final package
10. Aseptic area
11. Gas sterilization
12. Final product
13. Rest-room
14. Step-over bench


Operators position 1+2
IUD-magazin
insertion tube
flange
solid rod
assembled units
fixture
Operators position 3
assembled units
pouch
label
sealing
final packages

B. Equipment

Code	Equipment	Units	Capacity	Supplier	Estimated price US$
01	Extruder	1	Clamping pressure 20 tons	Arburg, West Germany	78,000
02	Electronic control system	1		Hunkar or Sikab, West Germany	10,000
03	Skeleton mould	1	4 cavities	Moderna Verktyg Söderköping Sweden	25,000
04	Hot runner system	1		"	14,000
05	Flange mould	1	8 cavities	"	22,000
06	Solid rod mould	1	4 cavities	"	20,000
07	Hot runner system	1		"	14,000
08	Pouch machine	1	1200/hours	Cloab AB, Stockholm, Sweden	20,000
10	Pouch tool	1		"	600
11	Heat sealing machine	1		"	800
					198,400
					200,000

IV. ESTIMATED COST REQUIRED FOR ESTABLISHING AN IUD PRODUCTION UNIT

Batch size: 100,000 units

	U.S. Dollars
1. Direct material cost	2,301
2. Capital cost for material	76.7
3. Direct labour	5,142
4. Control cost	700
5. Service cost	300
6. Production overhead	1,285.50
7. Cost for production equipment, payback 3 years	22,200
8. Research cost	-
Calculated cost/batch	32,005.2
Calculated cost/unit	0.32
Calculated cost excluding production equipment and research	
per batch	9,808
per unit	0.01

Calculated cost for one package

Package 1 x 1 IUD		
Cost for IUD	0.32	
Package cost	0.53	
	0.85	dollar/ package
Package 1 x 10 IUD		
Cost for IUD 10 x 0.32	3.20	
Package cost	0.75	
	3.95	dollar/ package
Package 1 x 100 IUD		
Cost for IUD 100 x 0.32	32	
Package cost	6.75	
	38.75	dollar/ package

1. Direct material cost for IUD

Batch size: 100,000 units

Material cost for polyethylene and polypropylene used for manufacturing:

	weight	cost/batch US Dollars
IUD skeleton	15 kg	75
Inserter	70 kg	350
Solid rod	80 kg	400
Flange	60 kg	300
Tie	1.4 kg	7
Barium sulphate	3.0 kg	24
Copper wire	14.5 kg	145
Direct material cost excl. pouch		1,301
Material cost for pouch and paper		2,000
Direct Material Cost		2,301 US dollars

2. Capital cost for raw materials and goods in process

Calculated months in stock/year: 2

Rate of interest = 10%

$$\frac{4 \times 10 \times 2301}{12 \times 100} = 76.7 \text{ dollars}$$

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		1.54 dollars	1694 dollars
		490 hours	6.42 "	3146 "
Assembling copper wire	200 hours		1.54 "	308 "
				5142 "

Cost for Grospackage

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

Material cost for label and filing box:	0.50 dollar
Direct labour	0.03 dollar
	0.53 dollar/ package

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

Material cost for label and box:	0.60 dollar
Direct labour	0.15 dollar
	0.75 dollar/ package

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

Material cost for label and box:	6.00 dollar
Direct labour	0.75 dollar
	6.75 dollar / package

4. Control cost

Raw material quality control/batch	600 dollars
Direct quality control in operation/batch	100 dollars
	700 dollars

5. Service cost for mould

Cost/batch IUD skeletons	150 dollars
Cost/batch solid rods	100 dollars
Cost/batch flanges	50 dollars
	300 dollars

6. Production overhead

25% of direct labour and machinery

$$\frac{25 \times 5142}{100} = 1{,}285.50 \text{ dollars}$$

7. Cost for production equipment

Calculated payback time 3 years
Investment cost: 200,000 dollars
Production first year: 300,000 units
Cost/batch 22,200 dollars

ANNEX I

Materials for IUDs

A. IUD skeleton

Low density polyethylene 0.917 - 0.919 gram/ml
Melt index = 1.2 - 1.7 gram per 10 minutes.

B. Copper wire in Copper IUDs

Copper 99. 99 % pure.

C. Tie

High density polyethylene containing 1% of iron oxide

D. Insertion tube

Low density or high density polyethylene

E. Flange

Polyvinyl chloride or polyethylene containing a certified colour.

F. Solid rod

Polypropylene containing 0.5% titanium oxide

G. Pouch

Polyethylene and polyvinylacetate on clear side and coated paper on the other. (More exact data in final report).

ANNEX II

Quality control of Copper-T intrauterine device

A. T-skeleton

The T-skeleton is made of polyethylene, containing 20% of barium sulphate. No antioxidants, plasticizers or other additives are added in manufacture of the T.

Quality of polyethylene

1. Type designation "Alathon 2005" or "Alathon 20" manufactured by Dupont Company, Wilmington, Delaware.

2. Melt index: 1.8 - 2.2 (according to ASTM method 1238).

3. Extraction test: approved (according to United States Pharmacopeia XVIII, class II plastics).

Quality of barium sulphate

According to United States Pharmacopeia XVIII.

Quality of moulded T

1. Tests before moulding:

   a) Ash content of moulding powder: 20 - 24%. Duplicate analyses are performed. If the average does not fall within the limits, another duplicate analyses may be performed. The average of the four values must fall within the 20 to 24 percent limit.

   b) Tissue reaction: approved. Ts moulded of sample of moulding powder must not cause unacceptable tissue reaction. Implant 1 cm length of each of eight Ts intramuscularly in two rabbits using 4 test implant sections and two negative control sections in each animal. Sterilize materials before implantation. Observe daily for evidence of irritation. After 14 days, sacrifice the animals and observe for gross and histologic evidence of tissue reaction. Reaction to not more than one in four pieces can be greater than that to strips of United States Pharmacopeia Negative Control Plastic Standard.

2. Properties of moulded T

   a) Dimensions:

      (1) Length of horizontal arms: 31.6 to 32.3 mm.

      (2) Length in direction of vertical arm: 35.7 to 36.2 mm.

      (3) Diameter of horizontal arm: Desired average 1.6 mm. Acceptable limits 1.5 to 1.7. Not more than 1 percent above 1.7 mm diameter. Sample 300 at random out of batches of

20,000 to 100,000. Average must fall between 1.5 and 1.7 mm. Not more than 10 above 1.7 mm.

(4) Diameter of vertical arm: Desired average 1.5 mm. Acceptable limits 1.4 to 1.6. Measure 300 at random of batches of 20,000 to 100,000. Not more than 10 can fall beyond either limit. (9 could be below and 9 above and still pass).

b) Flexibility of the horizontal arm: 5.2 - 6.3 mm.

Sample 50 units of each batch. Not more than 5 of the 50 may show a flexibility of less than 4.8 units or more than 6.5 units. None may show a flexibility above 7.0. A batch will be defined as units made with a single moulding mixture and in an uninterrupted manner, except for momentary turn-off.

The standard flexibility test measures the deflection in millimeters when a 20 gram weight is applied to the cross-arm of the T for 30 seconds at a distance 1.2 cm from the stem of the T. T units are subjected to test not earlier than 24 hours after moulding and after at least six hours equilibration at 24 $\pm 1.5^{\circ}C$. Readings made at other temperatures within the range $20^{\circ}C$ - $29^{\circ}C$ may be corrected by subtracting 0.125 units for each degree above $24^{\circ}C$ and adding a similar amount for each degree below. Temperatures must, however, be constant within $\pm 1.5^{\circ}C$ for 6 hours before reading.

c) Recovery of the horizontal arms after acute flexation: approved

The horizontal arms are folded and inserted to a depth of 6 mm in a hole of 4 mm diameter. They are allowed to remain in this folded position for 5 minutes and then removed and allowed to recover their shape under zero load for one minute. The recovery of the arms must be such that the tips of the arms are not displaced more than 5 mm from the horizontal. Sample 10 T's at random from a batch. If the average recovery is greater than 5.5 mm from horizontal, reject. If between 5.0 and 5.5, sample another 10 units. Average of 20 must be below 5.0 to be acceptable.

B. Copper wound T

The T-skeleton is wound with copper wire manufactured by Outokumpu Oy, Björneborgsverken, Finland.

Quality of copper

1. Grade 1 copper wire according to PDOF level of impurities (99.99%pure)
2. Diameter 0.25 mm $\pm$ 0.01
3. Length, 265 mm $\pm$ 10
4. Test for metals other than copper: approved

Spectographic analysis must show not more than the following concentrations of metals other than copper:

Element	Conc. ppm.	Element	Conc. ppm.
Pb	3	Te	3
Cd	1	Sb	2
Fe	10	As	3
Ni	13	P	1
Hg	1	Ag	50
Sn	1	Bi	1
Zn	2	Mn	2
Se	5		

Quality of copper winding

Winding must be uniform.

Ends of the wire must not protrude.

C. Ties

The ties are manufactured by Newton Filaments, Homer, New York and made of polyethylene, containing 1% of B 3016 Lakoline FD and C Blue No. 1.

Quality of polyethylene

Type designation Marlex 6009, a high density polyethylene manufactured by Philips Petroleum Company.

Quality of dye

1. Purified synthetic iron oxide with colour index no. 77499 or other dyes which have FDA approval for use in foods, drugs and cosmetics and which have been widely used in suture materials are considered reasonable.

2. Identity test: approved.

Properties of ties

1. Diameter: 0.25 mm

2. Length: 10.5 - 13 cm

3. Implantation test: approved.

Implant four 1 cm lengths of each lot of tie material intramuscularly in each of two rabbits. Also implant in each rabbit two sections of United States Pharmacopeia Negative Control Plastic Standard. Sterilize materials before implantation.

Observe daily for evidences of irritation. After 14 days, sacrifice the animals and observe for gross and histologic evidence of tissue irritation. Reaction to not more than one in four pieces can be greater than to strips of United States Pharmacopeia Negative Control Plastic Standard.

D. Insertion tube

The insertion tube is manufactured by:

1. Extraction test: approved (according to United States Pharmacopeia XVIII, class II plastics).

2. Dimensions:

   Length: 206 mm $\pm$ 2.
   Sample 300 (batches of 20,000 to 100,000) at random. Not more than 7 can vary from 206 mm by more than 4 mm.
   ID - Desired spec.: 3.7 $\pm$ 0.1 mm. Acceptable range 3.6 to 3.8 mm.
   Sample 300 (from lot of 20,000 to 100,000). Not more than 7 may exceed either limit.
   OD - Desired spec.: 4.4 $\pm$ 0.1 mm. Acceptable range 4.3 to 4.5 mm.
   Sample 300 (from lot of 20,000 to 100,000). Not more than 7 may exceed either limit.

E. Flange

The flange is made of polyvinyl chloride containing titanium oxide and B 3016 Lakoline FD and C Blue No. 1.

1. Diameter of centre hole: approximately 4.3 mm.

2. Resistance to displacement: approved.

   When flanges selected at random are placed on inserter tubes selected at random and allowed to age in place for from 24 to 72 hours, the resistance to displacement by a force increasing at the rate of approximately 0.25 pounds per second shall not be greater than 2.0 pounds. The desired resistance is 0.4 to 1.4 pounds. When this test is performed with 300 units, not more than 7 may violate either specification limit.

F. Solid rod

The solid rod is made of polypropylene containing 0.5% of titanium oxide.

Dimensions:

Length: 190 mm $\pm$ 4 mm from handle brace to tip.
Diameter at tip: 2.5 to 2.7 mm. Measure 300 (of batch of 20,000 to 100,000).
Not more than 7 can lie beyond these limits.

G. Package

The package is made of polyethylene or polyethylene and polyvinyl acetate on one side and polyethylene plus polyisobutylene rubber on the other side. The package is manufactured by Tower Products Inc.

1. Thickness of pouch: 0.1 mm $\pm$ 0.01.

2. Identification: a sample must give infrared spectrum essentially identical with that of reference sample H 0070.

Label insert

Printing and illustrations must be clear, neat and readily legible. They should be free of gross particulate matter and cuttings should be non-adherent.

Final package

1. The final package is sterilized by ethylene oxide treatment.

2. All components: wound T, inserter tube, flange, plunger and label must be present and the T must be in place in the inserter tube. Flange should be approximately 9 cm from end of inserter tube that contains the T.

3. The lot number must be readily legible on each package.

4. The seal must be of neat appearance and give a complete closure.

5. After sterilization, select 10 units at random from each sterilizer load. All must prove sterile in a test for sterility conducted in accordance with United States Pharmacopeia XVIII standards.

ANNEX III

Control of plastic package for Copper-T

Principle

This method covers procedures for control of the seals in plastic package, that they are of neat appearance and give a complete closure.

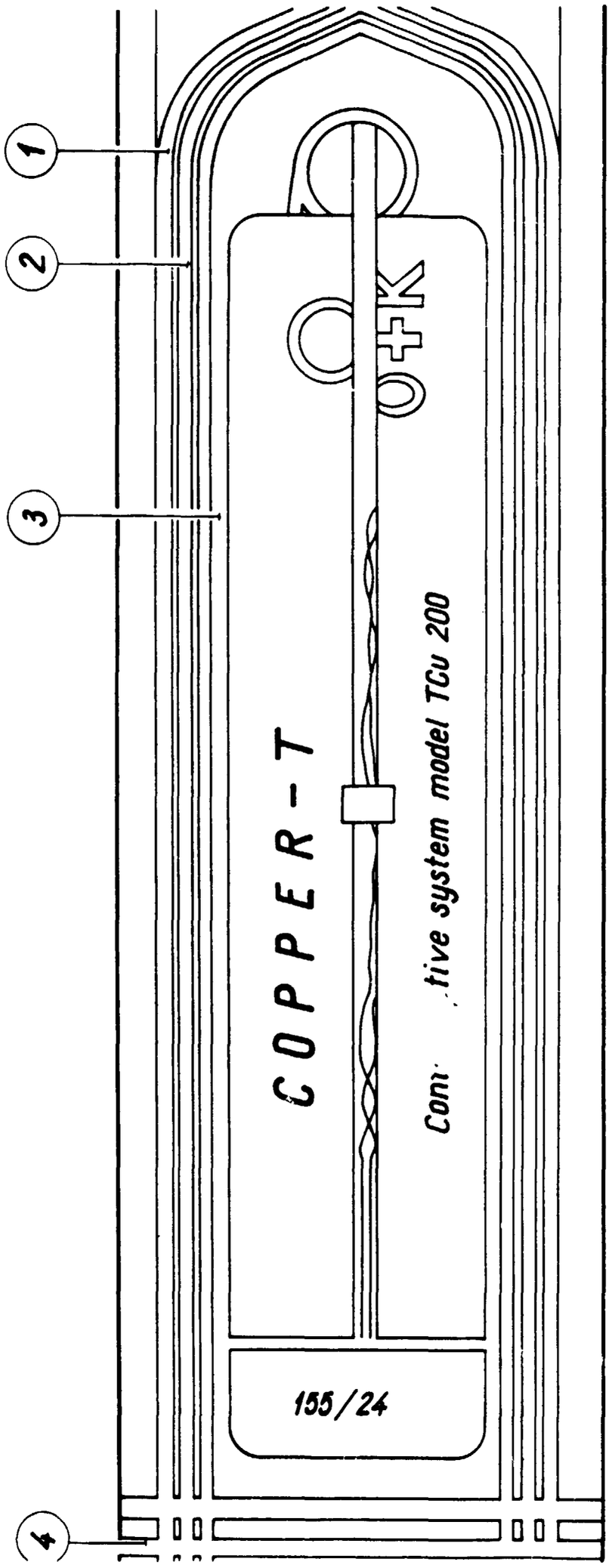
Procedure

1. Put the plastic package on a black bottom with the decorated cardboard downwards.

2. Observe the seals of the package. They should be transparent. Observe that further seals do not exist.

3. The seals nos. 2 and 3 according to enclosed figure may be partly milky, which means that they have burst.

4. Seals nos. 1 and 4 must not show milky parts. If that is the case, the package shall be rejected.


1
2
3
4
COPPER-T
Cont tive system model TCu 200
155/24

ANNEX IV

Shelf life of the Copper-T-Kabi

Four years from the date of manufacture.

Names and addresses of manufacturers involved

T-Skeleton	Dupont Company, Wilmington, Delaware, U.S.A.
Ties	Newton Filaments, Homer, New York, U.S.A.
Copper wire:	Outokumpu Oy, Björneborgsverken, Björneborg, Finland
Assembly of skeleton, ties and wire:	Outokumpu Oy
Packaging into poly-ethylene envelope:	Outokumpu Oy
Sterilization:	With Beta-radiation Ray-chem, Copenhagen
Final packaging:	AB Kabi, Stockholm, Sweden