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PRODUCTION AND MARKETING OF THERAPEUTIC STEROIDS

DP/CUB/92/005

CUBA

Technical report: Findings and recommendations*

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

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* This document has not been edited.

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CONTENTS

RECOMMENDATIONS

1. Although during this study period the means of implementing the objective of producing either AD and ADD by fermentation of phytosterols has not been realised, efforts to do so should not be discontinued. Other avenues of investigation should be followed up.

2. The pilot proving tests planned for phytosterol production should proceed.

3. Discussions should be arranged when possible to discuss with other parties the possibilities and indications of entering a research and/or teaching agreement for commercial development of fermentation of phytosterols to AD or ADD. Investigations into funding of such proposals should also be investigated.

4. It is recommended that Cuba give priority to the production of androst 4-en-3-one (AD).

5. Production of these steroids for which established methods are available should be implemented as soon as possible.

6. A stainless steel centrifuge should be procured as soon at possible to enable the production of testosterone enanthate to proceed. A unit of 500/650 mm ϕ is considered satisfactory. A figure of USD 35,000 fob investment has been suggested (but current firm quotation is needed).

7. The completion of installation of the micro-plant should be completed sufficiently for it to function. Funds needed amount to USD 78,000.

Completion of plant with installation of a further 30 lt enamel reactor unit could be delayed until later. The importance is to have functioning facilities.

8. A training programme, especially to cover the needs and implementation of GMP, should be instigated.

9. Planning should start in considering the details and best means by which full GMP can be achieved. Special attention should be given to the planning of the segregated estrogen processing area.

1. EXECUTIVE SUMMARY.

This project, entitled "Production and Marketing of Therapeutic steroids" under project No. DP/CUB/92/005, has been funded by the UNDP and UNIDO is the executing agency.

1.1 Objectives.

The main objective is to investigate the possibility of introducing to Cuba the process(es) of microbiological fermentation(s), using phytosterols produced from sugar cane by product (or cholesterol as alternative), to produce either one or the other (or both) of the synthetic intermediates androstenedione (AD) and androstadienedione (ADD).

These products are now preferentially used as basic synthetic building blocks for a variety of bulk active steroids. The choice of products proposed are initially of particular interest for domestic use, but later provide potential export opportunity.

The supreme objective is to provide Cuba with a domestic self-sufficiency with regards to raw materials for many steroid products. The production of AD/ADD will support the current availability nationally of hecogenin as the source for cortico-steroids.

The whole future of the steroid industry developing in Cuba probably depends on the success of this project since at times world market supplies availability cannot be relied upon, and price fluctuation can result from the supply and demand situation.

Beneficiaries of a satisfactory conclusion to the project will not only be the general Cuban economy and various sections of the Ministry of Health (MINSAP), especially IMEFA, but the population of Cuba as a whole through a more secure availability of supply of the steroid section of medicines. Most important in this sector could be the adequate supply of oral contraceptives.

An additional aspect is the saving of hard currency needed to procure the basic synthetic starting materials. This is of particular importance for the intermediates represent a high proportion of production cost.

1.2 Marketing.

Marketing of steroids is also considered part of the project. This aspect refers to export products since, in Cuba, the domestic market has only competition from imports controlled by the Governement.

The main target market has been considered to be domestic and for supplying formulation facilities available in Cuba. A possibility of export marketing is also considered and such could be achieved without causing significant reaction to cause concern to major steroid suppliers.

The report analyses the various steroids proposed in terms of formulated products and competitors.

Proposals have been made that the most appropriate export market for Cuba would be that of South America, both on account of locality and market growth potential. Other areas for investigation should include the Far East, Asia and Eastern European countries. Only the generic market is appropriate to Cuba.

In addition to domestic needs the report defines the levels available for export annually over the period 1993 to 2002.

Suggestions have been made regarding strategy for export marketing, which it is considered overall must largely be operated through approved agents who have experience in specific market areas and in steroid products. Registration of products for some export markets will need to be considered.

The bulk active market will probably be easier to infiltrate than finished formulated products, although such opportunities are not excluded. Production of either under strict GMP conditions will be mandatory.

1.3 Raw materials.

Raw materials are classified in three different groups:

a) sugar cane oil - as source of phytosterols.
b) phytosterols - as source of AD/ADD.
c) AD/ADD - as intermediates for steroid synthesis.

The use of sugar cane oil as the most suitable source for phytosterols is identified and the availability determined at 400 tons in 1993 rising to 2000 tons by 1995, remaining constant then until at least year 2002. Supplies are considerably higher than ever likely to be needed for use in fermentation.

Some stabilisation of the quality of sugar cane oil for the use in production of phytosterols is advocated.

Development of the use of cholesterol and phytosterols for production of AD and ADD by microbilogical fermentation has been summarized.

1.4 Location and sites.

This section again deals with the three aspects of phytosterols, fermentation and synthesis.

Production of phytosterols is not presently established in Cuba and some basic consideration has been given to possible locations for production.

For a National production of any significant size the obvious location would be in the Oriente provinces since all the present and proposed sugar cane wax refineries are located there. The use of a site which is already serviced with electricity, water, etc, would be a significant benefit. This size of unit would be expected not only to supply material for fermentation, but

also the pharmaceutical formulation and cosmetic industries as well as having product available for potential export.

For captive use in any development possible through fermentation, especially in the early years (as well for process proving tests), it is proposed that some existing plant facilities could be utilised. The most favoured is the Mario Muñoz factory which has spare capacity and is also the base for the steroid production unit.

For fermentation insufficient information is available to make any firm proposals, but utilization of a building shell and other areas becoming redundant at Mario Muñoz could house a suitable size fermentation unit.

Also in anticipation of the need for facilities to perform preliminary proving tests or scale-up operations in fermentation several sites were investigated. It has been concluded that the most promising is a preliminary facility being erected for operation by CQF organization using some existing equipments. Support for semi-industrial tests on limited scale might be needed, but could also probably be supplied at an IIIA installation. These would be subject to availability at the time and detailed suitability.

Steroid synthesis is established at a pilot level at Mario Muñoz and has been used as the basis for determination of production capacity. While adequate in early years it is pointed out that extension of facilities will be necessary after about 3 years operation.

Several processes in the laboratory are approaching the time when scale-up is needed. The micro-plant which is also sited with the production area will also provide an important training aid when functional.

1.5 Engineering and Technology.

This section also deals with the three aspects of phytosterols, fermentation and synthesis.

Technologies for the production of **phytosterols** have been compared with the conclusion that domestic production using "in-house" technology is most appropiate.

Since production of phytosterols does not currently exist in Cuba the situation has been looked at in some detail to ascertain the likely production cost of phytosterols. Effect of size has been considered, although strictly outside of the scope of the project. Costs have also been determined for the production of quantities needed only for fermentation input and as could be produced at Mario Muñoz.

It has been concluded that a production cost of phytosterols in dedicated units could fall within the range USD 13.56 to USD 17.10 per kg. These prices are likely to be too high for export marketing, but could be acceptable for national input to fermentation.

The price determined for small scale production at Mario Muñoz was determined at USD 15.50 per kg.
To allow for a margin of domestic profit a price of USD 20.0 per Kg is used in cost calculations.

Fermentation - to date it has not been possible to obtain any offers of fermentation technology which has been operated at commercial level. This most important aspect is still under very active pursuit.

The AD/ADD levels which are needed to satisfy the production schedules over a 10 year period projection have been determined. For AD these range from 44,8 kgs (1993) to 1,638.5 kgs (2002) while for ADD the needs range from 67.5 kgs (1993) to 459.5 kgs (2002).

Corresponding levels of phytosterols as input to fermentation are estimated at from 225 kgs (1993) up to 4,196 kgs (2002).

The costs of fermentation equipments at different levels have been procured and illustrate the effect of size on cost. The possibility of more economical procurement of plant, in some circumstances, is indicated through employment of a design/engineering/supply contract.

While it has not been possible yet to find a source of supply of technology for fermentation of phytosterols to AD + ADD, preliminary costings indicate a likely economy of size. For economic production certain necessary process parameters have been laid down and indicate that even then production levels below about 4,000 Kg AD per year could not be economic. Options for progressing possibilities are considered.

Synthesis.

The possibilities of synthesis of various products from AD and ADD are illustrated in flow sheets.

A review of the progress being made in synthetic routes, particularly starting from AD and ADD, has been presented and it can be concluded that reasonable progress has been made. Products from AD are represented by testosterone, spironolactone and danazol, while those from ADD cover estradiol esters and the nor-steroid, nortestosterone es intermediate for norethisterone. Other non-AD/ADD derived products such as oxymethalone and medroxy progesterone acetate of production interest are also covered and mention of elaboration of diene acetate to corticoids.

Production

Plant capacity has been analysed indicating bottle-necks, initially in vacuum drying and after some 3/4 years in the 100 lt. unit GR 100. A plant capacity of 400 kgs bulk active steroids is indicated before extra plant is strictly needed. Capacity for 700 kgs diene from hecogenin is also possible. the best times and approaches for plant expansion are discused. The needs for drying equipment and a centrifuge have been indicated and also the importance of completion of the installation of the micro-plant for scale-up and training.

Delays have occurred in production work, which is currently concerned with manufacture of mestranol and ethinyl estradiol from 18 kgs ADD. All materials has now been converted to

estrone. Mestranol had not previously been commissioned, but the first stage to estrone methyl ether has now been completed satisfactorily. Production of 4.5 Kg ethinyl estradiol required for the contraceptive formulation has been completed.

Plant capacity including drying has been roughly analysed in terms of hours occupancy and also in some detail by a concept known as litre-hours analysis. This concept was then applied to determine realistic production costs.

Personnel and Organisation

During the recent years an organisation has been set up for operation of the steroid production and research/development in Cuba under the description Labatorio de Investigacion y Desarrollo de Estarrides (LIDE) and this is considered satisfactory.

It is proposed that any production of phytoserols performed within the Mario Munaz Complex should be controlled by this establishment and also, should the fermentation of phytosterols be ultimately established in the same process area, this function and its staff should be responsible to the chief of LIDE.

Financial and Economic aspects

Only general outlines of parameters likely to be necessary for economic production of steroids intermediates AD and ADD have been presented. Lack of technology has precluded any financial or economic projections of this aspect. Financial and economic aspects of various possible production programmes for utilization and possible extension and GMP up-grading of the steroil unit have been considered.

CONCLUSIONS

Continued efforts should be made to procure or develop technology for fermentation of phytosterols.

Meanwhile proving tests for phytosterol isolation should be performed.

Production of steroids should be started on a regular basis at whatever level from imported intermediates for productions of domestic needs for products where technology is already proved with a view to a more extensive programme leading to export potential.

To produce all domestic products development work needs to be completed and it is most important that a functioning micro-plant is made available at the very earliest opportunity. As production programmes increase special attention must be given to segregation and satisfying GMP conditions.

Training programmes for process operation, safely and GMP requirements should be formalized. Dependant on the selected production programme some investments will be necessary, but the most immediate of importance for production is a small centrifuge for testosterone enanthates.

The early provision of a functioning micro-plant for scale-up and kilogram production is essential.

2. INTRODUCTION AND BACKGROUND.

2.1 Past.

The first active step towards production of synthetic steroids was taken in the form of a UNDP funded, UNIDO executed project DP/CUB/78/003. The object of this was to set up a pilot unit to utilize technology for the production of hecogenin form the waste juice of henequen. Isolation of hecogenin represented the first domestically produced starting material for steroid production, principially for corticosteroids.

A further project was funded by UNDP and executed by UNIDO under project DP/CUB/81/01 entitled "Development of Advanced Steroids Production in Cuba". This project which included transfer of techonology covered the production of classical steroids, corticosteroids and an important diuretic. Starting materials were principally diosgenin and hecogenin.

At the time the second project started diosgenin was the most important starting material for classical steroids and could also be used for corticosteroids if fermentation steps were included. It was thought at that time that diosgenin could be obtained from plant crops introduced into Cuba, such as dioscorea or Costus amongst others. An alternative plant species of Solanum providing solasodine, which can be rather similarly degraded as diosgenin to a common intermediate, was also under consideration and being investigated at the Medicinal Plant Centre. Neither of these possibilities has materialised.

Nonetheless project DP/CUB/81/013 resulted in the provision of a modern pilot production unit, of multi-purpose design, for production of several steroids by synthesis. Many unit processes were performed and several products satisfactorily produced during commissioning. A group of technicians and operators were trained and performed with satisfaction during commissioning.

2.2 Present.

While the original concept of project DP/CUB/81/013 was sound two things have changed.

Firstly, the realisation of domestic production of sources of diosgenin (or as alternative solasodine from Solanum) has not been achieved.

Secondly, in the international scene the importance of diosgenin as a base raw materials for production of classical and similar steroids has diminished to some considerable exent. It is still an important source material for corticoid production, but even this may change in the coming years.

The reason for the change was the availability in the international market, from about 1983/4 of alternative starting materials androst-4-ene-3,17-dione, (AD) and androsta-1,4-diene-3,17-dione (ADD) at very competitative prices with respect to diosgenin. These products, AD & ADD, were being produced by microbiological (fermentation) degradation of cholesterol and beta-sitosterol. While alternative synthesis methods had to be developed these starting materials provide a shorter route and more economic route to final products as compared

with diosgenin as starting material or even the intermediate dehydroepiandrosterone acetate prepared from it.

Using AD and ADD as starting materials is of particular interest to the Cuban situation. Synthetic routes from AD and ADD are significantly shorter than from diosgenin and consequently the capacity of the plant for producing final products is increased. Secondly not only will the range of imported additives be considerably reduced but, by judicious choice of final products, it may be possible to minimise the range of reactions performed and thus maximise individual chemical order levels. This should minimise both purchase prices and consequently product costs.

Work in the field of microbiological degradation has continued actively since the days when it was first introduced and the most recent work is concentrated on production of the intermediate 9-alpha-hydroxy-androst-4-en-3,17-dione which promises even further advantageous access into the area of corticosteroid production. Not only can the corticosteroid side chain be built up, but also easy access is provided for the ring C elaboration needed for halogenated corticosteroids without having to resort to additional fermentation steps.

Source materials for microbiological production of AD & ADD are principally cholesterol, beta-sitosterol, alpha-sitosterols or phytosterols mixtures (of beta-sitosterol, stigmasterol and campesterol mainly).

Cholesterol is potentially available in Cuba to a limited exent from cattle spinal cord. The alternative sources of cattle brain and sheep wool are not appropriate for Cuba.

Phytosterol mixtures may be obtained from, amongst others, sugar cane wastes and potentially Cuba has almost unlimited supply. Production of essentially pure beta-sitosterol (from tall oil or cotton seed oil) or stigmasterol/beta-sitosterol (from Calabar or Ordeal beans), alkaline refining of soy bean oil (by product of soap stock) are not appropriate to the Cuban situation.

2.3 Future.

This is the object of this project study.

The means of isolating the basic phytosterols at an attractive economic price must first be established. It will then be necessary to determine the means by which it may be possible to establish microbiological fermentation in Cuba, and the facilities needed in which to do so, to produce the essential starting materials, AD & ADD.

Technology is not likely to be readily available. Consideration will have to be given as to the available and best means by which such technology can be procured or developed.

Changes are also necessary in the synthetic routes to some of the final bulk products demanded in Cuba and this aspect will also be dealt with within this project both by provision of technology and development in the Cuban laboratories.

Production programmes to satisfy both domestic needs and provision of products to develop entry into marketing in the international field will be considered. Current and future production facilities and requirements will be analysed.

All these aspects will contribute in performing the techno-economic study to determine the possibility of producing AD and/or ADD from phytosterols derived in Cuba and from which a secure and developing steroid industry in the country can be sustained.

2.4 Project justification & possible beneficiaries.

It is of the greatest importance that the expertise and experience gained during the commissioning of the pilot production unit for steroids is not lost.

An idle plant is on no value. Domestic supply of a cheap and ensured supply of raw materials AD and/or ADD will permit the pilot plant to be operated most efficiently to provide steroids for domestic consumption and provide opportunity to investigate international export markets. Such utilisation can also provide confidence for the possible future installation of larger units.

In this way Cuba could conceivably be a significant provider of valuable steroid products.

Major beneficiaries can be defined as:

a) The Cuban economy.

b) The various formulation production plants of IMEFA.

The first to benefit is likely to be the new oral contraceptive plant which could be provided with all its estrogen requirements and a considerable level of progestogens from domestically produced materials. Also other tabletting units, especially No's 2 & 3 which will have steroid processing facilities.

Materials will also be available for the production of injection formulations in existing facilities and especially for any future facilities for injection products for contraception.

c) MINSAP, with respect to having several internal demands satisfied and to the opening of important lines of business for exportation.

d) The establishment ERON responsible for export marketing by extension of its range of products.

e) The establishment MARIO MUÑOZ through utilizing its existing pilot steroid production plant and possible exention of its activities. In addition to the opportunity to use facilities more efficiently opportunities for additional employment are likely to be improved.

f) The Cuban population in general through the likely availability of better supplies of steroid products and possible extention of formulations.

g) MINAZ through further extention of the use of sugar by-products.

3. MARKETING ANALYSIS AND MARKETING CONCEPT.

3.1 General.

Consideration has to be given in this project evaluation to both domestic marketing and export marketing.

While the most profitable marketing, taken at face value, would be of formulated products such would probably be the most difficult to promote. Sale of bulk active steroids has to be considered the prime marketing opportunity.

Since economic advantage and success lies in the possibility of Cuba providing its own basic starting material from natural by-products consideration may have to be given even to the marketing of the products AD and ADD. as with many productions there can be an economy of scale, which when this has been analysed might indicate production of more basic intermediates AD & ADD than can be readily consumed directly for further processing in Cuba. Other considerations may also have to be taken into account should any opportunities for joint venture production of AD & ADD be realised.

3.2 The Steroid Market.

3.2.1 Market size.

This can only be determined in terms of value of ethical formulated products since manufacturers do not reveal their production, purchase or consumption levels of bulk active ingredients.

Total world consumption by 1990, in formulated presentation of steroid products was about USD 35bn which represented about 2.6% of the total world market of ethical pharmaceutical drugs (USD 135bn). These figures exclude Eastern European production and consumption which probably rated about USD 9bn - 12bn for total pharmaceutical drugs.

The figures for Eastern Europe are considered to be very conservative with respect to potential since they correspond, due to shortages and funds, to a very low per capita consumption. In the USSR in 1988 consumption for all pharmaceutical drugs was reported at only USD 17 per capita against USD 115 - 144 per capita for various developed countries.

Cuban per capita consumption for all pharmaceutical drugs is recorded at USD 34. The figure is undoubtedly depressed by lack of availability of hard currency.

3.2.2 Growth rate.

The world market for all pharmaceutical drugs increased from USD 135bn in 1990 to USD 170bn in 1992, corresponding to an average annual increase in value of 12.5%.

Growth rate in steroid products, as with other pharmaceutical drugs, varies within therapeutic groups. Over the past decade an average growth rate in value terms of between 16% & 18% has been observed, although certain products have shown rates in the region of 30% p.a. for some years.

The overal market value of sales between 1985 & 1989 was doubled, corresponding to 20% p.a. while from 1990 to 1992 (as indicated above) the rate was 12.5% p.a.

In case of steroids a growth rate over the next 10 years of 6-10% p.a. of established products might be expected, although Cuban projections have been limited conservatively to a maximum of 5%.

3.2.3 Specific steroid groups.

Steroids may roughly be divided into the groups:

- corticoids
- estrogens
- progestogens
- androgens & anabolics
- diuretics

Detailed analysis of each group is not available but the following general facts are recorded.

a) The largest steroid market comprises topical cortico-steroids, being rated at USD 1.6bn in 1989. Hydrocortisone is the most important single corticoid whose growth in recent years has been significantly affected by the fact that several countries now permit its use in various OTC (over-the counter) products. Further significant growth exists in this area.

Corticoids used in inhalation formulations (for asthma and nasal inflammation) currently provide a particularly impressive growth area. The market in 1989 at USD 500m represented 30% of the value of the world market for all inhalation products. By 1991 sales had risen to USD 840m influenced largely by improved methods of application. The forecast is that by 1996 steroid inhalation products will represent as much as 40% of this market. Principle active ingredients are the patented products beclamethasone and budenoside.

Corticoids do feature in the long term strategy for steroid production in Cuba, but do not represent any particular element of this study.

b) Female sex hormones, estrogens and progestogens represent the second largest market group. Both estrogens and progestogens are each estimated to have a formulated market value of USD 500m.

Current market leaders are the conjugated estrogens (estrone and equilin sodium sulphates) and mestranol in the case of estrogens while progesterone and medroxyprogesterone lead as progestational agents.

Ethinyl estradiol is, in fact, more widely used than mestranol and both products will be important and major products in the Cuban strategy together with several esters of estradiol.

c) The third major group by value comprises the anabolics and androgens of which testosterone esters are the most important. Both products are included in the Cuban programme.

d) The final group consists of one major steroid diuretic product.

Diurectics are provided by four groups of compounds known as loop diuretics, thiazide diuretics, carbonic-anhydrase inhibitors and last group of K^+ (potassium ion) - sparing diuretics. One major steroid diuretic, spironolactone, has the activity of the last group.

The market for diuretics as a whole is large, but that for the steroid element is not available.

This product is very important for Cuba since importations have approached 300 kgs in a year at a value in the order of USD 100,000.

3.2.4 Bulk steroids market.

The value of the bulk steroids market can only be derived from the value of the formulated products. Any figure cannot be considered very accurate and it is impossible to readily determine the proportions formulated in-house by manufacturers and the amounts freely available on the bulk international market.

Some estimate of export sales could be obtained by analysing the import statistics of the various countries where these exist. Nonetheless experience shows the published figures can be notoriously misleading and it is not considered that such an exercise could warrant the time and expense necessary in carrying this out.

Estimations from the experience of cost relation of active ingredients to sales prices of formulated products leads to an estimate that a range of USD 70-175m represents the value of manufactured bulk product.

3.3 Market distribution

3.3.1 Exporting countries.

The USA and Western Europe (European Community) dominate exportations accounting for 70% in 1989. In line with the total market sales the export values doubled between 1985-1989.

Several developing countries also reported significant levels of exports in 1989. In descending order these were: Mexico (USD 24.8m), Hong Kong (USD 7.1m), Argentina (USD 6.8), Brazil (USD 4,5m) and India (USD 2.8m).

These figures represent total steroid exportations and no figures are available to indicate the formulated proportion.

Mexico and India, in particular, are known to have bulk production facilities for steroid products whereas the others rely more on bulk importations for formulation or re-exportation.

The only figures available indicating a relationship of bulk active steroids and the formulated products are ones which have been published in the UK.

Prices in m pounds sterling, fob.

Year:	1980	1981	1982	1983	1984	1985	1986	1987
Bulk hormones	21	19	13	19	27	30	40	32
Formulated	39	55	71	76	67	107	103	123

Bearing in mind the cost of bulk product in formulations, these figure indicate that the volume of bulk active steroids marketed as such exceed significantly those formulated.

3.3.2 Importing countries.

The principal importing countries for steroids reported in 1989 of the developed countries were: Italy (USD 202.8m), France (USD 182.6m), Japan (USD 85.2m) and USA (USD 73.5m). As with exports the proportions of formulated/bulk steroids are not available. Use of import statistics for these countries could be helpful in further analysis.

The leading imports of developing countries, also in 1989, were: Mexico (USD 30.2m), Brazil (USD 24.1m), India (USD 13.2m), Indonesia (USD 11.7m), South Korea (USD 10.1m), Chile (USD 9.7m), Colombia (USD 7.8m), Pakistan (USD 7.6m), Egypt (USD 7.1m), Argentina (USD 5.9m), and Venezuela (USD 5.8m).

With regards to the potential export markets for Cuba it is evident that the South American markets, which could be very appropriate, are very significant amounting to in excess of USD 80.3 m annual value. Currently this figure is likely to be in excess of USD 100m.

3.4 Production-selection-strategy Cuba.

Of consequence to the Cuban strategy are:

a) raw material availability.
b) Cuban domestic needs.
c) availability formulation facilities.
d) modest production excess to enter international market.
e) technological capability.
f) cost of production.
g) conservation of hard currency.

The starting materials AD and ADD are considered to be the most appropriate for the production of the bulk of the steroids which will be of most interest to Cuba.

While purchase of these intermediates on the international market should not be entirely discounted, problems can always be encountered with availability and price as well as reducing hard currency.

The project hopes to identify the possibility of providing self sufficiency of raw material supply and a price benefit as well as receiving drains on hard currency.

Production levels have been planned to satisfy increasing domestic needs of the most important steroid consumptions in Cuba while also allowing opportunity for gradual entry into international export markets.

Particular importance has been placed on supplying bulk active raw materials to largely service the needs of the recently erected and new oral contraceptive plant which will be operational in 1993.

Technologies for the production of the selected range of products have been considered. In general methods are available or can be provided for all phase 1 products. The development section will be well occupied proving the new methods, scaling-up and developing methods especially for the phase 2 products.

The immediate products selected for the strategic list are:

Phase 1:

- Ethinyl estradiol
- Mestranol
- Estradiol-3-benzoate, 17-valerate (& 17-cypionate)
- Testosterone propionate
- Testosterone enanthate

Phase 2.

- Spironolactone
- Norethisterone (and esters)
- Danazol
- Medroxyprogesterone acetate
- Oxymethalone (from hecogenin)

The recent establishment of an oral contraceptive plant for formulation in Cuba having a capacity of 500 million tablets per annum and which should be operable by mid 1993 has influenced the primary choice of estrogens, ethinyl estradiol and mestranol.

Some small productions of estradiol benzoate and valerate (& possibly cypionate if cost is not too high) are also planned. These are not constituents of oral contraceptives and will be processed for formulation in another unit.

The possibility of domestically producing some progestogen components for oral contraceptives has not been ignored.

In Cuba two progestogens are currently employed, levonorgestrel and norethisterone. Levonorgestrel is a fully synthetic steroid which cannot readily be prepared from AD or ADD and is excluded from considerations. Norethisterone (& its 17-acetate can be produced form ADD or possibly AD and is included in phase 2 of the strategy.

Although not listed norethisterone enanthate may also be included when clear plans can be seen of the provision of facilities for preparation of sterile injectable contraceptive products. A significant and growing market exists for such products.

Medroxyprogesterone acetate is also a component for injectable contraceptives, but is also employed in treatment of several disorders.

Testosterone propionate and enanthate were selected on the basis of considerable and growing consumption in Cuba. Formulation of these products are in the form for injection, either oil or aqueous, and will satisfy needs of existing formulation facilities.

Phase 2 products represent ones where processing methods are still being either checked or developed in the laboratory. Many are reasonably well advanced. In terms of volume and value spironolactone is the most significant Cuban bulk import.

Within the synthetic programme several other useful steroids will be produced. None are initially considered of prime importance in Cuba, but worldwide significant demands do exist. Products in this category are ethisterone and nortestosterone. Substantial quantities of ethisterone are consumed worldwide and nortestosterone, in the form of several of its esters, is an important anabolic steroid. It is currently imported into Cuba only in formulated form.

3.5 Utilization of selected bulk active steroids.

3.5.1 Cuban formulations.

Oral contraceptives
Tablets.

	Levo-norgestrel	Ethinyl estradiol	Mestranol	Nor-ethisterone
Norestra	0.25mg	0.05mg	_	-
Noretil	0.25mg	0.03mg	_	_
Trisnor A	0.05mg	0.03mg	_	_
B	0.07mg	0.04mg	_	_
C	0.125mg	0.03mg	_	_
Medrone-1000	_	_	0.05mg	1.0mg
Medrone-500	_	_	0.05mg	0.5mg
Aminor	0.03mg	_	_	_

Estrogens (& combination).
Injections.

Estradiol benzoate (-1 & -5)	1mg & 5mg/1mL ampoule
Estradiol valerate (Depo-estradiol)	10mg/1mL ampoule
Estradiol valerate /Testosterone enanthate (Androstradiol depósito)	4mg+65mg/1mL ampoule

Androgens.
Injections.

Testosterone própionate (Androgenona)	25mg/1mL ampoule
Testosterone enanthate (Androgenona deposito)	100mg/1mL ampoule

Anabolic.
Tablets.

Methandrostenolone (Metandienona-5)	5mg

Progestogens (other than for contraceptives).
Injections/tablets.

Progesterone	25mg & 50mg/1mL ampoule
Hydroxyprogesterone caproate	250mg/1mL ampoule
Medroxyprogesterone acetate	5mg tablets

Diuretic.
Tablets.

Spironolactone (Espironolactona)	25mg

Corticoids.
Injections, tablets, creams, opthalmic drops.

Betamethasone sodium phosphate	4mg/1mL ampoule
Triamcinolone acetonide	40mg/1mL & 200mg/5mL ampoule
Methylprednisolone	40mg/2mL ampoule
Prednisolone	5mg & 20mg tablets
Dexamethasone	0.5mg & 0.75mg tablets
Cortisone	25mg tablets
Fludrocortisone	1mg tablets
Hydrocortisone sodium succinate (freeze dried)	100mg & 500mg vials
Triamcinolone acetonide	0.1% cream

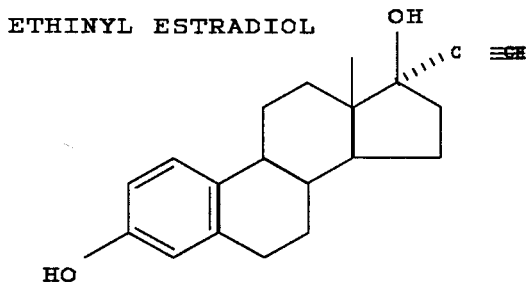
Other steroids imported in formulated form.

Danazol (Danocaine)	200mg x 60 capsules
Oxymethalone (Anadrol) (Anapolon)	50mg x 100 tablets
Nortestosterone decanoate (Nandrolone decanoate)(Deca-durabolin)	25mg & 50mg/mL ampoule
Nortestosterone phenylpropionate (Nandrolone phenylpropionate) (Durabolin)	25mg & 50mg/mL ampoule
Norethisterone enanthate (Noristerat)	200mg/mL ampoule

3.5.2 Compositions of formulated products marketed world- wide.

This analysis covers a typical cross section of the world-wide utilization of those bulk steroids included in the Cuban strategy to give an indication of the extent of use in export markets.

ETHINYL ESTRADIOL



An estrogen which, with one exception, is formulated together with another active ingredient. Majority of combinations are with progestogens and products mostly used as oral contraceptives.

Products with which ethinyl estradiol is co-formulated are: norethisterone, norethisterone acetate, cyproterone, lynestrenol (largely discontinued now), norgestrel, desogestrel, levonorgestrel, gestodene, ethynodiol diacetate and methyltestosterone.
A rather wide range of formulations & dosages may be experienced in different markets as the table indicates.

TYPICAL PRODUCTS CONTAINING ETHINYL ESTRADIOL.

Ethinyl estradiol	mgm 50	mgm 50	mgm 30	mcg 50	mcg 50	mcg 50	mcg 35	mcg 35	mcg 35	mcg 30	mcg 30	mcg 20	mcg 20	mcg 20	mcg 35	mcg 35	mcg 30	mcg 4.4	mcg 3.0
															35	35	40		
																35	40		
Norethisterone	-	-	-	-	-	-	1.0	0.5	0.4	2.0	-	1.0	-	-	0.5	0.5	-	-	-
															1.0	.75	-	-	-
																1.0			
Norethisterone Acetate	1.0	0.4	1.5	0.4	3.0	-	-	-	-	-	1.5	10	1.0	-	-	-	-	-	-
Cyproterone	-	-	-	-	-	-	2.0	-	-	-	-	-	-	-	-	-	-	-	-
Lynestrenol	-	-	-	2.5	10	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Norgestrel	-	-	-	0.5	-	-	-	-	-	.75	-	-	-	-	-	-	-	-	-
Desogestrel	-	-	-	-	-	-	-	-	-	.15	-	-	-	-	-	-	-	-	-
Levonorgestrel	-	-	-	.25	-	-	-	-	.25	.15	-	-	-	-	-	.05	-	-	-
																.075			
																.125			
Gestodene	-	-	-	-	-	-	-	-	-	0.075	-	-	-	-	-	-	-	-	-
Ethynodrioldiacetate	-	-	-	1.0	-	-	-	-	2.0	-	-	-	-	-	-	-	-	-	-
Methyltestoterone	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3.6	.667

Note: Table to be read across for ethinyl estradiol & down to locate combination product. With exception of product comprising ethynil estradiol alone, all products consist of only two components. Combination for diphasic and triphasic to be read in order printed.

mgm = milligram mcg = microgarm Quantities for all constituients other than ethinyl estradiol shown in mgm.

Bulk producers:

Schering Diosynth

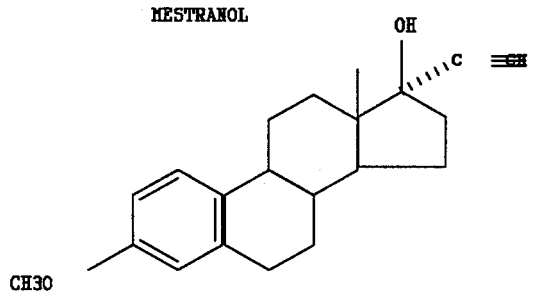
Formulators:

a) Principal	(+ other active ingredients)
Ortho	Norethisterone
Schering	Levonorgestrel, gestodene, norgestrel
Organon	Gestodene, (Lynestrenol)
Wyeth	Levonorgestrel, gestodene
Searle (Gold Cross)	Ethynodriol diacetate
Syntex	Norethisterone
Parke Davis	Norethisterone acetate
Cilag	Norethisterone

b) Lesser

Westmont Nicholas Roussel-Uclaf

MESTRANOL



An estrogen used in oral contraception products and for some female disorders such as uterine bleeding, pre-menstrual syndrome and dysmenorrhagia. The oral contraceptive with the largest market is Orthonovum which contains mestranol.

Mestranol is used in combination with progestogen.

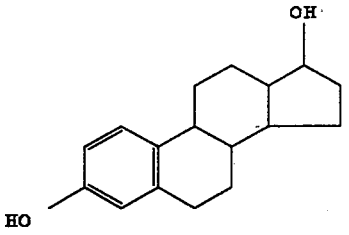
Typical products containing mestranol.

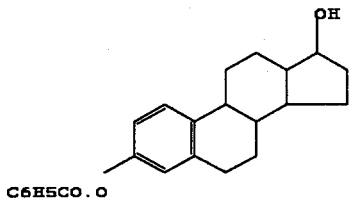
Mestranol	Norethisterone
0.05mg	1.0mg
0.10mg	6.0mg
(5)x0.125mg	-
(8)x0.025mg	-
(2)x0.050mg	-
(3)x0.025mg	1.0mg
(6)x0.030mg	1.5mg
(4)x0.020mg	0.75mg

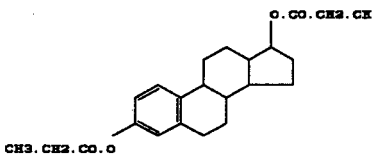
Bulk producers.
Schering
Diosynth

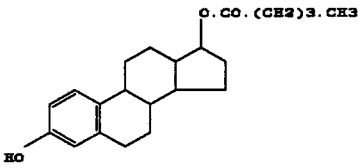
Formulators.
Ortho
Syntex
Searle
Organon
Ciba

ESTRADIOL AND ESTERS. (3-BENZOATE: 17-VALERATE: 3,17-DIPROPIONATE)









These are estrogens. Mostly are formulated alone, but in some instances together with other estrogens (estrone, estriol), with progestogens (progesterone, norethisterone acetate) or with the androgen testosterone enanthate. Presented as tablets, for injection, creams and as transdermal patches.

Used for treatment of post-menopausal deficiency states, prophylaxis of post-menopausal osteoporosis. Creams used for local treatment of atrophic vulvitis, vaginitus or urethritis. Have extensive use in HRT (Hormone Replacement Therapy) and for primary amenorrhagic lactation suppression.

Typical products containing estradiol and esters.

Estradiol	Estradiol Benzoate	Estradiol valerate	Estradiol diprop.	Estrone	Norethisterone Acetate	Estriol	Testosterone enanthate
	5 mg	8 mg			20 mg		180 mg
25 mg(tr)							
50 mg(tr)							
100 mg(tr)							
0.25 mg							
			5mg/1 ml(i)				
0.6 mg				1.4mg		0.27 mg	

Note: (tr) = transdermal patch: (i) = injection. Rest tablets.

The largest estrogen market is for "conjugated estrogens". Wyeth hold a virtual monopoly on this product. While not related to the current project, consideration might be given in Cuba to the production of conjugated estrogens at a later date since the market is so large.

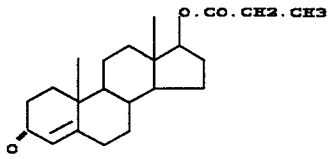
Bulk producers:
Roussel Uclaf
Schering
Diosynth

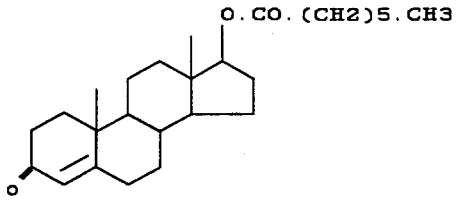
Formulators:

a) **Principal**
Schering
Organon
Ciba (especially transdermal).

b) **Lesser.**
Ayerst
Novo
Carnrick
Zofa
Weber
Paynes & Byrne

TESTOSTERONE ESTERS (PROPIONATE & ENANTHATE).





These products are mostly formulated alone or as a combination of esters. There are some combinations of testosterone enanthate with norethisterone, estradiol benzoate and valerate for treatment of primary and secondary suppression of lactation. A few other combinatios with non steroidal components are also marketed.

Products are used for post-menopausal hepatic cirrhosis and female mammary carcinomas. Also for male hypogonadism and osteoporosis due to androgenic deficiency. They are also used for hormone replacement therapy.

Most preparations are presented in ampoules for injection.

For completeness some other esters have been included in the table of products. Although not of special interest to Cuba these other esters could be readily produced.

Typical products containing testosterone esters (& testosterone)

Testosterone	Testosterone Propionate	Testosterone Enanthate	Testosterone Phenylprop.	Testosterone cypionate	Testosterone isocaproate	Testosterone decanoate	Testosterone undecanoate
			40 mg		40 mg		40 mg (cap)
	25 mg & 50 mg						
25 mg							
	50 mg (oil)	200 mg					
	30 mg		60 mg		60 mg	100 mg	
			250 mg				
	25 mg						
	50 mg						
	100 mg						
		250 mg					
	20 mg		40 mg		40 mg		

Note: (cap) = gelatine capsule. All others indicated as content/ 1 ml ampoule.

Bulk producers:

Schering	Roussel Uclaf
Diosynth	Upjohn

Formulators:

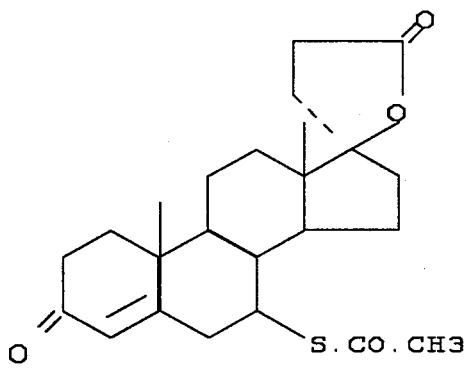
a) Principal

Schering (propionate & enanthate)
Organon (prop., phenyl prop., isocap., & undecanoate)

b) Lesser

Upjohn (Cypionate)
Aspro-Nicholas (Testosterone)
Merck (Propionate)
G. Richter (Phenyl propionate)
Paine & Byrne (Propionate)

SPIRONOLACTONE.



This product is usually formulated alone, but sometimes in combination with non-steroidal diuretics (Frusemide, Thiazide). Formulation is in tablet form.

Spironolactone is a diuretic known as a K^+ sparing derivative which inhibits exchange of Na^+ for K^+ ions the distal tubule inhibiting aldosterone.

Spironolactone is an important drug used in congestive cardiac failure, hepatic cirrhosis, malignant acites, nephratic syndrome and primary aldosterionism.

Typical products containing spironolactone.

Spironolactone	Frusemide	Thiazide
50mg	20mg	
25mg		2.5mg
25mg		
50mg		
100mg		

Bulk producers:

Boehringer Mannheim	Lab. Chim. G. Zoja Spa.
Schering	Secifarm
Diosynth	Searle
Gist Brocades	

Formulators:

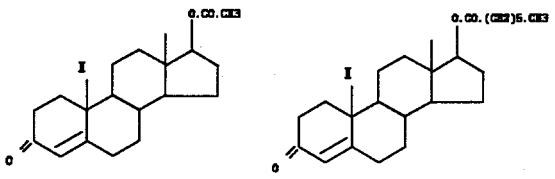
a) Principal

Searle (Gold Cross)
Hoechst

b) Lesser

Berk
Lagap
DOSA

NORETHISTERONE AND ESTERS. (ACETATE & ENANTHATE).



Generally presented in tablet form, but enanthate for injection.

Combined with ethinyl estradiol or mestranol for oral contraceptive use or with other estrogens, estradiol or estriol, for other uses.

Useful for menstrual disorders, as oral contraceptive, for hormone replacement therapy, for postponement of menstruation, dysmenorrhagia, menorrhagia and pre-menstrual syndrome. Also for prophylaxis of post-menstrual osteoporosis and disseminated mammerial carcinoma. Injection of norethisterone enanthate is used as long acting contraceptive.

Several of the earlier contraceptive progestogen components, such as lynestrenol and norethynodrel were effective through metabolism to the active norethisterone.

Typical products containing norethisterone & esters.

Norethisterone	Norethisterone acetate	Norethisterone enanthate	Mestranol	Ethinyl estradiol	Estradiol	Estriol
5 mg	-	-	-	-	-	-
1 mg				0.05 mg	-	-
1 mg	-	-	-	0.035mg	-	-
0.5 mg	-	-	-	0.035mg	-	-
0.4 mg	-	-	-	0.035mg	-	-
0.35 mg	-	-	-	-	-	-
-	10 mg			0.02mg	-	
-	10 mg	-	-	-	-	-
-	4 mg			0.05mg	-	
-	3mg	-	-	0.05mg	-	-
-	1 mg	-	-	0.05mg	-	-
-	1 mg	-	-	-	0.05 mg(p)	-
-	-	200 mg	-	-	-	-
0.5 mg	-	-	-	0.035mg	-	-
1.0 mg	-	-	-	0.035mg	-	-
-	-	-	0.0125mg	-	-	-
-	-	-	0.025 mg	-	-	-
-	-	-	0.050 mg	-	-	-
1.0 mg	-	-	0.025 mg	-	-	-
1.5 mg	-	-	0.030 mg	-	-	-
0.75 mg	-	-	0.020 mg	-	-	-
-	-	-	-	-	2 mg	1 mg
-	1.0 mg	-	-	-	2 mg	1 mg
-	-	-	-	-	1 mg	0.5 mg

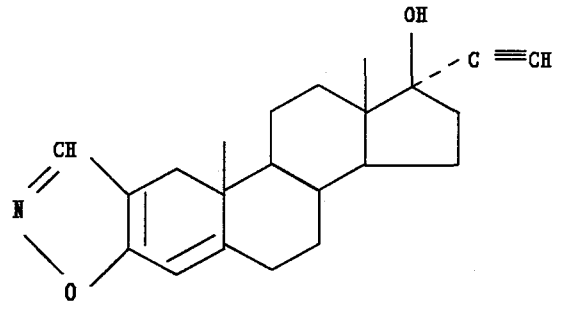
Note: (p) = transdermal patch. (i) = injection All others tablets.

Bulk producers:
Schering
Diosynth

Formulators:

Schering	Parke Davis
Syntex	Weber
Ortho	

DANAZOL.



Action of danazol is through suppression of pituitary gonadotrophin output; it has no inherent estrogenic or progestational activity and is only slightly androgenic. It is used mostly in endometriosis, but also for menorrhagia, benign breast disorders, premenstrual syndrome, gynacomastic and precocious puberty.

Danazol is used alone, in tablet or capsule forms.

Typical products containing danazol.

Danazol 100mg & 200mg.

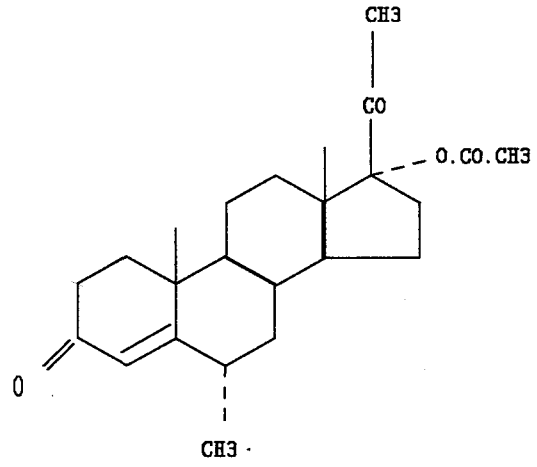
Bulk producers:

Schering
Diosynth

Formulators:

Winthrop

MEDROXYPROGESTERONE ACETATE.



Medroxyprogesterone acetate is a progestogen used for a wide range of menstrual disorders including premenstrual syndrome, severe dysmenorrhagia, dysfunctional uterine bleeding and amenorrhagia. It is also used as a depot injectable preparation for contraception and for chemotherapy of neoplastic disorders, mainly prostatic and breast cancer.

Medroxyprogesterone acetate is used alone and presented in tablet form or a suspension for injection.

Typical products containing medroxyprogesterone acetate.

Tablets: 10mgs; 100mgs; 200mgs; 250mgs; 400mgs & 500mgs.
Injection: 150mg/1mL.

Bulk producers:

Schering
Diosynth
Antibioticos
Cesquisa
Upjohn

Formulators:

Uphjohn
Farmitalia Carlo Erba
Leo
Biopharma

3.6 Marketing possibilities and potential.

3.6.1 Domestic possibilities.

With the existance of a generic policy in Cuba and no multi-national or foreign presence in the country domestic production can account for 100% of needs subject to adequate production levels of bulk active steroids and the satisfactory formulation standards and capacities.

The capacities of bulk production will be dealt with in detail when the technology and production programme is considered. Here the availability of products in formulated presentation is of importance and a brief analysis of present and future capabilities in Cuba is considered.

Formulation facilities in existence or planned to be built in Cuba

Formulation facilities, both operable and in course of construction, are listed below.

OPERATION	STATUS	CAPACITY	FACILITIES
Reinaldo Gutierrez	Operational	-	Limited steroid processing facilities; tablets only.
Oriente	Operational	-	Limited steroid processing facilities.
Tablet N°1	Established 1992, partly operational.	6000 million tablets per annum.	Not suitable for steroids.
Tablet N°2	Under construction, due 1993/94	6000 million tablets per annum.	Some capacities for steroids, but limited for estrogens.
Tablet N°3	Planned. Estimate operational 1995/n	5000 million tablets per annum	Some capacities for steroids, but limited for estrogens.
Anticonceptivos	Was due completion end 1992. Expect operational end 1993 - early 1994.	500 million tablets per annum	Enterely for hormonal oral contraceptive tablets (estrogens/progestogens).
Planned	No forecast date	2.6 million units	Initially only ampoules for injectables, including estrogenic steroids and others. Lypholization & vials excluded at moment.
a) Juan R. Franco b) Pedro Ballester c) Eduardo Reyes Canto	Operational Operational Operational	Three units having total capacity 2.9 million units.	Some capacity for nonestrogenic steroids.

The total capacity in units 1-6 inclusive for steroids is estimated at 2,500-3,000 million tablets p.a. of which 500 million tablets containing estrogen are accounted for in the contraceptive plant.

All of the establishments have not been visited, but it has to be assumed that when operational the new units will fully satisfy todays standards required for GMP (Good Manufacturing Practice). Conditions are especially important for the formulation of estrogenic steroid products, not only for product protection but also for operator security.

Supply of any products to any export market would require the highest GMP standards to be applied.

If steroid products continue to be packaged in the older establishments it would not be surprising if up-grading of facilities to meet current GMP requirements was found necessary.

Although no figures have obtained yet for corticoid formulating in **tablets** other steroid tablets were only produced in 1992 at a level of 14.1 million tablets. At forecast growth rates this figure could reach 16.2 million by 1997 and 18.6 million by year 2002. Such levels occupy only a minute proportion of available capacity.

Contraceptive tablets: At present some 3.3 million women are within the fertile age range and the level will be constant over the next 10 years. There is presently a shortage of oral contraceptives and the authorities consider that three times present supplies are needed. This would allow a campaign to be launched to promote oral contraception. If a 60% penetration of the domestic market was achieved almost 500 million tablets would be needed which is the full capacity of the new contraceptive plant. The market could be satisfied just up to this level.

Injectable products: The table below shows the 1992 level of ampoules prepared and forecasts for the next 5 & 10 years.

Year	Total ampoules	%Total capacity	Estrogen ampoules	%all ampoules	%Total capacity
1992	0.915M	31.6	0.311M	34.0	10.7
1997	1.062M	36.6	0.384M	36.2	13.2
2002	1.237M	42.6	0.474M	38.3	16.3

In this table only the capacity of existing units has been taken into consideration.

There is adequate capacity for domestic needs and some scope for export products.

It has not been possible yet to obtain the available capacity solely for estrogenic products and since these are forecast to increase at a higher rate than other productions due consideration should be given in a detail forecast.

No facilities for production of freeze-dried products, gelatine capsules or transdermal patches are currently available.

3.6.2 Export capabilities.

Tablets: as indicated in the previous section present domestic productions of non-corticoid steroid products would occupy less than 1% of total anticipated capacity for tabletting of steroid products. The only limit for export would be the level of orders obtainable.

In the case of **contraceptive tablets** the position is different. The levels of products available for export will be governed by the domestic effort to promote the preferential use of oral contraceptives for birth control. It is calculated that if a 60% penetration of domestic market is reached then 100% of the new oral contraceptive formulation plant capacity will be needed for domestic consumption.

Injection products: until the time that any further plant is erected it would appear that Cuba could have a modest capability in this area amounting to about 1.66M ampoules p.a.

There is no capability for vials of lyophilized (freeze dried) products nor for gelatine encapsulation or transdermal patches.

Bulk products: An analysis of the production forecasts will be given in the later sub-section 3.7.3.

Very modest levels will be defined for materials available for export either in formulated form or bulk and the proportions will depend on facilities and marketing success.

In any case the level of projected sales are insignificant with relation to the potential needs of world-wide formulation operations. Provided products are manufactured under good GMP conditions and meet the requirements of pharmacopeia, sales of products should present no problems at the right price.

If production can be established, the aspect of sales of AD and/or ADD has to be borne in mind. Any levels to be considered will be determined when the project is completed , being dependant on several factors - economy of production, possibly joint venture participation or simply consideration of the world market.

3.6.3 Marketing strategy.

To embark on a marketing strategy certain base guideline objectives should be answered.

This report will confine itself, to the marketing of bulk active steroids and formulated products. The possibility of marketing the phytosterol mixture itself and/or the basic synthetic building blocks, AD and ADD, may be considered separately at a later date when levels of production most suitable have been analysed and if marketing of such is considered appropriate.

The guideline objectives to be answered for marketing policy may be considered point by point.

a) Geographical area of operation: Havana, Cuba and within existing organization, but with external support agencies.
b) Basic strategy: Satisfying domestic market and finding market niche in world market.
c) Market shares aimed at: 100% domestic within 5 years (with relation to active principles in production programme). and maintenance thereafter.

For the export markets the production programme allows for varying percentages. All percentages are insignificant with respect to the world market.

Volumes forecast for export are from about 88.6kgs mixed steroids after 3 years to 608.2kgs after 10 years.

d) Product-market relationship: confined to old existing market (i,e. generic drugs) based on existing and expanding market penetration under competitive terms.
e) Markets aimed at: formulated & packaged, bulk formulated and bulk active steroids. Possibly intermediates also.
f) Regional market areas aimed at: South American, Asian, Eastern European and African. European market also for bulk active steroids.
g) Strategy: by competition on quality and price.
h) Aims: top quality, working to GMP, presentation, delivery, competitive prices and, most important, reliability.
i) Other considerations: possibilities existing for co-operation at marketing and/or manufacturing levels.

3.6.4 Marketing possibilities.

The generic market is the only one appropriate for steroidal supplies from Cuba.

The marketing of formulated and packaged steroid products will probably be difficult. Capacity is adequately available for tablets, with exception of oral contraceptives if the desired domestic market is satisfied. Ampoule sales will be rather restricted.

In the case of steroids the possibility for supplying formulated products may be somewhat greater than for other pharmaceuticals since more stringent and controlled conditions to meet

GMP and personnel protection are needed for handling steroids, especially estrogens. This situation may be of benefit to Cuban opportunities.

Many developing countries have already embarked on the provision of formulation facilities and will probably be more interested in bulk active products provided the technology is available also.

Cuba should have some geographical asset and contacts to make the South American market, which is reasonably considerable, attractive and attainable. Markets of Asia and Eastern Europe are also attractive being the ones of greatest potential for expansion.

One problem that can be expected, already apparent in some South American countries and Asian once and beginning to appear in some Eastern European countries, is the presence of multi-nationals who have set up formulation units to promote their branded products. Often capacity for formulating steroids is limited and formulated products may still be imported or are formulated by national companies.

The Health policies of more and more countries have moved to the priority procurement of generic products in place of branded ones. Such moves are always strongly resisted by the multi-nationals. Inspite of some generic scandals in the USA in the late 1980's the movement towards generics is likely to increase. Being capable of supplying generic products would give Cuba an opportunity to be an accepted producer and supplier, although multi-nationals will also be direct and serious competitors.

The method of marketing will need to be carefully researched. For the South American, it might have appeared appropriate to market directly through the agency ERON (established in 1991) to customers although presently it is understood that all business in this area is operated through agents. Government or other tenders could be dealt with directly in Cuba. The organization will need to work hard at its marketing policies and execution. Secure supplies will first need to be established before entering into contracted sales so as to ensure reliable delivery.

For Asian markets and others such as the Far East, Chinese and even Eastern Europe (perhaps assisted here by earlier contacts) it has to be recommended that consideration to be given to cooperation with existing traders and suppliers to these areas. This might be on an ad-hoc basis where the trader simply becomes the customer or through appointment of such traders as agents for Cuban products. This would be done under agreements made regarding commission rates, etc. It should be appreciated that under such agreement, particularly dealing with far away countries, the provision of consignment stocks might have to be considered. Many trading houses specialized in different areas and more than one agent would be necessary to cover all areas of interest, but not one necessarily in each country. In fact agents can be found where sales in their own country are a minor element of the total trade.

Where commercial contacts already exist consideration must be given to their exploitation, but it must also be remembered that a rather specialist market will be under consideration.

Business is likely to be conducted under one of the forms:

a) simple competitive offers or tenders.

b) tendering for Government contracts.
c) setting up long term contracts.
d) selling from consignment stocks
e) positive promotional marketing
f) barter

Apart from good quality products, with appropriate documentation, attention must be given to packaging whether for bulk or formulated products. Appropriate labelling, with hazard warnings as relevant, and quantity indication must be observed. In the case of any packaged formulated goods the quality of packaging will be especially important and any literature provided in the language of the recipients should be most carefully vetted for errors.

In all aspects for any form of product full GMP requirements must be met. This includes full redress for any faulty goods supplied and a system of re-call well established in such unlikely event of faulty products.

3.7 Past importations, future domestic needs and productions.

3.7.1 Past importations.

The importations in bulk of those steroids being considered for domestic production over recent years are recorded in the table below. Some products imported in formulated form are also included where domestic bulk production can be foreseen in the future.

Past importations of selected steroid products. **(All in kgs.)**

Steroid	1988	1989	1990	1991	1992
Ethinyl estradiol	0.68	0.96	1.61	0.91	
Mestranol	2.44	1.65	2.45	1.80	
Estradiol-benzoate	0.50	1.10	1.20	1.20	11.50
Estradiol-valerate	0.10	0.30	0.30	0.40	0.10
Testosterone-propionate	1.70	14.40	14.20	9.9	10.00
Testosterone-enanthate	7.20	27.10	42.10	34.90	19.56
Spironolac-tone	181.90	287.90	300.00	100.80	135.00
*Methandie-none	2.30	0.50	n/a	n/a	44.40
**Danazol					24.00
***Oxymetha-lone	0.64	0.40	0.13	0.52	0.40
Norethis-terone	47.90	31.70	n/a	n/a	n/a
****Levo-norgestrel	3.53	9.66	6.78	4.68	-
Medroxy-progesterone	4.40	2.00	8.00	4.68	n/a

Notes:

* Part formulated in Cuba & part (=9.9kgs.) imported in formulated tablets (packs 20x25mg).
** Imported in formulated capsules of Danocaine (60x200mg.)
***Imported in formulated tablets of Anadrol (100x50mg.)
**** This product is included only because of its relevance as a constituent of oral contraceptives. It is not planned to be manufactured in Cuba.

3.7.2 Projected future domestic needs.

The annual growth rate forecast by the Cuban authorities for each of the products under consideration have been applied to determine the domestic needs over the next ten years. Rates applied are probably mostly conservative. The 1992 production level has been used as a base for projections.

FORECAST DOMESTIC NEEDS 1993-2002 (All in kgs.)

Steroid	Year											Rate p.a Growth %
	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	
Ethinyl Estradiol	6.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	*
Mestranol	2.5	2.5	2.0	1.5	1.0	1.0	1.0	1.0	1.0	1.0	1.0	**
Estradiol Benzoate	11.5	12.1	12.7	13.3	13.9	14.6	15.3	16.1	16.8	17.2	18.5	4.9
Estradiol Valerate	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.07	0.07	0.07	1.0
Testosterone propionate	10.0	10.3	10.6	10.9	11.3	11.6	11.9	12.3	12.7	13.0	13.4	3.0
Testosterone Enanthate	19.6	19.8	20.0	20.2	20.4	20.6	20.8	21.0	21.2	21.4	21.6	1.0
Spironolactone	135.0	140.0	146.0	153.0	158.0	164.0	171.0	178.0	185.0	192.0	200.0	4.0
Methandienone	44.4	45.3	46.2	47.1	48.1	49.0	50.0	51.0	52.0	53.0	54.1	2.0
Danazol	24.0	24.5	25.0	25.5	26.0	26.5	27.1	27.6	28.2	28.8	29.3	2.0
Oxymetholone	0.4	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.5	0.5	0.5	2.0
Norethisterone	50.0	50.0	40.0	30.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0	**
Medroxyprogesterone		6.0	6.3	6.6	7.0	7.3	7.7	8.0	8.4	8.9	9.3	5.0

* An increase from 1992/93 corresponds to expected increased formulation capacity and positive promotion of oral contraceptive by SOCUDEF.

** Likely diminution due to prescribing habits domestically.

3.7.3 Production levels proposed.

PRODUCTION LEVELS PROPOSED. 1993-2202 (All in kgs.)

Steroid	Year									
	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002
Ethinyl Estradiol	18.0	21.0	24.0	40.0	60.0	60.0	70.0	70.0	70.0	80.0
Mestranol	12.0	12.0	14.0	17.0	19.0	21.0	31.0	41.0	52.0	55.0
Estradiol Benzoate	10.0	13.5	18.5	20.0	20.0	20.0	20.0	20.0	25.0	25.0
Estradiol Valerate	-	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Estradiol Cypionate	-	1.0	1.0	1.0	2.0	2.0	2.0	2.0	2.0	2.0
Testosterona Propionate	20.0	30.0	48.0	60.0	80.0	100.0	100.0	120.0	150.0	150.0
Testosterone Enanthate	10.0	20.0	48.0	60.0	80.0	90.0	120.0	150.0	150.0	150.0
Spironolactone	-	10.0	50.0	100.0	200.0	250.0	300.0	300.0	350.0	350.0
Methandienone	2.5	20.0	44.0	47.0	47.0	50.0	50.0	55.0	55.0	60.0
Danazol	-	6.0	18.0	24.0	26.0	26.0	26.0	28.0	28.0	30.0
Norethisterone	-	5.0	20.0	40.0	60.0	60.0	60.0	80.0	80.0	80.0
Medroxyprogesterone	-	2.0	6.0	7.0	10.0	11.0	15.0	15.0	20.0	20.0

3.7.4 Products available for export.

As indicated previously, it is proposed that up to 100% of the domestic demand should be satisfied by local steroid production. Bearing this in mind the next table indicates necessary purchases as (-) or product availability for export whether in bulk or formulated presentation.

EXPORT AVAILABILITY. (All in kgs).

Steroid	Year									
	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002
Ethinyl Estradiol	(12.0)	3.0	6.0	22.0	42.0	42.0	52.0	52.0	52.0	62.0
Mestranol	9.5	10.0	12.5	16.0	18.0	20.0	30.0	40.0	51.0	54.0
Estradiol Benzoate	(2.1)	0.8	5.2	6.1	5.4	4.7	3.9	3.2	7.8	6.5
Testosterona Propionate	9.7	19.4	37.1	48.7	68.4	88.1	87.7	107.3	137.0	136.6
Testosterone Enanthate	(9.8)	-	27.8	39.6	59.4	69.2	99.00	128.8	128.6	128.4
Spironolactone	(140)	(136)	(103)	(58)	36.0	79.0	122.0	115.0	158.0	150.0
Norethisterone	(50)	(45)	(10)	20.0	40.0	40.0	40.0	60.0	60.0	60.0
Medroxyprogesterone	(6.0)	(4.3)	(0.6)	-	2.7	3.3	7.0	6.6	11.1	10.7

( ) = Purchases needed

Note: Methandienone and Danazol have been ignored as potential export materials since production costs are uncertain. They might, in fact, prove to be valuable export items.

3.8 Bulk Steroid Prices

The following table indicates prices which have been applicable to purchase of bulk products on the international market during the ten years until 1993. They can be considered appropriate for medium levels of sales (10 Kg-500 Kg), premium prices applying for smaller purchases and lower prices at tonnage levels.

During 1991/92 some serious supply problems were experienced with respect to starting materials AD and ADD. This was partly due to cessation of production by Gist Brocades who sold their technology (but not production facilities) to Roussel Uclaf in 1991. Roussel Uclaf intend production only for their own captive use and will not offer material in the international market. Production was also suspended for some time by Mitsubishi in Japan, although this now appears to have been re-instated. Supplies from Schering and Upjohn could not satisfy demands. In consequence of demand, significant price increases were observed reaching highest levels in early 1992, but reducing again mid-year probably due to resumed availability from Mitsubishi.

Prices of AD and ADD are thought not to relate directly to production costs, but take into account prices of competing starting materials such as 16-DPA and DHA.

No attempt is being made to forecast prices of either starting materials or final products during the next ten years, but an essentially stable position relative to starting material and products will be assumed.

3.8.1 PAST, AND CURRENT, INTERNATIONAL PRICES OF BULK ACTIVE PHARMACEUTICALS AND STARTING MATERIALS AD AND ADD. Prices USD/Kg f.o.b.

Product	Year									
	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993
AD	65	65	70	70	80	105	105	-	230/180	163
ADD	135	135	165	165	190	240	240	-	403/325	325
Estrone	600	600	600	650	700	800	850	1200	1200	1300
Estradiol Benzoate	650	650	650	700	750	850	900	1261	-	1350
Ethinyl Estradiol	900	900	900	1000	1000	1100	1100	1364	1400	1550
Mestranol	-	-	-	1600	-	-	-	1740	1700	1700
Testosterone Propionate	350	350	350	380	400	400	400	430	410	430
Testosterone Enanthate	-	-	-	-	560	530	520	550	530	555
Spironolactone	-	-	-	-	-	-	370	430	480	500
Ethisterone	260	260	260	260	260	260	260	260	265	-
Norethisterone	-	-	-	-	-	-	-	-	2300	2300
Methyltestosterone	-	-	-	-	420	420	380	450	380	405
Methandienone	-	-	-	-	-	-	-	1330	-	1530
Danazol	990	990	990	990	950	950	950	930	930	-
Medroxyprogesterone acetate	-	-	-	-	-	-	-	-	1570	1600

The next table indicates purchase prices experienced in Cuba during 1992. In this case both f.o.b. prices and c.i.f. prices for Cuba are listed. On average for the range of values of steroids a factor of apprximately 1.17 is apparent.

Import duties levied on steroids and intermediates in Cuba are not clearly defined.

3.8.2 CUBAN IMPORTATION PRICES IN 1992 (Price USD/Kg)

PRODUCTS	F.O.B.	C.I.F.
AD	165.8	197.0
ADD	414.5	492.5
Estradiol Benzoate	1,845.6	2,155.6
Estradiol Valerate	1,905.4	2,225.4
Ethinyl Estradiol	3,080.0	3,590.0 *
Mestranol	1,700.0	1,984.0
Testosterone Propionate	481.5	562.4
Testosterone Enanthate	530.7	619.8
Spironolactone	495.7	579.0
Norethisterone	2,768.4	3,233.4
Methandienone	2,800.0	3,270.0 *
Danazol	978.6	1,145.0
Oxymethalone	2,179.5	2,550.9
Medroxyprogesterone acetate	1,569.2	1,832.8

* These prices are out of line with general international prices and probably was due to the effect of exceptional shortage of ADD in 1992.

3.8.3. - SALES VALUES OF PROPOSED PRODUCTION PROGRAMME

The values presented are based on f.o.b. prices in USD at the international prices quoted.

Product	UNIT: KG PRICE	SALES ('000 USD)									
		1993	1994	1995	1996	1997	1998	1999	2000	2001	2002
Ethinyl Estradiol	1400	25.2	29.4	33.6	56.0	84.0	84.0	98.0	98.0	98.0	112.0
Mestranol	1750	21.0	21.0	24.5	30.0	33.3	36.8	54.3	71.8	91.0	96.3
Estradiol Benzoate	1350	13.5	18.2	25.0	27.0	27.0	27.0	27.0	27.0	33.8	33.8
Estradiol Valerate	1800	-	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Estrogene sub-total	-	**59.7**	**68.8**	**83.3**	**113.2**	**257.7**	**148.0**	**179.5**	**197.5**	**223.0**	**242.3**
Testosterone propionate	430	8.6	12.9	20.6	25.8	34.4	43.0	43.0	51.6	64.5	64.5
Testosterone Enanthate	555	5.6	11.1	26.6	33.3	44.4	50.0	66.6	83.3	83.3	83.3
Testosterone sub-total	-	**14.2**	**24.0**	**47.2**	**59.1**	**78.8**	**93.0**	**109.6**	**134.9**	**147.8**	**147.8**
Spironolactone	500	-	5.0	25.0	50.0	100.0	125.0	150.0	150.0	175.0	175.0
Methandienone	1530	3.8	30.6	67.3	71.9	71.9	76.5	76.5	84.2	84.2	91.8
Danazol	930	-	5.6	16.7	22.3	24.2	24.2	24.2	26.0	26.0	27.9
Norethisterone	2300	-	11.5	46.0	92.0	138.0	138.0	138.0	184.0	184.0	184.0
Medroxyprogesterone acet.	1600	-	3.2	9.6	11.2	16.0	17.6	24.0	24.0	32.0	32.0
Dev.products sub-total *	-	**3.8**	**55.9**	**164.6**	**247.4**	**350.1**	**379.3**	**412.7**	**468.2**	**501.2**	**510.7**
GRAND TOTAL	-	**77.7**	**148.7**	**295.1**	**419.7**	**686.6**	**620.3**	**701.8**	**800.1**	**872.0**	**900.4**

* Dev = development

This production programme will be found to need some investments in plant after about 2/3 years and 5/6 years and will be considered later.

3.8.4 Sales Value of Domestically needed products.

The production levels of products needed entirely for domestic consumption are potentially capable of being essentialy made in existing equipments (some small investment needed in small centrifuge and final products crystalliser). The gross saving of such production is detailed next.

PRODUCT	UNIT: KG PRICE (USD)	DOMESTIC NEEDS KG	VALUE FOB ('000 USD)	VALUE CIF ('000 USD)
1) Established products				
Ethinyl Estradiol	1550	18.0	27.9	32.6
Mestranol	1750	2.5	4.4	5.1
Estradiol Benzoate	1350	12.1	16.3	19.0
Estradiol Valerate	1800	0.06	0.1	0.1
Testosterone propionate	430	10.3	4.4	5.1
Testosterone Enanthate	555	19.8	11.0	12.8
Sub total			**64.1**	**74.7**
2) Development products				
Spironolactone	500	140.0	70.0	81.8
Methandienone	1530	45.3	69.3	80.9
Danazol	930	24.5	22.8	26.6
Norethisterone	2300	50.0	115.0	134.3
Medroxyprogeste-rone	1600	6.0	9.6	11.2
SUB - TOTAL			**286.7**	**334.8**
GRAND TOTAL			**350.8**	**409.5**

Actual purchase cost for the above bulk active pharmaceuticals (cif) would be USD 406,600.

4. RAW MATERIALS.

4.1 Brief survey of major starting materials for steroid synthesis.

Starting materials for steroid synthesis are derived from a variety of vegetable and animal sources. In present times vegetable sources are of most importance.

Major sources which have been employed are represented in the following table:

Sterol	Source
a) Diosgenin	Dioscorea Sp.; Costus; Balanites; Trigonella.
b) Solasodine	Solanum Sp.
c) Hecogenin	Agave Sp.
d) Stigmasterol	Calaber bean; Physostigmine; Soybean oil.
e) Sitosterols	Vegetable oils; Cotton seed oil; Sugar cane oil; Tall oil.
f) Cholesterol	Sheep wool grease; Cattle spinal cord; Cattle brain.
g) Desoxycholic & cholic acids	Ox or pig bile.
h) Ergosterol	Yeasts; Lichens; Algae.

a) Diosgenin: produced from both wild sources (Dioscorea deltoidea, indigenous east & west areas of Himalayas) and cultivated species (best Dioscorea floribunda).
Deltoidea has the higher content and gives purer product but supplies can be limited and it is not profilic under cultivation. Floribunda provides high bulk production of tuber, content is lower on a % basis and contains pentogenin as impurity. This latter can be stripped off during processing.

Cultivation was exploited very satisfactorily in India for many years.

Diosgenin is utilized in chemical degradation to produce the intermediates pregnadienolone (16-DPA) and dehydroepiandrosterone acetate (DHA).

Diosgenin was used for many years as a basis for synthesis, but is now only really economic in use for producing corticosteroids when fermentation is used to produce various functions. In future, due to other fermentation advances the use of diosgenin is likely to diminish further.

b) Solasodine: extensively investigated and many species such as lacaniatum, nigrum, khasianum, incanum etc have shown promise. Harvesting problems are often encountered with the best species.

This source has only been commercialised to a limited extent, main production currently being exploited in New Zeland. Was planned as the steroid source for production in Indonesia but state of this project is not known.

Investigation of Solanum has been studied for some years in Cuba, but its value as a starting material suffers from the same problems as diosgenin where costs of additives is high and especially so when virtually all have to be imported.

Continuation of work in this field cannot be recommended.

c) Hecogenin: waste liquors of the fibre/rope making industry from sisal or henequen contain saponins from which hecogenin may be isolated by enzymatic fermentation and other techniques.

Widely investigated in areas of South America (particularly Brazil, Venezuela), México, Haiti and Taiwan, but utilization commercially mostly exploited from sources in East Africa. Glaxochem are the principal users. Quality is important and use of low content tigogenin is preferred. Cuba has already embarked on utilization of liquors of henequen and produce hecogenin of high quality at a limited level.

Use of this hecogenin is planned principally for production of various corticosteroids through the intermediate diene acetate.

When world prices are high it could be conceivable to use it not only for complex corticosteroids, but also for more simple such as hydrocortisone or prednisolone.

The production of oxymethalone through tigogenin (produced from hecogenin) is being considered and development is well advanced.

d) Stigmasterol: may be obtained from a specifically cultivated crop or as a by-product from other products. Direct crop sources are Calabar bean or Ordeal bean (Phyostigmae venenosum), while the more important source is the soap stock or foots provided by alkaline refining of soybean oil.

Crude products are mixtures of stigmasterol and alpha/beta sitosterols. Separation may be acheived by chemical and chemical/physical methods to provide pure stigmasterol.

Principal user of stigmasterol is the Upjohn Company of USA. Stigmasterol may be converted either chemically or by fermentation to progesterone. While the interest of Upjohn was initially in stigmasterol, sitosterols also were produced for which no use was initally known. The by-products were compacted and buried. At a later date when technology had been developed these proved a useful additional starting material for production of AD & ADD. It is possible to also convert the stigmasterol/sitosterol mixtures directly.

Soybean oil production in Cuba is not significant and this stigmasterol/sitosterol mixture is not an appropriate starting product for Cuba.

e) **Sitosterols/Phytosterol mixtures:** Sitosterols have gained commercial prominence because of their ready and commercially viable microbiological conversion to AD and ADD as well as their relative abundance. Commercial utilization, however, lies in relatively few hands.

Sitosterols are the most abundant and widely distributed of plant sterols (phytosterols) usually occuring in complex mixtures, alpha, beta & gamma sitosterols are described, but only beta-sitosterol is clearly defined as a pure compound. It is alternatively named stigmast-5-en-3β-ol. Alpha & gamma sitosterols are not clearly defined and are probably mixtures with campesterol or other sterols.

The principal sources of beta-sitosterols are soybean oil; cotton seed oil; tall oils and sugar cane oils or wax.

Soybean sterols contain stigmasterol together with beta-sitosterol & gamma sitosterol. Gamma sitosterol is a major component and, whereas Upjohn have more interest in stigmasterol, Schering AG and Searle have been principal users of gamma sitosterol.

Tall oil, produced as a by-product of alkaline pulping of such resinous woods as pine, contains considerable levels of beta-sitosterol in the un-saponifiable fraction.

Neither of the above sources fit in with significant process operations in Cuba and are not appropriate raw materials.

Sugar cane wax & oils from the wax contain significant levels of phytosterols with beta-sitosterol predominent. Lesser components are stigmasterol, campesterol, and brassisterol. The mixture is suitable for input to microbioloical fermentation to AD and ADD.

This must be considered a serious and interesting source of raw material on which to base the Cuban steroid industry and the possibility of commercialising its use and obtaining technology for fermentation forms the basis of this project.

f) **Cholesterol:** sources of cholesterol are of animal origin. Cholesterol was one of the earliest raw materials used for steroid synthesis.

Cholesterol may be extracted from sheep wool grease together with lanosterol. Alternatively extraction may be from cattle spinal cord or, to a lesser extent, cattle brain.

In earlier days cholesterol was degraded chemically, but this process became un-economic and was discontinued some 40 years ago.

Cholesterol is an excellent substrate for microbiological fermentation to AD and ADD. It is also used in preparation of calciferol, vitamin D_3.

Cholesterol has been prepared satisfactorily in Cuba from spinal cord. Quality is good, but quantity limited by raw material availability. It could provide a readily available source for preliminary or back-up raw material for production.

g) Desoxycholic and Cholic acids: these products are also available from animal origin, being collectively known as bile acids and produced from the bile of ox or pig.

Use of these materials has diminished significantly over the years, but in earlier days was the prime starting material for Roussel Uclaf, Merck, Schering and Organon.

Cuba has produced these products for many years, but output in now extremely low. They are not considered appropriate economic starting materials for steroid synthesis.

h) Ergosterol: is the most common of the fungal steroids-mycosterols. The principal source is yeast, saccharomyces cervisiae. It has never been a significant steroid starting material except for vitamin D.

Fermentation to ADD has been reported by a Hungarian group but this product is not a relevant starting material for Cuba.

i) Tigogenin: may be obtained as a by-product of hecogenin processing. In Cuba the "Coffee ground" produced contains a high predominance of hecogenin so no significant levels of tigogenin have to be dealt with. However, minor crops will contain a mixture of principally hecogenin & tigogenin. Separation of the mixture is laborious and such mixtures are probably best converted to essentially pure tigogenin by reduction.

Wolff Kishner reduction of hecogenin to tigogenin has been commissioned as raw material for production of oxymethalone.

j) Other sources: various other sources of sterols exist, but have no significant commercial application.

Apart from vegetable and animal sources many marine sources contain sterols. These are usually of more complex structure and commerical uses have not been exploited to date.

4.2 Selection of most appropriate raw materials for steroid synthesis in Cuba.

The most appropriate raw materials and starting materials for Cuba have been indicated in the previous survey.
They are:

- Hecogenin (Tigogenin)
- Cholesterol
- Phytosterols

Hecogenin (Tigogenin)

Production of hecogenin and commissioning for production of diene acetate, as intermediate for possible production of such corticoids as bethametasone, triamcinolone, dexamethasone and beclamethasone, have been performed.

Development work is in progress to produce oxymethalone from tigogenin, derived from hecogenin.

Cholesterol

Cholesterol can be produced in Cuba from cattle spinal cord. Technology and expertise are available and suitable plant for processing is also available.

The quantity of cholesterol which could produced is limited by the spinal cord availability and this is diminishing. A detailed assessment in Autumn 1992 suggested that 1,000kgs cholesterol could be produced during 1993.

Production cost was indicated to be about USD 24 per kg.

This product as starting material is considered to be appropriate only in the short term. Availability will be variable and the production cost is expected to be higher than that of phytosterols.

Used in fermentation it would be expected to give marginally better conversions than phytosterols mixtures due to its higher purity.

Phytosterols mixtures.

Phytosterols exist in a very large number of plants, usually consisting of a mixture of stigmasterol, beta-sitosterol & camposterol. Beta-sitosterl is usually the major component.

Stigmasterol, isolated after separation from sitosterols, from soybean oil was first employed in 1968 by the Upjohn company. Stigmasterol was used to produce progesterone either chemically or by fermentation, the latter now being preferred. Conversion then to hydrocortisone was also performed.

While no use was known for the separated sitosterols they were compacted and buried in the ground. Later developments showed the possibility of conversion of these sitosterols to AD and ADD. Sales from such production started early 1980's. The total mixture containing stigmasterol and sitosterols was also found suitable for microbiological conversion.

Phytosterols may be obtained from sugar cane by-products. Cuba being a major sugar producer has here the obvious potential to provide its own assured source of raw material on which the steroid industry can undoubtedly be based.

The economic production of phytosterols mixture from sugar cane wastes and subsequent conversion to the steroid synthesis building blocks AD and ADD forms the basis of this report.

4.3 Analysis of raw materials and their use.

Raw materials, in the context of the report, have to be dealt with under different headings. For clarity the following may be considered as raw materials:

a) basic indigenous raw materials - cattle spinal cord & sugar cane wastes: These may be processed to produce cholesterol and phytosterols mixture.

b) The raw material input materials, cholesterol and phytosterols mixture, used to produce the intermediates for synthesis, AD and ADD by microbiological fermentation.

c) The raw material input materials for synthesis, AD and ADD, used to produce the bulk active steroids.

d) Other raw materials in the form of additives (especially of domestic origin), services such as electricity & water and personnel.

The production of phytosterols from sugar cane oil alone is concentrated on in this report since the production of cholesterol is considered to have been delat with as far as is necessary under section 4.2.

4.3.1 Origin of phytosterol bearing sugar cane by-products.

The processing of sugar produces a variety of by-products, many of which are already utilized to varying degrees in Cuba. Indeed the development of the use of sugar cane by-products is one of the most advanced in the worls due to the efforts of the long established research establishment ICIDCA (Cuban Institute for Researh on Cane Sugar by-products).

The various useful by-products and the average production per 100kgs sugar produced from Cuban sources are indicated in the table below.

1,000kgs sugar cane produces: 275kgs bagasse (50% humidity)
25kgs molasses
25kgs filter mud (77% humidity
= cachaza

100kgs sugar

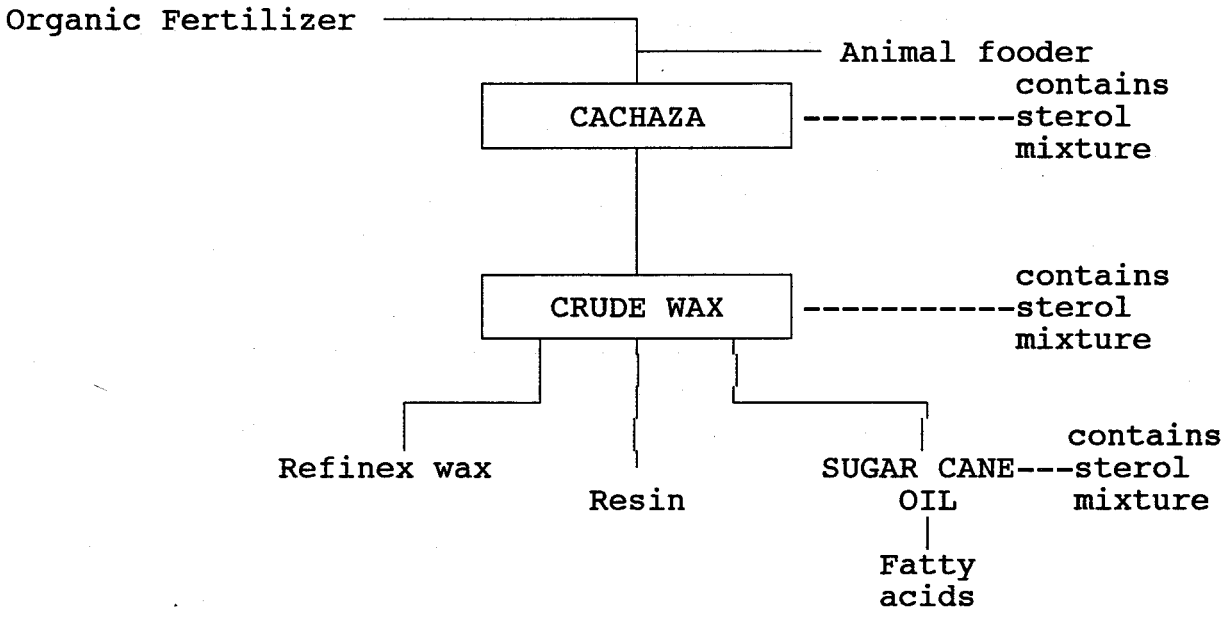
Bagasse is extensively used for animal feed products, for energy production, for paper and pulp and preparation of fibre board. It is also used for preparation of charcoal and to prepare the chemical furfural. All these aspects are covered in Cuba.

Molasses are used in Cuba for preparation of variety of yeasts, complexes such as molasses-urea and molasses-urea-pith, protein molasses, saccharin production and for the production of alcohol and in rums & spirits.

Other possible uses of molasses, not yet commercialised in Cuba, include citric acid production (for food & drinks industry), 1-lysine (amino-acid for human consumption), in fermentation for production of 1-ephedirne (pharmaceutical), for antibiotics (pharmaceuticals) or xanthan gums (food & cosmetic uses).

Filter mud or Cachaza is currently used in Cuba for dextran production, production of crude waxes which further processed to produce refined waxes, resins and sugar cane oil. Crude wax may also be used to produce other products of pharmaceutical interest. Has also a possible potential for production of biogas and waste waters for irrigation fertilizer.

The phytosterols are present in the Cachaza, crude wax and sugar cane oil. This, and product flow sheet, is illustrated below.



A comparison is given below of the proportions of derived fractions from processing of Cachaza of Cuban origin against some other published figures.

Source:	**1**	**2**	**3**	**4**	**5**	**Cuban**
Cachaza	100	100	-	-	-	100
Crude wax	10/12	-	-	-	100	10/12
Resin	0.3/0.5	-	-	-	20	2.5/3.4
Refined wax	5/6	-	-	-	47	3.3/4.2
Oil	4/4.2	-	100	100	33	3.3
Fatty acids	2/2.1	-	-	-	22	1.84
Phytosterol content	0.45/0.47	0.33	9	9.1	3.3	0.27/0.32
Isolated Phytosterol	0.36/0.38	-	6/7	-	-	0.18/0.21

All figures represent weights with relation to appropriate "100" base figure in column. All figures represent dry weight.

Reference sources:

No.
1 P.C. Goswani et .al. Curr.Sci.,1984 vol 53 No.17 p 917/919
2 S.Mathur et.al. Research & Industry 1988 vol 33 p 151/3
3 D.Werner/U.Hes DDR Patent 104513 (12.03.1974)
4 C.S.I.R. Indian Patent 163626 (27.05.1988)
5 A.O.Schubert et.al. Pharmazie, 1968 vol 23 p 454/461

With the exception of the figures reported in ref. 1 (where press mud from an Assam sugar factory was used) the Cuban figures compare well.

4.3.2 Cuban potential of phytosterol bearing products and phytosterol mixtures.

The most basic raw material containing phytosterols is the sugar cane itself. Considerations must always be given to availability and reliability of agriculatural crops as a source for isolation of a commercial product. In this case this aspect can be ignored, for even in event of most adverse growing conditions, disease or bad harvesting conditions the excess of availability relative to any likely level of phytosterols ever required is manyfold.

As with all plant materials variations in phytosterol contents can be expected dependant on species; growing conditions; harvesting time and conditions etc. Such variations are not likely to be very significant with respect to the economics of production of phytosterols. In fact levels of isolated phytosterols are much more likely to be dependant on the processing methods used to isolate them.

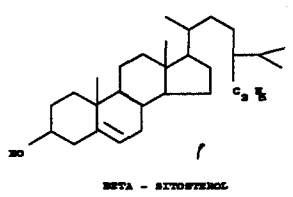
The maximum potential quantities of phytosterol containing materials available from an average annual production of 8 million tons sugar are shown in the table below.

Sugar cane	80 million tons
Cachaza	0.46 million tons-dry (2M tons wet)
Crude wax	46,000/52,000 tons
Sugar cane oil	20,000 tons
(phytosterol content)	1,600 tons
Pure isolated phytosterols	1,040 tons

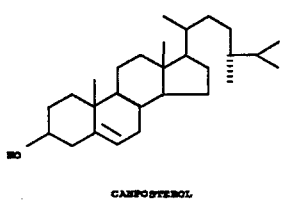
These figures illustrate the vast level potentially available, not taking into account other uses of by-products.

4.3.3 Isolation of phytosterol mixture.

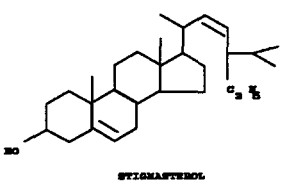
The desired product for use as input raw matreial for microbiological fermentation to AD and ADD is a mixture of sterols comprised of beta-sitosterol, stigmasterol and camposterol as major components.



BETA - SITOSTEROL



CAMPOSTEROL



STIGMASTEROL

The three possible by-product sources for phytosterols will be considered.

a) Cachaza

No analyses are available for Cuban material but the analysis given below for an Indian source is probably similar. It would be interesting to perform some analyses of Cuban materials for comparison.

Press mud (Cachaza)	100% (67% humidity)	100% dry
Total solids	32%	99%
Organic materials	20.3%	62.9%
Ash	9/11%	27.9/34%
Total nitrogen		0.4%
Phosphate (P_2O_5		0.4%
Potash		0.02%
Phytosterols		0.33%

With respect to phytosterol content in Cuban Cachaza this can only calculated from reported levels in derived sugar cane oil. These have been reported from 6-10% which could correspond to 0.27/0.32% in Cachaza provided the oil yields are reliable.

At this time Cachaza is not being considered as the appropriate by-product from which to isolate phytosterols directly.

However, the publication of an Indian group provokes interest. (S.Mathur et.al. Research & Industry 1988 vol 33 p.151/3). This claims that if Cachaza is allowed to ferment anaerobically not only is biogas produced, but also that phytosterol concentration is increased twelve-fold. If this could be confirmed, and if it could be established that during the fermentation enzymatic hydrolysis has occurred to liberate free steroids, the direct extraction of this material after drying could provide an interesting alternstive method for isolation.

b) Crude wax

Crude wax is produced by extraction of Cachaza with a solvent. Different producers may use different solvents for this stage, often governed by local availability and cost. Reported results do not appear to differ significantly.

Crude wax is a complex mixture of many compounds including C_{27} to C_{31} hydrocarbons, long chain saturated and unsaturated fatty acids (mainly linoleic and palmitic) esters, resin acids and the phytosterols.

Crude wax is not directly a suitable starting material for the isolation of phytosterols, but is best processed to remove the wax fraction and resins, leaving what is known as "sugar cane oil".

The more traditional way to perform this operation is to use isopropanol, but in Cuba an alternative alcohol is used. It is possible that the Cuban choice does not give optimal separation, but results are acceptable.

c) Sugar cane oil

This by-product is considered to be the most appropriate one from which to start to isolate phytosterol mixtures.

The obtaining of sugar cane oil from crude wax has been illustrated earlier in section 4.3.1

A use for refined, or hard waxes, already exists in Cuba and also for the resin by-product. Accordingly four plants are now in operation for refining crude wax. Another 6 are in course of construction and it is expected that all will be in operation by 1995.

All the plants are located in the Eastern Provinces, some 400km to 900km from Havana. Locations are Las Tunas, Holguin, Camaguey and Ciego de Avila. Approximate locations will be seen in section 5.

Availability: the availability of sugar cane oil is given in the table below.

1992	1993 First Quarter	1993 Last Quarter	1994	1995/2002
200 T	400 T	1,400 T	1,600 T	2,000 T
2 units	4 units	7/8 units	9 units	10 units

T= tons.

Total input of crude wax by 1995 will be 6,000 tons, some 10% utilization of Cachaza.

The production of sugar cane oil is expected to be far in excess of that needed for phytosterols production. It can also be used for chicken feedstock or is further potential for production of fatty acids.

Quality of raw material.

The quality and consistency of the sugar cane oils produced is a matter of concern. The production units are no doubt most concerned about the production of refined wax, but nonetheless the impression is that processing metthods are not well defined or carried out. Inconsistency is, apparently, not only between different production units but also within products from each. Varying amounts of residual wax and alcohol appear to be the problem. The process has not been observed, but problems may be due to variation in ageing and temperature control.

For considering a regular production of phytostrols the provision of a reasonably consistent sugar cane wax should be supplied. A specification needs to be set up for the sugar cane oil defined by bulk density limits with reported saponification values. A bulk density in the order of 0.915 would probably be appropriate with a saponification value in the order of 160.

The quality of sugar cane oils produced from different cane locations is likely to vary in phytosterol content and proportions or other constituents since it is derived from vegetable matter. No screening of qualities has been performed, but all oils are claimed to be high quality.

Some analytical figures relating to the content of phytosterols in sugar cane oils have been recorded. They fall within a rather wide range of 4-10%, but this could be a result of the actual oil, its wax and alcohol contents. A figure of 8.0% was claimed to be a reasonable expectation.

Analysis of oils has been performed by saponification, digitoxin precipitation and subsequent GLC analysis. It may be mentioned that some authors (M.Ktayama et.al. Agr.Biol.Chem. 1974, 38(9) p.1661/7) consider that the determination through digitoxin may be too low, particularly with respect to stigmasterol. The use of tomatine is though to give more correct analysis.

4.3.4 Starting materials for synthesis: AD and ADD.

AD and ADD can be considered as the raw materials for synthesis. They are now best produced by microbiological fermentation of cholesterol or phytosterol mixtures.

Brief history of development and use of microbiological fermentation methods in steroid chemistry.

Use of microbiological fermentation methods has revolutionalised many aspects of steroid synthesis.

Utilization of micro - organisms in organic chemistry started with Pasteur in 1857, but little more work was done until the end of the 19 th century. Steroid substrates were not used until 1937, when yeast was found to reduce a 17-ketone to 17α-hydroxysteroid. Several oxidation-isomerisation reactions were then discovered using impure yeast and these were interpreted as being due to bacterial contaminants.

Little further development was seen from 1940-1947, partly due to availability of good synthetic methods and also due to Second World War activities. These especially effected work of the German & Italian groups where promising work had started.

In 1947 the 7 - dehydrogenation of cholesterol using Arthobacter Sp. was recorded and followed in 1948 by the discovery of 7 - hydroxylation of cholesterol with Proactinomyces Sp.

The next step was the discovery of the use of steroids as sole source of carbon for microbial growth and the first illustration that cholesterol might conceivably be transformed by microbiological degradation to useful entities of substantially lower molecular weight. The importance of this work was not realized until a much later date. It was the real lead to the production of AD and ADD from cholesterol.

The next stage was a most important chapter in the microbiological transformation of steroids. It was only in 1949 that the real therapeutic value of cortisone was appreciated. Merck, in 1949, and Schering, in 1950, followed by others started the manufacture of cortisone by long and complicated synthesis from desoxycholic acid. Upjohn were stimulated to attack the problem by using a potentially more direct method of microbiological oxidation. Procedures for introduction of 11 alpha & 11 beta hydroxyl followed and in 1950 the first extensive publication was seen in a US patent.

Interest increased further with most of the major pharmaceutical houses such Merck, Pfizer, Schering, Syntex etc... intensifying research.

Discovery was next made that estrogens could be produced by microbiological means from 19-hydroxy-steroids, but this has not been applied commercially as chemical methods are still superior.

Finally valuable work was performed showing that a wide range of micro - organisms such as Pseodonomas, Mycobacterium, Corybacterium, Proactinomyces and others were capable

of using cholesterol as a sole carbon source and effecting microbiological degradation of the side chain as well as oxidative and reductive reactions to produce AD and ADD.

It was also shown that beta-sitosterol, essentially a somewhat cheaper source than cholesterol, could also act a sole carbon source.

Developments were made by several companies resulting ultimately in the large scale production of AD and ADD.

Patents were filed the earliest being issued to Hungarian group in Sept.1967 (Hung.Pat. 153831) followed by Noda Institute, Japan in June 1968 (US Pat.3, 388, 042), then by Gist - En Spiritusfabriek, Netherlands in May 1968 (Brit. Pat.1, 113, 887) and in Jan.1970 (US Pat.3,684,657) and in Sept.1973 (US Pat.3, 759, 791).

Industrial application started in the earliy 1970's and was later accelerated on account of shortages which developed in the supply of diosgenin. Also a greater accessibility of beta-sitosterol developed as a by-product of vegetable oils and others sources. In all five major companies started production. As indicated earlier availability of AD and ADD from these processes did not develop until the early 1980's.

4.3.5 Other raw materials.

The items under this heading which will be briefly dealt with are confined only to isolation of phytosterols from sugar cane oil and their purification. They are covered by:

a) Additives and solvents.
b) Service supplies such as electricity, steam, water and compressed air.
c) Personnel

a) Additives and solvents: The precise choice of additives and solvents to be used will be dealt with later under the "Engineerig & Technology" section.

Alkali hydroxides will be used. For costing purposes the imported price will need to be taken irrespective of which alkali metal hydroxide is used.

A 50 % solution of sodium hydroxide, of good quality, is produced in Cuba. While this might be procured for production use, it is understood that the current production level is no more than 22-24,000 kgs per year. Cost of this material is USD 304/ton.

Imported sodium hydroxide price is currently USD 560/ton c.i.f. and potassium hydroxide USD 890/ton c.i.f.

Solvents which might be used are 96% ethanol and acetone, 96% ethanol is produced in Cuba and it is likely that sufficient could be supplied to meet requirements since the solvent will recovered in the process for re-use. The domestic price for 96% ethanol is currently USD 0.33/lt.

Acetone is already imported into Cuba in significant quantities. If used, the solvent would be largely recovered and re-cycled. Current price at USD 1.11/kg or USD 0.88/lt. c.i.f.

Filter aid and charcoal would be used. A domestic form of filter aid is understood to be available and in adequate quantity. The price is reported at 1 Peso/kg.

Charcoal for de-colorizing would need to be imported as the quality of any local material, if available, would not be satisfactory. The price of imported material is currently about USD 3.6/kg.

b) Service supplies.

These may vary from area to area or installation to installation. Those costs which appertain to the steroid pilot production plant and other plant at Mario Muñoz will be used for calculation purposes. Particularly in the case of steam the costs could probably be considerably less for a plant in the sugar processing areas where bagasse may be used to fuel boilers.

Service costs which will be applied are as follows:

Fuel cost:	USD 110/140 per ton
Electricity:	0.067/0.849 cents per KWH
Water - mains	10 cents/m^3
- recirculated	14 cents/m^3
- treated	16 cents/m^3

c) Personnel.

Personel are an essential element to any processing industry. No problems are envisuaged in the training of personnel for the phytosterol processes and could be done in Cuba, as far as unit operation are concerned, at several establishments. For the staffing of any fermentation operation some external training will be desirable although the availability of personnel of sufficient calibre should not present any problem.

For synthesis a basic group of trained operators exists. They need the opportunity for sustained and continous processing to improve their skills further.

For costing purposes, while wages etc, are paid in local Peso currency, to cover dependant costs it is the policy to charge an element corresponding to 25% local payment in USD to the process.

5. LOCATIONS AND SITES.

In terms of the report as a whole, these aspects need to be considered in three parts. These are for productions of
a) phytosterol mixture from sugar cane oil
b) production of AD/ADD by microbiological fermentation
c) synthesis of bulk active steroids

5.1 Phytosterols from sugar cane oil.

The determination of the location and site for the production of phytosterols will be dependant on the ultimate aims.

Three main options are open:
- a dedicated unit
- use of an existing production unit having equipment suitable for the processing
- use of facilities at the Mario Muñoz factory where other steroid work is performed

a) Dedicated unit: Such an operation would really be outside the scope of this project study, but suggestions are made as to favourable posibilities.

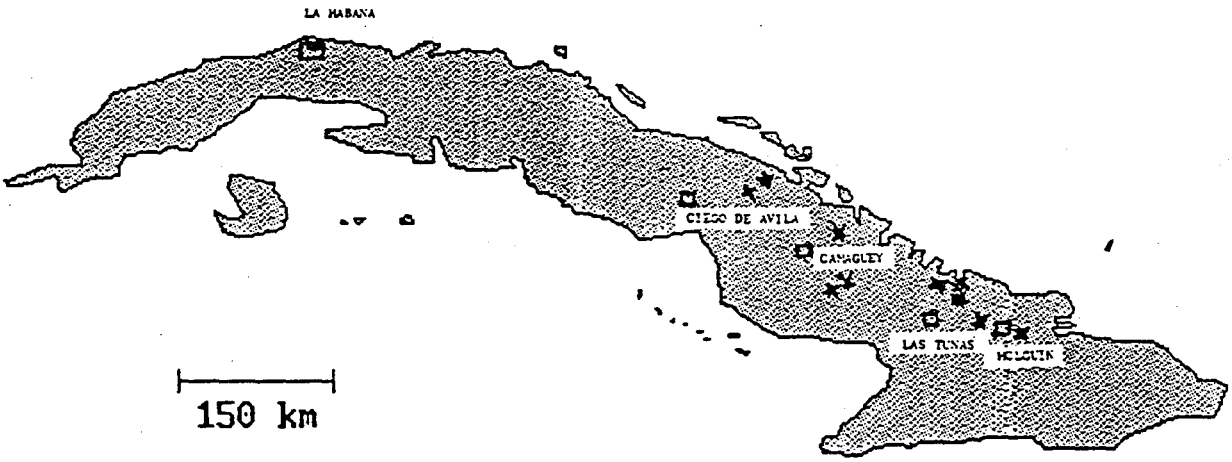
Again, although the implementatiom of setting up such a dedicated unit could be a purely domestic project, it has been considered necessary to look at it in some depth with regards to determinig both site size & plant equipment needs in order to reach an independant evaluation of the likely costs of output phytosterols. This is considered in the section headed "Engineering & Technology".

The size of a dedicated unit would not be expected to be determined by the demand of phytosterols for use in fermentation to produce AD/ADD, but by the overall picture including production of phytosterols also for use domestically in the pharmaceutical and cosmetic industries. Opportunity of export sales would also be considered.

Some consideration has already been given to this by the Cuban party and some preliminary evaluations carried out for a unit to process 400/500 tons of sugar cane oil to produce 20 tons of phytosterols. 6 tons has been sheduled provisionally for use in pharmaceutical products, cosmetics and use in fermentation, while the remaining 14 tons is intented for sale.

Such a unit might ultimately also be equipped for the isolation and further processing of fatty acids from the residues. Otherwise the residues may be used as chicken feed or for cooling of machines and bearings.

All the present and proposed factories for producing the sugar cane oil are situated in Orientes, roughly as indicated in the following sketch.



x = wax refining unit.

It would be most appropriate to situate a large plant also in the Orientes area, more or less centralised with relation to the units providing the sugar cane oil. The Las Tunas area could be appropriate.

Furthermore the selection of a site which is already serviced with facilities such as steam, water, electricity and possibly roadways, and with land available for building would greatly contribute to the economics of the project.

b) Existing facility.

This second option could, perhaps, be considered for operation at a level to satisfy only the needs of phytosterols for use in microbiological conversion to AD/ADD.

Such opportunity might be seen at the factory "Ocho de Marzo" where some preliminary development batches have already been processed.

It has been suggested that a production of 200/300 kgs/month phytosterols mixture could be performed. However, it is suggested that this is probably not the most beneficial use that this plant can be utilized for and a cost benefit against production of finished bulk products should be carefully performed before embarking on such a programme.

Some re-assessment of the full suitability of the existing equipment might also be necessary if a regular production was embarked upon.

Transportation of sugar cane oils of up to 900 km would be necessary. While gasolene is in short supply the tankers used run on diesel which is not such a problem and the transportation cost indicated of 56 Peso per ton of sugar cane oil (approximately 1 Peso per kg phytosterol mixture) is not prohibitive.

For regular production of phytosterols, this solution is not considered to be very attractive and does not fit in very well with the existing productions.

c) Third option.

The third option could be to consider production in existing facilities which could be freed or are currently under utilized at the establishment "Mario Muñoz".

Equipment for one of the possible processing methods is essentially free and available. The method which varies to some extent from that tested in "Ocho de Marzo" has not yet been scaled-up. The scaled-up of the method which involves simple operations and equipment should be performed. The essential hold-up in doing so is the availability of a satisfactory delivery of good quality oil. Because of variation in quality from the wax factory it is considered the appropriate quality be selected on site by a technically qualified person. Lack of fuel for transportation to do so is currently a problem which holds up this important aspect.

Subject to satisfactory scaling up (where no serious problems are foreseen) and checking some details with respect to drying capacity an estimated production of 50kgs phytosterols per week could probably be acheived.

Again transportation of the sugar cane oils would be involved and also disposal of the residual fatty acid bearing by-product. These could, though, be employed in uses in the near vicinity of Havana.

The advantage of this option is that not only is idle capacity available, but the type of processing and the nature of the product is more compatible with the operations carried out in this factory.

The production could also be used initially to provide a stock of phytosterols for fermentation development work and other purposes (eg. pharmaceutical or cosmetic or proof samples to promote interest in sales) would be most valuable.

5.2 Location and site - fermentation.

This aspect can only be speculated upon since insufficient information is available on detailed technology, operating conditions and scale.

Irrespective of the ultimate scale of fermentation which might be considered, whether technology can be procured from existing operators or from some development project, it is to be expected that some pilot proving runs will be desirable or necessary.

Various possibilities as to where to perform such work in Cuba have been investigated and possibilities for any early testing or proving runs do exist.

Choice exists between the following facilities which are either already installed or in an advanced state of installation.

5.2.1 Units where scale-up work could be performed.

a) Cuba-10 Project, Quivican.

This pilot unit is situated some 40 km to the south of Havana. It is a facility of ICIDCA.

The pilot area contains only one 10 lt. glass fermenter and one 500 lt. stainless steel (operating capacity 350 lt.). Facilities available for recording and control of parameters such as pH. O_2, temperature, foam & rpm, but no computer control. No downstream facilities in area.

The operation boasts another section in which a turbine and air lift fermenter are installed used for preparation of animal foodstuffs. These vessels are not suitable for steroid fermentation, but in the same unit a very wide range of downstream separation equipment is installed and would be very useful.

There are satisfactory microbiological laboratory facilities and high quality of personnel.

This facility suffers from the advantage of being a little remote from Havana and not having a spread of fermenter sizes for scale-up. An intermediate 40/50 lt. fermenter would make a considerable difference.

b) **Institute for Investigations in Food Industry - IIIA. Guatao.**

This unit is less isolated from Havana. When inspected the equipment was still being installed but was due completion end 1992.

With regards to fermenters this unit is very well served and appropriate for scale-up and small test production. Three fermenters are installed, one of 30 lts. one of 300 lts. and one of 3,000 lts. All have appropriate feed vessels and are constructed in stainless steel with full polish finish.

All appropriate controls for monitoring are available. Computer control is available on the largest fermenter and may be extended to all three.

While the fermenter arrangement is excellent, it does seem that the down-stream facilities are not appropriate for the different scales of operation and that there is a lack of liquid-liquid extraction equipment which may be required.

Consideration could be given to performing the fermentations in this unit and transferring products to another establishment , eg. Mario Muñoz, for down-stream processing. This would be cumbersome and not very desirable.

Since the pilot units have not yet been operated it is difficult to assess the expertice of the technicians, and especially for work which may be somewhat different to their normal experience with food products. Addition of some chemical engineer(s) and analysts to the team might be necessary.

c) **Cuban National Centre of Scientific Investigation: CNIC.**

This Centre has no facilities for carrying out work at greater than 15 lts. It has been working on the subject of fermentation of phytosterols to AD & ADD for several years and the experience gained both in the microbiological aspect and analysis could be of significant value . It has not been possible to evaluate the work performed, now at 10/15 lt. scale to assess its potential use commercially. There is also involvement of a third party in some aspects of the work. At the moment it must be assumed that the progress is not suficiently established for commercialization in the near future.

d) **Cuban Chemical - Pharmaceutical Centre: CQF.**

This Centre is not yet fully operational and is not expected to be so for another 2 years. Currently its research activities are performed at two centres and that covering microbiological work is housed at the Centre of CNIC.

When established will have an installation of fermenters ranging from 10 lt. through 100 lt. to 800/1000 lt. two of each being installed. These are primarily destined for antibiotic fermentation work.

Currently facilities in the laboratories are limited to 2x10 lt. 2x15 lt. and 1x40lt. stainless steel fermenter.

Additionally, however, an existing building is being fitted up with 1x15 lt. and 4x200 lt. SS fermenters together with make-up and feed vessels and some down-stream equipment. Laboratory facility, store and work area are included. This unit was planned to be ready by February 1993, but is inevitably delayed & the new completion date has not been forecast.

This unit has not yet been visited so its potential value is not clear and particularly the extent of down-stream equipment.

For work on steroids it would clearly be of benefit if the gap between the 15 lt. and 200 lt. could be bridged by a fermenter of about 40 lt., in which case perhaps a decision could be made to transfer the unit from the present CQF laboratory.

While the primary purpose of installing this unit was not for the benefit of steroid work it would to be the most attractive alternative if capacity could be provided when needed.

5.2.2 Possibilities for pilot fermentation buildings for production of AD/ADD.

While detailed technology is not available precise building requirements cannot be determined. Nonetheless it is possible to consider the possibilities, in principle, of opportunities for processing at the Mario Muñoz establishment. This is considered in many respects to be the most suitable area to be developed since it offers the opportunity of further centralisation of all steroid activities and advantages of direction.

At present a partly constructed building exists which, as far as can be ascertained, has little likelihood of being completed or used for the original purpose. The basic shell being completed, but still with possibilities for any necessary modifications could be very beneficial for expediting any production possibilities. The advantageous position of this building can be seen in the sketch below.

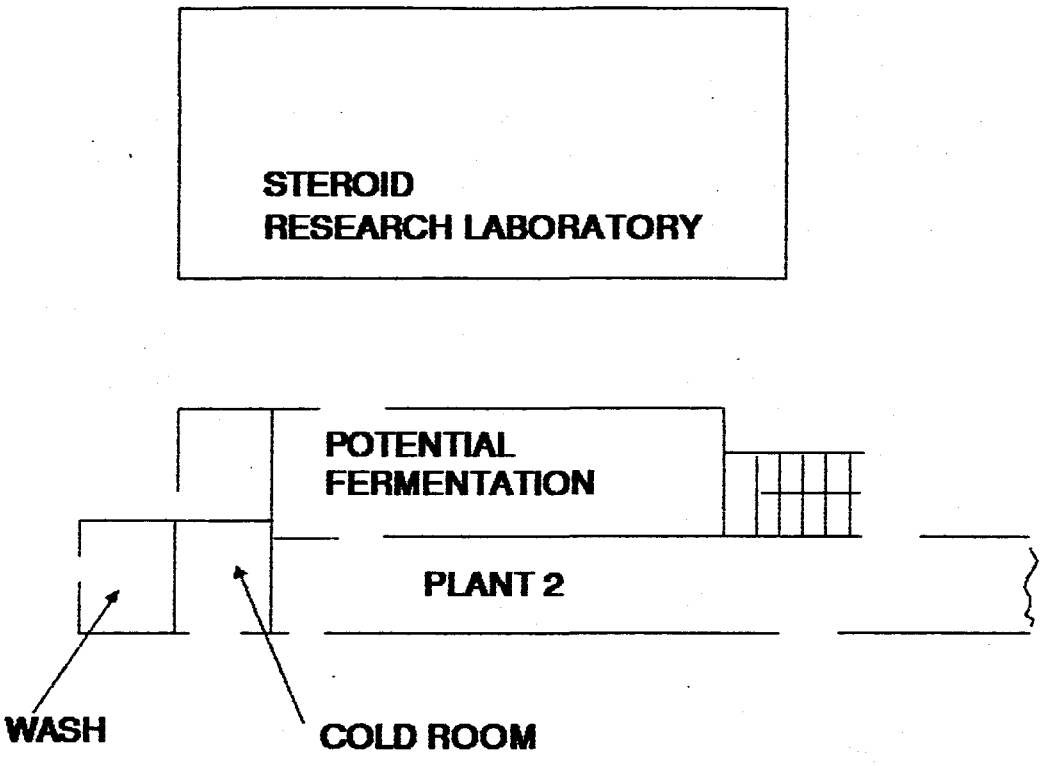
Building nucleus for integrated steroid production.

The relationship of the potential building to other steroid activities is clearly seen. The building will occupy an area of $108m^2$ (24m x 18m) as main production area together with adjacent rooms originally intended for centrifuging, cold room and washing/storage occupying a further $72m^2$.

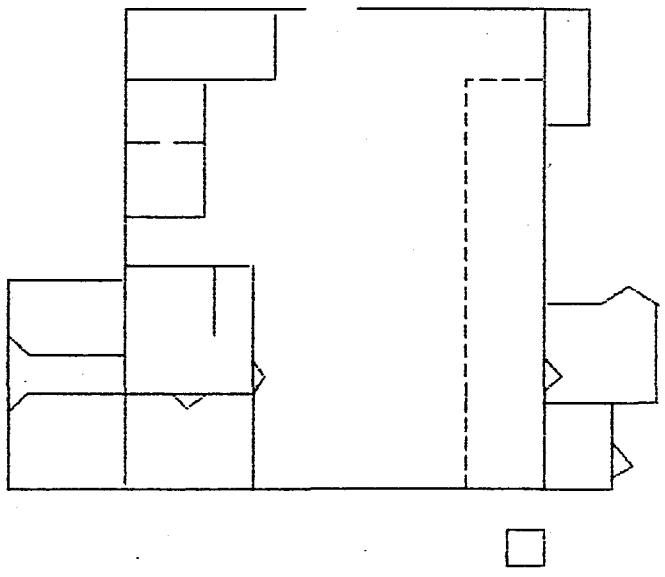
The main production area has a planned ceiling clearance of 5 meter but could be increased if necessart. Dependant on the scale of production fermentation and down-stream processing could be separated in the same general building. Should the processing scale be such that the main building was needed entirely for fermentation there is the possibility of converting the adjacent "Plant 2" for downstream processing since this area is likely to become available also due to changes in the Mario Muñoz production activities. Ceiling height is only about 3 meter, but adequate for isolation operations. The area would almost certainly need to be stripped of existing equipment and some cleaning and re-furbishing performed, but cost should be minimal.

For some investigative costing purposes to be found under the "Technology & Engineering" section on fermentation a generous building cost of USD 1,600 per m^2 has been assumed to provide facilities of sufficiently high standard as necessary for micro-biological fermentation and allowing for servicing of the building. Normal quoted prices for production areas are in the region of USD 300/350 m^2 for Industrial buildings and USD 400/450 m^2 for laboratories.

LAYOUT "MARIO MUNOZ"



HEIGHT FERMENTATION : 5 M
HEIGHT PLANT 2 : 3 M



STEROID PILOT PLANT

5.3 Location and site - steroid synthesis.

5.3.1 Laboratories.

The plan to centralize all steroid facilities at Mario Muñoz is running very many months behind schedule, due to construction materials problems.

Meanwhile research activities are being carried out within the CIDEM establishment. Progress is being made in spite of the very difficult situation regarding equipment and availability of raw materials and chemicals.

5.3.2 Micro-plant facilities.

A similar delayed situation exists with respect to the microplant. Several small reactor units have been collected for installation within the steroid process area. Additional necessary items have been idented for, but so far no funds released. Apart from these items installation of the existing vessels is held up for lack of piping, valves, etc for completion.

The completion of this unit must be considered very important since several processes are now being developed in the laboratory and are approaching the time when scale-up will be essential. The importance of this facility cannot be overemphasized both for scale-up and also as a training function.

5.3.3 Production.

The pilot steroid production unit installed under DP/CUB/81/013 is in good working order, but currently under-utilized due to shortage of raw materials and chemicals.

At the present time production is in progress. Commissioning of the production of mestranol is well advanced and the production of current needs of ethinyl estradiol completed.

One very important item (recommended in final report of DP/CUB/81/013) required for satisfactory operation under full operating conditions of the production programms is a small centrifuge especially needed for production of testosterone enanthate.

With the advent of regular production of steroids both for domestic comsumption and more particularly if export of products is contemplated the question of improving GMP requirements to the levels which can bear inspection will need consideration. This is referred to further in a section under "GMP" under "Technology and Engineering" but a formal audit should be performed either internally or with outside assistance.

During the 10 year projection of production, and certainly with the likely inclusion of some corticoid production, it will be found that some extension of plant and buildings facilities are needed as elaborated in the "Technology" section.

6. ENGINEERING AND TECHNOLOGY.

These aspects are to be covered in three parts.
a) Phytosterol production.
b) Fermentation of phytosterols to AD and ADD.
c) Steroid production capacity and future development.

6.1 PHYTOSTEROLS PRODUCTION.

6.1.1 Technologies for the production of phytosterols.

Technology in this section refers to the isolation of phytosterol mixture from sugar cane oil. The production of this raw material from Cachaza has been covered earlier in section 4.3.1/4.3.3.

The sugar cane oil fraction is composed essentially of long chain fatty acids, both saturated and unsaturated, largely esterified with lower and higher alcohols. Phytosterols are present in bound and free form.

Isolation of phytosterols has been known for many years, but large scale industrial production has not been exploited significantly due to the complexity and expense of many of the developed processes. A simple process employing low cost additives is most important.

Work on the isolation of phytosterols has been performed over many years in Cuba. Active development work is also being carried out in other parts of the world, especially in India.

Two partly developed methods are available in Cuba. Different saponification agents are used, different operational techniques are used to separate crude phytosterols and different solvents employed for purification by crystallization.

Both methods are essentially simple and it is considered that whichever one proves to be best is the most appropriate technology to use in Cuba.

Some more optimizing of the first method is needed and scaling-up of the second to provide more confident evaluation of the two.

For comparison and to justify the decision to recommended use of the Cuban procedure three typical published methods, two being from patents, will be considered.

The schematics of the three alternatives are given in the following pages, followed by that for the Cuban procedure.

Scheme 1. Reference: P.C. Goswani et. al.
Curr. Sci. 1984 vol 53 No. 17 p 917/9

This is really a laboratory method but does demonstrate the general procedure for production of sugar cane oil, particularly the use of isopropyl alcohol for wax fractionation from resins.

The method would be far too complex for commercial operation and uses very expensive barium for soap formation. Furthermore two relatively expensive ketonic solvents are used and although good solvents recoveries might be realized the operations would be expensive on power comsumption. Finally the use of chromatography over alumina for a relatively low priced fianl product would not be practicable.

Scheme 2. Reference: Dr. Werner Dopka & Dr. Ulrich hes.
DDR Patent No. 104513 Dec. 1974

The process used in this patent could not be economically operated. A very high level of potassium hydroxide is employed and the cost of this alone renders the method too costly. The use of anion exchange resin, at the stated level would involve huge columns. Finally the cost of recovery of the large volumes of mixed aqueous ethanolic and ethanolic/chlorinated solvent would be very high.

Scheme 3. Reference: Rajat Baran Mitra for CSIR, India.
Indian Patent No. 163626 Oct. 1988.

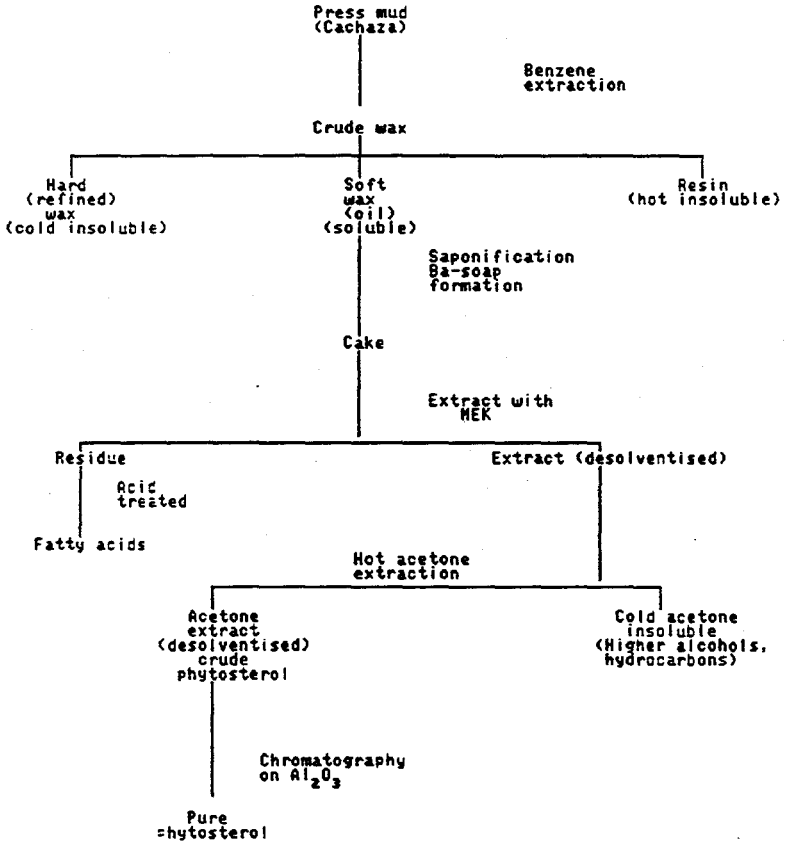
Saponification stage here is low cost, but no indication of foam problem normally experienced when saponification in water is indicated. Relatively large volumes of DCE are used since the cake (which also needs to be dried) produced after the saponification contains all the components still accounting for 94% of original input weight. Technique also appears to be important to get consistant results. Solvents used are relatively expensive.

Schematic for phytosterol isolation.

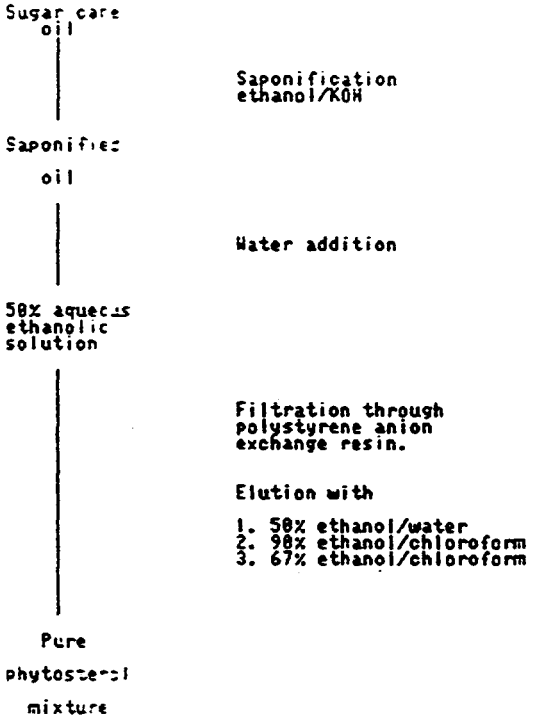
Four schemes are presented.

Schematic for phytosterol isolation

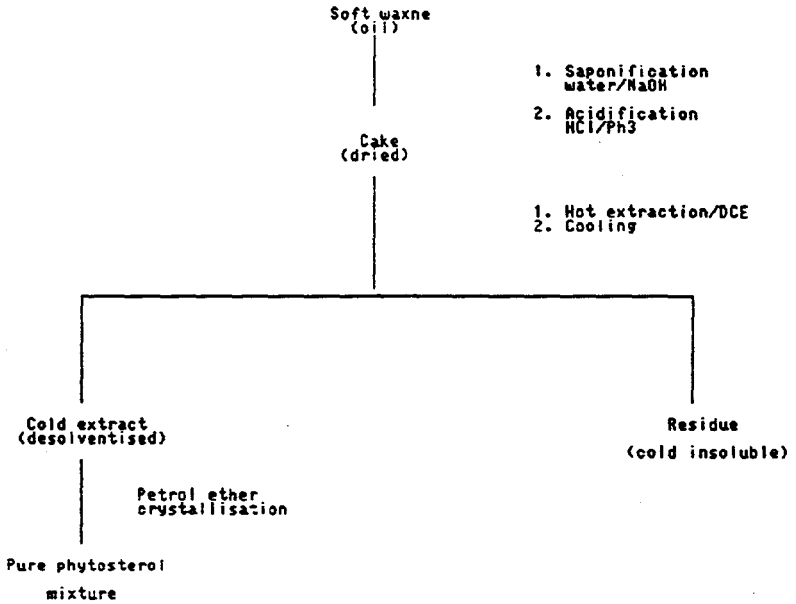
Scheme-1



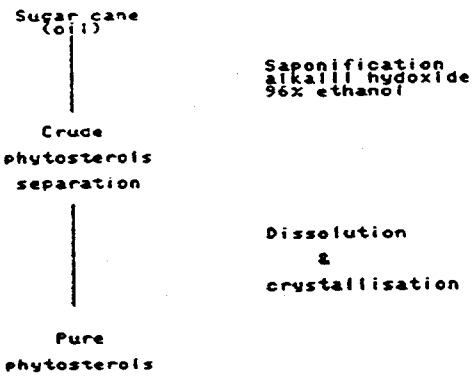
Scheme 2.


Sugar cane oil
Saponification ethanol/KOH
Saponified oil
Water addition
50% aqueous ethanolic solution
Filtration through polystyrene anion exchange resin.
Elution with
1. 50% ethanol/water
2. 90% ethanol/chloroform
3. 67% ethanol/chloroform
Pure phytosterol mixture

Scheme-3


Soft waxne
(oil)
1. Saponification
water/NaOH
2. Acidification
HCl/Ph3
Cake
(dried)
1. Hot extraction/DCE
2. Cooling
Cold extract
(desolventised)
Residue
(cold insoluble)
Petrol ether
crystallisation
Pure phytosterol
mixture

Cuban Scheme.



6.1.2 Production facilities for manufacture of phytosterols.

Locations and possibility of the production of phytosterols at different levels have been discussed already in section 5.1.

While any manufacture leading to the large scale production of phytosterols would undoubtedly fall under the initial auspices of ICIDCA, it has been considered in some detail but only the bare essentials needed to arrive at the conclusion will be reported since this is not the main object of this project.

The following factors have been taken into aacount to arrive at the determinations for the dedicated units which are the first consideration.

a) Three production levels of 10 tons, 20 tons and 45 tons per annum phytosterols output.

b) Assumed dedicated plants located in vicinity of sugar cane oil producing units and that site will already be served by electricity, steam, water, etc.

c) No cost of land included in capital costs since state owned.

d) Current costs of equipments used.

e) building, erection & other construction costs of varying structures currently prevailing in Cuba have been used.

f) Consumptions of steam, cooling water, fuel, etc have been calculated and costed on the basis of figures given for similar utility costs applied at Mario Muñoz. (Steam costs may be lower if bagasse used as fuel).

g) Chemical costs based on latest available fob (+ appropriate element for cif) for imported chemicals and delivered price for domestic (96% ethanol).

h) Cost of input oil (& output based on figure quoted as import price for oil used in chicken feed. This aspect will be discussed later.

i) The recovery of crude fatty acid mixture only is allowed for.

j) Main calculations are based on what is considered may be the more expensive of the technologies, but estimates are also made for the alternative.

Building requirements:

Capacity	Covered areas	Outside areas	Total cost USD

		(bunds)	including 30% contingency
10 tons	84 m^2	21 m^2	42,000
20 tons	201 m^2	74 m^2	99,500
45 tons	320 m^2	112 m^2	148,532

Equipment: basic.

Capacity:	10 tons	20 tons	45 tons

Items.

Reactors + condensers	7,000 lt.	20,000 lt.	44,000 lt.
Receiver/still	2,000 lt.	5,000 lt.	10,000 lt.
Crystallization unit	1,000 lt.	4,500 lt.	9,000 lt.
Storage	30,000 lt.	55,000 lt.	100,000 lt.
In-line filter	one off	one off	two off
Separator	one off	one off	two off
Driers	one off	one off	two off
Pumps, scales, misc.	-	-	-
Total equipment cost USD	425,510	676,920	998,940
Total installed cost USD	814,741	1,335,090	1,986,841

Factors proposed by The Institute of Chemical Engineers and Association of Cost Engineers, have been used. They were based on the appropriate level of installation, i.e. relatively low complexity and low instrumentation level. These factors are individually related to different types of equipments, e.g. reactors, pumps, centrifuges, storage, driers etc and cover the elements of erection, piping, instrumentation, electrical, civil (relating to floors, foundations & services), structures and lagging.

A contingency factor of 30% has also been included.

Installed costs were also estimated at the same levels of production assuming that the alternative second method of processing was used.

Alternative method.	10 tons.	20 tons.	45 tons.
Total installed cost USD	602,625	1,057,732	1,621,501

Chemical costs:

These initial chemical costs will be confined to additives. The effect of cost of sugar cane oil input and the value of the by-product fatty acids oil will be considered later with respect to the production costs of phytosterol.

Costs are given for both available methods. The former, which has been scaled-up, is listed undermethod 1 and uses potassium hydroxide as base. The second, method 2, uses sodium hydroxide.

Chemical cost per 1,000 kgs, phytosterol produced.

	Method 1	Method 2
Gross additives cost	20,585	53,818
Solvent recoveries	12,375	46,275
Net cost	8,210	7,543
Unit cost/kg in USD	8,21	7,54

Accuracy is very dependant on the solvent recovery efficiency.

6.1.3 Production costs - method of calculation.

For this exercise the following parameters have been applied.

Direct costs:
Overhead labour - supervisory, support staff eg Q.C. etc.
Factory & Administration overheads - covering auxiliary supplies, general utilities, communications (telephone, fax, etc, building maintenance & repair for convenience including any financial costs -using estimating figure at 15% of Direct cost.

Maintenance - labour and materials - using 4% of equipment depreciation figure.

Equipment depreciation - included for simplicity under Indirect costs. Straight line 10 year depreciation on cost used.

Building depreciation - Also included for simplicity in this section. Straight line 15 year depreciation on cost used.

Production cost - Direct cost + Indirect cost.

In the case of products for sale it would be necessary to add marketing costs to aarive at **Total costs of products sold** but this is not necessary in this exercise.

It might be noted that the Cuban system for determinig a **Total Production cost** does not consider a specific cost for marketing, but does add elements to cover Research Development (5% of Direct + Indirect) Contingency (also 5% of Direct + Indirect). This figure is referred to as the **Factory price.** Finally a profit margin of 5.4% is added to the Factory price to prive the **Total cost of Production.**

Care should be taken at not confusing Production cost as used in this report with the Cuban Total cost of Production.

Production cost determinations:

Projections are made for the two available methods assuming **dedicated units** of capacities 10 tons, 20 tons and 45 tons output phytosterols mixture per annum.

Method 1	10 tons	20 tons	45 tons
Additives net cost	82,100	164,200	369,450
Labour, utilities etc.	14,907	19,719	34,666
DIRECT COST	107,007	183,919	404,116
Admin; Main; etc.	20,996	34,608	70,244
Deprec. equipment	81,474	133,351	198,684
Deprec. buildings	2,785	6,627	9,902
PRODUCTION COST	212,262	358,505	682,946
UNIT kg. COST excluding oil	21,23	17,93	15,18

Method 2	10 tons	20 tons	45 tons
Additives net cost	75,400	150,800	339,300
Labour, utilities etc.	14,907	19,719	34,666
DIRECT COST	90,307	170,519	373,966
Admin; Main; etc.	17,636	31,489	64,261
Deprec. equipment	60,262	105,773	162,150
Deprec. buildings	2,785	6,627	9,902
PRODUCTION COST	170,990	314,408	610,279
UNIT kg. COST excluding oil	17,10	15,72	13,56

Sugar cane oil contribution.

The cost of input sugar cane oil, a by-product from the production of refined or hard wax as a saleable product, is not clearly defined. As a by-product it could be argued that the value is nil. On the other hand the product can be used in chicken feed and may be sold to farmers. On this basis it has been suggested that it should be valued at the same price as material imported and used for the same purpose. This was suggested to be at USD 700 per ton.

While this can be a valid argument perhaps with respect to hard currency saving it is suggested it does not represent the real cost of production and the figure must be too high.

It has not been revealed whether in the costing of the current production of refined wax all charges are made against the major product or apportioned over refined wax and resin or over all three products, refined wax, resin and sugar cane oil.

A similar dilemma exists with respect to a valuation of the by-product, crude fatty acids oil, from the phytosterol production process. This cannot presently be valued in terms of its potential to produce valuable fatty acids since the process has not been evaluated. All that is known is that each 100 kgs. crude fatty acids oil from which 56.8 kgs distilled acids can be recovered.

If the input sugar cane oil is treated as a by-product of no value, this output product should at present be treated similarly. If a valuation is agreed for the input sugar cane oil it is suggested that at worst the output oil should be given a similar unit value as it could also be made use of domestically. In fact the output oil should bear some added value, but the basis for allocation at this time is not clear.

Production costs including sugar cane oil cost.

These are best illustrated graphically to show the variation with value placed on sugar cane oil, but also assuming the output oil taken at the same unit value.

Using the method of valuation it is simple to calculate the production cost using the formula:

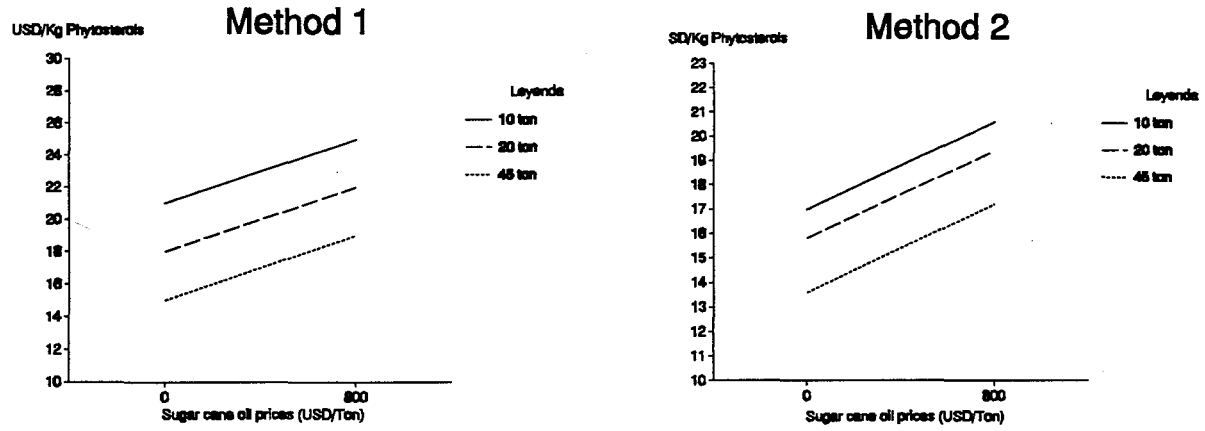
Production cost (zero valued oils) + 1.15 x(net added oil cost)

= Final production cost.

A production cost figure of USD 15.00 per kg. phytosterol mixture was indicated by the Cuban party for a 20 ton production plant, but was not a finalised figure. An input value of sugar cane oil of USD 700 per ton was understood to have been used.

Considering the accuracy of evaluation at this stage the agreement is not unreasonable.

Graphical representation of production cost relative to oil costs/values.



Production costs in non-dedicated facilities.

Insufficient information is available to determine the likely cost of production using facilities at "Ocho de Marzo", particularly with respect to depreciation of the relevant plant which could be used for the processing.

An estimation using the facilities at Mario Muñoz can be proposed since the plant usage can be reasonably defined and the majority of this is very old and fully depreciated. (It was understood that custom in Cuba is often to re-value plant but this will be ignored - however an increased element for repairs & maintenance will be allowed).

Production costing at Mario Muñoz.

The estimated possible production level is 2,500 kgs of phytosterols per annum.

Since the sugar cane oil will have to be transported for up to 900 km. It is considered that this transport cost must be included as a direct cost. Transportation charges have been indicated at 50 Peso per ton for 900 km. For calculation purposes this will be used as the USD equivalent.

Direct costs:	**USD**
Oil transportation	2,750
Additives cost	18,850
Labour etc.	7,450
	29,050
Indirect costs:	
Administration etc.	5,200
Maintenance	4,500
Depreciation	-
	38,750
Production cost:	
UNIT kg. COST exluding oil	15,50

Cost price phytosterol and sales potential.

Without resort to actual production cost calculations for fermentation to AD & ADD it is thought, at this stage, that a price of USD 15 - USD 20 per kg. for phytosterol mixture may not be unreasonable for local production. Much will depend on fermentation conditions, yield and particularly the depreciation element of installed equipment.

It is thought that the price of USD 15 - USD 20 per kg. produced may be too high for consideration of bulk sales of phytosterols. Such sales are generally under contract rather than on open market so it is difficult to establish a realistic price. At the moment only one indication has been received for 50 - 100 tons p.a. order at requested price of about USD 6.0 per kg. cif. this seems to be much lower than would be expected in reality.

Sales to the formulation industries of pharmaceuticals or cosmetics might realize better prices than for synthesis.

Market prices for beta-sitosterol itself also seem to be very unreliable - quotations have been received from about USD 50 to USD 500 per kg.
The real situation could probably only be determined when samples of typical materials were available for customer testing.

6.2 FERMENTATION TECHNOLOGY.

6.2.1 Required production levels of AD & ADD.

Bulk steroid consumption levels of AD & ADD.

For several products the methods of production are available and have been largely proved in commissioning, while others are in the course of being proved.

The products covered in this range, wich are derived from ADD are:
- ethinyl estradiol (commissioned)
- mestranol (commissioning in progress)
- estradiol benzoate (awaiting scale-up)

In the case of AD the following products have been proved in commissioning :
- testosterone propionate (from testosterone)
- testosterone enanthate (from testosterone)

Starting from AD in place of the former dehydroepiandrosterone acetate (DHA) requires new procedures. Commercially proved methods for improved conversion of AD to testosterone have been provided and are currently being checked in the laboratory prior to scale-up. This may be delayed due to lack of availability of additives, especially triethyl orthoformate. For all the aforementioned products firm conversion rates may be applied.

Methods for the synthesis of spironolactone, norethisterone, methandienone and danazol have been defined and here some expectation of yields can be fairly reasonably assumed.

The conversion factors applied are :

ADD products	x factor = ADD
Ethinyl estradiol	1.68
Mestranol	1.85
Estradiol benzoate	1.51
Estradiol valerate	1.79
Estradiol cypionate	1.65
Norethisterane	2.275
AD products	
Testosterone propionate	1.15
Testosterone enanthate	1.176
Spironolactone	2.80
Danazol	2.32
Methadiendione	4.00

Requirements of ADD & AD are calculated as follows from the production schedule forecast.

REQUIREMENTS FOR ADD & AD.

ADD DERIVATIVES	Year									
	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002
Ethinil Estradiol	30.2	35.3	40.3	67.2	100.8	100.8	117.6	117.6	117.6	134.4
Mestranol	22.2	22.2	25.9	31.5	35.2	39.9	57.4	75.9	96.2	101.8
Estradiol Benzoate	15.1	20.4	27.9	30.2	30.2	30.2	30.2	30.2	37.8	37.8
Estradiol Valerate	-	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Estradiol Cypionate	-	1.7	1.7	1.7	3.3	3.3	3.3	3.3	3.3	3.3
Norethisterone	-	11.4	45.5	91.0	136.5	136.5	136.5	182.0	182.0	182.0
TOTAL ADD	**67.5**	**91.2**	**141.5**	**221.8**	**306.2**	**309.9**	**345.2**	**409.2**	**437.1**	**459.5**
AD DERIVATIVES										
Testosterone propionate	23.0	34.5	55.2	69.0	92.0	115.0	115.0	138.0	172.5	172.5
Testosterone Enanthate	11.8	23.6	56.5	70.6	94.1	105.8	141.1	176.4	176.4	176.4
Spironolactone	-	28.0	140.0	280.0	560.0	700.0	840.0	840.0	980.0	980.0
Methandienone	10.0	80.0	176.0	188.0	188.0	200.0	200.0	220.0	220.0	240.0
Danazol	-	13.9	41.8	55.7	60.3	60.3	60.3	65.0	65.0	69.6
TOTAL AD	**44.8**	**180.0**	**469.5**	**663.3**	**994.6**	**1181.1**	**1356.4**	**1439.4**	**1613.9**	**1638.5**

6.2.2 Requirements of phytosterols for fermentation input.

These cannot be defined precisely. Most reported yields of various technologies range between 40% & 54% by weight on charged phytosterols. The best reported yield from one contact developing technology for ADD, in particular, report a yield in excess of 90% theory or 63% by weight. On isolation a yield of 54-57% by weight might be expected.

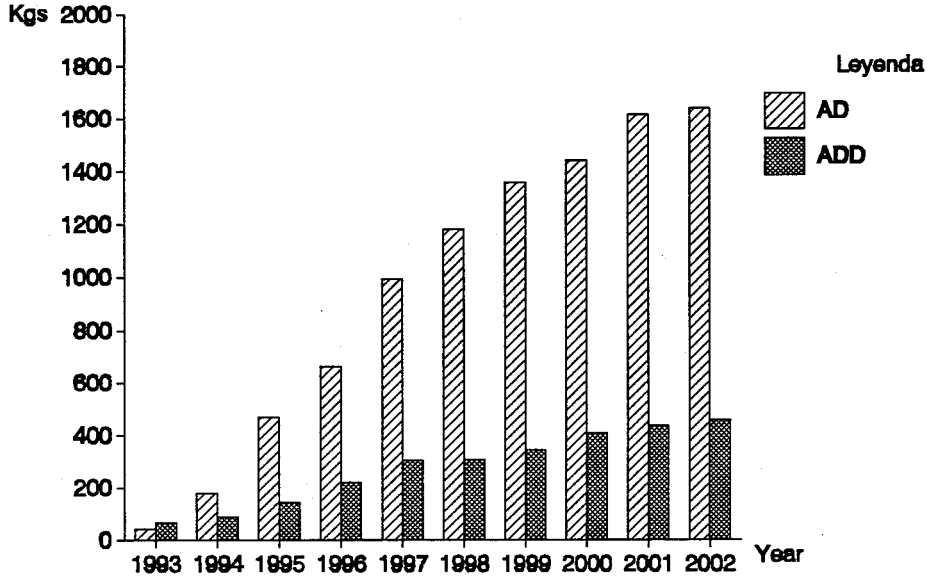
For calculation purposes it is proposed to use a yield for both ADD & AD of 50% by weight.

Phytosterol requirements are thus calculated at :

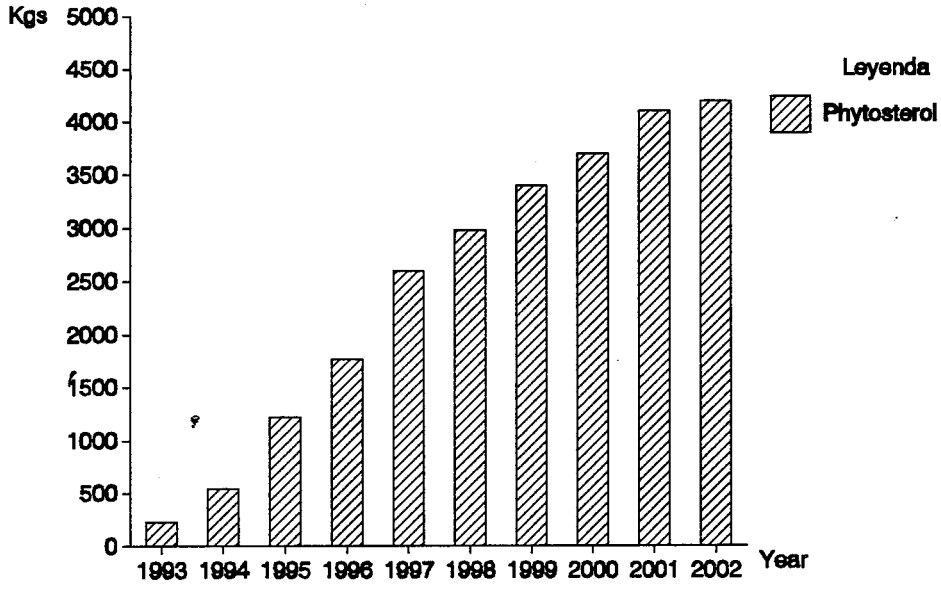
1993	1994	1995	1996	1997	1998	1999	2000	2001	2002
225	542	1222	1770	2601	2982	3403	3697	4102	4196 Kgs.

The figures from both sections 6.2.1 & 6.2.2 are more clearly illustrated in the graphical forms to follow.

Annual Growth AD & ADD Needs



Annual Growth Phytosterol Needs



6.2.3 Aspects of steroid fermentation technology & patents.

A choice of technology, as already mentioned, cannot yet be made due to lack of firm information.

In general, due to low water solubility of phytosterols, fermentation is usually reported at a substrate levels of 0.1% w/v, but some conditions have been studied to increase this to 1.0%.

Fermentation times depend much on conditions and have usually been reported at from 2 to 5 days.

The particular micro-organism used is usually found to produce a predominance of one product over the other. the common products, using appropiate micro-organism, are AD and ADD, but more recently work is concentrating on the production and isolation of 9α - hydroxy-AD. This is a most interesting starting material for cortico-steroids. It is of no interest with respect to the project.

The more specific the conversion, the simpler is the isolation and purification of the main product.

On the other hand, where both AD & AD are required in moderate amounts it might be appropiate to select a micro-organism to produce a mixture and separate, by known means, the two products chemically.

Alternatively, it can be argued that the major Cuban need is for AD and if a choice of technology had to be made it should be in favour of AD.

There could be opportunity also of converting AD to ADD also by fermentation (a higher substrate level is possible for this conversion), or having this done by another company in exchange for sale & provision of AD. Such a possibility has been established in principle with an Indian Company (CIPLA LTD.).

Patents

A patent search has been performed on micro-biological fermentation to AD & ADD without any significant revelations.

Most patents refer to early claims and few recent publications have been located.

Those abstracted, referring directly to fermentative conversions, are:

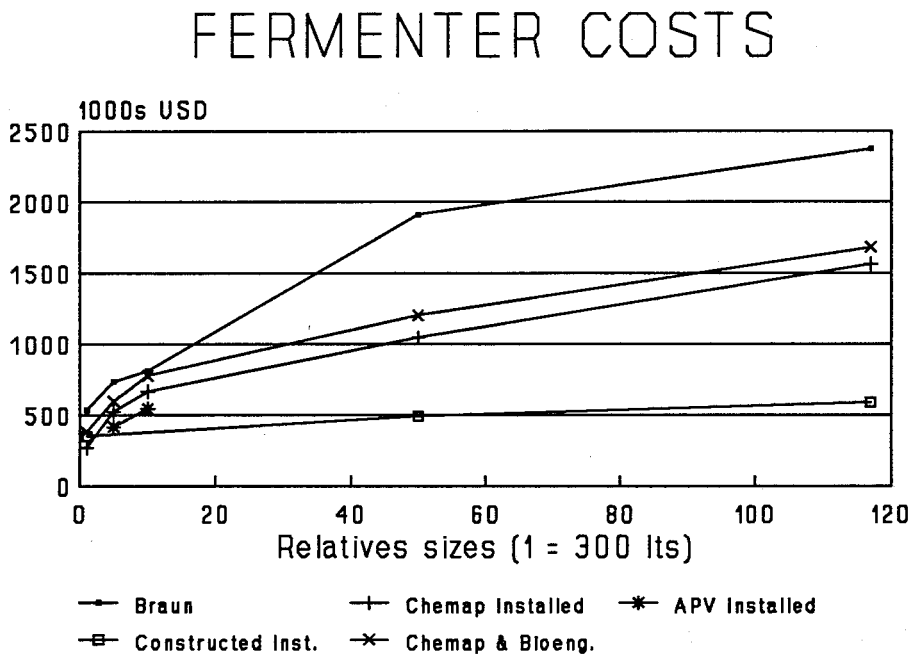
	Patent	Application	Patented
Hungarian	Hung 153,831	Sept 1965	Nov 1967
Mitsubishi	US 3,388,042	June 1964	Jun 1968
Gist-En-Spiritus	Brit 1,113,887	Oct 1966	May 1968
Gist-En-Spiritus	US 3,487,987	Apl 1967	Jan 1970
G.D. Searle	US 3,684,657	May 1970	Aug 1972
G.D. Searle	US 3,759,291	Dec 1970	Sept1973

6.2.4 Fermentation equipment.

While it is premature, because precise technology could not be obtained, to consider any details of engineering requirements, approaches have been made to several manufacturers to obtain some idea of current prices. Of particular interest was to obtain the relationship of size to cost. In the main offers have been for essentialy packaged units, but in addition a preliminary costing has been performed whereby component parts have been costed individually and used to determine a composite price.

The "package" units quoted are of very high design profile and as used in most high biotechnology applications. To some degree they are probably over-designed for use in microbiological fermentation of steroids to produce intermediates.

The results of the various quotations are given in graphical form:



It can be seen that the composed units are consideraly less expensive, though it is likely that design costs may need to be added unless turnkey technology can be procured.

The graph also shows, as expected, that pilot plant equipment up to 1,500 Lt is relatively expensive. Instrumentation costs are high and not proportional to the fermenter size.

The alternative representation in terms of cost per liter. given below, is revealing.

Cost per unit USD/Lt. for installed fermenters.

Manufacturer:	Chemap	Braun	APV	Bioengi-neering	Constructed
Installed size					
300 Lt.	905.2	1,785.0	-	905	-
1,500 Lt.	349.7	489.6	277.3	350	
3,000 Lt.	224.0	270.3	181.3	224	109.4
15,000 Lt.	77.4	127.5	-	77	29.1
35,000 Lt.	49.2	67.8	-	49	16.3

Procurement.

If technology can be purchased or licenced, the plant design should be included. It would probably be most economic then to consider building up the plant from component parts under an engineering contract.

Even if full design was not included it could still be worth considering to pay for the services of a fermentation engineering company for design, procurement & erection.

For procurement purposes great care should be taken in comparing the prices quoted to ensure they correspond to exactly the same specification. That similar care should also be taken in drawing up a specification, to determine it is appropriate and not either under- nor over-specified cannot be over-emphazised, particularly with this type of equipment. It can be crucial with respect to determination of project feasibility.

Other quotations.

Quotations have also been obtained for various down-stream activities, including drying, for inclusion in provisional cost evaluations at which follow.

6.2.5. Minimum economic size.

The cost of producing either AD or ADD from phytosterol will be found to vary considerably with production scale and batch size. The variation in production cost is due to the high cost of equipment and consequent high figure incorporated for depreciation,
which is particularly significant for small equipment.

Although precise production costs cannot be made in absence of access to firm process information reasonable assumptions can be made and applied to illustrate the position.

Operating parameters have been selected on various informations and documentations and must be considered achievable (as minimal aims)
for operation of any phytosterol fermentation production in Cuba. Under appropriate conditions a substrate level of 1% has been indicated possible. This level is considered essential and any operation at 0.1% as indicated in several other patented and literature sources does not seem feasible.

Fermentation time is also an important factor. Again 5 days fermentation has frequently been recorded, but here a maximum of 2 days is considered. Some documentation of satisfactory conversion in this time has been recorded.

The assumptions made then in the calculations are:
1) a substrate level of 1% for fermentation.
2) a fermentation time of 2 days; 2 batches per week.
3) employment of fully packaged agitated fermentors (at prices quoted within narrow limits by Chemap and Bio-engineering)
4) employment of one reactor only.
5) costs for down-stream processing estimated as considered appropriate.
6) building size & cost appropriate for production scale and depreciated over 15 years straight line.
7) equipment depreciated over 10 years straight line.
8) estimated direct labour costs.
9) estimated additives costs.
10) consumptions of fuel, electricity, compressed air and water consumptions determined roughly on basis of anticipated process conditions. Fermenter motor HP and air usage as appropriate 11) input price for phytosterols USD 20.0/kg.
12) yield determined from 90% utilization phytosterol, 67% weight conversion to AD, 90% isolation. Overall weight yield = 54.3%.
13) No allowance is made for any capital costs for utility equipments since, with the exception of compressors (for which estimate is included in equipment cost), it is anticipated that adequate levels of utilities will be available on site.

Plant equipment costs and depreciation figures for different size installations.

Equipment	Fermenter Size			
	1500 lt	3000 lt	15000	35000 lt
Installed fermenter	600,000	760,000	1,200,000	1,680,000
Water treatment	247,000	264,000	455,000	492,000
Harvest vessel				
Filter				
Extraction centrifuge				
Solvent recovery/crystallisation				
Drier, etc				
Compressors				
SUBTOTAL	847,000	1,024,000	1,655,000	2,172,000
Contingency 30%	254,100	325,200	486,500	651,600
Total installed cost	1,001,100	1,409,200	2,151,500	2,823,600
Depreciatioin charge	100,110	140,920	215,150	282,360

Possibility of advantageous use of an air-lift fermenter was consider. However, according to various manufacturers the cost of such equipment would only be 10% or, at best, 15% cheaper than the traditional type quoted.

Also little increase in price was indicated if a more intense or alternative stirring pattern is required (for example if working under two phase conditions).

Building cost estimates and depreciation

Two basic buildings have been considered, one of 50 m^2 for housing either the 1500 lts or 3000 lts units and one of 108 m^2 for housing a 15000 lt or 35000 lt fermenter. A building rate of $1,600 has been allowed to cover a high quality installation and utilities services, drains, etc.

VARIATION OF EXPECTED PRODUCTION COSTS WITH FERMENTATION SIZE

Anual Production (Kgs)	466	932	4660	10,873
Fermenter size (lts)	1500	3000	15000	35000
Production cost per Kg (AD)				
Phytosterols	37.0	37.0	37.0	37.0
Additives	3.7	3.7	3.7	3.7
Labour + anclllary	11.3	5.7	2.2	1.2
Utilities	18.1	15.5	7.7	7.0
Direct cost	70.1	61.9	50.6	48.9
Equipment depreciation	214.8	151.2	46.2	26.0
Building depreciation	11.4	5.7	2.6	1.1
QC, samples *	20.0	18.0	17.0	16.0
Maintenance	8.5	6.1	1.9	1.0
Administration	10.5	9.3	7.6	7.3
Indirect cost	265.2	190.3	75.3	51.4
Total production cost	335.3	252.2	125.9	100.3

INDICATIONS.

1) While costings are necessary only approximate it is very clear that production at low level would be expensive and could not justify investment in a pilot plant. For scale-up, etc existing facilities would be essential since the position deteriorates even more rapidly below 1500 lts.

2) Costs of different types of fermenters is not very significant. The design and/or type of fermenter should hence be chosen on a technological basis.

3) On the basis of the figures the minimum fermenter level would appear to be 15,000 litres, producing some 4,660 kgs. product per annum. This is about double the forecast domestic requirements by year 2002.

4) The level of 4,660 kgs. is not necessarily prohibitive since sales opportunities exist. At this point levels which could be sold in the International market have not been established, although one source indicated possible interest in the region of 2,000 kgs. per annum.

5) In the exercise it has been implied that only one fermenter be used. In practice it would undoubtedly be better to use more than one smaller unit (eg in place of the 15,000 litre fermenter use 3 x 5,000/6000 litres units.). The costs would be higher than for one larger unit, but significantly lower than for 3 complete installed smaller units.

6) The effect on production cost of the plant depreciation element can be clearly seen. The effect would obviously be reduced considerably by depreciating over a 15 year period which could be acceptable (this would effect taxeable profit levels and should be considered particularly if any joint venture were possible).

7) In view of the number of assumptions which have had to be made in this exercise it is considered impossible, and pointless at this stage, to make any further financial projections or detailed economic forecasts.

6.2.6 PROPOSALS FOR PROGRESS

Unfortuneately at the conclusion of this project and at the time of reporting it has not been possible to locate a source of technology which holders are prepared to either sell, licence or provide in any joint venture arrangement.

Sources of enquiries have not been exhausted and should any positive results materialise subsequent to the conclusion of the project period they will be communicated to the interested parties.

The only alternative options would, therefore, be to:

1) purchase the steroid raw materials AD and ADD on the open international market (for the meantime).

2) enter into a joint venture research/development programme on a commercial basis to develop suitable technology for the necessary conversions.

3) follow research only on a national basis to develop commercial technology.

4) decide not to pursue further any possibilities of self sufficiency.

5) provide source material for the toll conversion to AD (and possibly ADD).

An immediate solution only for provision of supplies has been discussed whereby a stock of some 300 Kgs of diosgenin, which has been held in stock for some time, will be converted to AD. While not an economic option, the cost of diosgenin and virtually all chemicals required for processing have been expended. This processing will also be useful as processing experience for the operators. An output of 80 Kgs AD is to be anticipated.

In view of the fact that no detailed technology is available it is not possible to present the full techno-economic study, projections and ratios for production of AD and/or ADD which were called for in the "Terms of Reference".

6.2.7 WHERE TO GO, AND HOW.

Various options will be considered.

1) **Purchase of AD and ADD on the open market.**

The problem here is that Cuba is reliant on outside influences and not self-sufficient as it strives to be. Obtaining AD & ADD on the open international market is possible, but subject to the possibility of shortages of supply which are then frequently coupled with variable and high prices. While Cuban production can probably cope with the prices (since final products are likely to follow suit) according to the projections made, lack of availability of material is very serious. Also, irrespective of price, considerable levels of hard currency are needed for the purchase of the intermediates which generally comprise a high proportion final product cost.

Production costs of the established products for Cuban manufacture, even using imported AD & ADD, can be seen to be reasonably satisfactory (see section 6.3.3.4). Overall profitability at low levels of production may be adverse due to the need to absorp depreciation of plant and buildings. These exist however whether production takes place or not (for calculation purposes it has been assumed that that plant still holds its original book value although now installed for some time and operasted at low level. The fact that a considerable level was also funded by UNDP funds has also been ignored since it should be seen that the operation is feasible in its own right.

2) JOINT RESEARCH PROGRAMME

When the financial benefits alone of domestic production are fully evaluated it may be clearly seen what annual and longer term advantages are apparent. This may gives an guideline as to the level of investment which might be considered reasonable to embark on a joint programme for long term benefits.

The production of AD and ADD can be considered side by side since the principal processing requirements are similar and the main strain of micro-organism Mycobacterium phlei also currently appearing to be that preferred.

Probably two main aspects are paramount: (a) micro-organism strain and (b) fermentation conditions.

Possibly screening for most suitable species may at the same time provide information as to which appears more suitable for each conversion. The subsequent work will be increased, and if not doubled, certanly significantly and with an increased need for funding.

Criteria to look for to set-up joint research programme.

a) The availability of a good strain for either one or other of the desired conversions.

b) An existing work programme preferably at some advanced stage for which a reasonably accurate forecast can be made for commercialisation.

c) Availability of facilities for scale-up and possibly pilot production.

d) Staff with scale-up experience.

Criteria considered necessary for posibility of an economic process.

1.- A strain of Mycobacteria which provides essentially selective production of AD or ADD. The production of a mixture might be thought advantageous if the ratio corresponds to the demand ratio of products but chemical separation cost are probably disvantageous against producing individual products and control of consistant ratios may be difficult.

2.- The major ingredients should be of domestic origin so far as possible. This will certainly apply to the major raw material which can be produced in Cuba. Other imported salts or carriers etc, should represent a relatively low element of cost.

3.- In view of the relatively high cost of equipment for fermentation and the conditions under which it should be installed and operated it is considered that any process for Cuba and at the levels which might be expected to be produced could need to have a high substrate level, minimum 1% w/v. This is contrary to all the earlier works which operated at only 0.1% w/v. Working at 1% may need to be 2 phase or using a carrier such are cyclo dextrins or other carriers.

4.- Fermentation time is also important and it is considered that the aim should be for not more than 2 days actual fermentation.

5.- High utilization of phytosterol is important (is the amount of phytosterol converted to 17 keto steroids) and also the efficiency of conversion of the utilised product (the maximum yield here is 69.2% w/w). A minimum utilization of 90% and conversion of 97% (67% weight) should be aimed at corresponding to a yield in broth of 60% w/w on charged phytosterols. An isolated yield of 54% might then be anticipated.

Any possibilities for co-operation and attributes from each partner need to be take into account.

6.- The major need in terms of quality of steroid intermediate in Cuba is AD rather than ADD although this latter is of extreme domestic importance for estrogen production. AD can be converted readily to ADD, but the reverse is not true. So although **AD is of lower value per Kg it is proposed that this production should be the prime aim in Cuba.**

Possibilities

Only 2 positive possibilities are presently known, a third being at a very early stage of investigation and not worth consideration except, perhaps as a last resort.

a) The first possibility is co-operation with an Indian group who have indicated positive interest. They claim to be able to offer availability of good strains of Mycobacterium for conversion to ADD. Claimed yields are very good, but the current limitation a low sustrate conditions (0.1% w/v) and prolonged (5 days) fermentation.
Work is in progress on AD, but is less advanced.

The group suggest they need one year more work to achieve commercialisation.

The cost for a join programme would likely be in excess of USD 100,000 and probably nearer to USD 300,000.

Talks with this group could be worthwhile.

It may be possible that the Cuban group who have worked for many years on AD and ADD conversions do not have the best strain or fermentation conditions while using oil for carrier and phytosterols solubilization up to a more acceptable level of 1% w/v. Either or both of this conditions may be the reason for low yields.
There may be further complication with the Cuban group collaboration with any other partner since the already have a working association with a Canadian group, although this is believed to relate only to conversion to ADD.

b) The second opportunity is that another Indian producer is currently performing the conversion of AD to ADD and would almost certainly co-operate, possibly by offering toll conversion of AD to ADD payment for which could be in terms of supply of AD for Indian use. Though less likely the possibility of licencing the technology could exist. Any installed plant in Cuba producing AD would be equally suitable for processing to ADD. Substrate level is good and also yield.

This source, however, does not have technology for production of AD and even if such should become available from another source this Company are not likely to be interested in any joint venture for the manufacture because of its other commitments.

3) **National Research.**

National work in fermentation of sterols to 17-keto steroids AD & ADD has been in progress in Cuba for very many years and also several jointly with Canadian research partners. Although it is claimed that suitable micro-biological strains are available for both production of AD & ADD every indication is that they are either not too efficient or are being used under un-favourable fermentation conditions since low yields are apparently quoted.

Considering the length of time spent on the subject so far and apparent lack of sufficient progress to be able to forecast an imminent commercialisation suggests that this source for progress cannot be relied upon.

It could, presumably, be possible for the group to be involved with another partner confining studies to the conversion of phytosterols to AD, since it is understood that work with the Canadians is confined to formation of ADD. In this co-operation the drive towards commercialisation appears to be absent.

For this latter reason it is suggested that although micro-biologists and other scientists might be drawn from this present group and further joint programme would be best directed through the chief of the steroid group, LIDE. It is possible that any joint programme might well be largely conducted in the laboratories of the co-operating party.

4) **Shelving the opportunity for self-sufficiency.**

This should not be considered at this stage without very serious thought or good reasons.

Self-sufficiency of a basic raw material supply has been the basis of the wealth of many Countries and Companies. It cannot be expected that any Country can be entirely self-sufficientttttt, but in this instance a real opportunity still exists in this area.

After the conclusion of this project paper the expert will continue with present avenues of investigation and initiate new onesw whenever possible.

Abandonment is NOT RECOMMENDED at this time.

To justify this, and to both illustrate and confirm the possibility of operating the pilot plant, an analysis in some depth of the production possibilities and costs for bulk active pharmaceuticals has been carried out. The resulting figures do illustrate that a breathing space exists providing supplies of AD & ADD can be procured. AD and ADD are currently available on the International market at reasonable prices. The position with rergards to AD is also being helped by the availability in Cuba of the diosgenin which will shortly be converted to AD.

5) Toll Conversion of Phytosterols (and AD)

This possibility has been investigated, as an interim step and a possible in-road towards obtaining technology, from the beginning of the project but without success. On return from the last mission the possibility of toll synthesis has been indicated as a possibility by the Hungarian firm Gedeon Richter. The possibility is not firmly established since several questions were raised. These have been answered and the subject pursued. Toll synthesis would not be an ideal solution, but might be considered if opportunity exists. The means for paying for toll synthesis would need consideration and might be agreed in terms of phytosterol supply or even in a three way arrangement including further conversion of part of AD to ADD paid for in terms of AD. Because of costs of transportation of raw materials and intermediates produced the arrangements might not prove to be very economic.

6.3 SYNTHESIS OF BULK ACTIVE PHARMACEUTICALS.

This interim report will confine itself firstly to a preliminary analysis of the capacity of the existing pilot steroid production plant with respect to the proposed production programme, and secondly a very brief consideration of plant and laboraty process developments.

6.3.1 Plant capacity: hour analysis.

Considering the use of AD and ADD as starting matyerials instead of dehydroepiandrosterone acetate effectively increases the plant capacity for final products. This is even more marked when compared with the use of diosgenin.

This is due to two reasons, (a) some synthetic routes are shorter -eg testosterone may be preparted from AD in two steps compared with 5 from DHA or 9/10 from diosgenin and (b) some rather simpler or shorter reaction conditions may be employed. Thus although the route to spironolactone is only likely to be reduced by one step the plant occupancy is likely to be significantly reduced and also the expensive stage of hydrogenation avoided.

It is difficult to define capacity simply in terms of kilogram product per annum since this is particularly dependent on mix of products. Analysis indicates, with the production mix proposed, the plant could be capable of some 400 Kgs per annum finished bulk steroids. It should also be capable of producing about 700 Kgs. diene from hecogenin.

Driers are not rated on a litre-hour basis since products cannot be mixed for drying. They are determined on an hours occupancy basis.

The concept of "litre-hours" and it usefulness will be elaborated in the next section, but a rough analysis based on straight vessel usage was also performed and reported in the third interim report is also presented here. The results of this analysis are given in summarized form below.

Plant filling summary (hour basis).

Available annual capacity = 6000 hours per annum.
Occupancy includes allowances for cleaning, change over product working on campaign basis.

Year	GR100	VG100	VS101	VS102	VG101	VS103	VG103	Vac.Tray	drydry
1993	2286	486	45	10	77	-	7	1461	93
1994	3178	866	198	162	220	-	11	1839	375
1995	4868	1151	316	399	516	-	22	3014	807
1996	7539	1637	517	780	790	60	27	4204	1330
1997	10310	2422	896	1580	1224	120	36	5828	2197
1998	10455	2536	899	1975	1413	150	43	5960	2588
1999	11666	2904	980	2300	1670	180	51	6108	2954
2000	13256	3135	1066	2311	1988	210	63	7895	3560
2001	14694	3339	1178	2701	2149	210	69	9102	3619
2002	15422	3506	1180	2701	2155	210	69	9622	3619

It can clearly be seen that there are two critical areas where consideration has to be given during the programme to further installetrion requirements. These are the provision of more capacity to relieve processes carried out in GR 100 and the other is in the area of vacuum drying.

An analysis follows indicating the breakdown of the occupancy of the critical unit GR 100 by the various products. This gives a good guide as to the most appropriate steps to be taken to increase capacity.

Analysis of product occupancy of critical plant GR 100.

Major users only are analysed.
Vessel GR 100 = 100 litre glass unit.

YEAR	EE	%	MES	%	EB	%	NE	%
1993	990	43.3	686	30.0	550	24.0	-	-
1994	1155	36.3	686	14.1	743	23.3	367	8.7
1995	1317	27.0	801	10.6	1018	20.9	1468	30.0
1996	2199	29.2	972	12.9	1100	14.6	2936	38.4
1997	3299	32.0	83	10.5	1100	10.7	4404	42.7
1998	3299	31.6	1196	11.4	1100	10.5	4404	42.0
1999	3849	33.4	1768	15.8	1100	9.4	4404	37.8
2000	3849	29.0	2339	17.6	1100	8.3	5872	44.2
2001	3849	26.2	2975	20.2	1375	9.3	5872	40.0
2002	4400	28.5	3147	20.4	1375	8.9	5872	38.1

EE = ethinyl estradiol
MES = mestranol
EB = estradiol benzoate
NE = norethisterone

6.3.2 Plant Capacity: litre-hour analysis.

This section will deal with a useful method known as "litre-hour analysis" which can be applied for analysing plant or production capacity, also as a means for evaluating realistic allocations of both equipment and building depreciation figures in order to determine meaningful forecast production costs when a variety of products are produced and especially when employing many stages.

Although determination of production costs will be dealt with later the determination of litre-hour depreciation absorptions will be performed in this section.

The "litre-hour" concept.

This concept is not an exact science, but can be useful not only as a tool to provide a method of allocation of certain overheads, but also for evaluation of plant capacity and for planning of plant expansions.

As the name implies, the calculation involves determination of volumes and times. The total litre-hour capacity of a unit is determined by multiplying the rated capacity of a vessel (eg VS 101 =250 litres) by the number of hours it is available for work (for 2-shift working this is taken at 16 hours per day, 5 days per week and 48 weeks per year totalling 3,840 hours per annum). For projection purposes a factor of 70% has been applied to allow for a maximum working capacity with respect to stated capacity. (For in-depth studies the actual maximum working capacity of each vessel may be used). Additionally to allow for change-over times in a multi-process, multi-product plant a further factor of 75% is applied.
Thus litre-hour capacity of unit =

0.525 x stated volume (litres) x available working hours.

Rating of Cuban steroid plant.

The Cuban plant may be divided essentially into seven units described as GR 100, VG 100, VG 101, VG 102, VS 101, VS 102 and
VS 103. The calculated litre-hour capacities to be used in calculations are tabulated below.

Litre-hour capacities of units (2 shift working).

	litre-hour capacity
GR 100	201,600
VG 100	201,600
VG 101	685,440
VG 102	4,536,000
VS 101	504,000
VS 102	1,512,000
VS 103	2,419,200
Total capacity	10,059,840

These figures may be employed in determining the proportions of depreciation of equipment or buildings which it is considered should be appropriate for the employment of each unit in production in terms of litre-hours.

Equipment depreciation allocations.

Allocations to the various units are based on installed unit costs. Where only basic unit costs are available, as in this case, generally used appropriate installation cost factors have been applied. In the case of unit VS 103 the cost of a hot oil generator, used solely for this equipment, is included.

Unit	Basic equipment cost (USD) '000	Estimated installed cost (USD) '000	% installed cost v total
GR 100	14.8	34.2	12.3
VG 100	14.6	33.6	12.1
VG 101	27.9	64.2	23.1
VG 102	19.6	35.2	12.6
VS 101	10.8	24.8	8.9
VS 102	14.9	34.3	12.3
VS 103	18.4	52.2	18.7

TOTAL		278.5	

From the total reported installed cost of the whole steroid plant, which includes, filters, driers, bins, mill, tools etc., the above % figures are used to determine the level of equipment depreciation which should be allocated to each principal unit. This assumes that the units each proportionately use all other items with respect to capacity. Division then of this calculated figure by each appropriate litre-hour rating produces various litre-hour absorption rates for the different units. These figures lend some accuracy towards determining realistic production costs of individual processes and products.

Litre-hour absorption rates for plant depreciation of Cuban steroid plant.

Total cost of all equipments installed = USD 578,461
Total annual depreciation applied = USD 57,846

Plant depreciated in this exercise straight line over 10 years and assuming no residual value.

Unit	Allocated value depreciation ('000 USD)	Litre-hour rating ('000)	Absorption per litre-hour (cents)
GR 100	7.115	201.6	3.53
VG 100	6.999	201.6	3.47
VG 101	13.362	685.4	1.95
VG 102	7,289	4,536.0	0.16
VS 101	5,148	504.0	1.02
VS 102	7,115	1,512.0	0.47
VS 103	10.820	2,419.2	0.45

	57.850		

The above absorption rates are used to determine the realistic figures to be used in any production costing when litre-hour consumptions for the processes have been determined.

Building cost depreciation allocations.

Figures for litre-hour absorptions of building depreciation may also be determined and applied to product costing.

In this case it is considered most appropriate to make allocations in proportion to the relative areas occupied by the major units and then proportion the total building depreciation figure. Finally, based on the litre-hour capacity of each unit, unit values per litre-hour can be assigned for use when determining process and product costs.

Litre-hour rates for building depreciation.

Areas covered by the defined units were determined and the proportions relative to the total covered area (ie including storage, drying, laboratory, packaging etc.) calculated. A uniform cost/m^2 has been assumed. The total building cost used includes any cost of external area such as bunding, effluent tank and similar civil works.

Total covered plant area = 582.5m^2
Total building cost = USD 330,000

Annual depreciation = USD 22,000

Buildings depreciated staight line over 15 years, no residual value.

Unit	Area occupied m^2	% total area
GR 100	8.1	13.2
VG 100	7.2	11.8
VG 101	9.9	16.2
VG 102	5.4	8.8
VS 101	9.0	14.7
VS 102	10.8	17.7
VS 103	10.8	17.7
	61.2	

The depreciations allocated to each unit are calculated using the above % and then a litre-hour absorption determined.

Unit	Allocated value depreciation ('000 USD)	Litre-hour rating ('000)	Absorption per litre-hour (cents)
GR 100	2.9	201.6	1.44
VG 100	2.6	201.6	1.27
VG 101	3.6	685.4	0.53
VG 102	1.9	4,536.0	0.04
VS 101	3.2	504.0	0.63
VS 102	3.9	1,512.0	0.26
VS 103	3.9	2,419.2	0.16

Again these figures may be used to determine realistic values to be used in any production cost determination when litre-hour consumptions for the processes have been calculated.

Calculation of litre-hours usages in processes.

As the description implies the method of calculation involves determination of reaction volumes and multiplying by the number of hours contained in the reactor or until it may be re-used. When process methods have been established this is not difficult.

Certain points should be noted
- when, during a reaction different volumes are used within the same reactor the largest volume is used for calculation purposes.
- allowance should be made for cleaning time.
- if a batch is left overnight in a reactor, even without attention when 2 shift working applies, this time is included.

This latter condition does mean that that it is not correct to assume that production levels can necessarily be increased by 50% if a third shift is worked. In event of three shift working a separate detailed analysis should be performed.

Plant capacity.

Litre-hour analysis is also a useful tool for determining the capacity of a plant for either a dedicated production or, as is more usual, when various mixes of products are involved.

Litre-hour consumptions have been determined for the products indicated in this report. The figures for products essentially established in production, viz. ethinyl estradiol, mestranol, estradiol benzoate, testosterone propionate and testosterone enanthate, should be reasonably accurate.

In the case of products for which syntheses have not yet been completed or scaled-up estimations of the consumptions which might be expected have been calculated on facts currently available and experience. While needing review as later information appears the figures may be used with caution for both plant utilization exercises and production costing (but see later section on production costs).

The results of the determinations are recorded in the following table.

LITRE-HOURS PER KILOGRAM DETERMINED FOR PROGRAMMED BULK ACTIVE PHARMACEUTICALS AND SOME INTERMEDIATES

Product	LITRE - HOURS / KG						
	GR100	VG100	VG101	VG102	VS101	VS102	VS103
Estrone	2489						
Estrone methyl ether	2378						
Ethinyl Estradiol	2872						
Mestranol	3475	77			150	60	
Estradiol	2489				14	108	
Estradiol Benzoate	2865				261	175	
Testosterone	4	31	46	611	87	73	
Testosterone Propionate	4	31	76	407	164	336	
Testosterone Enanthate	4	104	80	429	94	912	
Nortestosterone	2378	74			15	1081	
Norethisterone	2798	79			78	1379	
Spironolactone	229	8	1792	284	907	528	
Methandienone					960		
Danazol	713	16			42		
Medroxyprogesterone acetate		34			399	31	
Diene		22	381	2654	166	373	543

The above figures of litre-hour usages per kilogram for the production of various products have been applied:

(1) to determine the maximum capacity of any one product which could be produced in the existing plant.

(2) to show the extent of use of present capacity working at the levels of immediate domestic requirements and

(3) to analyse the plant capacity needs to satisfy the levels of the proposed 10 year production programme.

Maximum production levels for individual products.

MAXIMUM PLANT CAPACITY - INDIVIDUAL PRODUCTS.

Product	MAXIMUM LEVEL (KG)	% UTILIZATION OF UNITS						
		GR100	VG100	VG101	VG102	VS101	VS102	VS103
Ethinyl Estradiol	70	**100**	-	-	-	-	-	-
Mestranol	52	**100**	1.9	-	-	1.5	0.2	-
Estradiol Benzoate	70	**100**	-	-	-	3.6	0.8	-
Testosterone Propionate	3080	5.8	47	34	28	**100**	68	-
Testosterone Enanthate	1650	3.3	85	19	16	31	**100**	-
Nortestosterone	85	**100**	3	-	-	0.3	6	-
Norethisterone	72	**100**	3	-	-	1.1	7	-
Spironolactone	380	43	2	**100**	8	22	13	-
Danazol	283	**100**	2	-	-	2	21	-
Methandienone	525	-	-	-	-	**100**	-	-
Medroxyprogesterone acetate	1260	-	21	-	-	**100**	3	-
Diene	2400	-	20	**100**	105 *	59	44	40

note: **100** % = Limiting equipment.

\- = zero occupation.

* Not considered limiting equipment since only watering out and can be used in excess of 70 % of filling.

PLANT CAPACITY NEEDS FOR DOMESTIC LEVEL PRODUCTION

Product		LITRE - HOURS ('000)						
	Production level (kgs)	GR100	VG100	VG101	VG102	VS101	VS102	VS103
Ethinyl Estradiol	18.0	51.7						
Mestranol	2.5	8.7	0.2			0.4	0.2	
Estradiol Benzoate	12.1	34.7				3.2	2.1	
Estradiol Valerate	0.1	0.2				-	-	
Testosterone propionate	10.3	-	0.3	0.8	4.2	1.7	3.5	
Testosterone Enanthate	19.8	-	2.1	1.6	8.5	1.9	18.1	
Spironolactone	140.0	32.6	2.5	502.0	214.0	45.2	92.4	
Methandienone	45.3					41.8		
Danazol	24.5	17.5	0.4			1.0	28.0	
Norethisterone	50.0	140.0	3.9			3.9	68.9	
Medroxyprogesterone acetate	6.0		0.2			2.4	0.2	
Total	**328.6**	**285.0**	**9.6**	**504.4**	**226.7**	**101.5**	**213.4**	
Diene included	690		15.8	262	1831	115	257	375
Total (with diene)	**1018.6**	**285**	**25.4**	**766.4**	**2057**	**216.5**	**470.4**	**375**
Rated capacity		201.6	201.6	685.4	4536	504	1512	2419

(-) = minor use (<100 litre-hour)
(blank) = not used

These figures indicate that the existing plant cannot fully satisfy the full needs for Cuban formulation. Units GR 100 and VG 101 are of too small capacity. It will be noted, however, that in the case of GR 100 much of the capacity is taken up by the production of norethisterone and as will be seen by referring to the 10 year production plan it is not anticipated that the full level of such production is likely to be achieved before 1996/1997 since this process synthesis has to be completed in the laboratory and scaled-up. In fact by this time it is forecast that domestic consumption of norethisterone will have reduced by 60% although the overall production level is being maintained for an export market. Spironolactone is also likely to occupy up to 15% capacity of GR 100, but its main effect is forecast to be related to VG 101 taking up 73% of capacity. Again due to development time necessary this product also is not forecast to meet the Cuban domestic level requirements until 1996/1997.

Immediate levels of the other products can be accommodated in the existing plant, but as also mentioned elsewhere there is an urgent necessity for a small centrifuge for testosterone enanthate and a small crystallization unit advised for GMP reasons.

PLANT FILLING AT FORECAST PRODUCTION LEVELS 1993-2002

Unit		LITRE - HOURS ('000)						
Year		GR100	VG100	VG101	VG102	VS101	VS102	VS103
1993	1	122	2.6	2.3	12.4	8.6	18.3	-
	2	122	17.8	265	1843	123	275	375
1994	1	155	5.1	21.8	29.9	15.6	50.4	-
	2	155	20.3	285	1861	130	308	375
1995	1	228	9.7	97.1	85.5	35.9	138	-
	2	228	24.9	360	1916	150	395	375
1996	1	336	13.7	189	141	55.9	215	-
	2	336	28.9	452	1972	170	472	375
1997	1	457	19	371	246	91.5	323	-
	2	457	34.2	634	2077	206	580	375
1998	1	476	21.2	463	306	110	364	-
	2	476	36.4	726	2137	225	621	375
1999	1	551	25.6	555	364	129	419	-
	2	551	40.8	818	2195	244	676	375
2000	1	620	31.6	559	385	138	484	-
	2	620	46.8	822	2216	253	741	375
2001	1	684	33.7	651	443	160	522	-
	2	684	48.9	914	2274	2723	779	375
2002	1	724	34	651	443	161	524	-
	2	724	49.2	914	2274	276	781	375
UNIT LIMIT		**202**	**202**	**685**	**4536**	**504**	**1512**	**2419**

Analysis of this table shows that even at the levels of productions forecast over the 10 year period real bottle-necks still only occur in the units GR 100 and VG 101. The table indicates that consideration has to be given, at the latest, in 1994 to supplementation of capacity for products principally processed in GR 100 and fully operable in 1995. By modifying unit VG 100 about 9% of capacity of GR 100 could be relieved. Currently all estrogen products,which includes both intermediates and final products, are confined to one unit and use of VG 100 would violate this condition and should not be contemplated.

According to the production programme the production level of estrogens should rise from 56.5 kgs. in 1995 (which can be accommodated in GR 100 using 170,578 litre-hours) to 131 kgs. in year 2000 (requiring 400,811 litre-hours) and finally a proposed level of 160 kgs. in year 2002 (requiring 492,502 litre-hours).

These figures suggest that an appropriate plant of 400 - 450 litres capacity would be best considered, situated in a new segregated area, designated as a hazard area and confined to use with estrogenic materials. Dedicated separation equipment should be provided and a small crystallization unit which are also confined. Material flow to driers and packaging should also be considered during the planning exercise.

A second possible investment in equipment is implied for planning in 1995/1996 and operational late 1997. The capacity of the unit in this instance is VG 101. When capacity increase is indicated production of spironolactone is expected to occupy 52% capacity and processing to diene 38% capacity. The accuracy of this forecast will depend on the ultimate detailed spironolactone technology. The most likely appropriate solution here would be to instal a glass enamel reactor to be dedicated to the bromination of hecogenin. Such equipment would not need to be general purpose and consequently lower investment would be involved.

6.3.3 Costs of production of Bulk Active Pharmaceuticals from Intermediates AD & ADD.

In the case of the estrogens, ethinyl estradiol, mestranol and estradiol benzoate productions have essentially been established and for any price of ADD fairly precise production prices may be determined. The same is true of the androgens, testosterone propionate and testosterone enanthate with respect to AD.

For other products production methods are not established and production costs will be determined on methods still being developed in the laboratory. Some assumptions must be made in determining likely production costs, but do give an indication of the possibility of the success of the developments.

Production cost determination methods.

The methods used for calculation of production costs are essentially similar to those used earlier for phytosterol costing but, in view of the fact that several products are involved here, some further explanations of methods used may be helpful.

DIRECT PRODUCTION COSTS.

These comprise the total of the items:

Raw materials + additives,
Packaging,
Labour, complementary labour & Social security tax,
Utilities, electricity, fuel & water.

INDIRECT COSTS OF PRODUCTION.

These comprise the total of the items:

Equipment depreciation,
Building depreciation,
Quality control,
Sampling, Maintenance,
Administration expenses.

TOTAL PRODUCTION COSTS.

For the purposes of this report the total production cost of the various final Bulk Active Pharmaceuticals to be produced is taken as the summation of the DIRECT COSTS + INDIRECT COSTS.

Any profits derived will be available for funding research & development operations and contribute to subsequent production facility enlargement costs.

INDIVIDUAL COSTS ITEMS.

Raw material costs: these are taken as c.i.f. Cuban port. In case f.o.b. prices only are available a factor of 1.05 has been taken to determine the national c.i.f. price. No account is taken of any Customs duties which might be levied on intermediates or additives since the levels of imposition of such is not clear.

For the basic production costs of the various products the latest paid c.i.f. prices paid for AD and ADD have been applied. For AD this is USD 197/kg and for ADD USD 492.5/kg.

Packaging: has been included as a dirtect cost. Levels for typical packagings appropriate to the different products have been determined and applied accordingly. Costs vary from USD 3.52, through USD 3.00 to USD 1.20 per kg.

Labour man-hours: have been determined or estimated for all process stages involved in the production of the final product. While such wages are paid in Pesos a USD charge at a rate of 25% has been applied, as common Cuban practice, to production cost. The rate is USD 0.275/kg.
Ancilliary labour charges: according to Cuban practice amount to 9.09% of labour charge for complementary salary (holiday pay) plus a further 10% of labour + complementary salary to cover Social Security tax.

Utilities: these cover electricity (covering use for agitators, refrigeration, compressed air, boilers etc.), fuel (for steam generation) and various water needs (re-circulation, process, purified etc.). The consumptions are calculated so far as possible
and rates which have been supplied used to determine individual costs.

Rates used were:

Fuel	USD	140 per metric ton.
Electricity	USD	0.085 cents per KWH.
Water: Process & circulation	USD	10 cents per m^3
Softened (boiler)	USD	14 cents per m^3
De-ionised/distilled	USD	16 cents per m^3

Indirect costs.

Equipment depreciation: the procedure used here is based on the litre-hour concept described in section 6.3.2, being related to costs of processing units employed. The determined litre-hour valuations or absorptions are also reported in section 6.3.2.

A depreciation rate of 10% has been used corresponding to a 10 year straight line depreciation with no residual value.

The litre-hour rates determined for each basic equipment are extended according to the processes involved in the production of the final product.

Building depreciation: the procedure used is again based on the litre-hour concept, again described in section 6.3.2, in this case being related to the area of building occupied by the individual units. The determined litre-hour valuations are also reported in section 6.3.2.

Quality control: this cost has been applied at a constant arbitary level per kilogram for all prtoducts. This expenditure covers both analysts costs and depreciation of analytical equipment employed. The cost to be applied is USD 15.00/kg (of which USD 13.3 represents depreciation). The values applied accord with Cuban experience.

Sampling: this is also applied according to Cuban practice to cover the retention of intermediate and control samples. A fixed figure per kg. of USD 1.00 has been applied.

Maintenance: of equipment is used to cover labour & materials and is applied as a % of equipment depreciation. An element of 4% has been used, which is fairly standard for essentially new equipment.

Administrative expenses: it is understood that in Cuba administration expenses are taken to cover all other functions in the enterprise such as Directors salary & expenses, office salaries, warehousing, security, sales or marketing expenses, office equipment depreciation, car expenses etc. A fixed charge of 15% of DIRECT COST is applied and this custom has been followed.
Research & development charges are not normally included.

6.3.3.4 FORECAST PRODUCTION COSTS COMPARED WITH F.O.B & C.I.F PRICES

PRODUCT	WORKS PRODUCTION FOB (USD/KG)	INTERNATIONAL MARKET FOB (USD)	IMPORTATION CUBA CIF (USD)	PROJECTION PRICES USED (USD)
Established products				
Ethinyl estradiol	1549	1600	3590 *	1549
Mestranol	1750	1800	1984	1750
Estradiol Benzoate	1301	1350	2156	1301
Testost. Propionate	418	430	579	418
Testost. Enanthate	547	555	620	547
Development Products				
Norethisterone	1890	2300	3233 *	2216
Spironolactone	533	500	579	482
Danazol	832	1000	1145	960
Methandienone	2147	1530	3270 *	1469
Medroxyprogesterone acetate	1606	1600	1833	1536

** The prices for Cuban supplies are considerably higher than normal international prices, possible due to shortage at time of enquiry or level purchase.*

6.3.3.5 Capital requirements.

To achieve the production levels and range of products proposed in the 10 year programme, and additionally to move towards achievement of necessary GMP requirements, it will be necessary to consider some capital investments.
The principle anticipated items are listed below:

			Estimated Cost (USD)	
Year Expenditure	Item	Requirement	Hardware	Installed
1993/4	Industrial vacuum cleaner	GMP-cleaning	2,000	2,000
	Vacuum oven 12m³	Final products (non-estrogenic)	70,000	80,000
	Centrifuge 500/600 mm	Necessary for test. enanthate	35,000	40,000
	Building modifications	Packaging + GMP clean room; ventilation	4,000	15,000
TOTAL			111,000	157,000

			Estimated cost (USD)	
Year Expenditure	Item	Requirement	Hardware	Installed
1994/5	250 lt reactor unit	Production increase	35,000	80,000
	Mobile pressure filter	GMP	6,000	6,500
	Crystallisation unit (estrogens)	GMP	50,000	80,000
	Vacuum drying (extension) $1m^2$	Increase capacity	15,000	16,000
	Services extension	Installation	3,000	5,000
	Building for estrogens $48m^2$	GMP safety	-	15,000
	General Building modification (internal) $20m^2$	GMP	4,000	15,000
TOTAL			113,000	217,500

			Estimated cost (USD)	
Year expenditure	Item	Requirement	Hardware	Installed
1996/7	225 lt glass enamel reactor	Production capacity increase	62,000	142,000

6.3.3.6 Calculation of effect of input price of AD or ADD in major established products.

This analysis confines itself to those products essentially establish for production. It is not extented to those products for which firm costings cannot be established. Any price advantage due to local production against cif price of intermediates will reflect positive profit contributions. Viability of production of development products will be determined when processes have been established and scale-up. Efforts should be directed at achieving prices aproximately 20% below international prices. Production for domestic use may be acceptable at higher levels.

The effect of prices of AD or ADD are illustrated in graphical form below. From this production prices can be determine and hence profitability can be extrapolated at various production levels using these prices.

Breakeven prices are also illustrated in following tables.

ADD MAXIMUM PURCHASE PRICES FOR SELLING.

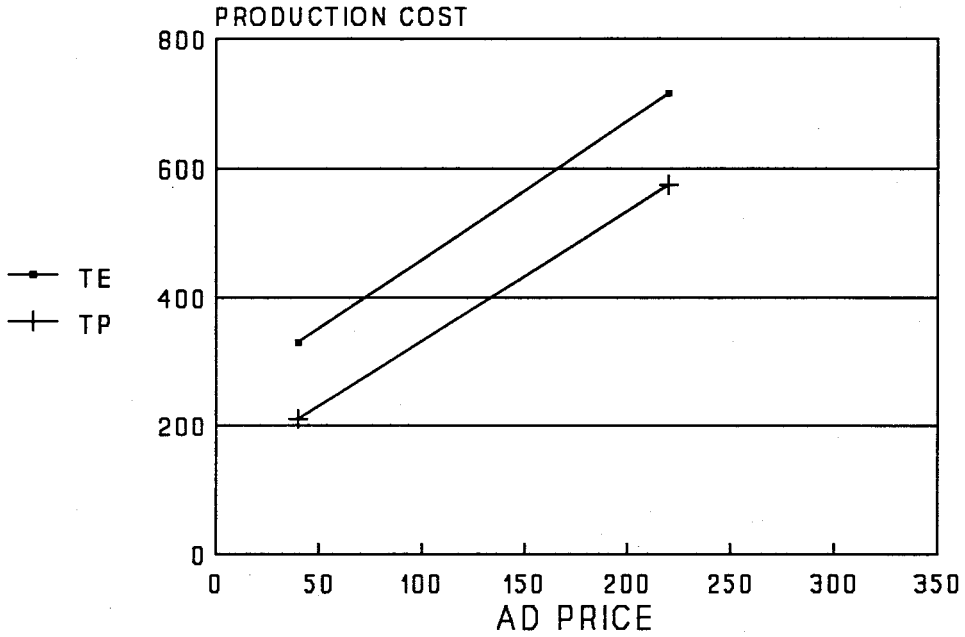
In USD/Kg	Selling Domestic	Selling Export
Ethinyl Estradiol	660	525
Mestranol	610	510
Estradiol benzoate	650	535

AD MAXIMUM PRUCHASE PRICES FOR SELLING.

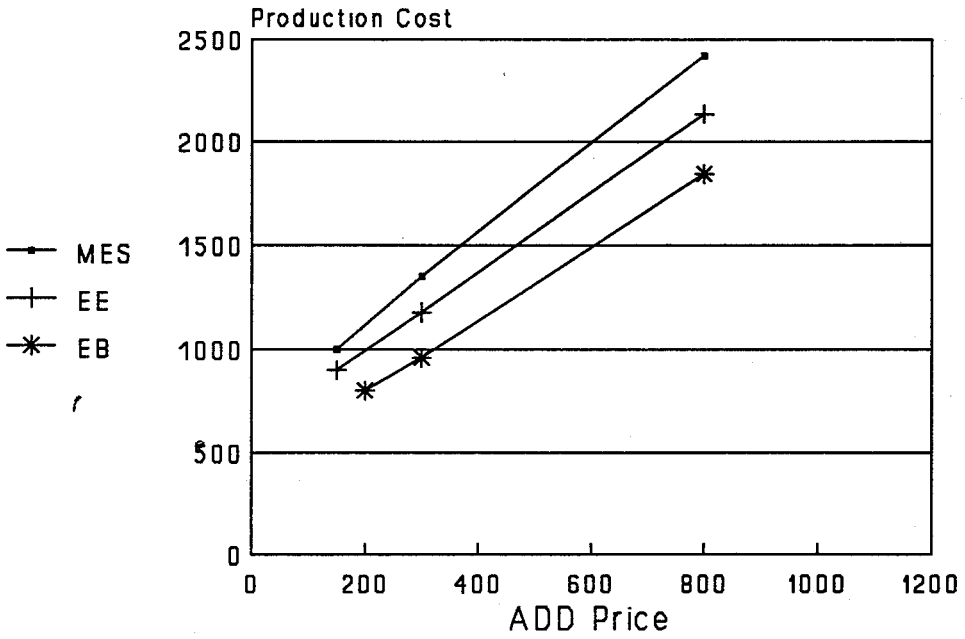
In USD/Kg	Selling Domestic	Selling Export
Testosterone propionate	262	208
Testosterone enanthate	272	210

With respect to production of AD and ADD the aim should be to produce domestically at a maximum price of USD 140/Kg for AD and USD 280/Kg for ADD.

AD PRODUCTS



ADD PRODUCTS



At these input prices the forecast production cost for products of domestic interest can be seen to be:

	USD/Kg
Ethinyl estradiol	1,140
Mestranol	1,295
Estradiol benzoate	1,025
Testosterone propionate	345
Testosterone enanthate	456
Spironolactone	406
Norethisterone	1,744

Benefits for establish products = USD 14,204 initially, rising by about 4% per annum.

Benefits for all scheduled products (produced directly from AD/ADD) = USD 55,164 initially, rising by about 4% per annum.

6.3.4 GMP CONSIDERATIONS IN PRODUCTION OF BULK ACTIVE PHARMACEUTICALS.

Some aspects of GMP with regards to operation of the steroid plant were given in a previous report (DP/CUB/81/019 dated 3.Dec.1991).

The present guidelines now presented cover in some more detail the requirements for the overall production of bulk active pharmaceuticals from receipt of raw materials to the distribution of final product.

While most emphasis is given to the chemical manufacture and materials handling the basic requirements for all other associated functions and personnel are covered.

The guidelines may be used for the evaluation of existing facilities and should especially be bourne in mind when any extension of facilities or any re-arrangement of facilities are contemplated.

1) OVERALL APPLICATION OF GMP PRINCIPLES.

Full GMP principles should be applied in the production of a bulk active pharmaceutical from the point at which it is recognized that the key factors governing the final quality of the pure bulk active pharmaceutical arise.

This is certainly true of the purification stage, but may also apply to the final stages of synthesis. As one moves back down the synthetic chain it is considered permissible to apply GMP principles in a progressively less rigorous, but still controlled manner. No relaxation on documentation is permissible.

2) PERSONNEL AND TRAINING

The ultimate quality of bulk active pharmaceuticals will reflect the capability and attitude of all staff involved in the manufacture and control.

Aspects to be considered under this heading are:

- a defined organization should exist which defines the role of responsible persons.
- Quality Assurance and Production must function independantly, with the authority necessary to ensure that product quality is not compromised.
- key personnel should be competent by virtue of qualification and experience to exercise the independent professional judgements required of them. As far as possible deputies should be nominated.
- adequate staffing levels in both Quality Assurance and Production should be provided to allow all defined procedures to be operated fully.
- all personnel concerned with both bulk active production and control should have written job descriptions and should be appropriately trained. Such training should be covered by written, approved programmes which include GMP principles as well as "on the job" and technical aspects.
- training should be recorded by the trainer and acknowledged by the trainee and on-going effectiveness monitored.
- other non-production staff whose duties take them into production areas should be given appropriate training, which should include relevant GMP aspects. (All other non-authorized personnel should be banned from production areas unless under supervision of a responsible person).
- high standards of personal hygeine and cleanliness must be demanded of all associated with the production process. Personnel must avoid contact with bulk active pharmaceuticals, intermediates and chemicals. Potentially compromising health conditions should be reported and dealt with appropriately. Absence or protection of lesions is also important.
- special attention should given to the cleanliness of facilities provided for showering and toilet.
- suitable clothing should be provided and worn by all involved with the manufacture and control of bulk active pharmaceuticals. Clothing should be changed frequently. (Especial precautions to be taken with estrogens).
- at the final stages of bulk active pharmacetical production the preferred standard of dress should be comparable with that required in formulation operations and will emphasis the need for high standards.

3) PREMISES AND FACILITIES.

- should be of adequate size and located, designed, constructed or adapted to suit the operations to be carried out in them.
- adequate services should be available and suitable areas for manufacture, testing and storage of bulk action pharmaceuticals be provided.
- all liquid and gaseous services, such as steam, water and air throughout the production and laboratory areas should comply with appropriate standards such as not to contaminate any bulk active pharmaceutical.
- back-up service should be available for critical processes in event of mains electricity failure.
- construction and finishes of buildings should be suitable for the operations to be carried out in them.
- walls and ceilings should be washable and, ideally, hoseable.
- floors should be impact resistant and adequately drained. Sloping should be incorporated to avoid flooding and drains preferably trapped.
- when pure bulk active pharmaceutical is exposed to the enviroment walls and ceilings should be covered with an impervious layer and be as ledge free and smooth as the plant and services allow.
- ventilation and extraction systems should be designed to afford maximum protection to the operators and also to minimise contamination of products and outside environment.
- exhaust and waste streams, such as vacuum exhaust, vents, extracted air, as well as liquid and solids streams, should not pollute the outside environment. This implies they should not exceed consent limits.
- waste products containers used should be readily recognizable and not resemble any product containers.
- premises in which bulk active pharmaceuticals are manufactured or stored should be capable of being made secure and only authorised personnel allowed to enter.
- any substances which may be possibly misused (whether legislation exists or not) should be stored in a suitable secure area and a register kept of movements into and out of the store.
- storage areas should be organized to ensure clear differentiation of raw materials, intermediates, bulk active pharmaceuticals, packaging and the other stocks. A system indicating the status of any material should exist.
- separate areas must be provided for potentially hazardous materials.
- suitable facilities should be provided for bulk deliveries to tanks including bunding and protection against static.
- buildings and all surrounding areas should be clean, orderly and free from accumulated waste, dirt and/debris.
- eating, drinking and smoking should be restricted to specific areas or rest rooms separate from manufacturing, laboratory or storage areas.
- for cleaning of areas only wet or vacuum methods should be employed. Compressed air methods should be avoided if possible.

4) PLANT AND EQUIPMENT.

General: plant and equipment should be designed, constructed and maintained to suit the processes and products for which it is designed:

- siting should be such as to avoid congestion.
- materials used in construction should not adversely affect the products being processed.
- equipment should be adequately labelled or numbered so identity is perfectly clear to operators.

Control of product contamination: typically the manufacture of a solid or liquid bulk active involves a purification stage of manufacture. This stage and drying of product, are the most important ones and control of contamination is critical. This will be considered first.

Final manufacturing stage: if more than one bulk active product is being produced in the manufacturing area the plant should be sited and arranged such that mixing of processes from different plants is impossible.

- all pipelines should be run to avoid contamination from the plants or processes previously performed in the plant.
- any mix-up of containers prior to loading raw materials must be prevented by correct storage and labelling. Containers should not be opened until the time of charging.
- a system of weighing or volume recording must be used to check the correct quantities of material are charged.
- re-use of re-cycled process liquors, recovered solvents, etc may be common practice but they should not effect the pharmacopoeial quality.
- all liquids and gaseous material which contact final bulk active product should be suitably fittered.

Final product drying it is of paramount importance that final product is protected from contamination by extraneous matter and other bulk active products. Operation should therefore be performed in a closed system or in areas where contamination can not occur.

The following should be observed:

- all gaseous materials which contact final bulk active during drying should be suitably filtered. This particularly applies to gases (especially air) used during blanketing and/or venting of driers and circulation.

Subsequent operations: these include milling, sifting and dispensing of the bulk active pharmaceuticals and similar preventive operations apply as for drying. Extraction should be employed whenever possible (with filtration containement of effluent stream).

Additionally:

- When containers are re-opened for sampling an area should be provided in which cross-contamination with other bulk active pharmaceuticals or extraneous matter is prevented.

Cleanliness of equipment: equipment should be suitable for being cleaned and the following especially observed:

- procedure should be specified and documented for cleaning all items of equipment.
- cleaning of plants items should be recorded.
- cleaning must be designed to include the washing of pipeline, heat exchangers and other relevant service equipment in possible contact with product as well as the main items of equipment.
- cleaning of plant items should be recorded.
- cleaning must be designed to include washing service equipment in possible contact with product as well as the main items of equipment.
- the status (cleanliness or otherwise) of any piece of equipment should be readily identifiable.
- washing of bulk active pharmaceutical (and intermediate product) plant is typically performed using a solvent in which the bulk active is known to dissolve. Testing of the wash liquors is the means of checking cleanliness.
- if plant is complex the stripping of some section of the plant followed by visual inspection or chemical testing may be the only means of ensuring cleanliness.
- cleanliness checks should be made on equipment before it is needed for processing. This should be done by a responsible person and appropriate documentation signed. Cleanliness checks should include visual inspection and/or testing for previous bulk active material and/or testing for extranenous matter.
- rooms in which a bulk active pharmaceutical is likely to contaminate its enviroment (dusts) should be adequately cleaned between the manufacture of different products. A defined cleaning procedure should be used and cleaning recorded.
- all cleaning procedures should be validated.

Weighing and measuring:

- equipments should be well maintained, cleaned and checked for accuracy regularly.
- measurement limits should be clearly indicated.
- all operations should be documented.

Continuous manufacture: this is rarely encountered in the manufacture of steroids but is included for completeness.
Requirements are similar to batch processing but additional considerations are:

- it is necessary that the plant be designed to ensure the bulk active pharmaceutical produced is homogeneous and of consistant quality.
- a suitable portion of the continuous manufacture should be identified as a discreet lot or batch, usually on a time basis. Labelling must match batch.
- the method and frequency of sampling should be clearly defined and samples taken representative of the bulk of the lot.

- consideration should be given to the defined procedure for cleaning of the plant to prevent the build-up of decomposed product or growth of micro-organisms.

Intermediate manufacturing.

The foregoing remarks have been specifically related to the manufacture of the final bulk active pharmaceutical. However, similar considerations should be applied to intermediates manufacture since cross contamination can be very costly if additional purification or separation methods need to be developed and applied or ultimate contamination of final bulk active pharmaceutical be realised.

While all previous comments are essentialy applicable some can be relaxed in severity in some cases. In others additional precautions may need to be considered.

Some relaxation is acceptable in the following cases:

- when a production campaign is being run, or plant dedicated to one reaction process the cleaning of the vessel between each batch may be relaxed providing only the same input product and reagents are being employed.
- for intermediate processing it is not normally necessary to employ filtered solvents for reaction or washing nor employment of filtered gases for blanketting (other than process requirements demand for purification) or transfer purposes.

Some general techniques to be applied in cleaning, from which those appropriate to the previous process conditions should be selected are illustrated:

- for removal of any intermediate or final product solid an appropriate solvent is selected in which such material is readily soluble.
- it is not sufficient to only stir with solvent to clean but, whenever possible, the solvent must be refluxed to ensure the reactor lid is clean.
- solvent must also be allowed to enter any condenser.

In the case of vertical condensers the flow of coolant should also be adjusted to ensure condensation also occurs at the top extremity.

- in the case of horizontal condensers a good rate of reflux should be maintained. This is normally sufficient but if there is any doubt that product has entered the condenser (due to boil over or frothing) consideration must also be given to physically washing the internal condenser services with solvent.
- after cleaning horizontal condensers by refluxing valves should be re-set to allow for destillation to ensure cleaning is complete in all lines.
- any U-bends or sample points should be thoroughly drained and ensured to be finally washed with clean solvents.
- particular attention should be paid to the cleaning of bottom discharge valves. If in doubt the valves may be dismantled and stripped.
- for cleaning pipelines it is preferable to circulate solvents whenever possible and not use a one-pass cleaning. It any doubt exist pipelines should be dismantled so that visual inspection is also possible.

- while condensers and their associated pipe lines may be thoroughly cleaned with the initial wash solvent (since pure solvent vapour is being employed) all vessels and other pipelines require at least two applications of fresh wash solvent. Thorough draining between each application should be applied.
- in some instances removal of stubborn solids may be found necessary and performed using mechanical assistance. Choice of cleaning brush or stick is important to prevent physical damage to the vessel surface, especially in the case of glass enamel equipment.
- even after cleaning by reflux it is good policy to also clean the internal lids of enclosed reactors using solvent in a high pressure spray since condensation of solvents over the entire surface cannot be ensured. Particular attention should also by given to various outlets eg thermometer pockets, pressure gauges etc where solid might collect in crevices.
- while cleaning precautions are mostly being directed at internal cleanliness of equipment, it should also be maintained externall in a constantly clean condition. The most significant danger here is for extraneous matter to enter the reactor through the charging hole. Attention must be given to no only the vicinity of the manhole (including sight glass), but also to any pipelines etc passing over such opening.

In multi-level plants design should be such that no extraneous materials from a higher level can enter a lower reactor.

- in some cases, more particularly of intermediate processing, it is should remembered that it may be necessary to use more than one solvent since all products present may not be soluble. Most frequently the second solvent may be water (eg to remove inorganic reagents). A suitable washing technique here is to completely fill the equipment (reactors) with water, drain and repeat rather than the technique of refluxing used with volatile solvents (to minimize energy costs as well as ensuring complete solubility).
- after cleaning equipment should normally be thoroughly dried. For this purpose acetone is frequently used for a final wash and reflux, solvent drained and the equipment throughly dried by application of steam heating and application of vacuum.
- when cleaning and drying are complete it should be ensured that the vessel is closed to the atmosphere.
- the cleaning of ancilliary equipment such as filters, bins, mills, driers etc is normally done manually with appropriate solvents or vacuum. Pressure jets should be avoided where dry solids occur.
- for pumps circulation of cold solvents is normally sufficient.
- for efficient working and general GMP all floor areas, drains, etc should be kept in a clean or orderly condition.
- special attention should also be given to the cleanliness of shower and, especially, toilet areas to prevent contamination by workers with microorganisms.

5) DOCUMENTATION AND SYSTEMS.

Production operation should be controlled and will be made more efficient by use of well-defined systems.

Supporting documentation and records help to ensure compliance with systems by recording all critical stages and paramenters of the process and their satisfactory execution. A reliable audit trail and also trouble shooting trail will also be stablished.

While production manufacture is of prime concern within this report the overall GMP requirements should be mentioned.

Aspects which need to be covered are:

- General Principles
- Specifications
- Quality Control Documentation and systems
- Manufacturing
- Filling, packaging and distribution
- Validation

General principles of documentation.

- in all cases documents should be clear, concise and permit recording of all critical elements of the related process.
- documents should be authorized, dated and systematically reviewed, an audit trail of revision maintained and all superceded copies recovered from use.
- all entries made should be indelible, in pen, signed or initialled.
- corrections are permitted but should not obscure any original entry and should be authenticated. Use of liquid paper must not be permitted.

Documentation.

To fully comply with GMP requirements documentation is necessary at a variety of functional operations. It is necessary for documents to be retained for reference. No specific retention times are laid down but guidelines are indicated below. These are minimum recommended retention time and are currently considered to satisfy the general requirement under liability implications and current legislation.

The guidelines for document retention are (a) Period of storage life plus 2 years for bulk active pharmaceutical having an assigned storage life or (b) 5 years from the last date of supply of any part of the particular lot or batch concerned when no assigned storage life exists.

These period are also considered appropiate for key production records such as:

1.- Completed batch records.
2.- Batch analytical and clearance records.
3.- Cleaning records for appropiate units, vessels, and containers (when used for final purification).
4.- Unit inspection and clearance record.
5.- Maintenance and clearance record of key instruments and measuring devices.
6.- In-process temperature and pressure records.
7.- Water, bulk solvent and environment test results.
8.- Packing and distribution records.

6) MATERIALS MANAGEMENT

GMP covers aspects of purchasing, warehousing and transportation of materials relating to the manufacture and packaging of bulk active pharmaceuticals.

Purchasing of materials to be used in manufacture and packaging should be made from approved suppliers in accordance with specifications agreed amongst departments covering Materials Management,
Production, Technical and Quality Assurance (Control). Use of an auditing programme as part of a supplier Approval Process can be beneficial.

Warehousing should give special attention to provision of facilities for:

- segregation of warehouse from manufacturing operations but intervening walls can be accepted.
- high value products, controlled and bonded goods need special protection.
- thorough cleaning and checking of incoming raw material.
- segregation area for sampling of materials such that contamination is avoided.
- receiving, proper storage and despatch of raw materials, intermediates, packing and component materials and products. Reception and despatch facilities should be separate.
- segregation of materials employing orderly separation, partitions or walls. Special care must be taken with regards to compatibility of raw materials.
- quarantine areas, so far as possible, for rejected materials, returned materials awaiting analysis, passed intermediate and final bulk pharmaceutical. Supplementary identification should be applied according to approved colour coded labelling system.
- controlled store for labels.
- storage of temperature sensitive materials in deep freeze or air conditioned rooms. These facilities should be equipped with recorders and/or failure warning devices. Regular checks should be performed on control equipment and records retained.
- provision of central weighing or bulk breaking facility may be considered. Such should be segregated from main storage areas and provided with dust control and adequate cleaning facilities to avoid cross contamination.
- discouragement of vermin, insects, birds and others pests. To facilitate inspection and necessary cleaning all racking should be positioned to allow adequate space between stock, fences and walls. A regular pest control programme should be operated.

Receipt and storage of Raw Materials should be strictly controlled:

- deliveries should be checked against details of order and delivery note before acceptance and also for damage or evidence of contamination.
- each suppliers batch of material received should have, or be given, an identification number which permits the tracing of the following in records: quantity received, date receipt, supplier and any Certificate of Analysis provided, results of test carried out according to specification and approval or rejection. The identification number should subsequently be recorded on production records of batches when used.

Receipt and storage of intermediates and bulk active pharmaceuticals.

Tranfer documents should be provided and materials not accepted into a warehouse until such are checked. All containers must be appropriately, and clearly, labelled.

Issue of goods for processing.

- no materials should be released for processing until all appropriate tests are completed. Where status labels are in use, as is recommended, "Passed" or "Released" labels should be applied and clearly visible before goods are issued.
- if, in special circumstances, it is necessary to issue raw material or intermediate before it has been fully tested a special procedure must be implemented to ensure that no batch of bulk active pharmaceutical made using that material is released until all testing in satisfactorily completed.
- all stocks should be used in rotation.
- after consideration of possible contamination any damaged bags or containers should be repaired, re-sealed or contents transferred to an alternative container. In such case a description label with contents description, identity number and weight must be applied.
- materials which fail to meet specification should be rejected by Quality Assurance, labelled and appropiate responsible persons informed.
- it may be decided not to reject a material which fails specifications, but to allow it use under strict control or for restricted purposes. Additional in-process control or testing of the output may be required.

Warehouse Control of Bulk Active Pharmaceuticals

- storage conditions should be stated on the label and complied with
- control systems should exist which only allow released materials to be distributed.
- selection, assembly and checking of orders should follow authorised written procedures.
- distribution records must be of such a standard that any product recall may be rapidly executed.

Transportation of Bulk Active Pharmaceuticals

Precautions to be taken are:

- to execute identification of products.
- that product cannot contaminate, nor be contaminated by, other products or materials.
- to take adequate precautions against adultaration, spillage, breakage or pilferage.
- to ensure material is maintained under appropiate environmental controls consistent with labelling and is protected against attack by micro-organisms or pests.
- existance of written procedures for checking vehicles covering, cleanliness, dryness, absence of contamination, strong odour, insects, pests and that packages are protected from weather or other external factors during transport.

7) RAW MATERIALS.

Specifications:

These should be based on quality required in terms of freedom from impurities and ability to give the required results in production processes. Physical properties sometimes must be taken into account as well as chemical.

Control

An Approval process for introduction of any new source of raw material should be in operation. A new source should only be accepted after mutual agreement between Purchasing, Quality Assurance (Control) and Production / Technical R & D departaments. Considerations to be taken into account are: (1) suppliers ability to routinely supply appropiate quality, (2) analysis of tender samples against agreed specification (3) need for assessment on pilot scale in reaction and (4) a supplier audit.

Analytical testing of routinely supplied materials may be reduced in consideration of various factors. These may be (1) on basis of safety (2) confidence in supplier including availability & Certificate of Analysis from an approved supplier and (3) if user tests are performed an each delivery.
Otherwise all batches should be subjected to at least an identity check and at least one batch per year fully analysed.

Raw Material Sampling.

Written procedures should define the number of samples to be taken from each type and quality of material, size of delivery and where sampling takes place.

Sampling equipment and containers must be clean and compatible with the material being sampled.

Containers from which samples are taken must be carefully opened and re-sealed inmediately. A label to indicate sampling has place should be affixed.

Retention samples must normally be preserved, but acceptable exclusions may be of gases, solvents, filter aids, fermentation media components, unstable compounds or other materials presenting a safety hazard.

In case of bulk deliveries of solvents in tankers it is most important that critical tests for identity and purity are performed from solvents taken from the delivery tanker before discharge is allowed.

In some cases tanker drivers may be able to present Certificates of cleaning for non-dedicated tankers but samples should still taken and checked before discharge.

Storage tanks should also be sampled and checked periodically since invariably they will contain mixed deliveries.

Retest periods

When sampled raw materials should be allocated a retest date, after which they should not be issued for use without additional testing. The period will depend on stability of material and it's importance in the process.

If bulk containers which may sensitive to light or moisture are opened to supply part consignments it may be necessary to re-test for quality/assay just prior to further issue (eg sodium borohydride, N-bromoacetamide or succimide).

In some cases retesting may only involve visual re-examination.

8) CONTAINRES, FILLING AND LABELLING.

Quality and cleanliness of containers, areas and procedures for filling and subsequent labelling of containers are of considerable importance specially for the bulk active pharmaceuticals.

Containers

The container(s) should safeguard the bulk active pharmaceutical from contamination by the environment and the converse during storage and transportation and be capable of doing so during the assigned shelf life of the product.

Containers (including liners) need to be controlled as for raw materials, testing programmers having previously demonstrated compatibility with product and shelf life in contact with packaging. Any change in packing components specifications should be assessed and validated.

Packages should be designed for easy handling and when possible security seals/ties of distinctive marking employed.

Any specific user specifications must be taken into account.

Filling and Packing

Full GMP criteria should be adhered to during filling operations. The area should be clean and segregated and clear of all materials not required. The area should be will lit and have appropiate surface finishes and not contain dust traps. Adequate ventilation, dust extraction or air handling facilities should protect operator, product and environs.

A record of regular cleaning and maintenance must be completed and available.

Formal documentation of packing operations of bulk active pharmaceuticals, to ensure correct components are used should exist. Such may be used to facilitate batch traceability.

Washing equipment must be well maintained and checked regularly with appropiate records kept. Simultaneous packing/filling opetations must not take place in any area to avoid mis-labelling or cross contamination.

Labels and labelling

All materials must be clearly labelled at all times to ensure identity and batch traceability. Where containers may be re-used old labels must be removed or at least completely defaced.

Raw materials should be labelled on receipt with an identifying reference number and approved title. Suppliers marking may be used but reference numbers must be employed for traceability.

Intermediates should be labelled with date, title and an identifying reference number.

In a multiproduct plant documentation should confirm the clearance of any of all materials associated with previous labelling operations.

Labels should be clear and unambiguous. Final product labels should be clearly printed and checked against approved copies released. final product labels will list the official product title, any specific company code, batch number, date, full hazard warning, quantity in container, limitations on storage conditions and expiry date as appropiate.

Issue of labels should be strictly controlled and covered by reconciliation system which will include for disposal of excesses or obsolete labels. Secure label storage is essential.

9) ENGINEERING

The engineering manager has a responsability for GMP wherever activities impinge on production and packaging activities and such should be included in the written terms of reference.

Primary concerns are:

- to ensure buildings, plant and service meet GMP requirements.
- to ensure satifactory calibration of measuring, recording and control equipment.
- to provide for avoidance of product contamination from plant, equipment and buildings.
- To develop written engineering standards and records to meet GMP requirements.
- To maintain programmes and records.

10) QUALITY ASSURANCE AND QUALITY CONTROL

While Quality Control is more familiar to production the concept of Quality Assurance becomes more frequently employed. These descriptions are not the same although they may be operated within one department.

Quality Assurance (QA)

Covers all activities and functions of an organization concerned with the attainment of quality. It is not the same as Quality Control, but duties are wider covering such aspects as setting up a QA policy and standards for a whole organitation and ensuring such are maintained.

Where a Quality Assurance department exists it does not reduce other departamental responsabilities.

An important duty of QA can be to co-ordinate programmes of self audits which should exist in various departments. Management should be committed in such activity to implement any relevant findings and QA co-ordination can be helpful in ensuring such dedication.

Quality Control (QC) is that part of the approval process concerned with the setting of specifications, sampling, testing and analytical clearance of raw materials, intermediate and bulk active pharmaceuticals (also for formulated products when applicable). It is also concerned with long term stability of pure bulk pharmaceuticals.

6.3.4.1 GMP position of Production Unit Mario Muñoz

Since the design and installation of the pilot steroid production unit at Mario Muñoz and many requirements for meeting GMP requirements have intensified in stringency, though not in principle.

No formal audit of the plant has been carried out, but some general evaluation has been made and the following found:

- it is considered that bulk active products can be produced for domestic use in the production area while meeting general GMP conditions, at least in the short-term and at the lower production levels. Nevertheless, special precautions must be taken and would be difficult as production levels increase.

- with increase in production segregation, problems will develop and it will be difficult to realize acceptance of scrutiny by customers (export or domestic).

- good training, operational systems, documentation and a truly informed appreciation and responsibility are all necessary aspects of GMP required to attain satisfactory production of bulk active pharmaceuticals. Some significant improvements in this area can be made.

- the importance of documentation cannot be over-emphasized. The basis of this has been established in the pilot steroid production unit, but should be constantly reviewed and improved as necessary.

Conditions to be considered:

1. Segregation of estrogen products, both for intermediates and further for final products, not only for synthesis stages but also extended to drying and packaging should be the first consideration.

   The original design incorporates an area especially for packaging of estrogens, including adjacent showering facilities. This area has been used in the meantime for other purposes and at the first instance needs to be thoroughly cleaned out.

   Attention must be given in the short term to the condition of ventilation since the situation of this has changed due to some building extension to house further drying and sifting rooms. In the longer term consideration must be given to transforming this, or an alternative area to a fully defined white area working under negative pressure.

   The subject needs to be analyzed in some detail to arrive at the best solution.

2. All other final products should also be produced in an enclosed, segregated area utilizing a dedicated crystallization unit. Different, non-estrogenic products, may be processed in this unit. Light partitioning could be acceptable with the current main production area. The most appropriate size of crystallization unit will be determined.

3. The acceptance of, and working under GMP as a most vital aspect of production has to be installed in all levels of workers. Formal instruction courses (as well as on-the-job-training) are to be recommended.

Documentation of presentation and examination to confirm teachings have been absorbed should be implemented. Such records for individuals could be combined with similar training records covering unit operations and safety courses.

It is clear, at the moment, that the seeds which have been sown with regards to working to GMP do not seem to have fertilised or developed to the extent which will be essential for a fully efficient operation. This is not a pointed criticism, but intended as constructive.

Considerations that have to be given to the future must include not only the provision of additional capacity to provide a high level production, but also especial attention given to the conditions under which these are installed. The two aspects which have to be borne in mind as most important are continued and more stringent attention to safety and to ever improving GMP satisfaction.

The plant unit which will need increasing in capacity is involved in two aspects - most steroids involved are estrogens and most reactions are ethinylations. This presents a product hazard (estrogens) and safety hazard (alkali metals).

For regular production (where other reactions may have to be performed at the same time in the building) there is an over-whelming argument for the provision of a specially contained unit housed in a hazard area. This should preferably be external to the existing building. but not remote from it.

It can be seen that this unit would probably not be necessary from the aspect of capacity until 1995/6, but it is most urgently recommended that immediate planning should be put into operation in order to implement such a unit at a much earlier date.

Other reaction conditions which may be met if the product spread is achieved also will need to be considered. The first is the use of ammonia for the production of norethisterone. This reaction could be performed in the existing area , but there will be a need for ancilliary scrubbing equipment for environmental control. this will not be expensive.

The second condition that will be met would be use of Grignard reagent for the production of methandienone (and also oxymetholone - a product not indicated in this report since it will be prepared from hecogenin via tigogenin). It is possible that the Grignard reaction in Cuba might prove to be too expensive for economical production of these products and such should be carefully checked when methods are clearly defined . Should this Grignard reaction be performed it must be done in a hazard area. The most appropriate arrangement would be to use an area allocated for norethisterone ethinylation and Grignard, leaving a second area solely for estrogens.

Ethinylations: an important comment on ethinylations is appropriate at this point. Ethinylation is an important process noticed to be used frequently within the product list. All are currently performed using potassium metal which is potentially very hazardous. A recommendation was made previously that the use of an alternative reagent lithium acetylide ethylene diamine complex should be investigated. This should be considered of top priority. It is understood that investigation has been held up by lack of the solvent ethylene diamine, but it is suggested every effort should be made to procure this to progress this work.

Other equipments.

The production analysis shows a high occupancy of vacuum drying facilities needed. At present only one vacuum oven of about 0.5 m^3 capacity is available which is too small for any regularity of production. Additional vacuum oven by drying capacity is certainly needed, but should be carefully sized taking into account not only current batch sizes but also for possible future batch sizes and it must be remembered that products cannot be mixed for drying.

Ideally, particularly for estrogens, consideration should be given to an agitated vacuum pan drier or Thermovac filter/dryer, to meet optimum GMP and safety handling requirements. This might be difficult to find in the correct capacity scale and prove difficult to fund. A 75 Lt agitated vacuum pan dryer complete with vacuum pump & condenser would cost in the region of USD 100,000 while a 200 Lt. Thermovac filter/dryer sells at USD 135,000. Prices would not be likely to be significantly lower for smaller units if indeed manufactured.

The need for a small FLP centrifuge for the production of testosterone enanthate has been emphasized previously (see DP/CUB/81/01), and is again endorsed.

6.4 Micro-plant.

Mention has also been made previously of need for the completion of procurement of some unit items and installation materials for the completion of the micro-plant required for scale-up, kilo production and also for valuable training facility. This unit is very important for satisfactory scale-up of the processes developing rapidly in the laboratory to use AD and ADD as starting materials, as well as such other products as medroxyprogesterone acetate and oxymetholone.

Current production.

For a variety of reasons less production work has been performed during missions thsn was planned.

Priority products, for which ADD was available, were the estrogens, ethinyl estradiol and mestranol. A stock of 18 Kgs. of ADD has been converted to estrone with fair success. The problems previously experienced in the production of ADD-ketal were satisfactirily overcome by a minor plant modification so that laboratory conditions could be more exactly mimicked.

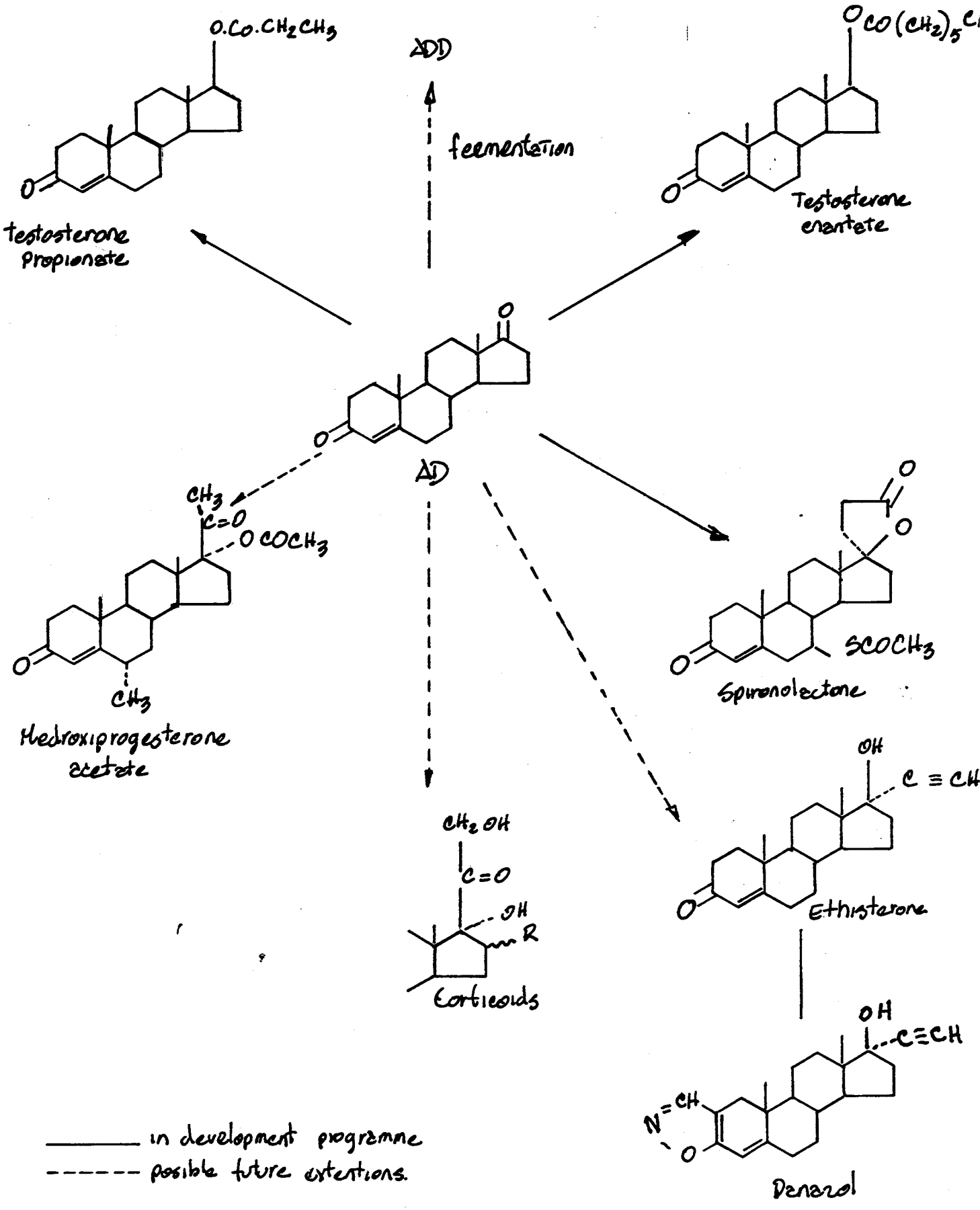
Mestranol has not previously been prepared on plant scale. The first stage, preparation of estrone methyl ether was satisfactorily performed using reaction conditions determined in the Cuban laboratory. Yield and quality were both up to standard. The ethinylation stage should have been performed during the last mission but was delayed.
After the mestranol has been produced the balance of the estrone will be ethinylated to ethinyl estradiol. Both products will be supplied to the oral contraceptive formulation facility.

6.5 INVESTIGATION OF SYNTHETIC ROUTES.

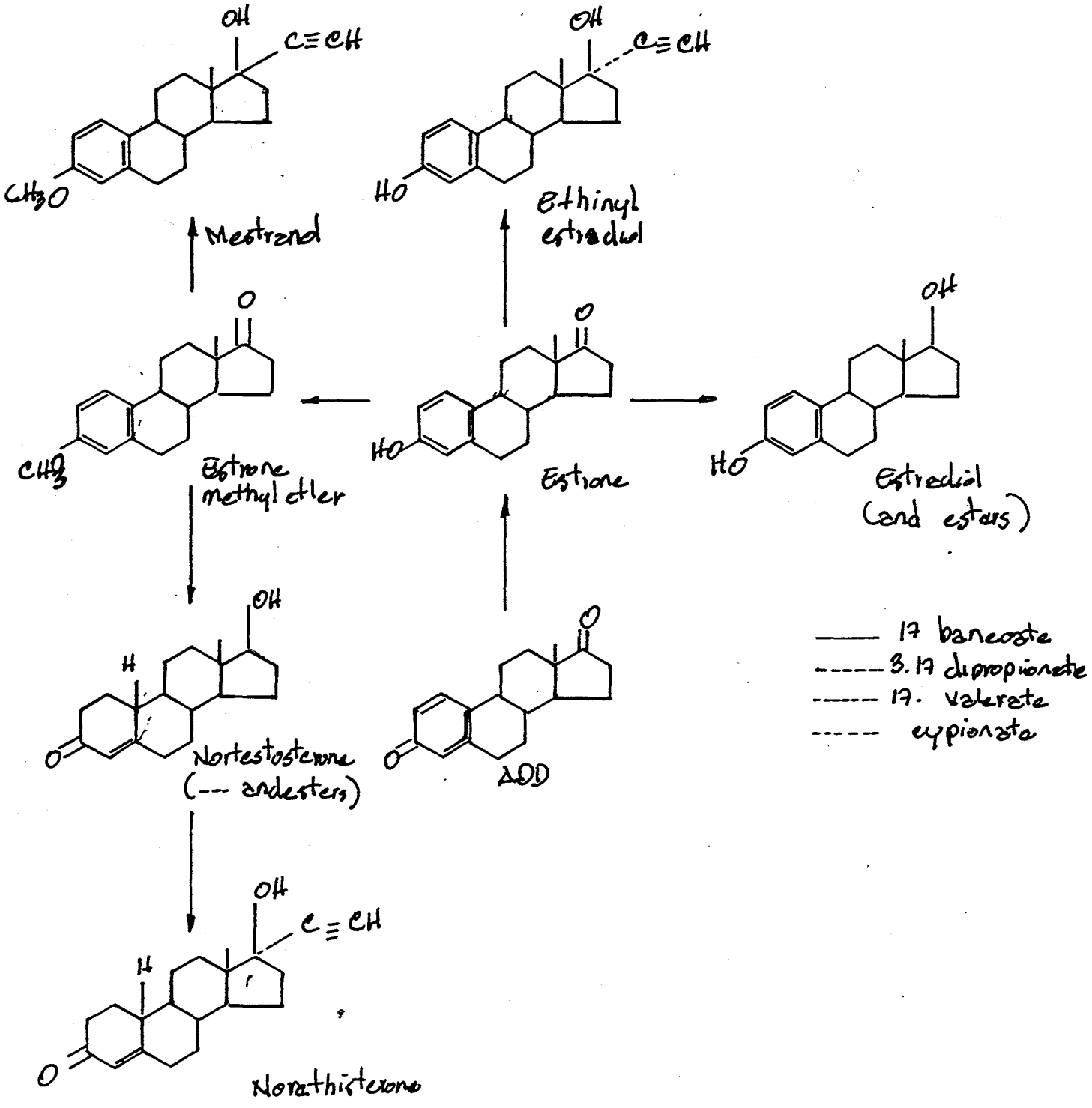
The flow sheets presented indicates some of the synthetic possibilities of using AD or ADD starting materials for the production of a wide variety of Bulk Active Pharmaceuticals.

Solid conecting lines represents the current product routes under development, while dotted lines represents possible extension later.

Utilization of AD as starting material



Utilization of ΔDD as starting material



Progress in development is steady, but at times decidedly adversely effected by lack of availability of many basic chemicals and also reasonable stocks of steroids intermediates.

Apart from ADD and AD, stocks of about 100 grs minimum each of at least intermediates such as ethisterone, methyltestosterone and nortestosterone would be very helpful.

The longest synthesis is that of spironolactone which is probably the least advance, due to shortage of additive chemicals. Considering the importance of the product it may be advantageous to augment resources in this field.

It is to be hope that when the new research laboratories are completed there will be greater incentive to achieving more rapid results.

Unfortunately the new facilities are not likely to start operation fully equipped and it is understood that some USD 30,000 appear to be needed to satisfy preferred requirements.

A very brief summary of programme and progress is being presented in this report.

AD to testosterone: conditions which have been exploited commercially have been supplied to the laboratory and are currently being tested. The method involves two stages of enol ether formation followed by reduction and enol ether hydrolysis. Recovery of starting material is included in the method and a high overall yield can be obtained at 84/90% by weight. This is considerable improvement over a previous method obtained from India.

AD to spironolactone: this investigation is at an early stage. The most appropriate route to follow has been agreed and has advantages of eliminating the stages of ethinylation/Kolbe reaction (which was very long and complex) and hydrogenation (expensive in catalyst) included in the original technology from DHA. A reagent has first had to be prepared to start this symthesis and the first two stages only are in course of investigation.

While the preparation of the specialist reagent necessary for this synthesis is acceptable considerable time was also devoted to preparation of reagent which should have been available off the shelf. This reagent, triethyl ortho-formate, is to be used by at least three members of the steroid group and lack of such chemicals can seriously delay more productive work.

AD to Danazol: work here has been confined to investigation of reaction conditions to form a hydroxy-methylene derivative of ethisterone and the coupling to danazol. Problems initially experienced with purification now seen to be resolved. the process can now be considered for scale-up and investigation of process volumens. The complete synthesis from AD consists of 4 stages and the first 2 produce ethisterone itself has been performed previously on 20 gm. scale successfully. Further work is likely to be delayed until further stocks of ethisterone are either prepared or procured. Since ethisterone can be procured at very low price on the world market consideration should be given to its use rather than manufacture from ADD, at least initialy.

ADD to Estradiol products: these proceed through the intermediate estrone which is already prepared on commercial scale.

Preparation of estradiol and the estradiol-3-benzoate were performed according to methods provided between the previous project and the start of this one. Results were satisfactory and the processes would benefit from scale-up when possible.

Preparation of estradiol-17-cypionate was also acheived via the di-ester. This is a very small volume product.

ADD to Nor-steroids: these products also proceed via estrone. Satisfactory preparation of estrone methyl ether, as intermediate for mestranol has already been mentioned. Small scale preparations of nortestosterone have followed provided methods with reasonable results apart from yield below standard. This is possibly a function of scale. Scale-up through 5 gms. to 10 gms.is in progress. This latter is the limit which will be possible with existing equipment in the laboratory. Some consideration will need to be given to procure larger equipment. a problemn may exist with the quality of Cuban produced ammonia. For small scale this is purified over sodium, but is not practical on larger scale.

Although not currently in the production programme, at a later date esters of the initial product nortestosterone will be prepared. Methods have been provided for such esters as 17-phenylpropionate, decanoate and isocaproate.

Two further stages will be required to convert 19-nortestosterone to norethisterone, but will require to wait until adequate raw material is available.

Products starting from other than AD and ADD:

These are:

(a) **Oxymethalone** which has been prepared in the laboratory from methylandrostanolone. This intermediate may be prepared from hecogenin via tigogenin. Satisfactory coupling has been acheived but the question of purification in satisfactory yield not yet resolved.

In the plant two large batches of hecogenin have been very satisfactorily reduced by the Wolff Kishner method to tigogenin. Laboratory work is proceeding with side chain degradation to determine the possibility of using the crude product.

(b) **Medroxyprogesterone acetate:** work on this only really started during the latter missions. The process consists of a 4/5 stage synthesis. The first stage has been reasonably optimized and work progresses on steps 2 & 3 now studied, final product, medroxy-progesterone acetate, has been produced.

In the case of this product it would probably be most appropriate to start from acetoxyprogesterone acetate although methods to produce this from precursors could be supplied.

(c) **Elaboration of diene acetate:** this is a somewhat long term programme and the stages of building up the side chain and modification of ring A are being systematically worked through.

General: Working conditions in the laboratory could be much improved with a more adequate supply in terms of range of glassware. Problems are also encountered often with spare items, particularly seals for vacuum work. A better vacuum supply might also help but only effectively if equipment is also in good order.

The situation in the control laboratory at Mario Muñoz is a very bad situation virtually no glassware and control equipment such as melting point often not available or in good order. Expenditure would not be high to rectify this and certainly something must be done before any significant production is under way.

Even though it is now anticipated that the new research laboratories at Mario Muñoz for the steroid group will be ready in another two months this must not be used to supplement control work. Such must be performed independantly in the provided control laboratory.

When the new research laboratories at Mario Muñoz are complete adequate funding is still needed to equip them to an efficient level. This is estimated at $30,000 including a computer.

A final problem which is observed, and can very seriously effect the speed of development is availability of some up-stream intermediates, eg ethisterone, methyl testosterone, nortestosterone, etc., which might often speed up development or indicate problems at later steps and could save much time in "in-house" preparation. It is suggested that this should always be borne in mind.

7. ORGANISATION OF PERSONNEL.

It is suggested that all functions relating to steroid products be contained under one organization from production of raw materials to production of final bulk active steroids as well as encompassing synthesis research (development) and fermentation development and initial production.

It is possible that changes might be beneficial or even necessary in the future dependant on various developments.

Initial proving of, and producing development quantities of phytosterols most likely can best be done at the Mario Muñoz unit and such best organised through the department of LIDE (Laboratorios Investigación Desarrollo Esteroides).

Some outside technical assistance might be given by ICIDCA or CIDEM since both have had involvements in method development.

ICIDCA may well retain a parallel development for process development and even direct involvement if a future date significant phytosterols production is contemplated. Should this be the case production duplication at Mario Muñoz would most likely be undesirable and be removed from LIDE responsability.

With respect to any development/scale-up work undertaken on fermentation it is suggested that this is divorced from any current work on steroid fermentation and from antibiotic fermentation.

A group should be formed an experienced micro-biologist with assitants and responsible to the head of LIDE. This group may well be involved in working in existing facilities on laboratory scale (possibly with coperation abroad) or being granted access to some local facilities in Cuba. Laboratory scale duplication would not be proposed and for initial scale-up, particularly with respect to timing some facilities outside of Mario Muñoz must be contemplated. Such might still be within the CQF confines.

Any production, to be at an appropriate economic level, is likely to be in excess of Cuban domestic needs but are considered best to be installed within facilities at Mario Muñoz if at all possible. The possibility of doing this would not appear to exist until a realistic process is developed or still can be procured by technology, licencing or transfer.

The installation of a pilot plant would not seen at all reasonalbe on a cost basis and any scale-up work or initial small production runs would seem to need to be performed in facilities of other Cuban organisations or with partners abroad.

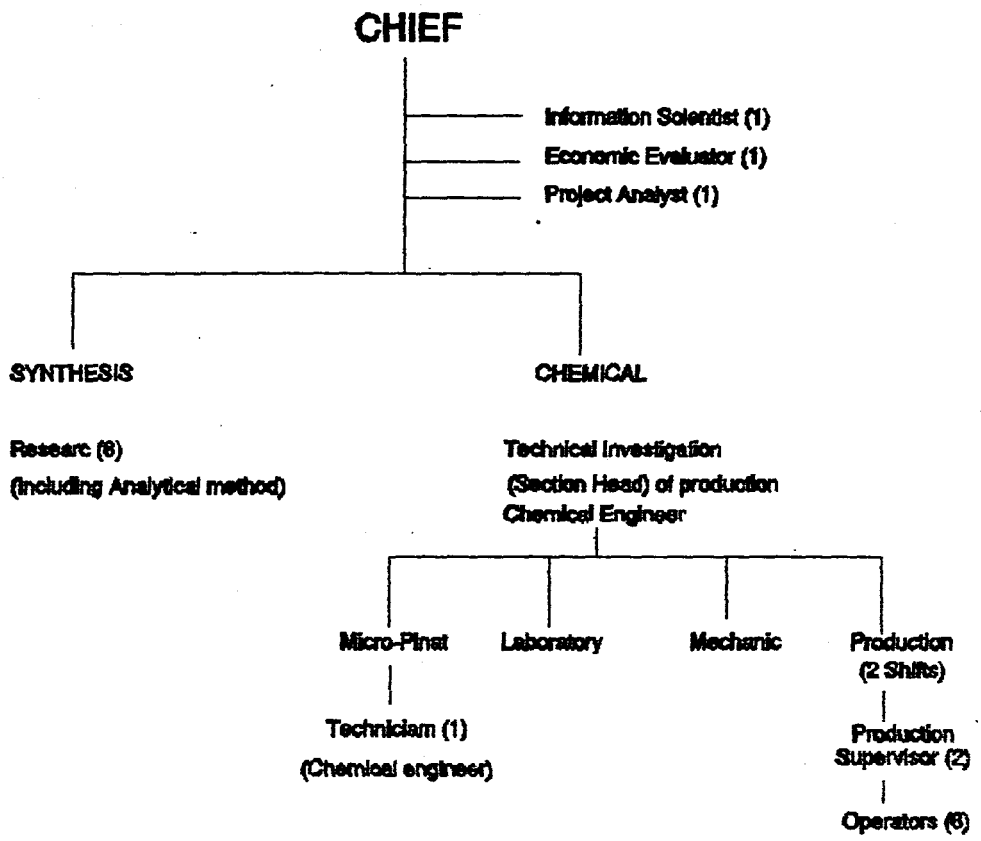
Two organisation chart are presented.

Firstly the current situation at the establishment LIDE is considered satisfactory in principle though suffering at the moment from operation taking place at 3 centres. Once the laboratory is complete all personnel will work within the same confines. At present a great strain is put in the chief of LIDE having to cover all centres which involves considerable travel (and long hours) and also that currently the position of section head of production is not covered.

The second organisation chart recommends, should developments take place in the field of fermentation, then this aspect should also fall under the umbrella of LIDE. This should apply to both developments and production. More smooth and rapid development is likely to result.

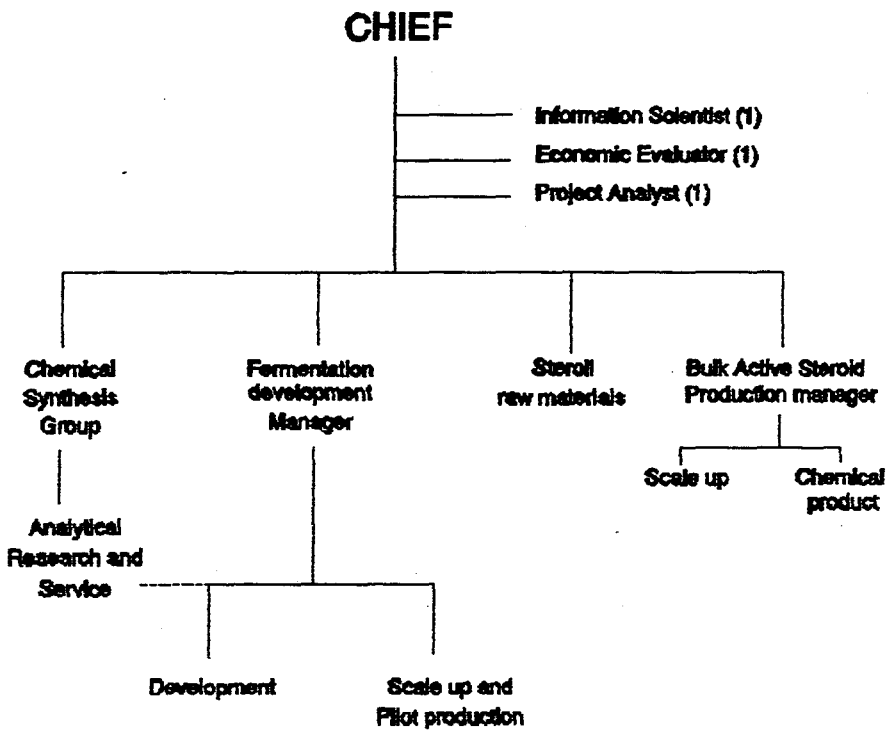
FUNCTIONAL CHART

(EXISTING)



FUNCTIONAL CHART

(PROPOSED)



Staffing

Current staffing levels are indicated on the first organization chart.

Levels for all staff are currently satisfactory although the position of section head of chemical technical investigation and production is vacant.

Adequate levels of operators exist for early production but is likely to be increased to be extent indicated in the following table which has been derived from analysis of production level needs. Two shifts working is assumed.

	Operators
1993	6
1994	6
1995	8
1996	10
1997	16
1998	18
1999	20
2000	20
2001	20
2002	20

8. FINANCIAL AND ECONOMIC.

Full financial analysis has not been attemped but the following summarised tables should help to illustrate various salient facts derived from utilization of the present pilot steroid production plant and following the proposed production programme and provide the basis for any projections.

In general this report deals with the production of Bulk Active Pharmaceuticals, but the influence of the annual constant production of diene acetate at a level of 690 Kg is also indicated.

8.1 Scenarios for Financial and Economic Evaluations

CONSIDERATIONS

(A) Fermentation

It has been previously indicated that it is not possible to project any figures for the fermentation of phytosterols since at this time technology is not available and too many assumptions would be necessary to be meaningful.

The parameters likely to be necessary for the economical processing of phytosterols by fermentation have been indicated and might be used as **guidelines for evaluating any process offered or developed.**

Processing at a level in excess of 4,000 kgs output AD should not be considered unrealistic. The markets available to Cuba may at present be limited since the major consumers, other than in-house manufacturers
(Upjohn, Schering and Mitsubishi) are the USA companies Searle and Syntex. One other significant consumer is Organon, Holland, where sales barriers should not exist. Other smaller consumers exist and it has been established that, provided suitable price, quality, availability and reliability of supply can be offered, the Indian company CIPLA Ltd would be very interested in being supplied with AD in the order of 4,000 kgs per annum. Currently other enquiries for supply of low tonnage lots of AD are circulating the market.

It has now been established that the world consumption of AD is in the order of 400 metric tons per annum, Searle alone consuming 100 metric tons. Although Searle held early patents on fermentation they no longer produce.

(B) Bulk Active Steroid Production

The financial and economical position with regard to the processing of intermediates AD and ADD to desired bulk active pharmaceuticals has been covered in some depth to determine the sense of establishing regular production in its own right for both domestic consumption and for export potential while still trying to establish the possibility and means of Cuban production of intermediates. An attempt is also made to indicate the value of domestic production of AD.

Various scenarios have been considered based on productive utilization of the steroid plant as it stands as well as considering further developments.

Installation of the present plant took place in the mid-1980's and commissioning completed during 1991.

The position with regard to initial investments appears to be rather confused for it is clear that the investments attributed to buildings must clearly include considerable expenditure which might have been more appropriately allocated to installation of plant and equipment.

Recorded investment costs were:

Buildings : USD 330,000

Plant and equipment : USD 578,000

UNDP contribution to above : USD 689,000

Additional pre-production costs : USD 456,000

This latter included expenditure on steroid intermediates and additives for commissioning, but unspecified volumes of such materials are still held in stock. Presumably also included would be elements for technology, technical assistance, overseas and domestic training, other missions as well as domestic engineering and technical expenditures. No breakdown could be readily supplied.

Since much of the plant was procured in the mid-1980's and installed over many years some devaluation must have occurred, but the current valuation of the investment could not be clarified and consequently the projections presented exclude the construction period and concentrate on production. This consideration is based on making use of the installation rather than letting it lie fallow.

For evaluation purposes the full purchase value of the plant, equipment and buildings have, nonetheless, been taken for depreciation considerations in determination of production costs.

In the scenarios presented consideration of various aspects of most consequence are presented. The scenarios represent typical possibilities of utilizing the facilities available and an attempt is made to quantify the values of each possibility and the sensitivity to the most important factors.

In all scenarios only production of bulk active pharmaceuticals has been considered although capacity is available for the production of diene acetate at a level of 690 kgs and oxymethalone from hecogenin.

The various scenarios considered and inputs may now be described.

Scenario A1

a) this assumes the utilization of the plant for production according to the full schedule proposed in section 3.7.3 with the exception that production of testosterone enanthate is excluded in year 1993 due to lack of the necessary centrifuge. This provides products for a build-up to all domestic needs and export possibilities. The further capital expenditures needed to achieve the programme, as proposed in section 6.3.3.5 have been included with the

exception of that in 1997 (USD 132,000) since this is only occasioned by the concurrent production of diene acetate.

b) **Total production costs** - all factory costs are derived from the individual production costs calculated essentially as indicated in section 6.3.3 except that in this scenario the full depreciation of plant and equipment (full cost depreciated over 10 years) and buildings (full costs depreciated over 15 years) have been charged against each years production.

Spares have been taken as an integral part of the maintenance charge.

As the layout of production costs in this section differed to a small extent from the earlier analysis the basic figures for each product concerned in the overall analysis will be represented here. They compare with those given in section 6.3.3.4.

c) **Net working capital** - minimum days coverage (mdc) and coefficient of turnover (coto) have been indicated on the projection sheets. A period of 90 days mdc has been used for inventory since all intermediates and virtually all additives have to be imported into Cuba.

The following calculations are used:

accounts recoverable : 1/12 x operating costs

work-in-progress : 1/12 x factory costs

finished products : 1/12 x (factory costs + administration)

accounts payable : 1/12 x factory costs

operating costs : total production cost, less depreciation

d) **Cash flow** - sales prices for domestic consumption have been taken at equivalent cif import prices, while for exports the international fob price is used.

Cash flows are based on production in existing units, but including improvements and capacity expansion as required and which are then depreciated fully in each subsequent year against production. No scrap value has been allocated against initial plant or building installation (strictly could be valued still at 1/3 cost), but investments during the production programme have been allocated scrap values according to the extents not depreciated within the programme. Investment in working capital is also included in scrap value.

e) **Economical evaluation** - has been considered by simply making cash flow adjustments applying a shadow exchange rate (SER) to all inflows and outflows involving foreign exchange. The ratio of SER to official exchange rate used was 1.2.

It will be appreciated that only a few of the units and products (those involving ethinylations and possibly spironolactone) approach 100% capacity and others still have significant capacity available for introduction of further production or increase in levels, even allowing for inclusion of diene acetate production.

Scenario A2

This scenario is similar to A1 except that 2 changes are made, one allowing comparison of cash flows and the other relating to net income statements and production costs.

Firstly, depreciation has been altered from 10 years to 15 years for plant and equipment and from 15 years to 20 years for buildings. These are both considered to be more appropriate to the actual conditions which apply to this level of installation.

Secondly, the influence of level of administration overheads is illustrated and can be compared in cash flow calculations. The Cuban method of applying 15% of factory costs for the type of productions involved, it is considered, can be misleading especially when particularly high priced products are involved. Although higher total raw material costs are involved and hence higher working capital requires funding the method may well imply higher costs than might be real. The levels applied in this scenario are arbitorily estimated but considered to be nearer the actuals which should be experienced.

Scenario A3

This scenario covers the application of depreciation according to levels indicated to be absorbed by the litre-hour determinations.

Here only a condensed product cost projection is presented together with the indication of actual annual capacity of plant filling.

The effect on Net Income is demonstrated but otherwise the scenario may be compared in turn with either A1 or A2.

Projections: Net Income statement and occupancy utilization.

Scenario B1

Here consideration has been given to analysing the situation of reducing the significant levels of capital expenditure involved in achieving the larger production levels of Scenarios A. It is also an attempt to determine whether any sense resides in considering only production of important domestic consumptions (even, perhaps, as a short term policy).

The first scenario has been confined to productions which are considered feasible with existing technologies covering the largely established products ethinyl estradiol, mestranol and estradiol benzoate, testosterone propionate and testosterone enanthate, and supplemented later with products methandienone and danazol.

The production programme is derived from the projected domestic needs (under section 3.7.2) for the appropriate products.

In the first year production of testosterone enanthate has been excluded since the procurement of a centrifuge in time for production in this first year would not seem feasible. Otherwise full levels are applied directly.

For the second year testosterone enanthate is included and also the products methandienone and danazol at full level since it is considered that process development of these products is sufficiently advanced to expect production to be possible during year 2 - provided a functioning micro-plant for scale-up is available in the near future.

Spironolactone has been completely ignored in this scenario since development is less well advanced, and although hopefully it will be satisfactorily developed during the period covered, its economics have to be more precisely evaluated.

In this scenario, for calculation of production costs, depreciation as absorbed by the specific production levels of products has been used based on original costs, but supplemented by full 10 year depreciation on plant and 15 year on buildings for new assets introduced during the programme.

The needs for capital expenditure are reduced to cover the need for a centrifuge (USD 40,000), some plant and building segregation (USD 35,000) and later a small vacuum oven (USD 20,000). These can be seen in the cash flow projection. As for previous scenarios scrap value is based only on new assets and working capital.

The methods of projection for new working capital and cash flow (including SER adjusted) are similar to scenario A1). In the case of SER adjustments the shadow price is not applied to sales since all are domestic but comparison is supplied for the export position.

Scenario B2

Since the production of methandienone and danazol have not yet been fully established this scenario has been reduced to the basis of producing only those products essentially established on production scale, ie ethinyl, estradiol, mestranol and estradiol benzoate together with testosterone propionate and enanthate. Production volumes again follow domestic needs, but testosterone enanthate production is excluded in year one.

In the cash flow the provision of further vacuum drying facility in 1998 is excluded in this scenario as current capacity would suffice.

Scenario C1

This scenario has been projected to consider the situation where production of intermediates AD and ADD from phytosterols could be envisaged in Cuba. Prices for the AD and ADD have been selected at levels which could be considered realistic possibilities given the technology availability. For AD a price of USD 140/kg has been selected and for ADD a price of USD 280/kg.

The proposed production programme for domestic plus export, as in the A scenarios has been applied and other conditions similar to scenario A1.

In the case where SER adjustments are necessary detailed breakdowns into foreign and domestic elements were made but are not presented other than indicating overall foreign % on cash flow statements.

In this scenario for net working capital calculations the inventory materials have still been calculated at a mdc of 90 days for both raw materials and additives although in practice with domestic production of AD/ADD the raw materials elements could well be reduced to a mdc of 30 days and thus reduce the overall net working capital requirements as well as administration overheads which are taken to include any short term loan investment for covering working capital. Due to lower factory costs the administration costs are automatically reduced.

Scenario C2

This has been prepared including only the absorbed depreciation to make allowance for other products which can be produced in the plant or for further increase in product levels where equipment availability is appropriate.

"Absorbed" depreciation levels

The full production programme has been analysed in terms of "absorbed" depreciation levels based on individual product costings. It can be seen that overall significant capacity remains in the plant.

This is partly covered by the "absorption" which will be attributed to the processing of hecogenin to diene acetate and which has been calculated to be equivalent to some USD 17,000 annual depreciation. Even with diene being produced spare capacity (as evident from plant filling tables in section 6.3.2) remains for introduction of further products or some higher product levels.

Overall capacity of plant filled in terms of "absorbed" depreciation
(bulk active pharmaceuticals only)
(Full programme)

Year	% plant equipment occupied	% building occupied
1993	7.5	2.4
1994	10.8	4.4
1995	17.7	9.2
1996	23.0	13.4
1997	26.1	18.8
1998	28.2	21.4
1999	32.6	24.8
2000	36.8	27.0
2001	40.6	30.3
2002	42.0	30.9

Projections in Appendix cover:-

Total production cost	A1	A2	A3	B1	B2	C1	C2
New working capital	A1	A2	-	B1	B2	C1	-
Cash flow - production and discounted	A1	A2	-	B1	B2	C1	-
Cash flow - production (SER adjusted)	A1	-	-	B1	-	C1	-
Net income statements (summary)	A1	A2	A3	B1	B2	C1	C2

8.2 Financial and Economic Evaluation Results and Analysis

8.2.1 Results and indicators

A summary of results is first presented, all more detailed projections being found in the Appendix.

Summary of Net Present Values and Internal Rates of Return

These figures are based only on production profiles over 10 years and represent utilization of existing facilities rather than being left idle. Initial investments are consequently ignored in this exercise because of uncertainty. The results will hence be relative rather than absolute and used for analysing various methods of treatment.

	Financial indicators		Economic indicators	
	NPV (18%)	IRR	NPV (15%)	IRR
Scenario	000 USD	%	000 USD	%
A1	- 48.4	14.4	+ 28.7	17.7
A2	+ 67.6	24.4	-	-
A3	- 48.4	14.4	-	-
B1	+ 67.9	45.6	- 25.9	8.9
B2	+ 9.1	23.8	-	-
C1	+ 157.5	31.9	+ 263.2	36.2
C2	+ 157.5	31.9	+ 263.2	36.2

Net Income Statements

These have been presented only in summarised form covering production year one, 5 and 10. Rates of return on equity relative to these projections have been calculated both on full original fixed asset values (ROE_1) and fixed assets adjusted to the extent of the plant value of USD 689,000 supplied by UNDP (ROE_2). In case of return on investment this has been based only on the situation of Cuban investment and working capital and reported as ROI_2.

These are summarised below, also including not only undistributed "profits" in year 10, but also indicating the levels of the most important elements affecting results, viz depreciation charged or absorbed and level of administration charges levied.

Scenarios		A1			A2			A3	
Year	1	5	10	1	5	10	1	5	10
Total Sales less variable costs	86.1	647.3	971.6	86.1	647.3	971.6	86.1	647.3	971.6
Non variable costs inc depreciation	161.8	672.3	977.1	133.5	603.6	894.1	86.9	584.9	907.2
operational margin =gross/net profit	-75.7	-25.0	-5.5	-47.4	39.7	77.5	-0.8	62.4	64.4
% total sales	-87.9	-3.8	-0.6	-55.0	6.1	8.0	-1.09	9.6	6.6
Accumulated undistributed profit	-75.7	-237.8	-342.0	-47.4	73.4	363.7	-0.8	143.9	423.3
ROE1 %	-8.3	-2.0	-0.4	-5.0	3.1	6.0	-0.1	4.9	5.0
ROE2 %	-34.6	-11.4	-0.9	-21.6	6.7	13.1	-0.1	10.5	10.9
ROI2 %	-30.4	-3.1	-0.6	-19.0	5.0	8.6	-	-	-

Scenarios		B1			B2	
Year	1	5	10	1	5	10
Total Sales less variable costs	63.9	193.2	216.1	62.0	76.8	84.5
Non variable costs inc depreciation	63.9	162.6	180.3	52.3	64.8	71.0
operational margin =gross/net profit	0	30.6	35.8	9.7	12.0	13.5
% total sales	0	15.8	16.6	15.6	15.6	16.0
Accumulated undistributed profit	0	123.3	270.6	9.7	56.9	121.8
ROE1 %	-	-	-	-	-	-
ROE2 %	0	10.4	11.4	4.4	4.1	4.6
ROI2 %	0	8.7	9.5	4.1	3.8	4.2

Scenarios		C1			C2	
Year	1	5	10	1	5	10
Total Sales less variable costs	86.1	647.3	971.6	86.1	647.3	971.6
Non variable costs inc depreciation	142.5	617.4	883.8	67.6	530.9	813.9
operational margin =gross/net profit	-56.4	29.9	87.8	18.5	116.4	157.7
% total sales	-65.5	4.6	9.03	21.5	18.0	16.2
Accumulated undistributed profit	-56.4	-65.4	220.2	18.5	314.8	988.4
ROE1 %	-6.2	2.3	6.8	2.0	9.1	12.3
ROE2 %	-25.9	5.0	14.8	8.4	19.6	26.6
ROI2 %	-22.9	3.8	9.9	7.5	14.8	17.7

Scenario	ROE_1 %	ROE_2 %	ROI_2 %
A1	-0.4	-0.9	-0.6
A2	+6.0	+13.1	+8.6
A3	+5.0	+10.9	-
B1	-	+11.4	+9.5
B2	-	+4.6	+4.2
C1	+6.8	+14.8	+9.9
C2	+12.3	+26.6	+17.7

Scenario	Cumulative profit at year 10	Depreciation "absorbed"	Administration overheads levied
	000 USD	000 USD	000 USD
A1	- 342.0	+ 1032.6	+ 677.9
A2	+ 363.7	+ 708.2	+ 383.0
A3	+ 423.3	+ 269.8	+ 677.9
B1	+ 270.6	+ 117.0	+ 189.6
B2	+ 121.8	+ 40.31	+ 81.63
C1	+ 220.2	+ 1032.6	+ 602.3
C2	+ 988.4	+ 269.8	+ 724.5

Pay-back periods

These have been determined from the Net Income Statements and may be used for comparison purposes rather than absolute.

Scenario	Payback period Initial level investment USD 219,000 (Grant adjusted)	Payback period Initial investment USD 908,000
A1	-	-
A2	7/8 years	est 13 years
A3	11/12 years	-
B1	8/9 years	-
B2	est 17/18 years	-
C1	6/7 years	10/11 years
C2	6/7 years	10/11 years

Note: Fixed asset investments during production period are also included, when incurred, in calculations.

Break-even analysis is not considered feasible for the production programmes involving a wide range of products and range of sales prices. Differing ratios of products are also involved over the production period.

For valuable breakdown analysis several criteria should apply and the most important ones not applicable in this study are that product mixes vary from year to year and sales value is not a direct function of the volume of products sold and further fixed operating conditions are not the same for all volumes of production.

Sensitivity analysis also cannot be applied in terms of quantitative effects, but the effect of most important factors are considered by comparison of the various scenarios.

Variable costs, such as energy, direct labour, utilities etc are relatively insignificant, particularly for the high priced products considered.

Sales prices are obviously significant, but are largely controlled by ruling international prices and they are found to vary with the costs of raw material intermediates which Cuba currently have to rely upon.

One aspect Cuba needs to be sensible of with respect to sales prices for the export market is the effect of carriage and freight since conversely the cif charges for importation into Cuba appear to be high at 16.8% Sensitivity to export price with respect to profitability should always be borne in mind but has not been allowed for in projections. On the other hand any exports from Cuba are likely to be of relatively low weights which can bear higher unit sales prices than quoted international prices, which is some compensation.

It should be borne in mind that cash flow projections have excluded any initial investments since these values are not clear and do not really relate to actual necessary plant or buildings for the processes involved. All indicators are relative.

The scenarios attempt to compare different situations. They cover the effect of depreciation and administration overheads while operating a full production programme including export sales potential using imported steroid intermediates. They also incorporate significant further investments to attain enhanced GMP and safety standards and provide adequate capacity for key products. These are represented in scenarios A1, A2 and A3.

The scenarios C1 and C2 are included to assess the situation when lower cost steroid intermediates produced in Cuba could be used, the production programme being similar to those of scenario A.

The scenarios B1 and B2 cover 2 different levels of production mixes for domestic use only to assess the financial and economic value of such low level production and also illustrate the benefits which might be derived from current developments and extending product range.

Before trying to analyse results some general comments may be covered.

The determination of the most appropriate way to cover allocation of depreciation poses a problem since plant is designed not only to cover the proposed products but also other productions and even then some spare capacity exists. For evaluation purposes it might then be argued that the most appropriate scenarios fall under A3, B1, B2 and C2. For all depreciation considerations it has been assumed that no depreciation had been incurred since purchase and installation so all results might be considered to contain hidden assets.

The method of determination of administration overheads can be seen to be most crucial to the results of evaluations. Using a percentage based on factory costs is not considered to be very appropriate, particularly in the case of high cost products since these should not incur any significant higher expenses than lower cost products except with respect to somewhat higher interest costs on loans for working capital. Administration overheads are under control of management and rather than the present estimation a detailed evaluation should be recommended.

8.2.2 FINANCIAL AND ECONOMIC ANALYSIS

While scenario A1 is not attractive in either terms of financial IRR, NPV or Net Income Statement comparison with A2 indicates, even using purchased steroid intermediates, and careful control of administration overheads a greatly improved financial IRR may be observed and reasonable level of undistributed "profit" at the end of 10 years production.

Economic evaluation may be derived from the indicators of NPV and IRR produced from cash flows with SER adjustment. Such has only been projected for scenario A1 but illustrates a reasonable level of IRR compared with the financial indicator. This is to be expected from the element of export production within the programme. While not calculated in detail for scenario A2 a figure for IRR of 28% should result.

One quantifiable benefit derived is the saving of foreign currency due to purchase of intermediates rather than finished bulk active products. Over the 10 year production programme this will amount to USD 529,128 derived only from domestically consumed products. An overall benefit of foreign currency comprising savings on domestic products and those derived from export sales would amount to USD 796,870.

The production of bulk active pharmaceuticals in Cuba from imported steroid intermediates can never be expected to provide any high profit margins since virtually all additives must also be imported.

In the case of intermediates AD and ADD prices are rather carefully manipulated by the suppliers relative to finished bulk prices. Cuba also suffers from a significant burden of cif charges since most additives are also imported from rather distant sources. Cuban sources indicate this can amount to up to 16.8% of fob prices which is a rather large margin to absorb in production costs.

Scenarios C1 and C2 indicate then the benefits which could be derived from domestic production of AD and ADD.

Comparison of scenarios A1 and C1 illustrate the dramatic improvement of financial IRR up to 31.9% and a healthy net income statement relative to A1. Utilizing the more appropriate levels of only absorbed depreciation improves the profit situation proportionately. This could be less desirable if a taxable profit situation existed.

Economic evaluation is similarly attractive with an increase to an IRR of 36.2% due to export sales benefit.

The direct quantified benefit in foreign exchange cannot be precisely determined since any element of importation of additives for fermentation is not known. The total figure would have a ceiling value of USD 722,000, but this might be no more over 10 years than 10% higher than actual benefit. Total benefit over 10 years in foreign currency would amount to USD 427,430. Scenarios B1 and B2 have been considered in the event that consideration could not be given to funding of the additional investments needed to execute the full programme.

B1 covers those products which it is considered can be produced within the first 2 years production and includes 2 products methandienone and danazol which will shortly be ready

for scale-up. This programme does depend on the provision of a functioning microplant operational within 4-6 months maximum.

Rather than allowing the steroid plant to lie idle it is seen from scenario B2 that it would be beneficial to operate it to produce at the least those products which have been fully commissioned, viz ethinyl estradiol, mestranol, estradiol benzoate, testosterone propionate and and, when a centrifuge is provided, of testosterone enanthate. A respectable financial IRR of 23.8% is observed and reasonable undistributed "profit" but low depreciation absorption. The economic indicator of IRR has not been presented, but in line with that of B1 will not look attractive. The reason for this is that all sales are domestic and not subject to the shadow exchange rate. This is probably a little misleading for the programme B2 will provide a foreign exchange benefit of about USD 148,160 over 10 years, 76% due to cif savings.

This programme could be improved by operating the installed plant to capacity, particularly for the more profitable estrogen products. A total complement of estrogen could approach 70 kgs per annum and might give an opportunity of investigating the bulk export market either as bulk products or further processed to formulated products.

Finally, scenario B1, when compared with B2, indicates benefits which can be derived from the introduction of new products through development. Financial indicators improve considerably and undistributed "profits" can more than double. This difference should be sufficient incentive for the incorporation of methandienone and danazol into the programme and this, in itself, justification for rapid completion of the micro-plant for scaling-up of these products and later for those in the larger programme.

Again the economic indicators are not attractive, but compared with scenario B2 a further annual saving of foreign exchange expenditure amounting to USD 371,600 can be expected, 61% due to cif savings.

9. CONCLUSIONS.

1. While it has not been possible to locate technology for direct commercialisation efforts will continue since it is recommended not to discard the possibility of introducing the fermentqation process.

2. Even purchasing AD and ADD at normal international prices it would be possible to produce products required for domestic use at prices close to or below fob prices, hence benefiting by at least saving most cif costs. At normal conceptions requirements it is forecast that this would amount to about USD 55,000 per annum gross.

3. It is recommended that proving experiments should be performed preferably at Mario Muñoz factory to prove the phytosterols isolation processes and select the prefered one.

4. While the present plant conditions can be controlled at low production level to provide satisfactory quality products if must be appreciated that meassures will need need to be implemented to improve to an acceptable level the GMP of the units. The isolation of estrogens is of highest priority.

5. Training in the meaning of GMP and its implementation in practice is needed to prepare for regular production.

6. So far as possible it would be appropriate to site all steroid development and production work at the Mario Muñoz establishment under LIDE.

7. First priority of steroid production in Cuba should be for domestic consumption as a means of reaching some degree of self sufficiency, preservation of hard currency and assisting in providing adequate supplies of medicines for the Cuban population especially in the field of contraceptives.

8. Reasonable production levels of required products should be developed to minimise production costs and absorb depreciation costs.

9. Opportunity exists for modest entry into international marketing of steroid products which might be in formulated form, but more likely bulk active pharmaceuticals.

10. Outlets for marketing will need to be set up when firm supplies of products are available. This is likely to be executed through agents.

11. An eleventh hour response has indicated the posibility of toll conversion of phytosterols to AD. The opportunity should be investigated.

10. RECOMMENDATIONS

1. Although during this study period the means of implementing the objective of producing either AD and ADD by fermentation of phytosterols has not been realised efforts to do so should not be discontinued. Other current avenues of investigation should be followed up.

2. The pilot proving tests planned for phytosterol production should proceed.

3. Discussions should be arranged when possible to discuss with other parties the possibilities and indications of entering a research and/or teaching agreement for commercial development of fermentation of phytosterols to AD or ADD. Investigations into funding of such proposals should also be investigated.

4. It is recommended that Cuba give priority to the production of androst 4-en-3-one (AD).

5. Production of these steroids for which established methods are available should be implemented as soon as possible.

6. A stainless steel centrifuge should be procured a soon at possible to enable the production of testosterone enanthate to proceed. A unit of 500/650 mm ϕ is considered satisfactory. A figure of USD 35,000 fob investment has been suggested (but current firm quotation is needed).

7. The completion of installation of the micro-plant should be completed sufficiently for it to function. Funds needed amount to USD 78,000.

Completion of plant with installation of a further 30 lt enamel reactor unit could be delayed until later. The importance is to have functioning facilities.

8. A training programme, especially to cover the needs and implementation of GMP, should be instigated.

9. Planning should start in considering the details and best means by which full GMP can be achieved. Special attention should be given to the planning of the segregated estrogen processing area.

Appendix

Financial and

Economic

Projections

TOTAL PRODUCTION COSTS. SCENARIO A1 in Thousand USD

Years	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002
Raw Materials	47.5	83.7	165.2	231.9	315.8	349.9	382.9	431.7	471.6	489.8
Additives	19.0	30.7	71.8	96.8	125.4	134.5	152.0	175.8	188.2	190.3
Utilities	0.7	1.0	1.9	2.5	3.3	3.8	4.5	5.3	5.9	6.0
Energy	0.4	0.8	1.8	2.5	3.6	4.2	4.8	5.4	6.0	6.1
Labour, Direct	1.4	2.9	6.3	9.5	13.4	14.6	16.3	17.3	19.4	20.1
Maintenance	0.2	0.2	0.4	0.7	0.9	1.0	1.2	1.3	1.5	1.5
Spares										
Factory Overheads	1.2	2.3	4.6	7.3	9.6	11.0	12.7	14.1	15.7	16.0
FACTORY COSTS	**70.3**	**121.7**	**252.1**	**351.1**	**472.1**	**519.0**	**574.3**	**650.9**	**708.2**	**729.8**
Admin. o/h	10.0	20.0	39.2	54.1	71.7	77.7	87.3	98.9	107.5	111.5
Indirect Sales Costs										
Direct Sales Costs	1.7	3.4	6.9	7.3	12.8	14.0	15.7	17.5	19.3	20.1
Depreciation - Equip.	57.8	57.8	61.8	72.0	90.7	90.7	90.7	90.7	90.7	90.7
Depreciation - Buildings	22.0	22.0	22.0	23.0	23.0	25.0	25.0	25.0	25.0	25.0
Financial Costs										
TOTAL PRODUCTION COSTS	**161.8**	**224.9**	**383.0**	**509.5**	**672.3**	**726.4**	**793.0**	**883.0**	**950.7**	**977.1**
% Foreign	70.7	75.9	77.3	77.7	78.2	78.2	77.9	78.1	78.0	77.9

NET WORKING CAPITAL. SCENARIO A1 in Thousand USD

Year			1993	1994	1995	1996	1997	1998	1999	2000	2001	2002
Coverage	mdc	coto										
Current Assets												
Accounts Recoverable	30	12	6.9	12.0	24.9	34.5	46.4	50.9	56.4	63.9	69.6	71.8
Inventory Material	90	4	16.6	28.6	59.3	82.1	110.3	121.1	133.7	151.9	165.0	170.0
Energy & Utilities	30	12	0.1	0.1	0.2	0.2	0.3	0.4	0.4	0.5	0,5	0.5
Spares	60	6										
Work in Progress	30	12	5.9	10.1	21.0	29.3	39.3	43.3	47.9	54.2	59.0	60.8
Finished Products	30	12	6.7	11.8	24.3	33.8	45.3	49.7	55.1	62.5	68.0	70.1
TOTAL CURRENT ASSETS			**36.0**	**62.6**	**129.6**	**179.9**	**241.6**	**264.9**	**293.6**	**333.0**	**362.0**	**373.2**
Current Liabilities												
Accounts Payable	30	12	5.9	10.1	21.0	29.3	39.3	43.3	47.9	54.2	59.0	60.8
NET WORKING CAPITAL			**30.2**	**52.5**	**108.6**	**150.6**	**202.3**	**221.7**	**245.7**	**278.7**	**303.0**	**312.4**
Increase in Working Capital			**30.2**	**22.3**	**56.2**	**42.0**	**51.8**	**19.4**	**24.0**	**33.0**	**24.3**	**9.4**
% Foreign			96.0	96.0	95.9	96.4	96.5	96.5	96.5	96.5	96.5	96.5

CASH FLOW (& DISCOUNTED CASH FLOW). SCENARIO A1 - PRODUCTION in Thousand USD

Year	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003 Scrap
TOTAL CASH INFLOW	**86.1**	**171.8**	**337.2**	**470.9**	**647.3**	**682.8**	**766.8**	**866.8**	**940.0**	**971.6**	**451.4**
Sales	86.1	171.8	337.2	470.9	647.3	682.8	766.8	866.8	940.0	971.6	
Other Income											451.4
TOTAL CASH OUTFLOW	**112.1**	**207.4**	**471.4**	**673.5**	**608.4**	**630.1**	**701.4**	**800.3**	**859.3**	**870.8**	
Increase in Fixed Assets		40.0	117.0	217.0							
Increase in Working Capital	30.3	22.3	56.2	42.0	51.0	19.0	24.0	33.0	24.3	9.4	
Operational Costs inc. Sales	82.0	145.1	298.2	414.5	556.6	610.7	677.3	767.3	835.0	861.0	
Cost Finance											
Repayments											
Corporation Tax											
Dividends Paid											
SURPLUS (DEFICIT)	**-26.0**	**-35.6**	**-134.2**	**-202.6**	**38.9**	**52.7**	**65.4**	**66.5**	**80.7**	**100.8**	**451.4**
Cumulative Cash Balance	**-26.0**	**-61.6**	**-195.7**	**-398.3**	**-359.4**	**-306.7**	**-241.3**	**-174.8**	**-94.0**	**6.8**	**458.2**
Net Present Value (at 18%)	-22.1	-25.5	-81.7	-104.5	17.0	19.5	20.6	17.7	18.2	19.3	73.1
Cumulative NPV	-22.1	-47.6	-129.3	-233.8	-216.8	-197.3	-176.7	-159.0	-140.8	-131.6	-48.4
NPV (at 18%)	**-48.4**										
I.R.R.	**14.4**										

CASH FLOW (& DISCOUNTED CASH FLOW). SCENARIO A1 WITH SER ADJUSTMENT in Thousand USD

Year	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003 Scrap
TOTAL CASH INFLOW	**103.3**	**206.2**	**406.6**	**565.1**	**776.8**	**819.4**	**920.2**	**1040.2**	**1128.1**	**1165.9**	**536.5**
Sales	103.3	206.2	406.6	565.1	776.8	819.4	920.2	1040.2	1128.1	1165.9	
Other Income											536.5
TOTAL CASH OUTFLOW	**135.6**	**246.7**	**569.9**	**789.8**	**710.4**	**739.9**	**821.4**	**937.6**	**1005.2**	**1018.0**	
Increase in Fixed Assets		48.0	137.4	254.4							
Increase in Working Capital	36.0	26.3	81.2	50.2	61.7	23.1	28.7	39.4	29.0	11.2	
Operational Costs inc. Sales	99.6	172.4	351.3	485.2	648.7	716.8	792.7	898.6	976.2	1006.8	
Cost Finance											
Repayments											
Corporation Tax											
Dividends Paid											
SURPLUS (DEFICIT)	**-32.3**	**-40.5**	**-165.3**	**-224.7**	**66.4**	**79.5**	**98.8**	**102.6**	**122.9**	**147.9**	**536.5**
Cumulative Cash Balance	**-32.3**	**-72.8**	**-238.1**	**-462.8**	**-396.4**	**-316.9**	**-218.1**	**-115.5**	**7.4**	**155.3**	**691.8**
Net Present Value (at 15%)	-28.1	-30.6	-108.8	-128.5	33.0	34.3	37.1	33.6	34.9	36.5	115.3
Cumulative NPV	-28.1	-58.7	-167.5	-296.0	-263.0	-228.7	-191.6	-158.0	-122.1	-86.6	28.7
NPV (at 15%)	**+28.7**										
I.R.R.	**17.7**										

TOTAL PRODUCTION COSTS. SCENARIO A2 in Thousand USD

Years	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002
Raw Materials	47.5	83.7	165.2	231.9	315.8	349.9	382.9	431.7	471.6	489.8
Additives	19.0	39.7	71.8	96.8	125.4	134.5	152.0	175.8	188.2	190.3
Utilities	0.7	1.0	1.9	2.5	3.3	3.8	4.5	5.3	5.9	6.0
Energy	0.4	0.8	1.8	2.5	3.6	4.2	4.8	5.4	6.0	6.1
Labour, Direct	1.4	2.9	6.3	9.5	13.4	14.6	16.3	17.3	19.4	20.1
Maintenance	0.2	0.2	0.4	0.7	0,9	1.0	1.2	1.3	1.5	1.5
Spares										
Factory Overheads	1.2	2.3	4.6	7.3	9.6	11.0	12.7	14.1	15.7	16.0
FACTORY COSTS	**70.3**	**121.7**	**252.1**	**351.1**	**472.1**	**519.0**	**574.3**	**650.9**	**708.2**	**729.8**
Admin. o/h	6.5	15.0	18.5	20.0	40.0	45.0	49.0	54.0	60.0	65.0
Indirect Sales Costs										
Direct Sales Costs	1.7	3.4	6.9	9.3	12.2	14.0	15.7	17.5	19.3	20.1
Depreciation - Equip.	38.5	38.5	41.2	48.0	60.5	60.5	60.5	60.5	60.5	60.5
Depreciation - Buildings	16.5	16.5	16.5	17.3	18.8	18.8	18.8	18.8	18.8	18.8
Financial Costs										
TOTAL PRODUCTION COSTS	**133.5**	**195.1**	**335.2**	**455.7**	**603.6**	**657.2**	**718.2**	**801.6**	**866.7**	**894.1**
% Foreign	77.8	77.6	82.0	81.6	82.1	81.9	81.8	82.2	82.0	81.8

NET WORKING CAPITAL. SCENARIO A2 in Thousand USD

Year			1993	1994	1995	1996	1997	1998	1999	2000	2001	2002
Coverage	mdc	coto										
Current Assets												
Accounts Recoverable	30	12	6.5	11.7	22.1	32.5	43.8	48.2	53.3	60.2	65.6	67.9
Inventory Material	90	4	16.6	28.6	59.3	82.1	110.3	121.1	133.7	151.9	165.0	170.0
Energy & Utilities	30	12	0.1	0.1	0.2	0.2	0.3	0.4	0.4	0.5	0.5	0.5
Spares	60	6										
Work in Progress	30	12	5.9	10.1	21.0	29.3	39.3	43.3	47.9	54.3.	59.0	60.8
Finished Products	30	12	6.4	11.4	22.6	31.8	42.7	47.0	51.9	58.7	64.0	66.2
TOTAL CURRENT ASSETS			**35.4**	**61.9**	**126.1**	**175.9**	**236.3**	**259.9**	**287.2**	**325.5**	**354.3**	**365.5**
Current Liabilities												
Accounts Payable	30	12	5.9	10.1	21.0	29.3	39.3	43.3	47.9	54.3	59.0	60.8
NET WORKING CAPITAL			**29.6**	**51.7**	**105.1**	**146.6**	**197.1**	**216.6**	**239.3**	**271.3**	**295.1**	**304.7**
Increase in Working Capital			**29.6**	**22.1**	**53.3**	**41.5**	**50.5**	**19.5**	**22.7**	**32.0**	**23.8**	**9.6**
% Foreign												

CASH FLOW (& DISCOUNTED CASH FLOW). SCENARIO A2 - PRODUCTION in Thousand USD

Year	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003 Scrap
TOTAL CASH INFLOW	**86.1**	**171.8**	**337.2**	**470.9**	**647.3**	**682.8**	**766.8**	**866.8**	**940.0**	**971.6**	**551.3**
Sales	86.1	171.8	337.2	470.9	647.3	682.8	766.8	866.8	940.0	971.6	
Other Income											551.3
TOTAL CASH OUTFLOW	**108.4**	**202.2**	**447.8**	**648.9**	**574.9**	**597.5**	**766.8**	**866.8**	**940.0**	**971.6**	
Increase in Fixed Assets		40.0	117.0	217.0							
Increase in Working Capital	29.6	22.1	53.3	41.5	50.5	19.5	22.7	32.0	23.8	9.6	
Operational Costs inc. Sales	78.5	140.1	277.5	390.4	524.4	578.0	639.1	722.4	787.5	814.9	
Cost Finance											
Repayments											
Corporation Tax											
Dividends Paid											
SURPLUS (DEFICIT)	**-22.3**	**-30.4**	**-110.6**	**-178.0**	**72.4**	**85.3**	**105.1**	**112.5**	**128.7**	**147.1**	**551.3**
Cumulative Cash Balance	**-22.3**	**-52.7**	**-163.4**	**-341.4**	**-269.0**	**-183.7**	**-72.6**	**33.8**	**162.5**	**309.6**	**860.9**
Net Present Value (at 18%)	-18.8	-21.8	-67.4	-91.9	31.6	31.5	33.0	29.9	29.0	28.1	87.5
Cumulative NPV	-18.8	-40.6	-108.0	-199.9	-168.3	-136.8	-103.8	-73.9	-44.9	-16.8	70.7
NPV (at 18%)	+70.7										
I.R.R.	25.1										

TOTAL PRODUCTION COSTS. SCENARIO A3 - PRODUCTION (SUMMARY) in Thousand USD

Years	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002
Raw Materials										
Additives										
Utilities										
Energy										
Labour, Direct										
Maintenance										
Spares										
Factory Overheads										
FACTORY COSTS	**70.3**	**121.7**	**252.1**	**351.1**	**472.1**	**519.0**	**574.3**	**650.9**	**708.2**	**729.8**
Admin. o/h	11.7	23.4	36.1	63.4	84.5	91.7	103.0	116.4	126.8	131.6
Indirect Sales Costs										
Direct Sales Costs										
Depreciation - total.	4.9	7.2	13.0	19.6	28.3	30.9	35.7	40.1	44.3	45.8
Depreciation - Buildings										
Financial Costs										
TOTAL PRODUCTION COSTS	**86.8**	**152.3**	**301.2**	**434.1**	**584.9**	641.6	713.0	807.4	879.3	907.2
% Foreign										

TOTAL PRODUCTION COSTS. SCENARIO B1

in Thousand USD

Years	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002
Raw Materials	28.5	89.0	90.3	91.6	93.4	95.2	97.0	98.8	100.6	102.4
Additives	11.2	30.3	30.6	30.9	31.4	31.9	32.4	32.9	33.4	33.9
Utilities	0.4	1.7	1.7	1,8	1.8	1.8	1.9	1.9	1.9	1.9
Energy	0.2	0.8	0.8	0.8	0.8	0.8	0.9	0.9	0.9	0.9
Labour, Direct	1.1	1.7	1.7	1.8	1.8	1.8	1.9	1.9	1.9	1.9
Maintenance	0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Spares										
Factory Overheads	0.7	2.2	2.2	2.2	2.2	2.3	2.3	2.4	2.4	2.4
FACTORY COSTS	**42.2**	**125.9**	**127.5**	**129.2**	**131.6**	**134.1**	**136.6**	**139.0**	**141.3**	**143.6**
Admin. o/h	6.6	18.9	19.2	19.5	19.9	20.3	20.7	21.1	21.5	21.9
Indirect Sales Costs										
Direct Sales Costs	0.1	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.5
Depreciation - Equip.	3.1	4.7	8.7	10.7	10.8	10.9	13.0	13.1	13.2	13.3
Depreciation - Buildings	0.4	0.8	0.8	1.9	1.9	1.9	1.9	1.9	2.0	2.0
Financial Costs										
TOTAL PRODUCTION COSTS	**63.9**	**150.7**	**156.6**	**161.7**	**162.6**	**167.6**	**171.6**	**174.5**	**177.4**	**180.3**
% Foreign	80.6	81.7	80.8	81.4	81.9	81.3	81.6	81.6	81.2	81.6

NET WORKING CAPITAL. SCENARIO B1 in Thousand USD

Year			1993	1994	1995	1996	1997	1998	1999	2000	2001	2002
Coverage	mdc	coto										
Current Assets												
Accounts Recoverable	30	12	5.0	12.1	12.3	12.4	12.7	12.9	13.1	13.4	13.6	13.8
Inventory Material	90	4	9.9	29.8	30.2	30.6	31.2	31.8	32.4	32.9	33.5	34.1
Energy & Utilities	30	12	0.1	0.1	0.1	0.1	0.1	0/1	0.1	0.1	0.1	0.1
Spares	60%	6										
Work in Progress	30	12	3.5	10.5	10.6	10.8	11.0	11.2	11.4	11.6	11.8	12.0
Finished Products	30	12	4.1	12.1	12.2	12.4	12.6	12.9	13.1	13.3	13.6	13.8
TOTAL CURRENT ASSETS			**22.6**	**64.6**	**65.4**	**66.3**	**67.6**	**68.9**	**70.1**	**71.3**	**72.6**	**73.8**
Current Liabilities												
Accounts Payable	30	12	3.5	10.5	10.6	10.8	11.0	11.2	11.4	11.6	11.8	12.0
NET WORKING CAPITAL			**19.1**	**54.1**	**54.8**	**55.5**	**56.6**	**57.7**	**58.7**	**59.7**	**60.8**	**61.8**
Increase in Working Capital			**19.1**	**35.0**	**0.7**	**0.9**	**1.1**	**1.1**	**1.0**	**1.0**	**1.1**	**1.0**
% Foreign			87.4	88.2	88.1	88.1	88.1	88.1	88.1	88.1	88.1	88.1

CASH FLOW (& DISCOUNTED CASH FLOW). SCENARIO B1 - PRODUCTION

in Thousand USD

Year	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003 Scrap
TOTAL CASH INFLOW	**63.9**	**185.0**	**187.1**	**189.6**	**192.2**	**197.0**	**200.9**	**204.8**	**208.1**	**216.1**	**95.8**
Sales	63.9	185.0	187.1	189.6	192.2	197.0	200.9	204.8	208.1	216.1	
Other Income											95.8
TOTAL CASH OUTFLOW	**79.6**	**220.6**	**183.2**	**150.4**	**153.4**	**176.3**	**159.1**	**161.9**	**164.7**	**167.5**	
Increase in Fixed Assets		40.0	35.0			20.0					
Increase in Working Capital	19.1	35.0	0.7	0.9	1.1	1.1	1.0	1.0	1.1	1.0	
Operational Costs inc. Sales	60.5	145.6	147.5	149.5	152.3	155.2	158.1	150.9	163.6	166.5	
Cost Finance											
Repayments											
Corporation Tax											
Dividends Paid											
SURPLUS (DEFICIT)	**-15.7**	**-35.6**	**3.9**	**39.2**	**39.8**	**20.7**	**41.8**	**43.9**	**43.4**	**48.6**	**95.8**
Cumulative Cash Balance	**-15.7**	**-51.3**	**-47.4**	**-8.2**	**31.6**	**52.3**	**94.1**	**137.0**	**180.4**	**229.0**	**324.6**
Net Present Value (at 18%)	-13.3	-25.6	2.4	20.3	17.4	7.7	18.1	11.4	9.8	9.3	15.5
Cumulative NPV	-13.3	-38.9	-36.5	-16.3	1.1	8.8	21.9	33.3	43.1	52.4	67.9
NPV (at 18%)	**+67.9**										
I.R.R.	**45.6**										

CASH FLOW (& DISCOUNTED CASH FLOW). SCENARIO B1 - SER ADJUSTED in Thousand USD

Year	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003 Scrap
TOTAL CASH INFLOW	**63.9**	**185.0**	**187.1**	**189.6**	**193.2**	**197.0**	**200.9**	**204.8**	**208.1**	**216.1**	**111.3**
Sales	63.9	185.0	187.1	189.6	193.2	197.0	200..9	204.8	208.1	216.1	
Other Income											111.3
TOTAL CASH OUTFLOW	**78.1**	**259.7**	**212.4**	**174.8**	**179.9**	**205.0**	**184.8**	**188.2**	**191.5**	**194.6**	
Increase in Fixed Assets		48.0	39.0			24.0					
Increase in Working Capital	21.3	42.5	0.9	0.8	1.0	0.7	1.1	1.3	1.3	1.2	
Operational Costs inc. Sales	56.8	169.2	172.5	174.0	178.9	180.3	183.7	186.9	190.2	193.4	
Cost Finance											
Repayments											
Corporation Tax											
Dividends Paid											
SURPLUS (DEFICIT)	**-14.2**	**-74.7**	**-25.3**	**14.8**	**13.3**	**-8.0**	**16.1**	**16.6**	**16.6**	**21.5**	**111.3**
Cumulative Cash Balance	**-14.2**	**-88.9**	**-114.2**	**-99.4**	**-86.1**	**-94.1**	**-78.0**	**-61.4**	**-44.8**	**-23.3**	**88.0**
Net Present Value (at 15%)	-12.3	-56.5	-16.7	8.5	6.6	-3.5	6.0	5.4	4.7	5.3	27.5
Cumulative NPV	-12.3	-68.8	-85.5	-77.0	-70.4	-73.9	-67.9	-62.5	-57.8	-52.5	-25.0
NPV (at 15%)	**-25.0**										
I.R.R.	**8.8**										

TOTAL PRODUCTION COSTS. SCENARIO B2 in Thousand USD

Years	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002
Raw Materials	28.5	33.2	33.3	33.4	34.1	34.7	35.4	36.1	36.5	37.6
Additives	11.2	14.8	14.8	14.8	15.0	15.2	15.4	15.7	15.8	16.1
Utilities	0.4	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7
Energy	0.2	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Labour, Direct	1.1	1.1	1.1	1.1	1.2	1.2	1.2	1.2	1.2	1.3
Maintenance	0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Spares										
Factory Overheads	0.7	1.0	1.0	1.0	1.1	1.1	1.1	1.1	1.1	1.2
FACTORY COSTS	**42.1**	**51.3**	**51.4**	**51.6**	**52.5**	**53.3**	**54.4**	**55.3**	**55.8**	**57.3**
Admin. o/h	6.6	7.9	8.0	8.0	8.1	8.3	8.5	8.6	6.7	9.0
Indirect Sales Costs										
Direct Sales Costs	0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Depreciation - Equip.	3.1	3.5	3.5	3.5	3.5	3.6	3.7	3.8	3.8	4.0
Depreciation - Buildings	0.4	0.4	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.5
Financial Costs										
TOTAL PRODUCTION COSTS	**52.3**	**63.3**	**63.5**	**63.6**	**64.8**	**65.9**	**67.2**	**68.4**	**69.1**	**71.0**
% Foreign	80.7	80.4	80.2	80.3	80.3	80.6	80.2	80.1	80.1	80.0

NET WORKING CAPITAL. SCENARIO B2 in Thousand USD

Year			1993	1994	1995	1996	1997	1998	1999	2000	2001	2002
Coverage	mdc	coto										
Current Assets												
Accounts Recoverable	30	12	4.1	5.0	5.0	5.0	5.1	5.2	5.3	5.4	5.5	5.6
Inventory Material	90	4	9.9	12.0	12.0	12.1	12.3	12.5	12.8	12.9	13.1	13.4
Energy & Utilities	30	12	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Spares	60	6										
Work in Progress	30	12	3.5	4.3	4.3	4.3	4.4	4.4	4.5	4.6	4.7	4.8
Finished Products	30	12	4.1	4.9	4.8	5.0	5.1	5.1	5.2	5.3	5.4	5.5
TOTAL CURRENT ASSETS			**21.6**	**26.3**	**26.2**	**26.4**	**26.8**	**27.3**	**27.8**	**28.3**	**28.6**	**29.4**
Current Liabilities												
Accounts Payable	30	12	3.5	4.3	4.3	4.3	4.4	4.4	4.5	4.6	4.7	4.8
NET WORKING CAPITAL			**18.1**	**22.0**	**21.9**	**22.1**	**22.5**	**22.8**	**23.3**	**23.7**	**24.0**	**24.6**
Increase in Working Capital			**18.1**	**3.9**	**-0.1**	**0.2**	**0.4**	**0.8**	**0.5**	**0.4**	**0.3**	**0.6**
% Foreign			88.0	89.2	88.2	88.2	88.2	88.2	88.2	88.2	88.2	88.28

CASH FLOW (& DISCOUNTED CASH FLOW). SCENARIO B2 - PRODUCTION in Thousand USD

Year	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003 Scrap
TOTAL CASH INFLOW	**62.0**	**75.0**	**75.2**	**75.4**	**76.8**	**78.2**	**79.8**	**81.2**	**82.2**	**84.5**	**46.6**
Sales	62.0	75.0	75.2	75.4	76.8	78.2	79.8	81.2	82.2	84.5	
Other Income											46.6
TOTAL CASH OUTFLOW	**67.0**	**103.5**	**94.7**	**59.8**	**61.2**	**62.2**	**63.4**	**64.5**	**65.2**	**67.0**	
Increase in Fixed Assets		40.0	35.0								
Increase in Working Capital	18.1	3.9	0.1	0.0	0.4	0.4	0.4	0.4	0.4	0.4	
Operational Costs inc. Sales	48.9	59.6	59.6	59.7	60.8	61.8	63.0	64.1	64.8	66.5	
Cost Finance											
Repayments											
Corporation Tax											
Dividends Paid											
SURPLUS (DEFICIT)	**-5.1**	**-28.5**	**-19.5**	**15.7**	**15.6**	**16.0**	**16.8**	**16.7**	**17.0**	**18.0**	**46.6**
Cumulative Cash Balance	**-5.1**	**-33.6**	**-53.1**	**-37.4**	**-21.8**	**-5.8**	**11.0**	**27.7**	**44.7**	**62.7**	**109.3**
Net Present Value (at 18%)	-4.3	-20.5	-11.9	8.1	6.8	5.9	5.3	4.8	3.8	3.4	7.6
Cumulative NPV	-4.3	-24.8	-36.6	-28.6	-21.7	-15.8	-10.5	-5.8	-1.9	1.5	9.1
NPV (at 18%)	**+9.1**										
I.R.R.		**23.8**									

TOTAL PRODUCTION COSTS. SCENARIO C1

in Thousand USD

Years	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002
Raw Materials	31.0	63.5	137.9	195.5	268.4	300.0	322.5	363.4	395.5	408.9
Additives	19.0	20.7	71.8	96.8	125.4	134.5	152.0	175.8	188.2	190.3
Utilities	0.7	1.0	1.9	2.5	3.3	3.8	4.5	5.3	5.9	6.0
Energy	0.4	0.8	1.8	2.5	3.6	4.2	4.8	5.4	6.0	6.1
Labour, Direct	1.4	2.9	6.3	9.5	12.4	14.6	16.3	17.3	19.4	20.1
Maintenance	0.2	0.2	0.4	0.7	0.9	1.0	1.2	1.3	1.5	1.5
Spares										
Factory Overheads	1.2	2.3	4.6	7.3	9.6	11.0	12.7	14.1	15.7	16.0
FACTORY COSTS	**53.8**	**101.5**	**224.8**	**314.7**	**424.7**	**468.7**	**513.9**	**582.6**	**632.1**	**648.9**
Admin. o/h	7.3	16.6	34.7	48.2	64.2	69.8	78.0	88.5	95.8	99.1
Indirect Sales Costs										
Direct Sales Costs	1.7	3.4	6.9	9.3	12.8	14.0	15.7	17.5	19.3	20.1
Depreciation - Equip.	57.8	57.8	61.8	72.0	90.7	90.7	90.7	90.7	90.7	90.7
Depreciation - Buildings	22.0	22.0	23.0	23.0	25.0	25.0	25.0	25.0	25.0	25.0
Financial Costs										
TOTAL PRODUCTION COSTS	**142.5**	**201.3**	**350.3**	**467.2**	**617.4**	**668.2**	**723.3**	**804.3**	**862.8**	**883.8**
% Foreign	57.8	47.8	41.5	39.4	38.2	36.9	36.7	37.5	35.4	34.8

NET WORKING CAPITAL. SCENARIO C1 in Thousand USD

Year			1993	1994	1995	1996	1997	1998	1999	2000	2001	2002
Coverage	mdc	coto										
Current Assets												
Accounts Recoverable	30	12	5.2	10.1	22.2	31.0	41.8	46.0	50.6	57.4	62.3	64.0
Inventory Material	90	4	16.6	28.6	59.3	82.1	110.3	121.1	133.7	151.9	165.0	170.0
Energy & Utilities	30	12	0.1	0.1	0.2	0.2	0.2	0.3	0.4	0.4	0.5	0.5
Spares	60	6										
Work in Progress	30	12	4.5	8.5	18.7	26.2	35.4	39.1	42.8	48.6	52.7	54.1
Finished Products	30	12	5.1	9.8	21.6	30.2	40.7	44.9	49.3	55.9	60.7	62.3
TOTAL CURRENT ASSETS			**31.5**	**57.1**	**122.0**	**169.8**	**228.5**	**251.4**	**276.9**	**314.2**	**341.0**	**350.9**
Current Liabilities												
Accounts Payable	30	12	4.5	6.5	18.7	25.2	35.4	39.1	42.8	48.6	52.7	54.1
NET WORKING CAPITAL			**27.0**	**48.6**	**103.2**	**143.6**	**193.2**	**212.4**	**234.1**	**265.6**	**288.4**	**296.9**
Increase in Working Capital			**27.0**	**21.7**	**54.6**	**40.3**	**49.6**	**19.2**	**21.7**	**31.6**	**22.7**	**8.5**
% Foreign			33.3	29.8	30.7	30.4	29.3	28.5	29.4	30.0	29.6	29.1

CASH FLOW (& DISCOUNTED CASH FLOW). SCENARIO C1 - PRODUCTION in Thousand USD

Year	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003 Scrap
TOTAL CASH INFLOW	**86.1**	**171.8**	**337.2**	**470.9**	**647.3**	**682.8**	**766.8**	**866.8**	**940.0**	**971.6**	**436.3**
Sales	86.1	171.8	337.2	470.9	647.3	682.8	766.8	866.8	940.0	971.6	
Other Income											436.3
TOTAL CASH OUTFLOW	**91.4**	**186.6**	**444.9**	**638.9**	**564.1**	**585.7**	**644.9**	**737.6**	**789.2**	**796.7**	
Increase in Fixed Assets		40.0	117.0	217.0							
Increase in Working Capital	27.0	21.7	54.6	40.3	49.6	19.2	21.7	31.6	22.7	8.5	
Operational Costs inc. Sales	64.5	125.0	273.3	381.5	514.5	566.5	623.3	706.1	766.4	788.2	
Cost Finance											
Repayments											
Corporation Tax											
Dividends Paid											
SURPLUS (DEFICIT)	**-5.3**	**-14.8**	**107.7**	**168.0**	**83.2**	**97.1**	**121.8**	**129.2**	**150.9**	**174.9**	**436.3**
Cumulative Cash Balance	**-5.3**	**-20.2**	**-127.9**	**-295.9**	**-212.6**	**-115.5**	**6.3**	**135.5**	**286.3**	**461.2**	**897.5**
Net Present Value (at 18%)	-4.5	-10.7	-65.6	-44.7	36.4	35.9	38.3	34.4	33.9	33.4	70.7
Cumulative NPV	-4.5	-15.2	-80.7	-125.5	-89.1	-53.2	-14.9	19.4	53.4	86.8	157.5
NPV (at 18%)	**+157.5**										
I.R.R.	**31.9**										

CASH FLOW (& DISCOUNTED CASH FLOW). SCENARIO C1 - WITH SER ADJUSTMENT in Thousand USD

Year	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003 Scrap
TOTAL CASH INFLOW	**90.5**	**164.0**	**361.4**	**515.6**	**715.0**	**751.0**	**845.2**	**964.4**	**1046.0**	**1082.0**	**388.2**
Sales	90.5	164.0	361.4	515.6	715.0	751.0	845.2	964.4	1046.0	1082.0	
Other Income											388.2
TOTAL CASH OUTFLOW	**109.4**	**213.3**	**483.2**	**698.5**	**588.6**	**617.0**	**678.3**	**739.1**	**827.2**	**836.0**	
Increase in Fixed Assets		48.0	137.4	264.4							
Increase in Working Capital	21.0	16.1	43.5	30.4	37.1	13.8	16.6	22.0	19.0	6.6	
Operational Costs inc. Sales	88.4	149.2	302.3	413.7	551.5	603.2	661.7	717.1	808.2	839.4	
Cost Finance											
Repayments											
Corporation Tax											
Dividends Paid											
SURPLUS (DEFICIT)	**-18.9**	**-49.3**	**-121.8**	**-125.8**	**126.4**	**134.0**	**166.9**	**225.3**	**237.8**	**246.7**	**388.2**
Cumulative Cash Balance	**-18.9**	**-68.2**	**-190.0**	**-315.8**	**-189.4**	**-55.4**	**111.3**	**336.8**	**574.6**	**820.8**	**1209.0**
Net Present Value (at 15%)	-16.4	-37.3	-80.1	-71.9	62.8	57.9	62.7	73.7	67.6	60.8	83.4
Cumulative NPV	-16.4	-53.7	-133.8	-205.7	-142.9	-85.0	-23.3	51.4	119.0	179.8	263.2
NPV (at 15%)	**+263.2**										
I.R.R.	**36.2**										

TOTAL PRODUCTION COSTS. SCENARIO C2 - PRODUCTION - SUMMARISED

in Thousand USD

Years	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002
Raw Materials										
Additives										
Utilities										
Energy										
Labour, Direct										
Maintenance										
Spares										
Factory Overheads										
FACTORY COSTS	**53.8**	**101.4**	**224.8**	**314.7**	**424.6**	**468.7**	**507.0**	**582.6**	**632.2**	**648.9**
Admin. o/h	9.0	20.0	41.8	57.5	78.0	84.2	93.7	104.0	115.1	119.2
Indirect Sales Costs										
Direct Sales Costs										
Depreciation - total	4.9	7.2	13.0	19.6	28.3	30.9	35.7	40.1	44.3	45.8
Depreciation - Buildings										
Financial Costs										
TOTAL PRODUCTION COSTS	**67.1**	**128.6**	**279.5**	**391.8**	**530.9**	**583.8**	**636.4**	**728.7**	**791.6**	**813.9**
% Foreign										

Appendix (Ref. Section 8.1) INDIVIDUAL PRODUCT PRODUCTION COSTS

	EE	MES	EB	TP	TE	METH	DAN	NE	MED	SP
Raw material	827.4	910.5	743.3	225.7	232.2	909.7	525.7	1119.3	1039.8	281.4
Additives	374.4	429.2	198.8	92.7	185.7	290.1	82.9	447.4	150.0	50.0
Fuel & utilities	9.2	10.5	14.3	21.0	21.6	20.0	20.0	20.0	20.0	20.0
Labour, direct	33.7	30.4	30.9	2.2	3.1	5.8	12.5	38.0	15.8	19.8
Maintenance	3.4	5.0	4.0	0.2	0.7	0.4	1.2	3.7	0.2	1.1
Spares	-	-	-	-	-	-	-	-	-	-
Factory overheads	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0
FACTORY COSTS	**1264.1**	**1401.6**	**1002.2**	**357.8**	**459.3**	**1242.0**	**658.3**	**1644.4**	**1241.8**	**388.3**
Administration overheads	187.2	207.6	177.2	51.4	66.6	184.3	100.8	244.0	184.3	55.9
Indirect costs sales	-	-	-	-	-	-	-	-	-	-
:Direct sales costs	3.5	3.5	3.0	1.2	1.2	3.5	3.5	3.5	3.5	1.2
Depreciation	94.9	137.1	111.8	8.1	20.2	15.0	36.2	104.8	8.3	37.3
TOTAL PRODUCTION COSTS	**1549.7**	**1749.8**	**1301.2**	**418.5**	**543.3**	**1444.8**	**835.8**	**1996.7**	**1437.9**	**482.0**

EE = ethinyl estradiol
EB = estradiol
TE = testosterone enanthate
DAN = danzol
MED = medroxyprogesterone acetate
MES = mestranol
TP = testostorone propionate
METH = methandienone
NE = norethisterone
SP = spironolactone

Annex 1

UNIDO comments on expert's mission report

The performed study underlines the feasibility of establishing the production of steroids active principles in Cuba, having into consideration the availability of raw materials (sugar cane oil), in quantities even higher than those needed. Identification of potential foreign partners and establishment of partnership agreements for foreign markets is compulsory as the internal market is not enough to ensure the optimal scale of production and satisfactory economic indicators. Having the quality of the produced sugar cane oil standardized, the product could be considered as the optimal source for industrial production of steroids in Cuba.

By producing Androstenedione (AD), the national pharmaceutical industry is opening the doors to enter into international market for testosterone and spironolactone among others, while having the availability of androstadienedione (ADD), possibility for penetrating the market of estradiol esters are opened.

For economically sound production of AD and ADD, it is compulsory to perform the isolation and purification of phytosterols from sugar cane oil on efficient basis and to be able to utilize updated technologies for the performance of fermentation process.

Through the introduction of the manufacture of the indicated products in local conditions, the production of oral contraceptives tablets in the plant which is presently under construction will be benefitted as the necessary active principles will be available in required quantities.

Once the oral contraceptives plant will be in operation

following the G.M.P. regulations, it could be possible to start the marketing promotion of locally produced steroids.

In order to achieve the desired results on the production of steriods, special attention has to be given to the establishment of some kind of agreement with international producers and/or researchers for the development of industrial fermentation of phytosterols utilizing locally available raw materials with the final objective to produce and commercialize AD and ADD.

Considering the toxicity of some of the products, special attention has to be given to the application of Good Manufacturing Practices and Good Laboratory Practices, as well as to the protection of personnel and environment. For the above, it is recommended to organize some training programmes for the personnel involved in the activities. Development of modern techniques for their application in the treatment of industrial effluents have to be carried out simultaneously. Considering the impact of the new technological development that Cuban economy might have, it is advisable to continue the support to the development of the steroids programme in Cuba.