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HIGH LEVEL CONSULTANCIES AND TRAINING

DP/SYR/86/009

SYRIAN ARAB REPUBLIC

Technical report: Pharmaceutical production in Syria*

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

Based on the work of J. T. Brown, expert in pharmaceutical industry

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* The views expressed in this paper are those of the author and do not necessarily reflect the views of the Secretariat of UNIDO. Mention of company names and commercial products does not imply the endorsement of UNIDO. This document has not been edited.

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ACKNOWLEDGEMENTS

The writer wishes to acknowledge with thanks the co-operation of Mr. M. Koudsi, the General Manager of THAMECO; especial thanks for co-operation and friendship are due to Mr. R. Chamaa, Technical Manager of THAMECO who provided a vast amount of information on the Company.

Finally, thanks for the administrative support and interest in the Project provided by the Resident Representative and staff of UNDP Damascus.

EXPLANATORY NOTES

1. THAMECO: The Arabian Medical Co., Box 976 Damascus, Syria.
2. Compatible products: product lines which may be handled in close proximity to each other bearing in mind the constraints of G.M.P.
3. Non-compatible products: the reverse of the above with special reference to dusty products (e.g. tablets) and clean products (e.g. injectables).
4. Class 1000: less than 1000 particles of size greater than 1/10 micron per cubic meter of air.
5. A.S.A: Acetylsalicylic Acid.
6. F.S.A.: free Salicylic Acid.
7. Exchange rate April 1989: Syrian Pounds 20 = US $1.00.
8. S.O.P.: Standard Operating Procedure.

ABSTRACT

Pharmaceutical production in Syria - DP/SYR/86/009/11-08.

Initial month of a 4 months split mission. Appraisal of existing facilities for the production of pharmaceutical dosage forms, review of projected expansion.

Existing facilities fully utilized, some non-compatible products consequently cohesive GMP not possible.

Requirements for new product types, no experience of technologies involved. Demand for expansion of output from 30% to 60% of National requirement for medicines.

New factory building nearing completion; recommendation for consolidation of compatible product types between the two units, minimum duplication to conserve Foreign Exchange, economies of scale, greater professionalism by specialization. Urgent need to nominate technical development chief with back-up engineering to expedite planning and equipment procurement for expansion of output at old plant and earliest on-stream date for new plant. On-going UNIDO assistance through Technical Assistance and Fellowships for some years to come.

INTRODUCTION

The following report relates to the first month of a 4 months split mission Project No. DP/SYR/86/009/11-08 Pharmaceutical Production in Syria.

The mission commenced 31 March 1989 and terminated 30 April 1989. Field work was mainly in Damascus, with a brief visit to a new facility under construction in Allepo.

The terms of the job description were:

a) to visit the pharmaceutical plants
b) identify product types
c) assessment of technologies employed
d) evaluation of equipment for production and QC
e) assess conformity with GMP
f) identify major bottlenecks
g) assess preventive maintenance programmes
h) report with specific reference to activities to be undertaken during the second phase of the mission

In addition, a general overview of pharmaceutical manufacture in Syria was called for. The authorities in Syria were extremely co-operative and within the limits of available time, all requirements of the job description were accomplished.

RECOMMENDATIONS

There are many recommendations in the body of the Report which deal with specific technical/mechanical problems experienced by operational departments in THAMECO. It is felt to be unnecessary to burden the major recommendations with these specifics. What follows, therefore, confined to major matters.

1) THAMECO must urgently appoint a Development Director with appropriate supporting staff, to organize the early start-up of the Allepo factory and to rationalize the product mix between Damascus and Allepo factories. Technical assistance is necessary.

2) THAMECO should prepare the designated rooms, as detailed in the text, so as to install the THIMON vial handling line in Damascus. The line should be validated, commissioned and used pending a decision on relocation to a more appropriate site. Standards for clean rooms must be developed. Technical assistance is necessary.

3) To provide greater storage capacity in Damascus, pallet handling equipment and racking should be provided.

4) In the interest of GMP, a Central Weighing Department should be introduced as specified.

5) In the interest of GMP, THAMECO's management style should be developed to include Key Executives. Initially a Production Controller and a Quality Controller should be appointed, with written, unambiguous job descriptions. Technical assistance is necessary.

6) Dust control equipment should be constructed and installed as specified to improve the working conditions in the Tablet Department. Technical Assistance is necessary.

7) In the complex technologies relevant to modern pharmaceutical industry THAMECO requires a new "window" through which to establish relationships and linkages to the world-wide industry. Technical assistance, study tours and fellowships are necessary. A number of UNIDO fellowships and a study tour have been detailed. THAMECO should request earliest implementation.

8) Background data should be developed to justify product Expiry Dates, as detailed in the text. Technical assistance is necessary.

9) THAMECO should review its raw water treatment facilities with the aim of providing flocculation and sedimentation stations, as specified. Technical assistance is necessary.

10) In view of the potential benefits to THAMECO of an extended relationship with UNIDO, alternative funding should be sought so as to enable direct contact between UNIDO and THAMECO. The mechanism of this should be identified by UNDP/UNIDO and advised to THAMECO for urgent implementation.

11) Before the commencement of the second phase of this project, certain activities in vial handling and dust extraction must be completed by THAMECO. It is reasonable to suggest that these should be accomplished by late July 1989; it is therefore, recommended that the second phase of 3 months should commence August or September 1989.

12) In the event that THAMECO should request the services of a QC expert for 1 month of the second phase, it is imperative that the proposed Fellowship for an analyst be completed before the expert is fielded.

13) To enable THAMECO to maximize its purchasing potential for Raw and Packing materials, some flexibility should be introduced into its tendering system.

1. BACKGROUND TO THAMECO

There are two active pharmaceutical formulation factories in Syria, located close to Damascus. Of these, THAMECO is operated by the Ministry of Industry; it is the subject of the following report.

The military operates the second factory DIMAS; its products are not so widely available to the general public as are the products of THAMECO.

The Ministry of Industry has commissioned a new factory at Allepo, some 400 km. North of Damascus. Buildings are nearing completion, equipment was planned to be purchased by way of a loan from the Government of France. Special terms are attached to the loan, so whilst THAMECO has received bids for equipment for Allepo no orders have actually been placed. Negotiations on the terms of the loan continue; however, the quotes received by THAMECO for equipment are probably no longer valid. It has been estimated that the cost of equipping Allepo factory as originally planned will be US $ 8 millions. A more detailed account of the Allepo unit is provided in Chapter 5.

THAMECO commenced operations as a very small unit in 1960. Its performance and potential were noted and upgrading of the original operation commenced in 1985. In addition to its own product range, THAMECO handled products, under licence agreements, of foreign principals. These agreements were terminated in 1987. Concurrently THAMECO was instructed to rationalize its product range (currently about 120 products) and to increase its output, so that, together with DIMAS output, some 60% of the Syrian demand for medicines would be provided.

Prices of medicines in Syria are strictly controlled; scheduled drugs and antibiotics are available only with a Doctor's prescription. This, together with shortages of medicines and higher prices in neighbouring countries has resulted in significant unofficial "export" of pharmaceuticals from Syria; consequently no reliable data exists regarding the real requirement of pharmaceuticals by Syria.

Currently the Company's product range includes:

- tablets, plain and coated
- capsules
- formulated infant foods
- suppositories
- ointments, topical/eye
- liquids
- injectable
- oral rehydration salts (UNICEF)
- antibiotic powders for reconstitution

Brief details of the technology employed is provided later in this report. THAMECO works a two shift system and employs in excess of 900 staff including: 27 pharmacists, 20 chemists and 15 engineers. Provision is made on the site for supervision of young children of female workers.

The factory buildings are located in a secure compound some 15 km. from Central Damascus. Staff is transported by contract buses and a number of cars for executives.

The buildings reflect their age but have been well maintained. Floors throughout are of locally produced Terrazzo tiles. Walls are masonry, generally finished with gloss enamel paint but with glazed ceramic tiles in certain critical areas. The wall/floor junctions are not coved. Ceilings are generally the original acoustic tiles, many of which are damaged and which do not conform to standards of GMP. In certain recently repaired areas non-absorbent metal ceilings have been installed. In the interest of GMP these ceilings should be installed throughout all manufacturing areas.

The factory water supply is from its own wells. The water is passed through a sand filter, pumped into a water tower and chlorinated.

Steam is not widely used and where it is required for a specific operation it is raised by small electrically heated steam generators.

Electricity is taken from the national grid system but significant stand-by generating plant is available as required.

Stores are small and cramped, pallet racking is not generally used. The inprocess store is vastly overloaded.

2. TECHNOLOGY EMPLOYED

Each department in THAMECO was visited briefly. The operations are outlined below, together with specific observations and recommendations which may improve output or GMP.

2.1. Tablet Making

Capacity of the department is 330 million tablets per year (based upon 240 working days).

Conventional tablet making technology is employed for wet granulation and direct compression (DC) formulations.

Blending is performed in a variety of Vee blenders, Manesty fluid bed equipment and Z blade machines.

Blending capacity is one bottleneck in the tablet making.

Direct compression is dependant on the use of DC raw materials. Heavy duty slugging machines are not employed.

Compression is performed on a number of old but well maintained presses by Killian, Horn and Manesty. The major unit however, is an almost new Fette 2000 press.

Film coating is applied to one product only, in pilot scale quantities. For additional information refer "Research Department" (2.15).

Tablet packing into strip and blister packs is also a bottleneck.

Observations and Recommendations

2.1.1. Formulations and stability problems have been experienced in respect of chewable ASA tablets. Unacceptable levels of FSA have been recorded. The probable reasons for this are:

- hydrolysis of ASA by high levels of water in the locally produced Ethanol used to dissolve the colour (tartrazine) used in the tablets.
- extended storage prior to packing.

It is not possible to reverse this hydrolysis; any batches which fail to comply with the pharmacopoeial standard for FSA must be discarded. Where moisture-sensitive materials are to be processed, direct compression or slugging is the preferred method. If solvents need to be used they must be anhydrous; isopropanol is the preferred solvent. When moisture-sensitive materials are to be stored for extended periods before packing, each bulk container should be protected by provision of approximately 1 kg. of dry silica gel packed in a cotton bag.

In order to process moisture-sensitive materials in non-air-conditioned rooms, it was suggested to THAMECO that a simple metal frame be constructed around the machine.

The frame is covered with heavy plastic sheet and the enclosed environment can then be maintained at low humidity by means of a small dehumidifier.

Should THAMECO wish to control the humidity in the Fette room, this may be done by the installation of 2 dehumidifiers each having capacity of 1.5 - 2 l. per hour.

2.1.2. THAMECO is experiencing problems of tablets capping and picking during compression. These problems are due to the poor condition of the faces of tablet-press tools. The problems will be reduced

and press-tools will have greater life if the faces are polished after use. A Manesty Punch Polishing Machine, specifically intended for this purpose had been partly installed but was not being used. The installation must be completed. The use of the Punch Polishing machine was demonstrated to THAMECO staff. It is necessary for the following items to be purchased from Manesty Machines Ltd:

- 2x burr holding chucks for the polishing unit
- 1 pack diamond polishing paste - coarse
- 1 pack diamond polishing paste - fine

2.1.3. The general standard of housekeeping in the tablet department was badly affected by inadequate dust collection facilities. Each tablet press is provided with appropriate dust collectors but the areas of mixing and granulating were provided with a system which was seen to be not working. The cause of the trouble was found to be the extractor unit, which had been correctly installed but was of poor design and had never been effective, hence it had been disconnected. It was explained to THAMECO staff that the blower unit had been installed down-stream of the filters, hence after the pressure drop across the filters there was insufficient suction at the dust collection points to have any beneficial effect.

The question of dust extraction was discussed at some length; subsequently THAMECO was provided with a basic design for a suitable unit and some initial calculations on airflow. It was not possible for the writer to discuss the proposed equipment with an independent engineer during the time at THAMECO, however it is strongly recommended that the equipment/calculations be discussed with an engineer and the equipment be fabricated in Syria as a matter of urgency.

Layout drawings and calculations are appended.

See Appendix 1: "Elevation of proposed dust collector"
2: "Plan of proposed dust collector"
3: "Initial calculations for proposed dust collector"

2.1.4. THAMECO is experiencing problems related to producing an homogeneous tablet granule particularly where small doses of active ingredients are involved. It was suggested that this may be overcome by the use of standard (or Lactose) granules. These are an inert granulation of Lactose and Starch with whatever granulating agent is preferred - normally Acacia powder is used. The material is wet granulated and dried in the conventional manner and stored until required for use, at which time the active ingredients and lubricants are incorporated. Selection of the relative quantities of Starch and Lactose is made according to the characteristics of hardness and disintegration - time required for the finished tablet. If a hard tablet with rapid disintegration is required, incorporation of Explotab (FMC) is recommended

2.1.5. Problems of tablet capping and flashing are being experienced. A production batch of Novalgin tablets was inspected at the wet-granule stage. It was found to contain a high proportion of ungranulated powder which had not been incorporated by the blender into the granule mass. It is not possible to compress powder - capping and flashing are the result. Increased blending time and/or 10% more granulating solution would help to resolve the problems of flashing and capping.

2.1.6. The technique to slugging is not sufficiently employed by THAMECO in its direct compression (DC) formulations. Whilst this omission may be acceptable when using raw materials specifically intended for DC (e.g. Asagran-Monsanto) it will be found to be troublesome when attempting to compress non-DC material. It is suggested that to overcome these problems THAMECO should install a slugging station i.e. a heavy duty press Manesty D3 or equivalent, fitted with large diameter flat faced tools. Generally, one pass through this machine followed by milling through a 16-20 mesh screen will produce a granule which will make a satisfactory tablet. Particularly difficult materials may require a second pass through the slugging machine; i.e. slug, granulate, slug, granulate, final compression.

2.1.7. If it desired to incorporate dry colour or flavour into a DC tablet, dry dispersible materials are available from Bush, Boake, Allen.

2.1.8. Isolation of tablet presses does not meet appropriate standards of GMP. With the exception of the Fette press which is in its own room, all other presses should be mounted on steel pallets to permit

them to be removed at the completion of a batch, by a small pallet truck. The presses should be moved to a service area where a steam lance should be employed to remove every trace of previous product; subsequently the machine should be serviced, lubricated, covered and placed in an appropriate store until

next required. A sketch for an appropriate pallet is provided in Appendix 4: "Steel Pallet for tablet presses".

Prior to reutilization, the empty press room should be completely washed down; any grease stains in the floor should be removed by steam lance.

2.1.9. The use of cotton mops for floor cleaning does not comply with hygienic standards of GMP. Being organic material, the cotton will support the growth of micro-organisms which will be distributed when the mop is next used to swab the floor. Cotton mops must be replaced with rubber squeegee style cleaners.

2.1.10. In-process control at the tablet pressing station must include both tablet weight and hardness. Balances are available at THAMECO for the former purpose but each press room should also be provided with a Monsanto Hardness Tester. Press operators should monitor weight and hardness every 30 minutes and report any deviation from specification.

2.1.11. The domestic style humidity meters currently installed in the tablet making and several other departments fail to provide an overall measure of RH throughout the department. It is recommended that use of a sling psychrometer will provide an accurate reading of RH at any point in a department.

2.2. Infant Food Department

This department was established as a turn-key installation for THAMECO by the Nestle Co. in 1979 to manufacture Cerelac.

Capacity is 8000 cans filled per shift and milk drying rate of 480 kg/hour.

It is a complex, self contained unit, having its own grain storage silos, steam and electricity generating sets, laboratories and machine shop.

Since the facility is now fully owned by THAMECO the products have been renamed THAMELAC (wheat based) and THAMERICE (rice based) respectively. The products are packed in cans or sachets. Whole grain wheat or rice and whole milk are the starting points. Cans are formed on site from imported printed tin-plate.

The original installation was contracted to the Schule company of West-Germany, equipment was procured from Optima, Rovema, Rieck and Melzian, Rolls Royce and others.

A resident engineer was provided by the Nestle Co. to supervise the operation; this is now entirely the responsibility of THAMECO staff.

The plant was seen to be fully operational; standards of QC have been maintained at a high level. However, as previously stated, this is a complex and expensive installation which would benefit from the appraisal of an engineer or chemist with hands-on experience of this type of operation.

Observation and Recommendations

2.2.1. THAMECO has experienced problems of rancidity in its infant foods. The writer suggested that some trials be made in which the air in the final pack is replaced by dry Nitrogen.

2.2.2. In view of the climatic conditions in Syria, it is also recommended that THAMECO should develop some product ageing data in a long term trial in which samples are stored at climatic extremes; monthly testing of chemical and physical condition will enable an extrapolated Expiry Date to be calculated. This date would subsequently be confirmed by analysis.

2.2.3. Assistance is required by THAMECO in sample-taking and Amino Acid analysis for the products.

A UNIDO fellowship has been proposed. Refer Appendix 17: "Suggested Fellowships No.2".

Should an on-going project be realized, technical assistance in plant operation and maintenance would be recommended.

2.3. Capsule Making Department

Capacity is 150 million filled capsules per year, packing is a bottleneck. THAMECO employs conventional equipment in this operation. Blending is performed in either an Alexanderwork (Herman Benseler) 100 kg. blender or in one of two Condor 240 kg. planetary blenders. Capsule filling takes place on Bosch machines, each has its own dust collection facilities.

Capsule polishing completes the operation. Risk of product cross-contamination is prevented by having a specific polishing blanket for each product type. Size 0.00 and 1 capsule bodies are handled; supplies are from R.P. Scherer, Elanco or Capsule Gel.

In-process QC consists of weighing a sample of filled capsules every 30 minutes.

The rooms are not humidity controlled but this seems to cause no problems.

Observations and Recommendations

2.3.1. Acoustic ceiling tiles are not appropriate for use in dusty areas; they should be replaced by non-porous sheet metal ceilings.

2.3.2. Blending stations should be segregated by a partition wall at least 2 m. in height to prevent cross-contamination between batches.

2.3.3. Dust extraction should be provided for blenders.

2.3.4. Filling machines should be screened as above.

2.4. Eye-drop manufacture

Capacity of filling line is 3000 bottles/hour. Capacity of solution preparation is 150 l. in a Chematec vessel.

2.4.1. To comply with GMP, eye drops should be produced either in clean conditions and terminally sterilized by steam; or produced in aseptic conditions. Neither requirement is being attained by the THAMECO process. It is recommended that eye drop manufacture should be removed from the general manufacturing area at THAMECO; it should be incorporated into a completely segregated clean area in which a range of mutually compatible products is handled to the absolute exclusion of non-compatible product types.

2.5. Oral Rehydration Salts

A standard UNICEF system is employed. It is confined to a single room which is not air-conditioned. It would be appropriate to provide some humidity control at the mixing and filling stations.

2.6. Suppositories

Capacity is 90000 units per day from 2 lines. This is a very small operation comprising a mass melting/blending station followed by a filling station where the fluid mass is injected into pre-formed plastic molds imported in rolls. After filling, the molds are chopped into strips of 5 or 6 suppositories and packed in cartons.

A suggestion was made for in-process control of fill-weights; a sketch of appropriate equipment is provided. See Appendix 5: "Suggested Method for i/p-control Suppository Filling Weight".

2.7. Ointments

This is a small section with excess capacity. It comprises an electrically heated steam generator heating two jacketed mixing vessels. A pump transfers the fluid ointment to a Celix filling machine which fills imported metal tubes; Batch No. and Exp. Date are embossed on the tube closure.

Observations and Recommendations

2.7.1. THAMECO is concerned about the losses which occur by pumping fluid ointment approximately 6 m. through 37 mm. plastic pipe. Two possible remedies were suggested:

a) Relocate the mixing vessels on a raised mezzanine as close as possible to the filling machine.
b) As the transfer of ointment from the jacketed mixing vessels nears completion, apply a small positive pressure of air in the mixing vessel. This will empty the vessel and force the residual ointment from both the transfer pump and the pipework.

2.7.2. The writer provided THAMECO with a suggestion for the construction of a simple steam heated immersion coil for melting bulk petrolatum in 200 kg. barrels.

2.8. Suspension Syrups

Capacity is 4.8 million x 100 ml. bottles per year. The syrups are produced in 6001 s.s. vessels; filled and capped on an automatic line.

Observations and Recommendations

2.8.1. THAMECO had experienced the problem of the preservative, Sorbic Acid, coming out of solution in a batch of Vitamin B-Complex syrup which had been exposed to near freezing conditions for an extended period. The writer suggested that re-solution would be achieved by placing samples of the affected product in an incubator at 37 C for several days. This was effective and it was suggested that the entire batch could be made fit for sale by allowing it to stand in the sun for several days. In view of this un-orthodox procedure it is recommended that THAMECO should retain a "keeping sample" and submit it to frequent QC checks as its Expiry Date approaches.

2.8.2. THAMECO must establish ageing data for its syrups by the method of climatic extremes cycling mentioned elsewhere in this report.

2.8.3. The syrups labels should be amended to contain the following phrases. "Store between 5-20 C". "Do not freeze".

2.9. Dry Syrups

THAMECO produces a dry, antibiotic powder for reconstitution with waster for oral administration, Batch size is 40 kg. or 100 kg. depending on the mixer used. Filling is by auger filler which gives some problems in the auger funnel,resulting in unacceptable weight variations in the finished pack. THAMECO is considering the possibilities of replacing the existing auger filler with a more appropriate unit.

2.10. Vial Filling

A most critical component of the medicine demand in Syria is for sterile antibiotics packed in rubber closed vials for use by injection.

Such is the urgency for the product range to be introduced that the major topic of discussion during the mission was the installation of an automatic line; as this is an area of utmost importance to THAMECO a fairly detailed account is provided below.

THAMECO had no previous experience of handling sterile powders for injection; it had no appropriate production space.

Pressure to introduce the product was such that THAMECO purchased a vial handling line from THIMON Co. of Aix les Bains, France. Subsequently an air-handling system was purchased from CAMFIL of TROSA, Sweden. Space for the installation was made available in THAMECO's existing production area.

The Thimon line comprises:

- washing station
- drying/sterilizing tunnel (300 C for 20 min.)
- filling/closing station
- seal crimping and labelling

together with conveyor belts and rotary tables.

Very soon after the equipment was received it was learned that the Thimon Co. had gone out of business and would be unable to provide the technical back-up related to installation, validation and commissioning of its equipment. This was a particularly serious situation for THAMECO which was now faced with the task of establishing a new and technically complex production operation which would, in Europe or North America, have justified a team of engineers and technicians being allocated a period of several months to complete.

THAMECO proceeded to the extent of moving the line into its allotted space, partially assembling it and unpacking part of the Camfil air handling system. This was the situation at the time of the writer's arrival in THAMECO.

On looking at the dimensions of the Thimon line it was evident that, with its associated changing rooms, preparation rooms, etc. it was too big to fit into the designated space. Many alternative schemes were tried, but each was found to be unsatisfactory in one way or another. In the interest of GMP it was agreed that the final production operation - labelling - would be separated from the rest of the line, to be undertaken only after the filled vials had been approved by QC. The floor space released by removal of the labelling unit would be converted into changing rooms. Thus a layout was prepared as shown in Appendix 6: "Suggested alternative layout for Vial Filling line".

The location of the air-supply was also clarified and is shown in Appendix 7:"Suggested layout of Air Systems in Vial Preparation and Filling unit".

Details of construction and finish of the rooms and the air flow conditions in the rooms was discussed and is summarized in Appendix 8: "Suggested layout Vial Department - some comments".

In view of the fact that all access to clean areas is off a general corridor, vestibules have been provided to act as buffer zones. Alternative methods for washing rubber closures for vials were discussed and two suggested methods are provided in Appendix 9: "Suggested method of washing Rubber Closures for vials" and Appendix 10: "Simple modification to a domestic, side impellor washing machine to make it suitable for washing Rubber closures for vials".

It is recommended that THAMECO should proceed with the installation of the Thimon line as discussed above.

The efficiency of the tunnel sterilizer must be validated by a statistically valid challenge, designed with the aid of THAMECO's bacteriologist. Should the accumulated data confirm the tunnel's value, GMP and SOP should be written for it.

The standards for THAMECO's clean rooms should be developed and implemented according to the best international standards; they should represent the standards for any future clean rooms built in Syria. Technical Assistance is necessary.

The vial handling line can be installed as detailed above, for the express purpose of allowing THAMECO to initiate its product, but

a) the entire installation is not perfect and
b) it should be viewed as a temporary expedient, to be upgraded at the earliest opportunity.

The necessity for THAMECO to follow an imperfect and temporary path, highlights the need for planned development by the Company, this topic will be discussed in greater detail in chapters 4 and 5.

A matter closely related to the precautions taken to ensure absolute freedom from particulate contamination in the handling of the vials themselves, is the quality and care of clothing worn by the clean room staff. Gowns and caps must be of monofilament, totally lint free material, stitched with monofilament thread - nylon is appropriate.

All fasteners must be able to withstand repeated washing and sterilizing by steam at 115 C. Wrist and ankle should fit tightly so as to prevent the escape of skin-scale and hair into the clean area. Shoes or boots must be of canvas or rubber, able to withstand frequent washing and sterilizing with chemicals or steam.

THAMECO must upgrade its laundry procedures to ensure that the conditions in which clothing is washed, dried, repaired and stored are no worse than the conditions which will apply in the aseptic rooms themselves, i.e. rinse water must be micron filtered and air conditions should be class 1000.

As the clean room clothing will not have come into contact with body fluids, sanitization will not be necessary; thus minimizing deterioration.

Recommendations

THAMECO must upgrade the finish of its designated vial filling area in accordance with proposals above.

A changing room must be constructed according to the drawings provided by the writer.

The Camfil air handling system should be installed; as should the Thimon line. Once installed the machinery should be commissioned and its performance validated.

At this stage UNIDO should be called upon to provide an Expert to review the situation, to write GMP appropriate for the operation and to provide SOP's relating to all aspects of the vial filing operation. A production team should be selected and trained.

A target date for completion of the above should be nominated. It is the writer's view that in view of the amount of preparation already made a realistic date for completion would be late July 1989.

2.11. Stores, Central Weighing Department

2.11.1. Raw and Packing Materials

Bulk excipients are stored on pallets in a series of individual stores measuring approximately 6 m. x 25 m. Storage is almost exclusively on the ground, consequently the volume of the stores is not used to best advantage.

Bulk antibiotics and other sensitive materials are stored in rooms as above but with air conditioning. Once again, the volume of the stores is not well used.

Packing materials are stored in individual racks; there is a limit of 1 m. imposed between the top of the material stack and the ceiling. Hence, it is understood that it is not allowable to make full use of the volume of the store.

It is suggested that THAMECO must expand its stores volume. The standard for pharmaceutical companies operating at long range from materials suppliers, is that total storage accommodation should be three times bigger than manufacturing areas. This is not achieved by THAMECO. Greater use could be made of the available volume in the existing stores by introduction of a pallet truck/lifter in conjunction with some angle-iron or tubular steel racking.

To quote an example of the pallet-lifter: The 'Big Jo' Walkie unit is self propelled by rechargeable battery. Its aisle width requirement is less than 2 m. due to the fact that it is controlled by an operator on foot; it has a lift height of almost 3 m. and capacity approximately 600 kg. There are many similar units available which would quite cheaply provide THAMECO with a worthwhile expansion of accommodation in its existing stores area.

2.11.2. Quarantine Store

The Quarantine Store is located far from the bulk stores, it is individually supervised and is provided with air conditioning. It is a small, low room not well suited to its purpose and not capable of any useful expansion. Proper segregation of batches is not possible, only careful control prevents confusion/mistakes from occurring.

It would be preferable if the Quarantine Store could be relocated to the general stores area so that proper racking could be installed and the previously mentioned pallet lifter used to ensure storage of all components of a batch in a single position, thus minimizing the risk of product mix-up.

The Quarantine Store should accept only complete batch quantities. Production Departments should not transfer incomplete batches to Quarantine. Wherever possible, one batch should occupy a single pallet. On no account should mixed batches be on a single pallet.

2.11.3. Spare Parts Stores

A separate area, under its own supervisor, the Spare Parts store is well stocked and clearly labelled.

2.11.4. Central Weighing Department (C.W.D.)

THAMECO intends to centralize the weighing of all raw materials prior to issuing them for processing.

The writer was asked to suggest a layout for a C.W.D. and also to indicate the type of documentation system which would be suitable. A layout is provided in Appendix 11: "Suggested Layout-Central Weighing Room".

A typical Weighing Document layout is provided in Appendix 12.

With minor modifications THAMECO's existing documentation system will meet the requirements of the standard form proposed.

A brief outline of the operation of a C.W.D. follows:

Supervision should be by a pharmacist on the staff of the Stores Department. In this role the C.W.D. supervisor would be in charge of bin-cards and stores inventory. The C.W.D. should be a self-

contained area large enough to accommodate a record keeping system in the supervisor's office, together with racking, benches, clean-up area, balances, pallets, etc.

Dust control equipment must be provided. On receipt of a Manufacturing Order from the Production Department, the C.W.D. pharmacist will record in his chronological Batch Register:

Date
Batch Number
Product-Name/Strength/Quantity
Expiry Date

He will requisition from the Raw Material Store, bulk packs of all Raw Materials together with their bin-cards.

After ensuring that correct materials have been provided, appropriate quantities will be weighed out by C.W.D. technicians, packed and labelled* for delivery and stacked on a pallet. One batch only should be placed on any pallet. Small volume items, colours, flavours, potent materials, etc. should be placed in a secure container, e.g. a wire mesh cage with lid, prior to being palletized. (*Details of an appropriate identification label are provided in Appendix 13).

After each measurement, the technician will sign the Weighing Document in the appropriate space; the C.W.D. pharmacist will validate the entry and countersign the Weighing Document. The bin-card will be adjusted to reflect the residual stock level.

All residual Raw Materials will be repacked into their drums, sealed with adhesive tape to prevent unauthorized opening and returned to the Raw Material Store.

The Production Department would be requested to collect the pallet of weighed material; an operator would be sent to the C.W.D. The C.W.D. pharmacist would sign the Weighing Document as having supplied the materials; the Production Department operator would also sign, acknowledging receipt of the material and responsibility for it.

Should an on going project be realized, technical assistance in computerizing stock-control would be recommended.

2.12. Supplies of Raw and Packing Materials

Raw Materials

Due to the high purity and chemical complexity of pharmaceutical Raw Materials, it is inevitable that Syria will be dependant upon overseas sources for its major raw materials for many years to come. Certain basic materials such as Sugar and Ethyl Alcohol are of domestic origin, but as seen in the instance of un-acceptable levels of F.S.A. developing in A.S.A. tablets due to the high water content of locally produced Ethyl Alcohol used in their manufacture, the low cost of the local product does not necessarily justify its use. Great care must be exercised when seeking to substitute a local Raw Material for an imported item.

THAMECO is required to place a public tender each year for its Raw Material supplies, but even from reputable foreign sources, price is not the only factor to be considered when purchasing Raw Materials; supplier reliability, willingness to respond promptly to an urgent request or to quickly replace faulty material must all be considerations in selection of a Raw Material supplier.

It is recommended that THAMECO's Raw Materials QC start a file system for each imported Raw Material. This would include data on physical and chemical characteristics of each batch from every supplier compared with the pharmacopoeial standards. Thus, if one Raw Material was supplied by 3 different suppliers over a period of years it is a simple matter to run through the characteristics of the

material from each supplier and to determine which supplier consistently offered the most suitable material.

Packing Materials

Printed paper and board products are generally purchased locally, against tender each year. This is an inflexible system which may force THAMECO to stick with a known supplier at a given price, rather than risk a new supplier whose price may be more attractive but whose delivery and reliability have yet to be determined. THAMECO should seek to clarify this situation in order to give itself the possibility of testing alternative suppliers without putting its annual demand for that item at risk. (The same flexibility should also apply to imported Raw and Packing Materials).

In respect of glass medicine bottles, THAMECO is 100% dependant upon imported goods, although the Syrian Glass Co., has expressed itself able to provide all of THAMECO's requirements. In an effort to validate this claim, a visit was made to the Syrian Glass Factory. There is no doubt that the bottle blowing unit has the resources to produce 28 mm. neck, pilfer-proof medicine bottles in volumes as low as 5 tones per day; however the blowing unit was unable to provide any details of the quality of glass which would be available. In context of pharmaceutical bottles it is vital that the correct quality of glass is employed or product deterioration may quickly occur; the Pharmacopoeial Sets-out exact standards for pharmaceutical glass containers. It was not possible to contact the Chemistry Department during the visit to Syrian Glass Co., but THAMECO should provide the Chemistry Department with photocopy of the Pharmacopoeial standards and request Syrian Glass to confirm in writing its ability and willingness to supply bottles to the required specification. Should THAMECO commence to take its bottle supplies from Syrian Glass, it should be agreed that the bottles are provided in relatively small trays, shrink-wrapped in plastic, to avoid undue entry of dirt whilst the bottles are in store.

Concurrently, THAMECO should start to investigate the use of polyethylene bottles for some of its liquid products - ageing data should be accumulated to permit a rapid change to plastic packs should this prove necessary. In order to reduce the risk of a batch of previously rejected plastic being re-worked as THAMECO bottles, the Company should consider the possibilities of either importing its own polyethylene granules and releasing them to the bottle maker only for a specific order or, alternatively, establishing its own blow molding unit for bottles and injection molding unit for caps.

2.13. Water Treatment

2.13.1. Softening

THAMECO's water is derived from its own wells. The hard water is treated in a plant constructed by WILOWERK AG of DORTMUND some 5 years ago. Initial treatment is by a sand filter from which filtered water can pass in two ways:

a) non-softened for special purposes
b) to the two column water softener followed by charcoal filter for other purposes.

Chlorination takes place and water ready for use is stored in a tower. There are several shortcomings with this facility:

a) the important first step of water-treatment with ALUM as a flocculate is omitted. Hence the effectiveness of the sand filters is greatly reduced.
b) the 'regenerate time' stage for the water softener is not functioning correctly.
c) the hydraulic pressure reservoirs have developed a fault such that the cycling control of the water pumps is not reliable with consequent risk of damage to the pumps.
d) one column is cracked; it has been repaired by welding; the column should be inspected for internal damage and replaced if necessary.

Recommendations

1) A flocculation station should be built into the raw water supply and loaded with block Alum. See Appendix 14: "Proposed chamber in inlet-water-line for flocculation with Alum".

2) THAMECO should contact either HONEYWELL Corp. or OMRON Co. to identify replacement control gear.

3) Damaged components should be replaced.

2.13.2. De-ionization and Reverse Osmosis

Water for 'special purposes' from the filter plant, not softened, is passed to a Millipore de-ionizer and reverse osmosis system. Difficulties are being experienced with this equipment; these difficulties have not been resolved by replacing the resin in the D.I. columns. The manufacturer of the equipment should be consulted for advice.

2.13.3. Distillation

THAMECO has a number of small electrically heated stills in Production and QC areas. It is understood that a new Finnaqua plant is on order.

Recommendations

Small scale electrically heated stills are expensive and may prove troublesome to operate. In its future planning THAMECO is urged to consider installation of a steam heated central distillation facility of the BARNSTEAD THERMODRIVE type. These units are modular and can be expanded to accommodate whatever volume of distillate is required. When fitted with a high-purity-column the distillate is guaranteed to be chemical and pyrogen free. An integral conductivity cell in the discharge line will respond automatically if the quality of the distillate goes out of specification; a dump-valve is operated which diverts all "non-spec." water to drain and an alarm is sounded to advise the operators of the fault.

Should an on-going project be realized, an expert appraisal of water supply both for Damascus and Allepo would be recommended.

2.14. Quality Control - QC

The QC Department comprises the following analytical procedures:

a) chemical
b) physical
c) optical/electronic
d) pyrogen - using rabbits
e) toxicity - using mice
f) microbiological

All Raw, Packing and Finished Goods are subject to QC procedures based upon the United States Pharmacopoeial.

Laboratories are spacious and well equipped with the best modern equipment. Repair and calibration of certain electronic/optical equipment is possible in Syria. It is un-necessary here to detail the equipment/procedures in use; the writer will refer only to aspects of QC in which THAMECO is experiencing difficulty.

2.14.1. Developing Analytical Methods: Relates mainly to microbiological testing of antibiotics. Equipment is required both for diffusion method and turbidity measurements. Special incubators are

also required. A programme for the interpretation and calculation of results is required. A method and equipment are needed for the analysis of Vitamin B12 when in association with other elements e.g. Iron.

2.14.2. Air Sampling: In view of the expansion of THAMECO's "sterile" and "clean" production activities, it is necessary that their ability to monitor clean-room conditions quickly and accurately is up-graded as a matter of urgency. Coulter or Rockwell equipment must be made available.

2.14.3. Stability of Electrical Supply: Optical/electronic analytical equipment is extremely sensitive to voltage fluctuations. The PYE UNICAM H.P.L.C. (PU4030) requires a voltage stabilizer urgently.

2.14.4. Expiry Dates: The writer was unable to develop a clear understanding of how THAMECO establishes Expiry Dates for its products. Hence a method will be suggested below, which the Company may wish to adopt if it has no better procedure already in operation. All products should be subject to cycling between the climatic extremes which they are likely to encounter, over an extended period. To achieve this, the standard procedure is to construct a climatic room in which the extremes of heat, humidity and cold can be cycled on a regular, preferably daily basis. Samples of all products are stored in the climatic room and are subject to complete analytical examination (as for Finished Goods) after a pre-determined period (normally 2-3 months). After two or three such examinations, a pattern will be seen, reflecting the stability of the formulation. From this pattern, it is possible to extrapolate an Expiry Date. The accuracy of the extrapolation should of course be proved by analysis.

2.14.5. Pharmacological Evaluation of Products

THAMECO currently has no means of measuring the efficacy/potency of its product range. Whilst its products contain well known and well tried molecules, the formulations which THAMECO has developed may, or may not, permit the molecule to function "in vivo" to the expected level. Clearly this is not too much of problem where THAMECO's formulations are based in those of foreign principals, but when the Company is faced with developing its own new products, particularly if up-to-date drug delivery systems are employed, then it is essential that expertise and equipment for "in vivo" pharmacology be available.

The area of QC in modern pharmaceutical industry is complex and requires specialist knowledge. It is appropriate to suggest that THAMECO would benefit from the visit of a QC expert for a period of 1 month, to study procedures, to identify equipment requirements and to assist in developing QC methods. A Job Description is attached (See Appendix 16: "Job Description follow-up mission - Instruments Analysis").

Details of a proposed UNIDO Fellowship in specific analytical procedures are appended. See Appendix 17.2: "Quality Control - Instrument Analysis".

Details of a proposed UNIDO Fellowship in pharmacology are provided in Appendix 17.3.

2.15. Research Department

Since terminating its licence agreements with foreign principals, THAMECO has found it necessary to reformulate a number of its products. This work is carried out by some 15 technicians, under the control of the Research Director, in spacious laboratories, well set-up with ERWEKA pilot scale equipment. Work is possible on traditional dosage forms only.

The Research Department is currently undertaking pilot-scale work on the film-coating of Nipefidine tablets in a small coating pan using Binks Bullows spray equipment. Subject to the successful outcome of these trials, THAMECO will proceed to purchase full scale spray coating equipment.

The writer would suggest that THAMECO should aim to install coating equipment which allows for flexibility in terms of batch size and coating procedure, rather than invest a great deal of capital in a large scale, fully automated facility.

2.16. Preventive Maintenance (P.M.)

An effective system of Preventive Maintenance is being employed by THAMECO.

The Company has an annual shut-down for 6 days in August, during which time building maintenance and major P.M. activities are undertaken.

At the completion of each production-run all machines are cleaned, inspected, lubrication is checked and parts changed where necessary.

In addition, there is a monthly maintenance check-up on all equipment.

In the particularly critical area of child-food production, each week the plant is shut-down for two days - Thursday and Friday - for cleaning and maintenance.

As mentioned elsewhere in the Report, THAMECO has one of the best stocked and operated spare-parts stores that the writer has seen in a comparable factory.

Currently the maintenance staff comprises 5 senior engineers, aided by 10 technicians. The Engineering Department has its own workshop which can undertake turning, milling and mild steel welding in addition to its routine fitting operations.

2.17. Good Manufacturing Practice - GMP

The nominated GMP within THAMECO is the US system. Implementation is the responsibility of the Technical Director.

Certain elements of GMP are seen to be working well, e.g. documentation and the alternating functions of Production/QC in the manufacturing process,etc.

In other areas GMP is seen to be weak, principally because it was not designed into the plant at the outset, but "applied" at a late stage to an existing operation which had itself grown in response to immediate requirements. Thus, non-compatible production lines operating in close proximity, cross contamination between mixing vessels, dusty working conditions and overcrowded In-Process Store are areas in which improvements are necessary.

It is the writer's view that improved GMP will result when some of the workload is taken from the Damascus factory by the new facility at Allepo. However, it is emphasized that the time to start installing GMP at Allepo is now, before the equipment is procured.

THAMECO has, in its new plant, a great opportunity to develop a very high class unit in which compatible products are manufactured according to the best standards of GMP. The same level of GMP will not be attainable if Allepo factory becomes merely a duplicate of the Damascus factory.

Technical assistance from UNIDO will be of value to THAMECO in the provision of GMP in the Allepo Factory.

The writer had agreed to THAMECO's request to give a short talk on GMP to senior technical staff; unfortunately time did not permit.

An important area of GMP which THAMECO should address promptly is the clear designation of Key Executives, each with his/her own un-ambiguous written Job Description. Thus, a Production Controller and a Quality Controller should be appointed and their individual and joint responsibilities should be agreed and implemented as soon as possible. This will represent a major shift in management style for THAMECO. Technical assistance is necessary.

2.18. THAMECO Executive Staff

In order to assist future Experts in THAMECO, a contact list of senior executives is appended. Refer to Appendix 17.

3. CONTACT WITH EXTERNAL PHARMACEUTICAL INDUSTRY

Pharmaceutical Industry cannot be viewed as an homogeneous, single technology industry. It comprises a number of widely different specialities, each with its own requirements and each developing world-wide at different rates. In order not to stagnate by isolation, it is imperative that THAMECO develops an active dialogue with all aspects of the industry, regionally and world-wide.

3.1. Personal Contact and Communication

THAMECO gained much of its early expertise from its relationships with foreign principals. Since its licence agreements were terminated, these relationships have been lost. For THAMECO's continued development it is imperative that alternative relationships are developed. THAMECO requires a new window* on the external pharmaceutical world (*vide Mr. M. Koudsi, General Manager, THAMECO).

Through its Fellowships, Study Tours and Technical Assistance programme, UNIDO can provide that window. The relationship with UNIDO should be seen as extending over a number of years, during which time THAMECO would have the opportunity to form fresh technical relationships through machinery manufacturers, specialist raw material suppliers, universities, public-sector pharmaceutical industry in overseas countries, etc.

Such relationships are essentially of a personal nature which can quickly be eroded if trained staff are lost to competing industries. Currently, in Syria, with only two active pharmaceutical companies, this is not a problem. The opening of the Allepo factory with its demand for qualified staff will bring additional professionals into the public-sector industry. However, it is understood that some 20 prospective pharmaceutical companies in the private sector have been granted licences by Syrian Government to establish their industries; they could represent significant erosion of the top experts from the public sector factories.

The question of an on-going THAMECO/UNIDO relationship was raised at a meeting of THAMECO/UNDP and the writer on the final day of the mission. Both THAMECO and UNDP expressed satisfaction at the way the mission had evolved; real benefits had been attained and a prospective future relationship had been explored in a general way. There was interest from both sides to develop the THAMECO/UNIDO relationship; it was suggested by UNDP that a revision in the method of funding, would permit a more direct contact between THAMECO and UNIDO.

It is recommended that a mechanism be identified and implemented as soon as possible to ensure that this financial change-over occurs. In the meantime the THAMECO/UNIDO relationship will start its evolution through the programme suggested below:

1) Study Tour (Refer to Appendix 16 for details)

The primary purpose of the Study Tour is to enable THAMECO's designated Development Director to experience at first hand the segregation of non-compatible product types and the handling of bulk infusion solutions. This experience will be invaluable in the rationalization of activity between the Damascus factory and the new facility nearing completion in Allepo.

2) UNIDO Fellowships (Refer to Appendix 17 for details)

Three Fellowships have been proposed:

1) Tablet Making Technology
2) Quality Control - Instrument Analysis
3) Pharmacology

of these, Nos. 1 and 2 are seen to be necessary as soon as possible. Fellowship No. 2 must be completed before a Technical Assistance Expert in Instrument Analysis is fielded.

Fellowship No. 3 is currently of lesser priority and may be deferred until THAMECO has resolved its more immediate QC/Research problems.

3) Technical Assistance (Refer to Appendix 18 for details)

The original terms of project DP/SYR/86/009 provide for one Follow-up Mission of 3 mm. In view of the urgency for Technical Assistance in Instrument Analysis, it may be appropriate to vary the terms of the project, thus providing 2 mm of Production Expert time and 1 mm of Instrument Analysis Expert time.

Job Descriptions are provided to cover whatever selection is made.

As previously stated, should THAMECO wish to have the services of an Instrument Analysis Expert, it is imperative that Fellowship No. 2 above is completed before the Expert is fielded.

3.2. Technical Journals

The writer observed no current technical journals during his visit to THAMECO. It is important that this situation be corrected and it is recommended that the following should be considered as a minimum subscription list:

- Drug and Cosmetic Industry (USA)
- Manufacturing Chemist (UK)
- The Lancet (UK)
- Pharmacy and Pharmacology (UK)
- International Journal of Pharmaceutic (Holland)
- Documenta Geigy (SW)
- Merck Index and Merck Manual (USA)
- Martindale Extra Pharmacopoeia (UK)

In addition, THAMECO should consider subscription to an Abstract Service similar to that offered by the Royal Institute of Chemistry in UK.

3.3. Trade Exhibitions

THAMECO senior technical staff should have the opportunity at least every two years, to visit one of the laboratory equipment exhibitions in Leipzig, Paris or London; and one of the machinery exhibitions, either Achemia or the Brighton Expo., organized by the Association of British Pharmaceutical Industry.

4. DEVELOPMENT OF PHARMACEUTICAL INDUSTRY IN SYRIA

During the initial month of field work it was evident that the development of pharmaceutical industry in Syria is governed by:

i) short term technical/mechanical problems
ii) medium/long term policy decisions

The writer was of immediate assistance to THAMECO in a number of areas categorized (i) above; of even greater importance, however, was the opportunity to identify a number of areas in category (ii) above, which if resolved, promptly will enable THAMECO to develop into a strategic industry both nationally and within the Arab countries.

THAMECO has already proved that it has the ability to manufacture a wide range of quality medicines; it has expanded its volume of production, it now needs to expand its product range and to consolidate its entire operation. Completion and commissioning of the new premises at Allepo will do much toward achievement of these goals.

As elsewhere stated, the concept of a homogeneous, single technology pharmaceutical industry is false. A number of widely differing specialities combine to form the pharmaceutical industry. Many of these specialities are compatible, some are absolutely incompatible. These facts must be bourne in mind when planning the development of the industry in Syria.

The production unit of THAMECO in Damascus is seen to be overcrowded. It grew in an ad-hoc fashion influenced more by the pressing needs of the market than by the rational development of a planned industry. Thus incompatible product lines are located in close proximity and a meaningful level of GMP does not exist.

The superficial "application" of GMP to an overcrowded factory would, at best, be an unsatisfactory approximation of GMP with consequent risk to product integrity and Company reputation. These facts are highlighted by the problems encountered when trying to install the Thimon vial handling equipment.

It is the writer's view that, it is important urgently to rationalize the production activities of Damascus and Allepo factories. Each should be redefined, to handle its own range of compatible products. It would be a mistake to develop Allepo as a duplicate of Damascus. The volume of work involved in making this rationalization is very considerable and would normally be undertaken by a team of engineers, draftsmen, production and QC people; a project of this magnitude would be expected to occupy several years.

The proposal by the Syrian Government that the Allepo factory should be modified to permit the production of sterile infusion solutions with a capacity of 4 million x 11 packs per year is a very compelling reason to consider the merits of developing the Allepo installation into a specialist sterile products unit. Thus pulling out existing sterile operations from Damascus and consequently providing floor space there to expand and develop its own product range. The benefits of such a policy include:

i) conservation of Foreign Exchange by avoidance of equipment duplication
ii) Reduced expenditure on dust-extraction and air handling equipment by reduction of the conflicting requirements of non-compatible product types
iii) economics of scale
iv) greater degree of professionalism amongst technical staff
v) ability to impose an acceptable level of GMP to each factory and thereby to define codes of GMP which will set the standards for other pharmaceutical enterprises wishing to establish in Syria.

The analysis of the foregoing is a complex matter. The writer strongly recommends that THAMECO should appoint a Development Director, with appropriate back-up team, to start planning THAMECO's development urgently. The Development Director should be given clearly defined terms of reference and should be free from the day-to-day problems of either the Damascus or the Allepo factory. Technical assistance is necessary.

5. THE NEW THAMECO FACILITIES AT ALLEPO

Allepo is the second biggest city in Syria, approximately 400 km. North of Damascus; the new factory is 18 km. South of the centre of Allepo and is conveniently located for both road and railway.

A one day visit was made, during which discussions were held with the construction manager, the electrical installation chief, the civil engineer amongst others. They advised that the buildings will be available for occupation by THAMECO early in 1990 at a finished cost approaching Syrian Pounds 100 millions (US $ 5.0 mill). Site dimensions are 200 m. x 600 m.; stores have a floor area of 16500 square meters; production area is 60 m. x 60 m. Water supply is from 2 wells; sewage treatment is located far from the wells; surface water is removed via the sewage plant soak-away. A sketch of the layout is provided in Appendix No. 15: "General Layout of Allepo Factory showing principal activities".

Observations

i) The cost of plant and equipment for Allepo is said to be US $ 8.0 millions. The availability of funds is tied to a loan from the Government of France which calls for 90% of the funds to be spent in France. Negotiations are proceeding; until resolved, the purchase of plant and equipment for Allepo is suspended. Tenders which were received by THAMECO in 1986 are now out-of-date.

ii) The original concept of Allepo as a duplicate of Damascus factory has been changed by the recent requirement for Allepo to produce 4 mill. x 1 l. containers of sterile fluids per year.

iii) Some of the designated areas at Allepo are oversize e.g. suppository manufacture. This is a small demand product, unlikely there will be any great increase in demand; one production unit, with appropriate equipment can easily supply the entire demand of Syria. Parallel situation apply in context of Eye Drops and Eye Ointments. The product mix between Allepo and Damascus factories must be critically reviewed.

iv) In view of the projected hand-over date from builder to THAMECO, it is urgent that a Development Director be appointed, to define the roles of Damascus and Allepo and to start the equipment procurement procedure for both plants. Machinery deliveries normally require 12 months minimum, hence urgent activity is necessary in this context.

Specific Points on the Building at Allepo

Care is required if any vibrating machinery is installed at Allepo as the dynamic floor loading is only 600 kg./sq. meter.

The water supply, coming from two wells, makes no provision for flocculation and sedimentation.

Horizontal ledges in production areas should be avoided.

Space designated for changing rooms should be re-evaluated, it is too small. A layout plan for an integral clean area with changing rooms is provided as Appendix 16: "Block Diagram Suggested Sterile Suite".

Location of electrical switch gear should be examined critically.

The expansion/contraction of sheet-metal duct-work may cause wall finish to crack in certain areas where no provision for movement has been allowed.

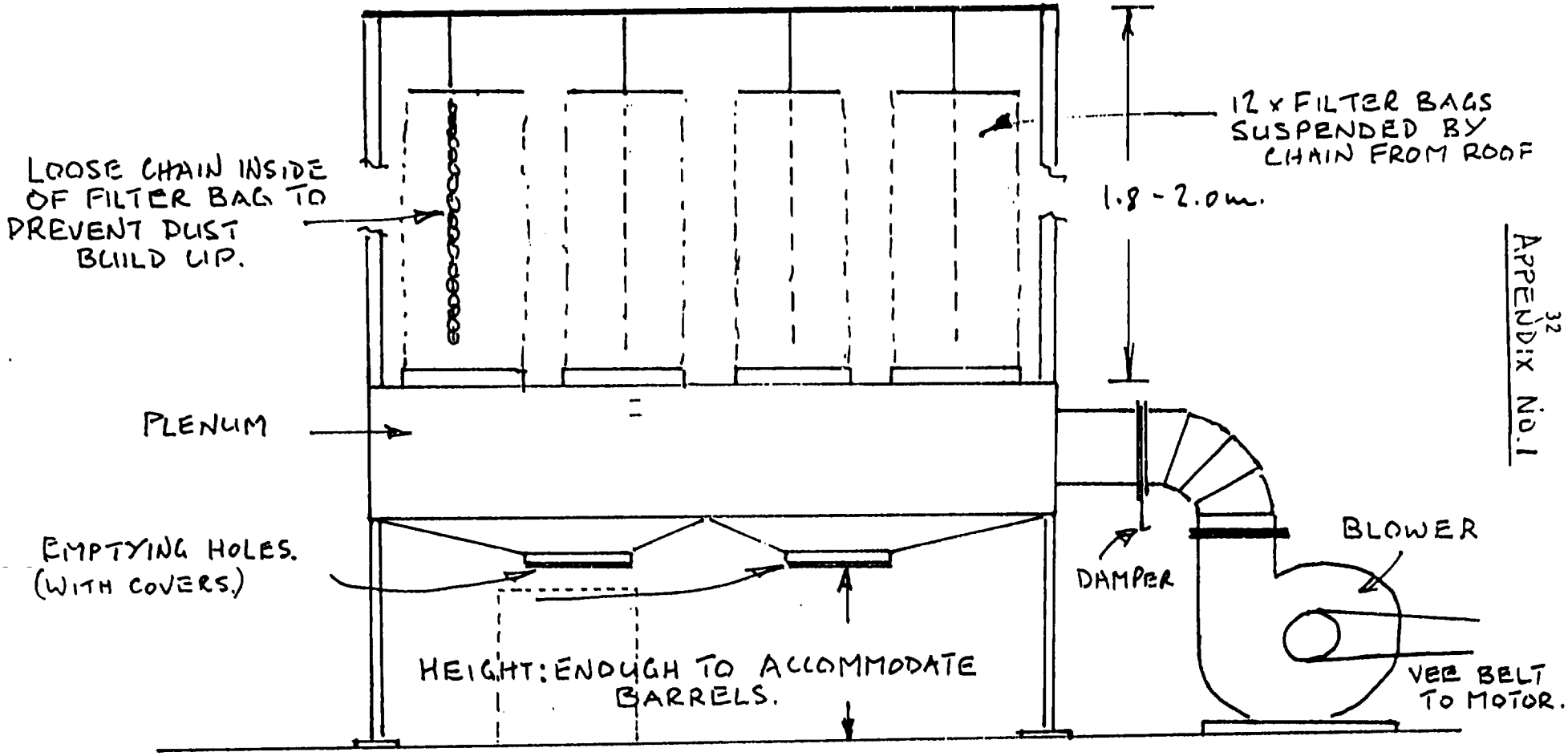
In wet areas, electrical supply to machinery should not rise from the floor.

Ample ventilation must be provided for air-conditioning chillers installed below ground.

The location of the boiler in the ointment making section makes no allowance for expansion of steam raising capacity should this become necessary as a result of increased demand for ointments.

Ointment preparation rooms should have floor drains to facilitate cleaning.

Distillation/water treatment equipment should be surrounded by a bund wall to contain any leaks/overflows.

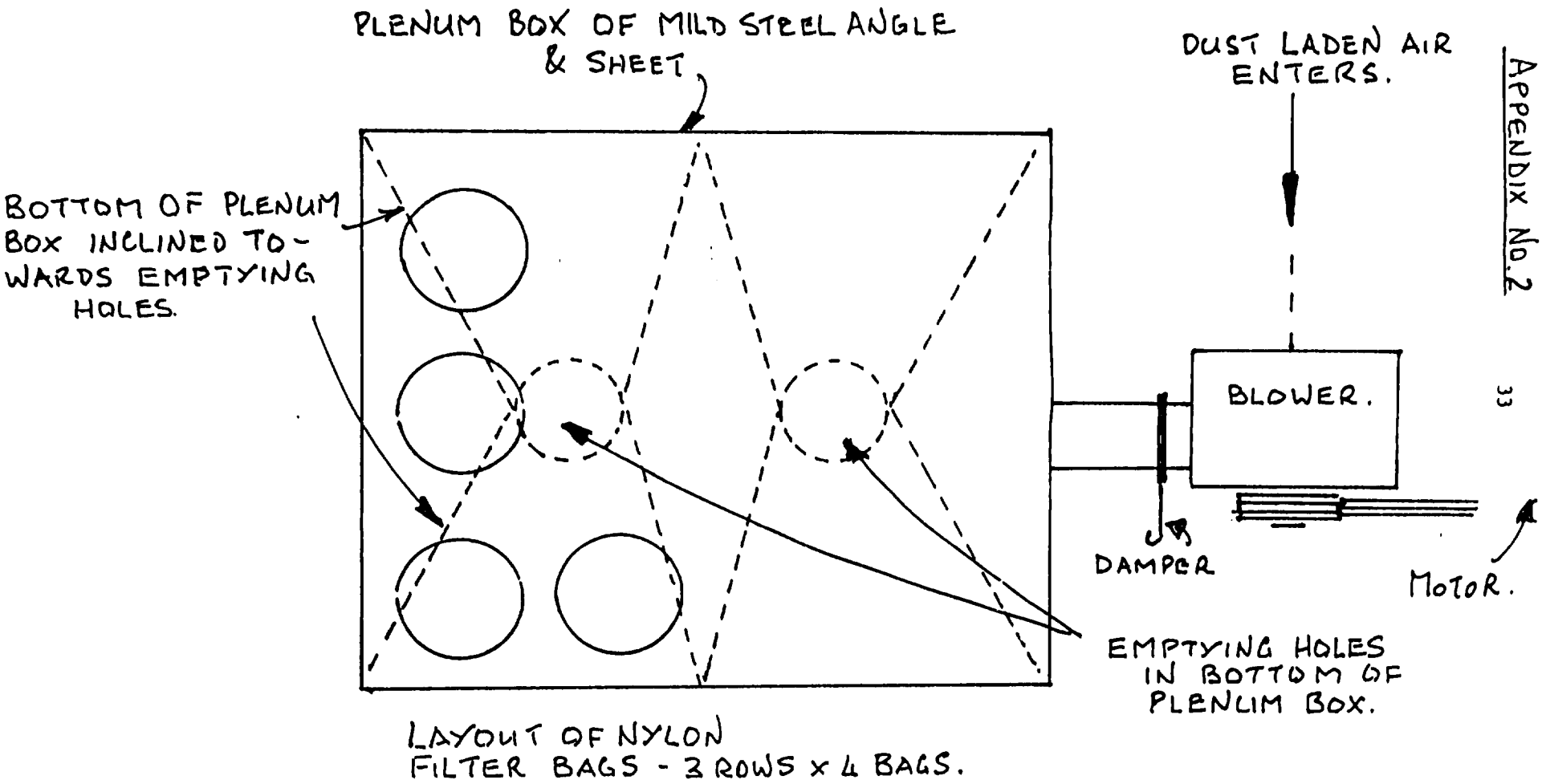


APPENDIX No. 1
32

THAMECO : ELEVATION OF PROPOSED DUST COLLECTOR FOR TABLET AREA

NO SCALE

17/4/89.



THAMELCO: PLAN OF PROPOSED DUST COLLECTOR FOR TABLET AREA.

NO SCALE

APPENDIX NO.3

THAMECO : INITIAL CALCULATIONS FOR PROPOSED DUST COLLECTOR IN TABLET DEPARTMENT.

(FOR DISCUSSION)

ASSUME THAT COLLECTOR PIPE AT TABLET MACHINE HAS DIAMETER OF 100 mm. i.e AREA OF OPENING (CROSS SECTIO. APPROXIMATES 80 cm^2.

THUS, FOR 6 COLLECTORS : AREA OF OPENING (CROSS SECTION)
$= 6 \times 80 = 480\ cm^2$.

ASSUME THAT REQUIRED VELOCITY OF AIR INTO COLLECTOR IS 250 m./minute i.e. 25,000 cm/minut

THEN, VOLUME OF AIR TAKEN IN BY 6 COLLECTORS IS $\frac{480 \times 25{,}000}{100 \times 100}$ m^3/minute

$= \underline{1200\ m^3/\text{minute}}$

SAY, FRICTIONAL LOSSES & LEAKS IN DUCTWORK REDUCE EFFICIENCY BY 20%, THEN BLOWER MUST HAVE CAPACITY OF $\frac{120}{100} \times 1200 = \underline{1440\ m^3/\text{minute}}$.

IN VIEW OF THE RELATIVELY LOW COST OF THE PLENU FILTER BAGS & DUCTWORK. IT WOULD BE PRUDENT TO BUILD THE UNIT CONSIDERABLY OVERSIZE INITIALLY TO ENABLE MORE COLLECTORS TO BE UTILISED AS NECESSARY_ SAY BLOWER CAPACITY 2,500 - 3,000 m^3/mi

DUCTWORK DIMENSIONS ARE GOVERNED BY TWO FACTORS :

a) DIMENSIONS OF BLOWER THROAT.

b) DIMENSIONS OF COLLECTOR PIPE - (i/d 100 mm in this example)

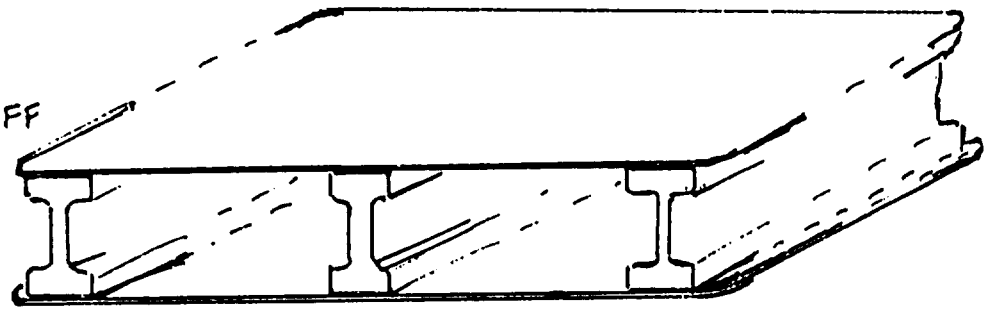
DUCTWORK MUST DECREASE IN CROSS SECTIONAL AREA (OPENING) AS ITS DISTANCE FROM THE BLOWER INCREASES.

Brown 17/4/89.

APPENDIX No. 4.

LOCATE TABLET PRESS WITH
4 x 19mm. NUTS/BOLTS.

TOP & BOTTOM FACES
4-6mm. M.S. PLATE.



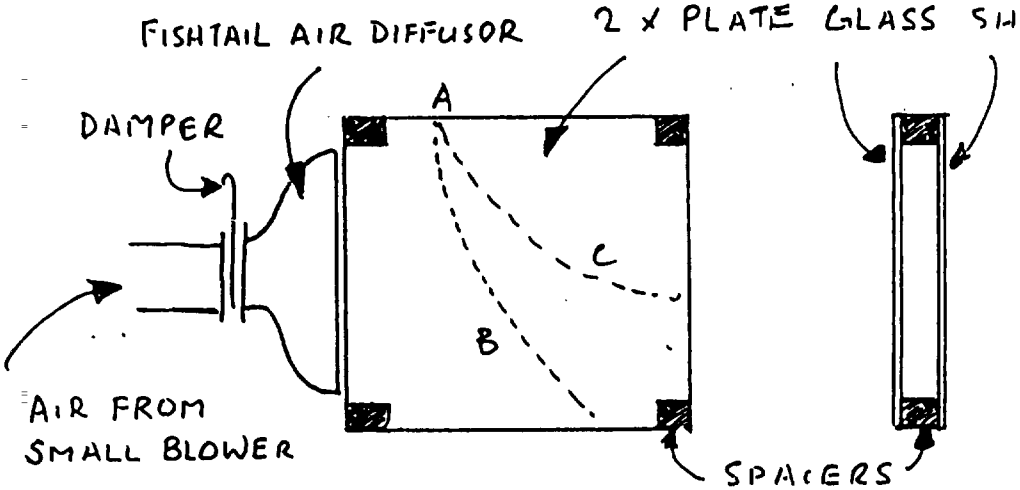
LENGTH & WIDTH DIMENSIONS
ACCORDING TO MACHINE TO
BE CARRIED.

M.S. I BEAMS 90 x 120 OR
100 x 150
AS AVAILABLE.

THAMECO: STEEL PALLET FOR TABLET PRESSES.

12/4/89.

APPENDIX No. 5.



A. SUPPOSITORY PACKS INTRODUCED.
B. TRACK OF CORRECT WEIGHT PACK
C. TRACK OF UNDERWEIGHT PACK.

OPERATION

THE UNIT IS TABLE MOUNTED, SLOPED ABOUT 30° FROM HORIZONTAL.
CORRECT WEIGHT PACKS ARE INTRODUCED AT 'A'. THE SLOPE AND AIRFLOW ARE ADJUSTED SO THAT THE CORRECT WEIGHT PACK FOLLOWS A TRACK AS 'B'. IT IS ALLOWED TO FALL INTO A DRUM FOR GOOD PRODUCT.
UNDERWEIGHT PACKS WILL FOLLOW TRACK C WHERE THEY CAN BE COLLECTED IN A REWORK DRUM AND THE MATERIAL INCORPORATED INTO A FUTURE BATCH.

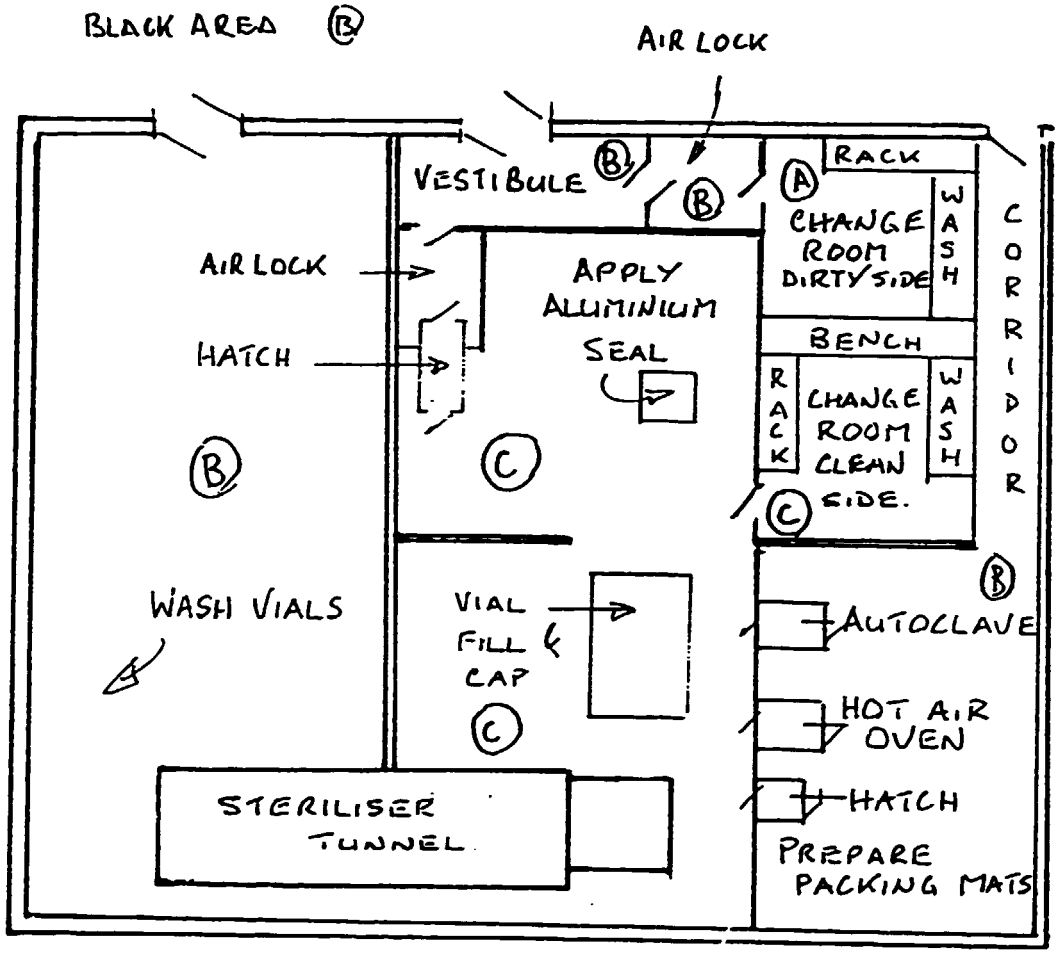
36

20/4/89.

THAMECO: SUGGESTED METHOD FOR I/P CONTROL OF SUPPOSITORY FILLING WEIGHTS.

APPENDIX No. 6

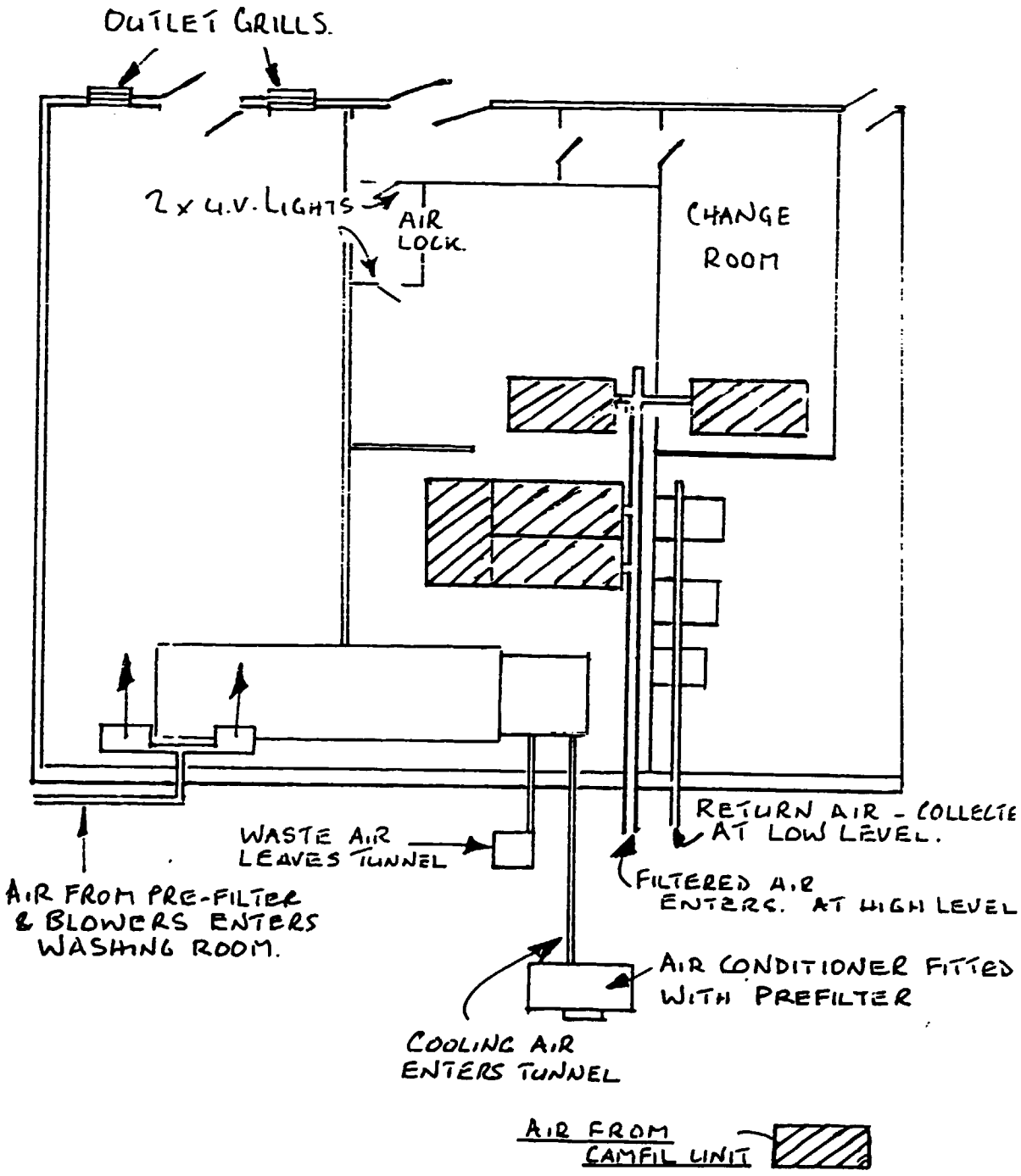
WHITE AREA (C)
GREY AREA (A)
BLACK AREA (B)



THAMECO: SUGGESTED ALTERNATIVE LAYOUT FOR VIAL FILLING LINE

19-4-89.

APPENDIX No. 7



THAMECO: SUGGESTED LAYOUT OF AIR SYSTEMS IN VIAL PREPN. & FILLING UNIT

18.4.89.

APPENDIX NO. 8.

THAMECO: SUGGESTED LAYOUT VIAL DEPT. USING EXISTING EQUIPMENT

SOME COMMENTS.

1. MATERIALS & STANDARDS OF CONSTRUCTION.

a) WHITE AREAS IDENTIFIED (C):

FLOORS - TERRAZO TILES, GROUND BACK & FINISHED WITH 3 COATS OF 2 PACK EPOXY FLOOR FINISH. COVED INTO WALLS. NO FLOOR DRAINS.

WALLS. - CERAMIC TILES TO AT LEAST 1.8m. ABOVE THAT HEIGHT FINISHED IN GLOSS ENAMEL PAINT. NO HORIZONTAL SURFACES - eg. WINDOW - FRAMES.

CEILINGS - ALUMINIUM SHEETS BEDDED IN SILICONE AND POP - RIVETTED. LIGHT FITTINGS TO BE FLUSH WITH THE CEILING.

DOORS - ELECTRICALLY INTER-LOCKED TO PREVENT TWO SIDES BEING OPEN SIMULTANEOUSLY.

b) GREY & BLACK AREAS IDENTIFIED (A) & (B) RESPECTIVELY.

EXISTING STANDARDS, PROPERLY REPAIRED AND FINISHED ARE ADEQUATE.

2. AIR SUPPLY.

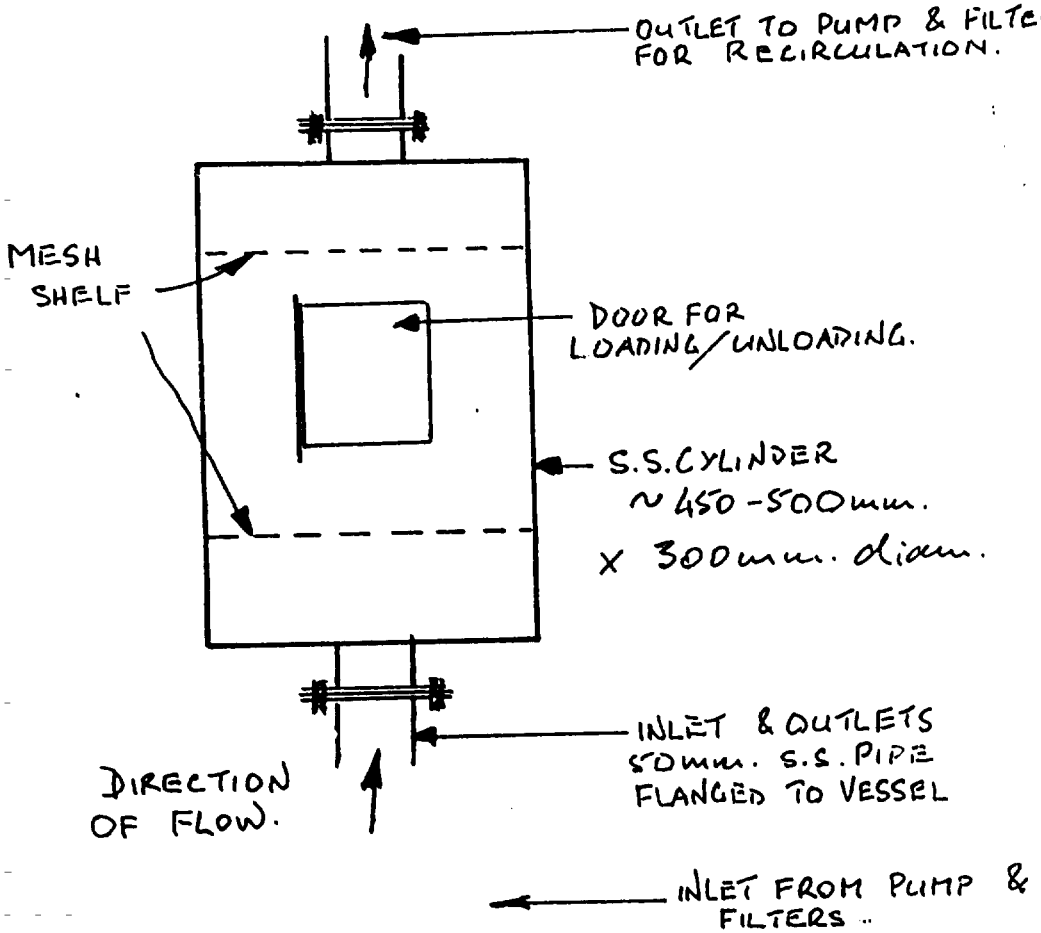
LAMINAR FLOW AREA - AIR AS PROVIDED BY PACKAGE UNITS ALREADY ON SITE.

WHITE AREAS IDENTIFIED (C) MINIMUM ACCEPTABLE STANDARD IS CLASS 1000. IF APPROPRIATE TERMINAL FILTERS ARE AVAILABLE CLASS 100 SHOULD BE UTILISED.
AIRFLOW SHOULD BE SUCH THAT THE ROOMS RECEIVE 16 CHANGES PER HOUR, i.e. BLOWER SHOULD PROVIDE APPROX 3500 m^3 PER HOUR. DUE TO IMPOSED HEAT LOAD FROM OPERATORS, MOTORS & HEAT STERILISED PACKING MATERIALS THE TEMPERATURE OF INCOMING AIR SHOULD BE 20°C OR LESS. DURING NONE-OPERATIONAL PERIODS AIR CHANGES MAY BE REDUCED TO 6-8 PER HOUR PROVIDED THIS DOES NOT REDUCE THE WATER GAUGE DIFFERENTIAL TO LESS THAN 1". DURING OPERATION W.G. DIFFERENTIAL SHOULD BE +2" (+50mm.)

10/4/89.

NOTE: ENAMEL = OIL BASED PAINT, NOT ACRYLIC.

THAMECO: SUGGESTED METHOD OF WASHING RUBBER CLOSURES FOR VIALS.



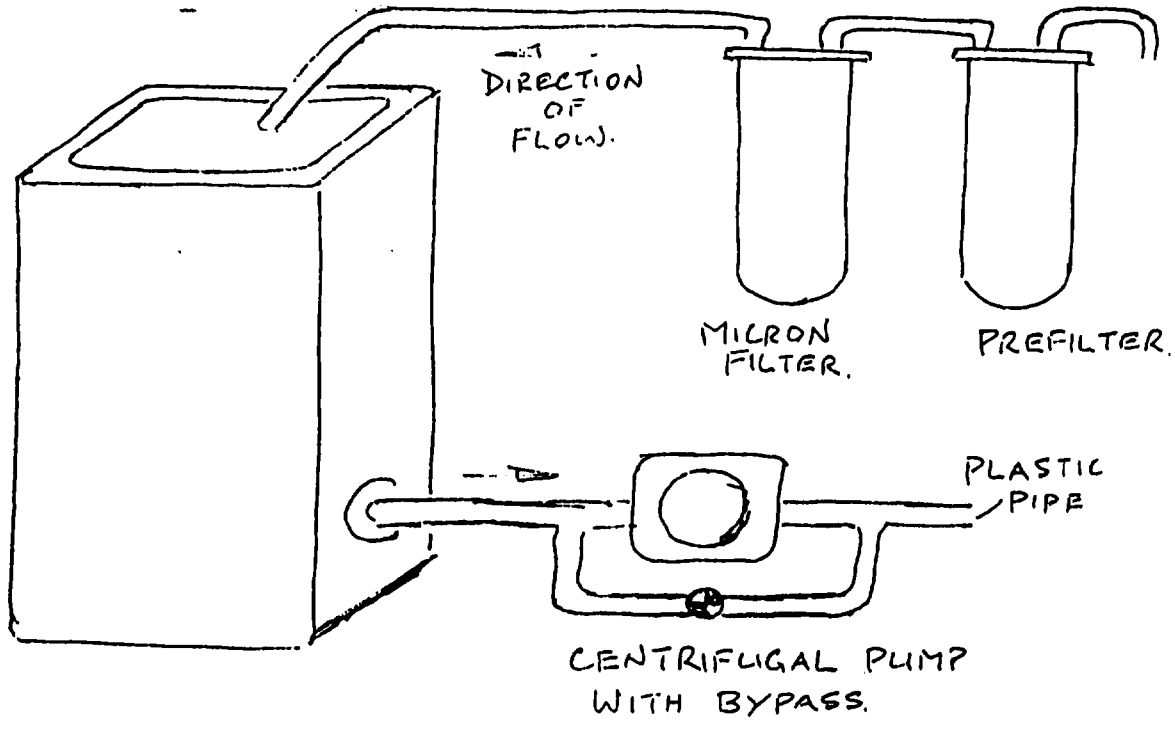
PUMP: CENTRIFUGAL - ½ - 1 HP. BY-PASS TO REGULATE THE PRESSURE OF WATER INTO THE FILTERS.

FILTERS: CARTRIDGE TYPE - PAL OR SIMILAR, IN TYPE 316 S.S. BODIES.
2 x PREFILTERS ON MANIFOLD
2 x MICRON FILTERS ON MANIFOLD.

PIPEWORK: SS. TYPE 304 OR 316

HEATING: STEAM MAY BE INJECTED INTO THE INLET PIPE IF REQUIRED. THE EQUIPMENT WILL THEN BE CLASSED AS A PRESSURE VESSEL & MUST BE PROVIDED WITH APPROPRIATE CONTROL & SAFETY VALVES. FILTER CARTRIDGES SUITABLE FOR THE WORKING TEMPERATURE MUST BE EMPLOYED. CARE SHOULD BE TAKEN THAT NO VOLATILE AMINES ARE CARRIED OVER FROM THE BOILER.

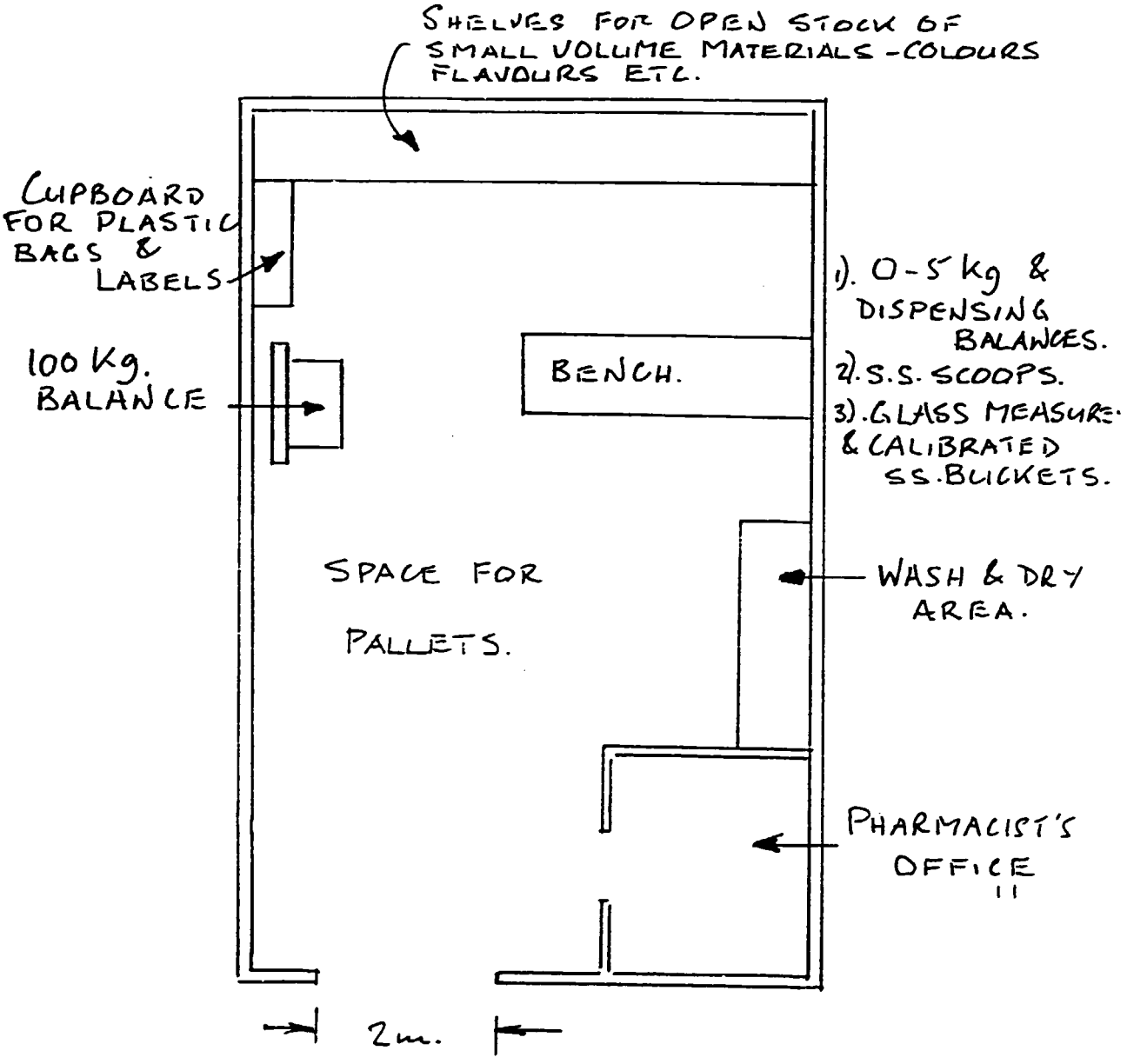
WATER QUALITY: DUE TO THE AGGRESSIVE NATURE OF D.I. OR DISTILLED WATER SOFTENED WATER ONLY SHOULD BE EMPLOYED.



THAMECO: SIMPLE MODIFICATION TO A DOMESTIC SIDE IMPELLOR WASHING MACHINE TO MAKE IT SUITABLE FOR WASHING RUBBER CLOSURES FOR VIALS.

11.4.89.

APPENDIX No. II



THAMECO: SUGGESTED LAYOUT CENTRAL WEIGHING ROOM

FOR DISCUSSION NO SCALE

13/4/89.

THAMECO.

WEIGHING DOCUMENT.

DATE ___ PRODUCT NAME/TYPE ___ BATCH NO.___ EXPIREY DATE.___

STRENGTH. ___ BATCH SIZE ___ kg/ℓ.

MATERIALS.	QUANTITIES. REQUIRED	QUANTITIES. SUPPLIED.	SOURCE	QC NO.	DISPENSED	CHECKED	DATE.
TOTAL							

COMMENTS

DELIVERED BY _____ RECEIVED BY _____

DATE _____

APPENDIX NO. 12. 43

THAMECO: SUGGESTED LAYOUT OF WEIGHING DOCUMENT FOR USE IN CENTRAL WEIGHING DEPARTMENT.

13/4/89.

THAMECO

DATE _____ BATCH NAME _____ BATCH NO. _____

PRODUCT STRENGTH _____

RAW MATERIAL NAME. _____ Q.C. NUMBER ____

QUANTITY _____

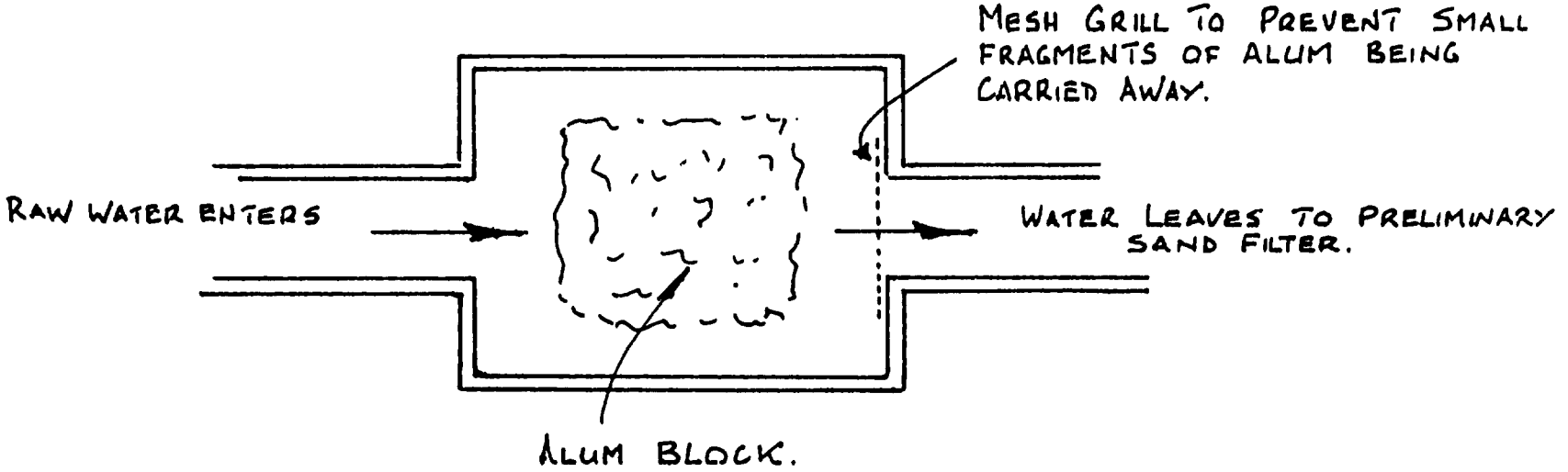
WEIGHED BY _____ CHECKED BY _____

APPENDIX No. 13

THAMECO : DETAILS OF IDENTIFICATION LABEL TO BE FIXED TO ALL RAW MATERIALS LEAVING C.W.D.

NOTE : THIS IDENTIFICATION LABEL IS PART OF THE BATCH RECORD. WHEN THE INGREDIENT IS USED BY PRODUCTION DEPT. THE IDENTIFICATION LABEL MUST BE STAPLED TO THE PRODUCTION DOCUMENTS TO PROVE THAT THE MATERIAL HAS BEEN USED.

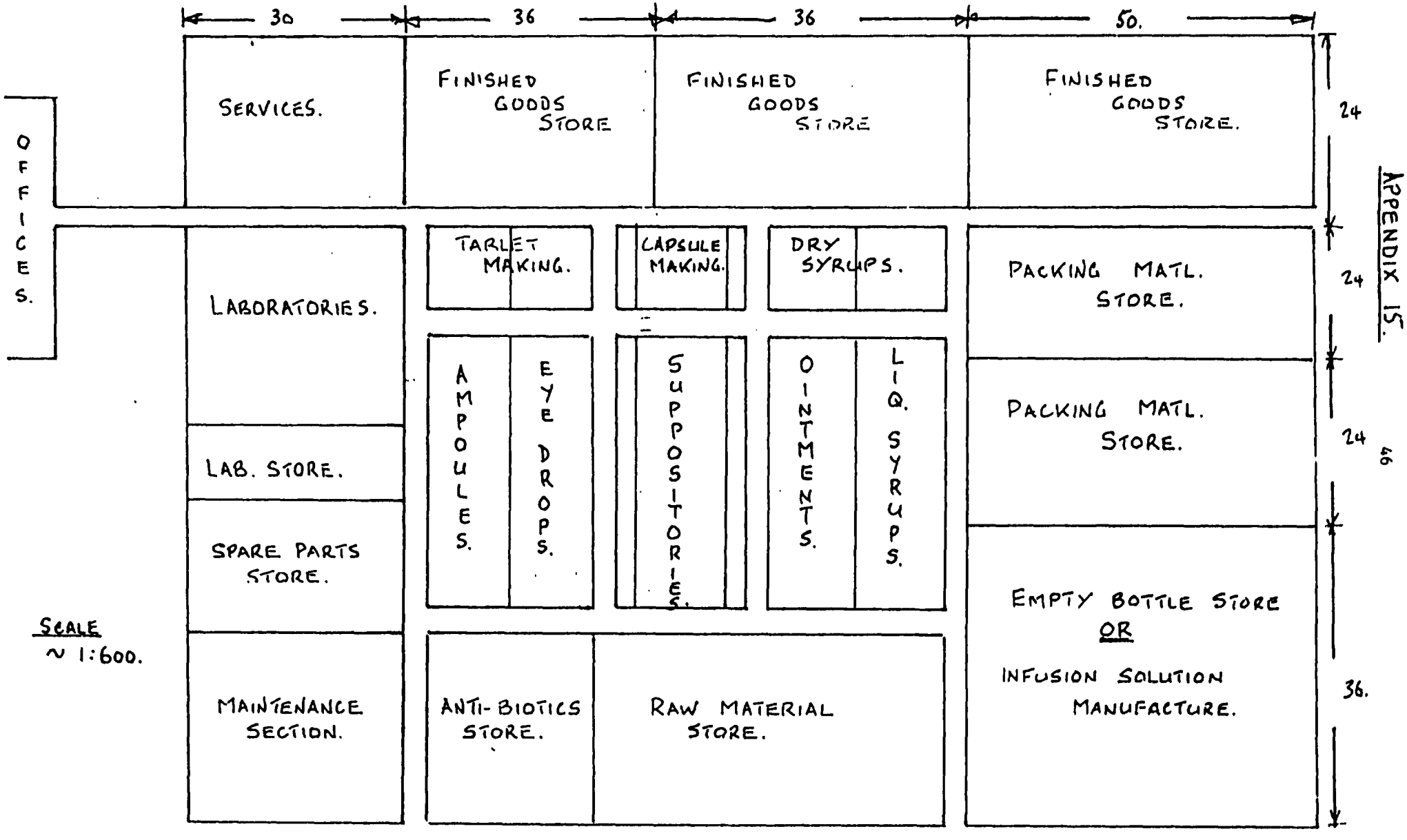
Brow 13/4/89.



DIMENSIONS NOT CRITICAL - APPROX. 1m. x 1m. x 0.75m. DEEP.

THAMECO: PROPOSED CHAMBER IN WATER INLET LINE FOR FLOCCULATION BY ALUM.

20/4/89.



THAMECO: GENERAL LAYOUT OF ALLEPO FACTORY SHOWING PRINCIPAL ACTIVITIES.

APPENDIX 15.

APPENDIX NO. 16

Outline of Proposed Study Tour

Candidate: THAMECO Technical Director
Duration: 1 month
Host: A large scale, multi-product factory, having properly segregated product lines, complying with high standards of GMP, producing large volumes of sterile fluids. The preferred host would be:

The Boots Company, Beeston, Nottingham, England.

Topics to be reviewed:

i) segregation of non-compatible product lines
ii) standards of GMP and SOP
iii) staffing of packing lines, production targets
iv) handling of large volume sterile fluids
v) preparation of small volume injectables

Should the Boots Co. not be available, the only alternative known to the writer would be the Government Pharmaceutical Organization (GPO) Bangkok, Thailand.

APPENDIX NO. 17

Suggested Fellowships

Fellowship No. 1

Tablet making technology
Candidate: pharmacist directly involved in tablet manufacture
Duration: 1 month
Host: the work should be planned with Fette equipment in mind. The Fette Co. may be able to nominate an appropriate host.

Topics to be reviewed:

i) granulation methods, wet/dry
ii) problems encountered during compression
iii) review of materials available for excipients, lubricants, disintegrants, special purpose ingredients.
iv) sources of colouring/flavouring agents
v) flow characteristics of powders
vi) influence of moisture on tablet compressibility
vii) maintenance of press tools
viii) film coating technology
ix) film coating materials and formulations

Notes:

a) THAMECO may wish to exclude items (viii) and (ix) until they have decided on the supplier of a film coating machine. At that time they may wish to send a candidate for training on that specific equipment.

b) In view of the climatic conditions in Syria, training time should be confined to film coating. Sugar coated products are unsuitable for Syria.

c) Prof. Hendrix of University of Ghent may have suggestions for a host if Fette Co. cannot comply.

Fellowship No. 2

Quality Control - Instrument Analysis
Candidate: graduate chemist/pharmacist. Analyst
Duration: 2 months - possibly split between two candidates
Host: month 1 PYE UNICAM
month 2 BECKMANN

Topics to be reviewed:

i) development of analytical procedures
ii) use of equipment and interpretation of results
iii) selection and preparation of reagents
iv) vitamin/steroid analysis
v) amino-acid analysis

If possible (vi) air sampling and efficiency of filters - a short period at Camfil, Trosa, Sweden would be appropriate.

Appendix No. 17 (Cont'd.)

Fellowship No. 3

Pharmacology - general procedures
Candidate: pharmacologist
Duration: 1 month
Host: to be identified

Topics to be reviewed:

i) establishment of pharmacological data base for existing products
ii) improvement of efficacy of existing products
iii) evaluations of new formulations
iv) routine screening of anti-allergenic products
v) formulation, testing and screening of non-steroid anti-inflammatories
vi) investigation of alternative drug delivery systems

APPENDIX NO. 18

Job description for Follow-up Mission

No. 1 - Production Expert

Expert: Senior industrial pharmacist/chemical engineer
Duration: 3 months (Refer to Note 1 below).

Activities

i) review the status of the vieal filling line, commission same
ii) review the status of improved dust collection and GMP in tablet making department
iii) review the status of raw water treatment
iv) in association with the Development Director, analyse the product mix to be handled by the Damascus and the Allepo factories
v) prepare drawings/layouts of specific areas at Damascus and Allepo so as to build in a component of GMP
vi) advise on the selection of plant and equipment for Allepo and for the better utilization of vacated areas in Damascus factory.

Note 1: The original terms of Project DP/SYR/86/009 provide for one only follow-up mission of 3 mm. In view of the urgency for Technical Assistance in Instrument Analysis, THAMECO may wish to vary the terms of the follow-up mission to include:

- Production Expert 2 mm.
- Instrument Analysis Expert 1 mm.

Job description - Follow-up Mission

No. 2 - Instrument Analysis Expert

Expert: instrument analyst, specific expertise in HPLC and amino-acid determinations
Duration: 1 month (Refer to Note 2 below).

Activities

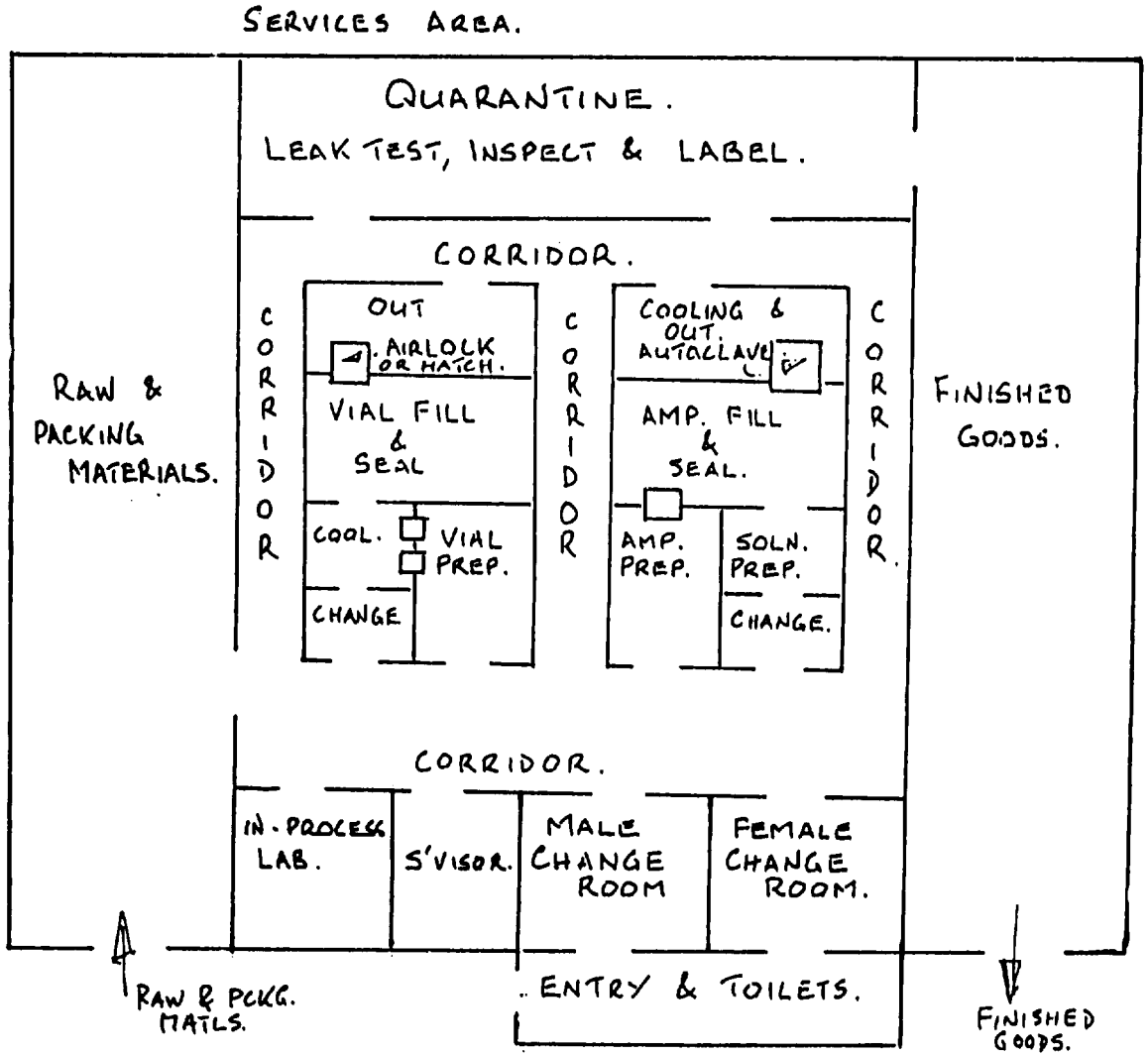
i) in house training of lab-staff on use of HPLC and amino-acid analyses
ii) sampling: selection and preparation of reagents
iii) reading and interpretation of results
iv) maintenance and calibration of equipment
v) development of analytical methods
vi) establishment of laboratory GMP

Note 2:

1. The Expert should be particularly strong in the use of Pye Unicam HPLC PU4030 and Beckmann Amino Acid analyzer equipment.

2. Should THAMECO elect to have the services of the Instrument Analyst detailed above, the duration of one month would reduce the period available for the Production Expert to two months, under the terms of Project DP/SYR/86/009.

3. UNIDO should not field the Instrument Analyst until the Fellowship detailed in Appendix 17 No. 2 has been completed.



THAMECO: BLOCK DIAGRAM SUGGESTED FOR STERILE SUITE

NO SCALE FOR DISCUSSION ONLY.

NOTE: ALL ORGANIC PACKING MATERIALS (e.g. CARTONS) MUST BE REMOVED PRIOR TO LEAVING R. & P.M. STORE.

SERVICES: STEAM
PYROGEN-FREE WATER.
ELECTRIC PANELS.
AIR SYSTEMS.
MAINTENANCE.

ALL SERVICES & DUCTWORK SHOULD RUN ABOVE STERILE ROOMS - ALLOWING SPACE FOR MAINTENANCE WORK TO BE PERFORMED WITHOUT DISTURBING STERILE ROOMS.

Brown 12.4.89.

APPENDIX 20

CONTACT LIST - THAMECO

Mr. Majed Koudsi	-	General Manager
Mr. Riad Chamaa	-	Technical Manager
Dr. Bassam Kabani	-	Research Manager
Miss Fadia Al Bezreh	-	Production Manager
Mr. Bassam Haffar	-	Planning Manager
Ph. Yasser Nahlawy	-	Head of Tablet Department
Dr. Youssef Hiba	-	Head of Formulated Foods Dept.
Mr. Hsen Talal	-	Head of Capsule Department
Mr. Ahmed Al Jazar	-	Head of Maintenance Department
Mr. Mouhamed Saka	-	Head of Air-conditioning Department
Mr. Nahida Andoura	-	Head of Documentation and In-process Control