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International Contraceptive Study Project
(I.CO.S.P.)

on

RAW MATERIALS AND LOCAL PRODUCTION OF CONTRACEPTIVES IN DEVELOPING COUNTRIES 1/

GLOBAL

PP/INT/75/015/11-02

Report prepared for United Nations Fund of Population Activities

by

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experts of the
United Nations Industrial Development Organization
acting as Executing Agency for the
United Nations Fund of Population Activities

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INTRODUCTION

In December 1974 a meeting was organized in New York by UNFPA in order to examine the data system, central procurement, world production of contraceptives, the availability of raw materials for contraceptive production and the possibility of local production of contraceptives in developing countries.

The donating Agencies and the UN organizations involved in this programme discussed the subject presented by UNFPA and decided that a worldwide study would be necessary to classify the various points above-mentioned.

The objectives of the study were divided into four groups:

1. Data system;
2. Procurement;
3. World production; and
4. Raw materials for contraceptives and local production of contraceptives in developing countries.

The responsibility for item 4 of the study was assumed by UNIDO on the basis that an interim report should be prepared for the IACC meeting in April 1975 and a final report in July 1975.

The first phase of UNIDO activity on this report started in February 1975 and continued through April 1975. The aim of this first phase was to collect more general information about this subject, while the second phase was designed to concentrate in detail on the findings of the first phase, with the addition of more information wherever necessary, and possible.

The interim result of the first phase study presented by UNIDO in the IACC meeting was:

1. The available information showed no significant shortage of raw materials; and
2. There is a considerable potential in developing countries for local production of contraceptives.

In April, the Committee decided to study further in detail and to look into the problems in more depth. For the second phase of the study, the actual situation of raw materials and local production in developing countries were analyzed, and studied in more detail.

It was found by UNIDO that contrary to the interim report the raw material situation in the world is faced with some difficulties concerning cost and availability of raw material (diosgenin), and that local production of contraceptives might be justified in developing countries.

The study on raw material and local production was organized and conducted by Mrs. Tcheknavorian, UNIDO staff member responsible for pharmaceutical and family planning programmes within UNIDO. She was assisted for carrying the first phase of the project by Mr. Awad, Pharmaceutical Adviser; Mr. Jewers, Steroid Chemist, and Mr. Noe, Organic Chemist.

To verify the findings of the second phase, a programme of visits to various countries was carried out by Mrs. Tcheknavorian assisted partly by Mr. Kékesy, Production Expert. The final report was analyzed and finalized at UNIDO headquarters with the assistance of Mr. Kékesy, Mr. Noe, who carried out the research work and presentation of technical data for the study.

CONCLUSIONS [illegible] PLAN

1. Raw materials for oral contraceptives

The facts obtained during the global survey showed that diosgenin is the most important raw material for hormone production today. The reasons are its suitability, i.e., chemical structure, the well-developed technology and corresponding to these facts, established industries based on the utilization of diosgenin for production. Until recently, all the other raw material resources, plant and animal, could not compete with diosgenin, except for stigmasterols in the corticosteroid industry. Rising prices for diosgenin have however changed this situation. Furthermore, at present (1975), the world demand for diosgenin is higher than its production. Both facts have resulted in other raw materials, and possibilities for total synthesis obtaining attention for possible industrial application. As one example, solasodin cultivation now appears in a new light whilst cholesterol and sitosterol microbiological side-chain degradations will be competitive if scaled up to plant scale. Other cheap sources for raw material, such as sarsapogenin however need further research work. The existing total synthetic methods are now already competitive and expansion of total synthesis will only depend on availability of large amount of investment capital for the setting up of production facilities. It can be stated that any further price increase of diosgenin in the next few years above US $ 80 per kilogram, will result in diosgenin losing its leading position as a steroid raw material for contraceptives.

The following technical recommendations can be made:

1. Improve the methods of collecting and harvesting of barbasco;
2. Study all aspects of cultivation of dioscorea to avoid the need for expensive collection from remote areas;
3. Improve the extraction of diosgenin from the plant material by application of better methods e.g. fermentation;
4. Study the techno-economic feasibility of the use of solanum in steroid production taking into consideration the increased price of diosgenin;
5. Promote further research work on the transformation of cheap steroid sources such as sarsapogenin which will be welcome in corticosteroid production and for oral contraceptives.

2. Raw materials for condoms

Special quality rubber latex, specially cured, treated and stabilised to achieve certain specific quality standards, constitutes the basic raw material for condom production.

Only a small amount of the world consumption of latex - 282,500 tons in 1972 - is used for condoms, most of the latex for condoms coming from Malaysia, the rest from Indonesia, India, China and some South American countries.

Condom and latex producers both feel satisfied with regard to the adequacy of latex supplies for condom production.

The price of latex, basically follows the rubber price and, therefore, fluctuates as prices for such commodities normally do. The rather low share of raw material in production cost, however, makes condom producers confident that even steep increases in price of latex would not affect the price of condoms very much.

The technology of latex curing, treatment, stabilization and colouring to meet the specifications for condom production, as well as the methods of testing to meet high standards, constitute major problems for developing countries wishing to produce condoms. UNIDO is ready to assist developing countries having both condom and latex production in their country, in adjusting the quality of latex, to the requirements of condom production.

Recommendations

Countries having condom production and available latex which do not meet the requirements of such production should try to upgrade the quality of existing latex to be used for local condom production.

3. Local production of contraceptives - General

One of the reasons for carrying out the global survey was the difficulty that might arise in raising enough funds to secure the success of the growing family planning programmes. The present system has until now been based mainly on donations from developed countries, notably Sweden, U.S.A. and U.K. In future, changes will have to be made if the system of family planning is not to come into difficulties. Local production of contraceptives is one of the solutions to overcome the difficulties mentioned above. Local production not only helps countries to save foreign exchange in times when family planning is no longer supported by donations, but local production makes countries more independent from foreign development and gives further impetus to industrialization.

It was the task of UNIDO to examine if, and under which conditions, local production can be carried out. The answer [illegible] local production is feasible is a clear "yes". UNIDO feels that local production, such as tabletting and packaging of oral contraceptives, as well as production of condoms in developing countries can be carried out without insuperable difficulties.

4. Local production of oral contraceptives

During the second phase of the global survey special attention was paid by UNIDO to the situation concerning local production. The justification for local production in developing countries could be based on available raw materials and facilities in the countries:

(a) Those countries having a well established pharmaceutical industry producing various types of drugs would easily produce oral contraceptives (formulating, tabletting, packaging) by adding or introducing a second shift to relieve production capacity for such an operation. It was found during the survey that the pharmaceutical industries in developing countries mostly do not use fully the capacity of their tabletting and packaging machines.

The major reason why the countries are not producing oral contraceptives is because they are short of hard currency for purchase of bulk material and secondly because the donating agencies supply finished products to these countries.

Therefore, the establishment of local production in the developing countries having a well established pharmaceutical industry could be achieved by the donating agencies providing bulk material to these countries instead of finished packed products.

This exercise will have an economical impact for both developing countries and donating agencies. As a broad indication, packaging costs are approximately 30 - 40% of production cost, therefore, more material could be provided for the same amount of funds by the donating agencies which they have difficulties in providing in view of the increase in demand of contraceptives in developing countries.

(b) Countries having raw materials and well established pharmaceutical industry should be assisted in [illegible] of oral contraceptives starting from raw materials available in the country.

This exercise will help the developing countries to develop a major industry based on available raw materials and avoid the re-importation of finished goods to the country which is not economically very desirable.

Such assistance will make the developing countries more independent and, in the future when the UN organizations and donating agencies are not in a position to respond to the increase in demand of contraceptives, the existing production units in developing countries could respond to their needs and provide the neighbouring countries the required contraceptives needed for the family planning programmes.

Based on the above-mentioned facts, the local production of oral contraceptives in developing countries could be justified on techno-economic aspects in countries that fall into one of the following two groups:

Group A - those developing countries having both the starting materials and well established pharmaceutical units and trained technicians to carry out chemical-pharmaceutical synthesis.

Group B - those developing countries having a well developed pharmaceutical industry, able to carry out local tabletting and packaging from imported or donated bulk material.

Recommendations

(1) Countries belonging to Group A (India, Mexico, Cuba) should consider carrying out all steps of oral contraceptive production from raw material to the endproduct in their countries. Such a step would make them more independent and would reduce costs for exports and re-imports, as it can be already seen in some cases. Those countries could also supply neighbouring countries with oral contraceptives.

(2) Many developing countries belonging to Group B have sufficient tabletting capacity which is sometimes not fully utilized and which could be used for tabletting of oral contraceptives without the need for considerable extra capital investment. Family planning programmes aimed at providing oral contraceptives to the developing countries should consider the utilization of local facilities for production of contraceptives, as a way of assisting the

developing countries in their economic development in accordance with the recommendations at the Bucharest Population Conference and Lima Conference of UNIDO. It seems advisable, with respect to the difficulties in raising enough funds, that the donating agencies consider providing those countries with bulk material for local tabletting and packaging. Since the bulk material is much cheaper than the ready packed tablets, this seems a valuable step to meet the rising demand for oral contraceptives for family planning purposes and will help both donating agencies and developing countries.

(3) Developing countries belonging to Group B, but having at present insufficient capacity to carry out oral contraceptive production, should be assisted in setting up local production facilities. To co-ordinate such activities, UNIDO is ready to examine the possibility of carrying out detailed plant design for local tabletting and packaging units - which can be set up after some modification to particular needs in different developing countries. The model facilities outlined above will be offered to the governments of developing countries interested in family planning and could be set up in those countries under UNFPA/UNIDO assistance.

(4) A programme of co-operation should be drawn up between developing countries having a pharmaceutical industry, and donating agencies, for production according to the demand of these countries and/or for surrounding neighbouring countries using donated bulk material.

(5) A programme should be worked out for giving priority to the local production even in the case of centralized procurement.

(6) The pharmaceutical industry in developing countries producing oral contraceptives should be assisted in training of personnel, maintenance of equipment and more rational ways of operation of production.

(7) Since packaging makes up a great part of the production costs of oral contraceptives, efforts should be made to utilize packaging material locally available for a cheaper packaging in developing countries. Apart from that care should be taken that the oral contraceptives donated by the family planning organizations should be distributed with a different packaging compared with the commercial brands to avoid formation of a "black market".

(8) Countries in which local tabletting is not feasible could take into consideration import of bulk tablets and doing local packaging according to their own "intentions".

5. Local production of condoms

Condom production has actually started in some developing countries, e.g., Korea, Taiwan, Indonesia, Thailand, India, Malaysia, Pakistan, mostly by affiliates of Japanese or English producers, by licence agreements and supply of equipment. It seems that local condom production is probably feasible also in many other developing countries.

The following recommendations are made:

(1) Rubber producing countries and countries with a big market for condoms - at least 200.000 gross/year - should think of domestic condom production. UNFPA/UNIDO is prepared to give technical assistance to those countries where necessary and appropriate.

(2) It is obvious that joint ventures between developing countries and big condom companies will not need assistance in technical know-how. It is however a matter of fact that those joint ventures during the starting periods have often faced many difficulties including government regulations, currency problems and import restrictions. UNFPA/UNIDO could help to overcome such difficulties and assist in preparing and examining new projects involving developing countries, and companies that provide know-how and equipment for joint ventures, and projects on turn-key basis.

(3) The countries where there are existing domestic condom manufacturers could receive technical assistance to improve quality and production, and assistance in marketing in order to upgrade these existing facilities.

(4) Family planning organizations in developing countries having a big demand for condoms that are however not willing or not in a position to produce condoms should at least take into consideration the possibilities for local testing and local [illegible]. The amount of foreign exchange

saved by imports of bulk condoms can be more than 50% because these final packaging steps make up more [illegible] of the production cost of condoms. Equipment cost for these labour-intensive steps are low compared to the equipment for the other steps of condom production. This could be a very good solution in countries with a market too small for domestic production.

(5) Since packaging makes up a great part of the production costs of condoms, efforts should be made to find cheaper solutions in packaging. Apart from that care should be taken that the condoms donated by the family planning organizations should be distributed with a different packaging compared with the commercial brands to avoid formation of a "black market".

(6) Donating agencies currently buy condoms in very big quantities, and mostly not on the basis of long term contracts. This results in small companies, especially those in developing countries, not being in a position to obtain orders, and some big companies having difficulties in making capacities available for such big orders. It is, therefore, proposed that a list be set up of condom manufacturers from which donating agencies might purchase condoms. Supply contracts should be concluded among the listed companies on a long term basis, so that manufacturers might adapt their production facilities to the demands of the donating agencies. This "pool" should be open to all companies that are willing to co-operate with the donating agencies and are ready to submit their products to a quality control of an independent testing laboratory accepted by both governments and agencies at any time. It must be pointed out that above all, manufacturers in developing countries should take part in such a pool. UNIDO could assist them in improving their quality to meet the requirements of international standards.

[illegible] PLACE OF UNIDO IN CO-OPERATION WITH UNFPA/UNICEF/ DONATING AGENCIES

During the survey, covering visits to developing countries, it became obvious that many developing countries would like to receive technical assistance from UNFPA/UNIDO for their family planning programmes, and they would regard this kind of assistance in the spirit of the recommendations of the World Population Conference for techno-economic development programme of developing countries which they believe is the most effective way of realization of a population programme.

Following these findings, UNIDO in co-operation with UNFPA/UNICEF and the donating agencies would be prepared to assist the developing countries in carrying out feasibility studies on local production and utilization of available raw materials and, furthermore, if a country has the potentiality and a well established pharmaceutical industry to assist this country with the production of oral contraceptives or expansion and improvement of its existing facilities.

UNIDO could carry out detailed regional technical studies leading to a programme for co-operation between UNICEF/donating agencies and the government responsible, for production of oral contraceptives. Furthermore, it could assist the government in transfer of know-how and technology, quality control and training of personnel for such production.

UNIDO could also assist countries with production of raw material from natural resources and transfer of technology and know-how for production of oral contraceptives based on available raw material especially diosgenin and solanodim.

This programme should be integrated with the programme of UNFPA/UNICEF and the donating agencies for assisting the developing countries in their family planning programmes. Close co-operation is necessary between the UN organizations and the donating agencies for the realization of a programme which is economically and technically feasible.

In addition, in all programmes of production of contraceptives in developing countries requested by governments or planned by UN organizations, UNIDO/UNFPA should examine the feasibility of such programmes, and assist in working out the technical requirements and providing further assistance if required.

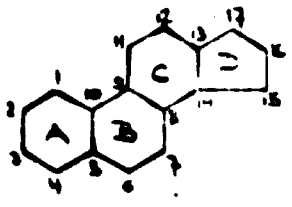
ORAL CONTRACEPTIVES - PRODUCTION AND RAW MATERIALS

1. Hormones used in production of oral contraceptives

Hormone contraceptives, especially oral contraceptives (the so-called "pill") play a dominant role in family planning nowadays. It seems surprising that it is only about 20 years ago that G. Pincus and J. Rock showed that alteration of the menstrual cycle of women by the administration of massive doses of progesterone could be used as method of contraception. Certain progesterone-like compounds, called progestins, at once became the objective of research of many steroid chemists such as F. Colton and C. Djerassi and within a few years several dozen orally-active progestins were synthesized and marketed as oral contraceptives.

In the case of most of the oral contraceptives used at present the hormones of the pill simulate pregnancy physiologically. They then prevent conception, because they act in the same way as the hormones naturally formed during pregnancy, and so prevent ovulation.

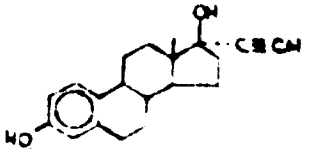
Most of the active components of the main oral contraceptives commercially available nowadays belong to the group of steroid hormones, which can be derived from the structure of sterane (cyclopentanoperhydrophenanthrene).



Apart from the groups of estrogens and progestins which are used in the pill, also the androgenic hormones and corticosteroids belong to this group of hormones. Their manufacture is therefore closely related to that of the hormones used in production of oral contraceptives. Some important examples of commercially used hormones are:

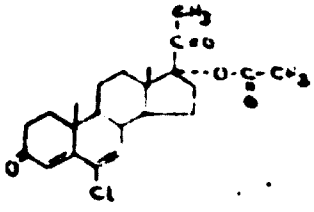
1.1. Estrogens: Estrogens commercially used at present are only

17α ethinylestradiol and its 3-methylether.

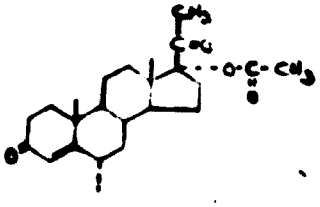


1.2. Progestins: There are several dozens of progestins commercially available, some of the most important are:

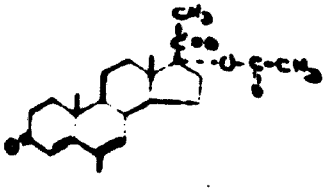
1.2.1. Progestins with pregnan skeleton (Pregnan-progestins)
Chlormanondiacetate (Gestafortin, Menova, Sequens)



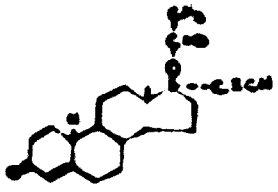
Medroxyprogesteronacetate (Provera, Depo-Provera, Provest)



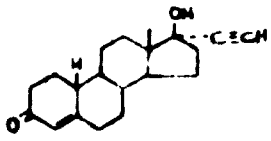
Megestrolacetate (Volidan)



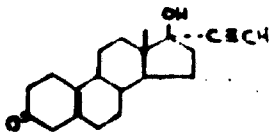
1.2.2. Progestins with 19-nor-androstan skeleton (19-nor-progestins)
Norethindroneacetate (Primolut-Nerlutate, Anovlar, Norlestrin)



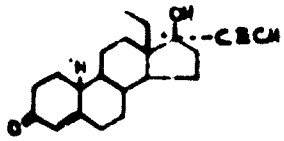
Noresthisterone (Primolut-N, Norlutin, Orthonovum, Norlestrin)



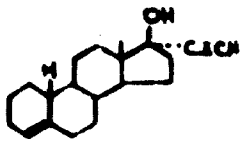
Norethynodrel (Rodilen, Enovid)



Norgestrel (Ovral, Eugynon)



Lynestrenol (Orgametril, Lyndiol, Noracyclin, Ovanon)



World market prices of some hormones per kg. are:

Norestisteron	US $	2.800
Noresthisteron-acetate		2.800
Norgestrel		15.000
Ethinodioldiacetate		3.200
Mestranol		1.600

Synthesis of the progestins and estrogens

Production of the pill can be divided into two main steps:

Synthesis of the progestins and estrogens

Production of the packaged pills starting from the bulk material

The first step requires detailed know-how and high skilled labour and experience in steroid chemistry, whereas the second step does not significantly differ from any other pill production.

Therefore it is not surprising that synthesis of the progestins and estrogens is carried out only in a few countries, such as U.S.A., Germany, Holland, France, U.K., Hungary, Japan and India., whereas tabletting and packaging facilities exist all over the world, even in many developing countries.

Production of the progestins can either start from simple organic chemicals leading directly to the hormone desired (total synthesis) or it can start from naturally occurring steroids (of plant or animal origin) which are extracted from the raw material and usually transformed to a steroid intermediate from which the active hormone is synthesised (partial synthesis).

Most of the progestins presently used are synthesized by partial synthesis. Total synthesis has gained importance only during the recent years, but its share in oral contraceptives production is continuously growing owing to a lot of research work in the total synthesis of progestins.

3. Raw materials and their isolation from their source material

3.1. Naturally occurring steroids of plant origin

3.1.1. Diosgenin

Diosgenin after being for some years the only source of raw material for most progestins on the market constitutes now the major source of raw material. It is a steroid sapogenin which is itself obtained by hydrolysis and extraction of the tubers of wild dioscorea, the true or tropical yam.

Commercially used dioscorea species, the tubers of which contain most diosgenin in the form of the glycoside dioscin (about 1-2% diosgenin of the wet weight and 4-7% of dry weight) are D. mexicana (cabeza de negra), D. Floribunda and most of all D. composita (barbasco) which are growing wild in central America, namely, in Mexico and Guatemala, and the African D. sylvatica. In India, O. Praseri in West Bengal and D. Deltoidee in Jammu and Kashmir and O. Nipponica in China while not so abundant as dioscorea in Mexico, were also shown to provide diosgenin in good yields.

As a rule these tubers are collected from wild growing species. Cultivation experiments were carried out and are still going on for dioscorea (e.g. Cuba, India). Low labour cost of the collectors and problems connected with cultivation, make the capital investment of a plantation unfavourable compared to the cost of the collected wild dioscorea. Exhaustion of wild growing yam, for which there is some indication, rising wages and rising demand may, however, favour cultivation of dioscorea in future.

In fact, the demand for diosgenin is likely to increase, as a result of the development of new anti-inflammatory agents which use diosgenin as a starting material. The demand for other steroid hormones which also use diosgenin is also expanding. The world demand for diosgenin is 1500 tons/year, the world production is only 80% of this demand.

3.1.1.1. Situation of dioscorea in Mexico

Mexico has been the main producer of diosgenin for many years. The production was 500 tons in 1968 and 1000 tons in 1974.

In recent years no dioscorea or diosgenin was allowed to be exported from Mexico. Only intermediates and finished substances - progesterone, oestradial, testosterone - and some corticosteroids were allowed to be exported.

Six companies have diosgenin and intermediate working factories mostly by agreements with Syntex in Mexico.

Syntex	Diosynth	Searle
Steromex	Schering	Beneficiadora

Syntex Headquarters until now have been in Mexico, and the finished products chemical and tabletting stages in California.

The Government does not produce oral contraceptives, but obtains them from local producers on the average cost of 26 cents per cycle.

The Government of Mexico last year nationalized the barbasco and diosgenin production and in February 1975 established a task force to study the possibilities of local production of oral contraceptives based on available raw materials. In addition the Government wishes to carry out the study independently and according to the result of the study, the Government will decide if future assistance from UNIDO or other UN organisations will be needed in this field.

In 1975 a company, Proquivemex, was established by the Government of Mexico and is responsible for harvesting and collecting the barbasco tubers. There is also interest in the natural fermentation of barbasco, an essential step prior to the extraction of diosgenin. The price of diosgenin on the market is US $60.0 per kg. Export of diosgenin by Proquivemex is allowed from this year - 1975.

3.1.1.2. Situation of dioscorea cultivation in India

A part of a report of [illegible] task force on the use of oral contraceptives in the national Family Planning Programme deals with the situation of raw materials for production of contraceptives in India as follows:

A major portion of dioscorea tubers now being produced in Kashmir is being sold exclusively by the Regional Research Laboratory, J. and K.,

through a system of tenders, to the highest bidder. This system allows manufacturers with international investments to acquire essentially all the available supply as they alone are able to pay high prices. It has been reported that new entrants of entirely Indian origin are unable to get this material. Dioscorea tubers have to be regarded as a scarce resource of national importance. As such there is a strong case for ensuring that the material is made available at reasonable fixed prices to all licensed manufacturers of steroids. This procedure is being followed by the Government with regard to all scarce raw materials. Dioscorea is also grown by farmers in the Mysore area, through the extension service and development work of ICAR and the encouragement given by certain pharmaceutical manufacturers. Here again the farmer's interest is dependent on high prices, assurance of demand and a return, at best equal to what is obtained from other crops. Again, the more widely known international companies are in a position to offer high prices. The farmers may sense the danger that such high prices now offered may decline, once dioscorea is more widely cultivated and this may lead to waning of interest in this crop. Since adequate cultivation is of national importance it is recommended that a central agency may be charged with the responsibility of growing, under contract, adequate quantities of dioscorea and prices should be adequate to stimulate interest. All such crops should be purchased by the central agency and distributed to manufacturers in an equitable fashion. This procedure could be applied to all new additional areas of cultivation and crops. Such an agency may also be asked to stockpile dioscorea to meet the demands for one to two years ahead, so that unexpected events such as plant disease, adverse climate etc. do not unduly upset availability. This procedure is being followed by the Defence Stores for Strategic Materials. Large excess stocks could be disposed off by exports, if necessary.

Against guaranteed prices and purchase of entire output, the agency could also ensure finance to farmers from banks. ICMR and ICAR could jointly suggest to the Government the formation of such a new agency or request an existing agency of Central Government such as National Seeds Corporation or CIMPO to take up this responsibility immediately. IDPL as a public sector organization should establish facilities for the production of diosgenin from dioscorea.

In view of the higher seeding to crop ratio (1:10), plant tissue culture was very suitable for quick propagation and the National Chemical

Laboratory may be requested to give priority to culture of dioscorea using this technique.

3.1.1.3. Isolation of diosgenin from the tubers

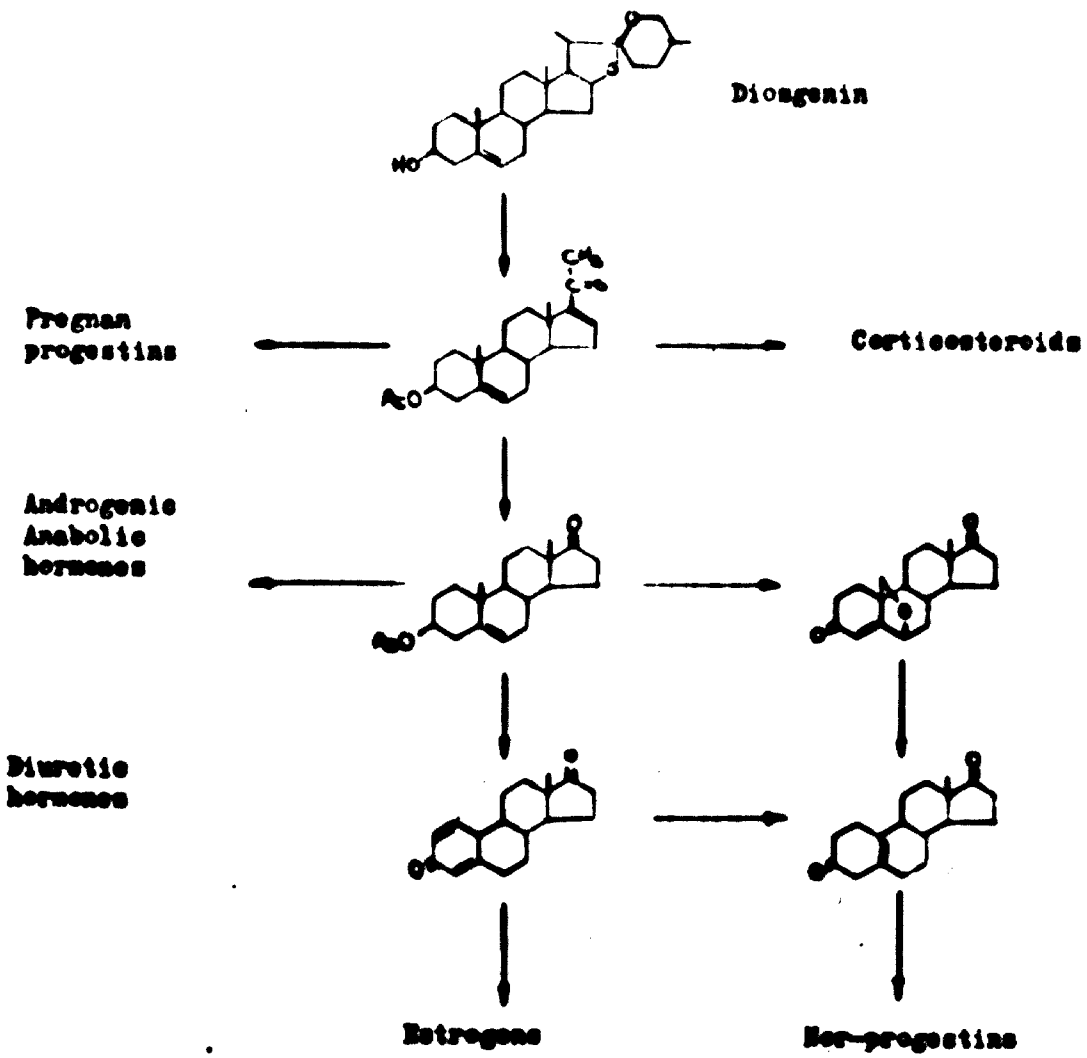
The process described here is according to the publication in Ind. Eng. Chem. 49, 136, 1957. The classical process for the isolation procedure most often employed by investigators the steroidal sapogenins were extracted by ethyl alcohol from the ground plant material, then acid hydrolized to liberate the sapogenin from the glycoside. The crude sapogenins were obtained by ether extraction of the hydrolyzate.

Nowadays the process of isolation involves direct acid hydrolysis of pulverized tuber followed by preferential extraction of diosgenin from the dried hydrolyzate by hydrocarbon solvents such as petroleum ether and heptane. In this process either fresh or dry tubers may be utilized. Dried tuber, prepared in an oven at 80° or in the sun, properly stored and handled under dry conditions loses no diosgenin over a long period of time. Fresh tubers can be only utilized if there is a relative short delay from harvesting to processing, because of rapid decrease in diosgenin content as rotting proceeds. Before hydrolysis tubers are milled. It is interesting that if dry tuber is used the yield of diosgenin will depend on the state of subdivision of the tuber during the drying operation.

The combined glycosidal form of diosgenin (dioscin) is split by the diluted mineral acids into its components, the sugars and diosgenin. After the cooling the hydrolyzates are filtered and then precipitated. After being washed free of acid with water, they are dried in an oven. These brown residues consisting of crude diosgenin soil particles and digested tuber cellulose are extracted with hydrocarbon solvents such as petroleum ether and heptane. Diosgenin is recovered from the solvent by evaporation. Another extraction process is based on the extraction of crude sapogenin from fresh or dry sliced tuber. Since the saponin of dioscorea is water soluble, a crude extract can easily be obtained by heating fresh or dry sliced tuber for several hours at reflux temperature and decanting the supernatant liquid. A still more concentrated saponin solution can be obtained by continuous hot extraction. Diosgenin can be obtained easily from these saponin extracts by adjusting the solution with HCl to 2N and selective solvent extraction.

3.1.1.4. Transformation of diosgenin to the steroid hormones

The structure of diosgenin is favourable for the transformation to different groups of commercially used steroid hormones. By degradation of the Rings E and F 16-dehydro-pregnenolone-acetate can easily be obtained (see Appendix 2), which is an important intermediate for the progestins with pregnan skeleton and for the production of corticoids too. Degradation of the pregnan side chain at the carbon 17 leads to dehydro-epiandrosterone-acetate which again is an important intermediate for the production of androgenic-anabolic and diuretic hormones. Dehydro-epiandrosterone-acetate is also the starting material for estrogens and nor-progestins using microbiological and chemical methods for the elimination of the 19 methyl group (see Appendix 2). All these production steps are very well elaborated also on large scale.

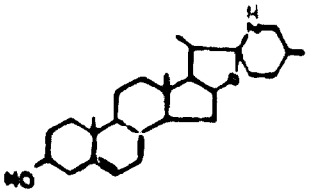


3.1.2. Solasodine

Solasodine is a steroid alkaloid, obtained from several solanum species (S. laciniatum, S. dulcamara, S. floribunda) which are cultivated in several countries (USSR, India, Hungary, Cuba). The solasodin content of the dry plant material is 1-2%.

Because of the relatively high cost of cultivation, solasodin was not competitive to diosgenin as long as the price of diosgenin remained low. The heavy price increase for diosgenin during the last years, from about US $ 20 to US $ 60, has opened up new possibilities for solanum cultivation.

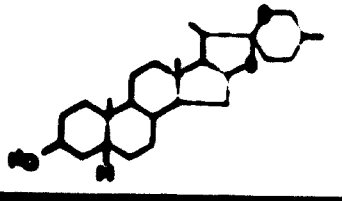
The structure of solasodin is very similar to that of diosgenin and the chemical methods for transformation are the same as in the case of diosgenin, which results in solasodin having the same advantage as diosgenin provided its price is competitive to that of diosgenin. Isolation from the source is easier than in the case of diosgenin, because of the basicity of the molecule.



Solasodine

3.1.3. Sarsasapogenin

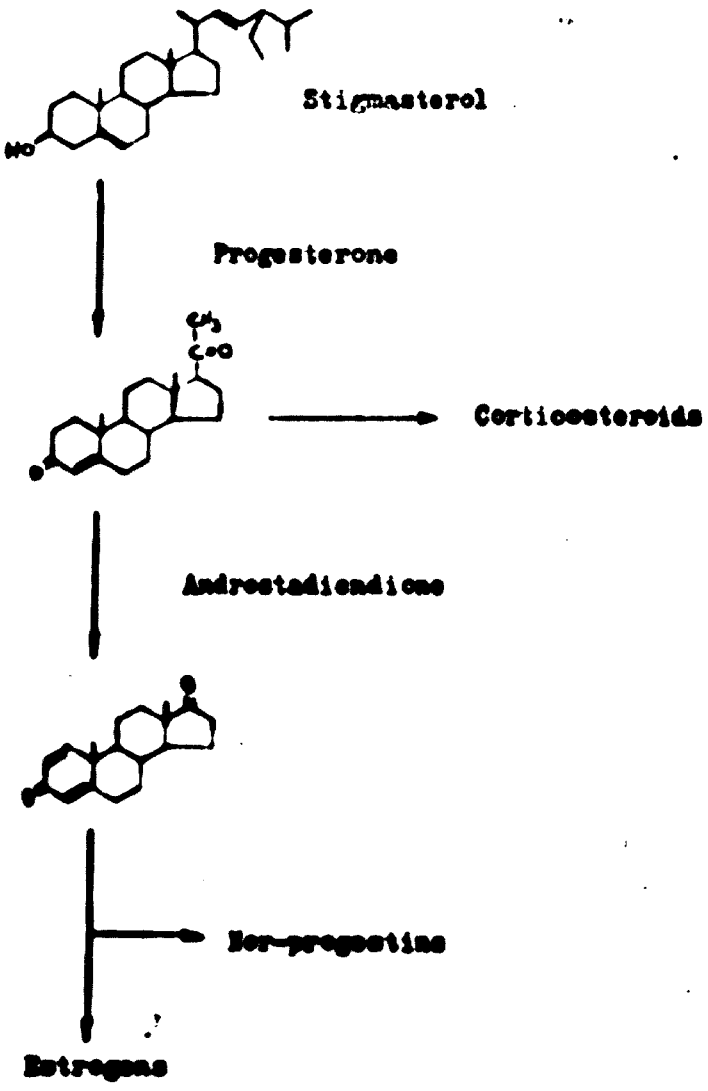
The seed of the fruit of Yucca filifera palms contains 7-9% of sarsapogenin saponin. Since the fruit of Yucca filifera is used at present, the seeds can be obtained easily as by-products in very great quantities at very low prices. The structure of the sarsasapogenin is very similar to that of diosgenin but unfortunately does not have the double bound between carbon 5 and carbon 6. To enable the transformation of sarsapogenin to steroid hormones it is necessary to develop new synthetic steps to introduce the double bond. These steps need further research work. It seems however that due to its very low price, sarsapogenin might become an important steroid source in spite of the difficulties mentioned above.



Sarsasapogenin

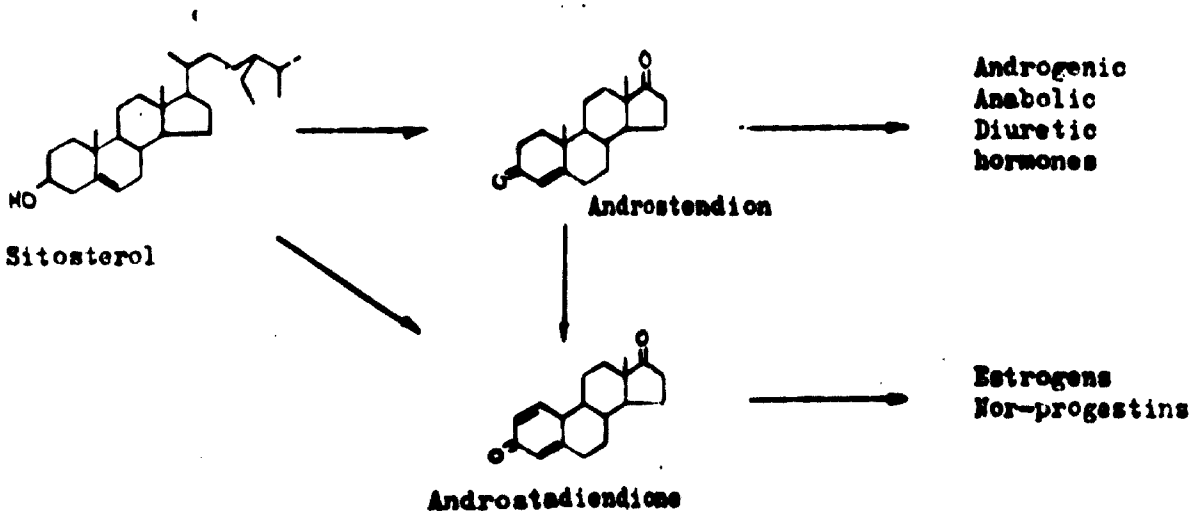
3.1.4. Stigmasterols

The main source of stigmasterol is soya beans. During refining of the soya bean oil a phytosterol mixture is available. This mixture contains 20% stigmasterol and about 60% sitosterol . The stigmasterol is separated from the other sterols by counter-current extraction. Stigmasterol contains a double bond in its side chain which opens the possibility of chemical side chain degradation to yield progesterone very economically. Progesterone is a good starting material for corticosteroids and thus stigmasterols are competitive to diosgenin as raw materials for corticosteroid production. There is also a possibility to obtain androstadiendione from progesterone by microbiological transformation. This compound can be used as starting material for the synthesis of estrogenic and progestin hormones too.



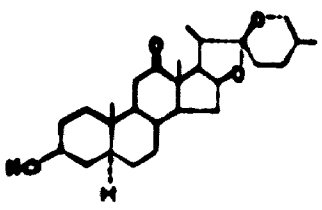
3.1.5. Sitosterol

Sitosterol is the plant steroid most widely spread over the world. It can be found in soya beans, all kinds of plant oils (sun flower, etc.) and also in tall oil which is a by-product of the pulp and paper industry. In the past sitosterol was not used as raw material for steroid production because the degradation of the side chain, which contai ne double bond, was encountered with many difficulties and gave only poo. yields. Only recently it was announced that Searle and Schering have developed microbiological methods on an industrial scale for transformation of sitosterol to androstendione or androstadiendione the first being a starting material for estrogenic and norprogestin hormones, as mentioned before.



3.1.6. Hecogenin

The juice of agaves such as Agava Sisalana has been shown to contain as much as 0,1% of hecogenin mixed with titogenin, but although industrial exploitation of this exists in East Africa, it has not proven to be a serious competitor of diosgenin because it has an oxygen function at carbon 12 and has no double bond at the positions 5,6. Therefore, it is used only for corticoid synthesis.



Hecogenin

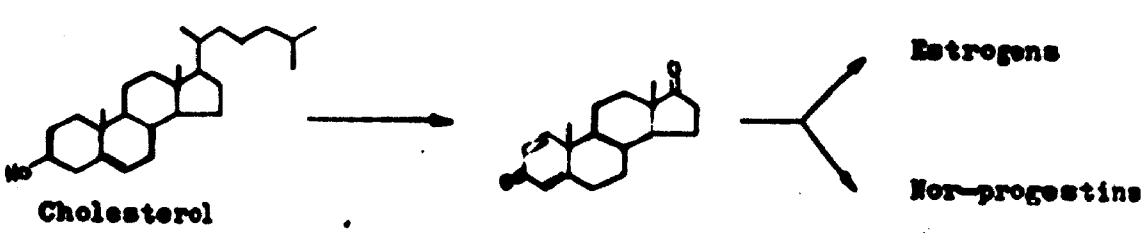
3.2. Naturally occurring steroids of animal origin

3.2.1. Cholesterol

Cholesterol is a cheap traditional source of steroid material. It can be obtained from animal material such as cord of cattle (1000 kg. yielding 40 kgs. of cholesterol), fish oil or wool grease from wool-scouring liquors. This latter source is a very economic one.

In the classical steroid synthesis which nowadays is no longer economical it was transformed to dehydro-epiandrosterone-acetate by chromic acid oxidation. The reason why this synthesis is not economically viable is its low yield of 33.6 kg. androstenolen-acetate from 600 kg. cholesterol (6,5%).

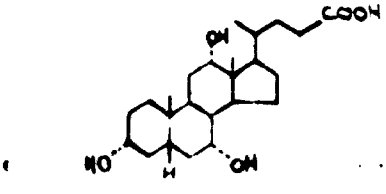
Cholesterol has achieved new interest as source of raw material for steroid production by the work of the researchers of the Noda Industrial Science Laboratory, notably K. Arima, in transforming cholesterol to androstadiendion by microbiological fermentation. In recent years Mitsubishi, based on the original technology, proceeded with studies for industrialization, and developed a process for which they claim that a drastic reduction of cost can be realized by the rationalized production method, and the very low cost of raw material. The patent for this new process has already been established in many countries and a series of contacts are being made with Mitsubishi, by the major steroid makers in regard to joint-venture or supply of raw material. The future will show whether this process will partly constitute diosgenin as a source of raw material.



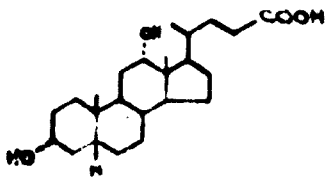
Cholesterol

3.2.2. Bile Acids

The bile acids of cattle have been traditional sources of raw materials for corticosteroid production and Roussel-Uclaf are still using them but because of the oxygen function at carbon 12 and the minimum double bound at carbon 5 and 6 it is not to be expected that bile acids will achieve importance as starting materials for oral contraceptives.



Cholic-acid



Desoxy-cholic acid

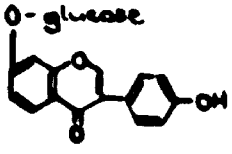
3.3. Other raw material sources

A lot of research work has been done to find other sources of raw material for hormone production.

The list of plants that could theoretically be used as sources of raw material is a long one, and they are widely distributed globally. A few of those reported are listed as follows:

Balanites triflora	Burma
Balanites aegyptiaca	Chad
Costus speciosus	India and related territories
Paris polyphylla	Pakistan, Nepal
Trigonella foenograecum	Ethiopia, Ecuador, Burma India, Pakistan, Morocco, Kenya, Turkey, Iran

Also certain Cordyline species growing in Australia produce steroidal sapogenins which can be converted into steroid intermediates. Apart from these sources being structurally related to sterane there are also other naturally occurring substances, that show estrogenic activity, such as genistine obtained from Lupinus polyphyllus and Scarothamnus scoparius Koch.



Also extracts prepared from some primitive animals show estrogenic activity. It seems worth mentioning that in many developing countries there are contraceptives or abortives traditionally used locally in remote areas which have not yet been scientifically examined.

4. Problems of raw material availability as seen by oral contraceptive manufacturers

The producers of oral contraceptives generally agree that whilst there was a shortage of diosgenin, they usually did not seem to regard this as a serious problem. Discussing the prospects of diosgenin in steroid production it would seem important to note that diosgenin is also the starting material for the production of corticosteroids and that only about 20-30% of its annual production goes into the synthesis of progestins and the much smaller amount of estrogens used in combination with them. The following comments were obtained from the producers.

4.1. Glaxo

Glaxo agreed that there is a shortage of suitable raw materials for steroid manufacture, and this could increase if oral contraceptive demand increased substantially.

Diosgenin and oestradiol are Glaxo's starting materials for oral contraceptives.

Glaxo would like to see an increased production of steroid precursors which would be on sale to contraceptive manufacturers. Failing this, Glaxo would take action themselves to safeguard their market position. They think that the present diosgenin price of US $ 40-50 was competitive. If a shortage remained it is possible that Glaxo would have to reduce oral contraceptive production as this is a less profitable line than corticosteroid drugs.

4.2. Schering

When questioned about raw material shortages for present and future production, Schering admitted that there had been an occasional diosgenin shortage, but they said that other sources and methods are available to meet current and future demands.

The company is no longer dependent on diosgenin for the production of oral contraceptives. The nor-steroids required for oral contraceptives can be synthesized by methods they have licensed from Wyeth. In addition, they can be synthesised from phytosterols, which - they claim - can be transformed microbiologically to androstendione by a unpublished process. (Confidential)

Adequate supplies of raw materials can be anticipated if demand of contraceptives requires 2X, 5X or 10X increase in [illegible] level - as Schering developed total synthesis methods for its steroids-based contraceptives. The capacity of production by total synthesis can be doubled and increased many times - if more, than 5 or 10 times increase is needed, this can also be done by some capital investment.

Sterols, phytosterols and diosgenin to lesser extent are their starting materials for steroid contraceptives.

4.3. Diosynth

It was agreed that diosgenin has been the cheapest raw material for the synthesis of oral contraceptives. However, the price of diosgenin has increased rapidly in the last three years: this in part has been the result of stockpiling by steroid manufacturers to safeguard their market positions and as such has exaggerated the shortage of the chemical.

At the present time there is no world trade in diosgenin - China is an exception, who has offered in the past small quantities for sale, a recent batch of which fetched US$ 105/kg. - and as such it is difficult to make an accurate assessment of the cost of the chemical. However, Diosynth was willing to provide the following data:

(a) Diosgenin trade has been at rate of 800-1000 tons/annum.

(b) About 40% of diosgenin has been used for manufacture of oral contraceptives.

(c) A diosgenin price of US$ 30-40 would be able to effectively compete with total synthesis and other steroid precurser in the manufacture of oral contraceptives.

(d) A diosgenin price above US$ 100 would effectively price it out of the market as far as progesterone manufacture was concerned.

Diosynth does not have any problems at present regarding the supply of raw materials for the manufacture of oral contraceptives; it has been able to satisfy all the demands made on it by producers. They claimed that the same situation does not exist for Syntex and Schering who have had to restrict supplies of steroid intermediates to their customers.

The company still has a licence from the Mexican Government for the processing of barbasco root and so they still expect to have supplies of

of diosgenin from Mexico in the near future. Syntex and Schering's licences have terminated recently and they have not been able to secure new licences to date.

Diosynth stressed that it is their policy to maintain their current position and to anticipate the changes which are occurring, including total synthetic routes and other sources of raw materials. They would not be drawn on what approaches they had in mind, but did say that they had been approached regarding fenugreek and were also watching the developments with phytosterol transformation and solasodine production.

They also gave what they considered to be the two major reasons for the shortage of diosgenin. Firstly, at the end of 1973 the Mexican Government had introduced generous subsidies for corn products, and as a result the barbasco collectors had given up collecting yams and had begun to work in the corn fields. This had reduced the quantity of yams being collected for diosgenin production.

Secondly, floods had occurred in the yam producing areas which had made barbasco collection impossible for a period of time. This had reduced the amount of yams reaching the factories, which produce diosgenin.

Diosynth stated that they did not consider that increased demand should effect the price of raw materials. A normal price of US$ 25-30/kg. for diosgenin ex Mexico or for equivalent should be maintained to 1980. However, when challenged they did agree that some consideration must be made for inflationary effects during the five-year periods, but were insistant that the price of the basic raw material should be maintained at this lower level.

When asked for their opinion on comparable prices for the various processes leading to androstendione, Diosynth was willing to offer the following information:

From a microbial oxidation of phytosterols to effectively compete with diosgenin at US$ 40/kg., the price of androstendione would have to be less than US$ 200/kg.

Present prices of raw materials are suitable - maximum price would be about $ 60 per kg. diosgenin - prices depend on market and supply -

sporadic exaggerated prices were due to unusual cases; collection was considered to be the factor which had the greatest effect on the price of raw material, and processing was considered to be relatively cheap.

Diosynth's plants in Mexico and Ecuador are the sources of their raw materials.

4.4. Syntex

They depend on dioscorea from their company in Mexico where some intermediates are produced. The final steps are processed in the USA.

Even if dioscorea is not increased two, five, ten times, they can depend on intermediates nearer to the final product stage which will be available commercially on world markets in two to three years. They are also developing methods for these intermediates.

Starting point until now has been dioscorea.

Synthetic and microbiological methods supplement diosgenin and there is no contraction or effect on their processes. In fact, they are making their own research on different methods, and have contact with producers using these production methods for collaboration.

Syntex developed Norethindrone and licensed it to Ortho and PD and licensed Norethindrone acetate to Schering and have their own oral contraceptives operation also. They have sufficient production facilities in Mexico and California to produce raw materials from diosgenin.

4.5. American manufacturers

The general finding was that raw materials, particularly diosgenin, was unlikely to meet projected demands although no shortages were foreseen through 1980 of the final products. As a result new methods would have to be used to satisfy the increased market requirements.

The U.S. manufacturers had provided the following information regarding their intentions:

Wyeth	-	will use total synthesis
Searle	-	will use microbial transformation of sitosterols and other plant products

Syntex	-	would be interested in securing alternative supplies of plant steroids
Upjohn	-	use stigmasterol: a microbiological approach is employed
Ortho	-	no data given: they have adequate supplies.

5. Possibilities for use of total synthetic methods

As mentioned before, the synthesis of the progestins and estrogens can be carried out either by partial synthetic methods or by total synthetic methods. Partial synthesis of oral contraceptives is characterized by the transformation of a steroidal skeleton of plant or animal origin to the progestins. Generally, there are three steps in partial synthesis:

(a) extraction of the naturally occurring steroid from its source;

(b) chemical transformation to an intermediate; and

(c) synthesis of the progestin from the intermediate.

Some information about partial synthetic methods can be found in the chapter on raw materials, and in Appendix 2.

Total synthesis methods start from simple organic chemicals. They have many advantages in the synthesis of norsteroids and estrogens but are however not well suited for the synthesis of androgenic and pregnan progestins, because the introduction of the 19 methyl group is a rather complicated operation and therefore not economical. Two types of total synthesis are commercially used at present. The synthesis of Roussel-Uclaf (annelating the rings as follows (CD → BCD → ABCD) (see Appendix 2). The synthesis leads to a racemic mixture which has to be separated. The other total synthesis by Wyeth and Schering annelates the rings as follows (AB → ABD → ABCD). In this synthesis there is a microbiological stereo-specific reduction so that a resolvation is not needed (see Appendix 2). Total synthesis enables production of steroids with new structural elements which by partial synthesis could not or only not economically be produced (e.g. production of the homologous 13-alkylsteroids). These steroids are sometimes more active and/or suffer from less side effects than the partially synthetized steroids. Another advantage of the total synthetic methods is that there is no need for a lot of special equipment so that most reactions can be carried out as in partial synthesis. Total synthetic processes are successful nowadays and they will be even more economical when production on a large scale is achieved.

6. Tabletting, packaging and quality control

In the second phase of hormone contraceptive production the hormones are brought into the pharmaceutical dosage form. The most widely used dosage form is tablets but parenterals also find some application (Depo-Provera).

The two main steps of second phase production of oral contraceptives are tabletting and packaging. Tabletting of orals does not significantly differ from any other pill production, with the exception that special care has to be taken for hormone protection.

Packaging of orals is usually done in a rather sophisticated way, because efficacy as a contraceptive is dependent on continuity of usage at the prescribed rate. Much ingenuity has been expended in creating packages that help the user remember to take one pill each day of a monthly cycle. Dial packs, compacts, bubble packs, calendar packs and many others have replaced the simple bottle.

6.1. Tabletting

Tablets are formed by compaction of powders, crystals or granulations. Like the newer therapeutic agents the hormones used in contraceptive production are of extremely high potency, thereby requiring only fractions of a milligram per dose. The tablet, therefore, consists mainly of inert filler material providing bulk so that tablets of suitable size for ease of handling can be manufactured. The fillers or excipients mainly used are lactose, mannitol, sucrose and microcrystalline cellulose. In addition other agents such as binders - starch paste, methylcellulose - lubricants - stearic acid, talcum - and disintegrants - corn starch, alginic acid, microcrystalline cellulose - are usually added to the tablet formulation.

The steps of tabletting are:

6.1.1. Milling

The ingredients to be used have first to be milled to a very small particle size and after that to be passed through a sieve.

6.1.2. Blending

The powdered ingredients except for lubricants and disintegrants are then carefully blended in mixers.

6.1.3. Wet granulation

The blended powder is then wetted with a solution or dispersion of the binders. The damp mass is screened to form coarse granules and dried. This can be either done by spreading the mass on trays and drying the granules in a hot air oven, or by a fluid-bed drying technique in which the damp mass is placed into a cylindrical container with a screened bottom. Heated air is then passed through the mass, causing it to be suspended in air and dried rapidly. This process has been modified so that the granulating fluid can be introduced to the air stream and can therefore granulate the powders and dry them in one operation. The dry granules are rescreened and then mixed with the lubricants and disintegrants.

6.1.4. Tabletting

The granulate which is now ready for compression is fed into a die cavity of the tabletting machine. The fill is volumetric and consequently the weight is controlled by changing the height of the lower punch which regulates the volume available for filling. Once the cavity is filled the upper punch compresses the powder mass into a tablet. After ejection of the tablet by the lower punch the cycle is repeated.

The equipment varies from small single punch machines which have one upper and lower punch and a die to large rotary tablet presses having up to 50 sets of punches and dies. The rate of production can therefore vary from 100 tablets per minute to 4500 tablets per minute.

6.1.5. Coating

Tablets prepared as above can be coated. Pan coating is the classical technique in which cores are tumbled in pear shaped pans. While the tablets are in motion they are wet down with a concentrated syrup containing a film forming agent such as gelatine, acacia or methylcellulose. When all surfaces have been wetted a dusting powder

such as flour or powdered sugar is added and tumbled under a flow of warm air. This is usually repeated several times. After this subcoating the process is continued by repeated applications of the heavy syrup without dusting powder to smooth out the tablet surface. The colour coats are applied if desired and then the tablet is polished with carnauba wax in a canvas or wax lined pan.

Nowadays coating is very often performed by means of a programmed system applicating a thin coat of polymeric material (film coating).

In another coating process known as Wurster coating the cores are suspended in air and coated by a coating solution that is introduced into the air stream.

6.2. Packaging

As mentioned before, packaging of oral contraceptives is done in a rather sophisticated way. The simple and cheap packaging in glass bottles is usually not used. Simple sealing between two plastic foils has also not achieved widespread application. The most common way of packaging is the so-called blister pack, in which a plastic foil is preformed, filled with the tablets and sealed with an aluminium foil. This whole process is done by one automatic packaging machine.

The second step of packaging is filling into boxes together with the instructions. This work can be done either by hand or by machines. In the least developed countries where labour is cheap packaging by hand often has advantages to the use of sophisticated expensive automatic machines.

6.3. Quality control

Testing of these tablets is done in a generally similar way to testing of other tabletted pharmaceuticals.

Tablet hardness: The resistance of the tablet to chipping, abrasion or breakage depends on its hardness. Hardness is usually tested with hardness testers, such as Strong-Cobb hardness tester. Another approach to the measurement of tablet hardness is the use of the Roche friabolator to determine loss in weight when weighed

tablets are exposed to rolling and repeated shocks resulting from freefalls within the apparatus.

Tablet thickness: Tablet thickness is determined with a gauge such as the Ames thickness gauge.

Tablet weight: There is a maximum allowed variation from the average weight of one tablet, which is controlled on analytical balances.

Tablet disintegration: To be absorbed, a drug must be in solution and the disintegration test is a measure of the time required under a given set of conditions for a tablet to disintegrate into particles.

Dissolution test: This test measures the time required for a given drug in a solid dosage form to go into solution.

Content uniformity: In order to ensure that every tablet contains the amount of drug intended the official compendia have introduced the content uniformity test. Testing methods are found in various pharmacopoeias and are mainly colorimetric thin-layer chromatographic, and titrimetric methods. Content uniformity test can also be carried out using spectrophotometric methods.

7. Local production of contraceptives in developing countries

7.1. Present situation of local production

There are only a few developing countries carrying out oral contraceptive hormone production (India, Mexico). On the other hand, the general situation is characterized by many developing countries having tabletting and packaging facilities in the private sector as affiliates and subsidiaries of the big companies (see Appendix 3) or government-owned pharmaceutical factories producing oral contraceptives.

7.1.1. Private sector

Visit to a local tabletting facility of oral contraceptives - P.T. Schering Indonesia (PTSI)

(a) PTSI is a foreign joint venture company, duly established under the Foreign Investment Law No.1/1967 engaged in the licence manufacture of a broad range of pharmaceuticals.

(b) The present share capital of PTSI is US$ 1,94 million.

(c) The shareholders of PTSI are

(i) Schering AG Berlin/Bergkamen	75,6%
(ii) Boehringer Ingelheim GmbH.	14,4%
(iii) Local Partner	10,0%

(d) Following oral contraceptives are at present being produced by PTSI:

FUGYNON / ED
NEOGYNON / ED
MICROGYNON 30 and 50 / ED

(e) In the second semester 1974 700.000 cycle-packs of NEOGYNON ED Fe were supplied in a "blue lady pack" especially designed by BKKBN in co-operation with PTSI, bearing all imprints in Bahasa Indonesia. This first purchase of BKKBN is a result of the withdrawal of US:AID from this field.

(f) It is intended to produce locally the three-month injectable contraceptive NORICEST. At present five clinical

trials in co-operation with BKKBN are being carried out.

The IUD COPPER T 200 will be introduced soon and BKKBN authorities have shown interest in this contraceptive device.

(g) PTSI commands a market share of approximately 60 - 65%.

(h) The present production capacities of PTSI for oral contraceptives, which can be reserved for supplies to the BKKBN are

4 million cycle-packs per year.

(i) (i) It would take at minimum 18 months to double this specific production capacity.

(ii) The estimated additional investment would be

approx.	DM 500.000	in buildings
and	DM 500.000	in additional production equipment
	DM 1,000.000*)	Total investment

(j) (i) The same time would be necessary to increase the production capacity by five times.

(ii) The estimated additional investment involved to increase the production capacity by five times would be

approx.	DM 1,200.000	in buildings
and	DM 3,100.000	in additional production equipment
	DM 4,300.000*)	Total investment

(k) The problems of raw and packing materials supplies from overseas, the delivery times and capital tied-up, resulting in a considerable financial burden and risk for the manufacturers have been discussed by PTSI with the Chairman of BKKBN and his Deputies on various occasions, and it is now PTSI's impression that the BKKBN authorities realise the need to come to some long term co-ordinated planning for the production and supply of oral contraceptives.

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1) The investments shown under (i)(ii) and (j)(ii) represent only the additional investment required for the increase of the production capacity. These figures do not reflect the additional investment becoming necessary due to the inevitable enlargement of the social installations such as sanitary installations, changing rooms, recreation facilities, canteen, kitchen, etc.

(l) The importance of raw material in production cost is much higher than in Germany. On the other hand, labour costs are lower, so that there are chances to come to the international price.

(k) Sugar, talcum, starch and some alcohols can be bought locally, packaging foils have to be imported from foreign countries.

m) The climate for investment is reasonable. Local producers are protected by import restrictions. It is foreseen that the share of Schering's local partner will increase to 30% within 10 years.

(o) The local partner is the distributor. Distribution activities are generally reserved for local partners.

(p) There is no patent law, and introduction of products is difficult for a company that is not well known in its field.

Mexico

In Mexico, several pharmaceutical factories exist which mostly are in private hands and with foreign investment. They are producing oral contraceptives for the public and private sector of the country.

The capacity of these factories is 10 - 13 million cycles/year in three shifts, whereas the actual production now is 0,5 million cycles/year in one shift. The factories could easily produce without any capital investment by just expanding the manpower to meet the target of 10 times the actual production. Therefore the international agencies providing oral contraceptives for Latin America could consider to formulate and pack the oral contraceptives needed for that region in Mexico instead of purchasing final-packed ones from developed countries where the manpower is more expensive and the transportation cost for the final product is much higher. In addition, a Mexican pharmaceutical factory owned by a Mexican company producing 80 different drugs would like to start the oral contraceptive production from imported bulk material and later to produce oral contraceptives from raw material available in the country. This factory has a well

developed packaging unit for pharmaceutical [illegible] which could easily be used, without any capital investment, for the packaging of oral contraceptives for the country or [illegible].

7.1.2. Government-owned pharmaceutical companies

In many developing countries, there are government-owned pharmaceutical companies to meet the requirements for pharmaceuticals in the public sector. These government-owned companies usually have well equipped and well operated tabletting and packaging equipment. These production facilities provide an ideal possibility of setting up local tabletting units for family planning purposes.

In general, the capacity of the pharmaceutical factories in developing countries is not fully used. Therefore, the production of oral contraceptives from imported bulk material can be carried out without significant capital investment. UNIDO has visited some pharmaceutical companies in Ghana, Egypt Cuba and India, and has found that all of them are well established and in the position to produce without any difficulty oral contraceptives needed in the country. Such a programme has been undertaken successfully by the Egyptian Government for the past few years.

India IDPL

In the Indian pharmaceutical industry for the public sector, IDPL (Indian Drug and Pharmaceuticals Limited) is a well established pharmaceutical unit with a production capacity of 200 million tablets/month and 49 different items. This unit has already started a programme for production of oral contraceptives from imported bulk material with existing facilities, without any additional investment. The production will start with 1 million cycles/year, and in two years this will be raised to 3 million cycles/year. The quality of the drugs produced in this factory meets the requirements of international standards. Furthermore, the factory is programming to produce the oral contraceptives from raw material available in the country, and research work on this has been carried out.

Cuba

Cuba has a well developed pharmaceutical industry which produces [illegible] different products. The amount of these products corresponds to 70 - 80% of the country's demand. As this factory is not working in its full equipment capacity, it would be feasible to produce the oral contraceptives in the same factory without any major capital investment. Furthermore, as Cuba has raw material a research and development programme is carried out by an experimental laboratory in Cuba to produce oral contraceptives and other hormone drugs from Diosgenin or Solasodin available in the country.

Ghana

GIHOC Pharmaceutical Division in Ghana is Government-owned industry which produced 700 million tablets and capsules, and 12 million ampoules per annum and there is a programme to expand its capacity in the near future. Right now, the factory is producing 57 different items and it has been taken into consideration by the Ministry of Health to produce the oral contraceptives needed in the country in the existing pharmaceutical unit.

UNIDO has visited the factory and found that they are in the position to produce oral contraceptives from imported bulk material without any technical difficulties and major capital investment.

7.2. Advantages of local production in developing countries

The following short list of advantages of production in developing countries is given:

(a) Better utilization of foreign currency funds as the import of bulk tablets for local packaging costs about 50% of the importa-

tion of the ready packs, while the importation of bulk starting material for tableting costs about 20% only.

(b) Creation of local skilled labour and trained technicians for the pharmaceutical industry in production, maintenance and quality control.

(c) Participation in the industrialization of developing countries which, in itself, has favourable effects on the family planning process.

(d) More independence from donations which may be subject to changes in the international economic situation.

7.3. Difficulties of local production in developing countries

(a) Shortage of foreign currency funds in developing countries for importation of equipment, bulk materials and packaging material.

(b) Shortage of local currency governmental budgets for purchasing the contraceptive produced for the public sector and family planning programmes.

(c) Governmental regulations and import duties.

(d) Shortage of technicians for production and maintenance.

(e) Difficulties in maintaining the quality standards.

(f) Problems of profitability and prices.

7.4. Analysis of local production of oral contraceptives

Discussing local production of oral contraceptives we have already mentioned before that the step of production of estrogens and progestins requires detailed know-how and trained technicians, whereas the second step of production, tabletting and packaging, does not differ significantly from any other type of tablet production. Regarding this, developing countries can be divided into two groups.

Group 1:

Countries having possibilities for synthetic production of inter-

mediates and oral contraceptive hormones from own or imported raw material of imported intermediates. These countries [illegible] to carry out tabletting and packaging themselves.

Group 2:

Countries having possibilities only for tabletting and packaging from imported bulk material or only packaging from imported bulk tablets.

7.4.1. Commercial production of steroid hormones

(a) Countries having raw materials, detailed know-how facilities and trained technicians (Group 1) meet all requirements to produce intermediates or endproducts of estrogens and progestins and carry out tabletting and packaging. Steroid hormone production can also be considered by other countries which do not have all or not enough raw material but have a highly developed pharmaceutical industry and are able to produce hormones starting from intermediates and to carry out tabletting and packaging.

(b) There are several cases of countries that have raw materials but, however, do not produce hormones but only intermediates which for their production require the same sophisticated technology as the final steps. The final steps of synthesis are carried out in other countries and the hormone endproducts are re-imported for tabletting and packaging. It is obvious that this system is disadvantageous because of the unnecessary transport costs. Therefore it would be necessary to provide those raw material producing countries with production facilities to carry out the whole synthesis in their own country, at least to supply their own demand in oral contraceptives. These countries could also provide neighbouring and other countries with oral contraceptives or bulk material for tabletting and packaging.

(c) Countries having possibility for oral contraceptive production from intermediates are sometimes faced with shortage of raw material. A supply of these countries with intermediates for synthesis of oral contraceptive bulk material could not only help to satisfy the own demand but could also serve as source

of oral contraceptives for developing countries. Supply of raw materials or intermediates to the manufacturing countries and delivery of the finished oral contraceptives to the developing countries could be arranged and carried out by the donating agencies.

(d) A country which intends to set up its own hormone industry must secure the supply of its own raw material, and also study carefully the situation of raw material in other countries and the development of total synthesis in their effects on local production economics.

(e) Establishing a facility for synthesis of oral contraceptives from raw material affords a capital investment of about 6 to 8 million US$ for a monthly capacity of 250 to 500 kgs. To set up such a plant detailed know-how, sophisticated engineering and supply of equipment must be secured.

7.4.2. Commercial packaging and tabletting

(a) In Group 2, there are many countries which have a well organised and developed pharmaceutical industry for tabletting and packaging. These countries could easily produce oral contraceptives from imported bulk material in existing facilities without any or only small investment, and without the necessity of acquiring very sophisticated technology.

(b) There are some countries which do not use their full tabletting and packaging capacities. These countries are in a position to carry out tabletting and packaging also for surrounding countries. This could be arranged by donating Agencies.

(c) Small countries in which tabletting is not economically feasible could be supplied with bulk tablets and do packaging according to their own intentions.

(d) The importance of packaging material should not be underestimated, since it makes up a considerable part of the production cost. Therefore, a further advantage exists for those countries which can produce packaging material locally.

8. Main types of hormone contraceptives

As far as dosage and combination of active components are concerned, the following main types of contraceptives are on the market at present:

8.1. Combined preparations:

These contraceptives contain progestins and estrogens in each pill and are taken continuously for 20 to 22 days. During the rest of the cycle either no pills or pills containing no hormones are taken.

8.2. Sequential preparations:

During the first 14 to 16 days, the pills contain only estrogens, during the following 5 to 7 days, a combination of both estrogens and progestins.

8.3. "Depot" contraceptives:

They contain progestins and estrogens and are generally used as 1, 3, 6 or 12 months injectables, or as one-month pills.

8.4. The "mini" pill:

The mini-pill is a late development containing only progestins in very low doses, the contraceptive activity of which is not based on prevention of ovulation but prevention of nidation (luteal supplementation).

8.5. Post coital hormone contraceptives:

8.5.1. Estrogens - contain high doses of estrogens and act as post coital contraceptives but suffer however from side effects.

8.5.2. Prostaglandins - these hormones do not belong to the group of steroid hormones. Much research work during the last years has resulted in this type of contraceptives now being available on the market.

8.6. Other types of non-steroidal contraceptives are either in course of development or are of relatively minor economic importance.

As a rule estrogens and progestins are contained in the pills in very low amounts (e.g. 0,05 mg. oestrogen, 1 mg. progestin in one tablet of 0,3 to 0,5 g., some new developed pills even containing less). For this reason, the share of the active compound in the price of contraceptives is unexpectedly low, when the cost of the pure hormone is considered.

Examples of some typical contraceptives on the market and their composition:

Anovlar 21: 21 coated tablets, each containing 4 mg. Noresthisteroneacetate and 0,05 mg. Ethinyloestradiol.

Eugynon 21: 21 coated tablets each containing 0,5 mg. Norgestrel and 0,05 mg. Ethinyloestradiol.

Lyndiol 2,5: 22 tablets, each containing 2,5 mg. Lynestrenol and 0,075 mg. Mestranol.

Neogynon 21, Neogynon 28, calendar pack with 21 coated tablets, Neogynon 28 contains 7 taolets containing no hormones, the tablets contain 0,25 mg. D-Norgestrel and 0,05 mg. Ethinyloestradiol.

Orlest 21 tablets, each containing 1 mg. Noresthisteroneacetate and 0,05 mg. Ethinyloestradiol.

Microlut: 35 coated tablets in calendar pack, each tablet containing 0,03 mg. D-Norgestrel.

Biosecurinn: 21 tablets, each containing 1,0 mg. Ethynodiol and 0,05 mg. Ethinylestradiol.

Continuin (40 tablets, Ethynodial diacetate 0,5 mg.)

9. Trends in the use of hormone contraceptives with special reference to the situation in developing countries

The trend in oral contraceptives production during the last decade has been towards a decrease of hormone content of the pill from several milligrams down to 0,5 mg. and less. The latest development, the so-called "mini-pill", contains only progestin in a very low amount. Side effects, such as bleeding, have however been observed in the use of this type of pill, so that it seems that the trend towards decreasing hormone content of the pill, which reduces the hormone caused side effects, may have come to an end.

Another type of contraceptive, the weekly or monthly pill, has been tested in Eastern Germany and in future may perhaps be of great interest especially in developing countries.

The so-called "paper-pill" has been developed and used with great success in China. It was not possible to get detailed information on this system of contraceptives from China.

The great expectations in recent years, for prostaglandins as contraceptives, have not yet led to success, and probably will not do so in the near future. Prostaglandins have however obtained their place as postcoital contraceptives.

The use of injectables, such as Provera, has had great success in Thailand. It must however be pointed out that this is mainly due to the successful medical service system in the hospital of Chieng Mai. In other countries, the side effects, bleeding and reduced fertility after cessation of the use of injectables, have militated against a greater usage of thie type of contraceptive.

It must be pointed out that careful selection of the formulations used by family planning organizations in developing countries is essential to secure success and high continuity rates of the use of such contraceptives.

As far as the donations through UNICEF are concerned, WHO act in an advisory capacity to UNICEF on the technical requirements of contraceptives for use in least developed countries. These Agencies held a meeting to discuss and evaluate available evidence on micro-pills;

namely, oral contraceptives containing less than [illegible] Unfortunately, the Chinese who have carried out [illegible] pills did not attend the meeting, and WHO consider that the evidence presented by Industry and that published in Western literature is not definitive. More information is still required on the effectiveness of these drugs, their side effects, and continuation rates. It will take WHO a further 2½ years to complete its study on the micro-pill.

WHO are also involved in research into progestational potency of oral contraceptives. They are interested in establishing whether different progestational levels are required for different ethnic groups. Thus more than one combination pill may be required, but only one progestational agent may be necessary to satisfy the different contraceptive need of the least developed countries. Norethisterone is being evaluated at 3 mg and 1 mg dose levels.

It is UNIDO's impression that the following factors seem decisive for successful oral contraceptives use in developing countries.

(a) Few side effects:
It is a matter of fact that women of a low educational standard are especially frightened by side effects of the pill and that these side effects have caused discontinuation very often.

(b) Pill formulation:
The influence of the formulation on different ethnic groups should be carefully studied and suitable preparations should be developed.

(c) "Long-time" contraceptives:
There is some indication that 1-week or 1-month pills or 3-month injectables show a higher rate of success than the daily pill and their development should be promoted.

(d) Good medical service will always be the basis of successful use of contraceptives.

CONDOMS - PRODUCTION AND RAW MATERIALS

1. Introduction

1.1. Condoms for family planning purposes

Although condoms have been in use for a long time they have in recent years received new attention as a means of family planning only. When family planning began to win social acceptance and national priority, in the 1950s, public interest tended to focus on the new medically approved oral contraceptives and IUDs, and it took several years for the advantages of condoms in family planning to emerge. The following are the most important advantages:

(a) it has no side effects;
(b) it is now reliable;
(c) it also offers protection against venereal disease;
(d) it is compact and disposable;
(e) it is a male contraceptive;
(f) it requires no medical examination, supervision or follow-up; and
(g) it can easily be distributed.

1.2. Types of condoms

Basically there are two raw materials for condoms: skin and rubber. Skin condoms are still in use in relatively low volume. They are said to transmit body heat much as the human skin does. Rubber condoms: In the 1870s the first rubber condoms were made by the cement process. In this process finely divided crepe rubber is dissolved in a volatile hydrocarbon. Upon removal the solvent evaporates leaving a film of rubber on the form. This operation is repeated until the thickness of the condom meets the requirements. Some condoms are still made by this process but, nowadays, the bulk of the world production is made by the latex dipping process which uses latex instead of crepe rubber.

As to the outer shape and design there are the following types of condoms:

(a) coloured;
(b) transparent;
(c) opaque;
(d) plain-ended;

(e) reservoir-ended;
(f) rippled;
(g) strictured;
(h) flocked, with a rough surface;
(i) dry (powdered);
(j) lubricated; and
(k) different sizes.

2. Raw materials

2.1. Natural rubber latex as raw material for condom production

Until about 1930 the use of the latex of natural rubber for making anything but crepe and smoked sheet was confined almost exclusively to a few small industrial processes. Then several developments occurred, such as the use of higher quantities of ammonia for improved preservation of the latex, the development of methods for concentrating latex to total solids of 60% or greater, and the development of better sanitary practices for storing and shipping the latex. These were some of the factors that propelled natural latex into the advanced technological state that it now enjoys.

2.1.1. Virgin latex

The solids content of fresh latex as it flows from a plantation tree of average age is between 30 and 36%. The latex solids from younger trees is sometimes as low as 20% and for older trees and trees that have not been tapped for a long period of time the solids can be as high as 45%. Although approx. 90% of the solids is accounted for by the rubber hydrocarbon, also present are enzymes, proteins, resins, sugars, tannin, alkaloids, mineral salts, and some bark constituents (30). Some of these nonrubbers are responsible for the stabilization of the colloidal particles of rubber in the serum. Others affect the colour of the latex, and still others are partially responsible for the physical characteristics of the rubber contained in the latex.

As it flows from the tree, the latex is almost neutral, but enzymic and bacterial action soon changes it into an acidic condition and the rubber tends to coagulate. In order to inhibit the coagulation and to keep the latex in a stable colloidal

condition, preservatives and bactericides are added as soon as possible after the latex comes from the tree. The most common preservative is ammonia, but formaldehyde, sodium hydroxide, soap, and certain bactericidal chemicals such as salts of pentachlorophenol are also used. The usual plantation practice is to place a small quantity of ammonia water in the collection cup so that the fresh latex flows into the stabilizer. After the latex has been collected it is taken to a station where additional ammonia is added in the form of a gas.

Ammonia is preferred over the other preservatives because it has bactericidal properties and increases the pH of the system, thus making it more stable. If there is too much ammonia present when the latex is used in certain processes, the ammonia may be decreased by simple aeration or by the action of formaldehyde, which yields hexamethylenetetramine. This last chemical is an accelerator of vulcanization and usually does not interfere in various latex processes. The disadvantages of using ammonia are the relatively high cost, disagreeable odor, and loss due to volatilization. Also, indications are that ammonia-resistant bacteria strains may be developed in latex which tend to lower storage life. Latex stabilized with 0.7% ammonia calculated on the weight of the latex (at 35–40% solids) exhibits a big increase in bacteria count during the first few days of storage and then it levels out and keeps this condition for some months. Besides its bactericidal property and its alkalinity, ammonia reacts with the naturally occurring fatty acids in the latex and these soaps formed in situ are absorbed on the rubber particles to stabilize the latex further.

2.1.2. Centrifuged latex

Because of the cost of transportation and the ease of application, practically all the latex used as such in industry is in a concentrated form. By far the most common type is centrifuged latex which is made by treating the fresh latex with a stabilizing agent such as ammonia and then passing it through a centrifuge (34). The fresh latex is stabilized with about 0.3% ammonia, and after centrifuging it is adjusted upward to 0.6%

to insure good storage life. This is called high ammonia latex in the trade and is referred to as ASTM + [illegible]. By varying the operation of the centrifuge, the relative quantity of the concentrate and the serum can be adjusted to an economic level. Approx. 80–85% of the total solids content of the fresh latex remains in the concentrate and the remaining quantity is in the skim.

The above two sections are quoted from Kirk–Ottmer Encyclopaedia.

2.1.3. Quality requirements in latex for condom production

This has to be high quality centrifuged latex. At present Malaysian latex is said to be best and in fact Malaysia is the world's greatest exporter of natural latex. The basis of the success of Malaysian latex is the well organized system of latex production and quality control in this country. Viscosity, acidity, stability, double centrifugation and other properties of latex play an important role in condom manufacture. Use of latex from mature trees, timing of storage, seasonal influences and other factors must be carefully observed. During recent years also other latex producing countries have become aware of the importance of constant good quality. India has had considerable success with its government rubber plantation on the Andaman and Nikobar Islands and there is also a project to use Indonesian latex in a condom factory to be built in Indonesia. In any case a close co–operation between latex producer and condom manufacturer will be essential to achieve successful condom production.

Natural rubber latex is still the best raw material for condom production and there is no indication that it will be substituted by synthetic rubber latex in the next future.

2.2. Price of latex

The price of latex basically follows the rubber price and therefore fluctuates as commodity prices normally do. Recently, the prices for rubber have fallen (in Malaysia at present M$ 1,30 per kg. DRC ASS1, 1974: M$ 1,50 per kg. DRC ASS1) which has resulted in many small holders converting from latex to palmoil production. On the other hand, future price increases due to speculation cannot be excluded. However, all these fluctuations of price will not have any significant effect on

the condom price. The actual production price of condoms can be estimated to be at least about US$ 1,50/gross, [illegible] price is between US$ 3,50 and US$ 7,00/gross. To produce 1 gross of condoms about 150 grams of latex (DRC) is needed, which costs about US$ 0,075. Thus even heavy price increases cannot have significant influence on the production cost of condoms.

2.3. Production and consumption of natural latex

Unlike crude natural rubber, the production of commercial latex is limited to relatively large, well-organized estates that employ an adequate technical staff. There are only about a dozen estates that produce natural latex. The following table shows the net exports of natural rubber latex in tons:

	Malaysia	Indonesia	Sri Lanka	Vietnam	Khmer Republic	Liberia	Total
1962	118,056	22,880	381	2,822	9,065	22,220	175,432
1967	146,094	24,587	90	1,307	14,500	26,857	213,435
1972	202,387	NA	NA	NA	NA	39,172	NA

These figures illustrate that there will be no shortage of latex in the case of heavy increase of condom production, since the consumption of latex for condoms is small. The world production in condoms may be estimated to be about 20 million gross. The weight of 1 condom is between 0,7 g. and 1,7 g. according to the thickness of the condom (0,03-0,06 mm.). This means that the total consumption of latex for condoms is between 2000 tons DRC and 5,000 tons DRC per annum. The estimated total consumption of natural rubber latex was 282,500 tons in 1972, the total production of natural rubber was estimated at 3,102,500 tons in 1972. Compared to those figures the amount of latex for condoms is so small that even a heavy increase in present condom production would not have a significant effect on the availability of latex. Other factors such as the development of other rubber industries will therefore have much more influence on price and availability of latex.

2.4. Availability of latex - Views of condom manufacturers

The condom manufacturers also agreed that there are no serious problems as far as latex is concerned. The following comments were

obtained:

2.4.1. London Rubber Industries, London

(a) LRI does not anticipate any raw material shortages whatsoever;

(b) Malaysia is the only source of latex used at present; and

(c) LRI does not anticipate that an increase in its latex requirements to enable it to manufacture 1 x 10⁸ gross additional condoms would have any significant effect on the use of latex. This is due to the small proportion of the world's latex production which is used for condom manufacture: a tenfold increase in demand for latex for condom manufacture would not in their opinion seriously distort the world trading patterns in latex.

2.4.2. Sagami Rubber Industries Co. Ltd., Japan

The situation concerning raw materials is the following:

Japan's condom manufacturers have a great experience in production of condoms from latex. Nowadays, Malaysian latex is preferred for condom production, because Malaysia provides a standard latex of high quality. Japan's producers prefer double centrifuged latex. Their requirements concerning viscosity, acidity, stability and other properties are very high and imported latex is tested carefully. It is estimated that raw material costs are 20% of the condom production costs in Japan. Sagami is very optimistic concerning availability of latex also in case of increase of production.

2.4.3. Sagami Industries (Malaysia) Sdn. Berhard

There is no shortage of latex at present, the quality of Malaysian latex is very good, since the system of quality control is good. Sometimes there are viscosity problems due to weather effects: Too much rain affects the quality, there are also seasonal influences, timing of storage is important. Suppliers are Harrison and Crosfield and other latex companies. It does not seem that there will be a shortage in latex, but low prices have resulted in many small holders converting from latex to palmoil. At present the price of latex is M$ 1,30/kg. DRC ASS1. This is cheaper compared with 1974, when the price was M$ 1,50.

2.4.4. Royal Industries (Thailand) Co. Ltd.

Germany know-how enabled the use of 60% latex from South Thailand. The latex is treated to obtain exact viscosity and exact colour. It took years to teach people to produce latex suited for condom production.

2.4.5. Hindustan Latex - India

(a) The main problem in condom production is latex. Hindustan Latex has a sound knowledge of latex technology, knowing well the importance of tapping from mature trees, double centrifugation, proper aging, etc.

(b) In time of shortage the use of latex from immature trees simply for reasons of profitable tapping should be avoided;

(c) There is now a very good latex available from Government plantation on the Andaman and Nikobar Islands. There, in a real tropical climate, plantations from Malaysian seedlings give month by month growing yields of latex processed according to the requirements of condom production. It is expected that the Perak plant will get its requirements of latex from the Andaman Islands.

(d) The demand for latex for condom production is very modest, therefore availability of raw material will be no problem.

2.4.6. Situation in Indonesia

Indonesia is an important latex producing country, its latex is, however, at present, not very much in use for condom production, although in the time before 1950 London Rubber Co. had purchased Indonesian rubber for condoms. It is planned that during the first stage of the joint venture of local condom production, a study on local latex for condom industry will be carried out and both Indonesia and London Rubber Co. believe that with improvement in technical processing, Indonesian rubber will meet the requirements of modern condom production. The small condom producing company in Central Java is said to use Indonesian latex at present.

3. Local production

An analysis of the present situation of condom consumption in developing countries reveals that in many countries most of the condoms are imported. Some countries such as India and Korea have rather big domestic condom factories. During recent years joint ventures and subsidiaries of the big condom producing companies have been established and are projected in

developing countries - Malaysia, Indonesia, India. Furthermore, in some countries, there are existing small domestic condom factories - Malaysia, Indonesia, Thailand - that however usually face problems of quality of their products.

3.1. Local production by The Latex Dipping Process

The condom consisting of a rubber sheath with a receptacle at the closed end, and a thin ring formed by rolling the rim, at the other end, is moulded from suitably compounded natural rubber latex. The steps of production are the following:

3.1.1. Compounding

Concentrated natural rubber latex, if possible double centrifuged, of 60% concentration is used as the raw material. After testing in the laboratory the latex is stored in the latex storage tank. It is then clarified and fed into the mixing tank where it is mixed with the compounding chemicals. These chemicals are prepared as a form of water dispersion (40%) of vulcanizer, accelerator, stabilizer and disperser in a colloidal state by ball milling before being added to the latex. Compounded latex is heated in the mixer to about 50°C and then held in storage to allow prevulcanization conditioning. It is then transferred to a tank for ageing. The aged latex is subsequently fed to the charging tank. Physical properties such as viscosity, mechanical stability, total solids and heat stability are adjusted here. The latex is then supplied to the moulding section.

3.1.2. Moulding and vulcanizing

Moulding is usually carried out as a fully-or semi-automatic process. Compounded latex is fed to the dipping tanks of the moulding machine. Glass moulds which are fitted to an endless chain are dipped in the compound latex. After drying they are dipped once again. The liquid level of compounded latex in the dipping tank is adjustable to decide the length of the condoms sticking on the glass moulds. The deposit obtained depends only on the viscosity of the latex and the speed of withdrawal of the former. Therefore, these factors must be most carefully controlled.

After drying the condoms are passed through the edge rolling section. From the final drying chamber, the condoms are dipped in ammonia water and "anti-stick" solution to make stripping easy. Stripping can either be done by hand, or by a stripping machine. Brushes, or a forced jet of chemical slurry are used in the stripping machine for removal of the condoms from the former. After stripping the condoms are partially dried and sent to the vulcanizing section. The moulds, after being stripped, are passed into the tank and are then washed and dried. In the vulcanizing section the condoms are vulcanized by heat in order to give the elasticity and anti-decay required into the half-finished products. At the same time, excess powder is removed.

Almost no labour is needed for dipping, but sophisticated equipment and exact tuning of the dipping process are necessary.

The moulding section also determines the capacity of a plant, which is always a multiple capacity of a single line. The monthly capacity of the automatic Japanese lines is about 20.000 gross per month. In Malaysia, a small company works with a 10.000 gross/month line. In any case, the smallest economically feasible capacity for condom production will be the capacity of the smallest automatic dipping line on the market. Malaysian condom manufacturers have estimated the minimum economically feasible capacity to be 1 million gross per year in a developed country, and 200.000 gross in one line in a developing country.

3.1.3. Testing

The electronic pinhole tester consists of a conveyor belt on which two rows of chromium plated steel moulds are fixed and driven by an induction motor. The condoms are inserted over the moulds, and the air trapped inside is pinged by allowing it to escape through a hole at the top of the mould. The mould passes then through a rotating sponge wheel fixed at the side of the moulds which tightens or fixes the condoms on the mould. This is to avoid any wrinkles in the condom while it is tested. Then these moulds are dipped into the inspection tank which contains a special soap solution. If there is a condom pinhole it will be

electronically detected in the inspection tank and the selection plunger immediately strikes at the pin located on the side of that particular mould. The pin will then protrude outside indicating a defective condom. The moulds with the condoms are then dried in the drying chamber, and after drying are rolled up by another sponge wheel. Whilst rolling up, a sponge wheel at the top presses the top of the mould so that it may not be stripped off at that point. The next operation of the machine is stripping. There are two positions in the line for stripping, one for the good condoms, and the other for the defective condoms. Stripping is done by another sponge wheel. Collectors are provided to collect the good condoms and the defective, rejected condoms separately. For quality control, there are several tests to which samples are subjected:

(i) Tensile strength;
(ii) Air inflation test;
(iii) Dimensional analysis;
(iv) Appearance test;
(v) Water leakage test.

The steps of testing and packaging are very labour intensive, and therefore, for example, Japanese manufacturers usually plan to carry out this part of production in regions of that country where labour is cheap.

3.1.4. Packaging

In the packaging section, the condoms are individually packed in laminated aluminium foils with suitable coatings and printed designs. The strip packing is done by machines. The packing of strips in cartons or packing cases is usually done manually. If the condoms are lubricated, the lubricant is added during the packaging operation.

As far as economic aspects of packaging are concerned, this is the most decisive step in condom production. Its importance can be seen from the fact that costs of packaging were estimated by some manufacturers to be more than 50% of the pro-

duction cost, and in fact it appears that the availability and price of aluminium packaging foils may influence the price of condoms much more than latex as the raw material. The reason for the great share in the cost of packaging lies in the commercial marketing of condoms. It is true that good marketing and packaging of condoms can increase consumption of particular brands of condoms very much as was noted in the condom campaign in Jakarta, and the condom industry in Thailand. It is surprising that in the private commercial sector, customers are not unduly concerned with high prices and even prefer the more expensive products. Regarding the question of high cost for packaging in aluminium foils, it should be examined whether it may be possible to find a less expensive, but nevertheless attractive and durable, type of packaging for family planning purposes. Indeed, in the Hirodh programme, has already made some steps in this direction.

3.2. Existing production capacities

The total annual world production of condoms can be estimated to be about 20 million gross, most of which is produced by a few big companies. The capacities of the condom manufacturers are usually almost fully utilized, with the exception of some small manufacturers in developing countries - e.g., Malaysia, Thailand. In the case of a heavy increase in condom consumption through family planning, however, additional production facilities would have to be installed to meet public demands. Production cannot be increased gradually, but only in steps, as multiples of the capacity of one line. A contract of 750,000 gross, according to London Rubber Industries, would justify installation of new condom machines. Therefore, condom producers really require long term contracts from purchasing agencies to justify additional machinery for increased production.

3.3. Developed countries - Producers' approach towards local production of condoms in less developed countries

3.3.1. London Rubber Industries, London

(a) LRI would be willing to consider joint ventures in which it had a controlling interest or in which it participated on a turnkey operation basis. LRI would then make its money from the sale of machinery and know-how. It would insist on the plant output being restricted to the country of manufacture as it could not afford to develop extra competitors.

(b) LRI would be willing to supply [illegible] packaging in LDCs. It considered [illegible] packaged 50,000 condoms/annum would [illegible] it would not consider the establishment of [illegible] packaging facilities to be desirable; this could result in local production which directly competed with its established markets, and it would not be a party to such a venture.

(c) LRI does not licence.

(d) LRI have no plans for expanding production in LDCs, apart from Indonesia where discussions with the Government are in progress, but they would be willing to consider when further information on likely demands for condoms is available.

3.3.2. Sagami Rubber Industries Ltd., Japan

(a) Sagami is ready to make joint venture projects in other countries. It is, however, difficult to select partners, careful feasibility studies are necessary and a lot of time is needed for government formalities. Since a 20,000 gross/year capacity plant is considered to be the smallest economically feasible capacity, a large investment is necessary, financial support from international agencies might be considered.

(b) To provide successful production in developing countries, the delivery channels must be well organized to avoid pile-up of condoms.

(c) In fact, Sagami has set up a condom factory as a joint company in Malaysia. The first line went into operation on 3-shift basis last September and the next line will start operation in February. Sagami has provided all the equipment and sent 3 expert engineers who are fully responsible for compounding, mixing, packing and testing. It took about 6 months until the same quality as in Japan was reached and it is hoped that Malayeia will become a good supplying company for home and export markets. The advantages of production in Malaysia are:

i) sufficient labour power;

ii) best latex source; and

iii) land is cheaper there than in Japan.

(d) One manufacturer sold a plant to India in 1968/69. There were, however, difficulties in the technical field and the Indian Government was not fully satisfied. Indian Government has asked for further advice from Japanese producers.

3.4. Difficulties of local production as seen by the developed countries' condom manufacturers

Some of the developed countries' condom producers have already had experience in setting up production facilities in LDCs. They gave the

following impressions on difficulties which have been encountered:

3.4.1. London Rubber Industries, London

(a) Availability of trained personnel has been a problem in establishing condom factories in LDCs. Latex technologists, engineers and effective managers pose particular problems. The time taken to train a latex technologist varies: about 3 to 6 months would be required to teach a chemical engineer or a rubber technologist the necessary skills; and up to 2 years could be required to train a graduate in Chemistry. Management training is more of a problem; this frequently requires radical changes in attitude on the part of the trainee before he can be taught to be a good manager.

Another major problem LRI has experienced in setting up factories in LDCs has been availability of U.K. staff willing to work overseas for protracted periods. The company has found that this factor prevents it from establishing more than two plants at any one time.

(b) Political problems, currency, and local traditions have been major problems encountered in setting up plants in LDCs. Import licence restrictions, use of local materials (latex and packaging materials were sub-standard) have been major difficulties encountered in the condom factory established in India. LRI also experienced difficulties following the installation of a secondhand machine at its Indian plant. The Indian Government changed the specifications for condoms following the start up of the plant which made the product sub-standard; this occurred after the Indian Government had given its blessing to the installation of the unit. LRI had informed the Government of the quality of the condoms which would be produced by the unit prior to its installation, and agreement had been reached to proceed with the installation of the machine. As a result, two years' condom production was lost whilst a new machine was manufactured, delivered and fitted.

Some governments insist on the location of a factory in an unfavourable site; the motivating factor here could be the introduction of industry into depressed areas. Sometimes, these regulations have to be opposed on technical grounds, and can delay or prevent the installation of a factory.

The company is having some difficulties in its discussions with the Indonesian government regarding the installation of a condom factory in that country. Social habits such as long lunch hours and holidays are particular sticking points at present and have to be resolved.

(c) LRI's experience in India has shown that finished product costs are greater in that country; this has arisen from the inability of the plant to work at maximum efficiency

due to Indian Government regulations. Labour costs in LDCs are generally less than the U.K.: testing and packaging would lower the finished product cost if a lower standard is acceptable. Experience in LDCs with LRI's products other than condoms has suggested that finished product costs are comparable to those in the U.K.

(d) The Indian plant had failed to produce a profit so far.

(e) Local specifications generally follow one of the international specifications and as such present no major problem. LRI did suggest, however, that Hindustani Latex has produced sub-standard condoms since the Japanese experts withdrew, and it is their understanding that the Indian Government is seriously considering lowering condom standards to enable Hindustani Latex's products to be marketed in India.

(f) Latex, lubricant, chemicals, packing materials and silicons have frequently to be imported and this can cause difficulties especially if the LDC has foreign exchange problems.

LRI has encountered difficulties in India due to Government decree that requires a proportion of the condoms produced in the Indian plant to be exported. Local packaging materials, which are suitable for packaging condoms for the Indian market, are totally unsuitable for the export markets. This requires the import of packaging materials; and this has produced some problems due to India's precarious foreign exchange position.

(g) Testing is similar to that used in the U.K.: namely, electronic testing. LRI admitted that it should be possible to train people to visually test condoms if labour intensive operations are required by the Governments of LDCs.

(h) Currencies can be a problem in the successful operation of a condom factory in an LDC. One example is cited above at (f). LRI would also tend to avoid the accumulation of soft currencies as difficulties may be encountered in converting these to hard currencies.

The company has also encountered difficulties in Iran due to the excessively long time taken to transact financial deals. This could be a possible factor in the loss of profit by a company sited in Iran if provisions are not made for this contingency.

3.4.2. Sagami Rubber Industries Co. Ltd., Japan

Sagami Japan mentioned the following difficulties during setting up their joint venture project in Malaysia:

(a) Obtaining and training good local engineers;

(b) [illegible] import [illegible] restrictions; and

(c) [illegible] obtain [illegible] water [illegible]

During the [illegible] survey, also the Sagami plant, Malaysia, [illegible] information on the setting up of this typical [illegible] proved in the section 3.5.

3.5. [illegible] - [illegible] - [illegible] Sdn. Bhd.

In [illegible], agreement for a joint venture was made. It took two years until [illegible] obtained from Malaysian and Japanese Governments. There were some problems in acquisition of land involving applications to be allowed to build in the industrial estate. Supply of electricity and water took also some time. The result was that the project, which had started in October 1969 with Mr. Ushiama coming to Malaysia, was completed only at the end of 1972. Production could start only in April 1973 when electrical power was obtained. During the starting period the quality of the condoms was lower - 30 to 40% scrap - and it took one year until the Japanese standard was reached. Financial standing during the first two years of production is recognized as difficult for new condom producers, but support from Japan helped to overcome all difficulties. There are also difficulties in building up a sales organization. Sagami has obtained so-called "pioneer status": for a maximum of seven years there are some preferences in taxation for new industries. These involve complying with some conditions: At present no more than 10% of the production must be sold in Malaysia; if production increases this might be changed to 30%. The quality of the company's products has now reached a very high standard, so that Sagami has applied for the SIM-mark to obtain another advantage of the pioneer-control status of imports. Dr. Leong Kwok Onn, Director of SIM, will play an important role in such decisions.

At present the monthly production is 40,000 gross, with a maximum capacity of 50,000 gross. Sagami believes that the minimum economic feasible capacity be 1 million gross per year for Japan and about 40,000 to 50,000 gross per month in Malaysia. At present most of the production is sold to Japan.

The estimated annual consumption of condoms in Malaysia is 30,000 to 40,000 gross - commercial market plus gifts - but there is a very considerable amount of smuggling so that the overall annual consumption can be estimated to be more than 100,000 gross with smuggling from Thailand, Singapore and Penang.

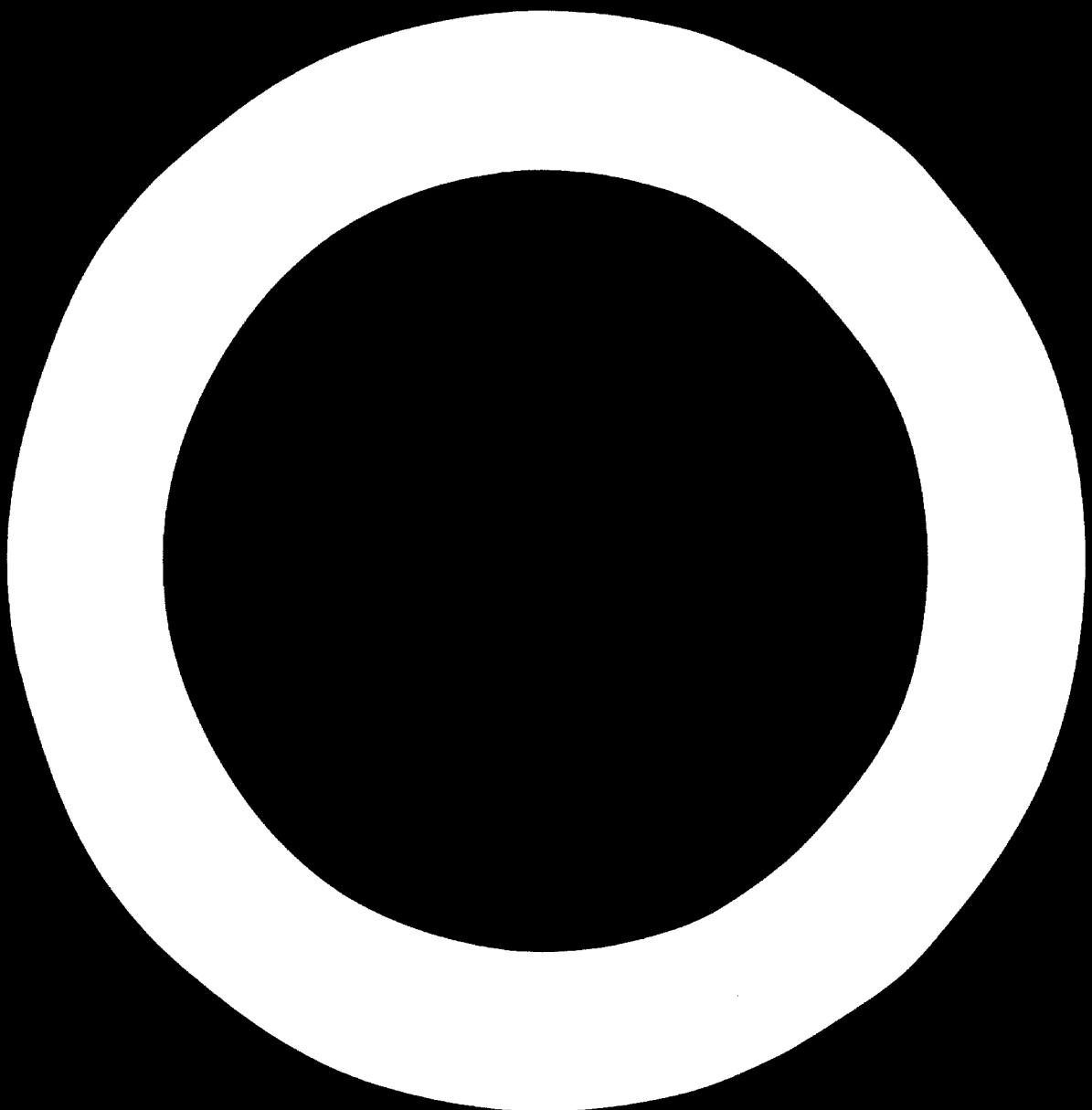
Sales and marketing are a problem for Sagami. The Islamic part of Malaysia does not use condoms for religious reasons. Therefore, the market for condoms is very low. At present most of the condoms used are imported, mainly from London Rubber Company. This firm has become synonymous for condom in Malaysia, because this company has been on the market for a long time. There are no restrictions on imports so far and since advertising is forbidden it is very difficult for a new product to be immediately successful in the market.

UNICEF and SIDA usually buy big quantities, but their orders are only once and they stop after that. Long term contracts would enable the company to adapt its capacity.

Sagami Malaysia has started to contact buyers all over the world, e.g. Greece, France and Italy, to sell bulk or packed condoms, but the effect of this campaign has been rather unsatisfactory.

As far as packaging is concerned there are problems about the aluminium foils. A company plans to produce the foils locally with "pioneer status". At present the quality of their products does not meet the requirements. It must be expected that the duties for foils will go up when the company obtains the SIM mark.

The five persons of Japanese nationality on the staff of Sagami Malaysia face some problems concerning visas. These are currently due to expire at the end of 1975 and from that time the number will decrease, to be substituted by Malaysian nationals. This may bring problems as far as production is concerned.



It must be pointed out that the lists of equipment and estimates of production costs given in this Appendix are only indicative, and are not data obtained from working production facilities. They can, therefore, only serve as a rough guide to the type of equipment that is needed for different stages of contraceptive production. To set up detailed equipment lists and flow sheets it would be necessary to have exact data, such as which contraceptive is to be produced, which technology and type of know-how is used, and where the facility is to be built. Note also that equipment prices are subject to uncertainty due to inflation.

1. Tentative list of equipment for the extraction of diosgenin from tubers on a small scale

Capacity per run	350 kg tubers (35 kg dry tubers)
Yield per run	3.5 kg diosgenin
Capacity	5 runs per day
Manpower needed	3 per shift
	$
1 micropulverizer	20,000 to 30,000
1 2000 l. vessel, glass-lined, with stirring equipment, vapour-heated, with condenser	60,000
1 decanter (stainless steel), or	35,000
1 centrifuge (glass-lined with variable speed)	30,000
1 fluidized bed dryer	20,000
1 1000 l. vessel (stainless steel), with stirring equipment, vapour-heated, with condenser	40,000
1 vacuum evaporator (pump and condenser)(stainless steel)	30,000
1 centrifuge (explosion protected)	10,000
1 rectifying column (solvent recovery)	5,000
	220,000
Piping and instrumentation, 50%	110,000
	330,000
Engineering costs, 10%	33,000
	363,000
Construction costs, 10%	36,000
Contingencies, 20%	72,000
	471,000
Buildings, 50%	235,000
	706,000

Raw materials needed for production of 17.5 kg diosgenin per day:

1750 kg fresh dioscorea tubers

1400 l. concentrated hydrochloric acid

5500 l. water

4000 l. petrolether (90% is recovered)

250 l. solvent mixture for recrystallisation (70% recovered)

2. Simple extraction unit for steroid raw materials

The following list gives a rough idea of equipment and investment needed for the extraction of about 500 kg of plant material per day.

	$
2 vessels (stainless steel or glass lined), with stirring equipment - each $7000	14,000
1 decanter (stainless steel)	35,000
3 vessels (stainless steel) - each $5000	15,000
2 circulating evaporators (stainless steel) - each $12,000	24,000
3 pumps - each $1500	4,500
1 separator	3,000
2 condensers - each $6000	12,000
3 hoods	4,500
2 boilers for water	6,000
Piping and instrumentation	18,000
	136,000
Space required 1000 to 2000 cu.m (300 sq.m x 4)	120,000
Total capital investment about	256,000

• Equipment for the transformation of diosgenin to its intermediate

It seems worth mentioning that transformation of diosgenin, if not carried out on a large scale, can be carried out by production in batch using large-scale laboratory equipment.

Capacity per run	about 5 kg diosgenin
Manpower needed	4-5 per shift

	$
2 50 l. reaction vessels, glass lined with reflux condensers - each $6000	12,000
2 100 l. reaction vessels, equipped as above	16,000
2 vacuum evaporators (stainless steel) with pump	12,000
1 50 l. vessel (stainless steel) with stirring equipment and drain valve	3,000
1 evaporator for about 20 l., with pump	3,000
3 5 l. flasks (glass) with heating jackets and condenser	1,000
1 centrifuge or 1 suction filter apparatus with pump	8,000
1 rectifying column with solvent recovery	5,000
	60,000
Piping and instrumentation, 50%	30,000
	90,000
Engineering costs, 10%	9,000
	99,000
Construction costs, 10%	10,000
Contingencies, 20%	20,000
	129,000
Laboratory equipment (without spectroscopic equipment)	12,000
	141,000
Buildings, 50%	70,000
Total capital investment	211,000

Chemicals needed for production of about 1 kg pregnenolone:

Acetate	CrO_3 - 1.2 kg
Diosgenin - 3.5 kg	$NaHSO_3$ - 410 g
Acetic anhydride - 10 l.	Benzene 50 l. (70% recovered)
Aluminium chloride - 350 g	Potassium carbonate - 2 kg
Sodium acetate - 850 g	Water and sodium chloride

4. Capital investment for a tableting facility of about 4 million units annual capacity

Weight of tablets produced daily	about 150-200 kg
Weight of progestine	about 0.3 kg per day

		$
(a)	Equipment for granulation	
	1 mixer	20,000
	1 centrifugal filter	4,000
	2 tumble mixers	8,000
	1 fluidized bed dryer	20,000
	Weighing machines	4,000
		56,000
(b)	Equipment for tableting	
	3 rotary pelleting machines, 12 dies capacity: 20,000 tablets per hour - each $10,000	30,000
	If bigger capacities afforded:	
	1 rotary pelleting machine (Fette) for 28 dies, capacity 180,000 tablets per hour	45,000
	28 dies	4,000
		49,000
(c)	Equipment for coating (suspension coating process)	
	4 coating pans - each $6,000	24,000
	Hoods and other equipment	3,000
		27,000
	(4 programmed system coating units - each $30,000	120,000)
(d)	Equipment for packaging	
	Equipment for packaging contraceptives into blister packs and filling into boxes	100,000 - 120,000
	(Normal sealing equipment	24,000)
	(Machine for packaging in glass bottles	12,000)
	(Machine for filling into boxes	35,000)

Space required

Tableting and packaging: 140 sq.m. x 3.5 =	500 cu.m.	60,000
Coating	180 cu.m.	25,000
Packaging	420 cu.m.	50,000
Stores, offices, workshop premises	900 cu.m.	
Control laboratory	100 cu.m.	
	2100 cu.m.	250,000

../.

5. Capital investment for a tableting facility of about 4 million cycles annual capacity (continued)

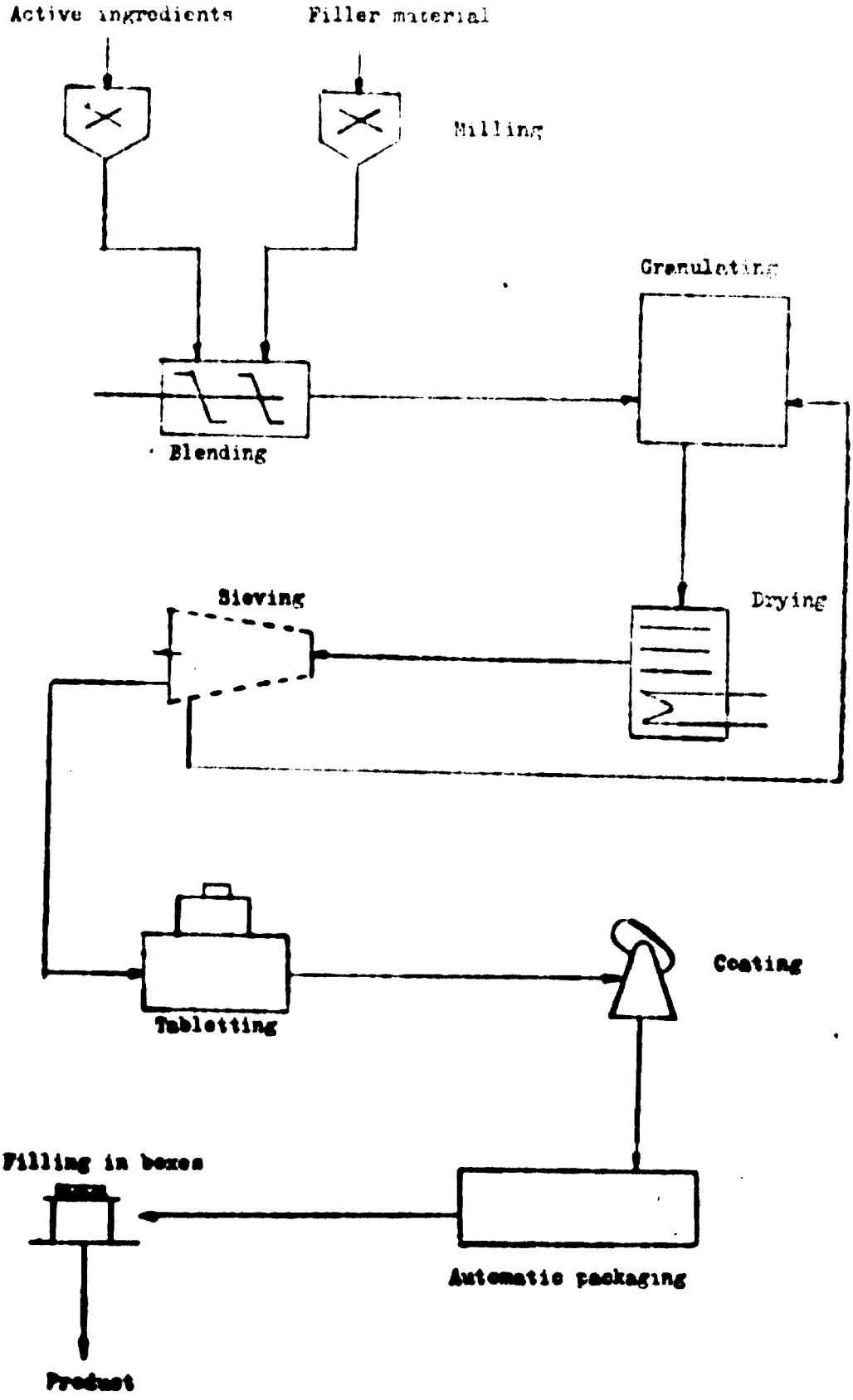
Total capital investment	$
Equipment	56,000
	49,000
	27,000
	100,000
	232,000
Buildings	250,000
	482,000

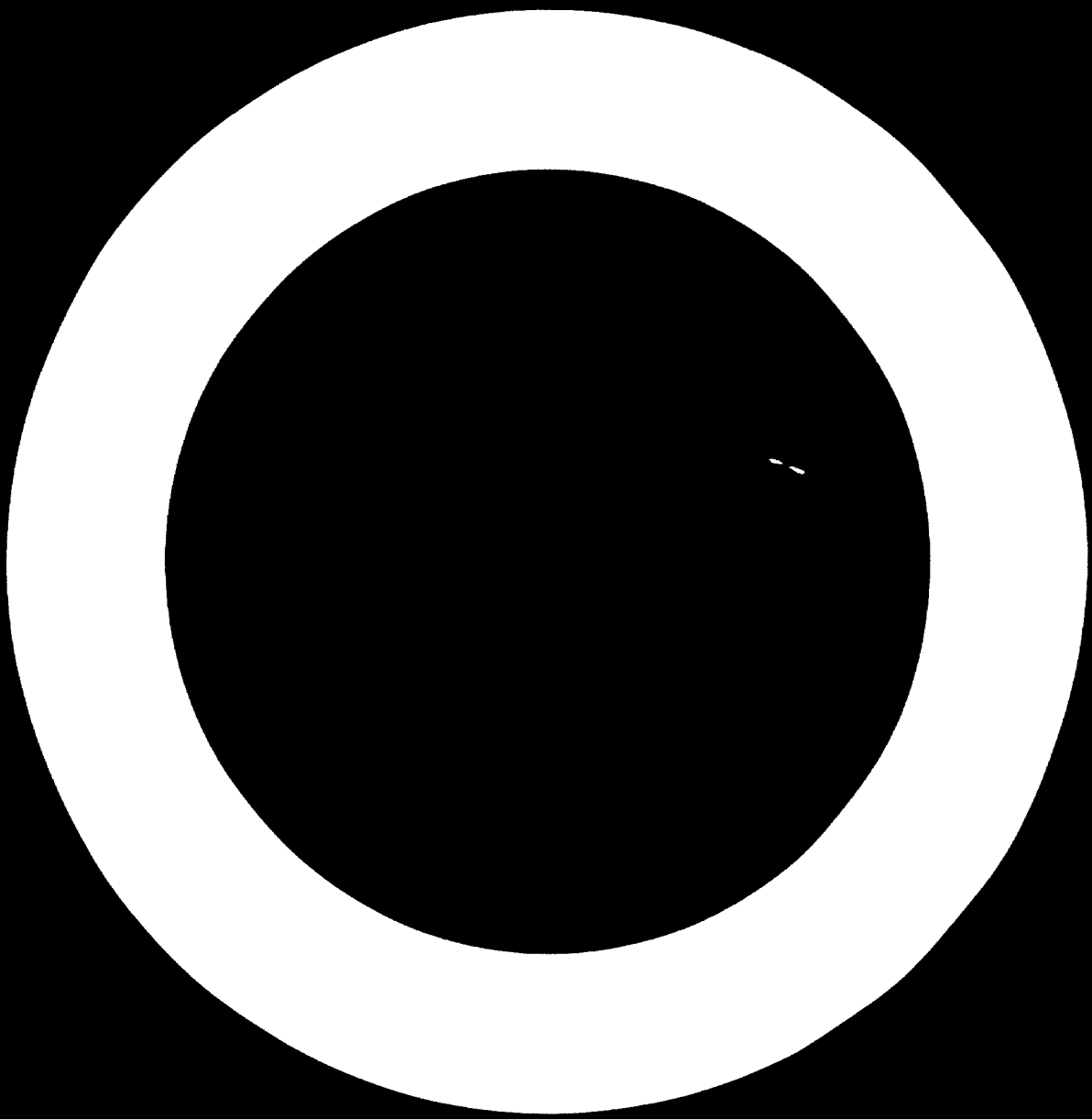
Estimated production costs for 4 million cycles per year:

Raw material	250,000
Packaging material ($2/sq.m.) 20,000 sq.m./year	40,000
Labour - 10 persons each $10,000/year	100,000
Utilities (100,000 - 200,000 kWh, 10,000-20,000 cu.m. water)	10,000
Depreciation, 10%	48,000
Maintenance and repair, 7%	34,000
	482,000

(Production price per cycle about $0.12)

THE TABLET AND ITS ADJUNCTS





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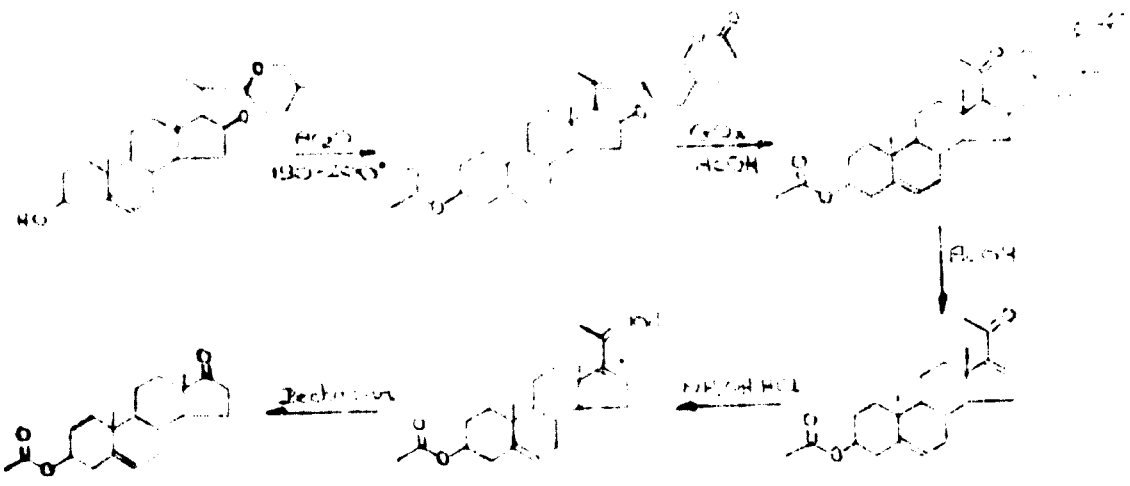
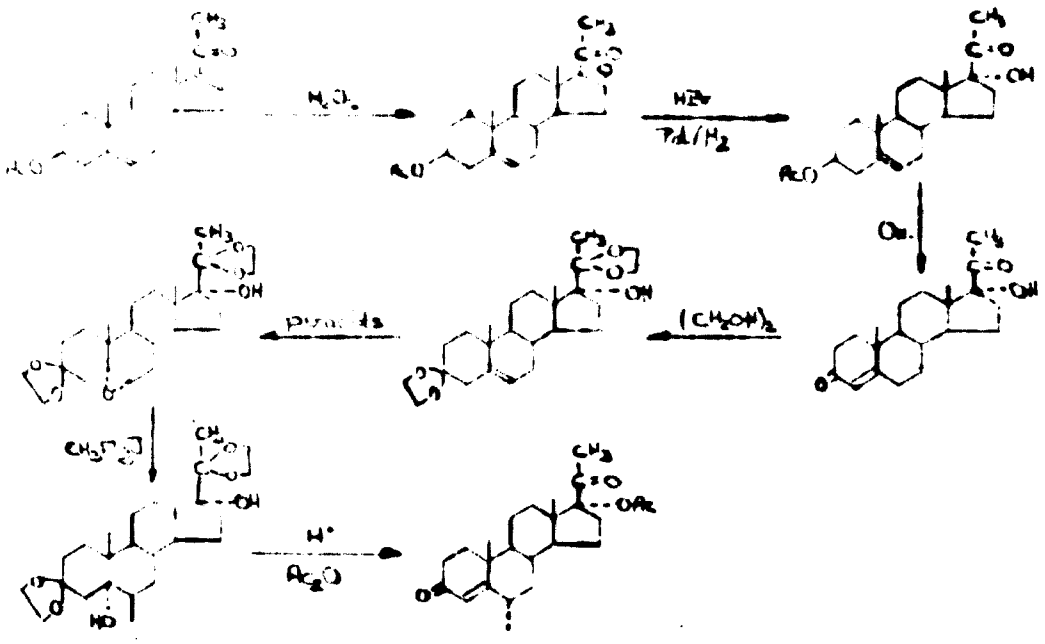


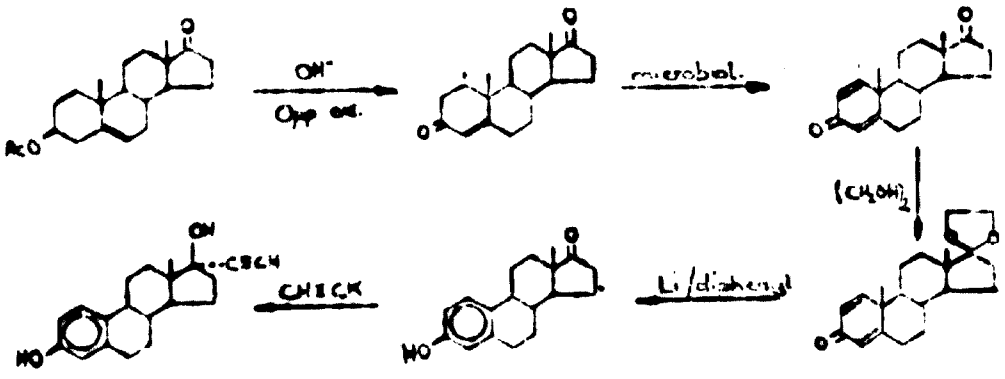
R.E. Marker developed the three steps transformation of diosgenin to 16-dehydro-pregnenolon-acetate which with some more recent improvements is the most common way of transforming diosgenin to an intermediate. Heating diosgenin with acetic anhydride results in ring cleavage and formation of pseudo-diosgenin acetate, which is converted to the 20-keto-16-acylate by chromic acid oxidation. Cooking with acetic anhydride results in 16-dehydro-pregnenoloneacetate which may be hydrogenated to yield the pregnenolone acetate. The first step is improved by catalytic amounts of Lewis acid or pyridine-chlorohydrate. Best results are obtained by cooking with n-octanoic acid and small amounts of acetic anhydride. The yields of oxidation are improved by the use of permanganate/periodate reagent of Lemieux and Rudloff. Converting 16-dehydro-pregnenolon-acetate to oxime is followed by Beckmann rearrangement to get dehydro-epiandrosterone-acetate.

2. Synthesis of hormones from intermediates



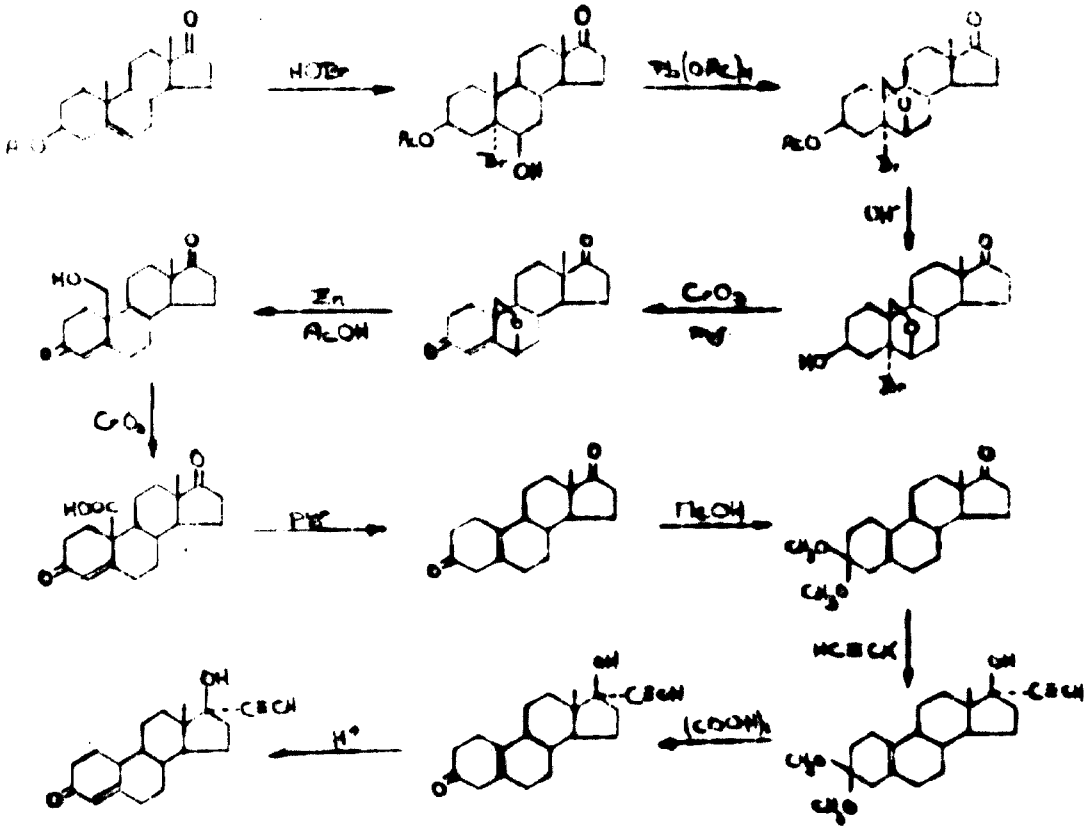
Starting from 16-dehydropregnenolone-acetate the 17α hydroxy-group is introduced by epoxydation, ring cleavage by hydrobromic acid and removal of bromine by catalytic hydrogenation. After introduction of the oxo group at position 3 by Oppenauer oxidation both oxo groups are protected as ethyleneketals. Peracid epoxydation of the rearranged double bond, ringopening by Grignard reagent and dehydratisation lead to medroxyprogesteronacetate. Recently some unadvantageous side effects in use of medroxyprogesterone-acetate have been found.

2.2. 17α - ethinylestradiol



Oppenauer oxidation after saponification of the dehydroepiandrosteroneacetate the 3 keto 4-en group is introduced. Microbiological dehydrogenation leads to androstadienedione. By ketalisation of the keto group at carbon 17 and reaction with diphenyllithium, estrone is obtained which can easily be transformed to 17α - ethinylestradiol by ethynylation.

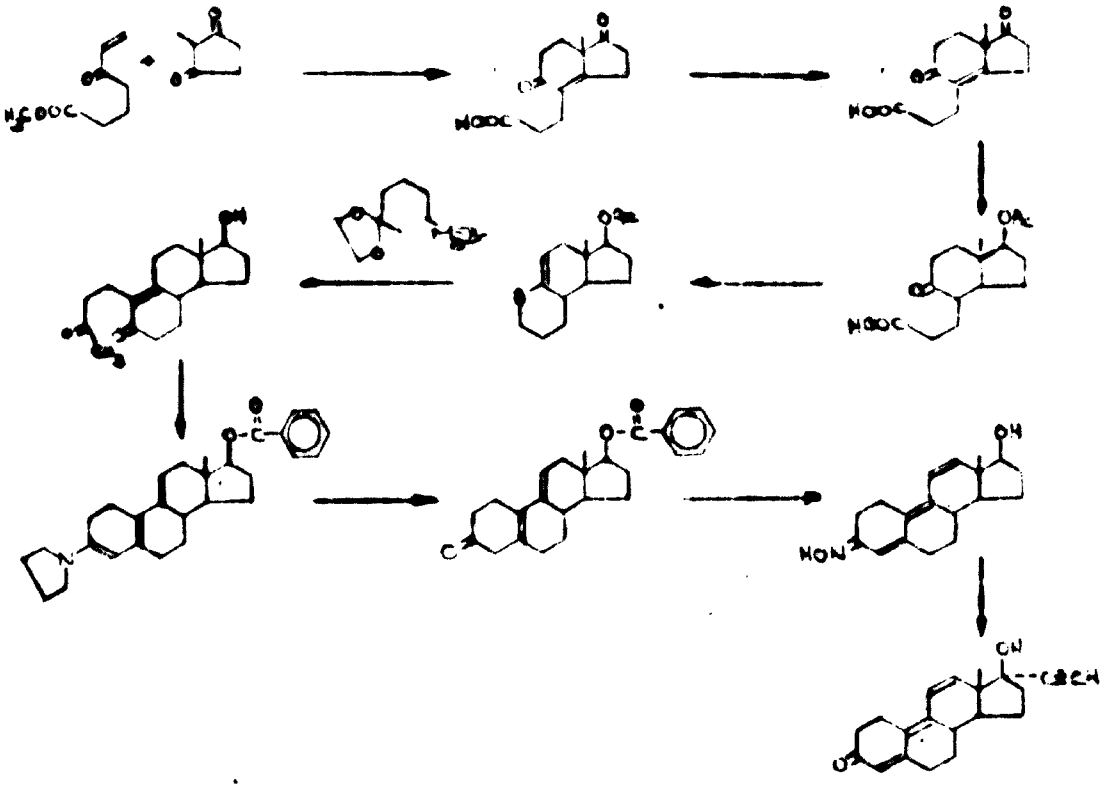
2.3. Norethisterone, Norethinodrel



Wettstein and co-workers have worked out a very successful synthesis which inspite of a rather great number of reaction steps has worked out to be very economical. It is characterized by the oxygen functionalization at the 19 methyl group. Reaction of 17-dehydroepiandrosteroneacetate with hypobromic acid and oxidation with lead tatraacetate yield a cyclic ether, which after saponification and Oppenauer oxidation can be submitted to reductive ring cleavage. The hydroxygroup introduced to 19 methylgroup enables chromic acid oxidation and subsequent decarboxylation to eliminate the 19 methyl group. Protecting the 3 keto in form of dimethylacetal is followed by ethinylation of the 17 keto group. Acidification with organic acids leads to Norethinodrel, whereas acidification with mineral acids leads to Norethisterone.

3. Norsteroids by total synthetic methods

3.1. Norgestrienone

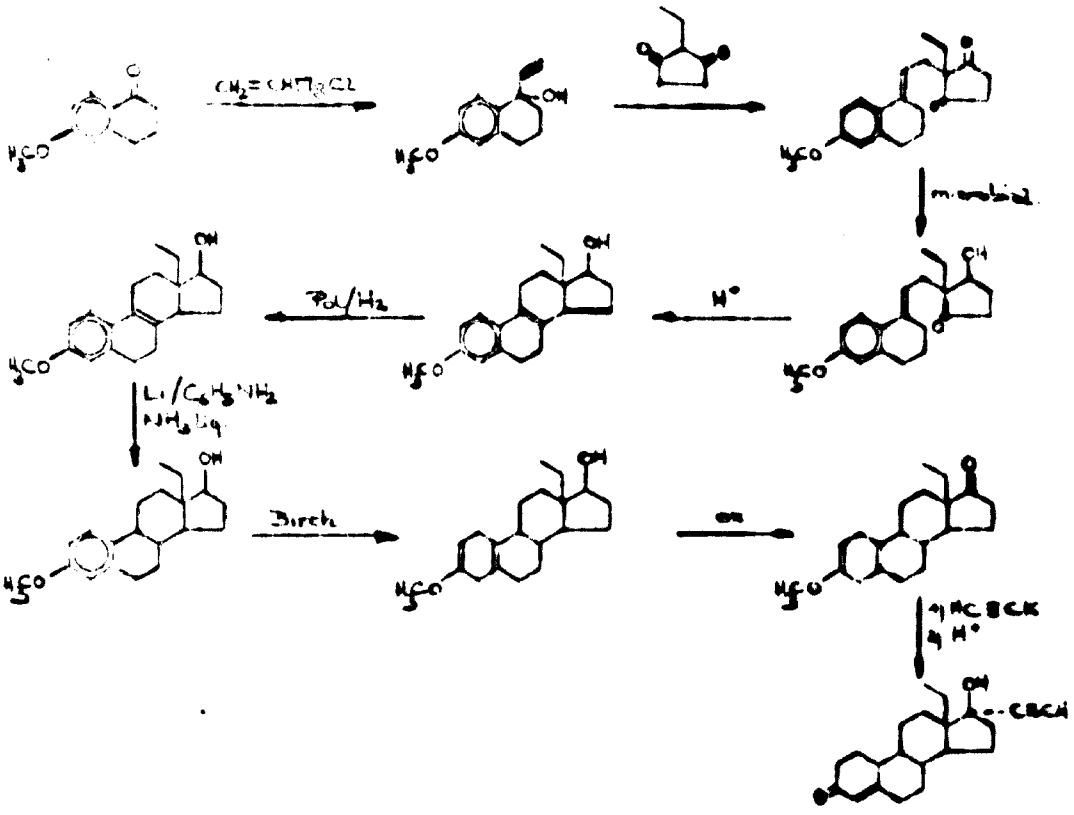


Roussel-Uclaf, France, has developed a very elegant process to synthesize Norgestrienone, which is the active ingredient contained in Planer.

By Micheal addition of 1,3-dioxo-2-methyl-cyclopropane and aldolcondensation the racemic indanederivative is obtained which after separation of the antipodes is reduced with $NaBH_4$ and formulated. Stereospecific catalytic hydrogenation and transformation of the formyloxy group into a acetoygroup leads to a trans-indanederivative which after treatment with acetic anhydride gives a enolic lactone. By reaction with 4,4-Ethylene-dioxy-pentyl-magnesiumbromide and subsequent benzoylation an intermediate is formed which after aldol-condensation and reaction with pyrrolidine yields the tetracyclic eneamine.

The eneamine is split, the benzoylgroup saponified and a further double-bond is introduced by DDC yielding Δ- 10(9), 11(12) - 19 - nortestosterone which is derived into its oxime. The 17 hydoxylgroup is oxidized, the oxogroup treated with ethylmagnesiumbromide the oxime-group is removed and norgestrienone is thus obtained.

3.2. Norgestrel



Another totally synthesized progestin successfully introduced to the market by Schering and Wyeth is the D-13-ethyl-17α-ethinyl 17β - hyaroxy gonen-3-on (Eugynon) which bears in position 13 the more active ethyl group instead of the methyl group.

6 -methoxy-tetralone reacts with vinylmeagnesiumbromide to yield the corresponding vinylalcohol. After reaction with 2-ethyl-cyclopentane 1,3-dione, seco-estrane-dion compound is obtained. By a stereoscopic microbiological reduction"seco-oleone" compound is obtained with the same structure at the carbon 13 and 17 as in the natural occurring steroids.

After treatment with acids the ring C is closed. Saturation of the double bound 14 by Pd/H_2 and of the double bound 8 by Birch reduction yields 13 ethyl-gona -1,3 5 (10) triene 3,17 β ol-3methylether. After Birch reduction in ring A, oxidation of the hydroxy group at 17 position followed by ethinylisation and acidification, norgestrel is obtained.

ORAL CONTRACEPTIVE MANUFACTURERS VISITED DURING THE GLOBAL SURVEY

The basic oral contraceptive production is mostly under the control of a few big pharmaceutical companies, which account for almost the whole of present global production. During the Global Survey most of these companies were contacted and their co-operation sought. Brief information about these companies as obtained by them during the Global Survey follows:

1. Schering

The company dated from 1851 when Ernst Schering opened the "Green Pharmacy" in Berlin; this was followed in the mid 1860' by the building of a factory at Wedding for the manufacture of chemicals. Since that time the company had undergone considerable changes; during the period between the two world wars, Schering AG developed into an international company.

Today the company consists of four divisions, which employ world wide about 19,000 people. About 10,000 are employed by Schering AG in Germany - approx. 6,500 are employed in Berlin and 3,500 at Braunsweig and 9,000 by affiliates. The turnover in 1974 for Schering was DM 1 billion, and for the group DM 1.75 billion.

The four divisions of Schering AG are:

1. Pharmaceutical Division - located in Berlin; it accounts for about 60 % of turnover.
2. Plant Protection Division - located in Braunsweig; it accounts for about 20 % of turnover.
3. Industrial Chemicals Division - located in Bergkammer; it accounts for about 10 % of turnover.
4. Electroplating Division - located in Nienburg; it accounts for 10 % of turnover.

[illegible] exports about 65 % of its total production; the Pharmaceutical [illegible]ion exports about 60 % of its production.

The company occupies about 700,000 sq. meters in Berlin; the Bergkammen [illegible] of approximately 2 x 10^6 sq. meters. During the [illegible] 1974 - 1978, DM 500 x 10^6 are to be invested in the Berlin facilities in order to enlarge and revamp the production, administration [illegible] departments.

The Pharmaceutical Division produces 7,000 different packages for marketing in about 130 different countries. This large number of packages is necessitated by differences in languages, presentations, [illegible] and regulations in the different countries.

The company has 350 cu meters of reaction vessels for pharmaceutical synthesis; half of these are located in Berlin and the other half in Bergkammen. A policy decision had resulted in the location of the synthetic work at Bergkammen; the reaction vessels in Berlin are used only for the final stages of recrystallization and purification of hormones and some other materials. This decision had resulted from a consideration of a host of ecological factors which made Bergkammen a more suitable site for large scale chemical synthesis.

The Berlin facilities are divided into three areas according to the operations performed in each location. Thus, normal, clean and sterile areas have been assigned to each part of the plant, and strict precautionary measures are taken to ensure that the appropriate procedures required for each area are adhered to.

We were then informed that about 40 % of the present oral contraceptive production arises from total synthesis.

Countries in which Schering manufactures oral contraceptives

a) Synthesis

Schering synthesizes oral contraceptives only in Germany

b) Tabletting and packaging

Schering has companies in 20 countries with tablet and package oral contraceptives. In addition, it has licensing agreements with companies in 5 other countries (see later).

Production of OC Preparations

OC preparations are manufactured in the following manufacturing plants:

1) Affiliated companies

Argentine
Austria
Brazil
Chile
Colombia
• Ecuador
France

•. Production will be started in late 1975

India
Indonesia
Iran
Italy
Korea
Mexico
Peru
Portugal
Spain
Taiwan
Thailand
Turkey
Uruguay

2) Licensees

Egypt
Finland
Morocco
Pakistan
Yugoslavia

3) Subcontract manufacturers

South Africa
Venezuela

The company had plans to expand its facilities for oral contraceptive production at its plants in India and Indonesia, and two plants are mooted for Ecuador and Venezuela.

No major expansion plans exist at present for production of contraceptives in least developed countries, however, the company has not encountered any special problems which could not be solved when setting up production facilities in LDC's.

2. Organon and Diosynth

Organon and Diosynth were two separate units of a holding company Akzo Pharma, which in turn was part of Akzo Holdings. Akzo [illegible] and a turnover of f 9 billion in 1974, and Akzo Pharma a turnover of f 5-600 million. Organon and Diosynth had been part of the same company until 1971, when Akzo had decided to separate the two units into separate and autonomous companies. Organon had been charged with responsibility for marketing, packaging and research on drugs, and Diosynth with the synthesis of bulk drugs which were sold to Organon and other companies.

For ease of marketing, Organon has divided its activities into 4 regions, namely:

1. Europe
2. North and South America
3. Middle East and the Indian sub-continent
4. Rest of world.

a) Partial synthesis - Holland

b) Tabletting and/or packaging in 30 countries all over the world, 19 Organon factories, marketing in 90 countries

Organon does not trade to any siginifacnt extent with China, although the company does have "know how" agreements with that country. Purchases of diosgenin have been made from China.

Organon is represented world wide in more than 90 countries. It has:

30 Organon National Companies

19 Manufacturing facilities including Argentina, Brazil, Columbia, Indonesia, India, Iran, Mexico, Pakistan, Philippines and Turkey.

4 Organon Research Centres located in the Netherlands, United Kingdom, France and the U.S.A.

Two thousand five hundred workers are employed at the Oss complex.

Organon always expands in least developed countries wherever feasible and successful;

3. Russel-Uclaf

Russel-Uclaf, France, the company which has started total synthesis in oral contraceptive production gave the following information about its activity in developing countries:

" Our company produces contraceptives in our affiliates in South American, Asiatic and African countries. We will increase production in least developed countries if demand increases;

a) synthesis in France;

b) tablet and/or package contraceptives in 20 countries;

c) no condoms

Production in Least Developed Countries

Brasil	Mexico	Argentina
Peru	Uruguay	Venezuela
Antilles	Guatemala	Morocco
Ivory Coast	Vietnam	India
Thailand		

At present, we have no major expansion plans for contraceptive production in least developed countries;"

4. Syntex

Syntex is deeply involved in the production of diosgenin. It has a Mexican and an United States branch and gave the following information:

" Our extraction and intermediate plants are in Mexico and our final transformation refinement, and control plants are in USA.

We produce OCs in Mexico and some Lation American countries. We sell and are ready to sell steroids for OCs production to any country that wants to produce them locally;

We have no present major expansion plans for local production in LDCs. We have existing OCs facilities in:

Spain	Mexico
Vietnam	Puerto Rico

apart from this in Europe and USA and importers in other countries."

5. Glaxo

Primary production of oral contraceptives is only carried out in the U.K., and this is performed under licence from Mead Johnson.

Overseas facilities will be provided at a later date.

Glaxo would only use existing spare capacity in LDC's to meet increased demands. It has no plans to make capital investment in these areas.

6. American Manufacturers

There are 5 big manufacturers of oral contraceptives in the United States: Wyeth, Searle, Ortho, Upjohn.

Three of the companies (Wyeth, Ortho and Upjohn) had indicated that they did not wish to receive visits from UNIDO staff connected with ICOSP, as they did not envisage any raw material problems.

Approach of the oral contraceptive manufacturers towards the setting up of contraceptive manufacture in LDCs

The results of interviews with European and U.S. manufacturers gave the following impression: production facilities in more than 24 countries exist; some of these are in the developed countries. Economic and/or politics normally determines the establishment of particular production facilites in LDC's.

It is a matter of fact that very often the reason for setting up is a government regulation either forcing the company to produce locally or protecting locally manufactured pharmaceuticals.

As far as the major drug manufacturers are concerned, the main criterion they use to make a decision on whether or not they should establish a production unit in LDC's is: " will it make money". Very little interest has been shown in third party ventures.

List of equipment for a 500,000 gross per year production line

(2 dipping machines each about 20,000 gross/month capacity)

1. Compounding

1 Centrifugal Separator
3 Vertical Cylindrical Mixers
1 Ball Mill Device
3 Latex Pumps
1 De-ionizing Device
Several Containers
1 Air Compressor
Several Tanks (latex receiver, scaling, ageing, service, charge)
1 Ammonia Preparation Unit
Miscellaneous Items (weighing balance, measuring cylinders, etc.)

2. Moulding

2 Mould Conveying Chains with Sprockets
6000 Glass Moulds
6000 Mould Holders
4 Motors
4 Reduction Gears
2 Drying Units
4 Edge Rolling Machines
2 Dipping Tanks, Hot Water Tanks, Anti-sticker Tanks, Stripping Nozzles
4 Conveying Chutes
4 Square Tanks
4 Dehydraters
Mould Washing Tanks and Washing Brushes as required
2 Chilled Water Tanks
Stripping, Slurry Hot Water Tanks, Slurry Pumps, Blowers, Heaters, etc. as required

3. Vulcanising

6 Vulcanising Machines
2 Quenching Machines
1 Cyclone Unit

4. Testing

1 Automatic Pinhole Tester (100 gross/hour)

5. Packaging

3 Automatic Strip Packaging Machines

6. Laboratory Equipment

1 Radiation Moisture Balance
1 Mechanical Stability Tester
1 pH-meter
2 Viscosimeters
2 Tensile Testers
1 Dumb Bell cutting machine
1 Rubber Ageing Oven
1 Drying Oven
2 Thickness Gauges

7. Utilities (steam boiler, soft water tank, water softening unit, water tanks and pumps, chiller device, working and electrical equipment, etc.

8. Piping Valves and Fittings, instruments and controls

9. Furnitures, Fixtures and Premises

Estimation of initial capital investment and tentative cost of production on the basis of 300.000 gross condoms per year (2 dipping lines)

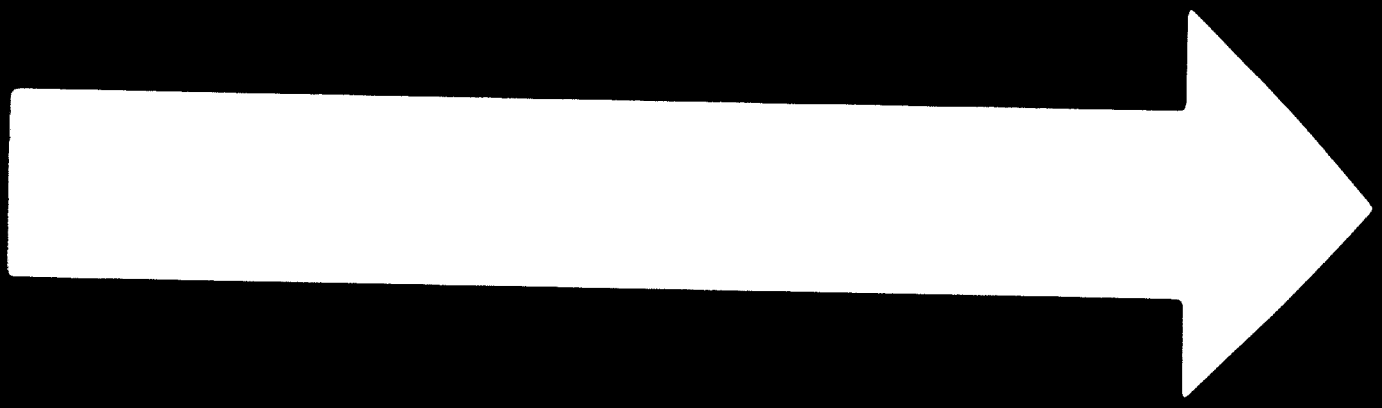
Capital Investment

Installed equipment cost (equipment, installation, piping and instrumentation) - the cost of this item can come up to more than 1,000,000 US $ depending on type of equipment.	US $	650,000.-
Laboratory equipment		20,000.-
Know-how fee		150,000.-
Building and site development (including administrative building, factory, workshop, staff quarters, welfare centre)		500,000.-
Auxiliaries (water supply, electricity supply)		150,000.-
		1,470,000.-
Contingencies - 10%		147,000.-
	US $	1,617,000.-

Annual Cost of Production

Latex and chemicals		140,000.-
Packaging material		160.000.-
Salaries (100 workers at US$ 4,000 per year)		400.000.-
Royalties (US$ 0.05 per gross)		25,000.-
Utilities		50,000.-
Depreciation (10%)		161,700.-
Maintenance and Repair (7%)		96,500.-
	US$	1,033,200.-

Equivalent to a Production price per packed gross of approximately US$ 2,07.-



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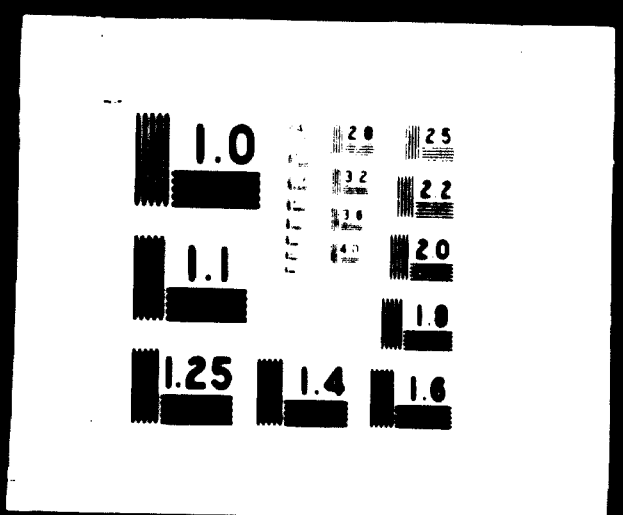
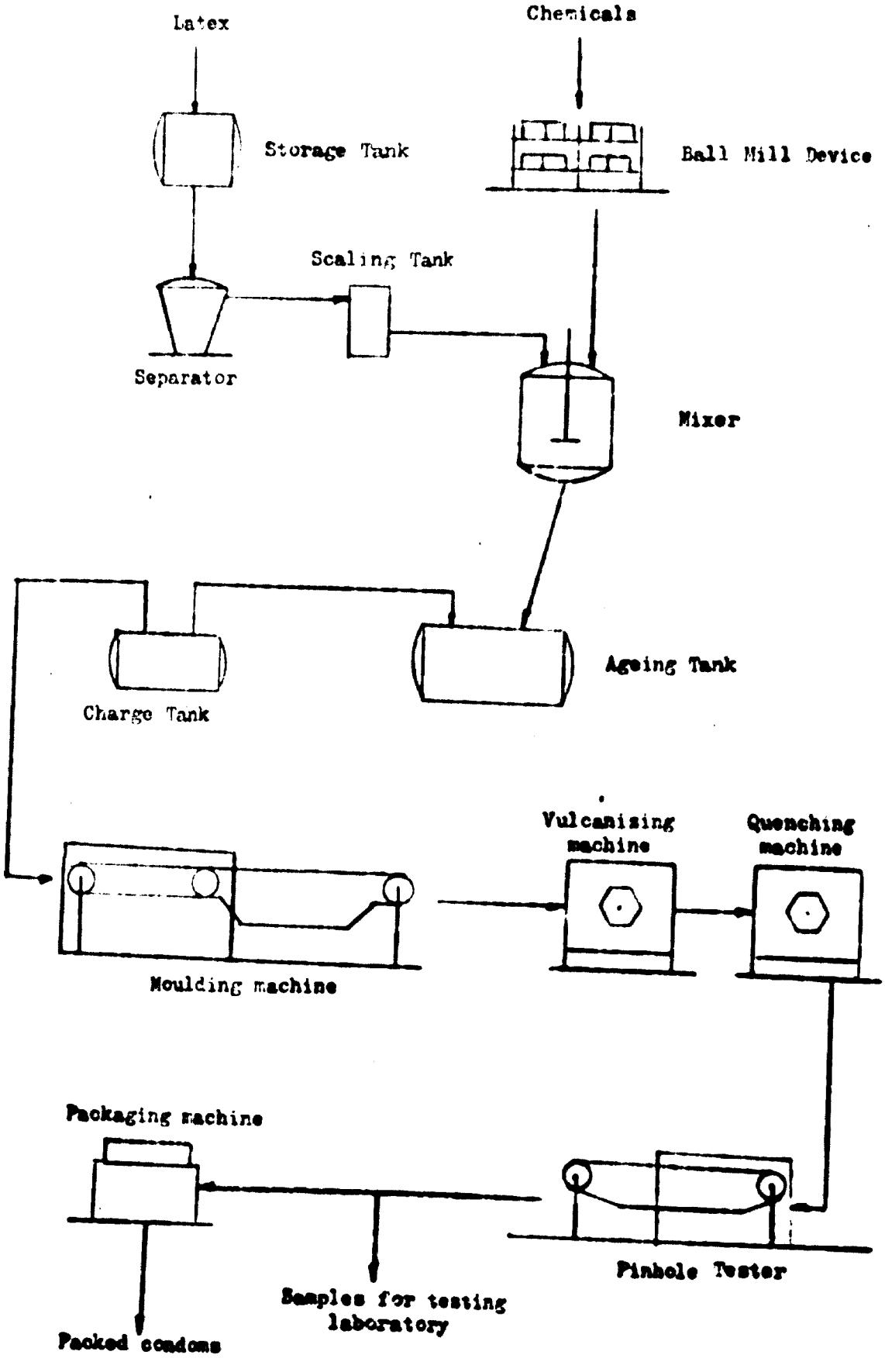


LATEX DIPPING PROCESS



1. Developed Country condom producers visited during the Survey

1.1. London Rubber Industries

The company was established in 1915 as a distributor of condoms mainly manufactured in Germany. Condom manufacture was commenced at Hackney in 1932 - the plant was later moved to Chingford. By 1939 it had become the leading U.K. supplier - over half was still met by imports. When the war commenced, imports from Germany stopped and the Government encouraged the expansion of condom manufacture in the U.K. The monopoly position produced at that stage, encouraged by Government, has persisted until today.

Production facilities are located in the U.K., India and the U.S.A. Production facilities in the three countries are:

U.K. 4.2×10^6 gross (mid 1975)
India 1.5×10^6 gross
U.S.A. 0.9×10^6 gross.

LRI packages condoms in Holland, Spain, Italy, South Africa and certain other countries.

a) LRI is not a major supplier to the public sector; the U.K. factory supplies about 100,000 gross at present. A new machine, capacity about 0.75×10^6 gross, is being installed at present, and when this is operational in mid 1975, LRI would be able to make available 1×10^6 gross of condoms (e.g. a ten fold increase on existing supplies) to the public sector.

The reason given for the installation of the new machine is the need to meet the more stringent standards operating at present (SIDA; FDA). The latex produced by the quicker growing rubber trees differs from that available from the older varieties, and this has made manufacture more difficult. The new machine is capable of overcoming these difficulties in forming good quality condoms.

Increased condom production to meet public sector demands would require the installation of new testing and packaging facilities. This would involve a considerable investment in ancilliary equipment and the employment of additional staff. LRI would be unwilling to make these investments without guaranteed contracts which would help to justify the capital expenditure. It may also be necessary to locate the new facilities at another site.

b) It is company policy at present to use only spare capacity for public sector work. A detailed cost-benefit analysis would have to be carried out by LRI if it were to change this policy. Three to five year contracts would be required, and the price obtained for condoms would be looked at critically.

c) Increased production facilities for packaging condoms would be required as mentioned in 1 (a) above.

d) As the company makes its own machinery, it would estimate a lead time of 6 months to 1 year for condom supplies up to 1×10^6 gross. For additional requirements, firm guarantees for multiples of 0.75×10^6 gross and 3-5 year contracts would be required. Lead time one year plus.

e) Financial considerations alone determine LRI's response to public sector tenders. At the present time the companies private sector growth is about 2 % per annum. This arises essentially from exports; the U.K. market for condoms has contracted slightly during the past eighteen months.

f) Lowering of standards of quality of packaging material are the only ways in which unit cost could be reduced.

g) Longer term contracts, preferably of 3 to 5 years duration, with inbuilt escalator clauses to allow for inflationary pressures could ensure more effective supplies to the public sector.

h) At the present time evidence suggests that only large machines which are continuously operated are capable of producing condoms of acceptable standard. However, it should be possible to produce smaller machines - minimum capacity 200 - 250,000 gross/annum - but nobody has succeeded so far to produce a satisfactory model.

i) LRI would be unwilling to accept payment for condoms in currencies of LDC's.

1.?. Sagami Rubber Industries Co Ltd., Japan

The following facts and opinions were given about condom production by Sagami-Japan:

a) Sagami has started condom production 45 years ago from imported latex and has done a lot of development in condom production from latex particularly in thickness, colour and shape;

b) Sagami is a private company which supplies the public as well as the commerical sector. It could easily extend its production facilities; big term contracts should, however, be given by purchasing agencies to ensure proper use of the increased capacity. At present, SIDA buys at a half year one year basis, sometimes contracts are suddenly stopped. This causes many problems for the manufacturers;

c) At present there is a cost inflation, especially concerning labour cost in Japan which will influence prices. Testing and packaging needing most labour will probably be transferred from the Tokyo region to parts of the country where labour is cheaper;

d) The introduction of sophisticated testing methods has resulted in the Japanese condoms being among the world top qualities. In 1965 SIDA had collected samples and prices to buy from Japanese producers. Since the Swedish standard was different from the Japanese standard, new testing methods were introduced by the Natural Material Testing Institute. After that 10 million condoms from Japan have been bought by the Swedish Government. Testing equipment consists of a fully automatic electronic testing system (wet system/where each condom is tested and a special testing laboratory with tests for elongation, tension strength, thickness, conductivity, water leakage, air inflation (25 litres) appearance and aging. One out of every 300 condoms is used during these testing methods.

e) The production process is highly automated. Latex and mixed chemicals are brought together in a vulcanization tank. The latex dipping is performed on highly automated machinery of 20,000 gross/month capacity. A conveyor, 400 ft long, carries a continuous cahin of glass moulds which rotates through the tank containing the specially compounded latex suspension. The forms are dried by hot air, dipped a second time and dried once again. They are then "cured" by a high temperature, carefully washed with hot water and thoroughly dried and dusted with talcum powder.

The finished condoms are rolled off the glass forms in the automation process, and the bare glass moulds are cleansed ready to repeat the entire cycle. The know-how of the whole process is Sagami owned and the specialized equipment is also manufactured by Sagami.

2. Condom Manufacturers in developing countries

2.1. Condom production in Thailand

Royal Tahi Industries, a private company, is the only local producer of condoms in Thailand. It holds about 20 % of the local market, 80 % being imported with Durex as leading brand.

In 1969, the plant was bought from Germany. It is semi-automatic and suited for all types of dipping goods, such as rubber nipples, toys and condoms.

The market share of Royal Industries in condoms has increased 30 % / year since 1972, all of the condoms being sold commercially. Condoms have not been sold to any agency, because capacity is too small and the prices are too high.

In the first three years, the company lost about US $ 200,000 because of deficient know-how. The problem was solved in 1972 when know-how was obtained from BAYER, Germany. Royal Industries has to pay 3 % royalties for that.

At present, capacity is too small to compete with Japanese condom manufacturers who at present produce more cheaply, by Royal Industries is working on a project of a plant for condoms which will be ready latest April 1976. Mr. V. Philaphongphanich intends to make use of loops from an old factory in Germany and to do the plant construction by himself. For that reason, the construction of this new 40,000 gross/month plant will cost only US $ 400,000 - 500,000. The present semi-automatic plant with 10,000 gross monthly capacity will be used for production of other goods only.

The success of KINGTEX is due to the modern advertising methods in newspapers and television. Royal Industries has done a lot of marketing for the regional market, and intends to concentrate mainly ofn the Thai market and that of the neighbouring countries. 70 % of production cost is packaging cost, "the more expensive a condom is, the better it is sold".

The main problems are that local production has no protection, and authorities do not buy locally, because they receive the condoms free of charge as donations. Royal Industries mentioned that once a tender came from UNICEF, but the quantity of this tender was too high (about three years capacity of Royal Industries Ltd)

2.2. Condom Production in India

2.2.1. Condom production of Hindustan Latex, Trivendrum

a) Installed capacity is 144 million pieces per annum in two production lines of 72 million pieces each;
b) Actual production is currently about 100 million pieces;
c) Doubling of capacity will be carried out through subcontracts to private parties and is expected to be completed and commissioned by June 1976 giving an annual capacity of 228 million (4 units);
d) Equipment for doubling capacity will be made in India;
e) Since the present plant is not the last word in condom production, it is hoped to set up the new plant using to the most recent development;
f) Packaging is at present in aluminium foil; it has been decided to use cheaper packaging, paper and poly. The shelflife of the new packaging will be about 3 years;
g) Chemicals and packaging materials are mostly Indian, only 1 % of the chemicals being imported;
h) Cost of production, including packaging are 20 Rp/gross. Selling price is about US $ 3.00 ex factory. (Note: 1 US $ 12.75 Rupees).
i) In a global UNICEF tender the quotation of Hindustan Latex was the lowest, but the contract was not given to Hindustan Latex;
j) Hindustan Latex is a Government-owned factory and therefore has to take care of social problems. Employment must be rewarded, only full time workers are employed. This makes the cost of production slightly higher from that of London Rubber;
k) Investigations have been carried out to establish a female protector contraceptive like C-film;
l) Hindustan Latex is capable of producing lubricated and coloured condoms.

2.2.2. Condom production of London Rubber, Madras

a) London Rubber, Madras, is a completely private enterprise;

b) London Rubber has recently doubled its installed capacity from 75 million pieces to 150 million pieces annually;

c) Government purchases condoms also from London Rubber Madras. London Rubber wishes to make over 10 million pieces directly under the brand name "Dyanak".

2.2.3. Future Government projects in condom production

a) It is projected to set up a 72 million per annum unit at Farakka in West Bengal. The site is ideally suited for the set up of a condom factory. It is on the banks of a river, an electric power line passes the site and housing is available. The building design is being prepared to take up expansion when the need arises;

b) In future, condom factories will be set up also on other places to expand capacity if necessary. A study was carried out whether all factories should be at the source of latex in South India or dispersed all over the country. The decision was made to disperse the factories since cost of transport of condoms is slightly more than that of latex and distribution is facilitated by regional facilities.

2.3. Condom Production in Malaysia

2.3.1. Sagami Industries (Malaysia) Sdn. Berhad

The factory is very modern and clean and well equipped with Japanese machinery. There are two automatic dipping lines, each capable of 1,000 gross per day with double dipping, and automatic stripping. Electronic testing is done as in Japan. There is only one packaging machine; most of the condoms seem to be sold in bulk. The testing laboratory is carefully equipped and testing is done in a very ambitious way. The factory is currently working on a 3 shift basis.

More information about this company can be found in the chapter of local production of condoms.

2.3.2. Life Industries Sdn. Bhd.

The company is a small private Malaysian enterprise

1. The factory started production in 1959.
2. The capacity of the only line is 300 gross/day in three shifts with an annual installed capacity of about 100.000 gross. At present only one third of the capacity is used.
3. The capital investment 6 years ago was M.$ 250.000 for equipment for production and testing, and M.$ 25.000 for equipment for packaging.
4. About 25 workers (mainly women) are employed. Most of them are working in product testing.
5. The salary of a normal worker is M.$ 0.60 per hour.
6. Life Industries is selling its own brand. At present the company is selling only on the local market but would like to export.
7. Following are the finished product costs (confidential)
   Manufacturers price M.$ 12.75/1 gross in aluminium foil with lubrification

   Agent's price M.$ 15.00
   Selling price M.$ 28 - 33

8. Prices are about 50 % with packaging in 1 polybag each condom. If packed 1 gross in each polytag, the price would be much lower in case of bigger orders - agent's price could be as low as M.$ 5.-
9. In packaging the major problem is the recent heavy price increase of 4-5 times for aluminium packaging material.

Life Industries face many problems because advertising for condoms is not permitted and it is therefore very difficult to introduce a new product on the market.

Life Industries would appreciate making contracts with other countries, especially LDCs.

The company's main problems concern marketing: There appears to be a considerable amount of smuggling of condoms in the country, and the company's production has not been accepted by NFPB, which distributes imported condoms.

There is one [illegible] line, [illegible] equipment [illegible], and one [illegible] for [illegible] testing. Both are not the latest models, but seem to work quite satisfactorily. Dipping is done twice, stripping is done by hand connected with a [illegible] ray inspection. After electronical testing, the condoms are powdered by hand and then each condom is blown up and inspected again. There is also equipment for a lot of other tests (blowing up, water, leakage, aging, water filling etc.). Life Industries assured the writer that testing is done carefully to meet BSI Standards. For packaging there is a small German machine that was not working at the time of the visit.

2.4. Project of Condom Production in Indonesia

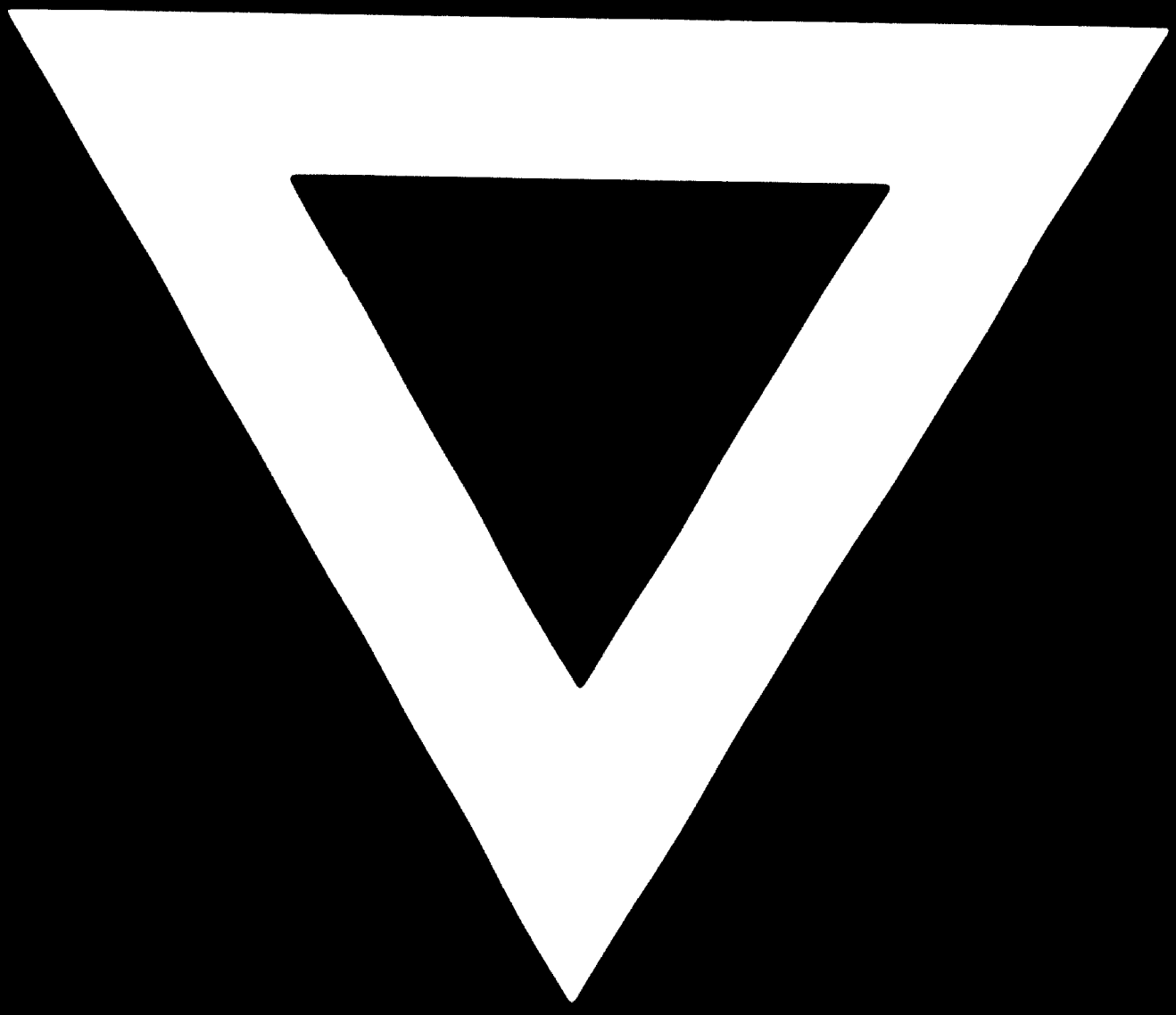
a) Before the Family Planning Programme started, there was a balloon producer in Central Java, who has started condom production. The products of this company are, however, not qualified for the use in Family Planning. It is still producing several types and sizes of condoms but cannot be recommended.

b) During the first Development Plan condoms have become more and more important, so that consideration was given to setting up a condom factory in Indonesia which would meet the requirements of Family Planning.

c) In 1973 an agreement on a joint venture was signed with the London Rubber Company for condom production in Indonesia and it is hoped that this factory will go into operatior by the end of 1975.

It is planned to setting up the operation in two stages. During the first stage of 1 1/2 to 2 years, condoms will be imported by London Rubber Company and only testing and packaging will be done in Indonesia, during the second stage complete production in Indonesia is planned, with the target being 350.000 gross/year in 1978/79. The project is in its administrative process. The Indonesian Government will be a 51 % shareholder and provide land, buildings and money. London Rubber Company will have a share of 49 % and will provide the machines and know-how.

d) The main problem in Indonesia is that the Government will be the major purchase of condoms and that the buying capacity of people is low. The future of condom consumption, however, is very promising due to the success of the BKKBN's activtities and it will be easy to double production.



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