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INTEGRATED DEVELOPMENT OF PHARMACEUTICAL INDUSTRY IN THE  
SYRIAN ARAB REPUBLIC

DU/SYR/92/008 + NU/SYR/92/008

SYRIAN ARAB REPUBLIC

Technical report: Findings and recommendations\*

(First Mission Report)

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

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

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United Nations Industrial Development Organization  
Vienna

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\* This document has not been edited.

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Much of the work for this mission was performed at the factories of the general sector company, Thamecc, mainly in Damascus, but also in the Serum Factory at Aleppo; I would like to express my sincere thanks to the recently appointed General Director, Ms. Rajwa, and her technical staff for the time they devoted to answering questions and providing the information which has been vital to the preparation of this report, and to the formulation of recommendations for the rehabilitation of the company.

A relatively short period of time was spent in reviewing the status of the private manufacturing sector, and I should like to express my sincere thanks to Dr. Z. Fadloun, Genl. Sec. of the Scientific Council of Pharmaceutical Industry, and to those factory operators who opened their factory doors to expose themselves to some direct and intense questioning.

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The Resident Representative of UNDP in Syria, Mr. K. L. Hla, has been greatly supportive of this project since its inception, and his forthright expression of principles is very much appreciated. Extremely valuable support and encouragement has been provided by Mr. E. Hagona, Deputy Resident Representative and by Ms. N. Kozak, Project Officer.

**CORRIGENDUM**

The writer is indebted to the Minister of Health of the Syrian Arab Republic, H. E. Dr. I. M. Shatti, for pointing out that the Pharmaceutical Industry in Syria has not, in fact, been privatised.

Dr. Shatti advised that the private manufacturing sector came into existence under the national Investment Law.

The Industry is covered by the topics and guiding principles embodied in Drug Policy in the Syrian Arab Republic.

From the time of inception of the industry, Government has established a framework of regulations, under constant review, for its control; Government has also established the office of Assistant Minister of Health, responsible for Pharmaceutical Industry.

The operating conditions in the industry are constantly monitored by the Ministry of Health Drug Inspectorate; standards for all medicines in Syria are constantly monitored by the Ministry of Health Drug Testing Laboratory.

The above mentioned facts are relevant whenever reference is made to "privatisation" in this, or in previous Mission Reports.

**EXPLANATORY NOTES**

- 1) Thameco            The Arabian Medical Co. Box 976 Damascus Syria
- 2) Dimas            The Syrian Military Pharmaceutical manufacturer
- 3) Exchange Rate Feb./March 1994: Syrian L42 = US\$1.00.
- 4) GMP              Good Manufacturing Practice
- 5) SOP              Standard Operating Procedure
- 6) QA               Quality Assurance
- 7) QC               Quality Control
- 8) LIMS             Laboratory Information Management Systems
- 9) MOH              Ministry of Health
- 10) MNC             Multinational Corporation
- 11) GD              General Director (of Thameco)
- 12) PMAS            Pharmaceutical Manufacturers' Association of Syria
- 13) STC             Short term consultant

**ABSTRACT**

The project DP/SYR/92/008 was conceived to enable the integrated development of pharmaceutical industry in Syria. The UNIDO component was to establish industry standards. The future of the public sector company Thameco, was subsequently seen by Government, to play a major role in the evolution of pharmaceutical manufacturing in coordination with the rapidly growing private sector.

In keeping with the original objectives of the Project, the UNIDO STC has reported on the standards of a cross section of companies from the private manufacturing sector.

In accordance with the requirement to evaluate Thameco, each technical and managerial element has been explored and reported. The report presents a blueprint for the administrative, managerial, and technical rehabilitation of the Company.



## INTRODUCTION

Project Number DP/SYR/92/008 was conceived at the time when the pharmaceutical manufacturing sector was planned to be privatised in 1989.

Until that time, the sector had comprised essentially two manufacturing operations in the public sector; namely Thameco and Dimas. Since the bulk of Dimas' production was not available to the general public, Thameco was the only national company represented in the market-place; the following work therefore is confined to the Thameco situation.

The legal and administrative infrastructure was appropriate to handle the relatively uncomplicated demands of Thameco at that time, and the Company was able to supply 40% of the market demand for pharmaceuticals. The Company has not operated along commercial lines. In that its activities were confined to the technical aspects of converting imported Raw and Packing materials into Finished dosage forms.

Its buildings were suitable to their purpose and the equipment provided was amongst the best available at the time. However, general wear and tear, coupled with lack of systematic maintenance caused a progressively rapid decline in the Company's ability to meet the demands placed upon it. Buildings were no longer up to the standards necessary for the safe handling of medicinal products and machinery stood idle through absence of spare parts. Thus, what the writer had described as "one of the best equipped public sector factories yet seen" rapidly became a worn out shell with an immense demand for capital investment if it were ever to be rehabilitated.

The national pharmaceutical legislation had not been significantly advanced when, in 1988, the decision was made to de-regulate the pharmaceutical manufacturing sector. Within a very short period of time there was a proliferation of new pharmaceutical factories throughout the nation, each one apparently set up according to its founder's interpretation of GMP. Since many of the founders were not pharmaceutically qualified or experienced, the overall picture was of an industry entirely devoid of standards operating within an administrative framework which was incapable of applying rational and objective control or direction.

Having witnessed the changes and the explosive, uncontrolled industry expansion, UNIDO offered to the Government of Syria a project for the introduction of standards for pharmaceutical production based upon internationally accepted norms. This project was subsequently incorporated into an ongoing WHO country program which became DU/SYR/92/008 + NU/SYR/92/008.

### SUMMARY

The project is a joint WHO/UNIDO activity which aims to strengthen the pharmaceutical sector in Syria through both the regulatory authority and the manufacturing sector.

The UNIDO component, first mission, is covered by the following Report.

Since the project is intended to benefit the nation of Syria rather than any segment of the manufacturing industry, the UNIDO STC has attempted to take a balanced view of the situation and fieldwork has been spread over a wide range of manufacturing plants. However, since there is also a specific requirement to rehabilitate the public sector company, Thameco, to its role as a supplier of low price, high quality medicines for the poor and needy people of Syria a major part of the STC activity has been spent in analysing the present status of Thameco and presenting concrete proposals for the rehabilitation of the Company.

The private sector has expanded to now include 38 factories. These range from a few large companies which would rate highly by international standards to the smallest companies operating out of badly converted domestic houses.

Awareness of, and compliance with GMP, Validation, ISO 9000, Product Profiles, etc. ranges from excellent to very poor. In some of the small factories even basic test equipment is not fully understood. Similarly, attitudes amongst the factory operators ranges from open and enthusiastic, to defensive.

With the exception of the larger companies and those with Multinational links which have access to their principal's specialities, the typical factory is attempting to create a market based on a small number of well-known, well tried molecules, with minor variations to present the impression of a novel medicament. These "brand name generics" are in a fiercely competitive market in which low price and aggressive promotion are the principal selling points. This does not appear to be an attractive market into which to relaunch Thameco; the writer is proposing that the company should consolidate in strategic products and seek to develop into niche markets.

The private manufacturing sector is estimated to be capitalised to a value of approximately US \$150m. On the basis of tablet making capacity it is estimated that there is an installed manufacturing capacity in excess of the national requirement. This fact, together with the limited market, limited product range and pricing policy gives cause to fear the development of a counterfeit drugs trade.

The private factory operators are looking for their survival to the export market. This will not be an easy one since all the neighbouring countries have well established, competent and aggressive industries, and historically, Syrian made products have not enjoyed a good reputation.

The private sector manufacturers, particularly those with major investments in non-productive equipment such as electronic and optical laboratory instruments, and electronic data processing equipment will find it difficult to recoup their overheads in the Syrian market where the cost of drugs has traditionally been low; inevitably there will be intense pressure for price increases. There is a risk that many of the smaller companies will not survive and that some of the larger companies, already operating at reduced capacity, may be forced to review their investment policies in Syria.

There is a feeling that in the private sector, Quality is a disadvantage. As in any manufacturing activity, high quality and low price are mutually exclusive. Thus, the manufacturers perceive that the industry will drift in the direction of the cut-price manufacturers who have not provided the analytical and validation facilities needed to properly control the quality of the product, and who have not installed the expensive systems required to support an acceptable standard of GMP. There is merit in this argument.

Also in the private sector there is a feeling that the regulatory authority represents a threat to their investment. By contrast, in the regulatory sector, there is a perception that the manufacturers are totally profit motivated and will resort to unethical methods in order to maximise their profit.

Arising from this mutual distrust, there is a tangible "us and them" mentality which does not provide a good foundation for the development of a high technology industry.

Industrial development is happening worldwide. In Syria, it has started with some excellent developments in the pharmaceutical sector which, if handled well can have great value for the nation. The government, and the private manufacturers must enter a dialogue, and accept joint responsibility for its sustained and satisfactory evolution.

By contrast with the rapid progress of the private sector, the public sector manufacturer Thameco, and the military Dimas, find themselves in difficult situation. After years of neglect their buildings and equipment are in desperate need of repairs and modernisation. The improved conditions offered in the private sector have caused serious staff erosion and the technicians remaining in the public sector are seen to have developed a sceptical attitude regarding the realisation of improvement for their situation.

Thameco was the main subject of the writer's investigation, therefore what follows should be read only in context of that company.

The company is administratively located within the Ministry of Industry GC which puts out an annual instruction regarding the total volume of items to be produced. The breakdown of items into individual dosage forms is provided by the Ministry of Health. All finished products are transferred to a third instrumentality, Pharmex, which looks after the commercial and distributive activities. There is clearly the possibility for a conflict of interests to arise in such a bureaucratic arrangement. For the survival of Thameco, this situation must be rectified promptly.

Thameco places great importance on appointing suitably qualified technologists to middle management production jobs and yet, for the most critical and difficult job in the entire company, that of General Director (GD), it has recently appointed a technical person who has no background in industrial management, thus continuing a policy which has seen the separation of three previous GDs since 1989.

Naturally, such a high rate of managerial change brings with it inherited problems for the new GD. The writer, in the role of uninvolved third party, has attempted to address some of these problems with a view to providing a clean start for the new GD.

The archaic system of procurement of imported raw and packing materials has resulted in Thameco losing some important sources. Additionally, unusable material has been purchased as a result of decisions made by a committee having no direct knowledge of the manufacturing processes involved.

The inability of Thameco to respond to urgent requirements for antibiotics and its frequent out-of-stock situation has attracted adverse comment from the authorities. This situation is not insoluble, but for its correction a total revision of the company's purchasing policy is needed.

On first contact with Thameco in 1988, it was the writer's opinion that Thameco was one of the best equipped public sector companies yet seen. This observation still holds true, but time and lack of spare parts has now reduced some of the equipment to the irreparable stage where it represents a risk to both product and operators. It is wrong for such equipment to be retained in production areas and, in the following report the writer has provided details of which equipment must be promptly removed from production areas.

The generally run down appearance of Thameco is due to three major causes. Firstly, the buildings were erected at a time when modular construction was not employed thus it has not been possible to restructure the internal layout to accommodate changes in equipment and technology. Secondly, the annual shut down for repairs and maintenance has been neglected for several years. Finally, there has been no policy for development of the industry.

It is not too late to rehabilitate Thameco, but instant improvement must not be expected. The company has been allowed to decline for too long and improvements will be both slow and expensive, however, with political ambition, Thameco can again play an important role in the supply of good quality medicines in Syria. There is nothing that the private sector can do which cannot be done at least as well by Thameco, however, failing the introduction of the necessary changes to remotivate the company, the private sector will take over the entire manufacturing sector in Syria.

Implementation of GMP in Thameco remains a difficult concept since the factory building itself will not provide a good starting point until renovation work has been completed. Thus, the current, reasonable standard of housekeeping is overshadowed by damaged walls, loose electrical wiring, dirty ceiling tiles, poor illumination, etc. A major building maintenance program is overdue, and

when completed it will be possible to introduce a meaningful level of GMP to the company.

The Ministry of Industry has responsibility for many factories in Syria, from paint to paper, ceramics to tires. Thameco is its only pharmaceutical factory. It must be emphasised that the standards appropriate to the manufacture of heavy chemicals, paint or leather have no place in the pharmaceutical industry. Consequently, for Thameco to approach the standards required by GMP it is imperative that the Ministry of Industry itself should conform to pharmaceutical standards when making renovations to the factory.

For several years the writer has been answering questions related to Expiry Dates. On every occasion, the answer has been the same. During the current mission the same questions have been raised. The writer has again explained that there is one method in use worldwide "Accelerated Aging" using a climatic cabinet. There is simply no alternative. A schematic diagram, together with operating conditions of temperature, humidity and time, have been provided to Thameco in order to permit them to construct their own facilities in keeping with the volume of samples with which they will need to work. A laboratory supplier's catalogue with illustrations of several small units has been brought to the attention of the technical staff. Finally, it has been pointed out that Dimas does, in fact, possess a climatic cabinet which is not in use and Thameco may wish to inspect it with a view to providing its own answer to this question.

The writer has offered to address a meeting with MOH and manufacturing people on the Expiry dates of raw materials and finished goods.

## RECOMMENDATIONS

The primary recommendations are based on the need to re-establish Thameco as a pioneer in the manufacture of high quality, affordable medicines for the people of Syria.

Thameco has immense potential, not yet matched by any private sector competitor. It could and should be the leading pharmaceutical company in Syria but it must be operated as a business, not as an institution.

The problems of Thameco are complex and interlinked, comprising Administrative, Managerial, and Technical components in that order of importance.

The recommendations are mentioned briefly in this section. A full account is provided in the substantive section of this report. For them to yield the desired outcomes, it is imperative that they be addressed in the correct sequence.

### PROBLEM 1: Thameco's situation

REASON 1: The company is in its present distressed situation because it was operated in a chaotic bureaucratic framework which became obsolete on the day that the industry was deregulated.

### RECOMMENDATION 1:

Place Thameco into a single administration, provide a small Board of Directors, with authority to facilitate the needs of the company and to make policy, provide an annual budget and run the company along commercial lines, within Government. Allocate funds for research and product development, human resource development, repairs, maintenance, and expansion. The structure of the company should be transparent and lines of authority formalised. The purpose is to convert Thameco from an institution into a business.

### PROBLEM 2: Management

REASON 2: The workload on the GD is daunting, managerial support is required.

### RECOMMENDATION 2:

On the understanding that Thameco's administrative chaos has been rectified, review the structure and objectives of the UNIDO component of Project No. DP/SYR/92/008 and request that it be extended to incorporate a management support project with possible SIS funding. Provide administrative assistance to handle the trivia and to permit the GD to concentrate on running the company.

PROBLEM 3: Fear of inherited mistakes.

REASON 3: The onerous penalties which have been imposed on Thameco for mistakes has had the result that many mistakes remain hidden.

RECOMMENDATION 3:

Identify all inherited mistakes, list them, notify the authorities. Act decisively to resolve the problems, advise the authorities when completed.

PROBLEM 4: Thameco's attitude

REASON 4: The staff is demoralised, confused and sceptical. There is an institutional mentality, conflict of interest, and a resignation that Thameco is destroyed.

RECOMMENDATION 4:

Evaluate the management team, introduce new talent and the technique of Management by Objective; reduce the overstaff situation to the optimal level; offer career path and human resource development together with a wage structure that does not oblige staff to take second jobs. Drive the company to its optimal production potential.

PROBLEM 5: Industrial overcapacity.

REASON 5: Uncontrolled expansion in the manufacturing sector, yet no increase in the number of molecules available and no increase in the size of the market.

RECOMMENDATION 5 :

Avoid confrontation with the private sector, consolidate into strategic products and expand productive capacity. Phase out unattractive brand name generics. Coordinate the activities of importers so as to protect the domestic producers. Implement a research project pipeline into niche products. Be alert to the possibilities of counterfeit medicines.

PROBLEM 6 : The Serum Factory

REASON 6 : Failure to reach agreement with Lequeaux

RECOMMENDATION 6 :

Settle for a compromise with Lequeaux, recruit the Production Controller, evaluate the management team, implement the training

component of the contract and operate the factory to its maximum capacity. If required, commission a duplicate of the existing facility.

**PROBLEM 7 : The Thimon Line**

**REASON 7 :** The Bulgarian offer to convert the Thimon line to a non-sterile filling unit has been revoked, Thameco needs engineering support to design and implement the changes on the machine and further support to install and commission it.

**RECOMMENDATION 7:**

Thameco to make policy decision on the intended use of the line and then, if necessary request UNIDO engineering support.

**PROBLEM 8 : Working Conditions**

**REASON 8 :** Old and badly maintained buildings accommodating technology for which they were not designed. Risk of product cross contamination and threat to worker's health.

**RECOMMENDATION 8 :**

Re-activate the factory annual maintenance shutdown which has been neglected for several years.

Provide a budget in the order of \$5 millions over three years to implement the specific recommendations which are provided in the body of this report. Provide and use protective clothing. When planning new development of the factory buildings do not employ unmovable structures; provide buildings with potential for change, use modular construction.

**PROBLEM 9 : Expiry Dates**

**REASON 9 :** Failure over several years to accept the simple methods for determination of valid Expiry Dates for Finished Products, and failure to adopt the Retest Date concept for Raw Materials.

**RECOMMENDATION 9 :**

Read, understand and implement the procedures spelled out in the body of this report. Purchase, or build, a climatic cabinet/room for use by the Research Department.

**PROBLEM 10: Materials Procurement**



REASON 10: Convolved and time wasting procedures result in Thameco having a "stock out" reputation.

RECOMMENDATION 10 :

Cut through the purchasing bureaucracy, request non-negotiable prices for absolutely specific Quality and Grade of materials, appropriate to their intended use. Compile Product Profiles in preparation for computerisation of the production operation. Schedule production according to market requirements and procure materials on this basis, using fax machine not the "Bid Book" method.

PROBLEM 11: Training

REASON 11: Thameco has failed to use training opportunities provided under the terms of previous Projects. There exists a serious deficiency of knowledge regarding the structure and operation of the pharmaceutical industry in Syria. It is difficult for administrators to identify the standards of the industry in Syria and to compare them with the standards which exist in other countries at a similar stage in their process of industrialisation. The general sector producer, Thameco, has only a superficial understanding of industry principles.

RECOMMENDATION 11 :

Following discussions with the MoH, Thameco, and UNDP, it was agreed that the recommendations for training as set out in the Project Document will have greater cost-effectiveness if condensed, intensified, and opened up to include senior members of the administration. It is suggested that the situation in Thailand most closely resembles that of Syria, and since the Thai government with UNIDO assistance, has been active in the development of industry standards this will provide an excellent location for implementation of the UNIDO Fellowship program. Not only will technical managers from Thameco gain valuable experience in their own, and related specialities, but they and administrators alike will have the opportunity to see what can be achieved by a mixed Public/Private sector operating in a country at a similar stage of industrialisation. Further, it will permit them to establish a perspective of the industry, and to evaluate the status of their domestic operation, so adding to their confidence in its evolution. In order to achieve the optimal benefit from the training, it is vital that the current UNIDO STC should join the trainees in Thailand in order to point out concrete examples of the matters which have been addressed verbally during the course of the Mission in Syria. Subject to the availability of funding, it is recommended that the number of trainees be increased from three to five/six, that the duration of the training should be maintained at 9 w/m but the time provided to each speciality be reduced to the maximum

consistent with the additional costs incurred by inclusion of the STC. The revised proposal will be discussed with the UNIDO backstopping officer during debriefing in Vienna and a revised list of trainees will be provided to the Syrian authorities as an addendum to this report.

### RECOMMENDATIONS CONCERNING THE PRIVATE SECTOR

Due to the changed emphasis of the project, which became Thameco oriented, relatively little time was spent with the private sector.

However, the writer's discussions, with the private sector operators, and with the officials who accompanied the factory visits, revealed an unhealthy "us and them" attitude.

Not only does the "us and them" situation apply between the factory operators and the Inspectorate, it is also evident between the ethical companies and some of the less reputable companies which are operating from badly converted domestic houses. A perception of "double standards" may arise within the industry.

This cannot be beneficial to the development of the industry. Mutual distrust between the manufacturers and the Inspectorate will be resolved only when mutual understanding is achieved. The risk of double standards cannot be beneficial to the reputation of the Syrian pharmaceutical industry, particularly in export markets; a potential purchaser needs to have absolute confidence in the quality of the offered material. This is the basic principle of the new standards for manufacturers known as ISO 9000. If Syria wishes to have a credible pharmaceutical manufacturing industry, it CANNOT ignore the standards imposed by ISO 9000.

The private manufacturing sector came into being as a result of Government policy, and over the period of its existence it has made great progress; the writer would venture to suggest that it is now amongst the most highly capitalised private enterprises in Syria. It has the right to have its case heard at the highest levels of Government.

The private manufacturers perceive that the inspectors do not have a manufacturing background and operate from a purely theoretical base. The writer can support this observation, since its rectification is one of the objectives of the current Project. Yet the manufacturers appear to have been negligent in that they have made no concerted move to present a cohesive statement of their own position.

It is recommended that the private sector should establish its own, completely independent, body (which has been nominated PMAS in the following report). The PMAS should develop its own internal standards for regulation of its membership and formalise them in the form of a Charter and Management Plan; which

would be binding on the entire private sector, both current and prospective members.

The Charter and Management Plan would be the official standard of the private manufacturers; under it, they would speak to Government with the single voice of a powerful industrial group.

The Government which allowed the private sector to come into being must now be attentive to its needs.

Dialogue is imperative to resolve the "us and them" situation, to resolve the differential in overheads between the ethical manufacturers who have invested heavily in non-productive capital equipment and those who have not, to resolve the painful question of the issue of manufacturing licences, and to assist in the training of the Inspectorate.

### THAMECO'S FUTURE ROLE

Thameco can play an important future role in the Syrian pharmaceutical manufacturing sector. However, before proceeding to review the future possibilities for the company, it is pertinent to pose two questions:

- a) is there a conflict of interest within the Government regarding its attachment to Thameco, yet its liberal treatment of the private sector?
- b) private owners are investing millions of dollars to compete with Thameco, the established leader; why then, is there so little confidence in Government circles, regarding Thameco, that it can take weeks to obtain answers to simple questions?

These are matters which are pertinent to whatever future Thameco may have. But they cannot detract from the reality that the company is currently the most capable manufacturer in the Syrian pharmaceutical sector, is arguably the most misunderstood, is in its current distress due to an unworkable administration, and has resources available to it which will not be equalled in the private sector for several years to come.

Properly structured and operated, Thameco could, and should be the leading pharmaceutical company in Syria.

Should this potential not be realised by the Government, and the company be transferred to alternative ownership, the writer is definite about the fact that a pragmatic, business-oriented owner could quickly reverse the deplorable slide which has typified Thameco's fortunes for several years.

There have been several efforts in the past five years by international agencies to promote some change in the company, but for various reasons there has been no response from the authorities. Valuable time has been wasted, during which, the private sector has made great progress.

It is not too late for one final effort to revitalise Thameco. However, this has to be the FINAL EFFORT since any delay will permit the private sector to gain market share which will henceforth exclude Thameco.

There is nothing that the private sector can do which cannot be equally well done by Thameco providing that the company and its administration are willing to make the effort.

Radical changes are overdue, they may appear as an affront to the traditional system but if Thameco is to survive there is no time to lament the past, every effort must be directed towards the future and the hard decisions must be taken now.

Thameco has played a pioneering role in the evolution of manufacturing in Syria. Over recent years, neglect of the buildings and aging technology, together with erosion of technical staff to the private sector has left the company at a crossroads. One direction implies the ultimate closure of the factory or transfer to a new owner, and disposal of its equipment. The other direction involves giving the company a major recapitalisation in terms of building renovation, replacement of superseded equipment, procurement of spare parts, together with remotivation of staff, planning the introduction of new technology, and rationalising the administrative chaos which has inhibited the company's performance for the entire time that the writer has known Thameco.

At the commencement of the current mission, the writer was requested to evaluate the company and to make concrete proposals for its re-instatement as a leader in the attainment of pharmaceutical self sufficiency for Syria. This request accords with the writer's own view that Thameco has much still to offer Syria, and that its role should be likened to that of the major state-operated teaching hospital, vis-a-vis the cottage hospitals, represented here by the private sector manufacturers.

There should be no misunderstanding, however, Thameco and the private sector are in the identical business, working with the identical molecules, and serving the identical market.

For the survival of Thameco it is imperative that the private and public sectors assume complementary roles. On no account should Thameco attempt to confront the private sector since it has access to promotional activities which are not available to Thameco.

The advent of the private manufacturing sector is, in fact, seen as an incentive to Thameco to modernise, to expand its capacity to supply strategic medicines, to seek and install innovative technology, and to serve as a training ground for pharmacy graduates wishing to enter industry. In the absence of the motivation provided by privatisation, there was a strong possibility that Thameco would settle complacently into its old ways and stagnate; to the detriment of the nation.

The "status quo" of pharmaceutical industry in Syria has been displaced by the developments in the private sector and it is necessary, now, to make some hard decisions regarding what has to be done to correct the situation as it applies to Thameco.

The principal cause of Thameco's deterioration must be attributed to the complex and diffuse institutional manner in which the company was forced to operate. With inputs from four different Ministries, the chain of authority had become so tenuous as to be unworkable. This is borne out by the company's inability to make any meaningful use of the technical assistance provided by UNDP/UNIDO over recent years.

Not only did the Company fail to utilise this assistance, it failed to offer any alternative strategies of its own. Thus, the internal management of the company was left in a vacuum, with no recourse, no direction, no plans, and

according to its professional middle management, no future; hence they left the company and took their skills to the private sector.

Worse still is the fact that Thameco is perceived by its administration as a "factory", to be treated in the same way as any other factory, despite the fact that the standards required to process heavy chemicals or leather have no place in the manufacture of medicines, injectables, and antibiotics.

Syria is in a state of change, to an industrial society; the old system, under which Thameco had operated, ceased to have credibility on the day that the pharmaceutical sector was deregulated. There can be no going back. The company's method of operation must be brought into line with the standards of pharmaceutical industry worldwide, or Thameco must be allowed to die with the dignity appropriate to an organisation which has served Syria well for many years.

The appointment of a new General Director (GD) at Thameco will not, in itself, cure the company's problems. It does, however, provide the opportunity to explore the associated changes which must be implemented if a cure is to be achieved.

First and foremost, the bureaucratic chaos of the company's administration must be rationalised to the extent that it is possible for the GD to actually MANAGE Thameco. If the company is to operate with the same efficiency as its private sector rivals, its manager must have the same freedom to make policy decisions and to exercise disciplinary control of the factory as do her private sector colleagues.

Ideally, Thameco must answer to ONE Government instrumentality. The willingness of that instrumentality to act in the Company's best interest, to make the hard decisions, and to implement the appropriate policies is the only way in which Thameco can be of real value to the nation. Hence, Thameco's future is dependant on political will, coupled with technology. Neither one, in isolation, will be sufficient.

Secondly, Thameco's "institutional" structure has resulted in the development of an institutional mentality in the second and third levels of management. To date there has been no formalised distribution of responsibility, and no evaluation of technical performance, particularly at the second level of management. The institutional mentality has also damaged staff morale and lead to scepticism in the workforce. In addition, there is an unhealthy problem of "personalities" in the company. Staff must clearly understand that they work for Thameco, and must give their total support to Thameco, and to the GD. If they cannot accept this condition then they are of no value to the company and should be released.

Further results of the failure of the company's previous style of management are demonstrated by the daunting, and costly, list of problems inherited by the new GD. It is imperative that these problems should be brought into the open now, at the commencement of the new management, in order that they may be disposed of, once and for all time.

Due to reluctance of staff to discuss these matters and to the sometimes conflicting reports provided by different individuals, it has been necessary to devote a significant amount of the project's time at Thameco to probing the underlying facts. The writer is, however, now confident that no major inherited problems remain to be uncovered. The issues, together with suggestions for their solution, are provided later in this report.

It is also important that the management team should be rated on its value to the future performance of the company, and on its commitment to the new GD. With the right management team, Thameco can develop the vibrancy which will set it on the track to success; with the wrong management team the company will continue to struggle and the new GD will find it impossible to remotivate the company.

Not only should the management team be evaluated, its members must clearly understand that the company is now in a competitive market and it is their own responsibility to support the GD to the extent that the Company will be successful. This situation will be fully realised only when the company introduces the system known as Management by Objective and the GD has the authority to take disciplinary action against team members who fail to attain the objectives identified in their Job Descriptions.

With these problems removed there is absolutely no reason why Thameco cannot operate as a very effective element of Syrian industry and meet the stated requirements of the Minister of Health that the company should play a leading role in the evolution of the national pharmaceutical industry.

The private sector is neither more skilful nor better equipped than Thameco. Technology-wise there is nothing that the private sector can do which Thameco cannot do. Indeed, whilst the private sector in general, is basing its production activity on "look alike" machines, cheaply built in India from European designs. Thameco currently has top-class European equipment on order with a total invoice price well in excess of \$ 1 million. It is a regrettable omission that suitable preparatory work to bring the factory up to a decent standard to receive the equipment has not been undertaken.

The differences between the sectors are to be found in the administrative system imposed upon Thameco; and the fact that the private sector is lean, aggressive, and hungry by contrast with Thameco which is lazy, institutionalised, and confused.

In view of the strategic value of Thameco, it may be appropriate to establish an autonomous "Board of Directors" comprising authorised, knowledgable, and experienced members of government. The chairman of this board would be answerable to the government Minister in whose portfolio the company resides.

The board would be structured so as to have responsibility for the effective operation of the company and to facilitate the needs of the company, rather than to issue directives about the technical details of the company's management. It should be restricted to the minimum size (four persons including the GD). Other members may be co-opted as necessary. Thameco's GD must have

equal status with each of the other members. This is seen to be a practical, working board, with authority.

During the fieldwork of this mission, the current status of the private manufacturing sector was reviewed, in order to determine the options available for Thameco. The writer has to express admiration for the professionalism with which many of the factories have been established. These factories represent a sincere effort, on the part of their owners, to prove that Syrian medicines can be favourably compared to medicines manufactured anywhere in the world. Not all of the private sector companies conform to the same high standards and there is a risk of double standards emerging.

However, it is evident that the installed capacity is considerably in excess of Syria's requirements. Thus, with the limited number of molecules available for processing, it is fair to say that the Syrian market is saturated with "brand name generics". There will be intense competition for market share based on considerations of selling price, promotion, and brand loyalty in that order of importance.

For this reason it would appear to be an unjustifiable expenditure to refurbish Thameco, merely to allow the company to compete with the mainstream private manufacturers in the generics market.

Thus, it is the writer's proposal that the company should:

- \* undertake a stringent review of its product range
- \* consolidate on strategically important products
- \* improve and expand its technology for manufacturing these products
- \* identify and develop into "niche" markets of sophisticated, high value items in the pharmaceutical, and related, fields.
- \* establish a research project pipeline utilising the excellent facilities already available to it, for products to come to market in three to five years.

Clearly, such a policy will not be attainable in the short term, but in order to perform the necessary preliminary studies of both the market and the technology it is important that the company should start, as soon as possible, to formulate its plans.

To achieve the standards of GMP, which are currently absent in Thameco, it is imperative that the installation of new or replacement equipment should be planned as a cohesive project rather than the ad hoc approach which has prevailed in the past. It must be understood that GMP cannot be incorporated into an operation as an afterthought. GMP must be designed and built into the system from the outset.

In order to provide Thameco with some technologies which it may wish to consider in its planning the writer has proposed the following:



- \* hormone and contraceptive tablets
- \* narcotics, tablets, injectables, and drops
- \* sterile powders packed in vials, including antibiotics
- \* transdermals
- \* mucolytic inhalers
- \* Interferon packing under licence
- \* contact lenses and their maintenance products
- \* formulated foods and infant products
- \* medical plastics, eg syringes and cartridges for dental anaesthetics
- \* sterile creams and burn dressings

Obviously it is neither possible nor appropriate to consider the group "in toto", and according to the company's own perception of its future direction, Thameco should assign a full time "project manager" to study the commercial and technical feasibility of the technology. Subject to positive feasibility studies, the technical planning can be initiated, firstly through a study of the relevant literature, secondly by contacts with equipment manufacturers, and finally with assistance from UNDP/UNIDO if appropriate.

There are possibilities that Thameco could stage a limited entry into chemical synthesis, producing kilogram quantities of microdose chemicals for its own use, and for sale to others. It is envisaged that pilot scale laboratory glassware would be employed. There is, however, the matter of Syria's position on Patent Legislation to consider before making any commitments to this line of action.

There are also possibilities that Thameco could commence the manufacture of fermented products, of vaccines and sera, and of modern diagnostic reagents. However, it is imperative that the company's operating system is updated to a level compatible with the introduction of the new technology before any new ventures are initiated.

For Thameco to achieve a level of efficiency comparable with that of the private sector, the company must modernise its systems in human terms by MBO (management by objective), and in documentation and control by computerisation. Installation of an Information Management System linking production, QC, commercial, financial, and research activities should not be delayed.

Subject to the progress achieved by Thameco in resolving its principal bottleneck: its administration, it may be appropriate to consider the possibilities of providing management support to the company for an extended period, funded by UNIDO's SIS budget.

## INDUSTRIALISATION

The current project, DU/SYR/92/008 is concerned with the integrated development of the pharmaceutical sector in Syria. This is not confined to the control of the recently deregulated private manufacturing sector but relates to the overall evolution of a new, high technology industry for Syria.

This evolution has implications for the industrialisation process in Syria which are just as real as are the benefits which will accrue to the nation through the target of self sufficiency in the provision of medicines.

Consequently, it would be an oversight to present this Mission Report without some brief reference to the economic and operational factors which are an inseparable component of the industrialisation process.

For many years, Syria has operated as a centrally planned economy, with directions flowing to the manufacturing sector down highly formalised pathways which demanded little, if any, intellectual input from the various officers who processed the messages. The officers were seen to function as "postmen" passing instructions down the chain, and referring queries up the chain. Thus arose a ponderous bureaucracy in which fast response was not possible; in which the managers of the manufacturing industries were saddled with the responsibility for the proper operation of their organisations but did not have the authority to enable fast response to the market forces which drive industry.

Further, the financial imperative which motivates industrial development was absent, since the industry was not operated on commercial lines but was directly supported by Government. This support had the effect of making pharmaceutical products in Syria, low cost items accessible to all. It also had the serious disadvantage of making Syrian pharmaceuticals very attractive commodities for sale by traders in neighbouring, high price markets.

With the advent of the deregulated pharmaceutical sector, has come the realisation that there exists a vast disparity between the style of modern management and the traditional system, to which the bureaucracy had become accustomed and which was the root cause of the problems experienced by the public sector company, Thameco.

Deregulation has displaced the status quo; and whilst there may be reluctance in some quarters to accept the fact that the clock has moved on, it cannot now be turned back without even more disruption of the system. The private sector is estimated to have invested in the region of \$150 million in plant and equipment. It represents a major force in the economy of Syria; a force which, if properly handled, can be of immense practical and financial value to the country.

Conversely, if mishandled and placed in an intolerable situation, the industry may find it necessary to review its investment policy with respect to Syria, resulting in the possible loss of a major health & manufacturing

resource, employer and tax payer. There is the additional risk of a "brain drain" of skilled middle management and technical staff.

There should be no doubt in the minds of policy makers that the private manufacturing sector, particularly those with MNC connections, are watching very carefully for the signs which will indicate to them whether the current industrialisation policy will lead to the economic liberalisation in which high technology industry can prosper. The fact that the national policy on pricing of medicines will result in dragging the entire industry down to the level of its poorest members is not calculated to promote the more ethical manufacturers to commit more capital to non-productive, yet vital, equipment.

Similarly, in the public manufacturing sector, there is an awareness of the opportunities represented by the private sector. This can be identified as one of the principal causes of the dramatic outflow of technical middle management from Thameco (Damascus) over the past three years and the inability of the company to recruit the vital Key Persons for its Aleppo factor.

The high-technology sector, of which pharmaceutical industry is a component, is now very dependant upon Internal Systems, Communications and Information Management for its efficient operation. This is particularly relevant in context of procurement of raw materials from overseas sources and acquisition/storage of data relating to manufacturing, Quality Assurance/Control, and stock control activities. With increasing pressure to attain higher standards of production efficiency and quality the investment in the non-productive hardware, software, and training to achieve these standards has to be offset against the profits generated by sales of the company's products.

There is a range of motivations in the new private sector, from the opportunist owner who sees pharmaceuticals as a means to a quick profit, to the serious manufacturer who has made all the necessary investments to ensure the quality of his medicines and yet sees his cut-price competitor, working from a badly converted domestic building, confidently expecting to receive a license to handle highly sophisticated molecules.

During the course of the fieldwork, the writer was given an explanation, by a medical doctor, of the method of measuring bio-equivalence in the human subject. The doctor implied, very strongly, that the manufacturers were cheating by using substandard materials to produce inferior drugs for which they were demanding high prices. It was stated that the medicines did not work, yet the bioequivalence tests were being performed on outpatients whose behaviour could not be factored-in to the interpretation of the tests. The doctor would not concede that the method of testing may give less than optimal results, it had to be the manufacturers who were wrong.

Such an attitude is both ill-informed and subjective; it can have no place in discussions related to the establishment of a major economic component of Syria's industrialisation.

When the ethical manufacturers hear this kind of comment,

and see the facilities which their competitors claim to be factories, they would surely be right in asking themselves why do they bother to risk their capital in an industry which is so devoid of objectivity.

The whole question of relationship between the industry and the regulatory authority MUST be brought into the open and clarified in dialogue between the parties. The facile device of applying GMP will not, in isolation, get to the root of the problem.

The private sector manufacturers have a valid argument when they complain about the price they receive for medicines in Syria. As currently structured, the cut-price operator stands to make the greatest profit, and the ethical manufacturer who invests in non-productive control equipment, and a well engineered factory, does so at his own financial risk.

A private sector manufacturer observed that, in the current situation, "quality is a negative asset". This opinion is reflected throughout the manufacturing sector; it has validity.

The new management style calls for a revision of the relationship between Supplier and Customer. This is clearly spelled out in the International Standards Organisation's publication ISO 9000 and its derivatives. ISO 9000 defines the necessary relationships between parties to attain the goal of Quality Assurance. It has just as much relevance between manufacturing departments within a factory as between supplier and consumer in any trading transaction. The several codes of GMP are simply distillations of ISO 9000 to represent the specific needs of the pharmaceutical industry.

Thus, for the Pharmaceutical (or any other) Industry in Syria to seek international recognition for the quality of its products, it is imperative that the industry is perceived to be aware of, and adhering to the philosophy of ISO 9000.

During the mission fieldwork it was evident that the private sector companies with MNC involvement were fully aware of, and incorporating the concepts ISO 9000 into their operations, whereas this was not noticeable to the same extent in the "Syrian only" companies.

The writer has offered to deliver an introductory talk, to the manufacturers and the MOH on the topic of ISO 9000 and its implications.

## STRATEGIES

One of the most obvious impressions gained by the writer during the field-work component of the mission was the very strong "us and them" relationship which exists between the Private Sector/Public Sector/Regulatory Sector.

From the manufacturing side, the Regulatory sector represents a threat to its existence; from the Regulatory side, the manufacturers appear to be totally profit motivated and liable to adopt any cost reduction activity which is available to them, including the use of cheap or substandard materials in their products.

Clearly this situation cannot be allowed to continue for it will result in the progressive worsening of relations between the sectors. The Government's factory inspectors will find that they experience mounting hostility from factory operators and the opportunities for unofficial activities will take on serious proportions. The ultimate result could see a dramatic reduction in the standards of the Syrian pharmaceutical manufacturing sector. This situation will not be resolved by the simple expedient of enforcing a code of GMP onto the manufacturers.

There needs to be a clear understanding between ALL the parties that this industry is here to stay, and here to offer the Nation the opportunity to realise its goal of self sufficiency in pharmaceuticals. The only way that this "us & them" situation will be resolved is by dialogue between the parties, and by a co-operative approach to the development of the framework within which the sector will be encouraged to evolve.

A first, and valuable step in this direction has been taken by the establishment of the Scientific Council of Pharmaceutical Industry within the Ministry of Health. The SCPI has a council comprising 20 persons from across the pharmacy spectrum: - Academia, Public Sector, Private Sector, Pharmacy Association and Ministry of Health; 60% of the members are from the Private Sector.

Further areas of joint action are seen, by the writer, to be necessary in order to allow the parties to develop more detailed understanding of the objectives of the sector as a whole and the problems being experienced by individual groups. In addition, there are activities which should best be undertaken by the individual groups themselves. These will be explored briefly below.

### 1. FOR THE PUBLIC SECTOR

In the rapid growth of the deregulated industry, the public sector manufacturers have fallen far behind in the matters of plant, equipment, training and attitudes. The general conditions in which they operate cannot be compared

favourably with the conditions prevailing in the new, privately owned factories. It is fair to say that, should Government at some time in the future introduce GMP Certification (see below), the public sector factories would either be forced to invest heavily in refurbishment and training programs or go out of business.

The needs and priorities of the military establishment are clearly separate and distinct from those of the general public and hence, they have not been specifically addressed in this mission. However the situation as it applies to Thameco has been addressed in some detail.

## 2. FOR THE PRIVATE SECTOR

Whilst being represented by a majority in the SCPI, the private sector needs to take a responsible attitude for its own internal structure and regulation. It must place itself above unsupported criticism that it is motivated purely by profit, and it must be clearly seen as a modern, technology-intensive/capital intensive industry which is capable of producing medicines to the very highest standards.

A start in this direction could be made by the sector setting itself up with a completely independent Pharmaceutical Manufacturers' Association of Syria, supported by a Charter and Management Plan for current and intending manufacturers. This would identify the immediate objectives of the private sector and its plans for the future. The requirements for intending producers are envisioned to be more rigorous than the Government's own constraints; thus membership of the Association would become a prerequisite of all manufacturers who wish to be identified as reputable producers of therapeutic materials for humans or for animals.

One of the first tasks of the Association would be to participate, with Government, in the current WHO/UNIDO supported training program for Factory Inspectors since this needs the total commitment of the manufacturing sector if it is to be of more than superficial value.

The function of the factory inspectors can be maximised only when the inspectors are perceived by the factory operators as having a working knowledge of the processes and equipment involved, together with an understanding of the basic economic and financial structure of any manufacturing operation. Failing this, the inspectors will be perceived merely as an outside interference, to be provided with the least possible assistance; thus, objective control of the industry will be very difficult to sustain.

From the viewpoint of the Inspectorate, it is equally important the factory operators understand and agree with the philosophies upon which the Inspectorate is founded.

Clearly, both the Inspectorate and the factory operators have much to learn from each other if this "us and them" mentality is to be overcome and the industry is to develop in a rational and balanced manner.

Consequently, the training of factory inspectors must be a joint responsibility of the manufacturing sector and the Government. It is suggested that senior members of the Inspectorate should be seconded to the manufacturing sector for a substantial period of time in which to gain "hands on" experience of the industry which they will subsequently be required to inspect.

Conversely, factory operators should be required to undertake some training (for instance lectures) in the Inspectorate division to assimilate their current thinking and to evolve policies for the improvement of the industry.

Such dialogue and coordination of activity is vital for the continued evolution of the manufacturing sector; and, should the manufacturing sector, for any reason, fail to evolve, there would be no further requirement for the Inspectorate.

An additional component of the role of the Manufacturers' Association is seen to be in the determination of conflict situations arising as a result of factory inspections. In order to develop a balanced perspective in this regard it would be of value for any conflict to be referred to a joint arbitrator drawn from the Inspectorate and from the PMAS. This peer group approach to evaluation and resolution of conflicts is seen to be more effective than the straight confrontational approach which would result if the Inspectorate were to deal with the situation without the support of the manufacturers' group.

During the fieldwork, discussions with factory operators revealed that the exportation of Syrian pharmaceuticals is curtailed by the unreasonable certification requirements placed on the products as a result of what was seen to be substandard goods supplied in the past. If this difficulty is to be overcome it is imperative that a trade delegation, from the PMAS, and supported by Government, should visit the target markets at the earliest opportunity to dispel this impression and to highlight the new and improved quality standards which are being developed in Syria. This market development activity is seen to be of the greatest importance since it is the writer's opinion that there is already production capacity installed in Syria far in excess of the National requirement.

### 3. FOR THE GOVERNMENT

For the balanced development of the pharmaceutical industry there needs to be a framework comprising a Drugs Policy, implemented by the Ministry of Health and an Industry Policy, implemented by the Ministry of Industry. In the absence of such a balance it is inevitable that bias develops in which the nation is the loser. Thus, for instance a strong inspectorate covering a weak industry would be counterproductive. Conversely a strong industry in the absence of a regulatory mechanism would be out of control. The emergence of the Manufacturers' Association, as described above, would be of the greatest value to the Government in evaluating the relative strengths of the Drugs Policy and the Industry Policy and assisting in the introduction of any adjustments which may be necessary.

The question of coordination of drug supply is one which should be addressed by government, in light of the installed capacity of the manufacturing sector. The private sector claims that it has invested millions of dollars in plant and equipment for processing ampicillin, yet it has been able to use the equipment for only two months of the year due to the importation of large quantities of Finished Product. Clearly this is a waste of resources, and it causes the manufacturers to question the motives of the importing authority.

The problems being faced in Syria since the pharmaceutical sector was deregulated are not uncommon in newly industrialised countries, and different strategies have been introduced to resolve them.

In Thailand for instance, there is a strong manufacturing sector comprising 181 companies of which 85% are nationals; the remainder being classified as Multinational. In order to protect its domestic producers, the Thai Government has imposed a 33% import duty on all manufactured pharmaceuticals entering the country. The population of the country is 57 millions of whom 60% are employed; the per capita GDP approximates US\$1200 and personal expenditure on pharmaceuticals approximates US\$10 per year. The major costs of health care must be paid direct by the patient but the Government has introduced two card schemes: Medicare which provides medical treatment free of charge for low income families and the Health Card which covers rural families requiring limited treatment. (ref.M.Carpio DP/ID/SER.A/1660 1993)

The writer was involved in an ESCAP (Economic and Social Commission for Asia and the Pacific) project based in Thailand during 1979; at that time the pharmaceutical sector had developed with no regulatory framework and there were some 30,000 pharmaceutical/pseudo-pharmaceutical products available in the shops: all based upon the standard, well tried/understood molecules (paracetamol, aspirin, etc.). Despite the industry already having production capacity in excess of the national demand, manufacturers continued to place orders for yet more production equipment. This would have led to a further annual increase in production capacity of 10%. (J.T.Brown/ ESCAP research).

Subsequent to completion of the study, the Thai Government introduced stringent controls on the industry, so that, in 1991 the Ministry of Public Health essential drug list comprised around 400 pharmaceuticals of which the two Government facilities (GPO) produced many for the public hospitals; the Thai pharmaceutical market totalled US\$ 541 millions and is ranked, worldwide, 35th largest. (M. Carpio).

The country has introduced a Patent Law to protect pharmaceutical products for a period of 20 years and Safety Standards have been introduced for all manufactured products, either domestic or imported.

With ongoing assistance from UNIDO and the manufacturing sector the Government has set up a Quality Assurance program for Validation in Pharmaceutical Industry based in Chulalongkorn University in Bangkok.

As has been mentioned elsewhere in this report, the newly expanded pharmaceutical sector in Syria will press strongly for price increases of domestically produced medicines.



They will support their claims by saying, quite rightly, that the non-productive overheads arising from investment in sophisticated and costly equipment for QC/QA and product validation must be offset by increased selling prices of their products. This problem will be exacerbated if they also have to provide independent data supporting Expiry Dates etc. for each of their products.

Again guidance may be gained from the Thai experience. The majority of the costs must be paid by the patient. The Thai Government has introduced two card schemes: Medicare which provides medical treatment free of charge for low income families and the Health Card which covers rural families requiring limited medical treatment. A Social Insurance scheme is also in force for all companies employing more than 20 workers. With minor differences a similar scheme is in operation in Australia. The Syrian Government may wish to consider some of these strategies when evaluating the price increase claims which will inevitably follow any demand on the manufacturing sector for greater non-productive investment.

A further strategy that the Syrian Government may wish to consider in the future is that of assessing the standards of QA/GMP/Validation of each individual manufacturer and issuing a GMP Certificate to those sections of the factory which comply to an agreed standard. Thus a factory may be Certified to produce uncoated tablets and ointments, another may be Certified to produce oral liquids etc. Obviously, this could become a highly contentious situation if it were seen to be imposed on the industry by the Ministry of Health alone. This is clearly an area in which a cooperative approach by the Ministry together with the PMAS would be beneficial.

## SUPPORT OF SENIOR MANAGEMENT

### Role of the General Director

The traditional role of the GD of Thameco has been that of an extension of the bureaucratic hierarchy, located in the workplace and obliged to accede to the directions of superior officers. The effectiveness of this style of management has to be questioned in the context of the problems which have overtaken the company during recent years and in the daunting task which the new GD must address, and resolve, if Thameco is to resume its status as a pioneer in the pharmaceutical sector of Syria.

It is the writer's responsibility to make evident the deficiencies of the system so that the system can be changed for the benefit of Thameco, and to allow the new GD some chance of attaining the goals set for her.

Over the course of several years and the tenure of four GDs, the writer has had ample opportunity to observe the management style of Thameco and has reported that the company's problems are essentially those of management and administration rather than of technology.

It has been noted that Thameco is a big company by any standards and, as such, demands professional management by a trained, experienced specialist. Yet all of the recent GDs have been pharmaceutical technologists rather than business graduates or MBAs.

It is incongruous to the writer that great importance has been placed upon filling the technical middle management positions (eg head of ampoule making, head of tablet making etc.) with pharmaceutically qualified personnel, yet the most demanding and critical position in the entire company has been repeatedly delegated to persons completely unqualified, by way of formal training or by experience.

It is appropriate to have a pharmacist as GD of Thameco but that pharmacist MUST HAVE the specialist knowledge, experience and aptitude to succeed in the job. Failing this, the job suffers, the company suffers and the GD is exposed to totally unreasonable trauma.

The writer has observed the incumbent GD attempting to handle three meetings concurrently, to deal with telephone calls and personal interruptions, whilst correspondence and letters demanding attention accumulate on the desk to be dealt with as "overtime". Clearly, active assistance in handling routine company business, (i.e. purely administrative matters) would remove much of the un-productive workload from the DG and allow time to be concentrated on the primary objective of restoring Thameco to a leading position in the Syrian pharmaceutical sector. It may be appropriate to appoint an assistant, on a probationary basis initially.

A factor which adds even greater difficulties to the job of the GD is that disciplinary action against non-performing staff members is almost impossible to apply. It has been noted elsewhere in this report that staff at all levels have been obliged to take second jobs to supplement their Thameco salary and, in fact, they do the minimum amount of work for the company and may be absent frequently. This situation leaves the way open for conflict of interest in that Thameco equipment and time may be used in ways which are not beneficial to the company. This is destructive to the overall factory morale and is an area that calls for early rectification.

The presence of the private sector pharmaceutical companies has increased the pressure on Thameco, but the traditional operating system has not been modified in any way to combat this. The GD must continue to accept full responsibility for the operation of the company but has neither the training nor the authority to effect the changes which are necessary to make the job possible.

The writer prepared a brief note for the newly appointed GD to point the way to avoiding some of the inherited problems which must inevitably resurface in the future; also provided as appendices to this report are a proposed Job Description for the GD and a proposal for setting up a basic Responsibility Chart.

It is imperative that the GD of a major Syrian institution should be equipped to do the job and be fully supported by a responsible assistant to handle the routine matters which currently erode management time. It is equally important that the system should be reviewed and liberalised so as to render the job possible.

At least a training course in basic management and an administrative assistant should be provided for the new GD of Thameco as matters of urgency.

Subject to the implementation of structural changes in the administrative arrangements of Thameco it would be appropriate to consider it as a new company and to make available some international expertise for an extended period to support the GD until the company is managerially restructured and capable of autonomous operation.

## INHERITED PROBLEMS AT THAMECO

### 1. MATERIALS

Many of the problems which have caused acute embarrassment to previous GDs of Thameco have been inherited.

Misunderstanding of raw material Expiry Dates has caused tons of material to be rejected. Despite frequent advice by the writer, in Mission Reports, and by personal communication, the authorities have steadfastly refused to accept that there is no such thing as an absolute Expiry Date for raw material.

Elsewhere in this Report the writer has provided again, a full account of the meaning of Expiry Dates for raw material and for finished goods. This must be read, clearly understood and implemented by all who have authority for the use of materials, either in the industry, or particularly in the Inspectorate.

Below is given a statement of the known, inherited problems as at April 1994.

OVERPEN: contains black particles; these cannot be removed by sieving or by magnet; they derived from the locally refined sugar used to prepare the product. FOR FUTURE PRODUCTION OF DRY SYRUPS THAMECO MUST USE SUGAR OF PHARMACOPOEIAL QUALITY.

This Overpen do not fit for public sale and should be destroyed.

TETRACYL: this comprises three batches of Finished Product with Expiry Dates of September 1993 and February/March 1994. It is estimated that the value of the material is in the order of \$35,000. Since this particular material is "out of date" because of the previously mentioned refusal to accept the meaning of raw material Expiry Dates it is the writer's view that the batches should be resubmitted for analysis to determine the exact status of their potency/degradation product. The results of this analysis should determine the future of the product.

AMINOPHYLLINE SUPPOSITORIES: these were withdrawn as a result of advice, from the manufacturer of the suppository base that a chemical reaction between the Aminophylline and the base caused the suppositories to go hard. The material should be dumped.

DECOSTAMINE: it was not possible to determine why this material has been put in suspension since its Expiry Date is July 1996. The so-called "rejected material" is mixed with good stock. It must be resubmitted for analysis and the decision regarding its disposal based upon the laboratory findings. Since the value of the product

is in the order of \$300 only. it should be dumped if the laboratory tests are in any way marginal.

TAMEVITE B1: this is an old material for which there is no market; it must be dumped.

ASCORBIC ACID: there is material which is plain and other which is coated. The plain material was sampled in 1987 but there is no sticker to identify whether it was approved or rejected. Since it is now probably ten years from the date of manufacture the material should be dumped. In the case of the coated material, it shows a retest date of November 1989. It should be submitted for retest as soon as possible and, if still in specification, it may be used.

NICOTINAMIDE: an excess quantity was bought from Merck and was sampled in January 1993; the results of the analysis are not known. Since Thameco no longer manufacture any products containing Nicotinamide, the material should be dumped.

MANNITOL B12: the product is no longer sold by Thameco; the material should be dumped.

THAMEVITE: this appears to be the end of a product run and since there is less than 35 kg, it should be dumped.

SUPRIME TABLETS: there is a quantity of 272 kg but it was not possible to determine the reason for it having been suspended. Since it has an Expiry Date of October/November 1995, it should be reanalysed and its future determined on the results of the laboratory findings.

CALCIUM d PANTOTHENATE: this is material for a product which Thameco no longer produces. It may be possible to sell it as raw material to another manufacturer, alternatively it must be dumped. Note: if to be sold to another manufacturer, Thameco must provide evidence that the material still conforms to pharmacopoeial standard.

FOLIC ACID: this material dated back to 1980; Thameco no longer handles the product; the material should be dumped.

## 2. MACHINERY

The new GD of Thameco has inherited in excess of \$ 1 million in new plant and equipment, there has been no preparation for its arrival or its installation in acceptable conditions of GMP. In some cases the terms of purchase included a component for installation and commissioning by the machine builder, in other cases there is no such provision. A danger here is that, according to Thameco's method of purchasing, the Performance Bond is refundable to the supplier after one year. It is improbable that all of this equipment will have been installed and commissioned within the refund period; consequently Thameco is at risk of accepting responsibility for equipment which it cannot install or operate - another Thimon Line fiasco.

There is a high level of naivety in such ad-hoc procurement of equipment in the absence of preparatory work and the new GD cannot be held, in any way, responsible for the difficulties which will undoubtedly be faced when this equipment descends upon the company. There is no merit in listing the equipment in this Report, however the details are all available in the Commercial Department; the GD should request a full inventory.

### INTENDED DEVELOPMENT AT THAMECO

The writer was shown drawings of the intended development at Thameco for the handling of antibiotic vials and capsules. It was reported that the intended development had "been rejected". It is not the purpose of the project to "reject" proposals; it is, however, very much the responsibility of the project to point out the shortcomings of a proposal and to make suggestions for their correction. The following applies:-

The present Thameco factory building dates back probably 30 years in conception and at the time it was built, suitable locally available materials were used in its construction. The design would have been appropriate for the technology to be installed. The method of construction, however was inflexible in that internal walls of brick and plaster are not capable of easy relocation should it be necessary to change the utilisation of a room or to change the layout of an area.

To look at the factory in 1994 clearly reveals that, what was appropriate when Thameco was built, is no longer appropriate; this is to a great extent the reason why the factory looks so broken down. For instance, many of the redundant electrical wirings, duct work and disused machines reflect the way the factory used to be. Old machines have been torn out and new ones, with their services, squeezed into the old spaces. Thus, the new machine is not ideally located and the remnants of the old machine are never completely removed. To the experienced observer, the factory has not been "planned".

The identical observations apply to Dimas, and the new factory buildings at Aleppo show exactly the same lack of flexibility. This is old style of factory construction is highlighted when comparison is made with some of the modern high technology buildings now constructed in the private sector .

This is what the writer was saying when the proposed extension was "rejected". The technology of building factories has changed to keep pace with the improved manufacturing technology which takes place inside. If Thameco wishes to be identified as a serious manufacturer, comparable to the private sector, it can no longer afford to operate in outdated premises and should definitely not be intending to construct yet another inflexible building. Similarly, the fittings provided within the building must be brought up to modern standards of hygiene, and, for instance, plastic laminated/"particle board" cupboards which are totally unsanitary and unfit for use in the pharmaceutical industry should all be replaced with modern stainless steel units as should marble topped sinks in production areas.

For its new structures, Thameco must be thinking along the lines of "modular construction". This is a method by which the outer shell of a building is designed as the load bearing component to support the roof and to provide maximum uninterrupted internal space.

The actual working areas are purpose designed around the machinery and staff which are required to do the job in the most efficient manner.

The working areas themselves are constructed of demountable metal and glass partitions and doors, with metal ceilings. These partitions offer the possibility that, at any time, they can be taken down and easily relocated to accommodate modifications in the technology of the production process.

Thus it is possible to provide a building in 1994 which will still have the attributes of a modern factory in the foreseeable future. Whilst the initial cost of such a building may exceed that of the old style building, the savings over years of use, the facility with which modifications can be made and the overall suitability for pharmaceutical operations will far outweigh the initial cost.

For maximum value, all services should be run across the tops of the workrooms. Walkways should be provided so that all maintenance can be performed from above, without the necessity of disrupting the integrity of the room itself. Thus, filters and light fittings can be serviced and cleaned without the maintenance staff having to enter the work space.

This is the modern concept of factory building and Thameco must be prepared to incorporate it into its future planning if it intends to remain competitive with the private sector and if it intends to be a credible manufacturer of pharmaceuticals.



## PROCUREMENT AND PURCHASE AT THAMECO

### 1. IMPORTED MATERIAL

Procurement of imported materials is a Production Department activity; it should only be initiated AFTER receipt of certified sales figures from the marketing organisation. These sales figures must forecast the projected sales for the forthcoming year; to be of any real value to the Production Dept. the twelve monthly requirement must be broken down into three monthly periods.

In view of the time delays involved in setting up production and packing lines it must be understood that the projected requirement for the first three month period cannot be changed; the second period's requirements are capable of some rescheduling; the final six month's forecast is totally flexible. However, the total annual requirement should not exceed the original forecast.

Wherever possible the concept of "Just in Time" (JIT) deliveries should be employed; this may present some problems in Syria due to the length of the supply chain but every effort must be made to minimise the stock of raw material held by Thameco. Minimal stock offers the following advantages:-

- a) reduction of the demand for foreign currency tied up in stock at any one time
- b) reduction of the risk of sensitive materials going out of date before use
- c) avoidance of mix-ups involving materials being used out of date-sequence.

### 2. RAW MATERIALS

Materials should be purchased from principals wherever possible, for instance vitamins from Roche, Aspirin from Monsanto, other companies able to supply bulk chemicals in the quantities required by a moderate sized manufacturer would be Dow Chemicals, Merck, Rhone Poulenc, S.K. Beecham, Roquette, etc.

Small or single drum quantities are best bought from one of the reputable European brokers such as Dolder AG., Select Chemie (Swiss) or Allwitt (UK).

In the best interest of product validation it would be valuable to have direct knowledge of the production facilities employed by the material manufacturer; this is not immediately possible in the case of materials coming to Syria from brokers. However, it is important that the country of origin of the material is known and all Purchase Orders for Raw Materials from brokers should require the broker to provide this information.

Additionally, a manufacturer's Certificate of Analysis must accompany each delivery.

The Purchase Order must specify that only material with a long Expiry Date should be shipped; this will avoid the problems which have arisen in the past of short dated raw materials being converted into Finished Goods with an unacceptably short shelf-life.

The purchase of cheap materials is false economy since they will probably not be easily capable of conversion into Finished Goods of consistent quality and efficacy.

The need for a single re-work of a production batch immediately inflates the actual cost of the raw material, and brings it in line with the price which would have been paid for high quality material at the outset. The cost of a second re-work, should that be necessary, obviously makes the real cost of the material higher again.

In an activity such as tablet making, the physical state of Raw Material is as important as its chemical purity. Only the user (i.e. the tablet maker) can appreciate which material is easy to work with and which is impossible despite the fact that each is chemically identical. The purchase of standard material is an integral part of Quality Assurance since it ensures that each batch of a product is identical in terms of physical and biological characteristics to every other batch of the same product.

Thus, when a product profile has been developed around a particular quality and grade of material there should be no variation of the material during the life of that product. If, for any reason, there is a change of material, then the resulting product must be regarded as a new product and a completely fresh product profile must be developed.

The question of determination of the proper price for Raw Material can only be resolved by the expedient of seeking bids from several different suppliers for the identical quantity of a material, this is best done by use of the fax machine since this assures that the prices quoted are absolutely current. An American weekly journal "Drug and Chemical Reporter" provides spot prices for every conceivable chemical, grade and quality and may provide a useful reference if required; this may, however provide misleading information if there is inconsistency in selection of the Quality and/or grade of material being priced.

It is unnecessary to provide raw material suppliers with details of the "points system" as set out in Thameco's Bid Book. The Purchase Order must state the exact specification for the material required in order that the prospective supplier has only one question to answer; "does the material that I am offering comply exactly with the requirements of the purchaser?". If the answer is "Yes" then the supplier will submit an offer.

It is strongly recommended that a company should standardise on a grade and quality of a material and take samples from several suppliers to determine which one has the optimal properties for the intended product; then THAT GRADE AND QUALITY ONLY should be specified in all future orders from THE SAME SOURCE. Only

in this way will product uniformity be attained. By this means, a company will find that its entire supplies of Raw Materials will derive from 4-6 different suppliers, this will enable an understanding to be reached between the suppliers and the Syrian user which will be beneficial to both parties.

Material suppliers are generally prepared to be very cooperative when they have developed a mutual trust with their customer. It is not uncommon for them to supply urgently required material "on credit" to customers with whom they have had several years of satisfactory trading. This facility offers great benefit to the user and should be the goal of every company which purchases materials from overseas suppliers.

The secret is to buy from only the most reputable sources and to provide the supplier with an absolute description of the required material.

### 3. PACKING MATERIALS

As with its Raw Materials, Thameco purchases almost all of its Packing Materials overseas. They are despatched by sea freight and as explained in the review of the activities of the Commercial Department, it can take up to thirty-three weeks for the materials to arrive.

The term Packing Material must be understood to include two varieties of material, namely Specific packing material, and General packing material.

#### a) SPECIFIC PACKING MATERIAL:

The term relates to any packing material which is Product or Company specific; for example pilfer-proof caps which are embossed with the Thameco logo, printed ampoule bodies, printed foil, printed cartons, etc.

It represents the company; the customer purchases a medicine on the basis that the manufacturing company is known and its products are trusted. Loss of trust means loss of customer; and the easy way that a rival can destroy the reputation of a company is by obtaining some of that company's specific packing material and making sure that the contents are in some way objectionable, e.g. by putting an insect into a bottle of cough medicine and recapping the bottle using a Thameco pilfer-proof cap.

Every time that Thameco ships specific packing material, there is a chance that some of it may find its way into the hands of a business rival, and Thameco's reputation is at risk.

In the days when there were only the two public companies this loss of reputation did not represent a real danger. Now, however, there are probably thirty companies which are equipped to use specific packing material of the type being imported by Thameco and this must be seen as a threat to the company's reputation.

The long term answer, is that the company must import plain packing material, to be printed in Syria, either by the user company, or by a printing contractor who is provided with exact quantities of plain stock ( eg pilfer-proof caps ) and the company's printing "slug" in order to do the job. On completion, the printer would return to the company the exact amount of printed material together with the printing slug.

In the short term, however, there is risk of malicious damage to the products of reputable companies.

The problem is not exclusively for the maligned company however, since the regulatory authority will have the greatest difficulty in proving that any objectionable material in a product actually arrived there as a result of carelessness on the part of the company purported to have made the product.

Now that there exists a highly competitive pharmaceutical manufacturing sector in Syria it is important that a specialist printing business should also be established

b) GENERAL PACKING MATERIAL:

This covers all other types of packing material and it is not liable to mischievous treatment by business rivals. Its manufacture requires extremely accurate cutting and folding if the material is intended for use on automatic packing lines. This is a peripheral industry to the manufacture of pharmaceuticals; its development in Syria should be encouraged.

## EXPIRY DATES OF THAMECO'S PRODUCTS

### 1. RAW MATERIAL

Regarding imported Raw Materials, the Expiry Date shown on the container is put there for the protection of the manufacturer; it represents the expected life of the material in the worst possible storage conditions, i.e. high temperature combined with high humidity. This Expiry Date is NOT ABSOLUTE, it is a GUIDE only and should be treated as such.

All Raw Material deliveries should be accompanied by a Certificate of Analysis. The receiving Company must confirm, in its own laboratories, that the data provided on the Certificate of Analysis is accurate in every way. Should this not be so, the Company has a legitimate claim against the supplier for providing substandard material. On completion of its analytical check the receiving Company must allocate a Re-Test date to the material.

Having confirmed that the material conforms to the required specification, the analytical results must be filed (on card or in computer) for future reference. Each grade of each material MUST HAVE ITS OWN CARD OR COMPUTER FILE. The data recorded on the card must show all of the pharmacopoeial standards for the material, together with the actual results obtained for the material under investigation. The card must show the date of the original analysis and also the retest date; it should be signed by the analyst.

At the time of retest, the material should once again be tested, but this time it is not necessary to perform those tests relating to impurities (such as heavy metals), which enter the material during its synthesis and cannot have changed during storage. The retest procedures may be confined to determination of activity level (potency) and of degradation product which may have developed during storage.

These figures for potency and degradation product should now be entered on the material's record card, immediately below the figures obtained in the first analysis. It is now a simple matter to compare the figures obtained in the first analysis with the new figures and see how the material is standing up to storage. Assuming that the material is still within specification a new retest date should be given and the material returned to store.

The same procedure should be followed at the next retest, and by this time a pattern should start to appear in the analytical results. This will indicate how stable the material is in the conditions in which it is being stored; and it is now possible, by a simple extrapolation, to estimate a date upon which the potency will fall below the pharmacopoeial limit or the degradation product will rise above it.

The most easy way to extrapolate the Expiry Dates is to plot the results of potency and of degradation product on a graph, against time. A line will

result which shows the decrease of potency over time; a second line will result which shows the increase of degradation product over the same time. It is possible to, theoretically, extend these lines until they reach the pharmacopoeial limit, at which time the material will no longer conform to the official standard and will need to be rejected. This is the extrapolated Expiry Date.

The analytical figures obtained at the next scheduled retest will be transferred to the graph and used to evaluate the accuracy of the extrapolated Expiry Date.

After sampling, the containers must be completely and hermetically resealed to prevent access of moisture during storage; the same care in re-sealing containers must be observed after each use of the material.

Storage conditions for the Raw Material must conform to the requirements printed on the supplier's label; failure to comply with these standards may result in accelerated deterioration of the material.

At some convenient time approaching the Re-Test date nominated by the Company, the material should be re-sampled, FROM THE BULK, not from the laboratory keeping sample, retested, and the results treated in the manner described above.

Whilst the material continues to conform to its specification, e.g. BP., USP. etc., then new re-test dates should be nominated and the bulk material returned to its correct storage conditions pending use or until the scheduled re-test.

The analytical and extrapolation work described above is the SOLE AND EXCLUSIVE RESPONSIBILITY OF THE QUALITY CONTROL DEPARTMENT. No material should be transferred to a production operation unless it is confirmed as being within the official standard and duly approved by the Quality Controller. Material which is not approved and signed by the QC Department MUST NOT BE USED IN ANY MANUFACTURING OPERATION.

In the case of Vitamins it is common practice to allow for an overage when formulating a product, this takes account of the deterioration which is inherent to Vitamins during bulk storage and during storage of the finished product. The same may apply to certain Antibiotics but in this case the development of toxic degradation products is inevitable.

There is no such thing as an absolute Expiry Date. The shelf life of any material, whether in bulk or as finished product, is critically dependant on its conditions during storage. In the case of inorganic material, such as Talc or Kaolin, the shelf life can be almost indefinite provided that access to moisture is avoided.

Organic materials however, are much more likely to deteriorate during storage and compliance with the manufacturer's storage conditions is the only way to obtain the optimal life from the material.

Whenever a material is OUT OF PHARMACOPOEIAL STANDARD IT IS REJECTED. This is an absolute condition; the material must NOT be returned to the store. It must be suitably marked with the words REJECTED, signed by the Quality Controller, and promptly disposed of.

Dumping of rejected material should be done in an environmentally and socially responsible manner. Incineration is the preferred method.

With proper procurement systems, proper storage conditions, proper QC procedures, and strict adherence to the FIFO (first-in, first-out) rule, the rejection rate for Raw Materials and Finished Goods will be reduced to a minimum.

It is not correct to enforce Expiry Dates in a generalised manner; it is the responsibility of the manufacturer to ensure that material in store, in all respects complies with the appropriate pharmacopoeial standard. If it fails to comply, it has no right to be in the store.

## 2. FINISHED GOODS

All finished goods must carry a Batch Number and an Expiry Date on their innermost packing, i.e. on the bottle label if the product is bottle packed, on the blister if the product is blister packed etc.

The Batch Number is self explanatory and clearly relates to the bulk batch from which the product was packed; this information is sufficient to trace the history of the product throughout its manufacturing, packing and Quality Control sequence.

The EXPIRY DATE (ExpDte.) is, however, less clearly defined; it relates to the date upon which the product no longer conforms to the standards established by the manufacturer or set out in the pharmacopoeia. The cause of this non-conformity is generally due to:-

- 1) the strength or potency of the product has fallen below that which is claimed on the label.
- 2) the degradation products of the components of the product have risen above the limits set out in the pharmacopoeia.

The reasons for the deterioration of the product are many and varied; they must all be allowed for when the ExpDte. is allocated to the product.

It is standard practice to establish ExpDte. during the "development stage" when the product is being progressed from the research laboratory to production scale. This progression may take several years in the case of an innovative new molecule. Several different trial formulations will be made up to test the efficacy, bio-availability and stability of the product; the formulation which gives the best overall performance will be selected as the one which goes into production.

Since a pharmaceutical product is a unit comprising medicament and immediate packing, it is imperative that the ExpDte. relates to the entire system and not to the medicament alone. The system is said to be "dynamic" because it responds to climatic changes of temperature and humidity.

Thus, leaving a product on a laboratory shelf where climatic changes are both slight and slow will not provide much data on how the product will respond when exposed to the climatic extremes to which it will be exposed when offered for general sale. So it is imperative that "aging data" for the product is related as closely as possible to the situation in which the product will spend the greatest part of its life.

Obviously, if this data were to be collected in normal, daily climatic variations it would require 3 years of exposure before a 3 year aging profile became available. This is too long a time to delay the introduction of a new product; so a process known as "accelerated aging" is employed.



Accelerated aging involves cycling the product through the harshest possible climatic conditions repeatedly over a short period of time; it is performed in a "climatic cabinet". This is a purpose built room equipped with heating/humidifying and cooling/dehumidifying equipment which can be cycled between extremes several times per 24 hour period. The selected extremes should represent the maximum temperature/humidity and the lowest likely temperature/dryness combination likely to be experienced by the product.

Assume that the cycling frequency is set at every 6 hours; then, in one calendar day of 24 hours the cycle of the climatic cabinet will have been through the equivalent of 4 calendar days; thus the aging will have been accelerated by a factor of 4 times. So a week in the climatic cabinet cycling 6 hourly has the same value as 1 month in normal conditions; the selected cycling conditions may have ranged between 40C/ 80XRH and 10C/ 40XRH.

By removing a sample of the product-under-test and analysing its critical parameters at intervals of, say, one month, it is possible to quickly determine the stability of the medication and its packaging, and by recording the analytical results in graph form to extrapolate a safe preliminary ExpDte. for the product.

This preliminary date would, in course of time be confirmed by analytical testing of the product in real conditions. It is likely that the ExpDte. derived from the climatic cabinet data will be considerably shorter than that derived from the real conditions but this is not important because the climatic data was on the "safe side" and presents no risk to the consumer; an extended shelf life may be attributed to the product after extensive testing of the product in real conditions. The manufacturer has been able to launch the product onto the market confidently knowing that its ExpDte. has been determined by rational methods, not just guessed at and does not constitute a danger to the consumer.

By this means, the manufacturer is confident that the Expdte. is valid for the product system, has been determined by objective methods, and can be proved to be accurate.

The use of ExpDte. is important since it protects the consumer from possible harmful effects of the deteriorated product. It also serves to protect the manufacturer against consumer claims that ill effects were experienced after taking a medication if the manufacturer can demonstrate that the product was, in fact, out of date.

In order to achieve the true value of an ExpDte. it is important that STORAGE CONDITIONS are also provided, in detail, on the innermost packing material. Storage conditions should be realistically achievable in the typical home or hospital and need be no more detailed than simply "STORE IN A COOL DRY PLACE", PLEASE "DO NOT REFRIGERATE", or "REFRIGERATE AFTER OPENING' etc.

### 3. DISPOSAL OF STOCK

Over a number of years Thameco has accumulated stock which is of no further value, because it is substandard or no longer used. It is bad practice to retain worthless materials and the following should be disposed of, in a responsible manner at the earliest opportunity :

Material/Batch No.	Quantity	Date	Reason
Mono Sodium Citrate #14982	13000 kg	1982	No application
Mono Sodium Citrate 31488		1988	No application
Sodium hexameta Phosphate 6423060	124 kg	1992	Substandard
Erythromycin 14883		1984	Substandard
Tween 80 22979	86.7 kg		Substandard
Castor Oil			Substandard
Tragacanth 27387	297 kg	1987	Substandard
Aspirin granulation			
Bismuth CamphoCarb.	340 kg	pre 1984	No application
Promethazine	10 kg	pre 1988	No application
Urea	30 kg	pre 1980	No application
Binitrate lysidine	23 kg	pre 1980	No application
Lithium Benzoate	23 kg	pre 1980	No application
Alginic Acid	13 kg	pre 1980	No application
Hexamine	3 kg	pre 1981	No application
Tartaric Acid	3.5 kg	1990	No application
Barbital	47 kg	1979	No application
Pyramidone	156 kg	1985	No application
Lidocaine HCl	5 kg	1985	No application
Kaozate	23 kg		No application

Chloroquine Phos.	2.5 kg	1989	No application
Phenobarbitone Acid	65.7 kg	1992	No application
Nicotinic Acid	0.535 kg	1989	No application
Acetarsol	368 kg	1977	No application
Charcoal	5711 kg	1977	No application
Nicotinamide	84 kg		No application
Lactic Acid	66 kg	1984	No application

NOTES: It may be possible to use the Charcoal as a filtering medium

Great care should be exercised in disposing of the Barbiturates because of their toxicity

The Aspirin powder is a very significant quantity; it is not soluble. Disposal should be in a pit which can be covered with earth as soon as possible. The location must be well selected to prevent the Aspirin entering the water supply or contaminating surrounding farming land

### STATUS OF THAMECO: WORKING CONDITIONS

As elsewhere noted in this report there now exists a strong attitude of scepticism in the staff of Thameco which stems from two principal sources; one being that a worker can get a "better deal" in the private sector and the other, that many promises for improvement have been heard over the years but little, if any, improvement has been realised at the level of the workers.

In performing the work for the Status of Thameco section of this report, the writer has taken particular note of the operating conditions within the Damascus factory and is quite definite that such working conditions would not be acceptable or tolerated in an industrialised country. The following applies:-

The buildings are no longer current; they reflect working conditions which are no longer acceptable in a pharmaceutical factory. Illumination, ventilation and dust extraction is in most areas totally inadequate. Decent changing rooms do not exist, female staff have been forced to paper over windows to obtain a degree of privacy. Rest rooms are not provided and staff are seen to be sitting on broken boxes on the floor since there are no alternatives. Flowers, vegetables and eggs are carried through the corridors of Thameco and street clothes are seen in workrooms. The condition of floors in some areas represent a risk of physical injury which the company would find extremely difficult to defend should a claim for worker compensation ever be taken to a court of law.

The non-functional dust extraction systems cause the workers to be exposed for long periods of time to high levels of systemically potent chemicals without suitable protective clothing or respirators. This clearly represents a hazard to the workers and to the products themselves.

Unprotected workers who spend 6 - 8 hours per day in an atmosphere heavy with the dust of antibiotics could well be expected to develop bacterial resistance or allergy to those antibiotics. The facilities for handling antibiotics would be condemned by a factory Health & Safety Inspector.

There is no policy within the company to protect special groups of workers from the environment or to protect the product from the possible dangerous effects of exposure to workers with respiratory or skin diseases.

Eye protection is not employed in laboratories where corrosive chemicals are in use.

Safety boots are not worn in areas where heavy pallets are in use; nor are they worn in workshops.

UV lights in sterile rooms are not controlled, workers may be exposed to high levels of radiation.

The risks of birth abnormalities in the children of pregnant female workers are openly discussed amongst the staff; they are aware of the existence of a risk but have no means of quantifying it, consequently it assumes irrational and terrifying proportions which do nothing to improve the morale of the workers and play a large part in the development of the scepticism.

The working conditions in Thameco have not been improved since the factory was built. They are outdated and require urgent improvement.

The matter of working conditions in Thameco is serious. It must be addressed and rectified to the maximum extent in the existing factory and should be properly incorporated into the planning and implementation of any extensions which the company may undertake.

Currently, staff morale is low and scepticism is high, yet there is an underlying enthusiasm for the company which could be revitalised if positive steps are taken to correct some of the deficiencies under which the staff is forced to exist.

**STATUS OF THAMECO : QC LABORATORY**

The QC laboratories at Thameco comprise what is now , an un-necessary complex of individual and independent departments doing what amounts to an identical job. Thus, there are labs for the Research Department, for the Injection Department, for the Child Food plant, and for the General Factory.

In the current status of Thameco, this degree of luxury can no longer be justified, and the entire QC set-up should be consolidated into a single laboratory for raw materials, a single laboratory for finished products and the appropriate in-process laboratories in the factory and the Child Food plant. (The term "single laboratory" is intended to mean a complex of specialities i.e. wet labs., instrument labs., biological labs., etc., which work for the entire factory, not for a single component).

Thus, it would be possible to undertake a complete modernisation of the QC equipment, much of which is of considerable age, and no longer fully operational. it is not seen to be relevant in the context of this Report to spell out the individual pieces of equipment which are in need of replacement in the several laboratories.

It is more appropriate to suggest a complete review of the QC function at Thameco, based on the LIMS (laboratory information management system) computerised principal. This will have the advantage of allowing Thameco to re-equip with modern technology, computer linked which will prevent the mistakes of the past where QC results have been hidden, or not correctly reported leading to many of the inherited problems described elsewhere in this Report.

Subject to high level decisions on the future direction of Thameco, work on the status of the QC Department should be held pending.

**STATUS OF THAMECO : COMMERCIAL SECTION**

The activities of the Commercial Section were reviewed with the head of the department and two assistants. Prior to the review, the writer had the opportunity to study a previous Tender Book.

The legal and financial obligations placed upon the prospective supplier by the tendering process as set out in the Tender Book are onerous and have obviously been unacceptable to some of the major manufacturers such as Roche and Monsanto, consequently a number of valuable material sources are not available to the company. Further, the leading antibiotics manufacturer, Beecham, has ceased to trade with Thameco on account of significant outstanding debts. In order to improve Thameco's reputation and to widen its supply options, these deficiencies should be rectified.

Thameco currently buys Raw and Packing materials from a wide range of sources including principals, brokers in the European Community, India and the Far East. One of the major brokerage houses, Dolder, is disqualified since it is registered in Switzerland which is not a member of the European Community. This appears to be a totally irrational situation in light of the importation of materials from India and S.Korea.

The Company currently uses 54 molecules of which 12 are antibiotics, 8 are vitamins and the remainder are therapeutically active chemicals. In addition, there are 77 excipients and 17 colours and flavours on the tender book. All of the listed items are currently legal in their countries of origin.

Thameco puts out two tenders per year and these are drawn up by hand. This is an immense undertaking and leaves many possibilities for transcription errors and omissions with consequential inability to carry the production/packing operation through to the Finished Goods state; hence the frequently heard observation of Thameco's "stock out" situation.

It is important that the Commercial Department is computerised as soon as possible, using appropriate hardware which can also handle warehousing and production activity through remote terminals. Thameco should investigate suitable equipment and software and make recommendations to the authorities for earliest procurement, software development, installation, validation, and operator training. This is an area in which the private sector manufacturers already have a big lead on Thameco and if the company wishes to be a serious member of the manufacturing group it should not delay computerisation.

The functions initially envisaged for computerisation in the Commercial Department include:-

- Stock Control
- Technical Standards for materials

- Comparison of offered materials against required standards
- Calculation of order quantities
- Raising of Purchase Orders
- Raising of Import Licences
- Raising of Letters of Credit
- Arrangement of Insurance Documentation
- Shipping instructions.

Additionally it could be programmed to post notification of low stock levels and to identify re-order points.

It has been noted that the private sector has a great ability to produce finished goods at short notice by contrast to Thameco and this matter was investigated with the Commercial Section. From the date upon which it is decided to place an order, typically six weeks will elapse before the Letter of Credit is opened. A further three weeks is required for the processing of the L/C through the Syrian bank, to the supplier's bank to the intending supplier. Delays in shipping the materials via Syriamar can add between one and three months to the delivery, however if the material comes by airfreight the delay can be reduced to just a few days. Delivery, by road transport, from the port of discharge to Damascus would typically require one to two days.

Thus, the most optimistic lead time on Raw Materials that Thameco can expect is thirteen weeks but this could extend to twenty-one weeks subject to the activity of Syriamar; the Commercial Department has no control over the delivery time of materials once the request for the L/C has been issued.

The situation for Packing Materials is worse since all materials have to be cut to size and printed before shipment is possible. This would typically add a further twelve weeks to the lead time making a total for Packing Materials in the order of thirty to thirty - three weeks.

An additional delay component not included in the above process arises from Thameco's evaluation of materials and prices by committees. There are two committees; the first evaluates the quality of the offered material, the second evaluates the price of the offered material. Together this requires nine signatures before an order can be initiated.

For Thameco to operate in a modern manner based upon Product Profiles, the *identical grade and quality* of a material MUST be employed in each and every batch of Finished Goods. Failing this, every change of raw material or excipient would have to be classed as a new product and that product would need to be revalidated according to standards of bio-availability/-equivalence, toxicity etc. Product Profile is the future direction of the pharmaceutical sector, and for Thameco to comply with the best standards of the industry it should be planning to move away from its traditional methods of material evaluation by committee and instead identify the CORRECT quality and grade of material for each product and purchase only THAT material in the future.

For Thameco to be able to respond instantly to urgent requirements for Finished Goods would require the company to carry at least six months additional buffer stock of all involved Raw and Packing Materials. Obviously this is



possible to arrange; instructions and authorization for the additional capital expenditure are required.

Once again the question of Expiry Dates for Raw Materials was explored with the Commercial Department together with technical staff. The material in question on this occasion being Acetylsalicylic Acid from the highly reputable supplier Dow Chemical (several batches are involved including Batch Number MM890111x79). Thameco seems to have been instructed (verbally) not to use the material since it had exceeded its Expiry Date. Yet there is no REJECT sticker on the drums and the most recent chemical analysis (1991, '92, & '93) indicates that it is still within the pharmacopoeial limit. There is no plan to use the material neither is there a plan to dispose of it. This is a nonsensical situation since there is reportedly 9,680 kg. of the material and its value is in the order of \$50,000. This is obviously a sensitive matter to Thameco staff and the writer was given a number of different accounts as to the status of the material.

In view of the value of the material it is important that the matter should be resolved by an unbiased referee. It has been proposed to Thameco that a representative sample of the material should be returned to Dow Chemical, together with an account of its storage conditions, Batch Number(s) and Thameco's own analytical results. Dow Chemical should be asked to perform and report on the necessary tests to determine the status of the material, and it should be used or dumped according to the data provided by Dow. It would be good administrative practice that, should a parallel situation arise at some future time, Thameco should be advised, in writing, with a complete justification of the decision.

## THAMECO - STATUS OF THE CHILD FOOD FACTORY

It is vital that the work discussed below in this section should be *undertaken and completed*, in the forthcoming annual shutdown of the Milk Factory. The extent of the job is such that the normal, one week, shutdown will be insufficient time to complete the work but this is not a reason to leave the factory in its current, run-down condition.

The principal problems of the Milk Factory are concerned with maintenance and housekeeping. The equipment is generally in sound condition but requires a complete overhaul, degrease, repaint and some repairs/spare parts; with attention it can operate for many years to come. Certain equipment in the factory and in the laboratory is now surplus to requirements and should be removed since it is a hazard; its removal will permit the remaining equipment to be better utilised.

Conditions appropriate to the processing of food and drugs are of special importance in order for the necessary standards of GMP to be sustained. Only when these conditions have been provided and the equipment overhauled will the Milk Factory be able to approach an acceptable degree of GMP.

The buildings and stores which house the Milk Factory are in serious need of attention. Walls, floors, ceilings, windows, services, doors and grills are all in a very poor state of repair and some are positively dangerous both to the product and to the personnel working in the plant. The conditions are so bad that the superficial daily cleaning has the effect only of removing the rubbish and gross contamination; the structural faults cannot be remedied in the normal course of housekeeping.

Floors are in bad condition, part ceramic tile/part cement and not level; they should be brought to a standard level with concrete and finished throughout the milk factory with an Epoxy floor treatment.

The Milk Factory was inspected in the company of the General Director of Thameco and the acting head of the Milk Factory; the following comments apply:

### 1. Milling Section:

Doors open, houseflies in the room. Hessian sacks, timber boards, broken pallets dumped in a corner, dangerous open pits require covers, machine chain drives uncovered with powder caked around shafts and chains. Fluorescent tubes uncovered, many not working. Electric wiring hanging in loose and dangerous condition. Drain channel in floor uncovered.

2. Grain store:

Grain covered by wire mesh only, risk of infestation by vermin, also risk of contamination by materials falling into it. Solid cover is recommended. The external grain silos require some de-rusting and regalvanising of the fastenings.

3. Drum Drier:

Condensation falling from the ceiling due to insufficient ventilation. Additional extractor fans required. General dirt on pipework; pump gland seal leaking badly.

4. Can Making:

Machines should be de-greased. Steel angle protectors should be provided on all columns to a height of 2 metre. Walls should be patched and ductwork repaired. Air blowers should be recommissioned if required, if not required they should be removed. The building expansion joint should be examined, repaired if necessary and re-covered. All light fittings should be replaced and electrical wiring fixed up.

5. Filling:

Ventilation should be improved and all loose wiring removed or refastened. The Instamat line which is no longer in use should be removed, together with miscellaneous parts in store rooms.

6. Vee Blender:

Replace shelf. Provide air entry so that the room can be operated with the door closed. Fit a filter to the ventilation fan. Remove notices taped to the walls.

7. Sifter:

Repair a stress crack in the ductwork with flexible material to prevent future cracking.

8. Stores:

Fit covers on ventilators to keep birds out. Repair roof where there is evidence of rain leaking in. Consider the possibility of expanding the stores to increase holding capacity and improve stock rotation. In the current situation it would be impossible for the storekeeper to take a stock inventory; the store should be provided with racks and pallets in the interest of inventory control, housekeeping, stock rotation(FIFO).

9. Laboratory:

Remove unwanted equipment, repair benches and cupboard doors, replace ceiling tiles.

Attention to the matters listed above will give the milk factory a fresh and clean appearance which will benefit the product, motivate the workers to take a little more pride in their jobs and help the regular cleaning staff to keep the factory in improved condition.

AMENDMENT: Late in the study of the status of Thameco, it was learned that purchase orders are placed, or are pending, for capital equipment valued in excess of US\$1 million for a new drum drier, filling machines, and cartooning machines for the department. The writer was not shown any engineering drawings related to the new installation, but it is now most important that the necessary improvements to the factory should be planned and implemented as a matter of top priority so as to facilitate the arrival of the new equipment.

**STATUS OF THAMECO : SERUM FACTORY**

The writer visited the Aleppo Serum Factory and inspected the facilities in the presence of the GD, the administrator, technical, and other staff. The following applies :

The installation is complete and fifty five batches have been produced with the assistance of Lequeaux. The documentation and SOPs provided by UNIDO were employed at all stages; they were found to be completely satisfactory.

The trial batches have been given an Expiry Date of July 1994; it is understood that there are some 500,000 x 1 litre filled bags in stock; with the selling price said to be SyrL 59 per bag, this represents a significant holding in stock which is apparently not able to be sold, for non-technical reasons.

It is understood that the Serum Factory has not yet been granted an operating licence by the MOH, on the grounds that it does not have a full complement of analytical equipment.

The Lequeaux installation is good. The standard of engineering and the selection of equipment presents no problems for the writer.

The overall condition of the factory buildings is good although there is evidence of settling in the structure; the cement used in the construction was of variable composition since the paint is flaking off badly in places.

There is a staff of about fifty persons who report for duty each day at the factory despite the fact that there is no work.

There is a leaking valve which needs attention in the Water Treatment system; the Filter Bank should be fitted with valves to permit the filters to be back-washed between batches, it may be possible to request Lequeaux to procure these valves on Thameco's account.

Thameco should consider the introduction of the two spare filling machines into the production operation in order to increase the hourly output. Masks and gloves should be worn in all production areas before the product is sterilised.

During trial runs, the polarimeter was found to be faulty; Lequeaux has taken it back to France for attention. Additional laboratory equipment is required : microscope, colony counter, laboratory refrigerator, materials for nutrients, and bacterial stains.

Test animals, rabbits, have experienced diseases of the outer ear, this has been successfully treated with Hydrogen Peroxide solution; alternative treatments are Chlorohexidine solution, and 70% alcohol. Whenever skin diseases are noticed, the infected animals must be immediately removed from the test-animal house, isolated accommodation until the condition is cured.

All stock (raw/packing & finished goods) are stored on the floor; racking and pallets should be provided. The site of the battery charger for the electric fork lift must be provided with a heavy gauge plastic sheet since acid spills are doing serious damage to the terrazzo floor tiles.

Thameco engineers advised that the Diesel generator set runs too hot; this is a question which should be referred to Lequeaux or to an independent engineer.

The writer has noticed that a purchase order has been issued for an additional air compressor; clearly, this item was bought on the recommendation of a non-practical committee since it is from a different manufacturer than the unit already installed. Thus, whilst the cost of the new unit may be, at first sight, less than the cost of a machine identical to the one already installed, by the time two separate batches of spare parts, oil filters, etc. have been added it would have been no more expensive to purchase the duplicate of the original unit.

A more critical stand-by machine than the air compressor is the boiler. The writer has already suggested in a previous mission report that a stand-by boiler should be installed, if for no reason other than to permit the original unit to be shut down for at least two weeks each year for tube cleaning and pressure testing. Again, the duplicate boiler should be from the same manufacturer as the original to economise on spare parts.

Thameco has an excellent installation in the Serum Factory, but there is still no appointed Production Controller. The Quality Controller is seen to have gained significant maturity and the contractual agreement for Lequeaux to provide training in France for both the Production and Quality Controllers must be taken as soon as possible. On completion of this training, together with the hands-on training to be provided by Lequeaux, in Syria the Quality Controller will be capable of fulfilling his Job Description.

The writer can see no valid reason why the Serum Factory cannot be issued with a manufacturing licence. The protracted dispute with Lequeaux should be resolved at an early date, by compromise, and the Serum Factory should be put to its intended use.

**STATUS OF THAMECO : BIOLOGICAL TESTING**

This comprises Toxicity and Pyrogen testing. Animal houses were clean and well kept. Laboratories were being rebuilt, nearing completion. Ventilation and temperature conditions were satisfactory.

Toxicity testing of Raw Materials using mice is performed on all antibiotic raw materials.

Pyrogen testing, using rabbits, can no longer be performed in these laboratories since the Ellab multipoint recorder has developed a fault, consequently it is necessary for the technician to take all samples for testing up to the Aleppo laboratories as and when necessary. A batch of Negamycin ampoules is currently held up in the Quarantine Store pending a retest on the technician's next visit to Aleppo.

It is recommended that Thameco should immediately order a complete replacement unit for the damaged equipment, and further, should run some trials on the now official Limulus test with a view to validating the results of its animal work. By this means, Thameco would be starting to fulfil the requirements of the Minister of Health, in pioneering work in the development of the pharmaceutical industry.

The question of training was discussed with the technician and it was learned that he had never, in fact, been trained in the job although he had been employed by Thameco for several years.

It is understood that there is a contractual agreement for the Lequeaux company to provide on-the-job QC training for the staff of the Aleppo Serum Factory and it would be appropriate for the Damascus technicians to be in Aleppo at this time as observers.

The laboratories have been comprehensively equipped to enable the performance of work far in advance of the current level; yet this equipment is standing idle and the only equipment which is needed at this time is out of action. Thus, the investment is wasted. The biological laboratory is maybe the only one of its kind available to industry in Syria, and should give Thameco an invaluable lead over the private sector in the development and testing of, for instance, topical products.

It is understood that skin cancer is becoming common in Syria; inevitably it will become more common. Thameco has the animals and equipment to be working on U/V blockout creams yet the laboratory is idle because its pyrogen tester is broken!

This situation can only be described as an appalling waste of existing technology, and a complete lack of imagination in the Thameco management team. If and when the private sector launches its own blockout creams, Thameco must

accept total responsibility for failing to make any use of the opportunity available it.

There must be a range of other possibilities for product development in the biological laboratory. However, it is not the purpose of this project to establish a research or development program for Thameco, so this single example must serve to illustrate the point that the company must look, for its technical survival, to the efforts of its scientists, and if that effort is deficient no amount of superficial change will revive the company.



**STATUS OF THAMECO: AMPOULE DEPARTMENT**

Conditions for manufacturing injection products are even more critical to the safety of the product than are the conditions for manufacturing oral or topical medicines. The status of the Ampoule Department at Thameco was inspected in the company of the General Director and the head of the department. The following points apply:

General to the department

Poor illumination, broken and dirty ceiling tiles with evidence of water leakage. Loose and disconnected electrical wiring, broken walls with excessive holes in them - no longer in use, damaged doors. The rooms must be completely cleaned out and repainted, care should be taken to remove all paint runs/splashes and drips. Paint on windows and doorframes must be removed with a scraper. Replace all broken ceramic tiles.

Office:

Provide partitioned area for weighing station. Replace damaged cupboard.

Preparation Room:

Remove unused door, provide cover for the radiator, remove un-necessary electrical wires and repair all damaged switches, remove unused pipework, repair or remove broken table, run the reverse-osmosis pipe correctly remove unused handles, Epoxy fill cracks in marble bench tops, provide new cupboard for cleaning materials, fit a cap on hole in the wall, repair shelf, repair doorframe, clean walls and ceiling. Repair motor on Leitz mixer. Fit gauge on storage tank and cap all unused fittings. Provide #316 stainless steel pipework to filters.

Reverse Osmosis room:

Fix ceilings, remove rubbish, provide accommodation for cleaning materials. De-rust all mild steel parts with Phosphoric Acid, treat with metal primer and paint.

Washing Room:

Fit temperature gauge on water tank, do not leave empty glass ampoules in the washing machine.

Autoclave room:

This area is pending the arrival of a new steriliser and is to be renovated when the new unit is installed.

Clean room:

The clean room was inspected as though by a factory inspector and a total of 22 faults was found, including; cracked table, holes in walls and under partitions, bare plywood in light fittings, vacuum cleaner oil leak, serious dirt and grease on u/v lamp and under all machines and tables, air gaps around doors, broken glass and broken ampoules in corners of the room, etc. These were pointed out and discussed with the supervisor. The use of UV lights is dangerous if workers are exposed for significant periods of time; arrangements should be made that these lights are switched off before workers can enter the room.

Autoclave:

Several points were noted in the autoclave itself; including loose panels and the use of mild steel machine screws where stainless steel should be used, however the most serious deficiency is that the door sealing gasket is so badly damaged at the bottom that it can no longer be considered effective and must be replaced as soon as possible.

Air supply:

There is some confusion about the purpose of one air inlet, this matter should be resolved and the inlet removed if no longer in use or identified as to its purpose if it is still used. A serious deficiency exists in context of the sterilising filters providing air to the room. These are routinely changed each year but are NEVER VALIDATED, thus their effectiveness is a matter of speculation. Since these are very costly components it is illogical to change them purely as a matter of course and casts serious doubt on the authority's understanding of the function of sterilising filters and on the meaning of GMP.

Changing room:

The Sterile Changing Room is completely unsuitable for its purpose; it is too small, has no hand washing facility, has no room for factory clothes/shoes, etc. and offers barely enough room for one person to change. It is a Sterile Changing Room in name alone. There is a large, unused area available adjoining the existing room and this should be converted into a proper changing room as discussed with the staff of the Ampoule Filling Department. The observations related to the use of UV lights apply to this room.

### STATUS OF THAMECO : CAPSULE FILLING DEPARTMENT

As in previous sections of the factory, the standards of the building and services require major work. Windows broken must be replaced, broken down machinery should be removed, useless and broken plastic containers must be removed, unpainted timber tables are cracked and broken - they are a threat to the product and should be replaced with hygienic stainless steel tables, the storage cupboards are beyond repair and must be replaced, the washing facility for equipment should be replaced, etc.

However, one of the most serious criticisms of the capsule area is the risk of cross contamination between products since the dust extraction system is non-existent and fine light dust is everywhere. The products handled in the capsule department are antibiotics and the consequences of cross contamination have serious implications. There is further possibility for product confusion in that the department has no proper containers for storing in-process materials; consequently on the day of the inspection, Erythromycin capsules were being filled on the machine and falling into a storage container still bearing the label of its original contents "Amoxycillin". This is completely unacceptable and proper storage containers are required immediately.

There is major risk to production workers by exposure for long periods to chemical agents and this is particularly serious when those chemicals are antibiotics. During the inspection visit it was very evident that the air was loaded with fine powder from the blending and filling operations and the floor was covered with powder yet the operators were protected with cheap paper dust masks of which there was no knowledge of their filtering ability; these were not in use by all operators and one individual was seen who's skin was all over white from the powder. Again, this is a totally unacceptable way to run a pharmaceutical factory.

As in other parts of the factory, the manager's "office" comprises a desk and chair in the main production area with the expected covering of dust and the continued exposure to active chemicals and antibiotics.

The lack of storage accommodation for tools and lubricants, as previously mentioned, means that the room is littered with boxes and cans which are absolutely unacceptable in the context of GMP.

Dust extraction in the capsule department is non-functioning.

Worn-out polishing belts have been allowed to accumulate since no one has the authority to dispose of them. They have no further value, they are a danger to the product, they should be disposed of by burning forthwith.

Cardboard boxes in which capsule bodies are received from suppliers are brought into the department to be opened for use. Cardboard is a notorious spreader of spores and it is not appropriate that they should be brought into a

manufacturing area. An ante-room should be provided in which all external packing materials are removed before goods enter production areas.

It is recommended that the existing capsule department be cleaned up to the best possible extent, correcting the deficiencies described above and a completely new facility built and equipped in a manner which will permit the continuing production of this important range of medicines in appropriate conditions.

**STATUS OF THAMECO : DROPS SECTION**

General comments apply.

Equipment is in acceptable condition although it is understood that the CGMER mixer is underpowered. This could be corrected by fitting a new motor.

The department is provided with laminar flow filters at the filling station but their efficiency is unknown, therefore they should be regarded as useless.

An un-acceptable amount of Finished Goods is stored in the Department since, it is claimed, there is no room for it in the store.

**STATUS OF THAMECO : ORAL REHYDRATION SALTS**

Equipment provided by UNICEF is in good condition although the filters are apparently not working, since the room is under a coat of dust. Improved housekeeping is required, as is external storage for finished product.

**STATUS OF THAMECO : DRY SYRUPS**

The same comments regarding the general condition of the buildings applies as previous. As in the Capsule Department, the amount of dust in the atmosphere is intolerable and represents a health threat to the operators.

However, the situation is more serious in the Dry Syrup department since there are large holes in the ceiling and the equipment should be considered as worn out. The cost of attempting to repair equipment of this type and age would be money wasted.

It is understood that the products of the Dry Syrup department are of the greatest importance to the children of Syria and it is accepted that the department cannot be stopped for correction of its faults.

It is therefore recommended that, as with the capsule department detailed above, the Dry Syrup department should be fixed up as well as possible in the short term so as to carry on production, whilst a totally new facility is constructed elsewhere on the Thameco compound, in accordance with the concepts of GMP, and equipped with completely new plant and equipment.

The working conditions in the department would be condemned by a factory Health & Safety Inspector and it is of immediate importance that workers are provided with protective clothing and instructed in its proper use.

**STATUS OF THAMECO : LIQUIDS MANUFACTURE**

The general comments regarding the condition of buildings applies to the liquids department.

All the machinery was examined and found to be appropriate for its use, except that in places, welding repairs had been left in a rough state, this will lead to rapid corrosion in the wet conditions which apply in the Liquids Department.

In one corner of the mixing room, a tiled bench ends very close to the tank-stand, making housekeeping in the corner almost impossible. When the room is refurbished, the bench should be shortened by 1 metre to resolve this problem.

**STATUS OF THAMECO : OINTMENT DEPARTMENT**

Comments general to the conditions of Thameco apply equally to the Ointment Department.

In the preparation, unnecessary manual labour could be reduced by melting paraffin base in its barrel and transferring to the mixing vessel by pump. The mixing equipment is in good condition; it is understood that the steam generator is to be replaced.

A significant amount of material is lost in transferring from the mixing vessel to the filling machine; in addition, an unacceptable amount of manual labour is involved in the operation; this is detrimental to the product in the case of sterile ointments.

The problem could be easily overcome by transferring the mixing equipment upstairs to the room exactly above the filling machine, and effecting the transfer by gravity. Thameco should request an engineer to check the floor loading of the upstairs room, and prepare drawings for the relocation of the mixing equipment if the floor is capable of supporting the load.

The filling room is clean and tidy, acceptable for packing non-sterile topical products, however, the laminar flow unit which is moved into position over the filling machine for handling sterile ointments is unsatisfactory.

It is recommended that Thameco should provide a new, purpose built facility for the production and packing of sterile ointments.

**STATUS OF THAMECO : PACKING DEPARTMENT**

The general observations regarding the condition of walls, ceilings, sinks, cupboards, wiring, etc., are relevant to the Packing Department.

The room is equipped with packing conveyors yet these are not in use because the operators prefer to work without them.

On the day that the writer visited the department, there was serious risk of product mix-up since four products were being handled concurrently in an unpartitioned workroom.

Since it is understood that a quantity of new equipment is on order for the Packing Department there is no merit in discussing the existing machinery. However, before any new machinery is installed the room must be completely refurbished and partitioned to prevent the possibility of product mix-up.

**STATUS OF THAMECO : QUARANTINE DEPARTMENT**

The Quarantine Department would be more appropriately known as the In-Process store, since "Quarantine" is generally understood to refer to new material entering the factory, pending QC release to the main stores.

The Quarantine Department was inspected with the department head. The department comprises several rooms which are clean and tidy, but the previous observations about the condition of the buildings, particularly ceilings and lights, apply in the Quarantine Department.

Air conditioners are installed, but on the day of the inspection, they were not in use. Storage conditions appeared to be satisfactory; however this could not be confirmed since there are no instruments in the rooms.

The rooms are filled to capacity. Goods are clearly identified and containers well sealed, with the exception of ampoules and ointments awaiting packing, in the upper room. Since these are homogenous batches there is no concern about product mix-up but it would be preferable if all containers were completely closed.

One particular batch of in-process Overpen is in the Quarantine Department pending rework for removal of foreign bodies. Its period in the Quarantine Department exceeds four months, it is recommended that prompt action should be taken to complete the rework and pack the material before it.

There are other materials in store at Thameco whose status is in dispute; these disputes commenced before the appointment of the current GD and they will be dealt-with elsewhere in this report under the heading of Inherited Problems.

**STATUS OF THAMECO : RESEARCH DEPARTMENT**

Thameco's future prosperity cannot be found by reverting to its traditional products. As stated elsewhere in this report, the "brand name generics" market is already oversupplied with manufacturing capacity and it would be of no value to relaunch Thameco in this direction.

Thameco has an excellent Research Department which will not be equalled by the private sector in the foreseeable future.

By contrast with its capacity, this facility is virtually standing idle. It has no research program and few pipeline projects. Thameco has no research policy.

Yet the department has the potential to do some pioneering work, which could not be done in any other pharmaceutical factory in Syria.

The main use of the department is in the investigation of the manufacturing difficulties which result from the company's policy of purchasing raw materials which vary from batch to batch. Thus, the department is concerned with trouble shooting rather than with research.

Clearly this is a waste of resources, both human and technical. In context of the staff of the department, unless they are properly employed, it is probable that they will become an addition to the "brain drain" which has already weakened Thameco's technical middle management. The company must evaluate the effects of losing its research department staff to the private sector. In view of the difficulties that it has had in recruiting Key Persons for the Serum Factory, Thameco should not presume that it will be a simple matter to restaff its Research Department.

In order to put the department to work, Thameco must develop a series of pipeline projects for products which it wishes to launch in five years time.



**STATUS OF THAMECO : LIBRARY**

A potentially valuable asset being used as a tea room, the library holds some valuable reference works but these need to be reviewed and up-dated. Additionally, the library is home to a large number of Product Profiles prepared by foreign principals for the registration of their products in Syria.

The preparation of Product Profiles for the Thameco range is an important component of Quality Assurance and it is suggested that the Library becomes the centre for this activity, using the works already there as models.

## ANNEX 1

## JOB DESCRIPTION

## GENERAL DIRECTOR

1. To establish and implement a Responsibility Chart.
2. To nominate authorised persons and provide job descriptions; delegate responsibility and monitor activities.
3. To liaise with national authorities in support of Thameco.
4. To establish and implement internal committees for GMP, Human Resource Development and Audits with appropriate subcommittees where appropriate; keep minutes and record progress.
5. To establish budgets for Staff Training, Staff Benefits, Company Operation and Maintenance and Project Development.
6. In close co-ordination with national authorities develop a 5-year plan for the consolidation of Thameco as a national asset and leader in Pharmaceutical Industry. Monitor and record progress.
7. In conjunction with International Agencies develop, introduce and implement up-to-date management systems.
8. In conjunction with representatives of the private manufacturers' group and the MOH, assist in the development of a national policy on factory inspection, self regulation by the industry, and resolution of disputes arising from factory inspections.
9. To arrange for the procurement of all necessary materials for the production of the required medicines as agreed with the authorities and supply the finished products in a timely manner.

**JOB DESCRIPTION****PRODUCTION CONTROLLER**

1. In conjunction with the Quality Controller, establish a written programme of GMP, SOP and QA appropriate for the operations being carried out at Thameco.
2. Select and train suitable staff for production areas, equipment operations and records. Training should be in accordance with a formalised protocol which should be reviewed each year. Training should be on-going and records should be kept.
3. Prepare job descriptions for responsible staff.
4. Establish standard manufacturing and packing lines, specify expected achievement levels.
5. Procure and store correctly, all necessary raw materials, packing materials, intermediates and finished goods.
6. Manufacture, store and distribute finished goods according to accepted standards of GMP and QA, in line with the quantities specified by management.
7. Maintain factory and surrounding areas in "Inspection condition" at all times.
8. In conjunction with the Quality Controller establish and implement a system of manufacturing and packing documentation based upon the system of Master Documents.
9. Continuously monitor the foregoing matters.
10. Report directly and independently to the General Manager.

**JOB DESCRIPTION****QUALITY CONTROLLER**

1. In conjunction with the Production Controller establish a written programme of GMP, SOP and QA appropriate to the activities at Thameco. Specific responsibilities should be clearly defined.
2. Establish, verify and implement all Quality Control procedures.
3. Establish written standards for all Raw materials, Intermediates, packing materials and finished goods.
4. Prepare written standards for all laboratory reagents.
5. Establish and validate a system of Expiry dates.
6. Establish and implement a system of Acceptable quality Limits (AQL) for all materials used in production.
7. In conjunction with the Production Controller, establish a system of manufacturing and packing documentation.
8. Independently of the Production Controller, approve or reject materials in accordance with 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.

## ANNEX 7

## OUTLINE OF WORK TO BE UNDERTAKEN BY UNIDO TRAINEES

- a) Observe manufacturing technologies in own and other specialities.
- b) Observe beneath technology to identify and study the systems on which the industry is based.
- c) Identify how technology and systems are integrated to yield Quality Assurance, particularly in relation to the phasing of Quality Control and Production operations.
- d) Study the compliance of the industry with the requirements of the selected code of GMP.
- e) Pay particular attention to the non-production activities and standards of Industrial Health & Safety, Housekeeping, Planning, Inventory Control etc.
- f) Study the methods of preparing SOPs and Product Profiles.
- g) Translate the findings into methodologies which will have application in the evolution of the pharmaceutical sector in Syria.
- h) Report and assist the UNIDO STC to prepare documentation and systems to be employed in the pharmaceutical industry in Syria.

## ANNEX 3

## FEATURES OF THE SAMPLE OF FACTORIES VISITED DURING FIELDWORK

Provided below is a brief picture of the individual merits of the factories in the order in which they were seen. There is no benefit to be gained by ranking the factories according to their attainment of GMP since the purpose of factory inspection is not to say that "this factory is better than that factory".

Factory inspections should reveal only whether an individual factory is a suitable facility for the manufacture of therapeutic goods.

1) DIMAS:

Only two sections seen: IV solutions and QC Department. Conditions were very bad, unsuitable for the preparation of IV solutions. Ceilings broken, dust-covered boxes in production areas yet visitors required to wear caps, gowns and masks. This contradiction leaves no doubt that the operators are out of touch with the norms of pharmaceutical production. Operators claim that their technology is still in 1984. They have no contact with the outside world of pharmaceutical manufacture, read no technical journals and seldom have expert visits. Autoclave temperature probes are not located in the drains where they would experience the lowest chamber temperatures. The factory is in urgent need of complete refurbishment and would not justify any claim to working in pharmaceutically acceptable conditions. Management is aware of its shortcomings, but equally aware that it has a production quota to meet and cannot afford the time to shut down the factory for the time necessary for renovation. To bring the factory to an acceptable standard would be an extremely costly exercise. The factory operators have not been accustomed to working in a controlled manner and have developed bad habits which will be extremely difficult to correct even in a completely renovated factory.

During the course of visits to the Syrian pharmaceutical industry over several years, there has been one question, regularly put to the writer yet apparently never satisfactorily answered; it relates to the determination of Expiry Dates for finished products. The writer has described the method, provided diagrams and brought brochures of commercially available equipment; this has evidently made no impression; since the identical question is still being asked in 1994. Yet, on the writer's first and only visit to Dimas, a Climatic Cabinet, the embodiment of hours of discussion, was seen in a corner of the QC department, standing idle presumably unwanted! This does not reflect well on the understanding of GMP or QA in Dimas. The presence of this equipment at Dimas has been discussed with the management and engineers of Thameco and it is brought strongly to the attention of the authorities by way of this Report.

2) SIFCO

A very small new company which has been nicely built with room for expansion. Internally good with ceramic tiles floor to ceiling throughout. Some unpainted timber was seen in production areas; this was pointed out as unacceptable, as was a single wet floor cloth in a doorway. These observations were well accepted by the staff who have an excellent attitude and are keen to do well and improve their business. Currently small range of products on which Sifco is consolidating its experience before attempting to diversify. Knowledge and implementation of GMP is good; however some training in the more sophisticated topics of Validation and QA would be of benefit. Sifco is complemented on its achievements.

3) MASSOUD AND BAHRI

A good factory, well set up with room for expansion. Documentation is good, in English. Records are well maintained. Staff well trained and personal hygiene is maintained at a high level by daily showers. Housekeeping is excellent as is "in process" control. The stores are small but well organised with palletted goods secured in wire cages. The Company has overseas contacts and experience; the benefits of this are clearly seen in its operations. One criticism is that non modular construction has been employed in the buildings and this places restrictions on the development of the working area; it does not, however have any adverse bearing on the company's fitness as a pharmaceutical manufacturer.

4) ADAMCO

The entire factory seen, excellent. First class system of documentation, in English, leaves no possibilities for ambiguities. Internal committees for factory regulation, improvement, GMP, Housekeeping, etc. Management has experience of overseas industry and this is reflected in the attitudes prevailing in the entire business, not only in the production unit. Knowledge and implementation of GMP/Validation/QA/GLP, etc. is very good and ADAMCO would be classified as operating at a very acceptable level of GMP.

5) CHAM

A small unit using a wet granulation method for the production of Paracetamol tablets. This is incongruous since the operator gained overseas experience with a MNC which lists Paracetamol as a major product and produces it by slugging; a cheaper and preferable method. With the exception of Production Documents, Cham is operated on a very ad hoc system which would not qualify as GMP. The operators had no understanding of Validation nor of statistical methods as applied to in process control. The operators showed a defensive attitude toward the visit and were not interested in noting comments which were intended to provide a measure of QA in their production unit. Cham was not seen to be a good example of pharmaceutical competence.

6) MPI

Concentrated on tablets, syrups and hard gelatine capsules, no plans for more sophisticated products at this time. Systems and documentation, in English, are extremely good and constantly reviewed/updated. The company operates a computerised Information Management System with 14 terminals in use, as recommended by one of its overseas principals. It operates monthly internal control committees on all aspects of factory operation, keeps minutes and takes follow up action. This is an excellent operation which is well up to European standards.

7) AVENZOR

This is a new factory nearing completion of the building stage; it has several overseas principals and their influence on the design, layout and implementation of the factory is very evident. Care has been taken to ensure that the factory is environmentally responsible and will comply with the very best standards of worldwide pharmaceutical technology. In view of the high level of technical support provided by its overseas principals it will be difficult to find fault with Avenzor.

8) MEDICO

Surroundings are not ideal for a pharmaceutical manufacturer, however the factory is well protected by a high wall and the exterior conditions have no deleterious effect on the manufacturing operations. Since the surrounding area has deteriorated to such an extent and the operator states that GMP cannot be built onto an old plant, Medico is in process of building a new GMP based factory in a clean location. The internal systems are good, housekeeping is of a high standard and the operation is well controlled. Medico would be classified as a very competent and responsible operation.



## ANNEX 4

## ADDENDUM TO FIELDWORK

DAM Pharma Laboratory

Plant visited with representatives of Drug Testing Lab., Inspectorate Division (MOH), Dimas, Thameco.

Overall impression was of a poorly converted domestic house which is not appropriate for the manufacture of medicines. Fresh paint had been applied but the substance of the building was not good, nor had it been repaired prior to painting. Loose wiring, broken skirting boards, ceiling fans, un-usable window blinds covered with dust etc., have no place in a pharmaceutical factory.

Job Description for the Quality Controller was seen, other documentation, SOPs, etc. were seen but they exist in names alone, since they are not formalised in their implementation.

Company has no policy on validation of balances, claims that the manufacturer's agent checks them monthly but no evidence provided.

Current USP/BP employed.

Products in manufacture are not identified eg no production documents available in the tablet pressing department relating to the product being compressed.

Packing materials not properly stored, risk of selecting incorrect items (labels/printed cartons).

Finished Products badly identified and the only evidence that they had been released for sale was a small piece of green paper attached to the shrink-wrapped cartons. A large piece of green adhesive paper was found in a box of rubbish in the Finished Goods store.

Housekeeping was not up to standard; lids were found behind radiators, Capsules were found behind machines. Blackboards provided for production line activity were not being used. Rough string had been used in place of PTFE tape for pipe jointing.

Operator advises that a new factory is being built and should be completed in two years, plans for the buildings were not produced.

Dam Pharma Labs would not be issued with a manufacturing licence by the writer.

In view of the fact that the manager claimed to be making efforts to set things right, he should be provided with a list of faults based upon the foregoing, instructed to correct them within three months and to present evidence

of his achievement, together with the architect's plans for the new factory and a committed date for its completion.

Should he fail to comply, his licence should be revoked and production halted. It is then the unambiguous responsibility of the factory owner to present to the Ministry, evidence of the improvements made to his operation and to show cause why he should be permitted to resume manufacturing.



UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION

Z. Csizer/sk

13 October 1993

**JOB DESCRIPTION**  
**DU/SYR/92/008/11-51**

- Post Title:** Industrial Pharmacist
- Duration:** 4.5 m/m (split missions)
- Date required:** 1 November 1993
- Duty Station:** Damascus with some travel to regional manufacturing centres
- Purpose of project:** To promote the domestic (public and private) pharmaceutical industry by introducing modern quality assurance system.
- Duties:** The expert should perform, in conjunction with the other experts, the following duties:
1. Establish a written programme of GMP, SOP and QA. Specific responsibilities must be clearly defined.
  2. Assist in recruiting and training of appropriate staff for production areas, equipment, operations and records.
  3. Establish production norms.
  4. Assist in procurement and storing correctly all necessary raw materials, packing materials, intermediates and finished goods.
  5. Advise on manufacture and distribution of finished goods according to GMP and QA standards, in line with quantities specified by management.
  6. Assist in maintaining production areas, stores and surrounding areas in "inspection condition" at all times.
  7. In conjunction with the other experts, to establish and implement a system of manufacturing and packing documentation.
  8. Continuously monitor the foregoing matters.

.... / ...

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Applications and communications regarding this Job Description should be sent to:

Project Personnel Recruitment Section, Industrial Operations Division  
UNIDO, VIENNA INTERNATIONAL CENTRE, P.O. Box 300, Vienna, Austria

9. Report directly and independently to General Management and UNIDO/WHO.
10. Prepare a final report on the above giving specific recommendations conclusions.

**Qualifications:** Senior Industrial Pharmacist with extensive experience of the practical and managerial components of operating pharmaceutical factories.

**Language:** English, Arabic will be an advantage

**Background information:**

Drug industry is expanding very rapidly. There is a great need to develop industrial standards and a well functioning national drug quality assurance system. Support of public and private drug industry is urgently needed to comply with codes of accepted manufacturing standards.

In the original WHO document the purpose of the industrial pharmacist mission is as follows:

1. To visit manufacturing companies and identify major areas in which standardization is necessary. Advise on appropriate levels of standardization and discuss with the inspectorate the standards to be adopted into the inspection system.
2. To consolidate the experience gained by UNIDO fellows during their industrial training overseas into a range of operating manuals for the industry.
3. To work with senior management and administration staff in the manufacturing sector and initiate guidelines for good manufacturing practices.

## UNIDO SUBSTANTIVE BACKSTOPPING OFFICER'S COMMENTS ON THE EXPERT'S REPORT

The Integrated Development of Pharmaceutical Industry in the Syrian Arab Republic is one of the most important UNIDO technical cooperation programmes in the pharmaceutical industry because it aims at addressing of all issues of the industry in a country and subregion which faces major economic, political and social challenges.

As a very highly regulated area in which the know-how is limited, restricted or even classified, the pharmaceutical and allied industries, both in the public governmental and the private sectors, have to create revenues and net results to achieve financial sustainability. The sustainable development of the pharmaceutical industry cannot, in the long term, be achieved by government subsidies. The industry should, therefore, be competitive. To become competitive, continuous quality improvement is needed.

It is interesting to note that based on a North American survey in 1988, the following rank importance of ten competitive abilities was defined:

1. Ability to offer consistent high quality;
2. Ability to keep timely delivery dates;
3. Ability to provide high performance products;
4. Ability to provide fast delivery;
5. Ability to introduce new products quickly;
6. Ability to provide after-sales service;
7. Ability to offer affordable prices;
8. Ability to offer a broad product mix;
9. Ability to obtain wide distribution; and
10. Ability to make rapid volume changes.

In addition to quality improvement, simplification and cycle time reduction of the manufacturing processes could lead lower production costs, and consequently can increase competitiveness. Since manufacturing activities account for approximately 35-40 % of all costs in the pharmaceutical industry, reduction of manufacturing costs and improvement of efficiency at all levels of operation can increase the results.

To increase efficiency the pharmaceutical industry should focus on the formulation and packaging (secondary) industry producing generic and over-the-counter (OTC) products and brand name products under licensing agreements.

It should also be emphasized that economically and ecologically (environmentally) sustainable development goes hand in hand. Due to the very strict international

regulations, economic growth cannot be achieved without taking care of the environmental regulations. Since the pharmaceutical industry processes a large number of chemicals and hazardous chemicals, aspects of safety, eco-toxicology and hazardous waste management should be very carefully taken into account.

The introduction of modern management techniques to manufacture quality products of high consistency may be one of the best investments in the long run for the development of a modern pharmaceutical industry. A brief description of a number of quality related programmes that have a major importance in the pharmaceutical industry is outlined hereunder. It should be noted, that the individual items are interlinked, certain areas are overlapping. Several items are, by now, parts of the regulatory requirements and therefore considered as driving forces in shaping the pharmaceutical industry. It should, however, be noted that in several aspects the internationally accepted requirements neither in their specific details nor in their general approach are identical. These differences can become clear not only from the facility and equipment requirements for pharmaceutical/biotechnological/biological plants but also from the quality specifications and from reports on the different regulatory agencies' inspections and auditing.

## 1. VALIDATION

The validation of the manufacturing and quality control processes for the pharmaceutical and health industry products assures a consistent production of the desired product with specified purity, safety and efficacy. Furthermore, validated processes operate at a controllable yields and predictable capacities and costs. According to the US FDA process, validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics.

Until recently, only the final steps of sterile and aseptic processing operations such as product sterilization, packaging sterilization, aseptic formulation and filling, sterility testing, etc., were validated in the manufacture of pharmaceutical and biological products. The validation of these operations focused on proving that they were maintained aseptic. As an increasing number of natural and recombinant biologicals have been licensed to be marketed as preventive, therapeutic and diagnostic products, it has become clear that subtle alterations in the techniques used to produce, concentrate, purify, fractionate and isolate these products can significantly influence the composition, configuration, activity, efficacy, safety and stability of complex biological molecules. Consequently, the downstream processing, but to a lesser extent even the upstream processing of biologicals are coming under the increased regulatory scrutiny of validation.

Process validation is necessary to identify the critical process parameters, establish an acceptable range for these parameters, and to provide a means of controlling them. Process validation is the means of studying or challenging a process to prove that it is doing what it purports to do. In order to prove that a process is doing

what it purports, in-process monitoring and control techniques must be in place and in-process specifications or alert and action limits should be set for the monitoring that is conducted on the process. If a process is to be introduced in the manufacturing operations, prospective validation could be used. This could involve designing a challenge of the process to determine whether the process effectively handles the challenge, meeting the pre-set criteria that are necessary for validation. Spiking tests could also be useful to establish in-process specifications and therefore they are extensively used in validation. Challenge and spiking tests in addition to the traditional process optimization techniques are also used to optimize yields. If in a pre-determined number of consecutive trial lots (in most cases 3 to 5 lots), the pre-established criteria are met, the process is considered validated (consistency tests). Each single unit processing step should be validated. After the process is validated, it must continue to be monitored and controlled on a routine basis.

If a process is already in use, concurrent validation and retrospective validation can be used to prove that the process is functioning according to design. This would involve the review of each individual step of the upstream and downstream processing. This review could lead to the optimization of the process, the establishing of new process monitoring and controlling criteria and new in-process control techniques and specifications of the phase and finished products.

The process validation and the maintenance of the validated processes resulting in products of a high degree of consistency require the introduction of computerized process monitoring and control techniques. The analysis, evaluation and interpretation of the data obtained during the above requires statistical process control.

Process validation is a prerequisite for efficient, productive and cost effective processes. The manufacturing processes must be revalidated whenever there are major modifications in the facilities, equipment, raw materials or processing conditions (parameters) that may effect product effectiveness, purity, safety or stability including changes in raw materials or equipment suppliers.

## **2. STATISTICAL PROCESS/QUALITY CONTROL (SPC)**

Statistical process/quality control (SPC) offers tools and techniques that are designed to monitor, control and improve the production processes. SPC assists in identifying and minimizing process variation, consequently it can be used to optimize processes and reduces work in process (WIP) losses.

The basic objectives of SPC are directed toward understanding process variability and therefore process improvement within reasonable costs and time. SPC can be regarded as a set of

statistical tools to support the broader philosophy of total quality control. The knowledge of statistics required for most of the widely used SPC techniques include means, ranges, standard deviation and fiducial limits, analysis of variance and parallel line assay. Therefore, SPC is relatively easy to apply and can effectively be used by plant operators and laboratory technicians/technologists. Recently, powerful softwares for PCs are available for SPC.

SPC focuses on monitoring, controlling and improving the quality of the process, not the product. By analyzing the parameters of manufacturing processes and/or quality control techniques, SPC provides personnel with the ability to validate process or test improvements. Computerized SPC packages, when integrated with automated process monitoring and control systems, analyze historical production parameters/product specifications and correlates them with the equipment performance data of a give production lot by using removable or embedded sensors.

TQM does not consist solely of statistical methods. Rather, it also consists of a set of techniques, some of which are very simple and effective, yet which requires little knowledge of mathematical statistics. Some of these techniques employed in TQC are: process flow charts, histograms, Pareto analysis, cause and effect diagrams, Gannt charts, control charts for variables and attributes in addition to pre-control charts and scatter diagrams and various goodness-of-fit techniques.

The key to successful and effective implementation of SPC is well-planned, focused and creative data collection combined with good problem-solving processes that lead to implementation action. In order for SPC to be effective, meaningful data must be collected at the right points within the process. The interpretation of the data obtained is the most sensitive part of the process, since statistical significance and significance in the process or test should clearly be differentiated.

To complement the use of SPC and enhance the process improvement effort, proper experimental designs and/or model experiments should be used. As a quick method to determine critical process parameters, Taguchi methods for conducting process evaluations can be applied. The results from the Taguchi methods can further be refined using factor analysis.

### **3. VENDOR PARTNERSHIP**

To establish and maintain a validated control of manufacturing processes and quality control techniques, all inputs must be under control. In particular, suppliers of raw and packaging materials have to meet the specifications. The goal of vendor partnership is to assure adequate quality materials that are guaranteed by the supplier. The vendor establishes documented evidence that its manufacturing processes are validated, and consequently they can consistently meet the required specifications and quality



characteristics. This type of vendor partnership can further be strengthened by vendor audits conducted by the pharmaceutical manufacturer (the buyer) or by a regulatory authority. Partnership with certified vendors for purchase of raw and packaging materials reduces quality control costs by reducing the number of tests to be performed on starting materials and also reduces the production lead-times by reducing WIP.

Vendor partnership creates a mutual problem-solving continuous-improvement focused relationship between customer and supplier. The result is higher quality and often lower materials and production costs, since agreements between buyers and vendors are replacing open competitive market. Long term commitments with certified and validated suppliers characterize partnership arrangements, therefore encouraging vendors to make productivity improvement investments and product and process development and improvement (R&D).

Vendor partnership has been developed with equipment suppliers and service industry, thus the ever-increasing cost of quality can very efficiently be controlled. The leading suppliers of the main pharmaceutical manufacturing, processing, service and infrastructural equipment are offering not only validated equipment but process validation in the purchase price. Service industry specialized for contract R&D, process improvement, validation of manufacturing processes and quality control techniques offering services such prices which are very reasonable for a pharmaceutical company without previous experience in these currently developed very specialized field. The cost of contracting out certain validation processes might be half compared to the purchase price of a instrument required to carry out the validation. In the new biotechnological industry the vendor partnerships play an important role to develop industrial and technological co-operation and not only improve but develop new quality requirements.

#### 4. JUST-IN-TIME (JIT)

Just-in-time is an approach to achieving excellence in a manufacturing company based on the continuing elimination of waste and consistent improvement in productivity. JIT is a concept that changes the basic philosophy for manufacturing and the goods that are processed into finished manufactured goods. The technical aspects of JIT involve linking and/or overlapping operations, reducing set-up times, reducing inventory levels, etc., to achieve efficiencies through the elimination of excess waste and inventories. Simply put, the philosophy of JIT calls for the production of only the minimum necessary units in the smallest possible quantities all meeting required specifications of quality in the least possible time and delivered on time. Quality-at-source is a fundamental concept of JIT. One can easily understand that JIT cannot be implemented without a well-functioning system of certified and validated vendors.

The benefits of such a programme are as follows:

- Reduction of manufacturing lead-times through the use of line balancing which reduces queues, reduces WIP, shortens set-up times and achieves efficiency through the adjustment of plant layout ( personnel, input and output/waste materials and product flows).
- Simplifies in-process monitoring and control.
- Reduces inventory levels of raw materials and packaging materials.
- Reduces the need for storage space, racks, conveyors, forklifts, computer terminals for inventory control and material support personnel.
- By certification of vendors and vendor partnership programmes where quality of raw materials are assured by the supplier, costly and time consuming release tests could be reduced and possibly eliminated. The materials could be utilized for production as soon as they delivered without staying in the quarantine area of the store. A long term vendor partnership would motivate the supplier to package the needed quantities in individual containers fitting easily and appropriately to the manufacturing equipment and processes where they are used. This would further reduce the number of quality control tests to be performed on the raw materials, the waste of raw materials due to their storage of an opened container and the manufacturing lead-times.

## 5. ZERO DEFECTS PLANNING

Zero defects is a performance standard. It is the standard of a craftsman regardless of his or her assignment. It is not limited to production efforts, in fact, some of the largest gains are obtained from service areas.

The objective of zero defects is to do it right the first time. That means concentrating on preventing defects rather than just identifying and fixing them.

Most human error is caused by lack of attention rather than lack of knowledge or experience. Lack of attention is created when we assume that error is inevitable or when due to the boring routine we are less observant. If we consider these conditions carefully and pledge ourselves to make a constant conscious effort to do our job right the first time, we will take a giant step toward eliminating the waste of rework, scrap and repair that increases cost and reduces individual opportunity.

In the validated manufacturing and control systems, the rejects also gain a different interpretation. A reject is not simply a scrap, but has value, since only a reject gives the chance to revisit the standard operation procedures (SOPs) and validation.

The zero defects programme requires active management participation and empowerment of employees. It needs team work, motivation, recognition policy with incentives and rewards, commitment, creativity, opportunity to influence and responsible for self. The planning of the programme should spell out at least the following elements:

- Dissatisfaction with the status quo,
- Vision of the desired state, and
- Determination of the first practical steps.

If committed to change the first practical steps could be:

- Contact,
- Awareness of change,
- Understand the change,
- Positive perception,
- Installation,
- Adoption,
- Institutionalization, and
- Internalization.

The cost of quality is the cost of not doing things right the first time. These costs arise from four major sources:

- Prevention costs,
- Appraisal costs,
- Internal failure costs, and
- External failure costs.

The two costs related to product failure are avoidable. There are two further cost categories which are not to be confused with the cost of quality. These categories, namely the cost of compliance and the cost of doing business, should also be monitored since they can also be reduced in the long term as a result of quality improvements.

The cost of compliance includes the expenses incurred to ensure compliance with various license agreements and requirements of regulatory agencies.

The cost of doing business includes items such as unavoidable manufacturing waste, material shrinkage, legal advice and minor variability in yields.

The objectives of a cost of quality study are two-fold: to increase the general awareness of the magnitude of the cost of quality and to establish clear parameters by which improvements can be measured. Conventionally, the results of such a study can be used to support additional capital expenditures in the prevention and appraisal areas that are designed to reduce the failure costs. In the new quality model the findings of a cost of quality study should be used to shift from quality-tested processes (appraisal) to quality-driven processes (prevention = quality assurance) and to apply quality improvement techniques such as the vendor partnership efficiently.

### **1. PREVENTION (QUALITY ASSURANCE)**

1. Re-education and re-training of personnel in quality assurance (metrology and validation), manufacturing and quality control (validation of personnel).
2. Supplier quality evaluations, establishment of vendor partnership.
3. Validation of facilities, equipment, laboratory animals and manufacturing processes/quality control techniques.
4. Equipment calibration.
5. Facility and equipment maintenance, and maintenance of supplies, and preventive maintenance.
6. Improvement of facility and equipment.
7. Process and testing improvements.
8. Reliability engineering.
9. Maintenance and compliance with GMP (SOPs, etc).
10. Maintenance of the operations strategic planning (OSP) and business requirements planning (BRP) systems and other corporate planning processes.

### **2. APPRAISAL (QUALITY CONTROL)**

1. Acquisition of improved testing equipment.
2. Raw material testing and inspection.
3. Packaging and component testing.
4. Environmental monitoring and validation.

5. Process and facility audits.
6. Hygienic testing of employees and validation.
7. In-process control and quality control of finished products.
8. Stability testing.
9. Trending of product quality.
10. Statistical quality control.

### 3. INTERNAL FAILURES

1. Raw materials and WIP losses and subsequent write-offs:
  - specifications and/or requirements are not met,
  - "accidental" (QA system and validation should be reviewed),
  - excessively poor yield,
  - expired dating,
  - scrap and leftover,
  - overfilling.
2. Finished goods write-offs and retesting.
3. Rework and reprocessing.
4. Retesting:
  - QC testing problems,
  - product-related retesting,
  - market-related problems.
5. Excessive in-house procedures and testing - revalidation:
  - plant is closed down - annual maintenance,
  - testing failures with similar products,
  - laboratory animal failures with similar products.
6. Equipment breakdown resulting in down-time.
7. Production delays and capacity bottlenecks.
8. Incident reporting and follow up.

9. Citation by the regulatory authority.
10. Excessive inventory carrying charges.
11. Expediting and rush orders.
12. Meetings concerning supply problems and testing problems that require corrective action.
13. Redesign of production and management processes.
14. Lost sales resulting from above problems.

#### 4. EXTERNAL FAILURES

1. Product recalls including lost sales revenues, lost customer's confidence.
2. Poor service level.
3. Customer complaints and the costs of any resulting allowances.
4. Legal settlement fees.
5. Licence revocation or regulatory changes to permit further competition.
6. Retest related to the failure at the regulatory agencies.
7. Substandard quality of raw materials.
8. Substandard quality of laboratory animals.

The introduction of the modern quality management techniques should be carried out in parallel to an extensive support/training programme to be offered to the senior management. The management support should also introduce a clear and transparent chain of command and an annual performance appraisal system as part of the human resource development through a restructuring exercise of the pharmaceutical industry.

In addition to the above given recommendations, which are focused to actions to be taken by the pharmaceutical industry, it should be the role of the government to create such an economic environment that would have a nurturing effect on the industry. In this context, it is interesting to note that in the South Asian region, where the pharmaceutical industry is growing very fast, a wide range of investment incentives are offered to improve the investment climate.

SUMMARY OF COMPARATIVE INVESTMENT INCENTIVES

(Based on a Survey of the S6V Group; with the Permission of S6V)

<u>Countries Surveyed</u>	<u>MAL</u>	<u>TWN</u>	<u>KOR</u>	<u>SNG</u>	<u>THN</u>	<u>CHI</u>	<u>IND</u>	<u>PHI</u>	<u>HKG</u>
<u>Against 39 Considered, Number offered</u>	32	29	27	27	27	26	21	20	19
<u>Basic Rights and Guarantees</u>									
Guarantee Against Expropriation	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Guarantee Against Losses due to:									
a) Nationalization	Yes	No	No	Yes	Yes	Yes	Yes	No	No
b) Damage Cause by War	Yes	No	No	No	No	Yes	Yes	No	No
c) Inconvertibility of Currency									
Remittance of Foreign Exchange earning and payments	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Repatriation of Capital	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
<u>Protection Schemes and Priorities Given     To Investors and Aliens</u>									
Employment of Aliens	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Patent Protection	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Preference in the Granting of Government Loans	Yes	Yes	No	Yes	Yes	No	No	No	No
Protection Against Unjust Competition:									
a) Import Competition	Yes	Yes	Yes	No	Yes	No	Yes	No	No
b) Government Competition	No	No	No	No	Yes	No	No	No	No
c) Local Competition	Yes	No	No	No	Yes	No	Yes	Yes	No
Real Estate Ownership by Alien Investors	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes

## LEGEND:

MAL = MALAYSIA  
SNG = SINGAPORE  
IND = INDONESIA

TWN = TAIWAN  
THN = THAILAND  
PHI = PHILIPPINES

KOR = SOUTH KOREA  
CHI = CHINA  
HKG = HONGKONG

	MAL	TWN	KOR	SNG	THN	CHI	IND	PHI	HKG
<b>Exemption from Taxes and Tariff Duties</b>									
Capital Gains Tax	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Corporate Income Tax	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Taxes on Imported Capital Goods	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Taxes on Royalties	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Taxes on Imported Raw Materials	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Withholding Tax on Interest on Foreign Loans (Tax Credit)	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes
Other Taxes and Fee	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
<b>Deductions from Taxable Corporate Income</b>									
Accelerated Depreciation Allowance	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes
Carry forward of Capital Allowance during the Relief Period	Yes	No	No	Yes	No	No	No	No	No
Carry forward of Loss	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Export Allowance/Deductions	Yes	Yes	Yes	Yes	Yes	No	No	No	No
Deduction of Organization and Pre-Operating Expenses									
a) Organization Expenses	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No
b) Preoperating Expenses	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Reinvested Profits	No	Yes	No	No	Yes	No	No	No	No
Investment Allowance	Yes	No	No	Yes	No	No	No	Yes	No
<b>Tax Credits (Direct Reduction From Corporate Income Taxes)</b>									
Investment Tax Credits	Yes	Yes	Yes	No	No	No	No	No	No
Tax Credit On Domestic Capital Equipment	No	Yes	Yes	No	No	No	No	Yes	No
Other Tax Credits	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No
<b>Extension of Incentive Availment Period</b>	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No
<b>Special Incentives</b>									
To Multinational Companies	No	No	No	No	No	No	No	Yes	No
To Exporters	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
To Offshore Banking Units	Yes	Yes	No	Yes	No	No	No	Yes	No
Other Laws Granting Benefits to Foreign Investor	No	No	No	Yes	Yes	Yes	No	Yes	Yes
<b>Assistance to Investor</b>									
Joint Venture Brokerage	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Technical Assistance	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Processing of Application and Other Requirements	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Source: 1988 Comparative Investment Incentives, Published by the SGV GROUP.



The author has recommended the promotion of the Syrian Pharmaceutical Manufacturers Association (PMAS). Such a professional association could, if established, be a forum where issues of common interest would be discussed. PMAS could lobby for a government policy for pharmaceutical industry, for government incentives, for human resource development at the level of higher education (universities, colleges, etc), for regulation of imported drugs. PMAS could also discuss the regional issues and opportunities for cooperation among the manufacturers of the region. Such cooperation can start issues of common interest e.g. pharmaceutical industry waste management.

To promote pharmaceutical industry of internationally accepted high quality, UNIDO has developed a concept for providing support to the national drug regulatory and quality control authorities as well as to the industry. Service centres of excellence could specifically be developed to offer services and information to the industry. To realize this concept a Pharmaceutical Technology Service Centre (referred to as Centre) was established with UNDP/UNIDO assistance at the Faculty of Pharmaceutical Sciences of Chulalongkorn University, Bangkok, Thailand, in close cooperation with the Federation of Thai Industry (FTI), the Pharmaceutical Industry Club (PIC), the Thai Pharmaceutical Manufacturing Association (TPMA), and Department of Technical and Economic Cooperation (DTEC) and the Food and Drug Administration (FDA) of the Ministry of Public Health. A brief account on the activities of the Centre is given as follows:

The Pharmaceutical Technology Service Centre is responsible for the following activities:

- A. Training of personnel at all levels in the pharmaceutical industry in current good manufacturing practices (cGMP) and quality assurance.
- B. Monitoring compliance with requirements of cGMP and auditing/self auditing. A few most frequent occurring examples of non-compliance are as follows:
  1. Inadequate layout due to incorrectly designed material, product and personnel flows.
  2. Cross contamination due to the above.
  3. Unmonitored environmental conditions such as atmospheric pressure, airborne particle count, temperature, humidity, etc. particularly in aseptic area.
  4. Inadequate stability of the products.
- C. Provision of services required by the pharmaceutical industry as follows:
  1. Advice on planning and designing new manufacturing facilities with optimized layout.

2. Establishment of criteria for the construction of clean rooms and production of rooms of special/toxic substances, such as penicillin, steroids, etc.
  3. Selection of the right construction materials for the interior portion of the manufacturing plant or laboratory (i.e. insulations, water or vapour barriers, interior finishing and coating, etc.)
  4. Designing model types for production service facilities and equipment required.
  5. Assistance in selection of manufacturing equipment.
  6. Establishment of appropriate standard operating procedures and sound/effective preventive maintenance programmes for equipment, facilities and building(s).
  7. Identify, order or design and fabricate calibration equipment required for validation of instruments and machinery.
  8. Designing a portable waste water plant and other pollution control equipment adapted to the capacity of the pharmaceutical production plant.
- D. Introduce the basic GMP documentation in the pharmaceutical industry as standard operating procedures (SOPs), batch production records (BPRs), test records (TRs), etc.

The Centre was opened on 17 April 1991 and became effectively functional and operational as of October 1991. Since then it has become well accepted both by the Thai Pharmaceutical Industry and the FDA. The Ministry of Health has expressed interest in cooperating with the Centre and to promote its activities. Several neighbouring countries expressed interest to utilize the services provided by the Centre. Recently, representatives of the Ministry of Health of Laos visited the Centre.

It is strongly felt that the Pharmaceutical Technology Service Centre in Bangkok, Thailand, could be expanded to provide services to the neighbouring countries and the countries in the region. High level government officials of Laos and Vietnam have shown interest in participating in the programme and during their visit also expressed interest to use the services of the Centre. Its scope of activity could also be expanded to provide an independent testing facility for carrying out analytical tests on pharmaceuticals on the market in order to identify suspected sub-standard quality and counterfeit products.

It is strongly recommended that the services of the Pharmaceutical Technology Service Centre, which are provided, and by now actually delivered approximately 150 governmental and private pharmaceutical industry in Thailand, should be used for training of the professional staff of the Syrian pharmaceutical industry. It should be emphasized that the Centre, by reaching financial sustainability within

the first year of its existence, by mid-1992. in this very competitive field, proved its excellence and could offer Syrian professionals a very intensive fellowship / study tour programme at a very reasonable price.

Finally, it should be noted that UNIDO has developed a technical cooperation programme on waste water treatment and biodegradation of organic pollutants generated by the pharmaceutical industry. Such a programme is being implemented in Jordan. Since the project on Integrated Development of Pharmaceutical Industry in Syrian Arab Republic is executed jointly with WHO, it gives a very good example for inter-agency cooperation. Furthermore, the technical and technological competence and industrial experience of UNIDO can well be demonstrated to WHO and other United Nations agencies not only through the subject project in Syria but through any relevant programme or project of UNIDO in the pharmaceutical and allied industries.