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HIGH-LEVEL CONSULTANCIES AND TRAINING

DP/SYR/86/009

THE SYRIAN ARAB REPUBLIC

Technical report: Pharmaceutical production in Syria, third visit, November 1992*

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 John T. Brown, expert in the pharmaceutical industry

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Vienna

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* This document has not been edited.

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TABLE OF CONTENTS

Introduction

The following report relates to a two month extension to project number DP/SYR/86/009: Pharmaceutical Production in Syria.

The extension was granted specifically to :-

Finalise the preparation of the Project Document entitled "Pharmaceutical Standards" in co-operation of the National Authorities and the WHO expert.

To work with the engineers of the Lequeux company and technical staff of Thameco in Aleppo on the commissioning of a facility for the annual production of 4 million litres of sterile injection solution; the Serum Factory.

To work with the Thameco engineers and technicians in Damascus on the installation and commissioning of a facility for the aseptic handling of antibiotics packed in vials; the Thimon line.

The following report should be read in context of the two previous UNIDO reports dated 28 April 1989 and 28 June 1991.

Explanatory Notes

1.Thameco: The Arabian Medical Co., Box 976, Damascus Syria

2.Exchange rate October/December 1992 Syrian Pounds S42 = US $1.00

3.GMP: Good Pharmaceutical Manufacturing Practice

4.SOP: Standard Operating Procedure

5.QA: Quality Assurance

6.QC: Quality Control

7.Key Persons- the Quality Controller and the Production Controller

8.MOH: Ministry of Health

9.MOI: Ministry of Industry

10.TNC: Transnational Corporations

Other References

1.Executive Action Document, National Drug Control Laboratory in Damascus - Dr. Jan Karlsen WHO consultant
12 Nov. - 14 Dec 1991
2.Towards a National Drug Policy for the S.A.R. - preparatory workshop report: Hogerzeil, Saleh, Herxheimer
22 -24 Dec. 1991
3.Mission Report Jan Karlsen Nov./Dec. 1991 Project ICP/EDV/011/VD
4.Drug Policy in S.A.R. - conference - 10pp. Copy provided as Appendix No. 36

Acknowledgements

The writer wishes to acknowledge with thanks the cooperation of the Thameco management and staff in Damascus and in Aleppo.

Great assistance was provided by the General Manager of Thameco Miss Fadia Al Bezreh and the Research / Technical Manager, Dr Bassam Kabani.

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The Regional Adviser to WHO, Eastern Mediterranean, Dr A. Saleh was invaluable in guiding the preparation of the Project Document DP/SYR/92/008 so as to integrate it into an ongoing WHO Country Project.

In the UNDP Damascus, thanks for the great interest and time devoted to the project by the Resident Representative Mr K. Hla, to the Project Officer Miss Nadia Kozak and to the Finance and Administration Sections.

Abstract

*Two month extension of Project DP/SYR/86/009 Pharmaceutical Industry in Syria.

*Cut back in Government expenditure on pharmaceutical manufacture.

*Further development of private sector drug manufacture.

*Public sector, Thameco, grossly disadvantaged, structural changes required, company acts as price regulatory mechanism.

*Status of the Thameco/ Lequeux installation - Serum Factory.

*Status of the Thimon line - downgraded to non sterile production

*Preparation of project document DP/SYR/92/008.

Chapter 1

SUMMARY AND RECOMMENDATIONS

1. After prolonged experience with Thameco between 1989 and 1991, it is clear that the company's underlying problems have not changed; the private sector has moved ahead at great speed and developed from the "me too" generic activity into license agreements with TNCs for domestic processing of speciality products with consequential inflow of sophisticated technology from the principals. The capital investment in private sector manufacture is estimated to be approaching US $ 100 millions.

2. Thameco is grossly disadvantaged vis-a-vis the private sector, working within an institutional framework which may have been acceptable when Thameco and Dimas were the only producers of Pharmaceuticals in Syria, but is totally inadequate for the changed circumstances of 1992.

3. The company has experienced attrition of its technical management from 45 pharmacists in 1989 to currently 13 pharmacists; they are confused, unhappy and reluctant to continue to work for Thameco. Their salaries and conditions of employment have not changed despite the fact that the same position and responsibility in the private sector would offer 8 - 10 times the Thameco salary.

4. Stock-outs continue to plague the company; the principal cause being the protracted lead times between initiation of tender and receipt of goods. This can exceed 12 months; with proper trading practice it should seldom exceed 8 weeks.

5. Thameco retains the potential to provide a valuable service for Syria by producing low price/ high quality medicines for the average wage earner. The Company's continued existence serves as a price control mechanism for generic type products; the prices of TNC speciality drugs cannot be controlled by this mechanism.

6. Thameco's current framework is resulting in the slow destruction of both the company and its staff; the authorities should seriously evaluate the need for, and the status of Thameco, using the objective UNIDO mission reports for guidance, and act promptly and decisively according to their decision.

7. Evidence for Thameco's uncompetitive status as an employer is starkly displayed by its continued inability to recruit a Production Controller for its US$ 3 million Serum Factory in Aleppo, this is despite months of advertising. The Quality Controller who has in fact been recruited is a newly graduated pharmacist with no industry background and insufficient experience to safely fulfil his Job Description. The fact that his salary is Syrian Pounds 2,500 per month, by contrast to the SP 25,000 per month being paid by an Aleppo private sector manufacturer, for the equivalent position, brings Thameco's problem into perspective.

8. The products of the Serum Factory are of a very critical nature, any mistake during the manufacturing process could result in the death of a hospital

patient. It is unreasonable to place the responsibility for their safe processing in the hands of underexperienced staff, yet the management is left with no alternatives within its existing framework.

9. The writer is opposed to running the Serum Factory until the appropriate numbers of qualified, experienced and trained senior technical staff, supported by qualified deputies is permanently available. The writer is also opposed to running the Serum Factory with Dimas staff on an expediency basis.

10. The Serum Factory cannot achieve its designed output of 16,000 x 1 litre packs in an 8 hour work day; the law should be varied in this unique and exceptional situation to permit the factory to operate on a split-shift basis.

11. The UNDP funding for DP/SYR/86/009 is now exhausted; the writer will explore the possibility of UNIDO SIS funding when in Vienna and also will attempt to secure some ongoing technical help for the Serum Factory through the UK Government cost sharing scheme British Executive Service Overseas (BESO).

12. UNIDO recommendations for installation and commissioning of the Thimon line have not been implemented; Thameco has wisely elected to downgrade the machine to a non-sterile operation, UNIDO assistance will not be required.

13. The Project Document for DP/SYR/92/008 has been modified to integrate it into an ongoing WHO/ MOH country programme supporting the National Drug Testing Laboratory and the Drug Inspectorate.

14. It is suggested that UNDP / UNIDO maintain a watching brief on Thameco /Serum Factory through DP/SYR/92/008 and when the situation warrants be prepared to provide further assistance through a GMP based project.

15. Technical suggestions made by UNIDO remain valid and should be implemented by Thameco at some convenient time. For quick reference they are listed below:-

Refer to 1991 Report

a) Raw Water	page	12.1	Alum flocculation
b) Laundry	"	14.4	Air-supply, ceiling
c) Electricity Supply		14.5	Power Factor
d) Boilers		15.6	Standby unit, hotwell
e) Air Quality		15.7	Particle counting, sizing
f) Quality Control		16.10	Provide facilities
g) Key Persons		16.11	Recruit/train urgently
h) Boiler Room		18b	Lifting Equipment
j) Stores		18c	Racking
k) Water Treatment Rooms		19d	Bund Walls
l) Distilled Water Store		19e	Reduce Floor Loading
m) Emergency Exit		20h	Generator Room

Refer to 1989 Report

a) Increase storage volume in Damascus by providing racking and pallet handling equipment.

b) Provide central weighing department in Damascus
c) In the interest of Quality Assurance appoint Key Persons
- Production Controller - Quality Controller.
d) Validate Expiry Dates by means of accelerated ageing tests in climatic cabinets.
e) Review Raw Water treatment.
f) Provide effective dust extraction in tablet and capsule department.

Chapter 2

CONDENSATION OF MISSION REPORTS 1989 - 1991

1. Over the period April 1989 - December 1992 UNIDO has provided six man months of pharmaceutical production expertise to the Syrian public sector manufacturer, Thameco.

2. In 1989 the mission was seen by Thameco to be completely technical and to advise on some specific manufacturing difficulties. It was evident that some much deeper problems were preventing the Company from achieving its very considerable potential. Thameco gave the impression of being stagnant. However, the equipment was excellent, the management keen and the staff was proud to work for "their company", Thameco. Thus it was felt that with some objective appraisal and assistance it would be possible for the potential to be realised. The recommendations from the 1989 mission were basically technical, related to Thameco's perceived manufacturing difficulties, however in an effort to provide " a window on the (pharmaceutical) outside world " a number of UNIDO Fellowships and a Study Tour were proposed, utilising funds already available to the Project.

3. The 1991 mission revealed dramatic changes in the pharmaceutical sector; deregulation of the industry had occurred and over thirty private sector factories had exploded into being at a cost then estimated to be US $ 20 millions. Thameco, meanwhile, had failed to take up the UNIDO Fellowships / Study Tour, had not implemented the suggestions arising from the previous mission and, most significantly, lost many of its invaluable technical middle management to the vastly superior salaries and conditions offered by the private sector (for instance salaries increased by a factor of 10 X). The private sector was seen to be producing a " me-too" range of brand name generics in direct competition with Thameco products.

4. Thameco was however, proceeding with a US $3 million Serum Factory within the buildings of its planned factory at Aleppo. Concurrently, it was evaluating offers for machinery and equipment to a value of US $ 10 millions for the development of the remainder of its Aleppo premises as a comprehensive pharmaceutical factory, complete with laundries and the full spectrum of Quality Control facilities; to be in fact a modern version of the Damascus factory. UNIDO advocated caution in this approach and made a number of recommendations for improvement and consolidation of its existing operations, particularly in view of the erosion of technical management.

5. A matter of considerable embarrassment to Thameco in 1989 and in 1991 was the Thimon line, a "look alike" Robert Bosch machine for the aseptic processing of dry antibiotics for injection. The equipment had been with Thameco for several years, there were no instruction books and the Thimon Company had gone out of business. In addition, the area nominated for the machine in the Damascus factory was totally unsuitable both in location and floor space. However suggestions had been made in 1989 for its utilisation but not implemented by Thameco; in 1991 the location and floor space constraints had been relaxed a little and considerable time was spent devising a " best compromise" installation which would have provided an adequate operating ambience.

6. The main emphasis of the 1991 Recommendations, however, was no longer on technical matters but directed at the cause of Thameco's apparent stagnation, its institutional framework, constant "stock-outs" and most seriously its drastically reduced, unhappy and confused, technical management. An extension of two months was granted by UNDP to the project to allow UNIDO to assist in the commissioning of the Aleppo Serum Factory and to commission the Thimon line.

7. An imbalance in the development of Drug Policy vis-a-vis Industry Policy prompted UNIDO to suggest a Project, with MOI/ Thameco as the counterpart to produce some Industry Standards for Syria, which, by integration with the rapidly developing Drug Policy, would provide the Quality Assurance framework to control the rapid development of the private sector industry.

Chapter 3.

THAMECO IN 1992 - AN OVERVIEW

This chapter should be read in conjunction with Chapter 2 of the UNIDO report dated 28 June 1991.

1. The status of the pharmaceutical sector, particularly MOI/Thameco has changed significantly between the termination of the previous UNIDO mission (June 1991) and the commencement of the present final mission, October 1992.

2. There has been a severe cutback in Government investment in its industry; plans for the comprehensive development of the Aleppo factory - some US $ 10 millions - have been shelved, temporarily at least. However, the Serum Factory which was already being fitted out in 1991 has continued and is nearing completion.

3. The drug control and regulatory framework has developed within the Ministry of Health with support from WHO. There has been no parallel development within MOI, which has nominal responsibility for Thameco.

4. There continues to be intense activity within the expanding private manufacturing sector yet Thameco continues to operate as it did when it was one of only two pharmaceutical manufacturers in Syria (the other being Dimas, owned and operated by the military).

5. "Out of stock" is a comment frequently voiced about Thameco, not surprisingly since the methods of procurement of all imported materials are so complex and protracted that it can take upwards of 12 months between issue of tender for raw material and actual receipt of the material in Syria. In view of the ease of modern communications a typical "lead time" for material deliveries should not exceed 8 weeks; a lead time of 12 months is totally unacceptable.

6. In the new, deregulated industry climate of Syria, Thameco is grossly disadvantaged by holding to these traditional methods, management is reduced to moving from crisis to crisis, at the expense of running the business in a safe and effective manner.

7. Thameco also finds itself disadvantaged vis-a-vis the sector in general in the following ways:-

* working within an establishment which functions as a "landlord" rather than a policy making or an industry regulatory authority.
* working within premises in Damascus which are overdue for refurbishment.
* having an increasing inventory of broken down equipment for which spare parts are not available.
* moving from a strictly non-commercial operating mode (when Thameco and Dimas were the only drug manufacturers in Syria), with no real market experience, into the commercial free- for- all represented by the young and aggressive private sector.
* inability to react quickly to changed circumstances.
* a declining government investment programme.

* inability to attract appropriate numbers of qualified staff, due to its low salaries and uncompetitive conditions of employment.

* attrition of its technical staff to the attractive conditions offered by the private sector

* a generally confused, unhappy and reluctant workforce

8. The current problems of Thameco cannot be solely attributed to its in-house administration and management. The major constraint to Thameco's performance is the rigid infrastructure within which it is forced to operate and until this is changed any in-house management will face identical problems.

9. During the first UNIDO mission in 1989, the factory was described as "---one of the best equipped public sector factories yet seen---". At that time it was able to supply 40% of the National demand for medicine; it employed 45 pharmacists and had a proud and cohesive workforce. During the second UNIDO mission in 1991, it was evident that the Company had been allowed to stagnate, there had been no visible investment in major equipment, few of the 1989 UNIDO recommendations had been implemented, the number of employed pharmacists had been dramatically reduced and many of those still employed were simply waiting for the best salary offer to move into the far more attractive positions offered by the newly deregulated private sector. The mission report of 1991 made the following comments:- "--- Thameco's principal requirement ---is its staff, and this is where the private sector manufacturers have the ability to destroy the Company, by syphoning off its experienced mid-level technical staff with offers of greatly improved rates of pay---Thameco Departmental Manager would typically earn SP 3000 per month --- in contrast the private sector is offering SP 20,000 for a similar position with equal responsibility

Thameco does not just need " staff" or " more staff" it needs " Quality Staff". It must retain what it already has. The private sector has issued the challenge, Government must react quickly and positively or risk losing a strategically important component of Syria's health care system which has traditionally been able to meet 40% of the Nation's requirement for medicine -".

9. The final UNIDO mission October/December 1992 revealed that (with exception of the Serum Factory) few, if any, of any of the 1991 recommendations had been implemented. Thameco's most chronic problem, its mid-level technical pharmacists had now been reduced to 13 only, their rates of pay and conditions had not been improved, they were confused, unhappy and reluctant to continue to serve the Company. In Aleppo, the situation is even worse; the Serum Factory has not been able to recruit any pharmacist for the crucial position of Production Controller and the nominated Quality Controller does not have the experience necessary to perform his job.

10. Despite the best efforts of Thameco's in-house management team, there is no evidence that the situation is about to improve. The Company continues its decline, the external pressures for it to perform become more intense, criticism increases and yet the potential value remains.

11. The status of the public sector manufacturer needs to be very carefully evaluated; if correctly used it has great potential to make available to the average Syrian national good quality medicine at an affordable price whilst still allowing the private sector manufacturers to produce their " brand-name generics"

and to diversify into joint venture and license agreements with TNC partners for the production of speciality medicines.

12. The writer has watched the decline of Thameco over a period of 4 years; the causes of the decline are at the structural rather than the operational level. The Company, its management and staff are being destroyed in the process; within the existing framework there appears to be no possibility for the decline to be halted, let alone be reversed.

13. It was in this industrial climate that the 1992 mission was conducted.

Chapter 4

ACHIEVEMENT OF THE JOB DESCRIPTION

The final mission of project DP/SYR/009 comprised three elements:-

* in Damascus - to install the Thimon line for the aseptic processing of antibiotic powders
* to re-write the Project Document for DP/SYR/92/008
* in Aleppo - to assist in the commissioning of the Serum Factory

1. In relation to the Thimon line, the writer was intended to work with the engineers and technical staff of Thameco, to install/ commission the Thimon line.

1.1 The writer completed the 1991 mission with the clear understanding that a major component of the 1992 mission would be to commission the Thimon line. Much time had been spent in preparing layout drawings, relocating departments and suggesting modifications to the machine to improve its aseptic characteristics. However, for several reasons, Thameco has elected not to proceed with installation of the Thimon line for antibiotic handling but to downgrade it to a non-sterile powder operation. The Company has been in contact with a Bulgarian pharmaceutical manufacturer which has an identical machine and has offered to make appropriate modifications to the Thameco machine. In view of potential problems arising during use of the Thimon line and the lack of manufacturer support, this is seen to be a very rational decision, hence, no UNIDO time was spent in this area.

2. In relation to project proposal SYR/92/008 the original UNIDO draft entitled " Industry Policy " had been submitted to the Syrian authorities for information.

2.1 Its main thrust had been to correct a perceived imbalance between the relatively well developed Syrian Drug Policy and the inadequate nature of Industry Policy. Initial work in Damascus indicated clearly that the project heavy emphasis on Industry had been misplaced and that the project would have greater potential value to Syria if it were to be incorporated into an ongoing WHO/MOH programme supporting the National Drug Control Laboratories and the Drug Inspectorate.

2.2 Discussions with the WHO Regional Advisor revealed that the current WHO/MOH emphasis on drug policy through Quality Control and Inspection did not adequately address the basic concept of Quality Assurance, which states that the Assurance of the required Quality of a pharmaceutical cannot be achieved by testing the end products alone. It was recognised that Q.A. can be realised only through the integration of the two disparate elements of Drug Policy and Industry Policy. Thus it became clear that the UNIDO proposal was exactly complementary to WHO/MOH policy and on this understanding the project was redrafted.

2.3 Copy of the Revised Project document is submitted as a component of this report.

3. In relation to the Serum Factory.

3.1 Thameco had contracted for the provision of a turnkey plant for the production of 4 million X litre plastic packs of sterile intravenous solutions per year. The contractor,Lequeux being an independent subsidiary of the Getinge Company of Sweden, a world recognised manufacturer of sterilisers.

3.2 At the date on which the Thameco/Lequeux contract was signed, Thameco had plans to establish a comprehensive pharmaceutical factory in its extensive buildings at Aleppo. This facility was scheduled to include, interalia, sterile manufacture with dedicated laundry and laboratory accommodation for biological/micro-biological Q.C. procedures.

3.3 The timing of the final mission and the writers arrival in Aleppo had been scheduled by Thameco to coincide with the start up and commissioning of the Serum Factory.

3.4 On arrival at the Serum Factory, it was seen that the basic Lequeux engineering and installation had been completed in a very professional manner under the supervision of a Lequeux site engineer. With minor adjustments the plant is operational. It was inspected over a period of three weeks; clarification of several technical matters and minor procedural adjustments were required. Clarifications provided by Lequeux senior engineering staff were completely acceptable and the writer is satisfied that the installation is of a very high standard.

3.5 As a result of the UNIDO recommendations in 1991 concerning the laundering of sterile garments, Thameco/ Lequeux have provided a dedicated laundry and steriliser within the Serum Factory. However, this installation imposes a heat and humidity load, which had not been calculated into the original air treatment parameters; consequently it has not been possible to provide a sterile air supply to the laundry. It has also been necessary to leave the laundry without a ceiling so as to permit the heat and steam arising during the washing, drying and sterilising cycle, to escape. Clearly this does not comply with the requirements for a sterile laundry but it is the best possible compromise within the physical limitations of the facility. This deficiency should be corrected by Thameco at some convenient time after taking over the Factory from Lequeux.

3.6 Training of Thameco technicians had a high level of achievement but was constrained by the Company's inability to provide a Production Controller; hence the major training was concentrated on the Quality Controller and the Administrator. Documents relating to GMP, SOP and Factory Rules were prepared by the writer with specific assistance from Lequeux senior engineer. They were explained at length to, and understood by Thameco. They will be transcribed into Arabic for regular use. The list of documents is itemised in #j of this chapter and drafts are appended.

3.7 The entire staff - approximately 25 persons - was addressed on general matters related to the industry. Three topics were discussed at length, in English, translated immediately into Arabic, and recorded in writing by Thameco. Duration was two hours, the topics were :-

* Responsibility - personal / corporate.
  - factory rules / consequences of non observance.
  - GMP / QC / Quality Assurance
* Hygiene - housekeeping.
  - personal hygiene.
  - human particulate contamination.
* Pyrogens - nature and effect.
  - origin and prevention.

3.8 The engineering staff - six persons- were addressed on specific matters, including:-

* Maintenance - QA / Machine Logs.
  - Preventive Maintenance.
  - Annual Shutdown / Pressure Vessel inspection.
* Break Downs - financial cost of unplanned stoppages.
  - economics of using Lequeux engineers to resolve specific problems
* General - matters related to the design, operation and inspection of equipment, provided by Lequeux.

3.9 Acting as Thameco's technical adviser, in the event of dispute with Lequeux, involved a significant period of time.

a) As mentioned in #3.2 of this chapter the original plan for the Aleppo site had included a complex of laboratories for general chemistry, biology and microbiology - the laboratories.
Subsequent to a change in Government investment policy, these plans were shelved, temporarily at least, and so the laboratories were lost, leaving the Lequeux as the only laboratory on the site. In view of its size, location and standard of equipment it is clear that the Lequeux laboratory was intended to be an In-Process check station only. It had not been intended to duplicate the laboratory of the main factory.

b) Working within the spirit of the 1989 contract and officially unaware of the changed status of the laboratories, Lequeux continued to provide its In-Process laboratory. Thameco, however, working to the letter of the contract, expects Lequeux to --- guarantee quantity, quality and specifications ---" of the products. This requirement clearly cannot be met by the In-Process laboratory. Further, the biological indicator tubes used to verify autoclave performance will not satisfy Pharmacopoeial standards for proof of sterility of finished product; this calls for filtration and microbiological testing which has not been provided by Lequeux. A parallel problem exists in reference to pyrogen testing, however, this may be capable of early resolution since Thameco is in process of completing animal houses and Lequeux is providing test equipment.

c) Other areas of difference between the Companies, concern the unwillingness of the contractor to initiate test runs according to a previously established timetable. Thus, although the writer's mission was timed to cover commissioning of the plant, it was not possible to witness even a single full scale production run.

d) Due to a complex overlapping of cleaning, maintenance and production operations, the plant will produce its designed output of 16,000 X 1 litre bags per day, only by operating on a "split shift" system. This requires the factory to remain open for 12 hours per day, although each individual worker will be employed for the standard 8 hours (excluding overtime). Until raised by the writer, the possibility of split shift working had not been envisaged and it appears to be in breach of Syrian Law, which limits work to an 8 hour day. However, it would have been clear at the outset of this project in 1989, that to produce 16,000 packs in a total elapsed time of 8 hours would add, at least, 50% to the cost of distillation, steam raising, filling, overwrapping, solution making, water storage and sterilising equipment. This is an important matter and it is recommended **that in the unique and exceptional case of the Serum factory the Law should be varied to permit the Factory to achieve its target.** In addition, due to the expected long hours and intense work load, it is imperative that Key Persons - Production Controller and Quality Controller are fully supported by qualified and trained deputies.

e) The situation is exacerbated by the fact that the original signatories to the contract are no longer employed by their respective companies. It is understood that a meeting of senior officers of both companies has been convened; at the time of this report no date had been set. Certainly no concrete outcome can be expected before this mission terminates on December 8, 1992. Arbitration cannot be ruled out since each party could make a case against the other, based upon perceived non-performance. However, many of these perceived failures are insubstantial and due to lack of clear understanding between the parties. The implications of arbitration have been discussed with Thameco in Aleppo and in Damascus.

f) Of greater concern to the writer than the contractual matters described above is Thameco's inability to recruit an adequate number of appropriately qualified technical management staff to run the Serum Factory. To date only the Quality Controller has been appointed, the other Key Person, the Production Controller has not been appointed. This is a serious omission since the complex nature of the plant, its logistics, its designed output and the critical standards demanded by intravenous products call for a high level of technical maturity, experience and authority from both the Production Controller and the Quality Controller. As explained in #3.6 above, the writer provided a "crash course " in factory operations to the Quality Controller and the Administrator. This however, does not qualify them to operate a factory of this nature and sensitivity. Lequeux is contracted to provide training in France for the Production and Quality Controllers, each for two months, followed by further work with a French pharmacist on the actual equipment in Aleppo for a further month. In order to maximise the value of this training it is imperative that Production Controller and Quality Controller are trained concurrently, so that they share a common understanding of the production / Q.C. operations and can clearly recognise their responsibilities towards their own jobs and their joint responsibility to attainment of the high standards of Quality Assurance demanded by this product range.

g) In order to alleviate this problem in the short term, it is understood that Thameco has arranged with the military factory, Dimas to "borrow" some Dimas staff to assist in the start up of the plant. The writer is opposed to this

expedient for the following reasons:-

* Dimas is known to operate in a far less stringent manner than is planned for the Serum Factory; once introduced into the Serum Factory, bad habits could become extremely difficult to correct.

* Whilst it does in fact produce intravenous solutions, Dimas is not specifically experienced on the Lequeux plant, which could lead to misunderstandings and conflict between Dimas / Thameco and the Lequeux commissioning team.

* The Dimas solution is a short term expedient only, at most for a few months, by which time the Government will have developed specific expectations of the Serum Factory; these will not be sustainable in the absence of its own senior technical management team when the Dimas support is removed.

* To force the issue by insisting that the Factory "must produce" could be a recipe for disaster and cost the Company the remains of its already tarnished image.

h) In terms of providing ongoing direct technical help to the Serum factory, for UNIDO this is not a possibility within the terms of SYR/86/009 or any other currently foreseen project. However, the possibilities for SIS assistance will be investigated with UNIDO in Vienna. Action has been initiated to secure some assistance on a cost sharing basis through the British (Government) Executive Service Overseas (BESO) programme, by which retired executives of major UK companies may be made available at relatively little cost to the host company. This matter will be followed up by the writer and advised directly to Thameco.

j) A list of documents prepared by UNIDO, discussed, explained and understood by Thameco for use in the day to day operations of the Serum Factory is provided below.

Document Name	Appendix Number
Responsibility Chart	1
Job Description - Production Controller	2
- Quality Contoller	3
Factory Rules - No. 1 House Cleaning	4
- No. 2 Personal Hygiene	5
- No. 3 Prestartup Procedures	6
- no. 4 Complaints & Recall	7
- No. 5 Validation of Balances	8
Laboratory Practice	9
Standard Operating Procedures	
- No. 1 Rinsing mixing tanks	10
- No. 2 Filling mixing tanks	11
- No. 3 Raw material introduction/ Weighing	12
- No. 4 Solution making	13
- No. 5 Preparation for Filling	14
- No. 6 Filling, Sealing & Inspection	15
- No. 7 Overwrapping	16
- No. 8 Sterilising	17
- No. 9 Packaging	18

Other Appendices

Chapter 5

FUTURE ACTION

1. For Thameco in general:-

1.1 The viability of Thameco is now in the balance as never before. In the overall context of pharmaceutical manufacture in Syria, Thameco is grossly disadvantaged and destined for imminent collapse unless prompt and positive action is taken to give it freedom to compete on an equal footing with the private sector manufacturers.

1.2 UNIDO has produced 3 mission reports dated April 28 1989, June 28 1991 and the current report. They provide an objective overview of what was described as "--- one of the best equipped public sector factories yet seen---"; they go on to describe the progressive decline which has taken place over the 4 year period to date, leaving Thameco in a moribund condition with disillusioned staff and a badly tarnished image of stock outs due to the constraints imposed by its institutional framework. These problems have been brought into sharp focus by the dynamism of the recently deregulated private sector.

1.3 Future action for the Serum Factory and Thameco Damascus will have no meaning unless and until the Company's underlying problems are corrected.

1.4 The objective tools to support this correction have been provided; UNIDO can do no more, urgent action should be taken by the Syrian authorities.

2. For Serum Factory.

2.1 The most pressing need for Aleppo is to recruit the Production Controller and together with the Quality Controller urgently commence training with Lequeux in Paris and subsequently with a French pharmacist in Syria.

2.2 During the final training stage in Syria, it would be extremely valuable for the deputy Quality & Production Controllers to be present.

2.3 Future action also in need of urgent attention involves provision in Aleppo of accommodation, furniture and equipment to provide comprehensive Quality Control facilities for all Raw / Packing Materials and Finished Goods, by chemical, biological and microbiological methods. It is understood that this action has already been initiated by the technical management of Thameco; in view of the extreme urgency of the situation it will be of great value if the traditional tender system of procurement can be waived in favour of a direct purchase authorisation.

2.4 The Serum Factory requires an immense amount of assistance to achieve and sustain its designed capacity within an appropriate framework of Quality Assurance and GMP. Such assistance is not available in Syria. Funding for Thameco from UNDP within SYR/86/009 has been exhausted by this final mission. Future plans for projects in the drug sector are of a much more general nature and will not have the ability to provide the same amount of attention to an

individual operation. However, within the context of any forthcoming project, related to the drug sector, UNDP/UNIDO should maintain a watching brief on the status of Thameco and the Serum Factory with a view to provision of further assistance in the area of GMP when the situation warrants.

2.5 The writer will explore with UNIDO, Vienna the possibilities of SIS funding for the Serum Factory and also will contact the UK Government scheme BESO; the writer will deal directly with Thameco in this latter matter.

Chapter 6

OUTLINE OF ADDRESS TO SYRIAN PHARMACEUTICAL MANUFACTURERS ASSOCIATION

Date: October 31 1992 Location: Damascus MOH
Attendance: About 50 persons; private sector/ public sector/Drug Inspectorate.
Opened by H.E. Dr. Iyad Shatti - Minister of Health.
Convened by Dr Habib Abboud - Director of Drug Testing Laboratories and Drug Inspectorate.
Previous Speaker Mr M. Okopski, Technical Manager, Eli Lilly Basingstoke, U.K.

Topic: Our Common Interest : The Drug Industry
Built on STANDARDS - Drug Standards
- Material Standards
- Equipment Standards
- defined by Pharmacopoeia

What are " Industry Standards"?
Are they covered by GMP?
GMP is a GUIDE to Good Manufacturing Practice;
merely having the guide book is no guarantee of having Good Manufacturing Practice.
To build a house according to a GUIDE is to invoke LUCK
Remove LUCK provide FOUNDATIONS
What do STANDARDS mean/refer to?
Mean: clear, unambiguous parameters, agreed and accepted worldwide
Refer to: everything that happens in the industry which does not relate to the dosage form
Basically three components:- SOP
Engineering
Methods

Expansion SOP - Rules for Housekeeping. personal hygiene etc. inprocess control/ sampling; FIFO/ documentation systems etc.

Engineering - International standards for motors, switch gear etc. but what about domestic constructions - duct work etc. possibilities for contamination dead space, Legionnaire's disease etc. We need STANDARDS for objective proof that things are being done correctly.

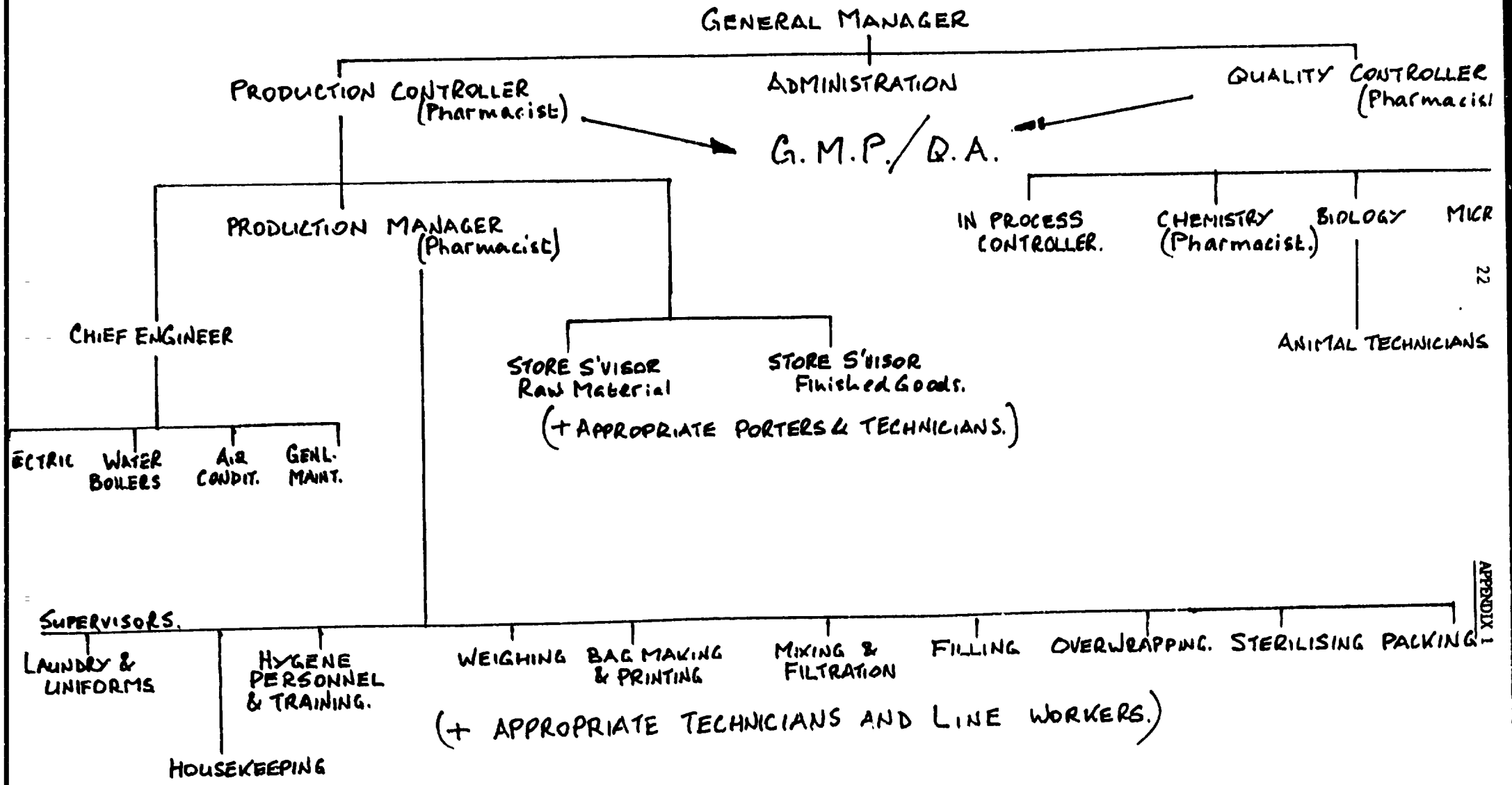
Methods eg. clean room garments - conditions for air/water/laundry; how to test for sterility; what equipment to use; where to test ie. at the knees/ seat or in the middle of the back. May seem like a lot of effort for a sterile gown but this is an integral part of our responsibilities and part of the overheads which soak up our profitability.

Thus we come full circle Drug Standards plus Quality Control integrated with Industry Standards plus GMP results in QUALITY ASSURANCE.

Appendix No. 1

THAMECO ALEPPO — SERUM FACTORY

RESPONSIBILITY CHART TECHNICAL STAFF — NOVEMBER 1992



APPENDIX 1

Provisional JOB DESCRIPTION : PRODUCTION CONTROLLER - ALEPPO

1. In conjunction with the QUALITY CONTROLLER establish a written programme of G.M.P.,S.O.P.,and Q.A. Specific responsibilities must be clearly defined.

2. Recruit and train appropriate staff for production ares equipment,operations and records.

3. Establish production norms.

4. Procure,and store correctly,all necessary Raw Materials,Packing Materials,Intermediates and Finished Goods.

5. Manufacture and distribute Finished Goods according to G.M.P. & Q.A. standards,in line with quantities specified by management.

6. Maintain Production Areas,Stores and surrounding areas in "Inspection Condition" at all times.

7. In conjunction with the Quality Controller establish and implement a system of manufacturing and packing documentation.

8. Continuously monitor the foregoing matters.

9. Report directly and independently to General Management.

Provisional JOB DESCRIPTION : QUALITY CONTROLLER - ALEPPO

1. In conjunction with the PRODUCTION CONTROLLER establish a written programme of G.M.P.,S.O.P.,and Q.A. Specific responsibilities must be clearly defined.

2. Establish,verify and implement all Quality Control procedures.

3. Establish standards for all Raw Materials, Packing Materials,Intermediates and Finished Goods.

4. Prepare written standards for all laboratory re-agents

5. Establish and validate a system of Expiry Dates.

6. Establish and implement a system of Acceptable Quality Limits (A.Q.L.) for all materials used in production.

7. In conjunction with the Production Controller establish a system of manufacturing and packing documentation.

8. Independent of the Production Controller approve or reject materials in accordance with the standard test results.

9. Establish and implement " In Process" test procedures.

10. Provide appropriate accommodation and safeguards for all aspects of Chemical,Microbiological and Animal testing.

11. Continuously monitor the above matters.

12. Report directly and independently to General Management.

APPENDIX 4

THAMECO ALEPPO FACTORY RULES — SERUM FACTORY NUMBER 1 — HOUSE CLEANING

Manufacture of Serum is a very demanding activity. Conditions of air, water and engineering have been designed exactly to minimise the risk to all users of the products.

Failure to comply with the basic rules of house cleaning will result in conditions deteriorating which puts the product at risk.

House keeping is of prime importance and is the unambiguous responsibility of the Production Controller, working through a suitably qualified and trained supervisor.

Beware that house keeping standards often deteriorate gradually so that it is not easy to quantify the extent of the deterioration.

The following points are particularly important, they are not exclusive:-

a) the supervisor should be carefully selected and trained

b) training should be reviewed at least every six months

c) the supervisor must be provided with a detailed, written job description,which must be explained verbally to the supervisor by the Production Controller

d) the supervisor must be provided with appropriate staff to fulfil the requirements of the job description

e) the supervisor must be provided with appropriate equipment to fulfil the requirement of the job description

f) the supervisor must maintain a daily cleaning log, which is monitored and signed by the Production Controller each week. All deficiencies such as damaged woodwork or painted surfaces,broken glass windows etc., inoperative lights must be recorded

g) the log must clearly indicate the cleaning and sanitising methods which are in use.

Basic procedure is as follows:-

1. All toilets, showers and wash hand basins are to be cleaned and sanitised daily.

2. All lockers and changing rooms are to be cleaned out each day and doors left open, personal belongings must not be allowed to accumulate.

3. All waste, paper, plastic etc. is to be removed from production areas immediately upon completion of production activity.

4. All horizontal surfaces, window ledges, tops of doors etc. are to be freed of extraneous material daily.

5. All walls are to be washed and sanitised weekly

6. All black area floors and corridors are to be vacuum cleaned daily.

7. Corridors and floors in clean areas are to be washed daily with detergent solution and sanitised.

8. Sanitising agents should be varied at least each week to avoid development of resistant strains of micro-organisms.

9. In stores, air conditioning plant rooms and other warm, dark,moist or humid areas great care must be employed to prevent insect and/ or vermin contamination. All rubbish must be removed and the area sprayed regularly with an appropriate aerosol. Care must be taken to protect raw and packing material from the aerosol.

APPENDIX 5

THAMECO ALEPPO FACTORY RULES — SERUM FACTORY NUMBER 2 — PERSONAL HYGIENE

In the production of Intravenous Solutions personal hygiene is of greatest importance. The human body is probably the most serious source of particulate contamination in the entire factory. It is the most difficult to control.

Contamination from air, water, and machines can be controlled by good design and engineering; human contamination can only be controlled by paying maximum attention to personal hygiene. Each individual must take personal responsibility for following the hygiene standards set by management.

Human contamination has two principal sources:-

a) skin flakes
b) hair

People generate contamination even when sitting still. The level of contamination increases rapidly as the activity level increases; the following table refers

ACTIVITY	PARTICLES PER MINUTE
Sitting or standing with no movement	100,000
Simple arm movements	500,000
Average movement	1,000,000
Walking slowly	5,000,000
Walking quickly	7,500,000

Particles 0.3 micron or larger
Reference: Design & Operation of Clean Rooms : Dr P. Austin

The most important means of reducing human particulate contamination are:-

1. Limit the number of staff working in critical areas to the minimum required to do the job properly.
2. Provide and use correctly suitable protective clothing.
3. Install and implement the highest standards of personal hygiene.
4. Reduce operator movement to the minimum by efficient work practices.

The above demands a serious commitment from the Company and from each individual worker; rigorous supervision from management is imperative. Factory rules are intended to benefit the workers and to protect the product; they must be obeyed at all times.

Only factory clothing and footwear to be worn in the factory.

Food and drink not to be brought into the factory.

Smoking is forbidden in the factory.

Showers must be taken before entering clean areas.

Any worker leaving a clean area for whatever reason must follow the entire routine before re-entering the clean area eg. after toilet visits, after rest breaks etc.

Any worker having skin infection or abrasion, hair or finger nail infection, common cold, intestinal, respiratory or diarrhoeal diseases must report the condition to the supervisor. They should be sent home or given alternative non-critical work until the condition is completely cured.

Management should provide regular medical checks, at least every six months, for staff working in clean areas.

APPENDIX 6

THAMECO ALEPPO SERUM FACTORY

FACTORY RULES NUMBER 3 PRE-START UP PROCEDURE

Before any manufacturing operation is commenced the following procedures must be observed. This is the joint responsibility of the Production Controller and the Quality Controller together. They, or their nominees, must together inspect each area to be used and each machine or other equipment which will be involved at any part of the manufacturing operation

The following points must all be completely satisfied and a "Production Diary" dated and signed by both persons must be filled before any manufacturing activity is permitted

1. All work areas and surroundings must be clean and free from any material not specifically concerned with the current batch, particular attention must be given to raw or packing materials or documents relating to previous day's activity

2. All controllers and warning devices (particularly Magnahelix air pressure sensors) must be working correctly

3. All machine guards and covers must be undamaged and in place

4. Each machine, tank,filter bank etc. must carry a sticker to show that it has been cleaned, sanitised and serviced as appropriate.

5. Each piece of major equipment to be used must be clearly identified with a card bearing the following details:
Date, batch number, quantity, product description/standard and machine identity eg. "mixing tank # 2 " , "filter bank # 3 " etc.
On completion of the production run these cards should be attached to the manufacturing document as part of the batch record

6. All personnel should be dressed in an appropriate manner for their work. Clothing must be in a good state of repair and all fastenings done up correctly

7. All personnel for critical areas must confirm verbally that they have observed Factory Rules No. 2 "Personal Hygiene" and are free from any condition which may be prejudicial to the product.

APPENDIX 7

THAMECO ALEPPO SERUM FACTORY

FACTORY RULES NUMLER 4 COMPLAINTS & PRODUCT RECALL

1. All complaints about a pack or product, from whatever source must be immediately channelled, in writing, to the Quality Controller, in order that a full picture of the status of complaints may be put together revealing any trends

2. A complaint may lead to the need for a product recall. Any action taken as a result of a complaint must be prompt and in accordance with a written procedure. Such procedure should be clearly understood by all persons concerned with its implementation.

3. Records of complaints should be regularly reviewed by Quality and Production Controllers together with the General Manager. Specific problems should be addressed immediately.

4. A written recall procedure must be capable of implementation at any time, day , night and holidays included. Persons responsible for initiation of a recall include:

the Quality Controller
the Production Controller
the General Manager
or their appointed and trained nominees

Action may be initiated by the group or by any individual member of the group

5. Having established a recall procedure it should be tested for effectiveness and practicality. It should be reviewed from time to time. In the event of changes in senior staff, new comers must be thoroughly trained in the operation of a product recall.

6. In the event of a recall the Directorate of Drug Control at MOH must be informed immediately. Also all drug distributors and agents must be instructed to quarantine their remaining stocks and to recall that which is in the market; any defective material which is in transit at the time of the recall must be immediately quarantined when it reaches its destination.

7. All recalled material should be immediately placed in quarantine, pending investigation and disposal instructions.

8. A notification of recall must include:

a) product name, strength and batch number
b) nature of the defect
c) action to be taken
d) urgency of the action to be taken
e) warning to recipient to retain this notification in order that goods in transit can be checked

APPENDIX 8

THAMECO ALEPPO SERUM FACTORY

FACTORY RULES NUMBER 5 VALIDATION OF BALANCES

1. This factory rule refers to all balances in the factory and in laboratories.

2. Each balance should be identified by a unique number which is clearly marked on the instrument itself.

3. A record card should be established for each balance and must be kept with the balance at all times and be available for inspection

4. Validation of balances shall be divided into two segments
   a) for daily action by production staff
   b) for weekly action by Q.C. staff

5. Daily activities are:-

5.1. check that the balance and its surroundings are clean and completely free from extraneous material, dust etc.

5.2. check that the balance is perfectly level and not resting against any object which could influence or limit its ability to swing freely.

5.3. check that power cords and recorder/printer connections are in good condition.

5.4. check for absence of liquids or powders under the weighing platform.

If the foregoing is absolutely correct the balance may be used for any weighings within its designed capacity.

6. Weekly activities are:-

6.1. 1 through 4 above

6.2.if 1 through 4 above are absolutely correct the Quality Control inspector should use a Standard Weight (say 50g for analytical instruments and say 2kg for production balances) to verify that the balance is reading and printing accurately.

6.3. if the balance complies with all the above mentioned standards, the inspector should sign and date the balance record card. Failure to comply with the above mentioned standards should result in that balance being taken out of service until the fault is corrected.

APPENDIX 9

THAMECO ALEPPO SERUM FACTORY

LABORATORY PRACTICE

1. Control laboratories must be designed and equipped to fully support the operations performed in them.

2. Ample storage should be provided for the orderly keeping of standards, retention samples and documents.

3. Chemical, microbiological and biological laboratories must be separated from each other and from production areas.

4. Animal houses should be completely segregated from production and laboratory areas.

5. Animal and microbiological waste must be carefully disposed of, preferably by incineration. Whilst waiting disposal such material must be safely stored.

6. Sensitive laboratory equipment, eg. balances and optical equipment should be properly protected and located so as to function correctly.

7. Physical equipment eg. balances and optical equipment should be regularly validated and serviced by trained technicians. Equipment logs must be kept up to date showing work done and dates for future service visits.

8. Any equipment seen to be malfunctioning or overdue for service should be withdrawn from operation.

9. Operating instructions (the manufacturer's instruction book) should be filed for easy access for all laboratory equipment.

10. Where possible analytical methods should include a stage to verify that equipment is working correctly eg. use of a standard solution or a blank measurement.

11. Control laboratory equipment must be kept clean and appropriately protected.

12. Laboratory personnel should wear clean protective clothing and protective equipment when dealing with hazardous materials.

13. All analysts' records and calculations should be kept in a bound book together with basic data on which calculations and test results were derived. This record must be retained by the laboratory for at least three years after the date of the final entry.

14. Where contract analysis is performed the nature and extent of the analysis should be agreed, in writing, between Thameco and the Contractor. Signed protocols of all test methods should be available for inspection in Thameco's laboratories. The method and volume of sampling should be agreed, as should the formal retention of test records and keeping samples.

15. Although analysis and testing has been performed by a contractor, responsibility for the finished products rests entirely with Thameco.

SAMPLING PROCEDURE

Correct sampling procedures are of vital importance in the development of the Quality Assurance profile of a product. Correct sampling procedure imply that the samples are statistically representative of the batches of materials from which they are taken. It is important that sampling procedures, approved by the Quality Controller are employed at all times. Sampling instructions should be in writing and provide the following details:-

1. the method of sampling
2. the equipment to be used
3. the quantity of sample to be taken
4. instructions for subdivision of the sample
5. the type of container to be used for keeping the sample and the instructions to be provided on the container label.

Special precautions for sampling sterile products should be directed towards getting a truly representative cross section of the load.

A very common cause of spoilage of raw material is that containers which have been sampled are not properly reclosed by the sampler. Consequently contaminants are able to enter the container and spoilage due to moisture will make the raw material unfit for use. The responsibility for closing of all sampled containers rests solely with the sampler.

Each sampled container should be clearly identified with an adhesive label showing:-

material name
manufacturer's batch number
date sampled
signature of sampler

This label should be placed beside the red " QUARANTINE " label.

Raw material sample size should be sufficient to permit subdivision into three equal parts; the first for immediate testing, the second as backup for the first sample and subsequent testing, the third part to become the Quality Assurance record and be retained as a keeping sample for at least one year after the raw material itself has been completely used.

It is important to be able to directly compare sequential batches of raw material. Therefore Raw Material Cards, set out as below, should be kept up to date; this will reveal trends in Raw Material quality and identify reliable suppliers.

APPENDIX 10

THAMECO ALEPPO SERUM FACTORY

STANDARD OPERATING PROCEDURE

NUMBER 1 RINSING MIXING TANKS

Number of operators - 1 Duration - 10 minutes

Note: During the rinsing operation all tank openings, except one small triclip must be closed.

Mixing tanks must be rinsed each day before production commences.

When changing from one product formulation to a different formulation tanks must be thoroughly rinsed.

Production activities should be planned in a manner which permits the weakest solution to be prepared first eg.

first batches- water for injection
later batch- normal saline
last batches- dextrose/saline

Procedure:
1. Connect flexible rinsing hose equipped with rinsing nozzle onto the tank.
2. Open the supply line carrying apyrogenic rinsing water to the tank.
3. Open the tank drain valve.
4. After ten minutes close the rinsing water supply valve, allow time for any rinsing water in tank to flow to drain. Close the drain valve.
5. Disconnect and remove the rinsing water supply line and the rinsing nozzle. leave the triclip open.

APPENDIX 11

THAMECO ALEPPO SERUM FACTORY

STANDARD OPERATING PROCEDURE

NUMBER 2 FILLING MIXING TANKS

Number of Operators - 1 Duration - 20 minutes

Note: Manhole must be closed during filling.
Leave the rinsing triclip port open during filling to avoid pressure build up.

Procedure:
1. Check tank level on digital display and confirm that tank is empty.
2. Open apyrogenic water supply line to tank.
3. When tank is 30% filled the agitator will start automatically.
4. When tank is filled to working capacity a green signal light will automatically be switched on.
5. This green light will remain on during the mixing/filling cycle until the tank is once again empty.
6. During the filling operation a sample of water must be submitted for In-Process Quality Control and must be approved before any additional processing takes place.

APPENDIX 12

THAMECO ALEPPO SERUM FACTORY

STANDARD OPERATING PROCEDURE

NUMBER 3 RAW MATERIALS - INTRODUCTION & WEIGHING

Number of Operators -1 storeman
1 pharmacist /supervisor
1 weighing room technician

Note:Weighing is a critical activity, particular attention must be paid to personal hygiene, handling, and cleanliness of all containers and equipment. All balances and equipment must have been prepared in accordance with Factory Rules No.5.

Procedure:

1.Raw material must be transported to Room 37 by the storeman. The outer wrapping must be removed and taken away by the storeman.
2.Unwrapped material must be transported to Room 8 (airlock) by clean room staff and the second wrapping removed.
3.The material (dextrose) is poured into previously tared plastic containers, fitted with lids and suitably labelled, each container should be loaded with approximately 30 kg. of Dextrose.
4.Transfer the number of containers necessary to give the required weight of Dextrose plus one spare container with Dextrose to make the final weight adjustment.
5.Before weighing, enter the following data into the printer:
Date Batch Number
Product Description
Balance Identification Number
Tare of Container
Identification of Supervisor
6.Proceed to weigh the raw material until correct amount is obtained.
7.Have procedure validated by I-P Quality Control.
8.Remove all printouts from the printer and attach to the production document.
9.Label each container with a completed transfer ticket
10.Transfer the raw material to the mixing department and ensure that it is accepted and signed for by the mixing supervisor.

APPENDIX 13

THAMECO ALEPPO SERUM FACTORY

STANDARD OPERATING PROCEDURE

NUMBER 4 SOLUTION MAKING

Number of Operators - 1 supervisor Duration - 20 minutes
1 technician

Note:Filling is a critical activity, particular attention must be paid to personal hygiene, handling and cleanliness of all equipment and containers.

Procedure:

1.Ensure the mixing tank is labelled with :-
Date Batch Number
Description
Tank Number Identification of Supervisor.

2.Ensure that tank is filled to working capacity and that agitator is running.

3.Open loading port (Manhole) and slowly pour the raw material into the water, avoiding any build up of undissolved powder on the bottom of the tank. This will require approximately 10 minutes.

4.When all raw material is added and dissolved submit for I-P Quality Control.

5.If solution fails to comply with standard, make the adjustments and submit a further sample for I-P Quality Control.

6.Close tightly all openings of mixing tank.

7.Attach to the tank a notice " Warning Vessel Under Pressure".

8.When signalled by the filling supervisor, open the compressed air line to the mixing tank. A pressure of 2 bar will automatically be maintained. Check this on the manometer.

APPENDIX 14

THAMECO ALEPPO SERUM FACTORY

STANDARD OPERATING PROCEDURE

NUMBER 5 PREPARATION FOR FILLING

Number of Operators - 1 supervisor Duration - 30 minutes

Procedure:

1. Check that the filtration line corresponding to the tank in use has been cleaned and sterilised and that the nonreturn valve is orientated to the filling position.
2. Remove the "Filter O K " sticker and attach to batch records. Do not use the filter bank if it does not carry a "Filter O K " sticker.
3. When ready to commence filling signal the mixing supervisor to apply transfer air pressure to the tank.
4. Vent filter housings commencing with that closest to the mixing tank.
5. Rinse the filter bank, pipework and filling pumps with fresh solution; fill and set aside 2 X 1 litre bags from each filling pump.
6. Submit sample bags to I-P Quality Control to ensure that solution at the pumps is within specification.
7. When approved by I-P Quality Control proceed to filling the batch.

APPENDIX 15

THAMECO ALEPPO SERUM FACTORY

STANDARD OPERATING PROCEDURE

NUMBER 6 FILLING, SEALING & INSPECTION

Number of Operators - 1 supervisor
13 (fillers
(inspectors

Note:Each filling station must be provided with :-
* a tray of tube closures (stoppers)
* a trolley of printed PVC bags
* a labelling machine with sufficient labels
a reserve of stoppers in a closed container must be kept in the filling room.
The first two filled bags from each filling station will contain indicator tubes.

Procedure:
1.Switch on the filling pumps:- first open the pump valve then open the solution supply line
2.Attach an empty PVC bag to each filling spout
3.Fill to capacity, remove, and insert tube closer
4.Pass closed bag to inspector
5.Inspector checks bag for:-
Print
Fill
Seal
Absence of leaks when pressed
Absence of visible particulate contamination.
6.If OK Inspector applies sticker showing:-
Manufacture Date
Expiry Date
Batch Number.
7.If not OK, set the bag aside and call Supervisor.
8.Place good bags on conveyor to Overwrapping Department.
9.Near the end of the filling run the Supervisor will count the number of reject bags and advise the Overwrapping Supervisor.
10.At the end of the filling run, stop the filling pumps by attaching PVC bags to the filling spouts, close the supply line and finally close the pump valve
11.At the end of the day, or when changing between batch formulations, the filling line, filters and pumps must be rinsed for 10 minutes with apyrogenic distilled water.
12.After final rinse, submit a water sample to I-P Quality Control for confirmation of freedom from undissolved salts and/or Dextrose.

APPENDIX 16

THAMECO ALEPPO SERUM FACTORY

STANDARD OPERATING PROCEDURE

NUMBER 7 OVERWRAPPING

Number of Operators - 1 supervisor
4 technicians

Note: a)Off-take conveyor must be working to allow removal of overwrapped bags.
b)Supervisor must ensure that all pockets are continuously filled.
c)Should the Overwrapping Machine have to be stopped for any reason, except emergency, it must be stopped by pressing the normal "STOP" button not the "EMERGENCY STOP" button.
d)Polypropylene overwrap film must be brought to room 37 by store staff and then to Overwrapping Room by technicians. Film must be stored overnight in Overwrapping Room to allow it to stabilise to the room conditions and provide a perfect seal.
e)The Overwrap provides mechanical strength for the PVC bag during the sterilising cycle. To maximise this there should be a minimum of air spaces within the sealed overwrap.

Procedure:

1.The first 12 bags from the Filling Department will contain steriliser indicator tubes. Overwrap these bags and set them aside.
2.Provide 4 autoclave trolleys with all shelves except the lowest, removed. Align them with their locking mechanism in the same direction.
3.Place two trolleys beside the offtake conveyor and commence loading.
4.Into each bottom shelf load 3 bags per row for 11 rows = 33 bags.
5.Fit the second shelf and load 6 bags per row for 11 rows = 66 bags.
6.Continue loading each succeeding shelf with 66 bags until the trolley is completely filled. It will contain 1 row of 33 bags plus 7 rows of 66 bags = 495 bags.
7.The Supervisor will load 3 bags, containing indicator tubes randomly, but well separated in each trolley.
8.When the first two trolleys are completely filled replace them with the two empty trolleys and continue to fill as directed in # 4,5,6 above.
9.A full autoclave load comprises 1,980 bags, when 3 trolleys and 6 shelves of the final trolley have been filled 1,815 bags will have been loaded.
10.The Overwrapping Supervisor must check with the Filling Supervisor how many reject bags remain in the Filling Room and add this number to 1,815. The total number represents the number of litres of solution which have been withdrawn from the mixing tank. The Overwrapping Supervisor will subtract the total number filled from 2,000 and advise the Filling Supervisor how many more bags remain to be filled.
11.When this figure is reached the Overwrapping Supervisor will advise the Filling Supervisor that the batch filling is completed.
12.Any residual solution in the mixing tank will be let to drain.

APPENDIX 17

THAMECO ALEPPO SERUM FACTORY

STANDARD OPERATING PROCEDURE

NUMBER 8 STERILISING

Note: a)Sterilisation is achieved by exposing the load to 121 Celsius for 20 minutes.
b)Heating up and cooling time must be added to give the total autoclave cycle time.
c)Air support pressure during heating, sterilising and cooling is 1.2 bar.
d)Final temperature of bags at the end of the complete cycle is 60 Celsius.
e)These parameters are already programmed into the autoclaves in the fixed cycle position (Key Switch on "Fixed")
f)Other parameters may be programmed by placing the Key Switch in "Adjustable" position
UNAUTHORISED CHANGE OF PROGRAMMED PARAMETERS IS ABSOLUTELY FORBIDDEN
g)If a change is required for any reason it may be effected only by the Production Controller in conjunction with the Quality Controller and with the understanding and written authorisation of Thameco Senior Technical management
h)If a change of steriliser parameters is made it must be reflected in a revised SOP and a revised Production Document.
j)The following values are measured and displayed on the autoclave instruments during the cycle:-

* Chamber Temperature
* Chamber Pressure
* Temperature in the Dummy Load
* Elapsed sterilisation time
* Actual sterilisation time constantly updated during the cycle (Fo).

Procedure:

1.Fit a new chart into the autoclave recorder
2.Place the 4 loaded trolleys in front of the autoclave with their locking mechanisms correctly aligned.
3.Load them into the chamber in sequence.
4.Ensure that they are locked together.
5.Insert a temperature probe in one bag - the DUMMY LOAD- and place it in the door basket.
6.Close the autoclave door and commence the sterilisation cycle.
7.Check that the recorder chart is rotating and that the pens are correctly set.
8.At the end of the sterilisation cycle the "Cycle End" indicator lamp will be illuminated.
9.Check the chamber internal pressure on the pressure gauge. If no overpressure is indicated, the door may be opened. If overpressure is indicated do not open the door; advise the Supervisor and the Maintenance staff.

10.Remove the 4 trolleys using the winch and unlock them from each other.
11.The Overwrapping Supervisor must remove the indicator tube bags and reconcile the number of tubes collected with the number originally put in. If the number of indicator bags cannot be reconciled any further work on the batch is forbidden. Failure to achieve reconciliation may be cause for the batch to be rejected.
12.Collect the dummy load from the autoclave door pocket and keep it with the batch. Do not allow the dummy load bag to be confused with, or mixed into, the main load. It must be kept with, but separate from, the main load. If the dummy load is damaged or empty after sterilisation the load must be considered non-sterile.
13.Transfer the indicator tube bags to Quality Control for incubation.
14.Transfer the dummy load bag to Quality Control for inspection; if it is found to be normal in every way, it may be destroyed.

APPENDIX 18

THAMECO ALEPPO SERUM FACTORY

STANDARD OPERATING PROCEDURE

NUMBER 9 PACKAGING

Note: Each carton must be clearly labelled showing:-
*Name/Strength of Solution/Pharmacopoeial Standard
*Batch Number and Product Code
*Manufactured Date/Expiry Date
*Number of Bags and Volume per Bag
*Storage Conditions
*Name and Address of Manufacturer.

Procedure:
1. Transfer autoclave trolleys to packing conveyor.
2. Remove bags, starting with the top shelf, place them on the conveyor.
3. Reject any bags which are imperfect.
4. Pack the bags into cartons, 5 bags per carton.
5. Close and label the cartons.
6. Stack the closed and labelled cartons onto pallets in 5 layers of 8 cartons ie. 40 cartons per pallet.
7. Use the pallet truck to transfer the filled pallets to the wrapping machine, and wrap.
8. One batch comprises 10 pallets, each of 40 cartons of 5 bags ie. 2,000 bags; confirm that this is correct for each batch. Report any batches which do not comply.
9. Use the pallet truck to transfer the wrapped batch to the Finished Goods Quarantine Store to await Q.C. approval for transfer to Finished Goods store.

APPENDIX 19

THAMECO ALEPPO SERUM FACTORY

STANDARD OPERATING PROCEDURE

NUMBER 10 UTILISATION OF MIXING TANKS

Note:There are 4 tanks each with its own digital display. Each tank / display must be uniquely identified. Any tank may be reserved for the rinsing function; for the purpose of this SOP it is assumed that tank number 4 is the rinsing tank.

Procedure:

1.In tank No. 1 prepare batch No. 1 - duration 1 hour. Submit for In-Process Q.C.
2.In tank No. 2 commence preparation of batch No. 2 - duration 1 hour
3.On receipt of In-Process approval for batch No. 1, pressurise the tank, position the "WARNING, VESSEL UNDER PRESSURE" notice and commence filling.
4.Complete preparation of batch No. 2 in tank No. 2 and submit for In-Process Q.C.
5.In tank No. 3 commence preparation of batch No. 3 -duration 1 hour.
6.On receipt of In-Process approval for batch No. 2 prepare tank No 2 for pressurisation and filling when batch No. 1 is completed.
7.Complete preparation of batch No. 3 in tank No. 3 and submit for In-Process Q.C.
8.Filling of batch No. 1 will be finished during completion of batch No. 3.
9.Tank No. 1 will now be almost empty and must be isolated from the filtration/filling station and prepared for mixing of batch No. 4 as follows:-

*Close the air supply valve
*Open the drainage and then the outlet valves
*Allow the tank to drain and depressurise to atmospheric pressure
*Remove the "WARNING" notice
*Rinse the tank with apyrogenic water
*Close all valves.

Tank No. 1 is ready to be used for mixing batch No.4.
Repeat this procedure on tanks No.2 & No.3 until the daily output of 8 batches has been attained.

THAMECO ALEPPO — SERUM FACTORY. — APPENDIX 20.

DOCUMENT NUMBER 1 — PRODUCT SPECIFICATION — MASTER DOCUMENT NO:

DOCUMENT PREPARED BY: CHECKED BY: DATE:
DOCUMENT REVISED BY: CHECKED BY: DATE:

PRODUCT NAME : THAMECO REFERENCE : DATE:
PHARMACOPOEIAL STANDARD

DESCRIPTION: AN OVERWRAPPED, COLOUR CODED, PRINTED PVC BAG WITH INTEGRAL HANGING LOOP, CLOSED WITH A SEALED GIVING TUBE, BEARING AN IDENTIFICATION TICKET SHOWING MANUFACTURE DATE, EXPIREY DATE AND BATCH NUMBER.
VACUUM SHRINK WRAPPED IN POLYPROPYLENE AND TERMINALLY STERILISED BY STEAM.
BULK PACKED IN CARDBOARD CARTONS CONTAINING 5 x 1L. BAGS.
CARTONS SEALED AND LABELLED WITH INFORMATION:-

- MANUFACTURER NAME AND ADDRESS.
- CONTENTS NUMBER AND VOLUME.
- PRODUCT NAME STRENGTH AND PHARMACOPOEIAL STANDARD.
- PRODUCT REFERENCE CODE.
- BATCH NUMBER, DATE OF MANUFACTURE, EXPIREY DATE
- STORAGE CONDITIONS: BELOW 20°C, NOT STACK MORE THAN 5 CARTONS

SAMPLING INSTRUCTIONS: RESAMPLING: EVERY 6 MONTHS.

THAMECO ALEPPO SERUM FACTORY

APPENDIX 21.

DOCUMENT NO. 2 RAW MATERIAL SPECIFICATION

MASTER DOCUMENT

DOCUMENT PREPARED BY: CHECKED BY: DATE:

DOCUMENT REVISED BY: CHECKED BY: DATE.

MATERIAL NAME: THAMECO REFERENCE CODE

PHARMACOPOEIAL STANDARD:

MATERIAL DESCRIPTION:

APPROVED SUPPLIER(S) :

SAMPLING INSTRUCTIONS: A.Q.L. %

TEST FOR IDENTITY & PURITY:

LIMITS:

STORAGE CONDITIONS:

RETEST INSTRUCTIONS:

THAMECO ALEPPO SERUM FACTORY APPENDIX 22.

DOCUMENT No 3. PACKING MATERIAL SPECIFICATION MASTER DOCUMENT.

DOCUMENT PREPARED BY: CHECKED BY: DATE:
DOCUMENT REVISED BY: CHECKED BY: DATE:

ITEM NAME: THAMECO REFERENCE CODE:
PHARMACOPOEIAL STANDARD:

ITEM DESCRIPTION:
APPROVED SUPPLIER:

ACCEPTABLE DIMENSIONS:

SAMPLING INSTRUCTIONS: AQL %:
STORAGE CONDITIONS:
RETEST INSTRUCTIONS.

THAMECO ALEPPO SERUM FACTORY. APPENDIX 23.

DOCUMENT NO. 4 : WEIGHING DOCUMENT. MASTER DOCUMENT.

DOCUMENT PREPARED BY: CHECKED BY: DATE:

DOCUMENT REVISED BY: CHECKED BY: DATE:

PRODUCT NAME: THAMECO REFERENCE NO. DATE:

BATCH SIZE: BATCH NUMBER:

RAW MATERIAL REQUIRED	STANDARD	QUANTITY PER PACK	QUANTITY PER BATCH.

WEIGHING DETAILS : REFER STANDARD OPERATING PROCEDURE NO. 3.

MATERIAL	BATCH NO.	ANALYTICAL CERT. NO.	WEIGHT REQUIRED	WEIGHT TAKEN	DATE	WEIGHED BY	CHECKED BY

MATERIAL DELIVERED BY : Date:

RECEIVED BY :

THAMECO ALEPPO DOCUMENT NO.5 SERUM FACTORY. APPENDIX 24.

SAMPLE PAGE OF GOODS RECEIVED NOTE (G.R.N.) BOOK.

G.R.N. NUMBER: DATE:

RECEIVED FROM

MATERIAL DESCRIPTION:

PHARMACOPOEIAL STANDARD :

MANUFACTURER'S BATCH NUMBER:

QUANTITY : NUMBER OF CONTAINERS:
QUANTITY PER CONTAINER: Kg/Litres.
TOTAL QUANTITY: Kg/Litres.

CONDITION OF GOODS

PHYSICAL DAMAGE: CONTAINERS.
WATER DAMAGE: CONTAINERS.
OTHER DAMAGE CONTAINERS (PROVIDE DETAILS)
TOTAL NUMBER OF DAMAGED CONTAINERS _____

PLACE GOODS IN QUARANTINE STORE, APPLY QUARANTINE STICKERS

COPY THIS DOCUMENT:
ORIGINAL TO PRODUCTION CONTROLLER.
SECOND TO QUALITY CONTROLLER.
THIRD TO ADMINISTRATION
FOURTH RETAINED IN STORE

THAMECO ALEPPO — SERUM FACTORY — APPENDIX 25

DOCUMENT NO. 6: IN PROCESS CONTROL — MASTER DOCUMENT

DOCUMENT PREPARED BY: CHECKED BY: DATE:
DOCUMENT REVISED BY: CHECKED BY: DATE:

PRODUCT NAME: THAMECO REFERENCE: DATE:
BATCH SIZE: BATCH NUMBER: SAMPLED BY:

TESTS PERFORMED	PHARMACOPOEIAL STANDARD	ACTUAL RESULT	PASS	FAIL

RESULTS. a). THE BATCH COMPLIES WITH ALL PHARMACOPOEIAL STANDARDS AND IS RELEASED FOR FILLING.
b). THE BATCH FAILS TO COMPLY WITH PHARMACOPOEIAL STANDARDS AND REQUIRES ADJUSTMENT AS FOLLOWS:

SIGNATURE OF QUALITY CONTROLLER:
DATE:

DOCUMENT No. 7. APPENDIX 26.

SAMPLE OF QUARANTINE LABEL TO BE APPLIED BY STOREMAN IMMEDIATELY ON RECEIPT OF ANY MATERIALS.

THAMECO ALEPPO SERUM FACTORY

MATERIAL IN QUARANTINE

DATE RECEIVED: G.R.N NUMBER:

MATERIAL:

SUPPLIER:

CONTAINER No. of CONTAINERS

NOT TO BE USED

TO BE PRINTED IN BLACK ON RED ADHESIVE PAPER.

DOCUMENT No. 8. APPENDIX 27.

EXAMPLE OF FORMAT OF "SAMPLED" & "APPROVED" STICKERS.

THAMECO ALEPPO SERUM FACTORY

APPROVED

DATE APPROVED: APPROVAL NUMBER:

G.R.N. NUMBER:

THAMECO MATERIAL NUMBER:

MATERIAL

QUANTITY

APPROVED BY:

TRANSFER TO STORES.

TO BE PRINTED IN BLACK LETTERS ON GREEN ADHESIVE PAPER.

TO BE PRINTED IN BLACK LETTERS ON WHITE ADHESIVE PAPER.

MATERIAL SAMPLED FOR TESTING

G.R.N. NUMBER:

DATE SAMPLED:

CONTAINER No. of CONTAINERS.

SAMPLED BY: DATE:

DOCUMENT No. 9.

APPENDIX 28.

EXAMPLE OF "REJECTED" STICKER

THAMECO ALEPPO SERUM FACTORY

REJECTED

DATE GRN. NUMBER

MATERIAL

SUPPLIER: QUANTITY:

REMOVE TO REJECTED STORE.

AUTHORISED BY:

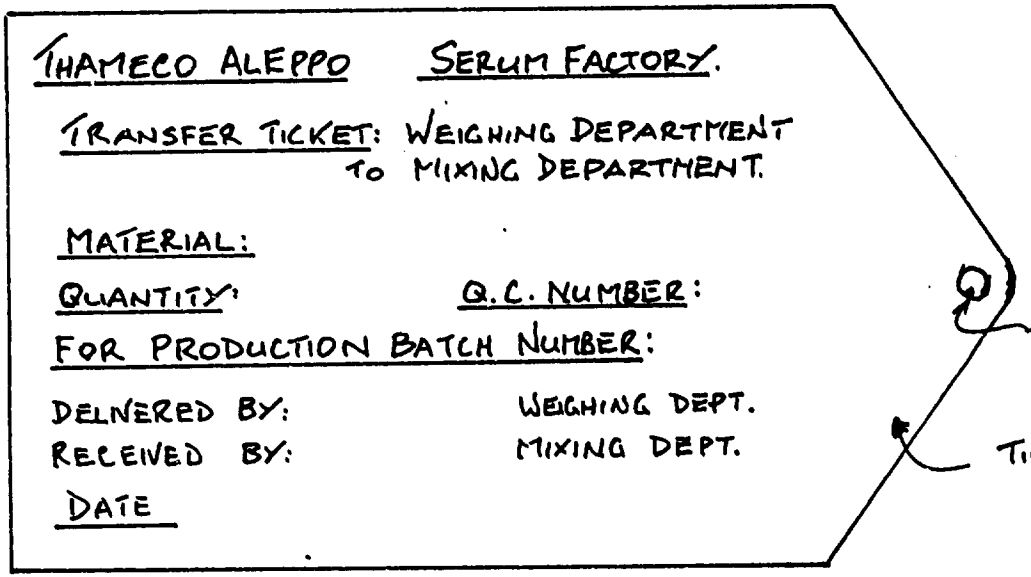
TO BE PRINTED IN BLACK ON RED ADHESIVE PAPER

DOCUMENT No. 10.

APPENDIX 29.

EXAMPLE OF TRANSFER TICKET FOR WEIGHED MATERIAL TO PASS FROM WEIGHING DEPT. TO MIXING DEPT.

ON COMPLETION OF TRANSFER, TICKET MUST BE CLIPPED TO "MIXING DOCUMENT" AS PART OF THE BATCH RECORD.



HOLE FOR ATTACHMENT TO BAG.

TICKET TO BE CUT FROM LIGHT CARTRIDGE PAPER OR CARDBOARD.

THAMECO ALEPPO DOCUMENT NO.11 SERUM FACTORY APPENDIX 30.

SAMPLE PAGE SHOWING LAYOUT OF 'PRODUCTION BOOK.'

MANUF. DATE	EXPIREY DATE	THAMECO CODE No.	PRODUCT NAME AND STANDARD	BATCH NUMBER	STRENGTH	BATCH INITIATED BY

DOCUMENT 12 APPENDIX 31.

IHAMECO ALEPPO SERUM FACTORY

SIMPLIFIED A.Q.L. SAMPLING INSPECTION CHART.

BATCH SIZE (UNITS)	AQL 0.10%			0.15%			0.25%			0.40%			0.65%			1.0%			1.5%			2.5%		
	n	P	F	n	P	F	n	P	F	n	P	F	n	P	F	n	P	F	n	P	F	n	P	F
2 - 50	ALL			ALL			ALL			ALL	0	1	ALL	0	1	13	0	1	8	0	1	5	0	1
50 - 90					0	1		0	1		0	1		0	1	13	0	1	8	0	1	5	0	1
91 - 150		0	1		0	1		0	1		0	1		0	1	13	0	1	32	1	2	20	1	2
151 - 250		0	1		0	1		0	1	32	0	1	20	0	1	50	1	2	32	1	2	20	1	2
251 - 500		0	1		0	1	50	0	1		0	1		1	2	50	1	2	50	2	3	20	1	2
501 - 1200		0	1		0	1		0	1	125	1	2	80	1	2	80	2	3	80	3	4	32	2	3
1201 - 3200		0	1	80	0	1	200	0	2		1	2	125	2	3	125	3	4	125	5	6	50	3	4
3201 - 10,000		0	1		0	1		0	2	200	2	3	200	3	4	200	5	6	200	7	8	80	5	6
10,000 - 35,000	125	1	2	315	1	2	315	1	3	315	3	4	315	5	6	315	7	8	315	10	11	125	7	8
35,000 - 150,000	500	1	2	500	2	3	500	2	4	500	5	6	500	7	8	500	10	11	500	14	15	200	10	11

n = Sample
P = Pass
F = Fail.

EXAMPLE: SAY NECK TUBES 10.000 Received AQL = 0.4% SAMPLE SIZE = 200
NOT MORE THAN 2 REJECTS - BATCH PASS.
3 REJECTS - BATCH FAILS.

Ref. DEF 131A LONDON H.M.S.O.

APPENDIX 31

THAMECO ALEPPO — SERUM FACTORY. — APPENDIX 32.

DOCUMENT No. 13. MIXING DOCUMENT — MASTER DOCUMENT No.

DOCUMENT PREPARED BY: CHECKED BY: DATE:

DOCUMENT REVISED BY: CHECKED BY: DATE:

PRODUCT NAME: THAMECO REFERENCE No.

BATCH SIZE: BATCH No. DATE:

MIXING TANK No. REMOVE "TANK CLEANED BY " STICKER AND ATTACH TO THIS DOCUMENT.

MATERIALS: REMOVE "TRANSFER TICKETS AND ATTACH TO THIS DOCUMENT.

PROCEDURE: FOLLOW STANDARD OPERATING PROCEDURE No. 4.

MIXING COMMENCED: TIME MIXED BY:

MIXING COMPLETED: TIME

IN-PROCESS CONTROL: SAMPLE TAKEN BY TIME TAKEN

RESULTS OF IN-PROCESS TESTING BATCH APPROVED REJECTED

ADJUSTMENT REQUIRED.

RESULTS OF RE-TEST IF SOLUTION WAS ADJUSTED BATCH APPROVED REJECTED

ATTACH Q.C. DOCUMENTS TO THIS FORM.

THAMECO ALEPPO — SERUM FACTORY. — APPENDIX 33.

DOCUMENT NUMBER 14 — FILTRATION FILLING & OVERWRAPPING — MASTER DOCUMENT No.

DOCUMENT PREPARED BY: — CHECKED BY: — DATE:

DOCUMENT REVISED BY: — CHECKED BY: — DATE:

PRODUCT NAME: — THAMECO REFERENCE: — DATE:

BATCH SIZE: — BATCH NUMBER:

REFER TO: S.O.P. NUMBER 5 PREPARATION FOR FILLING
NUMBER 6 FILLING SEALING AND INSPECTION
NUMBER 7 OVERWRAPPING

REMOVE "FILTER OK" STICKER FROM FILTER BANK AND ATTACH TO THIS DOCUMENT.
ATTACH ONE COMPLETED BATCH No., MANUFACTURE DATE, EXPIREY DATE STICKER TO THIS DOCUMENT

TIME FILLING STARTED
FINISHED

TOTAL TIME FOR THE BATCH.

BATCH YIELD: NUMBER OF BAGS IN TROLLEY No. 1
No. 2
No. 3
No. 4 _____

EXPLAIN ANY DISCREPANCY IN RECONCILIATION :-

TOTAL NUMBER OF FILLED BAGS
NUMBER OF WASTED BAGS. _____
TOTAL YIELD FROM THE BATCH _____

SIGNATURE OF SUPERVISOR:

THAMECO ALEPPO — SERUM FACTORY — APPENDIX 34

DOCUMENT NO. 15 STERILISATION — MASTER DOCUMENT NO.

DOCUMENT PREPARED BY: — CHECKED BY: — DATE:

DOCUMENT REVISED BY: — CHECKED BY: — DATE:

PRODUCT NAME: — THAMECO REFERENCE: — DATE:

BATCH SIZE: — BATCH NUMBER: — EXPIREY DATE:

PROCEDURE: FOLLOW OPERATING PROCEDURE No. 8.

AUTOCLAVE USED : No. 1 / No. 2.

BATCH RELEASED BY Q.C. FOR STERILISING YES/NO. ATTACH Q.C. RELEASE FORM TO THIS DOCUMENT.

DUMMY LOAD BAG CORRECTLY POSITIONED IN AUTOCLAVE DOOR YES/NO.

NEW RECORDER CHART FITTED YES/NO.

STARTING TIME : — FINISHING TIME :

TOTAL AUTOCLAVE TIME :

REMOVE RECORDER CHART AND ATTACH TO THIS DOCUMENT.

REPORT ANY ABNORMAL CONDITIONS OF THE STERILISATION CYCLE:

SIGNATURE OF SUPERVISOR: — TIME: — DATE:

RAW MATERIAL COMPARISON CARD.

DOCUMENT No. 16 APPENDIX 35.

RAW MATERIAL NAME: STANDARD: THAMECO CODE:

DATE		SUPPLIER	Q.C. NUMBER	TESTS PERFORMED/MONOGRAPH LIMIT.				APPROVED REJECTED	SIGNATURE DATE.
RECVD.	SAMPLED			PURITY	pH	OPT. ROTATION			

In implementation of the Directives of President Hafez Assad concerning self-reliance and scientific research, the Ministry of Health, in collaboration with the World Health Organization, in coordination with the Pharmacists' Association and the Medical Association, and with the contribution of public institutions and parties concerned with drugs, decided to hold a Conference on Drug Policy in the Syrian Arab Republic under the auspices of Dr M. Iyad Shatti, Minister of Health.

DRUG POLICY IN THE SYRIAN ARAB REPUBLIC

Introduction

Drugs are an essential component of the provision of health services, whether preventive or curative. Hence it is only to be expected that in any country a drug policy should evolve, along with ways and means of dealing with drugs, within the framework of the general objectives of health activities and the fundamental principles which constitute the basis of that country's health policy.

Thus, it seems imperative at this juncture to carry out a review of the most important foundations of the health policy in Syria. That policy can be briefly described as follows.

(a) The Government functions within a general framework, sanctioned by the President of the Republic, whose prime basis is self-reliance and self-sufficiency. The social objective sought by the State in the field of health is to bring about the attainment, by the whole population, of a level of health that will permit them to lead a socially and economically productive life. It is the objective generally known as Health for All by the Year 2000; it constitutes a part of the overall social and economic development process.

(b) The State is responsible for the health of the people, and must provide the prerequisites of health care in collaboration with all public sectors, and within the framework of economic pluralism, so as to assign to each individual, sector and institution a role in attaining the required level of health care.

(c) The basic health sector providing health services is a government sector, which in the implementation of its mission cooperates with the joint and private sectors, through comprehensive central plans.

(d) Primary health care is the essential part of the health service structure geared to achieving geographical coverage by basic health services, with special emphasis on preventive medicine.

(e) University training is linked to the actual needs of society in this field.

The Syrian Arab Republic has made considerable progress in the attainment of its health goals through successive five-year plans; over the past few years, emphasis has been given to the issue of drugs and related questions, and to the formulation of a clear drug policy in line with scientific developments and emerging economic realities.

Components of the national drug policy

I. Objectives of the formulation of a national drug policy

II. Public sectors concerned with the question of drugs

III. Criteria for selection of drugs

IV. Drug registration

V. Basis for pricing of drugs

VI. Drug supplies

VII. Drug quality assurance

VIII. Drug classification

IX. Drug information

X. Health education and the safe use of drugs

XI. Training of technical and administrative staff

XII. Research and development in drugs and pharmaceuticals

XIII. International technical cooperation

I. Objectives of the formulation of a national drug policy

The major features and objectives of the drug policy, in line with overall health objectives, are as follows:

1. Provision of drugs of reasonable quality and price in quantities sufficient to meet the health needs of the population.

2. Adoption of a national list of essential drugs which constitutes a general framework for local manufacture and imports of drugs, to be undated in accordance with national circumstances.

3. Promotion of and support for local production of drugs, and restriction of imports to drugs that cannot be produced locally.

4. Continuation of and support for the pioneering role of the public sector.

5. Encouragement of the joint and private drug sectors, guiding them to complement the work of the pioneering public sector so as to achieve the highest possible coverage of drug needs.

6. Promotion of the manufacture of drugs under their generic names and avoidance of duplication.

7. Encouragement for the acquisition of expertise and technology, with emphasis on transfer of technology.

8. Promotion of local production of materials required by the drug industry (starting materials, packaging materials, etc.).

9. Establishment of a national drug information centre.

10. Support for scientific research on drug manufacture and control, to ensure access to safe and effective drugs.

11. Training and development of technical and administrative staff working in the drug sector.

12. Rationalization of drug consumption and organization of drug information, with special emphasis on the List of Essential Drugs during courses and other forms of training.

13. Organization and strengthening of drug distribution outlets and networks to ensure equitable distribution and easy access to drugs by patients.

14. Unification of all bodies dealing with the manufacture, importation, control and regulation of drugs into one entity.

II. Public sectors concerned with the question of drugs

1. *Technical Commission on Drugs* (TCD)

The Technical Commission on Drugs is the body that approves drug policies, importation plans, and local manufacture. It is headed by the Minister of Health, and comprises experts from the Ministry of Health, the Pharmacists' Association, the Medical Association, the schools of medicine and pharmacy, public sector drug factories, and *Saidaliya*, together with representatives of other bodies concerned with drugs.

The functions of the Commission are as follows:

(a) Supervision of drug policy, follow-up of its implementation in line with the approved strategy.

(b) Determination of the medicinal drugs required for treatment (List of Essential Drugs).

(c) Adoption of the plan for the provision of drugs, including:

  (i) Plan for local manufacture by the public, joint and private sectors.

  (ii) Imports plan.

(d) Issue of licences for local drug manufacturing establishments.

(e) Issue of licences for the local manufacture of drugs.

(f) Selection of imported drug categories and approval of their registration.

(g) Supervision of all matters relating to medicinal plants, and approval of plans for their study, processing and importation.

(h) Establishment of specialized subcommittees and determination of their terms of reference.

2. *Ministry of Health*

(a) *The Directorate of Pharmaceutical Affairs* undertakes the following activities:

  1. Implementation of the decisions of the Technical Commission on Drugs.

  2. Implementation of drug regulations.

  3. Issue of import licences for starting materials needed for the local drug industry.

  4. Registration of imported drugs approved by the Technical Commission on Drugs.

  5. Licensing of locally manufactured drugs approved by the TCD.

6. Issue of certificates of origin for locally manufactured drugs.

7. Supervision of the importation and dispensing of narcotic substances.

(b) *The Directorate of Drug Control, and subsidiary committees in the Governorates*, undertake the following activities:

1. Implementation of the decisions of the TCD.

2. Monitoring of local drug manufacturing establishments run by the public, joint and private sectors.

3. Control of imported and local drugs.

(c) *TAMECO (Public Sector Drug Factories)* is an institution of the Ministry of Industry, producing medicinal preparations, baby formulae, and some veterinary preparations; it comprises:

(i) In Damascus: The Damascus Drug Factory
The Baby Formula Factory
The Veterinary Drug Factory

(ii) In Aleppo: The Aleppo Drug Factory
The Serum Factory

All products of TAMECO are sold to *Saidaliya*.

3. The *Al-Dimas Factory* for the manufacture of drugs and sera is a subsidiary of the General Establishment for Blood and Medical Industries, comprising a branch for the manufacture of solutions for injection, and other departments for pharmaceuticals (such as capsules, ampoules, tablets, liquid syrup, dry potions, ointments, suppositories, etc.).

Production plans for this factory are formulated under the supervision of and in the light of proposals by the TCD. Its products are distributed to the Military Medical Services, *Saidaliya* and the *Ministry* of Health.

4. *The General Establishment for Drug Trading (Saidaliya)*, is an economic service institution of the public sector with exclusive rights to the importation of drugs and the distribution of imported drugs and drugs manufactured locally by the public sector (TAMECO-DIMAS). It imports drugs in accordance with technical specifications and prices approved by the TCD, and determines the internal sale prices of such drugs on the basis of prices at the place of origin; it then distributes them to all parts of the country through its outlets in the governorates.

Policy on drug services management aims at:

(a) Unification of all bodies concerned with the manufacture, import, control and regulation of drugs into a single entity.

(b) Development of the administrative structure concerned with drugs in order to specify factions and ensure proper coordination.

(c) Establishment of a national drug information centre with a view to developing it into the main source of all drug information and development in the field, for the benefit of personnel in the pharmaceutical and health sectors.

III. Criteria for selection of drugs

1. Safety, quality and efficacy are prerequisites for the administration of drugs to patients.

2. Selection of drugs, whether imported or locally manufactured, is conducted with reference to a national list of essential drugs; this list constitutes an important part of national drug policy. The national list of essential drugs has been adopted in the light of the health, social and economic realities in our country and with a view to meeting the basic needs of our society.

The list was compiled in coordination with the competent health authorities and in collaboration with WHO. It is regularly updated to keep pace with scientific developments and the health situation in Syria.

IV. Drug registration

1. The registration file must contain the medical justification for registration, in addition to information pertaining to efficacy, safety and cost. It is important that complementary drugs remain at a minimum. The file must contain the following information:

(i) Composition of the preparation.

(ii) Pharmacological and pharmaceutical studies thereon.

(iii) Clinical and curative information.

(iv) Information on manufacture and analysis.

2. . Registration fees determined and charged at the time of licensing the product go to the Special Fund for Drug Research.

3. All local and imported drugs registered are reevaluated regularly and reregistered in accordance with the evaluation.

V. Pricing of drugs

1. *Local drugs.* Prices of local drugs are determined on the basis of cost, in addition to the following considerations:

(a) Cost of production including starting materials, filling, packaging, cost of quality assurance and potential wastage.

(b) Price incentives related to research, development, expertise and the technical performance of the factory.

(c) Cost of distribution, including transport, storage and promotion.

(d) Profit for manufacturer, distributor, and pharmacist.

2. *Imported drugs.* Prices are based on the cost of importation, as approved by the TCD.

VI. Drug supplies

Drug supply plans require an integrated statistical data base on the drug situation in the country, and on movements in that situation.

Drug requirements for the local market are met by imports or local manufacture of drugs, with emphasis on supporting local manufacture until drug security is achieved.

1. *Imports*

Drugs registered with the Ministry of Health in terms of technical aspects and price are imported through SAIDALIYA; the types of drugs imported are determined on an annual plan drawn up by the TCD, taking into consideration the plan for local manufacture.

2. *Local manufacture*

The drug policy aims at promoting and supporting the local manufacture of drugs in order to attain self-sufficiency in this field and dispense as far as possible with the import of drugs, by:

(i) Steering drug manufacturers to give priority to the production of essential drugs in sufficient quantities to meet the needs of the local market, and exporting any surplus of local drugs.

(ii) Directing national investment in the field of medicaments towards the manufacture of starting materials and other requisites of local production.

(iii) Creating the necessary technical capacity to manufacture pharmaceuticals.

(iv) Setting up drug control laboratories and facilities for research and development.

(v) Paying continued attention to the technical expertise required for this industry, and the control thereof.

(vi) Emphasizing the principle of transfer of advanced pharmaceutical technology.

(vii) Facilitating the importation of starting materials and production requisites, and promoting the consolidated purchasing of such materials.

(viii) Supporting the Central Laboratory for Drug Control to make it the most advanced reference laboratory, and enhance its capability to analyse all drugs; and giving priority to providing it with expert technical staff.

(ix) Strengthening drug control procedures, as regards both administration and inspection, so as to enhance their role at all stages of manufacture and distribution.

(x) Supporting public sector drug manufacture, especially by:

(a) giving priority to the manufacture of strategically important substances in public sector establishments;

(b) ensuring the constant flow of foreign currency needed for implementing the manufacturing plans;

(c) creating appropriate incentives for public sector personnel concerned with the production of drugs;

(d) organizing training courses for public sector personnel;

(e) ensuring that the public sector seeks to meet all the needs of public health facilities;

(f) achieving sufficiency for the public sector in supplying important items required for children;

(g) giving the public sector a pioneering role in the manufacture of basic drugs.

(xi) Developing and updating legislation and regulatory decisions relating to drug manufacture and control.

VII. Drug quality assurance

Drug quality assurance entails strict control of starting materials and finished products alike, including:

(i) Legislation, regulations and directives concerning quality assurance;

(ii) emphasis on the importance of drug control in all governorates;

(iii) development of technical staff capable of carrying out quality assurance;

(iv) strengthening of the certification and registration system by applying the WHO Certification Scheme.

Storage and distribution

Appropriate storage and distribution are two important elements in the supply of pharmaceuticals to the population as a whole, including remote parts of the country. To ensure this the following points ought to be taken into consideration:

1. The existence of appropriate distribution depots (temperature, humidity, lighting, etc.).

2. Proper means of transport and maintenance.

3. An appropriate administrative and technical system.

4. Strengthening the role of continuous training and development of personnel responsible for storage and distribution, such as pharmacists, technicians, administrators, inspectors, accountants, depot supervisors, and packaging and transport workers.

VIII. Drug classification

Drugs can be classified by their curative importance as life-saving drugs, essential drugs, and other drugs. This classification helps to direct efforts toward ensuring supplies in accordance with priorities, whether by local manufacture or by imports.

Drugs can also be classified by the method by which they are dispensed, as follows:

(i) prescription drugs for which the pharmacist keeps a record of supplies issued (narcotics);

(ii) prescription drugs (antibiotics, hormones, cardiovascular drugs, etc.);

(iii) OTC drugs (painkillers, Aspirin, paracetamol, some cough syrups, etc.).

Drug policies in this respect aim at developing or revising occupational legislation and regulations relating to the dispensing of drugs, at defining the terms governing the exchange of drugs within the same category, and at ensuring the safe and rational use of drugs.

Medicinal plants are considered an important means of treatment and may be used to benefit mankind, provided that:

(i) health conditions that could be treated with medicinal plants are defined;

(ii) ways and means of recognizing these plants and their active ingredients are devised, together with ways of making their use medically, socially, economically and culturally acceptable;

(iii) studies to evaluate the clinical efficacy and safety of drugs derived from such plants are conducted.

To this end, and to make optimum use of medicinal plants that are found or could be cultivated in Syria, it is desirable to establish a national committee on medicinal plants to undertake the study and regulation of such plants.

IX. Drug information

Information on drugs and the dissemination of promotional material have an effect on the supply and use of drugs; the undertaking and control of these activities are an essential part of drug policies.

Drug information is disseminated as follows:

1. Publication of an annual national drug manual, which is updated regularly.

2. Organization of continuing education seminars and lectures for health personnel.

3. Drug newsletters publish objective and reliable information.

4. The media disseminate the drug information newsletter approved by the competent health authorities.

5. Distinction between drug information and commercial promotion of drugs.

X. Health education and the rational use of drugs

The drug policy emphasizes the importance of prescribing and dispensing drugs in the appropriate manner, by physicians and pharmacists, as well as their use by patients and people in general. It reviews the problems of wastefulness, improper prescription of drugs, excesses in self-medication, and the treatment of minor ailments which do not require any medication; it also reviews the use of new and expensive drugs, especially when alternative, safe, high-quality and efficient drugs are available at reasonable prices. To ensure optimum use of drugs, the following measures must be taken:

(i) incorporation of drug information and sound methods of prescribing drugs into medical curricula (medicine, pharmacy, dentistry and nursing);

(ii) dissemination of separate scientific information on the rational use of drugs, particularly the information published by WHO and other bodies concerned with health and drugs;

(iii) organization of training courses and continuing education programmes on methods of prescribing, dispensing and handling drugs, for physicians, pharmacists, and paramedical personnel;

(iv) implementation of education programmes for the population on the safe use of drugs;

(v) continuous coordination among bodies concerned with drugs: the Ministry of Health, medical, pharmacists' and dentists' associations, schools of medicine and pharmacy;

(vi) emphasis on the role of teaching hospitals in educating medical staff about rational prescription practices.

XI. Training of technical and administrative staff

Implementation of the goals and components of drug policy requires the availability of appropriately trained technical, administrative and health personnel who can carry out their functions efficiently in all fields related to drugs and drug management, through:

(i) defining human resources needed for various facilities concerned with drugs;

(ii) taking the necessary measures to ensure continuing training and education for all technical and administrative staff, and strengthening cooperation in this respect with specialized agencies such as WHO and the International Federation of Pharmaceutical Manufacturers Associations;

(iii) drawing up long-term plans for the development of human resources, in keeping with developments in the drug situation;

(iv) emphasizing the role of universities and academic institutions in the development of technical staff in line with the actual needs, both qualitative and quantitative, of the drug sector, and in the development of teaching systems and curricula;

(v) making as much use as possible of regional cooperation (technical cooperation among countries in the same region), fellowships and international scholarships, conferences held in and outside the country, and training offered by WHO collaborating centres, with emphasis on the exchange of expertise in this regard;

(vi) creating a system of incentives for personnel working in the public sector to ensure the continued cooperation of efficient and competent staff, and to tackle the problems of pharmacists working in the public sector in the same way as those of pharmacists in the private sector.

XII. Research and development in drugs and pharmaceuticals

This constitutes one of the main features of national strategies for health for all by the year 2000. Investment in this field yields considerable benefits such as:

(i) preparation of technical human resources capable of leading the process of drug development in the country;

(ii) development and improvement of available drugs;

(iii) dispensing with drugs at present being imported;

(iv) reducing imports of starting materials and other requirements of the drug industry;

(v) devising new types of drugs that are more efficient and safer.

All this helps to create better possibilities for attaining drug security. Research and development in the field of drugs cover not only pharmacy, medication and toxins but also basic research on chemistry, biology, immunology and biotechnology, together with industrial techniques, their transfer and adoption. They include health systems research to evaluate the effects of drug policies and the availability of essential drugs, not to mention economic and planning studies related to drug policies. They also cover behavioural studies on the social and cultural aspects of drug prescription at different levels of health care.

Emphasis must be given to research oriented towards the manufacture of basic and alternative materials, and other requirements of the drug industry.

Drug research priorities are determined by defining needs for new, more efficient, less toxic, and more stable drugs and vaccines, appropriate for conditions in the area and the types of diseases prevalent there, in addition to research on other, less prevalent diseases such as AIDS.

The drug policy aims at encouraging coordination and consolidation of the strenuous efforts being made by all bodies and agencies concerned with drug research, including the Ministry of Health, public and private sector factories, research centres and universities.
To achieve such coordination and consolidation, the potential for drug research must be realistically explored, and an integrated plan for research and development must be formulated; a national fund for supporting drug research, financed by charges on the registration of drugs and from other sources, must also be established.

XII. International technical cooperation

The national drug policy aims at achieving optimum use of limited resources and at strengthening technical cooperation among countries and with international health organizations, particularly WHO, and especially in the following areas:

(i) drug evaluation;

(ii) exchange of drug information;

(iii) quality assurance and cooperation for quality control among regional laboratories and other similar laboratories;

(iv) Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce;

(v) pharmacopoeias and regional reference specifications;

(vi) inspection of drug factories;

(vii) technology transfer;

(viii) research and development;

(ix) drug-purchasing tenders;

(x) manpower training and development;

(xi) studies on drug classification and use;

(xii) use of computers in pharmaceutical work and drug control;

(xiii) drug emergencies.

APPENDIX 37

UNIDO Backstopping Officer's technical comments

Mr. Brown's report is comprehensive and clear and provides a group of constructive and practical recommendations, appropriate to help overcome the present very critical and declining situation of Thameco. The backstopping officer fully supports the expert's recommendations and believes firmly that urgent measures should be applied in order to preserve Thameco's potential and capability for providing the country's middle and low income sectors of the population with good quality and accessible priced drugs, within the framework of the pharmaceutical industry's increased privatization and market competition. In addition to the expert's two previous reports, the Thameco management has in this document a valuable tool for the company's work organization up to currently accepted international standard procedures, and specially for the commission and stable operation of the new Intravenous Infusion (IVI) Plant supplied by LeQueux/France.

Following the solution of the legal and organizational matters that are now preventing the IVI Plant commissioning and slowing down Thameco's functioning and competitive efficiency, and upon receiving a request from the Syrian Government and the UNDP office, UNIDO would be ready to support and assist Thameco in the start-up of the IVI plant.

Regarding the project document prepared in cooperation with WHO for drug policies and drug industry standards, UNIDO recognizes the importance of the project objective and is ready to fulfil, and if necessary, to increase its participation in technical assistance and training, according to the previous proposal of Mr. Brown, prepared after his second visit to Syria.