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08636

RESTRICTED

DP/ID/SER.A/172
4 July 1978
English

INVESTIGATION OF PRODUCTION OF CONTRACEPTIVES

SI/CUB/75/808

CUBA

Technical report: Equipment maintenance in the pharmaceutical industry, and oral contraceptive production

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

Based on the work of Sudhir M. Dixit and Iain M. Maclean

United Nations Industrial Development Organization

id.78-4315

Explanatory notes

References to dollars ($) are to United States dollars, unless otherwise stated.

The monetary unit in Cuba is the peso. During the period covered by the report, the value of the peso in relation to the United States dollar was $US 1 = peso 0.75.

A slash between dates (e.g. 1970/71) indicates a financial year.

ABSTRACT

Two experts were sent on mission to Cuba as part of the project "Investigation on the Production of Contraceptives" (SI/CUB/75/808)[1] of which the United Nations Industrial Development Organization (UNIDO) was the executing agency.

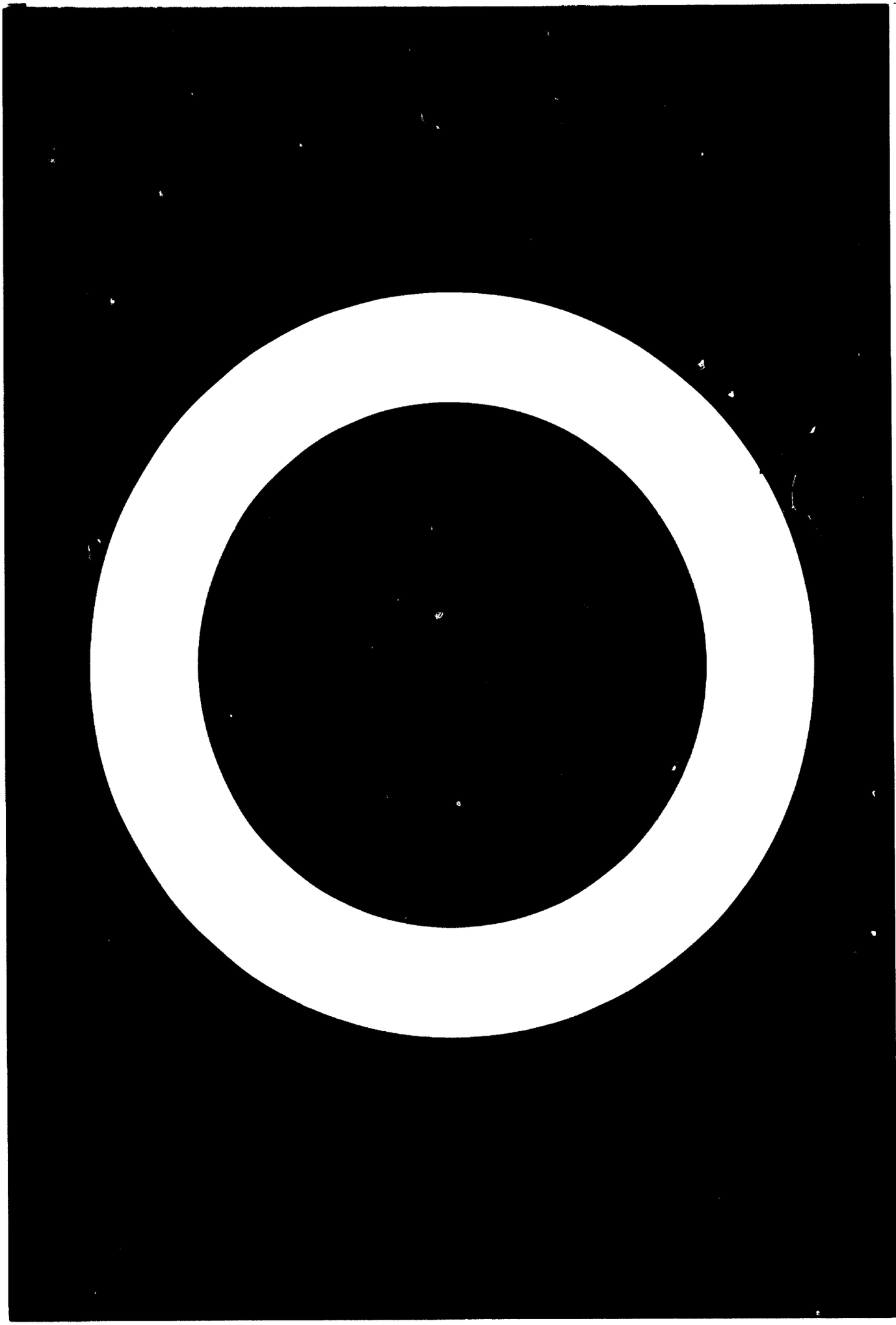
The duties of the experts were to study, and advise on, the pharmaceutical industry, in general, and oral contraceptives, in particular. The entire system of operation in the contraceptives industry was studied, from drug registration to final distribution, with particular reference to oral contraceptives. Engineering was studied in relation to its effect on product quantity, quality, environmental contamination, and health hazards.

There are too many products. Outdated prescribing habits exclude the wider use of new and more efficient formulations and therefore require unnecessary production which is a drain on convertible currency.

There is much scope for improvement in manufacturing conditions in general and hygiene standards in particular. Recommendations have been made for better layouts with air conditioning to reduce the risk of contamination and for the concentration of production.

Some modification to formulae and packing as well as tighter control of quality of the three oral contraceptive tablets would be advantageous. The provision of raw material for oral contraceptives is dependent on the cultivation of Dioscorea and subsequent pilot plant production of diosgenin. This could take up to six years. Methods of production were discussed and a method of degradation of side chains of diosgenin was supplied; subsequent steps were also discussed and modifications were suggested. In the case of mecogenin appropriate published methods have been supplied to achieve synthesis of corticosteroid intermediates.

1/ On 1 January 1977, the project number was changed from IS/CUB/75/008 to SI/CUB/75/808.



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INTRODUCTION

In 1975, UNIDO conducted a global survey on contraceptives, which included the supply of raw materials and local production. This survey involved visits to developed and developing countries to collect accurate data for the preparation of the report. During the visit to Cuba the development of useful sources of steroid drug precursors that can be obtained from Cuban plants was discussed and a draft document on the establishment of a pilot plant for the production of these precursors was finalized.

The project "Investigation on the Production of Contraceptives" (SI/CUB/75/808)[1/] was requested by the Government of Cuba in April 1975 and approved by the United Nations Development Programme (UNDP) in July 1975. The Ministry of Public Health was designated as the government co-operating agency and the United Nations Industrial Development Organization (UNIDO) as the executing agency. The purpose of the project was to investigate the possibilities of expanding the production of contraceptives from locally available raw materials and of establishing the production of intrauterine devices.

Two experts - one an adviser on oral contraceptive production and the other an adviser in maintenance of equipment for the pharmaceutical industry - were sent to Cuba on this project on 29 January 1978 for one month (annexes I and II). They studied, and advised on, the following aspects of the pharmaceutical industry, in general, and oral contraceptives, in particular:

(a) The development of this industry in the post revolutionary period, and its importance and recognition for the economy of the country;

(b) The machinery and maintenance systems of the industry;

(c) The system of operation: registration of drugs, development of drug formulation, quality control, production, costing and distribution of drugs;

(d) The introduction of oral contraceptives;

(e) Raw materials for oral contraceptives;

(f) Intrauterine contraceptive devices.

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I. FINDINGS ON THE PHARMACEUTICAL INDUSTRY

Development

A report[1/] made for WHO provides information on production units and distribution of drugs before and after the Cuban Revolution.

> "Another significant aspect of the transition to socialism in the health services is seen in the pharmaceutical industry. Before the Revolution, of course, drug production and distribution were entirely in private hands. In 1958 there were about 500 drug companies in Cuba, but the great majority were only distributors of imported products. The basic plan of the Ministry of Public Health (MINSAP) was to nationalize and rationalize the drug industry for both production and distribution of pharmaceutical products, but this was carried out in stages. Initially, when conflicts developed between labor and management in the pharmaceutical manufacturing company, the Ministry of Labor intervened. Some of these companies were taken over by the Ministry of Labor, and then transferred to the Ministry of Industries. In 1959 and 1960 some Cuban owners of drug companies left the country, as did many of the foreign owners; these companies were taken over directly by the Ministry of Industries. Then in March 1961, this Ministry carried out a general plan for governmental drug production. Of the original 500 drug companies, a study by the Association of Cuban Laboratories in 1959 had shown only 110 met minimal standards, and only 72 of these accepted control criteria. The rest sold unethical or poor-quality products. Of these 72, the Ministry of Industries selected 14 which were considered reasonably efficient, and those that had not been acquired by one of the methods noted above were taken over (nationalized), with compensation."

The latest information, based on meetings with MINSAP reveals that there are 18 enterprises under MINSAP, of which 8 are purely formulation units and 1 chemical. Other remaining enterprises are optical and orthopaedic equipment, maintenance, Central Control Laboratories, MediCuba for import and export of allied requirements of enterprises and medical equipment (annex III).

Importance and recognition

It is clear from the many visits to factories, colleges, and training and research establishments that remarkable progress has been achieved in industrial

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1/ Milton J. Roemer M.D., Cuban Health Services and Resources.

development within the 20 years since the Revolution. If the present momentum continues, and if adequate technical assistance can also be provided during the next decade, the future economic prospects seem bright.

It is also clear that for good economic reasons, priority in capital allocation and in the training of technicians goes to the industries on which the economy primarily depends. The sugar industry is the prime example. However, following the price drop in the international markets, there has been some diversification including fishing and mining of metals. It is not anticipated that the pharmaceutical industry, which is mainly engaged in dosage formulation of imported raw materials, will, in the near future, influence the balance of payments unless production of raw materials is started.

Machinery and maintenance

For the reasons stated above, it is clear that the funds available are very limited, particularly in the form of convertible currency, so the training of engineers is vital for prolonging machinery life and for building in Cuba some less sophisticated items of plant. Hence, it is necessary to carefully consider, on a priority basis, the most profitable use of whatever capital is made available and to devise a training programme that will provide, as early as possible, the manual and technical skills of which there is a shortage.

Organizational structure

The consultants were unable to find any plan showing the present management structure, maybe because it is under review. While it was not part of their brief to consider the management structure, this can have considerable bearing on the performance of an enterprise and they therefore felt justified in making a few comments.

The vice-minister or the pharmaceutical industry has reporting to him three directors responsible for projects, technical and economic functions respectively. The directors of the 18 enterprises are also responsible to him directly.

The projects director controls, as part of his department, a staff of 15 professional engineers. A non-technical director of maintenance is responsible for approximately 114 professional and technician engineers of whom 40 in 6 disciplines come under a professional university trained engineer, and 74 in

10 disciplines report to an accountant via a technician. The remainder of the engineering force consists of about 100 maintenance people who are based at various establishments and who are responsible, through site directors, to the technical director (chemical).

The experts believe that there is too much fragmentation in this arrangement and that sometime in the future - when the competence is available - a better plan would be to have an engineering director with line responsibility for all of the central engineering enterprises to deal with engineering design, execution of new works, including erection, installation and contracts where applicable, planning, costs, and specifications for all machinery and parts. The placing of orders could still be done elsewhere.

Until it is convenient or desirable to make such a change the engineering operation should be controlled by a professional engineer responsible to the technical director. He should have functional responsibility only for maintenance at the factories that are large enough to support their own maintenance force, but would provide direct service to the smaller establishments. He would also have a functional responsibility for the engineers with the project director.

There should be a unified control to ensure that good and common standards are maintained, but full responsibility should lie with the factories for all aspects of the work including administration, production, quality control, maintenance, costs, personnel, and planning. Therefore, the site director is responsible to the higher or central control for all these functions on his site or sites. This does not appear to be fully realized at present since there is evidence of a lack of generally accepted standards of control of quality, hygiene, maintenance and costs.

It would therefore appear that a primary requirement is a well-defined chain of command, a clearly established delegation of responsibility with job descriptions and an accountability for performance against set criteria, particularly on costs and production.

Industrial engineering

Labour costs are relatively low by Western standards and consumer durables are in short supply at this early stage of industrialization, but this situation may well change during the next decade and labour costs may become a larger proportion of the added value in processing raw materials.

Having regard to the above, but primarily to reduce waste of both raw materials and finished products and to make better use of all available resources, it is strongly recommended that an industrial engineer be employed. This may take some time as a university graduate would have to be selected. He should have the equivalent of at least six months experience of industry in Cuba (it is understood this would normally form part of his university training) followed by not less than one year, and not more than two, in one or more large efficient factories, preferably pharmaceutical, in a developed country.

This person would initially be responsible to the technical director and would develop a small department of two or three people to serve the industry. The cost would be repaid many times and there would be a continuing monitoring of manufacturing costs and methods.

Maintenance

Of the factories that comprise the pharmaceutical industry, the experts visited the six that mainly produce tablets and that are controlled from Reinaldo Gutiérrez, the largest unit of the group. They also visited factories producing ointments and injectables.

There are some fifty buildings constituting 18 enterprises, each of which is a centre of control. Some of the buildings may be quite close to the control while others may be many kilometres distant.

The R Gutiérrez group, for instance, consists of six manufacturing or packaging sites two of which are centered on R. Gutiérrez and two more centered on Andrés Berro which is six kilometres away. The six sites are administered from R. Gutiérrez which also supervises maintenance and quality control. Prior to the arrival of the experts, some transfer of production, together with the installation of air-conditioning, had started involving Andrés Berro and its two satellites. Plans were being drawn up for transferring some plant to R. Gutiérrez from one of its nearby associates. The experts took part in the discussion on this and felt that there should be full integration of the other two sites with R. Gutiérrez. The quality control laboratory for R. Gutiérrez is at present at one of the other two sites, and the maintenance service to them is supplied by R. Gutiérrez.

There are many problems associated with the planning and production of so many different products, more than 200 products in the R. Gutiérrez complex,

which are made in different sizes and packs. There is also the question of contamination. Nevertheless there is a very strong case for extending R. Gutiérrez with the attendant advantages of unified maintenance as well as administration and quality control. Other savings would result. The least costly extension would be a second floor, and this appears to be feasible as there is sufficient space for segregation of contaminants.

Documentation of maintenance work is quite well organized with a programme of planned maintenance and with time and materials for this and other maintenance work appropriately recorded. The information is not yet being used by the cost office to establish the components of unit cost (in this case 1000 strips) attributable to maintenance. Nor is it used to determine the annual cost of maintaining individual machines, thereby indicating when replacement becomes advisable. This should be introduced as soon as possible.

A more positive system is suggested using a time-clock card for recording working hours that list materials and provisions for signed checking of quality and completion time. At present, planning of maintenance is done along with the central maintenance enterprise and practical assistance is given from the centre as required.

It is important that, as far as it is reasonable according to size, the manufacturing sites should be autonomous. Therefore they should be equipped with the appropriate tools to enable all normal maintenance to be carried out. The maintenance workshop should be provided with all necessary tools including spanners of the correct size. There should be an arc welding plant and an oxy-acetylene welding plant, also two small portable drills and one bench drill at least 15 mm in size. There should be a 6-in. or 8-in. lathe preferably with gap bed.

These should be considered minimum requirements but as funds become available additional equipment should be provided after discussion between the head of engineering and the factory administration.

This might allow the addition of a small milling machine or a shaping machine, and possibly another drill and some tools for light sheet-metal work The electricians must have access to testing equipment for voltage, current and resistance checking.

It would appear that the present maintenance operation is understaffed, taking into account the average age and type of machinery, the degree of training available, and the fact that workers have to visit other sites to carry out maintenance. Under present circumstances therefore an enterprise such as R. Gutiérrez could probably justify a maintenance work force as high as 10% of the total employment. This figure would include supervision, assistants, boiler operators and all people providing an engineering service. With training and rationalization of sites, 8% should be a rough guide considering the high manual content of the manufacturing operation at the present time.

Standards of maintenance, as well as some general standards, varied from one factory to another which is simply a matter of management competence and control. It is therefore recommended that responsibility for maintenance should be as much the function of the head of the enterprise as is production. This will allow the central engineering group to concentrate on providing the industry with the technical, managerial and manual skills necessary to improve the operating efficiency, planning and execution of new developments and the carrying out of major modifications to existing plant and equipment. Some maintenance support will still have to be provided to smaller sites. The quality of work being done in the central group called the Maintenance Enterprise was very good considering that the men doing it have not received any formal training. Work particularly noted was the opening and repair of small sealed refrigerator units, coil winding, sheet-metal work and carpentry. The central workshop was well equipped with machine tools and it is understood that attention is being given to utilizing the machines more efficiently.

The utilization efficiency of the packing and tabletting operation did not appear to be high; records over one week on a selected packing machine showed it to be 64.6% on paid time but 70% on working time. (A midday break of 45 minutes is paid.) For a tabletting machine the corresponding figures were 63.6% and 67.3%. A machine for mixing, granulating and drying gave an efficiency of 90% based on the number of batches made compared with the number planned. The lost time on the packing machine included 18% for mechanical reasons.

The management is up against difficult problems with regard to training, availability of spares, variation of raw material etc., but even before these problems are remedied a more critical and constructive approach to maintenance problems is possible and can produce better results.

It could be helpful to try, even as a short-term experimental measure, sending a senior technician or professional engineer from the central enterprise for up to one month to R. Gutiérrez or any factory having similar maintenance problems. He would study the maintenance operation, identify the problems and make recommendations that would be included in a written report for consideration and action by management. The examination should include especially the stock of spares and possibility of local manufacture. Two examples of plant at risk or in difficulties are:

(a) Two compressors for air-conditioning are running 24 hours a day with no reserve;

(b) Packing machines frequently lose time because of unsatisfactory seals.

In isolated cases, special requests should be made for importation but it is appreciated that this must be very limited and assistance should be asked for from colleges, universities and other industries. They could help with specifications and testing for local manufacture when this is beyond the ability of the central workshop.

Air-conditioning and exhaust systems

These systems form an important and integral part of the production operation of most pharmaceutical factories and it is recommended that more careful attention should be given to their design and operation.

Some of the faults that the experts noticed may also be found in the developed countries of Europe and Asia but, if good working standards are required, attention must be given to the movement and quality of air in the working environment. The technical and managerial knowledge is available and should be applied to this problem. It is worthwhile stating a few basic principles:

(a) It is more expensive to cool than to heat;

(b) Heating of air contributes to reduction of relative humidity and therefore the minimum amount of refrigeration should be used which, along with reheating, provides the optimum combination of relative humidity and dry-bulb temperature. For general application for tablet work, the level would be 45% relative humidity and a dry-bulb temperature of 22°-24°C. For hygroscopic products the relative humidity may be reduced to 35%-40%;

(c) Approximately 90% of air should be recirculated and 10% fresh air introduced;

(d) Filters should be used in the air return system before the evaporator and heater, and a manometer should be placed outside the plant chamber to show by pressure differential across the filter when the elements require cleaning;

(e) The conditioned area should be well sealed with windows locked shut and entrance lobbies or air lock provided;

(f) There should be no wash places in the conditioned area;

(g) Direct sunlight should be excluded:

(h) A slight positive pressure should be maintained in the area;

(i) Where non-conditioned exhaust systems are required, a supply of outside air should be introduced remote from the extracting fan or fans. This will avoid short circuiting and draughts in adjacent areas;

(j) Where protection of the environment is necessary air filters must be used. Windows should be kept shut.

Training of engineers

There is an excellent training operation going on which has been developed over quite recent years. The output, which is far below demand, is creamed off to the priority or mainly export industries. The pharmaceutical industry is not so far enjoying the fruits of this training; with the exception of a handful of professional and technician engineers, the engineering section is staffed with people who have not received formal training.

Two colleges for training engineering tradesmen were visited and the quantity and quality of equipment available for practical training were impressive; it included relatively sophisticated machine tools, and even iron casting and electric-arc steel furnaces had been acquired. A well equipped metallurgical laboratory with excellent testing equipment was seen. The colleges are not yet supplying any of their output to the pharmaceutical industry.

Because of external pressure the colleges have, for 1978, reduced to one year the curriculum, which previously required two years to complete. This is a retrograde step but it is intended to extend the training to two years again in 1979 The allocation of college output is at present directed by the Government. It is clear that the training of engineering workers at present employed is essential and a training programme outline was drawn up at a meeting with technical and training staff. It will involve a two-year course which will be theoretical and practical with some nine months on machinery specific to the industry. To minimize interference with production, small groups of about 15 workers will be selected for a part-time work, part-time study programme. It is intended to raise the standard of maintenance efficiency, particularly in its diagnostic aspects. The expectation is that by the time this programme is completed it will be possible to obtain a trained intake from the colleges. The training should be extended eventually to a minimum of three years, of which at least nine months should be on machines that are special to the industry.

The training of professional engineers at university level is well established and includes extensive periods of practical training in industry. As soon as possible a form of sponsorship should be established in the industry. Students would be selected from school and sent to the engineering schools or colleges to be trained as qualified workers or medium technicians. (A medium technician has a more advanced technical training that fits him for a supervisory position.) At the end of the first six-month period, the student should be interviewed and a decision taken on the question of his/her suitability. He or she may have also decided against continuing the training. Interviews should continue at six-month intervals to maintain the interest of the student and to consider any problems such as a desire to change specialization. Such interviews should occupy at least 30 minutes and there should be a full and free exchange of views between the student and the person conducting the interview. The same person should see the student on each occasion.

If possible, without serious interruption and loss of continuity in college training, the student should, after one year, spend six months in a pharmaceutical factory on a programmed variety of maintenance work with qualified workers. If this is not feasible then the last year should be spent in the factory to achieve qualification. If six months is spent in a factory in the middle of the course a further period of six months should be included at the end to complete the three year course.

Training of mechanics should include elementary electricity in addition to the use of hand and machine tools. As an incentive, and to provide specialist knowledge, selected top grade students should be sent overseas for from three to six months in a pharmaceutical factory to receive special training on a type of machine in use in the industry, the programme to be arranged before departure. One such student might be selected each alternate year. The training objective must be clear and might be stated as: to provide, in addition to a good general education, the necessary technical, theoretical and practical training to enable the individual, with minimum assistance, to diagnose faults, make parts, carry out repairs and maintain and install equipment and machinery of the pharmaceutical industry.

A useful contribution to training could be made, with the assistance of an international organization, by arranging with the Cuban authorities, on the basis of a five year period, for:

(a) A small number of qualified and medium technicians to have short periods, as mentioned, in overseas factories and with emphasis on the diagnostic and performance aspects of maintenance on the special machines used in the industry;

(b) Two or three senior professional engineers to have, say, six months gaining experience of plant design and of management techniques in the industry.

Costs

Although the records are available for time and materials on all maintenance operations, the cost office is not at present using this information to provide a cost control service to management and it is recommended that such a service should be provided as soon as possible. Such cost information, set alongside the annual budget by monthly breakdown, will show the plus and minus variations and more detailed information on individual machines or machine groups that will enable management to take whatever action is indicated. Clearly there is no justification for providing detailed cost information unless management is prepared to discuss it regularly and to act upon it.

Machine characteristics

Circumstances may exist that require machines to be purchased from specified countries but it is recommended that, for reasons of standardization of spare parts and to benefit from present maintenance and operating experience, machinery should be bought from the same manufacturers as at present. In any event, there should not be more than two suppliers of each type of machine.

Because a machine is old, it should not necessarily be replaced. A decision should be based on two criteria:

(a) The cost of maintaining it has reached a stage where replacement is justified in relation to the capital cost and depreciation on a new machine;

(b) Replacement by a machine having a substantially higher output and/or technological advance would so reduce unit costs as to recover, over 10 years or whatever cost recovery period has been laid down for the industry, the capital investment.

A number of guidelines are given below that may be helpful when considering the purchase of new machines:

(a) Ease of cleaning;

(b) Ease of maintenance, that is, designed for good accessibility and easy dismantling;

(c) Where possible bearings should be used that do not require lubrication;

(d) Lubrication points grouped and marked to indicate the frequency of lubrication, daily, weekly, monthly etc.;

(e) Good cost/value ratio;

(f) General reliability;

(g) Long life. (Wearing parts can be made from locally available materials.);

(h) Detailed working and maintenance instructions should be available from the manufacturer in the language of the country;

(i) Sophistication. Electronics etc., should be within the competence of the available standard of technological training;

(j) Contact should be made, before buying, with other users of the machine to obtain as much information as possible;

(k) It can be useful, before parts of a new machine begin to wear, to make sketches of any expendable parts for which replacements are not held in stock. Also, component parts should be subsequently purchased direct from the manufacturer of the parts.

It is important that the central engineering technical department as well as the responsible maintenance department should be involved together with the technical and production department in discussions on the purchase of new machines.

The experts observed that, since their arrival, two new Italian coating machines and a Hassia packing machine were not working on production although they were received many months previously. Careful attention should be given to drawing up a machine specification to ensure that it will do the job exactly as intended; this may include sending samples to be coated or packed, as the case may be. These samples are then held as the standard against which production must be judged and full payment should not be made until the manufacturers have, through their representative, shown that the machine can reproduce that standard.

The price quoted for the machine should include recommended spares, installation and operating instructions and, in the case of a machine of a type not already in operation, sending a man to check and test the machine and to train the operator for one week.

Summary

The engineering operation has available good basic standards of technical knowledge and documentation and there is a desire to use the knowledge gained.

In order to provide a more effective maintenance service and to strengthen the engineering function generally the following points require careful consideration:

(a) Improved organizational structure and delegation of responsibility;

(b) Practical and specialist training of manual workers on the machinery of the industry;

(c) More positive application of known standards in day-to-day maintenance work;

(d) Wider experience to be gained by technicians and professional engineers by spending time in selected overseas factories engaged in the manufacture of pharmaceuticals;

(e) A more positive system for maintenance control should be introduced for jobs lasting more than one hour. This would involve the use of a time-clock card on which materials used would be listed and on which the person responsible would sign for the quality of the work;

(f) Before any further visits by an expert or consultant take place, it is important that substantial progress should be made in training at all levels. This could take at least one year.

System of operation

To evaluate quality, quantity and the machinery of the pharmaceutical industry, the experts studied the industry from the stage of registration of drugs to their distribution.

One advantage is that the total system is under one ministry, hence the introduction of a drug from its development to distribution takes place within a short time However, short cuts have been taken which could have undesired effects with respect to the efficacy of the product. In addition, there is neither competitor activity nor a feedback from consumers that can influence a change for the better over the existing system.

Registration of drugs

The registration of drugs, introduction of new drugs, and deletion of some existing drug formulations are done by the Commission of the National Formulary of Cuba, which is comprised of the National Paediatric Group, Internal Medicine Group, Gynaecology and Obstetrics Group, Ministry of Industry, Health Ministry, and representatives of the Drug Technical Laboratories.

Remarkable work has been done by the National Formulary in reducing the number of drugs from 30,000 to 1,200. However, considering the country's raw material and packing material resources (80% of this material is imported),

transportation costs, foreign exchange, production facilities, availability of trained personnel for production and maintenance of special machinery, it is suggested that the Commission of the National Formulary should give due consideration to the check-list of drug preparations for use in hospitals and those needed for the practice of medicine in developing countries published by UNIDO and WHO. This list may help them to consider the future of certain formulations, for example, sodium salicylate tablets and liver injection. Through conferences and meetings with the medical profession, it may be possible to modify prescribing habits and eliminate some of the drugs in view of the availability of modern drugs.

The National Formulary, when introducing a new formulation, should evaluate such facilities for product development as the following:

(a) Raw materials availability and their characteristics. Since most of the raw materials are imported from different countries using varying processing technologies, the variation in the physical characteristics of certain raw materials with respect to bulk density, particle size etc., affects the efficacy of formulation;

(b) Acceptability studies - feedback from field studies for modifications in the delivery system;

(c) Further product refinements based on acceptability field study findings;

(d) Stability studies done on the formulation packed in the proposed packing material;

(e) Continued product refinements based on technological advances and experiences followed by stability studies;

(f) Procedures for quality control using conventional and advanced spectroscopy and chromatography methods;

(g) Introduction of dissolution tests in certain formulations;

(h) Finally, the most important evaluation, the environment, skill, layout and machinery required for such drugs.

Development of drug formulation

The development of drug formulation in Cuba is done at the well equipped Laboratorio Técnico de Medicamentos with an experienced technical staff, headed by a director, of 64 university qualified professionals, 58 medium level technicians and 210 workers.

This unit is composed of the departments listed below.

Department of Technology. This Department investigates new formulations and their preparations on a small scale It has three branches: parenterals, liquids and semisolids, and tablets. The equipment in this laboratory consists of a wide range of spectroscopy equipment, a pH meter, potentiometric titration equipment, polarographic analysis equipment, small units for dosage formulations, ovens, humidity chambers and a gas/liquid chromatograph.

It is surprising that with such modern equipment available in this laboratory and with expertise available, no stability studies are carried out. Details of stability studies have been discussed with this group and a method recommended for the estimation of the shelf-life of the product (the product being packaged in the form in which it will be marketed). A stability study model in case of suspensions was discussed and the details for the use of dialysis and electrophoresis methods will be sent from India. It was apparent during the discussions that the initial technology for new products is developed by this section and is passed on to the production enterprise for production.

The problems in production arising from variations in the quality of raw materials are handled on the spot and there seems to be no co-ordination or feedback.

The experts studied the variation in particle size of raw materials from various countries. The discussion with production personnel of such problems revealed that they vary the processing method to obtain the product within the pharmaceutical limits, but the effect of such process variation and variation in raw materials on the efficacy of the product has never been established.

It is recommended that a study be made of the physical properties of the raw materials of certain drugs from various countries, for which minimum effective concentration is critical, such as particle size, bulk density and crystalline nature and of the procedures to be followed by production laid down by the Departments of Technology and Technological Control. The data from the dissolution rate studies that are recommended will be the deciding factors for the procedure. Based on these studies, this laboratory should insist that the Department of Procurement of Raw Materials (MediCuba) procure raw materials from those countries that have been supplying materials of the desired specifications. Initially it may be wise to do this in the case of raw materials such as aspirin, meprobamate, digoxin and tetracycline.

Department of Technological Control. This Department deals with quality control specifications, and methods of chemical, microbiological and pharmacological quality control. These methods are adopted by the quality control departments of various enterprises for the analysis of raw materials and finished products. The Department also undertakes the inspection of factory premises, quality control and production documents.

Department of Norms. This Department lays down the norms to be followed by different levels of industry: enterprise, branch and national.

Department of Quality Control. A department of quality control is attached to each enterprise manufacturing a given dosage form. For example, one such department at Mirassou is responsible to the director of the R. Gutiérrez enterprise and controls the quality of tablets and granules manufactured at R. Gutiérrez, Mirassou, Aldabó, Andrés Berro, Abella, and Iturrioz. The quality control technicians perform their work satisfactorily as far as determining the identity, percentage, purity or assay, and other pharmacopoeial tests of raw materials and finished products. However, the conditions and standards for the built-in quality of a product, which is a function of production, need to be established by Quality Control and followed up to ensure that production takes all essential precautions. The conditions to be established are: a proper and tidy layout; dust-free atmosphere; use of proper apparel; proper manufacturing conditions - humidity, temperature and ventilation; elimination of cross-contamination owing to the use of unclean equipment; a good air-conditioning system; proper storage of raw materials and finished products: labelling; and documentation. These conditions are responsible for the potency, uniformity and stability of the products and assure quality and efficacy. In addition, in certain cases, detailed specifications should be set of active ingredients and special tests to ensure that a product of the same efficacy and stability is obtained from the raw materials from different countries using varying processing technologies. This responsibility should be studied more critically as it has been seen how the variation of particle size and crystalline nature of five consignments of aspirin and meprobamate had an effect on the disintegration time of these products. However it is not only the disintegration test but also the dissolution test that need to be studied of many drugs for which minimum effective concentration is responsible for efficacy and rapid toxic concentration in the

body is undesired. The production personnel do alter the formulation process to compensate for changes in order to achieve correct disintegration time, hardness, and friability, but there is no established correlation between the effect of such variations and the dissolution rate.

Since most of the raw materials are imported, Quality Control assumes more responsibility in view of the waste of foreign exchange, time required for delivery of the consignment and impossibility of replacement in case it is rejected. Since the Department of Quality Control is also under the Department of Technological Control, the following procedures, which are common to all the enterprises, are recommended:

(a) The Planning Department, before requisitioning materials or sending the requisition to the Purchase or Import Department, should consult Quality Control and show them the format of detailed specifications before placing the order. Here Quality Control can, based on their experience of the past performance of this supplier, add or insist on certain data to be furnished in the next consignment: packing, particle size etc. The exporter must furnish a standard format of quality. The Certificate of Analysis must accompany the consignment;

(b) After unloading, the shipment must be kept in a quarantine area and stored under conditions that are required for production. Quality Control must check the label, batch number, product name, name of manufacturer, date of expiry etc. Batch number on the containers must tally with those given in the Certificate of Analysis and on the invoice. The physical condition of individual cartons of the consignment must also be checked;

(c) Methods of sampling must be defined and the size of the sample for the consignment must be established. This holds good for both the raw and packing materials. One supplier had sent for trials cellopoly rolls and the entire consignment was of cellophane. This was detected much later by which time the guarantee period was over. The reason may have been negligence on the part of the supplier or a typographical error on the part of indentor. To avoid the latter, it is advisable that the indenting department and the Department of Quality Control check that the order as typed is in accordance with their requirements. To avoid negligence on the part of the exporter, many countries appoint internationally or government recognized laboratories that collect a sample of the consignment from the exporter and analyse or retain the sample in case of disputes, rejections etc.;

(d) Considering the deterioration in the properties of raw materials and packaging materials, the first in first out (FIFO) method should be insisted on by Quality Control regarding the usage of material. Quality Control should classify and categorize the raw materials with clear instructions to the stores to give the raw materials for reanalysis or checking after remaining unused for longer than six months, six to nine months and nine months and longer, before or at the time of taking them for processing. In such classified raw materials, Quality Control should carry out one test that will determine the uniformity and the content of the raw material. In certain cases

Quality Control should carry out, with the Development Department, the actual performance test (a small amount of dosage) and analyse the product. In case of any variation or interesting finding, proper instruction to be followed while using such a raw material will be issued to the production department so that it does not take any spot decisions;

(e) The dispensing or the issue of raw materials to production should be checked by Quality Control to ensure that correct materials accurately weighed or measured into clean, properly labelled containers are used by production;

(f) The documents showing the manufacturing and packaging operations carried out should be checked by Quality Control. They should indicate to production any variations in parameters, in the sequence of process steps or in yield that are found against the theoretical yield of units;

(g) Other functions include checking of: (i) machinery cleanliness at the time of start and change of product or batch; (ii) the use of correct labels with required information or proper legible printing on the foil of the required information; and (iii) adequate control during the process of manufacturing and the packing operations to ensure the uniformity and compliance with appropriate specifications before proceeding to the next step, e.g., moisture content of granules or disintegration time of the various intermediate stages of coating from a core stage to final stage of coating; leak test at specific intervals on strip packs during strip packing; the assay on an active ingredient that is in minor quantity as compared to other ingredients before compression or before filling and packing in the case of liquids and ointments etc.

The recommendations given in the foregoing paragraphs should not be taken as totally lacking in the present system of quality control. These are documented in this report to make the people concerned aware of the importance and autonomy of the Quality Control Department so that this Department contributes substantially to the built-in quality of products by assuming a more effective role.

In most cases, the analytical methods are fool-proof and the method and size of sampling are standardized but some lapses may take place that are due to an unusual and undesirable distribution of production departments at different sites distant from Quality Control by a few kilometres.

Production

The production operation was studied through visits to the six establishments that comprise the R. Gutiérrez Enterprise and two other enterprises, namely, Roberto Escudero, ointments, and Juan R. Fraco, injectables. At R. Gutiérrez the following aspects of the production operation were considered:

Machinery layout
Storage facilities and conditions
Air-conditioning and ventilating systems
Mechanical handling
Process technology
Documentation of processes
Technical skills available
Housekeeping standards
Maintenance
Production planning

Since it was found that generally accepted standards of working, under the above headings, were not being fully complied with the experts visited various training establishments for engineers and technologists from university level down to qualified workers. The standard of training appeared to be good at all levels. The machinery was purchased after the 1959 Revolution from well established suppliers in the countries of origin. It includes mills; mixing, granulating and drying machines (which are quite sophisticated); tabletting machines; and packing machines. Two of the packing machines are convertible for strip and blister packs. Although relatively high output machinery is used the potential output of the machines is not fully achieved because of inadequate maintenance and multiplicity of products which result in frequent changes of plan and of product.

Because of inadequate air cleaning equipment, excess dust remains in the atmosphere and is deposited on all surfaces including exposed and moving parts of machines. This poses a risk of cross-contamination as well as possible damage to the machine.

The experts considered, with members of engineering and production management, where and how air-conditioning and ventilating plant should be used, which areas should be provided with it and in which order of priority. Because of the climatic conditions in Cuba it is considered that all preparation, processing and packing areas should be air-conditioned eventually. This will be expensive and is another reason for recommending the maximum degree of rationalization that is feasible.

Hygiene. The general housekeeping standards in some factories were below what the experts consider to be a desirable level and, if this is due to a shortage of cleaning people, it is strongly recommended that steps should be taken to improve this situation as soon as possible. Regular cleaning of the inside of ducts should not be overlooked.

With regard to hygiene, the use of gloves and nose masks is not general. During the very hot months of the year it may be difficult to impose rules in this respect until air-conditioning is installed in all working areas, but efforts should be made to obtain a suitable washable type of glove that does not promote perspiration. At present, wet and dry granules, raw material additions, sampling at compression and sorting for reworking are all handled with bare hands. In one factory the production of "slugs" was taking place within 3 or 4 feet of a large door open to nearby dusty ground. In another, a green colour was being used in coating pans and a red colour from previous work was in evidence on the equipment.

At the Juan R. Franco factory the standards of hygiene appear to be closer to expectation as far as layout and equipment were concerned. However, it was noticed that ampoules were being removed from dusty containers and washed at the same time as an autoclave door was being opened and closed, all in the same room, with movement of men and materials.

The protective garments worn are not made of synthetics such as dacron or nylon and therefore are not free of lint. Because of these factors and the quality of ampoules (glass particles) the speed of visual checking (70 per minute) seems to be high. To sum up, the documentation of process parameters is satisfactory, and the machinery is up to date, but it is necessary to raise standards of hygiene and tidiness and to give closer attention by managements to matters of detail in order to ensure a high level of quality.

Production planning. Greater accuracy is necessary in production planning, which may be a matter for guidance from a senior person. For instance, where 550,000 tablets of one product are required in a year and a batch size is 250,000, then three batches are correctly shown to be produced, but to cover a 5% loss a total of four batches is listed which would be nearly twice the requirement. It is thought to be unlikely that four batches will actually be produced but the plan should be much tighter. If this form of planning is accepted it could result in a heavy production loading in the early part of the

year and a slack period at the end when it is found that the requirement has been met already. One purpose of planning should be to balance the production load as evenly as possible and to allow for maintenance, holidays etc.

The experts discussed at some length the possibility of developing R. Gutiérrez as a main tablet plant and transferring equipment and machinery from two other small factories 1 kilometre and 4 kilometres distant from it. It was agreed that it would be useful to prepare drawings with the ideas put forward although it was appreciated that improving the present manufacturing and environmental standards may have a higher priority when allocating whatever funds are available in the immediate future.

Capacity. There should not be any problem with regard to production capacity of solid dosage forms in general and contraceptives in particular within the next five years. It is essential, however, that trends should continue to be monitored year by year to allow sufficient time to procure and train the people required to provide the additional output.

Although the increase is likely to be fairly gradual and therefore the intake of workers and professional people spread over a few years, to obtain technical personnel and train them in the industry can take a considerable time. Generally, in tablet manufacture, where an increase in consumption is anticipated with two working shifts and a little overtime working, there is approximately 50% of reserve available. Even allowing for maintenance time with a third shift, and assuming that there could be at least 10% improvement in working efficiency, it should be possible to increase total through-put by more than 50%.

Oral contraceptives

The Government of Cuba does not have a family planning programme, its policy being to provide contraceptives for those who wish to plan their family. The pharmaceutical industry has been producing oral contraceptives since 1963 which doctors were prescribing only for medical reasons.

These preparations were restricted and were sold through a pharmacy under prescription. Later, their sale was restricted to hospitals till 1975. After seven years of restriction, the National Group of Gynaecologists and Obstetricians gave approval, with some modifications, to the old formulations and approved the introduction of three formulations in tablet form:

Norethynodrel 1 mg + mestranol 50 µg

Norethisterone 1 mg + mestranol 50 µg

Norethisterone 0.35 mg

These three formulations are now freely available in more than 1 000 pharmacies in Cuba. The distribution is throughout the country with central control of production and inventory. The transfer of stocks from certain areas of poor sales demand to areas of greater demand is possible.

Product introduction and registration

Oral contraceptives were not new in the true sense but introduced for the first time in Cuba in 1975; they were made with the country's own processing and packing technology skills. The trial lots were given as clinical samples and the effectiveness of the contraceptives motivated the successful launching of the contraceptives in the country. There seems to be no feedback from the consumer or any documentation showing data on side effects or the effects of long-term administration. The omission of some aspects of the biomedical development phase of the drug, such as the study of physiological mechanism, animal experiments and teratological studies, is understandable since it is not truly a new drug, but a programme for monitoring the users of oral contraceptives with the consumers' medical history, habits, complaints during use and medical check up during use should have been started during the trials and continued.

According to Dr. Ory,[2/] each woman must be matched to a method of fertility control based on her health and circumstances and the matching process should be accompanied by a programme for monitoring users of birth control and for giving to potential users the information gained by the surveillance. Even though currently available methods of contraception are effective and relatively safe, the risks involved in their use vary from method to method and even within types of contraceptives. He produced data showing how complications arise when other factors such as smoking and a high cholesterol level interact with the oral contraceptive and concluded that such surveillance data, based on findings and feedback, can be used to make oral contraception even safer than at present. Similarly, in the product development phase, at least methods of quality control and data on stability studies and layout facilities to avoid cross-contamination should have been assessed or evaluated.

2/ Dr. Howard Ory, Chief of the Centre for Disease Control's Family Planning Evaluation Division of the United States to the House Population Committee.

Projection of oral contraceptives to be used in the next five years

While evaluating the projection of quantity the following points were considered:

(a) The need for such a study. Even though there is no compulsion from Government or no organized family planning programme, (i) the percentage of working women is increasing, and (ii) the Government, through social workers in hospital, gives information on methods of contraception besides other information to the women under the national programme of health care for mother and child;

(b) Information on methods of contraception is given under the public education programme through radio and television. Hence, as people know more about the use of a contraceptive they will ask for it as it is now on free sale;

(c) The lactational amenorrhoea period is also reduced to 3-6 months because of urbanization, industrialization, mothers working outside the home and the availability of safe and nutritions breast milk substitutes;

(d) The average menarche age is 11 years, the age period for marriage is between 15-17 and the social mores of the country necessitate the use of oral contraceptives between menarche and marriage. Each year the need for oral contraceptives for married and unmarried teenagers will increase. Menopause is at 43-44 years. In the calculation of the next five years demand, the consumers in the age periods 10-14 years, 15-29 years and 30-44 years have been considered (table 1).

Table 1. Estimated requirements for contraceptive tablets, 1978-1983

Year	Number of women (10 to 44 years)	Number of consumers	Number of tablets required [a/]
1978	2 880 000	134 000	46 500 000
1979	2 955 000	160 800	52 260 000
1980	3 020 000	192 900	62 692 500
1981	3 050 000	231 400	75 205 000
1982	3 115 000	277 600	90 220 000
1983	3 150 000	333 100	107 575 000

a/ The total number of tablets required is calculated by multiplying the number of estimated consumers by 260 and adding 25% of this quantity i.e. the expected consumption to be kept as stock.

This projection of quantity is based on information and assumptions such as a 1.8% growth rate in population to be maintained and the age composition of the population, i.e. the ratio of males to females, eligible women as consumers of contraceptives as a percentage of the total population and as a percentage of the total female population in the next five years.

(e) The Government, in the next five years, will not impose any restriction on the size of the family or introduce any family planning programmes. However, the mother and child care programme and audiovisual media for public education will deal more often and intensively with the methods of contraception. The industrial growth will also make more provision of jobs for women. This factor will contribute substantially to the consumption of oral contraceptives in the coming years;

(f) Consideration was also given to the following three aspects:

(i) The preference of the medical profession to recommend an intrauterine device (IUD) or oral contraceptive;

(ii) Propaganda for the use of condoms;

(iii) Encouragement for the termination of pregnancy by suction and evacuation.

Oral contraceptives have been used since the end of 1975 or early 1976, therefore 1977 has been taken as a base year for the calculation of their production and consumption (table 2). The IUD has been in use since 1972. It is felt that the IUD will be the first choice for contraception by the medical profession in the next five years. However, there seems to be no documentation of information on insertion failures, expulsion data, inflammatory diseases and removals due to bleeding and pain. The reason is that there is no definite programme to assess or evaluate contraceptive methods. It is a matter of choice for the consumer based on the consumer's education gathered through the audio-visual media.

Table 2. Production and consumption of contraceptive tablets, 1977
(In packs of 20)

Stock on 1/1/1977	Production	Consumption	Number of consumers packs (13 each)
406 295	373 401	511 133	39 318

Conclusions and recommendations: quality control

The three oral contraceptives, out of which two have mestranol as the estrogen and norethisterone and norethynodrel as progestins, are formulated without a stability study. The enterprise, after one year or in certain cases after six months, reanalyses the shelf sample of production batches from the reference room. One such report was shown to the experts of the analysis of formulation of a tablet containing norethisterone: the initial contents were 103% and after one year, 107%.

The raw materials are analysed as per the pharmacopoeial standards but in mestranol-norethynodrel tablets only the major active ingredient, i.e., norethynodrel is analysed. The identification of mestranol is not done. It was suggested that a suitable thin layer chromatography (TLC) method be developed to identify the same.

The other tablet formulation containing norethisterone and mestranol is not analysed at all and the method is under development.

The tablet containing 0.35 mg of norethisterone is analysed as per the pharmacopoeial methods.

The tablet containing norethindrone and mestranol or norethynodrel and mestranol could be analysed by gas chromatography using XE-60, 3% as liquid phase. The published method and the chromatograph showing the separation and the details of parameters was passed on.

Since all the active ingredient absorb at 240 nm, the separation and the identification of individual components by TLC should be the first objective followed by the assay based on its C ≡ C content and uv spectrum. A method to identify these components by TLC has been suggested and is under development.

A method using silicic acid impregnated with silver nitrate and the solvent system will be sent to Cuba. It is recommended that stability studies should be carried out on the blister pack and bottles containing these formulations at ambient and accelerated parameters.

Conclusions and recommendations: production

The general working conditions and machinery have been evaluated in the section and these evaluations, with recommendations, hold good for oral contraceptive production facilities also.

The procedure for the issue of raw materials to the production department for formulation of oral contraceptive tablets is not foolproof. The stock card does not show the proper documentation and the columns entered are just sufficient to show the inventory. The material issued does not indicate the batch number of formulation for which it is issued. It is recommended that each issue of raw material, with its identification assigned by Quality Control, denotes the product and batch number for which it is issued. In this way, stock reconciliations can be made and the cause of any problem arising in the product can, with the stock card and the documents of manufacturing job card, be detected.

The sifting, milling, granulation, and blending during the formulation is done in non air-conditioned, open rooms and the initial mixing of raw materials with dry starch is done in a polythene bag by manual mixing. This can create a dust detrimental to the operator and environment and can cause losses, since both the ingredients are in small quantities. Mixing may not be thorough and uniform. The use of a small blender ("V" shaped or double cone of 10 kg capacity) was recommended.

Also recommended was a ball mill or micropulverizer of 4-5 kg capacity for the initial process of trituration of colour, active ingredient and starch, and a bigger blender of 75 kg capacity for final blending.

The provision of two dust extraction units was recommended, one connected to each hopper. The hopper covers should have one opening in the centre connected permanently to the dust extractor. There should be a hinged flap that can be opened at the time of charging granules to the hopper. There should be a positive flow of conditioned and filtered air at the entrance of the cubicle or room where operations of formulations are being carried out and a powerful exhaust with filtration and recycling system at the rear top of the cubicle.

This system will direct the generated dust at the source to the exhaust system.

The air handling system for oral contraceptive processing and tabletting should be completely separate as far as ducting and filters are concerned, although refrigeration and heating services can come from a central plant. In the formulation, rather large amounts (up to 10% of the batch) of a fairly costly material, microcrystalline cellulose, are added to increase hardness and

reduce disintegration time. The addition is necessary because of the non-cohesive nature of the active ingredient and the possibility of chipping of tablets during packing in the rotating disc before they are guided to the chute or channel.

The following modifications are suggested to eliminate completely or to reduce the proportion of microcystalline cellulose required to 1%: use an acacia solution (1%-1½%) in the present starch-gelatin solution and increase the proportion of lactose from 80 to 100-120 times that of the active ingredient. The proportion of lactose could be kept to 80-100 times active ingredient if the quantity of acacia solution is gradually increased and microcrystalline cellulose used up to a maximum of 1%. The success of such modifications will be assessed through stability studies of a tablet from the compression machine and not merely by the conventional process control and quality control methods.

Present and future capacity

The projected increase in the use of oral contraceptives is shown below. This could, in theory, be handled on one tabletting machine by one shift within six months annually up to 1982. In practice, more than one machine may be used.

Year	Days (single shift)
1978	64
1979	72
1980	86
1981	103
1982	124
1983	148

The above forecast is calculated from the following data: average output of a compression machine per day is 727,470 tablets. The yearly prognosis for the next five years has been divided by the daily output to get the number of days per year. The days calculated above include the days required for a 25% reserve stock level of oral contraceptives.

Requirements for the training of technicians

The training given in the medium technical school and university is quite intensive, as is evident from their syllabus.

Frequently, the microbial counts of the exposed parts of the operators are taken and shown to them. With their knowledge of microbiology and of such tests, they become thoroughly conversant with the technological requirements but because of lack of persuasion from senior staff, the precautions taken by the technicians are much below the expected standards. From the process technology view people

seem to be quite conversant and efficient with the process and the machines but the importance of personal safety and products safety is not truly realized.

In view of this, it is suggested that the films on good manufacturing practices and safety be shown to people at all levels so that they are constantly reminded of theory and its practical applications. The older staff who are not qualified can in a short time have a better understanding of the procedure.

It is sometimes found that the older operators resent advice but it is possible, by tactful personal discussion with them and by continual encouragement and use of the films, to develop the right attitude to this important issue. In time, it is hoped that an improvement will be shown because the workers will make constructive suggestions themselves.

It is necessary that the technicians working in the oral contraceptive formulation unit are provided with a suit of pure cotton so that dust is not attracted to them as in the case of synthetic yarn. Hands should be covered by gloves and nose/mouth masks and head gear should be worn. Ideally, dressing and undressing should be done within an air lock. Regular and frequent medical examinations should be a feature of the protection system for the workers. In the case of oral contraceptives, and in other special cases, this should be monthly although in other cases the medical check may be done annually.

Development of a new pack

The existing pack is a carton type of a very thin board and is quite suitable for literature insert and product protection. However, in view of the lower rate of packing in cartons as compared to the output on strip packing machines, as evidenced by the following data, two packs have been submitted in the form of a catch cover which will help to hold the blister tray and can accommodate the printed leaflet. The present method of packing the strips separated in cartons has two disadvantages:

(a) Performance cannot be assessed;

(b) Mixing of batch during packing can take place. With this catch cover, the strips of insertion of leaflet will have to be geared to the machine speed. A greater number of people will be required to match the packing of strips in catch cover. In view of this a layout has been proposed of placing the machines in other directions by turning and shifting in the same area.

The packing data are:

(a) Packing of tablets in blister pack, 40,800 blister packs per shift;

(b) Insertion of leaflet and blister pack in the carton, 9,600 per shift by 15 people.

Raw materials

A UNIDO expert recommended Agave fourcroydes as the source of hecogenin, an ideal precursor for the synthesis of corticosteroids, and Solanum laciniatum as a promising source of solasodine. He suggested also a pilot plant for extraction of hecogenin.

There are 19 species of Dioscorea available in Cuba and some of them are rich sources of diosgenin which may be suitable raw material for oral contraceptives.

The experts visited the Experimental Station and found that the work on the cultivation of Dioscorea and Solanum was at the nursery stage. It is recommended that at least one acre of land be used for the cultivation of at least seven or eight species of Dioscorea and then the correct species should be chosen for further cultivation. The same should be done in the case of Solanum laciniatum.

Transformation of hecogenin. Considering the availability of equipment, methods, and raw materials, it was advised that the research group at the Synthesis laboratory should undertake the work on hecogenin, which is readily available, with two objectives: the synthesis of corticosteroids by the hecogenin route and, more important, the development of technical skill by the group in carrying out and scaling up organic reactions because of the abundance of this raw material. In view of this the group asked the experts for information on the following steps of conversion of hecogenin:

1. Degradation of the side chain to C_{21}
2. Transferring of the keto group at position 12 to 11
3. Introduction of a 9, 11-double bond
4. Epoxidation of the 9,11-double bond and introduction of F at position 9
5. Introduction of the double bond Δ^1

The method for degradation of side chains has been supplied and work has been undertaken on its development. After a careful survey of the literature, methods have been supplied for the above conversion steps, i.e., for steps 2 to 5, and suitability and commercial feasibility were discussed.

These methods are applied commercially elsewhere with modifications, however, their success depends upon the design of experiments to change the parameters, polarity of solvents, condensing agents and their concentration, mode of addition etc. Since hecogenin is available in quantity it is advisable that these methods be tried and scaled up to operation at a 5-litre flask level as phase I.

The work on microbiological hydroxylation at C_{17} and C_{21} may be assigned to the group at CNIC. CNIC is a research centre where applied and pure research work in different fields such as chemistry, electronics and bioengineering is carried out with the objective of achieving processes of industrial application. This laboratory was visited by the experts who were impressed with its talent, capability and equipment. Excellent work has been done in the microbiological degradation of bagasse, a sugar industry by product. Many other projects are also nearing completion.

For the steroid project, it is recommended that this laboratory should preferably undertake microbiological transformation work in the following areas:

(a) Besides C_{17} and C_{21} hydroxylations, as mentioned above, separation and microbiological transformation of sitosterol, which is present in the 11% sterol fraction in the oil that constitutes as much as 40% of the wax obtained as a by-product in the sugar industry. Considering the large quantities of this wax available annually, even if only 1%-1.5% is separable as sitosterol, the project will be quite feasible. The work to be carried out by CNIC will be independent of this project but can be started as early as possible;

(b) Work on the introduction of the double bond Δ^1 could be undertaken by this laboratory on 4-androstene-3, 17-dione, which will be supplied by a synthesis laboratory.

Choice of raw materials. With an oxygen functional group at position 12 and no 5,6-double bond, hecogenin cannot be an economical raw material for oral contraceptives. The most accepted raw materials are either diosgenin or solasodine. Considering the inadequate development work on the cultivation of the Dioscorea and Solanum species that is being done at the Experimental Station, it is felt that it will take six years from now to get a sizeable quantity of diosgenin or solasodine for pilot plant extraction. The pilot plant, which is being procured for hecogenin extraction, will also be useful for both diosgenin and solasodine extraction.

The Experimental Station should aim at achieving 70-75 kg of diosgenin per acre per year. The suitable areas for cultivation will be the places where northerners, as Cubans term the cold winds, do not bring down the temperature below 10°C in winter and the temperature in summer does not exceed an average of 30°C. Advantage could be taken of the summer for drying roots, taking care against rot. An average yield of 1.5 kg of diosgenin per 100 kg wet roots as a basis for calculation would require a yield of 5,000 kg wet roots per acre to achieve 70-75 kg of diosgenin. It is recommended that efforts be concentrated on the cultivation of Dioscorea because in similar climatic zones and practically neutral fertile soil this crop has always been a success unless spoiled by extreme conditions of temperature or humidity. In addition, Solanum laciniatum has been considered only as a promising source of solasodine and nothing definite is known regarding its economic viability.

The transformation of diosgenin. The method to degrade the side chain of diosgenin and solasodine to a C_{21} compound was given. Better yields have been obtained with this method and it is preferred to the existing methods as it is operated at atmosphere pressure. This method works on an industrial scale also but has one disadvantage in that the length of time is much more than with other methods. In view of this, it is felt that up to operating at the 20-l flask level, this method should be used. At the level of a 50- or 100-l pilot plant, the method involving pressure should be used. Later operations may be carried out in a glass-lined vessel of 500-l capacity. The details of this method were also given.

The conversion of a C_{21} compound to a C_{17}. This method (Beckmann transformation) has been carefully reviewed and compared with the existing method. Some modifications have been suggested with respect to the variation in the temperature at the time of addition of phosphorus oxychloride and at the time of work-up of the reaction. The method for the preparation of 16-dehydropregnenolone acetate (DPA) oxime has also been discussed and modifications have been suggested.

It is recommended that the reaction be carried out and scaled up from a 5-l glass assembly to a 20-l glass assembly to operate up to conversion of 2-3 kg of 16-DPA oxime. Other experiments should include hydrogenation and hydrolysis of 16-DPA, synthesis of methylandrostenediol and methyltestosterone, and 17α-hydroxyprogesterone. The methods for these could be dispatched at a later date.

In view of the difficulty in procurement of chemicals and equipment because of lack of foreign exchange, it is recommended that, until the methods outlined above are employed the synthesis laboratory should undertake and standardize the work-up to operating in 20-l glass flask assembly.

For the steps after these reactions, it is recommended that the technology of manufacturing of steroid intermediates and oral contraceptive ingredients should be procured and transferred, with the aid of an international organization, from a country or enterprise that can offer the technology and training facilities to the technicians. For the synthesis laboratory to standardize these steps will involve time, a large variety of equipment, the import of costly chemicals and their use in substantial quantity for standardizing the process, e.g., the introduction of the Δ^1 double bond by dichlorodicyanobenzoquinone, aromatization by lithium diphenyl and oxygen functionalization at the 19-methyl group by the lead tetraacetate oxidation method. The list of equipment and chemicals to be procured for the steps recommended to be carried out by the synthesis laboratory is given in annex IV.

The steps suggested to be carried out in the synthesis laboratory on hecogenin and diosgenin will help them to develop experimental techniques, design experiments to decide suitable parameters, scale up the reactions in general and develop an analytical approach and aptitude for applied research work.

Intrauterine devices

The use of IUD is relatively new in Cuba and there is no documentation regarding insertion failures, expulsion, inflammatory diseases or removal due to pain and bleeding. It is possible, if the information is recorded for some time, and the need for this type of information is publicized, that physicians may prefer to prescribe tablets. The increasing urbanization, industrialization and easy administration of a tablet and its ready availability may raise considerably the demand for oral contraceptives.

The manufacturing machinery and equipment will not be inexpensive and new skills and technology will have to be developed to make these devices.

The experts did not have sufficient experience of the plant that would be required, or the cost of it, to be able to provide any assistance.

It is recommended that such information be sought from an international organization.

Before a decision is taken to proceed with manufacture, senior members of technical and engineering management should visit two factories in Europe or Asia where IUDs are being produced.

II. CONCLUSIONS AND RECOMMENDATIONS

1. A modification to the engineering organization structure would be beneficial.

2. An industrial engineer should be employed to study and improve methods of operation, materials handling and cost reduction.

3. A more positive control of maintenance at all establishments is required. This includes costing methods and the provision and use of control information. The procedural paperwork in use is acceptable at present but this could be improved in the future.

4. The understanding and use of air-conditioning and ventilating systems must be developed.

5. In-plant training of engineering personnel already in the factories should have a high priority and should be linked with basic college training of a theoretical and practical nature. There is a growing need for more professional engineers and technicians.

6. Professional engineers particularly in the pharmaceutical industry, should be given more industrial experience.

7. Closer attention must be paid to the ordering of machinery to ensure that it serves the purpose for which it is intended.

8. Standards of hygiene are not good and can be improved in most of the places visited. The attitude of management needs to be changed, with support from the highest levels.

9. Further rationalization of products and manufacturing sites is desirable.

10. Accurate planning is necessary.

11. Copies should be purchased of Good Pharmaceutical Manufacturing Practices, 1977, published in English by Her Majesty's Stationery Office in London.

12. Proper documentation of feedback from oral contraceptive consumers, and a programme for monitoring the users is desirable.

13. Although the technology of manufacture is acceptable the control of quality is not of a desirable standard. The use of thin layer and gas chromatography in the detection and estimation of oral contraceptive ingredients in the formulation should be developed.

14. A separate layout for oral contraceptives has been suggested with the addition of a few machines such as a double-cone blender, dust extractor units and a ball mill. These will contribute towards uniformity of formulations and reduction of contamination hazards. A change in the formulation ingredients, such as the quantity of adjuvants necessary, followed by a stability study is recommended.

15. A simpler pack of the catch-cover type, which will accommodate the printed matter and hold the blister tray in position, has been suggested. Samples of two types have been supplied for adoption if of interest.

16. Large-scale cultivation of Dioscorea should be undertaken and the plant recommended for hecogenin extraction can also be used for diosgenin extraction. The side-chain degradation and synthesis of a few intermediates of the pregnane and androstane series should be developed by the Synthesis Laboratory. Assistance with technology and training should be sought from an international organization so that after the initial experience in steroid chemistry there would be minimum delay in developing manufacture.

Annex I

JOB DESCRIPTION

Post title:	Oral Contraceptive Production Adviser
Duration:	Two months
Date required:	As soon as possible
Duty station:	Havana, Cuba
Purpose of the project:	To assist the pharmaceutical industry of Cuba to improve production of oral contraceptives and programme the expansion of this unit.
Duties:	The expert will be connected to the Ministry of Health and will carry out the following duties: 1. Evaluate the quality and quantity of oral contraceptives currently produced in the country. 2. Project the quantity of oral contraceptives used in the next five years. 3. Evaluate the Quality Control Laboratory for such production and introduce, if necessary, more efficient analytical methods. 4. Evaluate the existing machine and advise whether additional machines or equipment are needed for current production and for the expansion programme. 5. Advise on the most suitable and economical packaging for oral contraceptives for tropical climates. 6. Prepare a training programme for technicians for the production of oral contraceptives.
Qualifications:	Pharmacist or chemical engineer with wide experience in production and quality control of drugs, specifically oral contraceptives.
Language:	Spanish; English acceptable
Background information:	Cuba has a well developed pharmaceutical industry which produces approximately 300 different products. The amount of products produced in the country meets 80%-85% of Cuba's demands. Although the Government of Cuba does not have a family planning programme, the country's policy is to provide contraceptives for those who wish to plan their family; therefore the pharmaceutical industry in Cuba started to produce oral contraceptives in 1983.

As the demand for oral contraceptives has increased, the Government wishes to expand the existing production with the aim of satisfying the country's demands and, if possible, for export purposes. In addition, the Government wishes to develop the production of oral contraceptives based on locally available raw materials.

Annex II

JOB DESCRIPTION

Title:	Adviser in maintenance of equipment for the pharmaceutical industry
Duration:	Two months
Date required:	As soon as possible
Duty station:	Havana, Cuba
Purpose of the project:	To evaluate existing machinery and assist the pharmaceutical industry of Cuba to develop a maintenance programme for its machinery and equipment.
Duties:	The expert, in co-operation with the Ministry of Health, will carry out the following duties: 1. Visit the different units of the pharmaceutical industry in Cuba. 2. Evaluate the existing machines and equipment in the production and quality control units. 3. Advise a maintenance programme for equipment. 4. Advise on maintenance of machinery, if necessary. 5. Prepare a list of spare parts possibly needed. 6. Prepare a training programme for technicians.
Qualifications:	Mechanical engineer with wide experience in maintenance of machinery and equipment for the pharmaceutical industry.
Language:	Spanish; English acceptable.
Background information:	Cuba has a well developed pharmaceutical industry with a production of approximately 800 different products. The amount of product produced in the country meets 80%-85% of the country's demands. Although the Government of Cuba does not have a family planning programme, the policy of the country is to provide contraceptives for those who wish to plan their family. Therefore the pharmaceutical industry in Cuba started to produce oral contraceptives in 1968. As the demand for oral contraceptives has increased the Government wishes to expand existing production with the aim of satisfying the country's demands and, if possible, for export purposes.

Annex III

ENTERPRISES OF THE PHARMACEUTICAL INDUSTRY

Listed below are the enterprises (by product or function) of the pharmaceutical industry.

Tablets and dragees
Injectables
Ointments
Liquids
Eyedrops and lyophilized products
Large-volume injections
Biological production of vaccines
Opotherapeuticals
Wound-dressing materials
Medical instruments and furniture
Eye equipment (spectacles and lenses)
Orthopaedic equipment
Pharmaceutical (in Oriente Province)
Maintenance
MediCuba (Import/Export)
EMSUME (Import/Export)
Central Control Laboratories
Experimental Station for Medicinal Plants

Annex IV

EQUIPMENT AND CHEMICALS FOR THE SYNTHESIS LABORATORY

Equipment

Six three-neck glass flasks with ground joints, of 500 ml, 1-l, 2-l, 5-l and 10-l capacity and three 10-l flasks with flanges to accommodate openings.

Three heating mantles, for the flasks, with thermostatic control.

All necessary adapters, vacuum bends, seals for stirrer, thermometer pockets, vacuum taps or plungers with ground-glass joints to make a reflux and distillation assemblies using each size of flask as in the first paragraph above.

Two vacuum pumps, Torr (0.01 mbar).

Two vacuum desiccators.

Glass stirrers to fit the assemblies.

One fume cupboard, width 2 m, length 4 m, height 3 m, with inside lining of fibre glass reinforced PVC, with two powerful non-corroding exhaust fans at the top of the back wall. The sliding glass door to be divided in 2-3 parts so that it is not too heavy to operate easily.

Chemicals (commercial grade)

Hexane - 100 l

Toluene - 100 l

Benzene - 50 l

Pyridine - 50 kg

Phosphorus oxychloride - 50 kg in small packages of 5-20 kg

Acetic anhydride - 50 kg

Acetic acid - 100 kg

Hydroxylamine hydrochloride - 10 kg in small packages of 500 g

Mineral acids - 50 l each

Chromum trioxide - 25 kg in small packages

Lead oxide - 5 kg

Dichlorodicyanobenzoquinone - 1 kg

Magnesium ribbon or turnings - 500 g

Hydrogen peroxide solution (20 vol %) - 20 l

Raney nickel alloy - 500 g

Palladium chloride - 100 g

Charcoal - 5 kg

Diethyl ether - 10 l in small packages

Sodium metal - 1 kg

Sodium borohydride - 100 g

Lithium aluminium hydride - 50 g

Bromine - 5 kg

Potassium acetate - 1 kg

Sodium hydroxide - 10 kg in small packages

Ethyl acetate - 10 l

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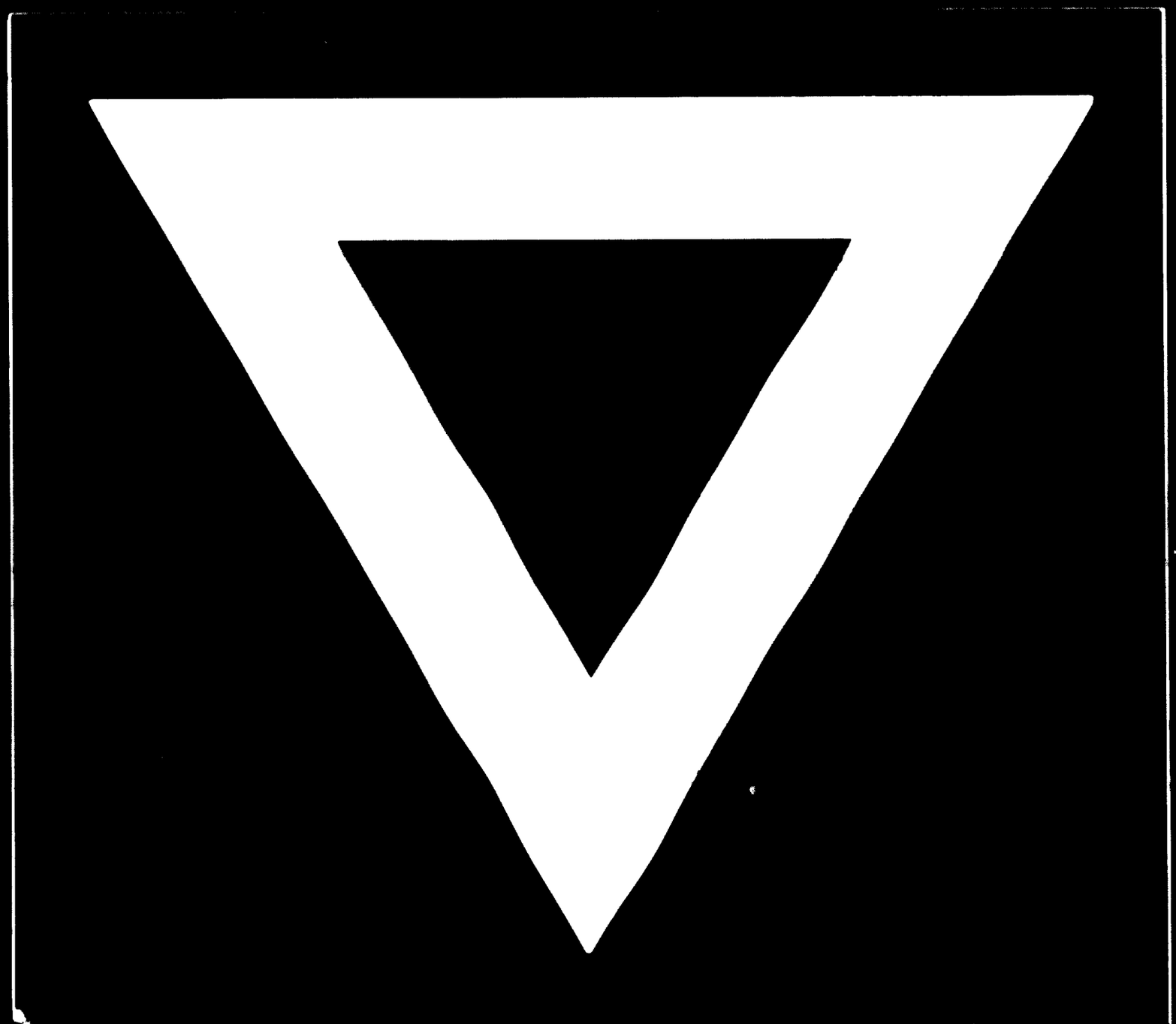

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