OCCASION

This publication has been made available to the public on the occasion of the 50th anniversary of the United Nations Industrial Development Organisation.

DISCLAIMER

FAIR USE POLICY

CONTACT

Please contact publications@unido.org for further information concerning UNIDO publications.

For more information about UNIDO, please visit us at www.unido.org

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION
Vienna International Centre, P.O. Box 300, 1400 Vienna, Austria
Tel: (+43-1) 26026-0 · www.unido.org · unido@unido.org

20283

RESTRICTED

DP/ID/SER.A/1660
20 July 1993
ORIGINAL: ENGLISH

ix, 188 p.
tables
graphs
diagrams

DEVELOPMENT OF THE PHARMACEUTICAL INDUSTRY IN THAILAND

DP/THA/88/018

THE KINGDOM OF THAILAND

Technical report: Quality assurance in pharmaceutical industry with specific reference to validation*

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

Based on the work of M.M. Carpio, quality assurance expert

Backstopping Officer: Z. Csizer, Chemical Industries Branch

United Nations Industrial Development Organization
Vienna

* This document has not been edited.

V.93-87500

TABLE OF CONTENTS

ABBREVIATIONS AND ACRONYMS

AFTA	Asean Free Trade Agreement
ASEAN	Association of South-East Asian Nations
CIDA	Canadian International Development Organization
CTA	Chief Technical Advisor
DP	Development Project
DTEC	Development of Technical and Economic Cooperation
FAO	Food and Agriculture Organization
FDA	Food and Drug Administration
FTI	Federation of Thai Industries
GATT	General Agreement on Tariffs and Trade
GDP	Gross Domestic Product
GMP	Good Manufacturing Practices
GPO	Government Pharmaceutical Organization
HRD	Human Resources Development
IDA	International Development Agency
IMF	International Monetary Fund
MOI	Ministry of Industry
PTSC	Pharmaceutical Technology Service Centre
Q.A.	Quality Assurance
Q.C.	Quality Control
QIT	Quality Improvement Team

R & D	Research and Development
SOP	Standard Operating Procedure
THA	Thailand
TPMA	Thai Pharmaceutical Manufacturers Association
UN	United Nations
UNDP	United Nations Development Program
UNIDO	United Nations Industrial Development Agency
VAT	Value Added Tax
WHO	World Health Organization

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

* For a Detailed List on Appendix III refer to the next 3 pages.

Appendix iii

Audio-visuals and Handouts used in Process Validation Workshops:

- Standard Operating Procedures
- The Quality Assurance Triangle
- An approach to the Validation of Pharmaceutical Process
- Validation of Pharmaceutical Operations
- Introduction
- Validation Overview
- Glossary
- A checklist for Validation Working Groups
- Validation (Samples, Methodology, Calibration, Data)
- Handling and Receiving Samples
- Samples for Validation
- Key Points for Processing
- Historical Data
- Assessment of Data
- Recording, Handling and Validating Data
- Design
- Organization
- Validation of Sterile Products
- Inspection and Reporting Quality Assurance Deficiencies
- Guide to Quality Assurance Programs

Appendix iii - Cont.

- Data
- Working Environment
- Equipment and Instruments
- Analytical Methods
- Key Considerations (New Methods)
- Documented New Methods
- Modification of Analytical Testing Methods
- Glassware
- Specification of Volumetric Glassware
- Reagents and Solutions
- Reagent Quality
- Media
- Reference Standards for Analytical Testing
- Special Attention for successful Tableting Process
- Tablets
- Wet Granulation Process
- Tablet Presses
- Tablet Process Validation
- Aseptic and Sterile Operations
- An Equipment Installation Protocol
- Sterile Products

Appendix iii - Cont.

- **Equipment Installation Protocol**
- **Sterilizing Oven Validation Sheet**
- **Steam Sterilizer Validation Protocol**
- **Minimal Internal Organization for the Implementation of a basic Validation Program**

ABSTRACT

A technical Mission to Thailand was undertaken by a UNIDO Technical Expert to support the Project "Development of the Pharmaceutical Industry in Thailand" (UNDP/UNIDO DP/THA/88/018. The main objective was to provide technical training on pharmaceutical manufacturing process validation. The audience for the training activities consisted of professionals and senior technical personnel who are involved in the manufacturing and quality control of pharmaceutical products in Thailand. In, addition, the Technical Expert reviewed the year to-date (March 1993) activities of the Pharmaceutical Technology Service Centre.

1.0 A BACKGROUND ON THAILAND

A SUMMARY OF INFLUENTIAL FACTORS ON THAI PHARMACEUTICAL PRODUCTS

In 1991, Thailand's pharmaceutical market totalled US $541 million. Accounting for 24% of South-East Asian sales, Thailand ranked third in this market. Worldwide, Thailand ranked as the 35th largest pharmaceutical market.

In January of 1992, Thailand introduced a value added tax (VAT), to be applied for all goods and services, including pharmaceutical products. This rate was set at 7%, however, small businesses were to be partially exempt, having to pay a reduced rate instead. In addition, the government imposed a pharmaceutical price freeze, placing prices at October 1991 price levels.

In February of 1992, an amendment to the patent law was passed in Thailand. This amendment provided for patent protection for pharmaceutical products, extending the protection period from 15 to 20 years. Products already the market were not protected, however retroactive protection was offered to patent applications filed prior to the law's enforcement. In addition, local manufacture of a patented product was no longer required.

A Pharmaceutical Patent Board was to be set up, in order to monitor prices. Patent holders, under the new law, will be required to provide details on their pharmaceutical products sold in Thailand and abroad. These details would include not only prices but also internal production and distribution costs. The board could take action if it appeared that a patented product was being sold at an unreasonably high price, if a price increase was higher than the consumer price index, or if the board felt that public demand was not being met.

In addition, safety standards have been set up for pharmaceutical products manufactured either locally or imported. To help in the

control of pharmaceutical manufacturing, a registry for generic names was established.

In terms of health care, the majority of costs must be paid directly by the patient. The Thai government 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. In terms of future coverage, the government has been considering expanding the health card scheme cover to urban areas. In addition, private health insurance is available from both specialist and general insurance companies. The private sector covers care in the form of western-style hospitals and general practice physicians, as well as treatment through traditional Thai practitioners.

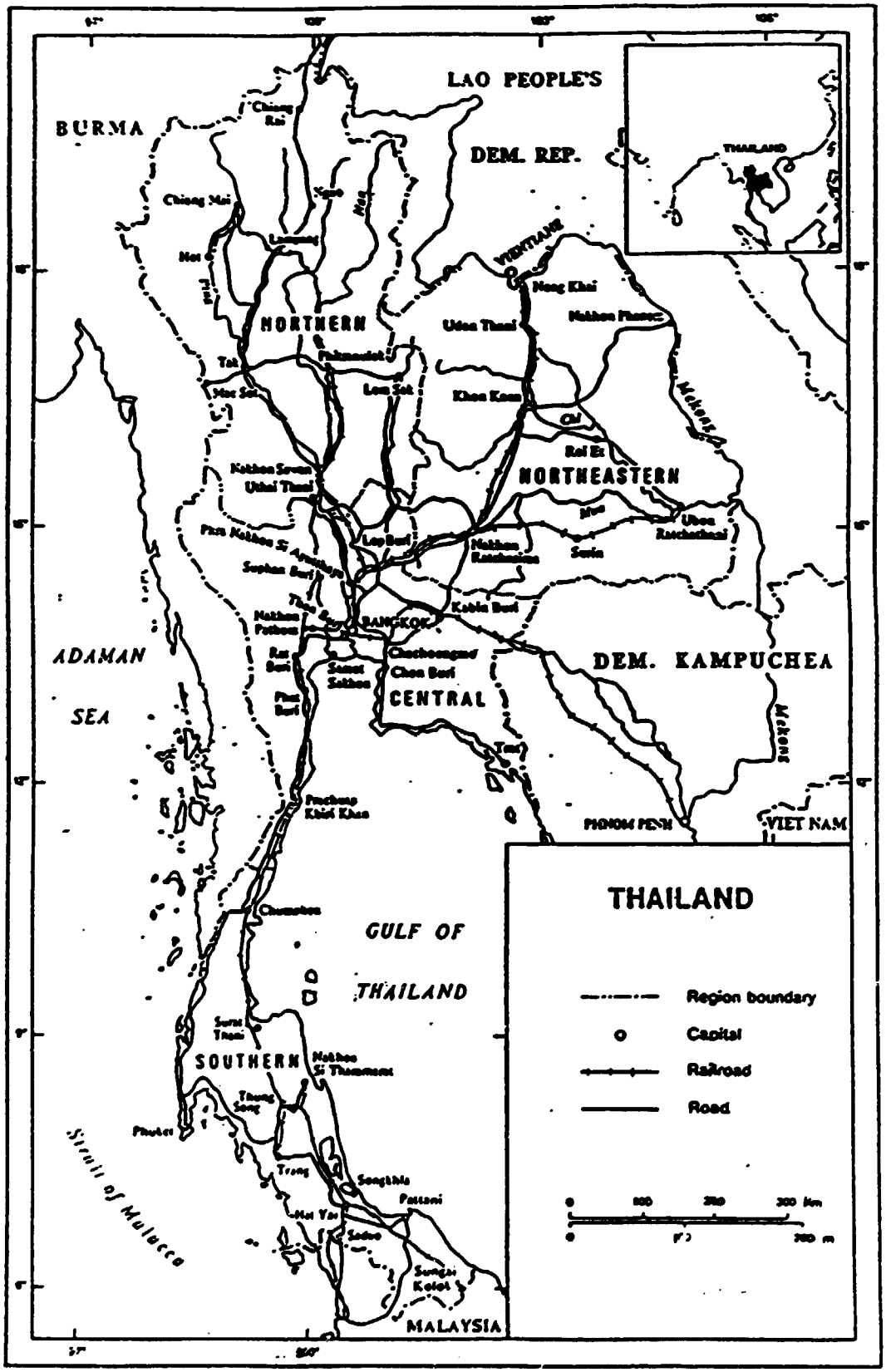
In 1991, a social insurance scheme for Thai workers was also introduced. This plan covered people working for companies and institutions employing more than 20 workers. This was based in part on a commitment included in the Fifth National Economic and Social Development Plan (1982 - 1986). This health care commitment by the government revolved around the introduction of a social security system, initially slated for industrial employees, but meant to eventually include the entire population.

1.1 A COUNTRY PROFILE

Location, Climate and Topography

Thailand is located in the centre of the south-east Asian mainland. It covers an area of 198,115 square miles or 513,115 square kilometres. Thailand is bordered by Laos to the north and east, by Myanmar (Burma) to the north and west, Kampuchea to the south-east, and Peninsular Malaysia to the south. The southern portion of Thailand extends down the Malay Peninsula and lies between the Andaman Sea and the Gulf of Thailand (refer to Figure 1).

Figure 1:


LAO PEOPLE'S
DEM. REP.
BURMA
THAILAND
VIENTIANE
Nong Khai
Nakhon Phanom
Udon Thani
NORTHERN
Phitsanulok
Loei
Tak
Mae Sot
Khon Kaen
Mekong
Roi Et
NORTHEASTERN
Nakhon Sawan
Uthai Thani
Phra Nakhon Si Ayutthaya
Lop Buri
Nakhon Ratchasima
Surin
Ubon Ratchathani
Suphan Buri
Kanchanaburi
BANGKOK
Nakhon Pathom
Ratchaburi
Samut Sakhon
Chachoengsao
Chon Buri
CENTRAL
DEM. KAMPUCHEA
ADAMAN
SEA
Prachuap Khiri Khan
PHNOM PENH
VIET NAM
GULF OF
THAILAND
Chumphon
Surat Thani
SOUTHERN
Nakhon Si Thammarat
Trang
Phuket
Songkhla
Pattani
Sadao
Sungai Kolok
MALAYSIA
Strait of Malacca
Region boundary
Capital
Railroad
Road

In Thailand, the north and north-west regions, along with the southern peninsula are mountainous areas. The central area consists of a fertile alluvial plain. The climate in Thailand is tropical and consists of 3 distinct seasons: the hot season (February to May), the rainy season (May to November) and the cooler season (November to February).

Population and Demographics

The population of Thailand was an estimated 57.6 million people in 1991, with a labour force of approximately 32.6 million workers[1]. In 1990 the majority of the population (64.1%) were aged 29 and younger[2] (refer to Table 1). The projected annual growth rate was 1.3% (estimated for 1990 - 2010)[1].

The vast majority of the country's population are Thai, while the remainder of the population is comprised of both Chinese and Malay people. Buddhism is the principle religion, but other religions are also present. The official language is Thai, however English is widely used in government and business circles.

The national population density in 1990 was 284 per square mile (110 per square kilometre)[2]. Around one-third of the population lives in Thailand's central plain area. The urban population was placed at 16% of the total in 1985, according to the WHO. The largest city in 1989 was metropolitan Bangkok, with more than twice the population of the second largest city, Nakhon Ratchasima (see Table 2). Bangkok, the capital, is also the main port, and industrial and commercial centre.

1. Source: Thailand: Coping with the Strains of Success, International Review Series, UNIDO, March 1992.

2. Source: Statistical Handbook of Thailand (National Statistical Office).

Table 1: Thailand - Population by Age and Sex 1990

Age Group	% of Total Population	% of Age Group Male
All Ages	100.0	50.0
0 - 9	22.4	50.6
10 - 19	21.9	50.8
20 - 29	19.8	50.7
30 - 39	14.4	49.9
40 - 49	8.9	49.9
50 - 59	6.5	48.0
60 - 69	3.9	47.2
70+	2.2	42.9

Source: National Statistical Office

Table 2: Population of Thailand's Largest Cities 1989

	000's
Bangkok Metropolis	5,833
Nakhon Ratchasima	2,361
Ubon Ratchathani	1,902
Udon Thani	1,799
Khon Kaen	1,667

Source: National Statistical Office

The Economy

Thailand's Gross Domestic Product (GDP) was Baht* 2,051.2 billion in 1990[2]. The GDP per capita figure for the same year was Baht 27,470 (using a population figure of 56.34 million for 1990)[2].

Thailand has good agricultural resources and is also the world's third largest producer of rubber and tin. In addition, zinc has also become an important resource. Natural gas production supplies over 10% of Thailand's total domestic energy needs. Thailand also is one of the world's leaders in the production of shrimp. In 1989, agriculture, forestry and fishing contributed 17% of GDP, while manufacturing contributed 24% (see Table 3). This economic profile has changed from 1988 where 66.4% of workers were employed in the agriculture, forestry and hunting (fishing) trades, and only 8.4% were employed in manufacturing activities (see Table 4).

This change in Thailand's economic profile was greatly influenced by the government's plans and attitudes. Internationally Thailand is a member the following organizations of ASEAN, the Colombo Plan, FAO, GATT, IDA, IMF, UN, UNIDO, WHO and the World Bank. Further, in October of 1991, the members of ASEAN, including Thailand, announced the establishment of a single market, the Asian Free Trade Area (AFTA), to be implemented over the next 15 years. This move however, has not yet been implemented.

Changes in Thailand's sixth National Economic and Social Development Plan (1987-91) aimed at an annual economic growth of 5% and the creation of 3.9 million new jobs. The Thai government intended to shift emphasis from the expansion of state services to improvements in industrial efficiency and quality, and also aimed at encouraging the private sector.

* For comparison purposes the 1st quarter of 1993 showed 1 USD = 22 Baht.

Table 3: Contributors to GDP for 1989 (estimated)

	% GDP
Agriculture, forestry & fishing	17.4
Banking, insurance & real estate	4.9
Construction	7.2
Electricity	2.7
Manufacturing	23.6
Mining & Quarrying	3.8
Ownership of dwellings	3.1
Public administration & defense	4.2
Services	14.2
Transport & communications	7.6
Wholesale & retail trade	11.4

Source: National Statistical Office

Table 4: Contributors to Employment 1988

	% employed
Agriculture, forestry & hunting	66.4
Commerce	9.8
Construction	2.4
Electricity, gas, water & sanitation	0.4
Manufacturing	8.4
Mining & Quarrying	0.1
Services	10.2
Transport, storage & communications	2.2

Source: National Statistical Office

The Government of Thailand:

Thailand is a constitutional monarchy. In September 1992 the present constitution was introduced.

The Head of State and the head of the armed forces is King Bhumibol Adulyadej (King Rama IX), who succeeded to the throne in June, 1946.

Legislative power rests with the bicameral National Assembly, which consists of a 270 member Senate and a 360 member House of Representatives. Members of the Senate, who must not be members of any political party, are appointed by the King (on the advice of the Prime Minister) Each member of the Senate serves a six year term. On the other hand, members of the House of Representatives are elected and serve a four year term.

The King appoints the Prime Minister on the advice of the National Assembly. The Prime Minister does not have to be an elected official. Executive power is exercised through the Council of Ministers. The King appoints up to 49 ministers, who do not have to be elected members of the House of Representatives. The ministers can be appointed through the advice of the Prime Minister. The current Prime Minister is Chuan Leekphai, who was appointed in September, 1992.

In terms of local government, Thailand for administration purposes, is divided into 73 provinces (changwats), each under the control of a governor. Each province is subdivided into districts (amphurs), subdistricts (tambons) and villages (mu-bans). Heads of subdistricts and villages are elected by the people of those communities.

1.2 HEALTHCARE IN THAILAND

The Ministry of Public Health is responsible for the overall organization and administration of public health and most medical services. It is comprised of six major departments. The Office of the Under-Secretary of State coordinates the work of the various Ministry of Public Health departments.

Key departments include the following:

The Department of Medical Services	-	responsible for psychiatric services for the entire country; deals with national health laboratories, pharmaceutical analysis, food and beverage analysis, toxicology, clinical pathology, medical research, and the Virus Research Unit.
The Department of Health	-	oversees dental health, rural water supply, sanitation, environmental and occupational health, and family and school health.
The Thai Food and Drug Administration (Office of the Food and Drug Committee)	-	responsible for food and beverage control, pharmaceutical and psychotropic substances, and cosmetics.
The Department of Communicable Disease Control	-	covers venereal diseases, tuberculosis, leprosy, malaria and other communicable diseases.

The Ministries of Education and Defense alsc manage some hospitals. The Board of Primary Health Care (through the Ministry of Public Health) helps to set up, coordinate and promote primary health care activities. Locally, there are 73 Chief Medical Officers, one for each of the provinces (changwats), who are responsible to the Under-Secretary of State, and handle health education, and prevention services.

A commitment to introduce social security - initially for industrial employees and eventually for the whole population was included in the Fifth National Economic and Social Development Plan (1982 - 86). The Sixth Plan (1987-91) for the most part continued to pursue the objectives of the Fifth Plan. The plan would stress disease prevention, expansion of health care facilities, integration of traditional medicine with public health care, improved training for nurses, midwives and other health workers, improvements to the pharmaceutical distribution system, and a goal to increase the number of pharmacists and dentists in the workforce. This plan was reportedly successful, Baht 54 billion was budgeted for improvements to the health care system for the 1987-1991 period. This compares favourably to the Baht 1.44 billion spend by the government in 1980 on pharmaceuticals.

In terms of health care professionals, most of the services are performed by the public sector, although the private sector is expanding. Most doctors dispense drugs, and their fees include the cost of pharmaceuticals. Health care personnel are unevenly distributed though, with about 40% being based in Bangkok. With the majority of patients preferring cheaper advice and medication, pharmacists or traditional Thai practitioners are frequently sought. In addition, rural health care through health centres (organized by the Ministry of Public Health) rely heavily on paramedical staff, often volunteers.

1.3 THE PHARMACEUTICAL INDUSTRY IN THAILAND

The pharmaceutical industry in Thailand consists mainly of three groups: importers, distributors and manufacturers. The Thai government, under the 1977 - 1981 National Economic and Social Development Plan, aimed at encouraging national production of essential raw materials for pharmaceuticals since local supply was inadequate. This domestic shortage still exists today, as much of the raw materials are still being imported (refer to Table 5 for the balance of trade figures). According to IMS figures[3] only 3% of locally produced pharmaceutical products are exported, while 65% of pharmaceutical imports are raw materials. Finished products constitute 35% of imports. This severely constricts Thailand's ability to produce inexpensive local pharmaceuticals, reduces the ability to ensure adequate supply, and lessens control on quality improvements.

The Thai pharmaceutical market is very segmented with approximately 181 registered manufacturers. Three trade associations partially represent these drug companies. The Pharmaceutical Producers Association (PPA) represents research based companies who are associated with foreign companies. The Thai Pharmaceutical Manufacturers Association (TPMA) represents pharmaceutical manufacturers. The Bangkok Pharmaceutical Trade Association represents small local distributors.

To-date in 1993 there are 181 companies who are registered with the government, plus 2 Government Pharmaceutical Organizations (GPOs). Of these 181, 154 or 85% are national companies, and 27 or just under 15% are considered multinational companies. In total 78% of these companies reside in the Bangkok area. Of course many other pharmaceutical companies exist in Thailand who are not registered.

3. Market Research International Ltd., IMS Data Thailand Branch.

Table 5: Balance of Trade Figures for Pharmaceutical Imports (1986 - 1988)

(in Baht Millions)

	Exports	Imports	Balance
1986	230.5	1,658.6	-1,428.1
1987	267.1	1,517.4	-1,250.3
1988	405.4	1,968.2	-1,562.8

Source: Pharmaceutical Producers Association of Thailand

Table 6: Top Ten Leading Pharmaceutical Companies in 1991*

US $ Mil	
14 - 16	Teck Heng Yoo
12 - 14	Thai Nakorn Patana; GPO
10 - 12	Glaxo; Hoecht; Roche
8 - 9	SmithKline Beecham
7 - 8	Merck Sharp & Dohme; Bristol-Myers Squibb; Janssen

* Based on Sales Through Retail Pharmacies and Hospitals

According to IMS data, ten leading pharmaceutical companies accounted for 24% of total market sales in 1991 (see Table 6). In 1991, the leading 25 companies took 42%; the top 50, 58%; and the top 75, 69%. 36 companies contributed 50% of sales; and 97, 75%. Pharmaceutical sales through retail pharmacies and hospitals totalled US $ 433 million in 1991.

In terms of product sales, the ten leading product classes in 1991 (see Table 7) accounted for 52% of total market sales, with antibiotics, analgesics and antacids/antiulcerants leading as the top three.

The IMS Thailand Hospital Index for 1991 estimated distribution channels as follows:

- 42% of sales went to drugstores (36% being direct sales and 6% through wholesalers)

- 40% of sales went to private and government hospitals (20% of sales were through the GPO, and 19% of sales being direct from other manufacturers and 1% through wholesalers)

- 13% of sales went to health centres and private clinics (12% direct and 1% via wholesalers)

- 2% of sales to the consumer was sold direct by the GPO

- 3% of the manufactured goods were exported.

As stated above, in addition to the GPO supplying a small percentage of pharmaceuticals directly to the consumer, the GPO is also the main distribution point from which government facilities receive their pharmaceuticals. Further,

the Ministry of Public Health produces an essential drugs list which lists around 400 pharmaceuticals. The GPO produces many of these products, hence government facilities such as public hospitals are supplied by the GPO. Other products can be tendered, with the GPO assessing bids on the basis of price.

Pricing for pharmaceutical products varies, distributors generally mark-up prices by 20%, while wholesalers or retailers can mark the product up by anywhere from 10% to 30%.

Imported pharmaceuticals are currently subject to a 33% import duty which adversely affects prices. However, in January of 1992, the members of ASEAN introduced the Common Preferential Tariffs (CEPT) scheme. The objective of this scheme is to gradually reduce and remove tariffs on products including pharmaceuticals over the next 15 years. In addition, changes brought about in the February 1992 patent law, which extended patent protection from 15 to 20 years is also influencing market prices on pharmaceuticals.

The government through the FDA controls the manufacture, importation, sale and quality control of pharmaceuticals. Hence, the FDA plays an important role in medical manufacturing regulations. The FDA issues licences or certificates to pharmaceutical manufacturers who follow GMP guidelines. These guidelines are based on WHO specifications. The FDA also issues certificates based on different dosage formats, such as liquid dosage forms, ointments and cream products, sterile goods, and solid dosage forms. It should be noted that for the year to-date 1993, only 30 pharmaceutical companies in Thailand produce sterile products.

Table 7: Top Ten Leading Product Classes for Pharmaceuticals in 1991*

US $ Mil	
75 - 80	Systemic Antibiotics
30 - 35	Analgesics
26 - 28	Antacids/Antiulcerants
22 - 24	Cough and cold therapies
14 - 16	Vitamins
10 - 12	Systemic antirheumatics; I.V. solutions over 100cc
8 - 9	Systemic Sex hormones
7 - 8	Bronchodilators/antiasthmatics; topical antirheumatics

* Based on Sales Through Retail Pharmacies and Hospitals

A licence from the FDA is also required to import pharmaceuticals. In addition, the FDA carries out compulsory inspections of pharmaceutical manufacturers. Random samples circulating in the market are also inspected for quality. Product recall decisions are also made by the FDA with the offending manufacturer given six months for recall completion.

It should be noted however, that neither manufacturers, nor doctors are legally required to report on adverse drug reactions. Many unregistered pharmaceutical manufacturers are also supplying "counterfeit drugs" to the national market.

In 1992 the government introduced regulations disallowing the marketing of drugs produced through non-GMP manufacturers. This, coupled with an emphasis to keep pharmaceutical prices down, in a market containing many small diversified manufacturers could result in a strained manufacturing economy. The role of the FDA has become paramount in its role among the local pharmaceutical producers (see Table 8 for numbers on current GMP certified producers). In addition, market research carried out by the Thai FDA shows that the government must make efforts to educate the public on the significance, and cost effectiveness of internal GMP programs (see Table 9).

Table 8

NUMBER OF PHARMACEUTICAL COMPANIES
IN THAILAND WITH GMP (APRIL 1989 - FEB. 1993)

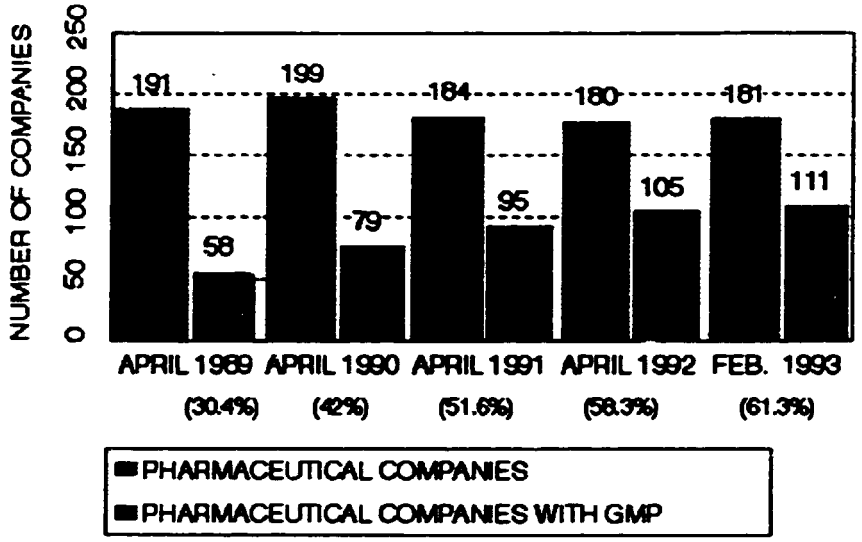


Table 9

Companies Surveyed Who Do Not Yet Have a GMP Certificate:

Reasons Why:

	%
Lack of Money	44
Lack of Personnel/Human Resources	46
Do Not Feel that the GMP Programs would be Cost Effective	87

2.0 THE CONCEPT OF QUALITY ASSURANCE

The concept of Quality Assurance is applicable to any manufacturing operation. Quality Assurance could be defined as 'the sum of total organized arrangements made to ensure that the products will be of the quality required by the intended use'. The Standard Operating Procedure (SOP) is a key tool in the Quality Assurance Triangle (see Figure 2). SOP's provide a step by step written account of a procedure, fully documented and detailed. These operating procedures become building blocks in the manufacturing process. They describe methods to be followed and performance and specification levels to be achieved. The SOP's serve as a training tool, especially for new employees. SOP's also act as technical references, maintaining the standards which help ensure quality in manufacturing is achieved (see Figure 3).

Good Manufacturing Practices (GMP) is that part of quality assurance which is aimed at ensuring that products are consistently manufactured to a quality appropriate to their intended use. It is thus concerned with both manufacturing and quality control procedures.

Because a system requires people to make it work, a substantial portion of the quality assurance effectiveness depends on the organizational capability of the manufacturing enterprise. In order to implement the quality assurance concept into any manufacturing sector, a combined effort is necessary with the participation of the industry, the government, educational institutions such as universities and/or technical, colleges and non-government organizations related to the target industry and/or to any particular aspect related to it.

For successful implementation of the quality assurance concept in any manufacturing sector it is necessary to establish comprehensive and effective training programs. These programs should be directed at the different groups responsible for the manufacturing process. The objectives of these programs should contribute knowledge and information on the basis of the concept as well as introducing the requirements for compliance to existing regulations.

Figure 21

The Quality Assurance Triangle

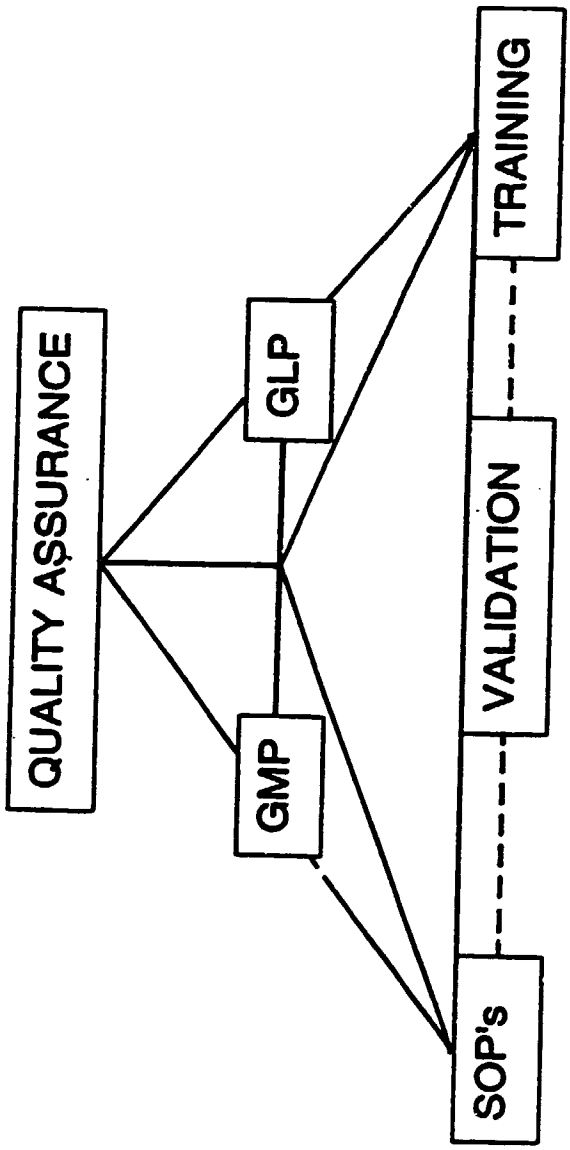
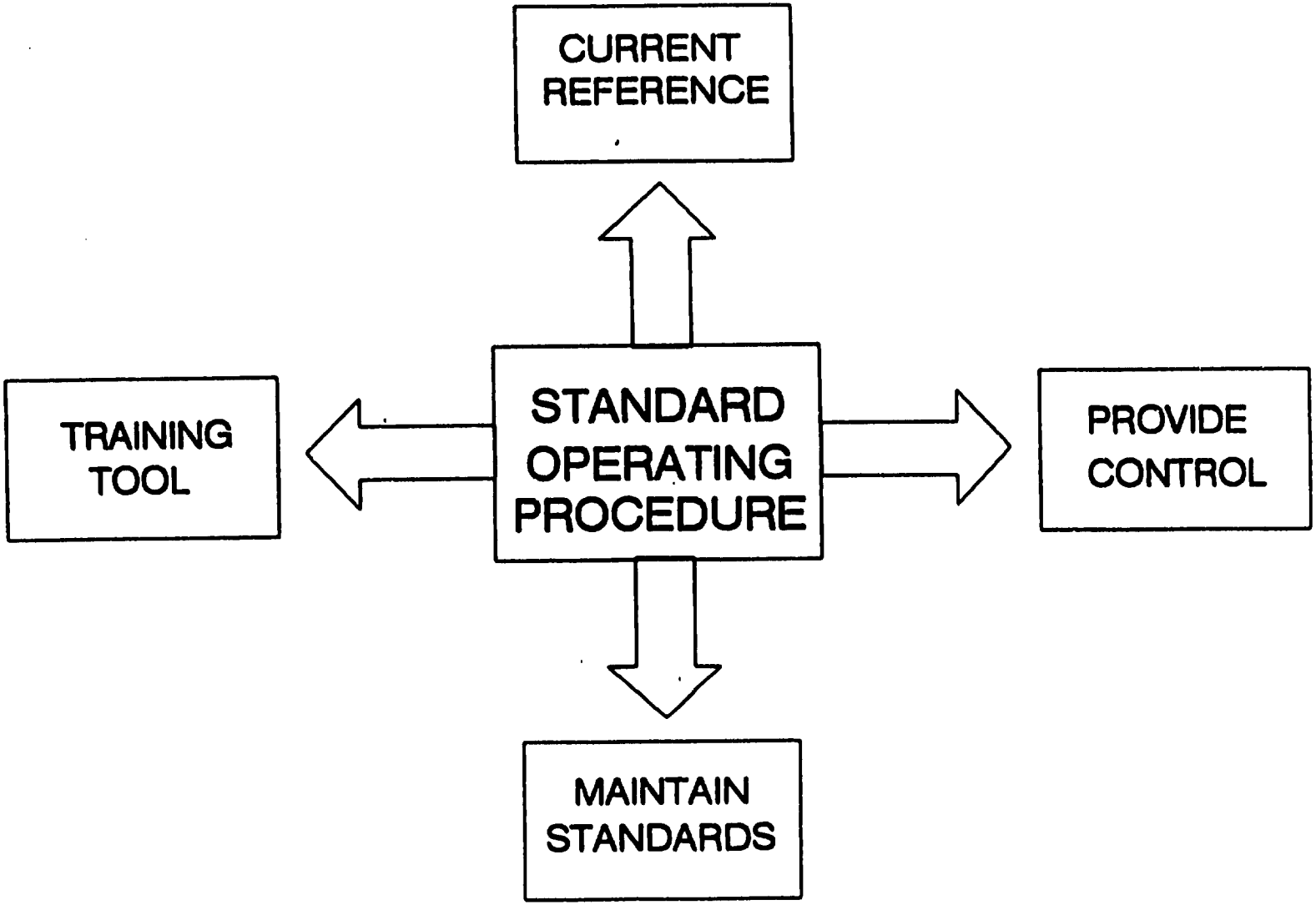


Figure 3:

Standard Operating Procedures



3.0 PROJECT BACKGROUND

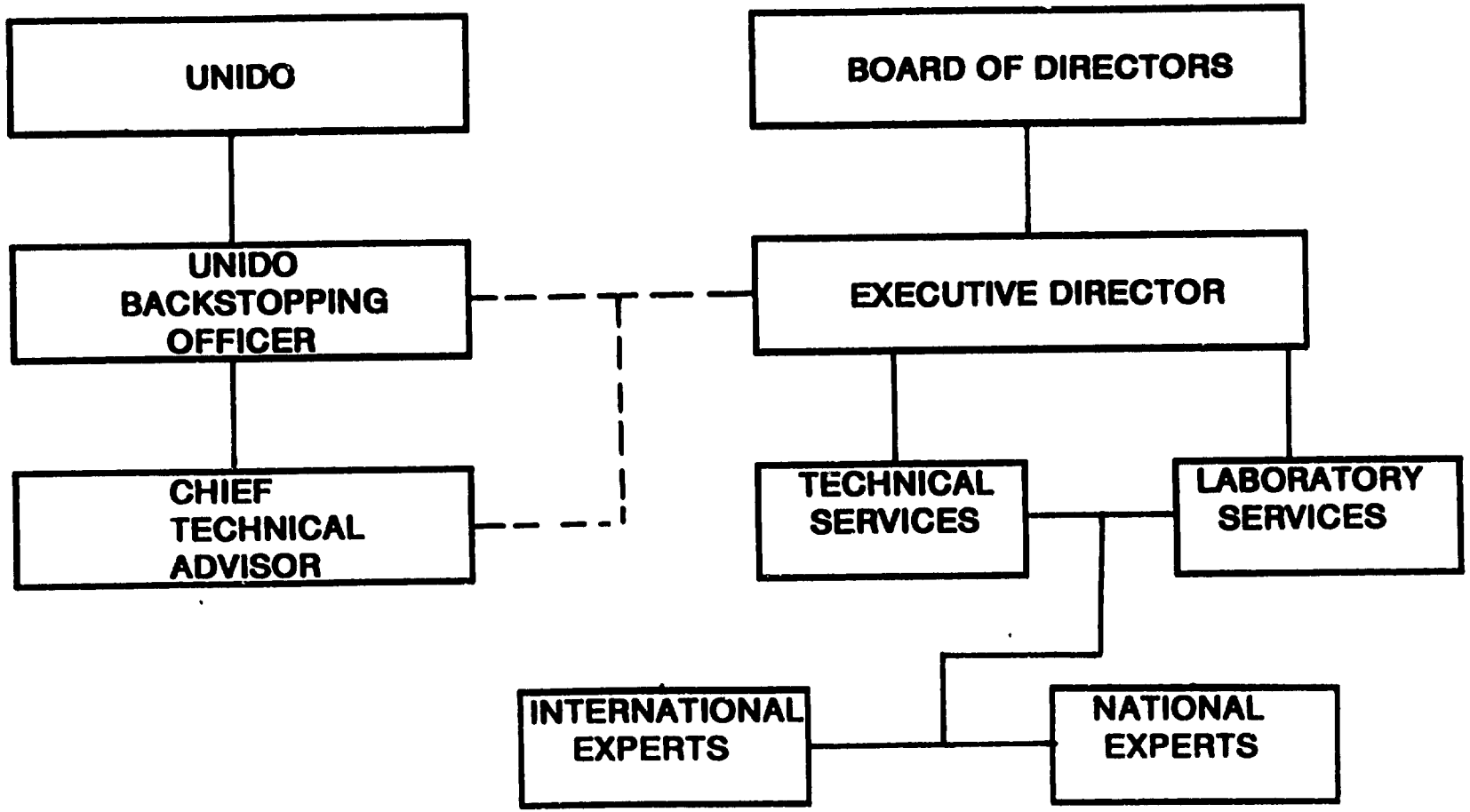
The Royal Thai Government in conjunction with UNDP/UNIDO acknowledged the need to develop the pharmaceutical industry in Thailand. Guidelines for GMP were issued by the Thai FDA, however, both the FDA and the Thai industries faced problems in the application of GMP. In 1987 the Government established the Quality Improvement Team (QIT). The QIT is composed of representatives from Inspection, the Technical Division of the FDA, the Drug Analysis Division, the TPMA, the GPO, and Academicians. The function of QIT is to give advice to pharmaceutical manufacturers and to promote compliance with the current GMP regulations. To-date, QIT has visited over 60 factories, of these, the majority were found to be in need of technical assistance in implementing GMP guidelines.

In 1989, 58 out of the 191 pharmaceutical factories or 30.4% were granted GMP certificates by the FDA in various dosage forms (refer to Table 8). Although this number has increased since, today it is still far from the FDA's goal which established that 100% of the pharmaceutical manufacturers will meet the GMP criteria targeted for the end of the seventh National Economic and Social Development Plan (1996).

As a result of the difficulties faced by the pharmaceutical industry in Thailand, the Royal Government in conjunction with UNDP/UNIDO and members of industry and universities, set up the framework for a Pharmaceutical Technology Service Centre (PTSC) (see Figure 4). This centre was established at the faculty of Pharmacy at the Chulalongkorn University in Bangkok. UNIDO provided support through its organization and supplied international technical support, and financial assistance for procurement, as well as management support for the project. The PTSC's objective was to aid in assisting the development of the Thai pharmaceutical industry.

Figure 4:

Organizational Chart for the Pharmaceutical Technology Science Centre



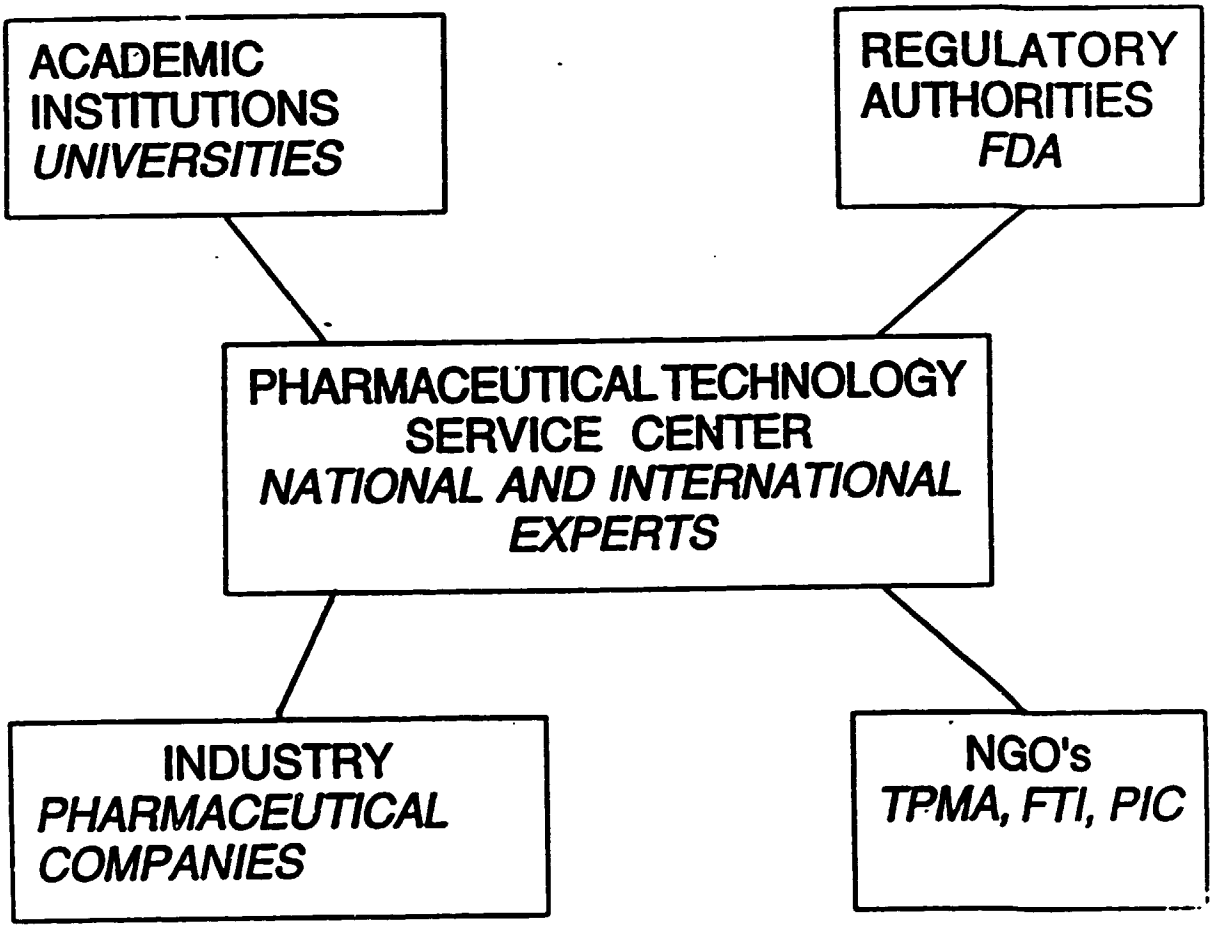
During April 1991, the UNIDO Pharmaceutical Technology Service Centre of the University of Chulalongkorn was officially inaugurated. The PTSC's role was to bridge the communication gap between government, industry and academics (see Figure 5). In addition, the PTSC was to address the main problems of the pharmaceutical industry in Thailand. These hindrances included limited manufacturing technology, lack of product quality improvement knowledge, and a shortage of crucially skilled manufacturing personnel. The Thai Pharmaceutical Manufacturers Association (TPMA) contributed about 1.3 million Baht (U.S. $52,000) for the start up of the Centre, while the University provided the physical facilities for offices and quality control laboratories. A formal "Agreement Document" outlining the terms for long term cooperation was finalized, and Dr. D. Prasan, Associate Professor, of the Faculty of Pharmaceutical Sciences, Chulalongkorn University, was appointed to the position of Director of the PTSC. UNIDO assembled a project team and identified a Chief Technical Advisor (CTA) to the project.

Later in 1991, a two day seminar was organized by the PTSC aimed at the executives of the local pharmacies, in order to stimulate potential interest for the Centre.

The objectives established for the PTSC included a requirement for improving local GMP (Good Manufacturing Practices) levels, in order to meet international quality standards. The Centre would enable local pharmaceutical companies to introduce GMP's in their production plants through training of company staff at the top, middle and production levels. Through seminars and workshops on GMP and/or pharmaceutical technology related topics, the Service Centre would serve to educate and inform local manufacturers, and would enhance its own reputation and credibility both within the industry, and the FDA authorities.

Figure 5:

The PTSC in Relation to Other National Institutions



On May 10th, 1992, during the general meeting of the Thai Druggist Society (2,000 participants out of 6,000 total in the country), it was announced that from now on, regulations would not allow drugs to be marketed from non-GMP manufacturers. GMP Certificates issued by the FDA thus became industry incentives.

Another PTSC goal was to sustain and elevate effective Quality Assurance procedures and practices in the Thai pharmaceutical industry. Quality Assurance would be supported through the use of prepared and detailed SOPs (Standard Operating Procedures) and written guidelines on GMP. These well documented manuals would help to maintain quality assurance in the industry. Through gradual implementation of Quality Assurance Standards, the Centre would play an important role as mediator and/or facilitator between the FDA and the industry. In addition, through the FDA's approval, the Centre would become a certified laboratory, thus increasing its attractiveness and importance to local manufacturers.

Further, the PTSC would eventually act as a referral centre for other national control laboratories and could become the headquarters for technical assistance, providing pharmaceutical product and process development information and consultancy services to other Asian countries for both the private and public sectors. On a regional basis, the Centre could be expanded to serve countries such as Vietnam, Cambodia, Laos, the Philippines, Burma, Indonesia, Nepal, etc.

Finally, a Project Planning Committee was established which aimed at monitoring, effectively controlling and ensuring that the various objectives and outputs were being achieved both in terms of priorities and the time frames. The representatives of the UNDP in Bangkok and the Royal Government of Thailand (MOI-DTEC) had expressed on several occasions doubts and/or concerns about the long term financial sustainability of the Service Centre. Reassurances and justification were requested at that time. Together with international expansion, October of 1994 became a target for financial viability.

4.0 THE TECHNICAL MISSION

On January 19, 1993 a Technical Mission was undertaken in Thailand to support the project UNDP/UNIDO DP/THA/88/018 "Development of the Pharmaceutical Industry in Thailand".

The mission's objective was to provide technical support to the Pharmaceutical Technology Service Centre (PTSC) in the implementation of training programs and technical assistance in the area of quality assurance, particularly pharmaceutical process validation. The terms of reference for the mission are shown in Appendix i. The training activities were directed to professionals and to the senior technical personnel who are responsible for manufacturing and quality control of pharmaceutical products. These products originate from different pharmaceutical companies located in the Bangkok area. In addition, a series of miscellaneous activities were conducted such as a joint PTSC/FDA/TPMA seminar held for owners and senior management in the pharmaceutical industry. This seminar focused on the overall aspects of quality assurance and good manufacturing practices including policies and procedures for compliance to existing regulatory requirements. These seminars had over 200 participants representing over 100 institutions including pharmaceutical manufacturers. Also, a GMP and process validation seminar was held at the faculty of pharmacy at Mahidol University and a paper on "Trends in Biotechnology" was presented in a seminar organized by the Pharmaceutical R & D department of Chulalongkorn University (refer to Appendix ii).

During the mission the technical expert organized four workshops:

a) validation of solid dosage forms

b) validation of sterile products

c) validation of water treatment

d) validation of quality control testing

The technical workshops had a duration of two months with one session per week of approximately 3-4 hours each on each of the four previously mentioned topics. Each session included oral presentations coupled with a task force approach utilizing active participation and discussions. Audio-visual aids were prepared to complement the training activities (see Appendix iii). Case studies and handouts based on actual Thai companies were also analyzed and discussed. Experiments on standardization and calibration were conducted in the quality control groups. Check lists, forms and handouts were also prepared and distributed among the participants. It is important to note that there was no evidence of attrition occurring in these workshops.

The general outline for the workshops is presented in Appendix iv, and the list of participants appears in Appendix v.

During the field mission the technical expert visited six pharmaceutical manufacturing companies, and conducted GMP audits and also toured the GPO manufacturing facilities (including the biological division). The technical expert visited and met with the senior authorities from the FDA and participated in hosting the visit of senior FDA authorities from Laos.

In addition, the technical expert also collaborated with the director of the PTSC in other project activities such as reviewing the project plan, the program requirements and business development activities.

Appendix vi presents a list of individuals visited and interviewed during the mission.

Regular updating meetings were held at the UNIDO offices in Bangkok. Participants in these meetings were comprised of the UNIDO officers responsible for the project, along with the director of the PTSC.

A briefing session was conducted at UNIDO Vienna for two days prior to the field mission. A four day debriefing after the mission included the participation by the project backstopping officer and other UNIDO officials.

5.0 THE PHARMACEUTICAL TECHNOLOGY SERVICE CENTRE

5.1 The Organization

The Pharmaceutical Technology Service Centre is a semi-autonomous institution located within the Faculty of Pharmaceutical Sciences at Chulalongkorn University in Bangkok, Thailand. The Centre has been functioning effectively since 1991.

The Centre has an executive director who reports to a board of directors. The Centre has a permanent staff consisting of four people: one administrative member and three technical personnel including the executive director. In addition, the Centre has two UNIDO's technical experts one of whom is an associate expert. The Centre has the support of a chief technical advisor from UNIDO and receives input from other short term UNIDO experts on specialized areas of pharmaceutical quality assurance. The Centre also has a pool of national experts, composed of professionals from the universities and individuals from the pharmaceutical industry. These individuals are experienced in research and development, processing, testing, local pharmaceutical manufacturing, quality control, quality assurance, processing, and R & D.

5.2 The Facilities

The Centre's physical facilities contains a laboratory equipped with up-to-date analytical instruments. These instrument are capable of performing qualitative and quantitative analysis necessary for pharmaceutical raw materials and products. The Centre also has basic audio-visual equipment used to complement the delivery of training activities.

The Centre is in the process of organizing a small library with information on GMP, quality assurance, international GMP requirements and other miscellaneous information related to pharmaceutical quality.

5.3 Training Activities

The Centre designs and administers training programs on quality assurance, GMP and process validation geared towards professionals working in the pharmaceutical industry. In addition, the Centre (in collaboration with the FDA and TPMA) promotes GMP through conferences, seminars and plant visits.

Since the PTSC's establishment two years ago, the Centre has been conducting a broad range of educational activities and programs for the pharmaceutical industry. It's track record is impressive, as evidenced by the fact that the Centre had administered over 20 training activities which encompassed over 1,000 participants (see Table 10). The percentage of companies participating since 1990 is presented in Table 11. The activities of the PTSC are summarized in Figure 6 and Appendix vii.

In addition, the Centre acts as a focal point for technical advice on quality assurance, SOP formulation, GMP and analytical testing for the pharmaceutical industry. Through its training programs, the Centre provides working groups with hands on experience in a wide variety of applications. For example, individuals learn, formulate, and assemble the critical components of SOP's, which are the building blocks for good manufacturing practices (see Appendix viii for examples of Master SOP's produced by the PTSC). The Centre collaborates on these and other educational activities with the FDA and different universities through the pharmacy faculty.

TABLE 10

NUMBER OF PARTICIPANTS INVOLVED IN THE TRAINING ACTIVITIES OF THE PTSC (1990 - 1993)

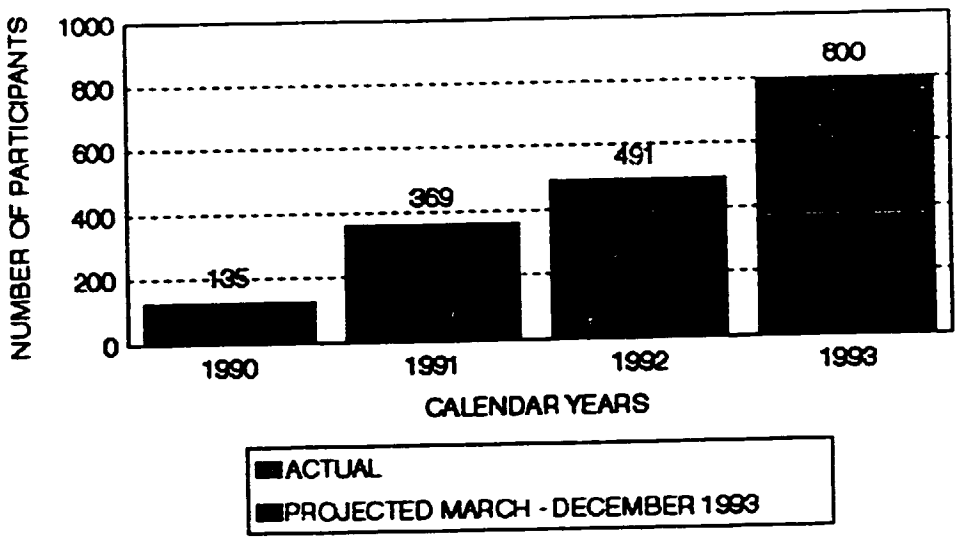


Table 11

COMPANY PARTICIPATION IN THE PROGRAMS OF THE PHARMACEUTICAL TECHNOLOGY SERVICE CENTRE (1990 - 1993)

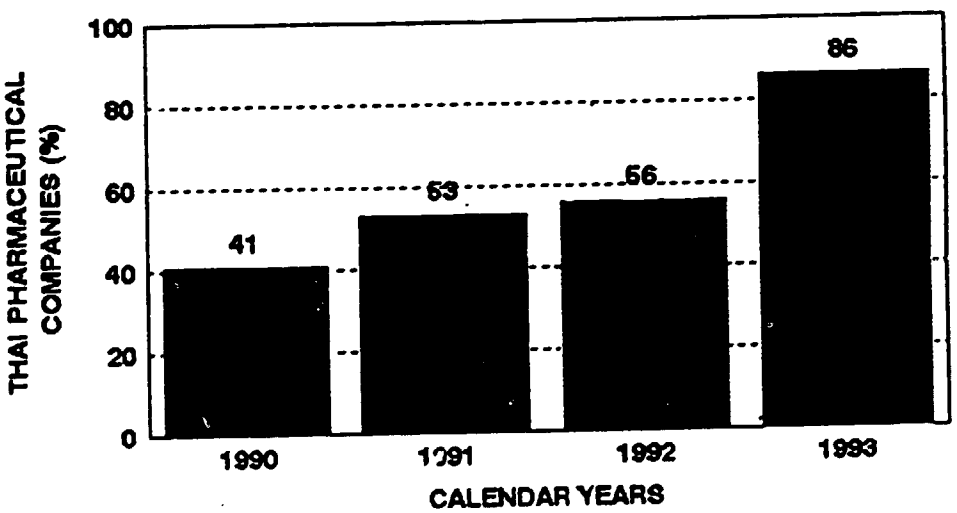
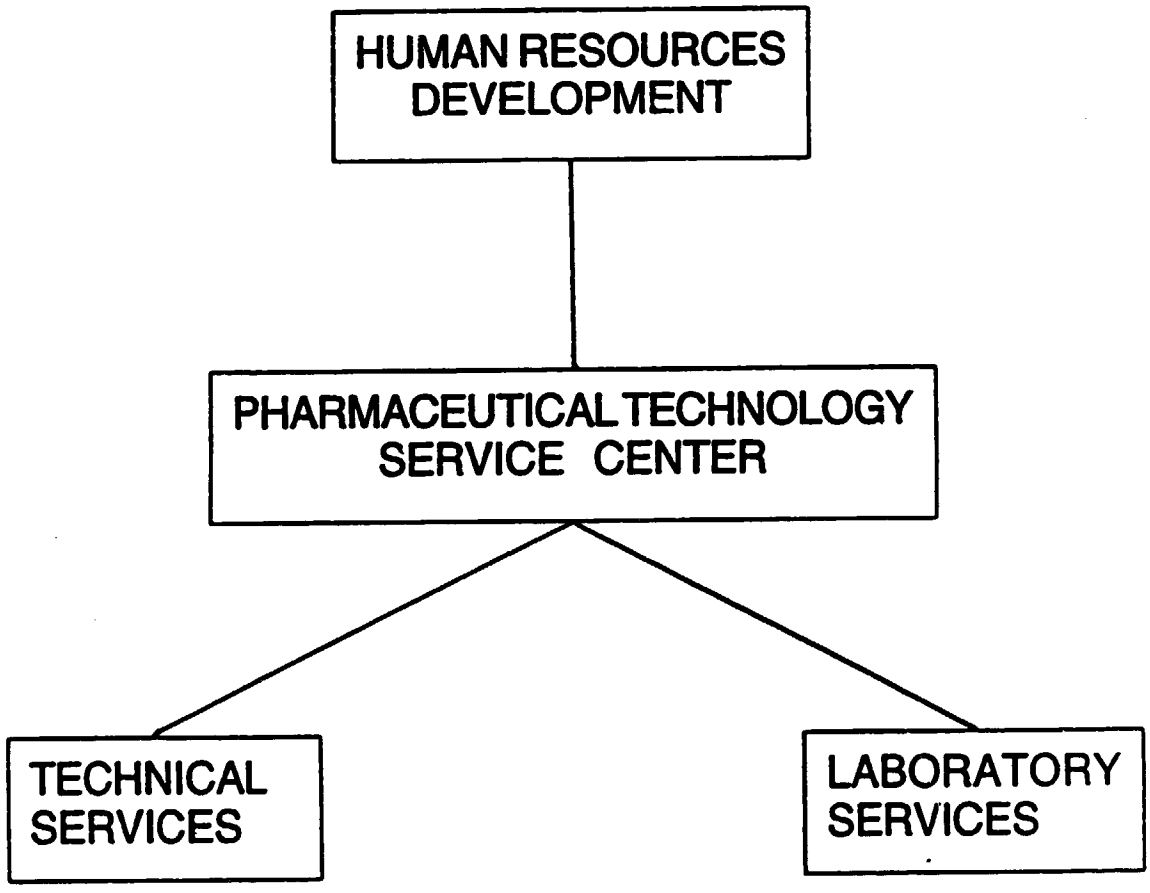


Figure 6:

The Pharmaceutical Technology Service Centre and its Activities



5.4 Laboratory and Technical Services

The Centre's laboratory services perform analytical testing on raw materials, and on different dosage forms. The performance capabilities include the use of:

- HPLC (High Performance Liquid Chromatography)
- A Dissolution Tester
- A UV Spectrometer
- A Coulter Multisizer Particle Analyzer
- A Viscometer
- A Tablet Hardness Tester
- An IR (Infrared Spectrophotometer)

The department is also responsible for R & D, standardization of testing methods, and is fully furnished to carry out stability programs.

Technical services provides assistance in hands on implementation of Quality Assurance methods and procedures. In 1992 the PTSC undertook assisting Medicap Ltd. a local pharmaceutical manufacturer in implementing a system necessary to comply with regulatory requirements for GMP certification. This certificate was essential to allow the exporting of pharmaceutical products to Australia. Medicap Ltd. is at present regularly exporting to Australia. Currently the Centre is pursuing similar technical support agreements with other national companies.

5.5 Partnership For Success

There are several characteristics unique to the PTSC which enhances its success:

a) The organizational structure:

this gives the Centre the required neutrality and flexibility to explore cooperative ventures with government institutions, non-governmental organizations, universities, the industry and with international organizations.

b) The different backgrounds of the technical, national and international experts and collaborators (which combines the experiences from academia, industry and other related organizations):

these combinations give the Centre the necessary tools to promote and develop human resources in the area of quality assurance and GMP for the pharmaceutical industry in Thailand.

c) The participation of high profile national experts from the national industries and the university sector:

gives the Centre the necessary credibility and cultural understanding which facilitates the acceptance for an effective delivery of educational activities and programs which are necessary for the promotion of quality assurance and GMP.

5.6 Strategy For Delivery

The Centre has developed a step-by-step methodology for the delivery of its training activities. The education method is based on the "train the trainers" approach. The delivery systems consist mainly of workshops and working groups which are highly participatory. The working groups vary from 6 to 10 people from the industry. The Centre appoints a coordinator or group leader who is a member of the university and/or the industry. It is their responsibility to lead, monitor, coordinate and direct group activities and discussions. These working groups are very active and their members have "hands-on" experience with pharmaceutical manufacturing, process development and/or testing. The group activities are complemented with technical input from UNIDO international experts. This experience forms a base which becomes a strong asset in the development of tailor made training material and programs used in the implementation of the workshops. These workshops are delivered mainly by national experts (the exception being special sessions delivered by UNIDO international experts and/or through combined efforts).

The main goal for the training activities is to ensure that the professional and senior technical staff develop the necessary technical knowledge, skills and awareness of quality assurance and GMP guidelines and procedures. These abilities are vital for understanding the various manufacturing activities inherent in the pharmaceutical industry. In addition, some of the educational activities are directed at increasing awareness among senior management in order to foster and encourage compliance with existing GMP pharmaceutical regulations.

The PTSC offers a variety of training activities for professionals who work in the manufacture of pharmaceutical and cosmetics products. The audience for PTSC activities are mainly pharmacists and chemists who are involved in manufacturing and/or quality control activities.

6.0 THE FUTURE OF THE CENTRE

6.1 Potential areas for expansion

The PTSC'S future endeavours should include a review of its original goals and objectives. A comprehensive strategic plan should be developed to propel the Centre into even higher ranks. The Centre should strive to be perceived as a leading regional organization geared to the development of human resources in the different aspects of quality assurance for the pharmaceutical manufacturing sector. In addition, the Centre could aim to develop a data base which could serve as a regional reference centre for Thailand and its neighbouring countries. The Centre could also become the source of know-how for the implementation of similar programs in the region.

A significant number of women are present in the Thai pharmaceutical industry. It is necessary therefore, that the centre take the initiative to develop specific training activities for women. Training should aim at developing the necessary skills (management and technical knowledge) which will enhance and increase the participation of woman in the Thai pharmaceutical industry. As a first step towards the development of these specific training programs, the PTSC should identify the needs and requirements for professional and technical development of the female work force.

As the Thai pharmaceutical industry develops, the need will be increased for training and for technical assistance in implementation and maintenance of quality assurance activities. This will open a window of opportunity for the PTSC to expand their activities in the areas of technical assistance to companies which require this type of service. The centre should develop a strong technical team of

professionals and technical personnel for provision of the necessary technical assistance for the region.

The PTSC training programs have proven to be successful for the Thai pharmaceutical manufacturing sector. As a result, the centre should develop comprehensive training materials which are necessary for the delivery of effective training programs and educational workshops.

Collaboration and harmonization between government institutions (such as the FDA) and universities and the pharmaceutical industry is the foundation for the present success of the centre. As a result, the centre should continue to open more avenues in order to increase harmonious relationships with other national and international institutions.

Although the training programme was developed in a Thai context, the training materials could be applied to other countries in the region. So far, the government of Laos is interested in a form of technical collaboration with the PTSC for technical assistance and training in quality assurance for its pharmaceutical sector. At present Laos appears to be involved in preliminary discussions for a technical cooperation program between the government of Laos, the World Bank and the Canadian International Development Agency (CIDA). This program is examining the possibilities of developing an institution similar to the PTSC in Laos.

The diffusion of the Centre's activities in particular the HRD programs across neighbouring countries is as important as the training activities themselves. The PTSC should design a strategy geared to creating awareness in the regions for the centre's present activities and future programs. For the period of 1993 and 1994 the Centre had developed a tentative workplan which is presented in Table 12.

Table 12

The PTSC's Tentative Workplan for 1993 and 1994

Stability workshops/Seminar	1993				1994			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Stability workshops/Seminar	-	x	-	x	-	x	-	x
Stability Co-Service	-	-	-	x	x	x	x	x
Analytical Testing Services, Raw Material and FinishProducts	x	x	x	x	x	x	x	
Training of Analyst Testing/GLP	-	-	x	x	x	x	x	x
GLP workshop/Training	-	-	x	x	x	x	x	x
Miscellaneous Service (Calibration, Plant visits)	x	x	x	x	x	x	x	x
SOP working groups (Training the trainers)	x	x	x	x	x	x	x	x
SOP workshops Middle management	x	x	x	x	x	x	x	x
SOP-Hands-on Training (Tailor to companies) Supervisors & Seminar operator PTSC	x	x	x	x	x	x	x	x
Validation working groups	x	x	x	x	x	x	x	x
Seminar- Upper- Middle Management	x	-	x	-	x	-	x	-
Workshop- (Validation)	-	x	x	x	x	x	x	x
Hands-on-training	-	-	-	-	x	x	x	x
Update Training on Validation	-	-	-	-	x	x	x	x

6.2 Needs and Requirements

The following topics will be reviewed as to current requirements and future needs for the Centre:

- Physical Facilities
- Training Activities
- Human Resources
- Equipment & Accessories
- Financial Support
- Strategic Planning
- Development of a Comprehensive Data Base
- Collaborative Efforts
- Social Environment

In order to be able to achieve its new objectives the PTSC will be required to incorporate the following points:

Physical Facilities - The Centre needs to expand its current facilities in order to become more independent with respect to space needed for training activities, space required for a data base and for some additional office space.

Training Activities - The Centre needs to develop the additional audio-visual material which will serve to complement present and future training activities. This material should be developed locally in order to incorporate elements relevant to the Thai culture. The audio-visual material should be complementary to currently

existing materials and should be organized into comprehensive packages to assure continuity and sustainability.

Human Resources - The development of necessary human resources is the major key for the success and longevity of institutions such as the PTSC. The Centre should identify the skill requirements associated with present and future needs. These requirements should become an integral part of the overall planning and strategy of the Centre. The Centre should continue to seek alliances with local and international institutions who have the necessary resources required to complement the Centre.

Equipment & Accessories - The Centre is equipped with some modern analytical equipment for conducting analytical testing of most pharmaceutical raw materials and some dosage forms. However, it is necessary to consider assistance in the procurement of additional equipment and critical spare parts. This would help to guarantee the operation of laboratory services for the time necessary to generate the resources needed to achieve financial independence and

sustainability. A detailed list of suggested equipment and accessories is presented in Appendix ix.

Financial Support - Even though the Centre has been able to generate some local revenue from training and technical services activities, it is evident that the current administrative and technical infrastructure is insufficient for the development of the necessary steps required to generate the required revenue. This sensitivity should be considered by UNIDO in order to support the Centre with the required tools to develop the necessary approach to seek financial independence.

Strategic Planning - It is essential that the Centre be able to consider mid and long term activities. This exercise should be incorporated as an important dynamic instrument to aid in planning the centre's future activities.

Development of a Comprehensive Data base - Reliable statistics and current information on local, regional and global trends in the pharmaceutical industry are necessary and important in order to provide a context and a reference point for training

activities and technical support for the pharmaceutical industry. As a result, is necessary for the centre to organize a comprehensive data base, which will provide direct access to the necessary information. As well, the centre should have a comprehensive plan to disseminate specific information on quality assurance to the national and regional pharmaceutical industries.

Collaborative Efforts - The centre should continue to collaborate with the FDA in the development of policies related to quality assurance for the pharmaceutical industry. This should include some advice on policies and technical assistance needed to sustain the capacity of the reference centre for specific quality assurance and/or technical activities.

Social Environment - The importance of having a social environment conducive to enhancing equal participation of women in the pharmaceutical industry labour force should be stressed as being one of the focal points for the Centre's future activities.

7.0 RECOMMENDATIONS

In order to provide a framework for these recommendations, the technical consultant organized this section as follows: the facilities and equipment; human resources; the programs; the strategic approach; human resources development; and the project.

These recommendations are directed to the Pharmaceutical Technology Service Centre as well as to the UNIDO project coordination team.

THE FACILITIES AND EQUIPMENT

The current physical facilities of the Centre are very limited. Consideration should be given to expand the existing facilities by the incorporation of adjacent space to accommodate an environment for training activities as well as a suitable space for a library and data base. The incorporation of this additional space will enable the rearrangement of the existing offices so that proper space could be allocated to the Centre's different activities.

Consideration should be given to reorganize the laboratory facilities to facilitate "hands on" training activities, in addition to the analytical testing and research and development activities currently being performed in the laboratory.

HUMAN RESOURCES

The roles and responsibilities of the permanent and associated staff should be reviewed, and if necessary, updated. The roles and responsibilities should be clearly outlined in order to facilitate the management of the Centre. Also the project should document all

of the requirements for human resources, both in terms of present and future activities (for example the role of the national experts).

In order to ease the administration burden of the director of the Centre, the board should consider the identification and appointment of an assistant to the director to be responsible for the administration activities of the Centre. This position should report to the director.

The associate UNIDO expert should concentrate time and effort in assisting the PTSC in activities already identified as the Centre's objectives and priorities.

UNIDO should consider continuing to assist the centre with short-term international experts on SOP, GMP and process validation rather than providing assistance in the areas of ventilation and air systems as originally planned at the project inception. In addition, it appears that Thailand already has a significant pool of national expertise in ventilation and air conditioning.

THE PROGRAMS

The PTSC existing strategy for the development of human resources in quality assurance has been effective. The implementation of a step-by-step approach to 'training the trainers' by means of working groups and workshops has been successful (see Appendix x for a list of companies who have participated in PTSC activities). Emphasis should remain on the 'hands on' approach to working group participation in the subjects of SOP's, validation, GMP, and GLP, in order to promote quality assurance in the workplace. At present, the credibility of the Centre is well established and the level of expectations among the Thai pharmaceutical industry is high. Therefore, the Centre should continue with this approach for the implementation of current and future activities.

Consideration should be given to strengthen and expand the Centre's current activities such as the development of human resources in quality assurance activities, technical assistance in GMP implementation and laboratory support services for analytical testing.

The presentation of technical seminars to the pharmaceutical community should also continue as a complement to the human resources development activities of the Centre.

Plant visits to selected companies gives a good opportunity to PTSC personnel to continue to assess the local working environment in the Thai pharmaceutical industry. It also provides a good opportunity for interaction with company management and technical staff and maximizes the exchange of technical advice. These visits also help to update the Centre as to the industry's needs and requirements. The PTSC should also implement a service to pharmaceutical manufacturers to assist in the implementation of self inspections and trouble shooting programs.

The PTSC should design and incorporate a monitoring and evaluation system for the activities of the Centre. The results of these evaluations should serve as a guide for any necessary adjustments to improve and/or maximize the Centre's activities.

Consideration should be given to the incorporation of specific programs on communications and management skills as a complement to current human resources development activities.

The Centre should consider the establishment of a data base on pharmaceutical quality with comprehensive material on all quality control and improvement activities for the pharmaceutical industry.

The Centre should consider the incorporation of a program for women in the Thai pharmaceutical industry. A preliminary need assessment study should be conducted to identify the structure of the Thai pharmaceutical industry and quantify the participation of women. Consequently the Centre should establish a special

committee to formulate the necessary projects to create the proper environment for the development of the necessary skills of women in order to increase the level of participation in the industry.

THE STRATEGIC APPROACH

A strategic approach to the future activities of the PTSC could be the key for achieving sustainability and expansion of the Centre's current activities. Therefore it is appropriate, that the Centre review their strategy and formulate a plan of action that responds to the needs of the national and regional pharmaceutical industries.

The collaboration of the Centre with the private sector, non-governmental organizations (NGO's), educational institutions and government organizations should continue. It is the Centre's neutrality that is a corner stone for acceptance and universal success. This, coupled with the technical capability and ability to deliver could be the key for the growth and sustainability of the institution.

HUMAN RESOURCES DEVELOPMENT

The single most important factor in the implementation of quality assurance is the development of human resources.

Human resource development (HRD) includes education, training, research, institutional development and communication. This leads to the evolution of values, attitudes, motivation, organization and mobilization of people in pursuing higher levels of quality in the manufacture of pharmaceuticals in Thailand. The Centre should continue to provide assistance in all these areas.

The Centre should incorporate managernent activities which complement the implementation of GMP such as planning and organizing activities and inventory management.

Particular attention should be given to the development of hands-on training programs to assist the pharmaceutical companies to reach the operational level. Also attention should be aimed at increasing effective participation of company personnel since a system requires people to make it work.

The PTSC should organize a comprehensive selection of audio-visual materials on quality assurance, GMP, and Q.C. to be used in the implementation of training and educational activities.

THE PROJECT

It is important that UNIDO continues to support the activities of the PTSC. UNIDO also should consider supporting the Centre's new initiatives such as the regionalization of the Centre's activities and equity development.

The PTSC should continue to act as the Centre for knowledge and expertise in quality assurance for the pharmaceutical industry, with special attention to human resources development.

UNIDO's input of technical expertise as well as its aid in equipment procurement and project management has been essential in establishing the Centre. This, coupled with the local input provided by the TPMA has enabled the Technical Service Centre to achieve its initial objectives as planned at the project's inception.

It is recommended that UNIDO considers using this model formulated in Thailand for PTSC for use in other countries. In addition, to help ensure the financial viability and sustainability of the PTSC in Bangkok, it is suggested that efforts are made by the PTSC to expand its activities to other countries with similar pharmaceutical experiences.

Appendix i:

The Technical Mission - Terms of Reference

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION

dr.A.Atger 15.1.92

. . . . . JOB DESCRIPTION
DP/THA/88/018/11-02 Rev.

Post Title : Quality Assurance Expert

Duration : 3 months

Date required : ASAP

Duty Station : Bangkok, Thailand

Purpose of the Project : To develop the Pharmaceutical Industry in Thailand

Duties :

1. The expert should work with the Chief Technical Adviser to set up the office and the "Service Center", especially in the concern of the laboratory
2. Coordinate with the Service Center for training arrangement.
3. Meet and discuss with FDA, FTI, TPMA and University Authorities
4. Provide training to the Service Center staff, in the area such as GMP requirements.
5. Arrange and conduct training offered to the Service Center in the area such as Calibration and Validation Technique, S.O.P. and Document Preparation, Auditing, Quality Control, Quality Assurance Management.
6. Provide technical advise and consultation to pharmaceutical factories regarding GMP.
7. Conduct a specific training and advice the manufacturers of sterile products.
8. Prepare separate comprehensive manuals for the application of GMPs and SOPs.

Qualifications : Pharmacist with extensive (10-15 years) experience as Quality Assurance Manager.

Language : English fluently written and spoken

Background information : The main problems confronting the pharmaceutical industry in Thailand are :

- limited pharmaceutical manufacturing technology
- lack of know-how to improve the product quality, and
- lack of skilled personnel in certain aspects of manufacturing.

Furthermore, there is no engineering consultancy in the country who can advice on plant layout, construction techniques, material of construction and selection of equipment and facilities in order to comply with the current Good Manufacturing Practices.

The FDA, established the Quality Improvement Team (QIT) in 1987. The QIT is composed of representatives from inspection, Technical Division of FDA, Drug analysis Division, TPMA, Pharmaceutical Association of Thailand, Government Pharmaceutical Organization and Academicians. The QIT has so far, visited over 60 factories. Majority of the 60 factories are believed to be in need of technical assistance.

The projects expects to have trained a large number of executives and technical staff of various pharmaceutical companies on CGMP. These companies will also greatly benefit from the services which are to be made available in the newly established Service Center which will charge appropriate fees for services rendered for operating /maintenance costs of center.

Therefore, hence forth the FDA can be more strict in imposing the requirements of CGMP rules after being given the FDA the period to adjust may have to cease their operations. At this stage, the estimated percentage of those manufacturers who would comply with CGMP is 52% of the 192 manufacturers.

Appendix ii:

A Cost Effective Approach to Quality Assurance Management and Developments and Limitations of Biotechnology Research

STRATEGIC PLANNING

TO IMPLEMENT QUALITY ASSURANCE

IN A COST-EFFECTIVE WAY

- **INFORMATION ANALYSIS**
- **DEVELOPING A STRATEGY**
- **IMPLEMENTATION**

INFORMATION ANALYSIS

- RESEARCH FACTUAL INFORMATION ON Q.A.
- ESTABLISH A TASK FORCE AND/OR A PROJECT TEAM
- DETERMINE AND ASSESS CURRENT SITUATION
- IDENTIFY KEY PROBLEMS
- DETERMINE PRIORITIES
- DRAFT TENTATIVE PLAN

DEVELOPING A STRATEGY

- SET CLEAR OBJECTIVES
- ELABORATE A BASIC STRATEGY
- IDENTIFY AND DETERMINE ORDER OF ACTIVITIES
- ASSESS YOUR RESOURCES
- ESTABLISH A PROPER BUDGET
- DEVELOP A PLAN OF ACTION
  - IDENTIFY ACTIVITIES INTERACTION
  - GROUP ACTIVITIES BY SIMILARITY
- SET PROPER CONTROLS AND MONITORING SYSTEM
- SET AN ORGANIZATION STRUCTURE (AUTHORITY AND RESPONSIBILITY)

IMPLEMENTATION

- REVIEW PLAN OF ACTION
- MAKE NECESSARY ADJUSTMENTS
- LAUNCH PLAN (STRUCTURE)

ORGANIZATION

- PROVIDE DEFINITION, ORDERLINESS AND OBJECTIVITY
- ENABLE THE UNDERSTANDING OF ROLES, DUTIES AND RELATIONSHIPS
- ELIMINATE REDUNDANCIES
- FACILITATE COMMUNICATION
- PROVIDE SENSE OF BELONGING
- FACILITATE MONITORING AND CONTROL

PLANNING

- DETERMINE CLEAR OBJECTIVES BY PRIORITY
- IDENTIFY PROCEDURES
- ESTABLISH COMMUNICATION NETWORK
- ESTIMATE COST AND BENEFITS
- ASSESS SUPPORT SYSTEMS REQUIRED
- ESTABLISH QUALITY CONTROL PROCEDURES TO ENSURE THAT THE OBJECTIVES ARE MET
- EVALUATE ALTERNATIVES
- ESTABLISH A PROMOTION ACTIVITY (TO CHANGE ATTITUDES)

QUALITY ASSURANCE BENEFITS

- INCREASE PRODUCTION QUALITY
- MINIMIZE DOWN TIMES
- INCREASE PRODUCTIVITY
- REDUCE REJECTIONS
- REDUCE REWORK
- INCREASE SAFETY
- IMPROVE INVENTORY CONTROL
- OPEN NEW BUSINESS OPPORTUNITIES
- ASSIST IN PROCESS OPTIMIZATION

ACHIEVING THE RIGHT BALANCE

- MANAGEMENT vs ADMINISTRATION
- EFFECTIVITY vs EFFICIENCY
- OVERSEEING vs DOING
- INNOVATING vs STATUS QUO

DECREASE THE WORRY OF UNEXPECTED MANUFACTURING AND TESTING HICCUPS

DEVELOPMENT OF THE QUALITY ASSURANCE SYSTEM

- HIGH QUALITY HUMAN RESOURCES
- CLEAR STRATEGY
- EFFECTIVE ORGANIZATIONAL STRUCTURE
- CLEAR OBJECTIVES
- EFFECTIVE CONTROLS

RESPONSIBILITIES OF QUALITY ASSURANCE TEAM/GROUP/DEPARTMENT

- DEFINE COMPANY'S GMP STANDARDS
- MONITOR COMPLIANCE (AUDITS)
- RECOMMEND CORRECTIVE ACTION
- SUPPORT TRAINING ACTIVITIES

RESPONSIBLE GROUP SHOULD HAVE DIRECT REPORTING LINE WITH MANAGEMENT

ORGANIZATIONAL CONCEPT OF THE QUALITY ASSURANCE GROUP SHOULD BE COMPATIBLE WITH THE COMPANY STRUCTURE.

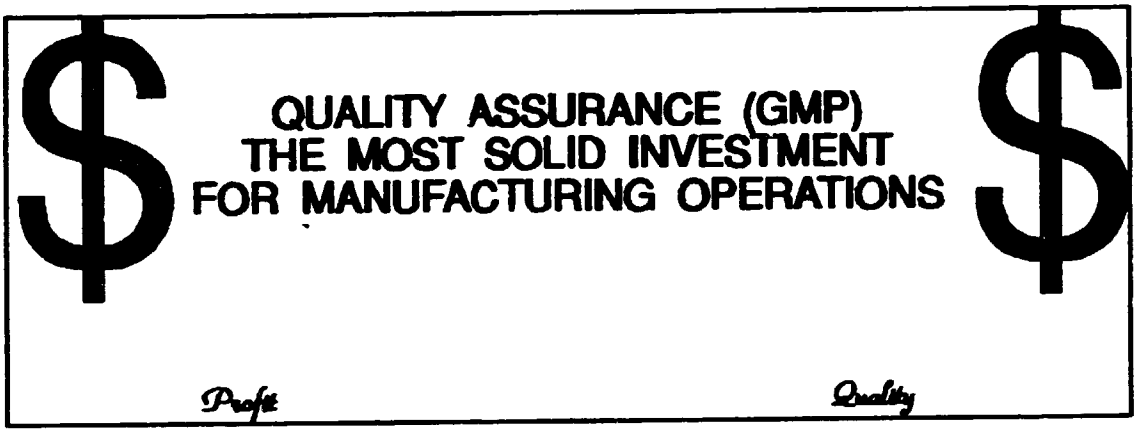
MANAGEMENT COMMITMENT IS ESSENTIAL FOR THE IMPLEMENTATION OF A COMPREHENSIVE QUALITY ASSURANCE SYSTEM.

SUMMARY

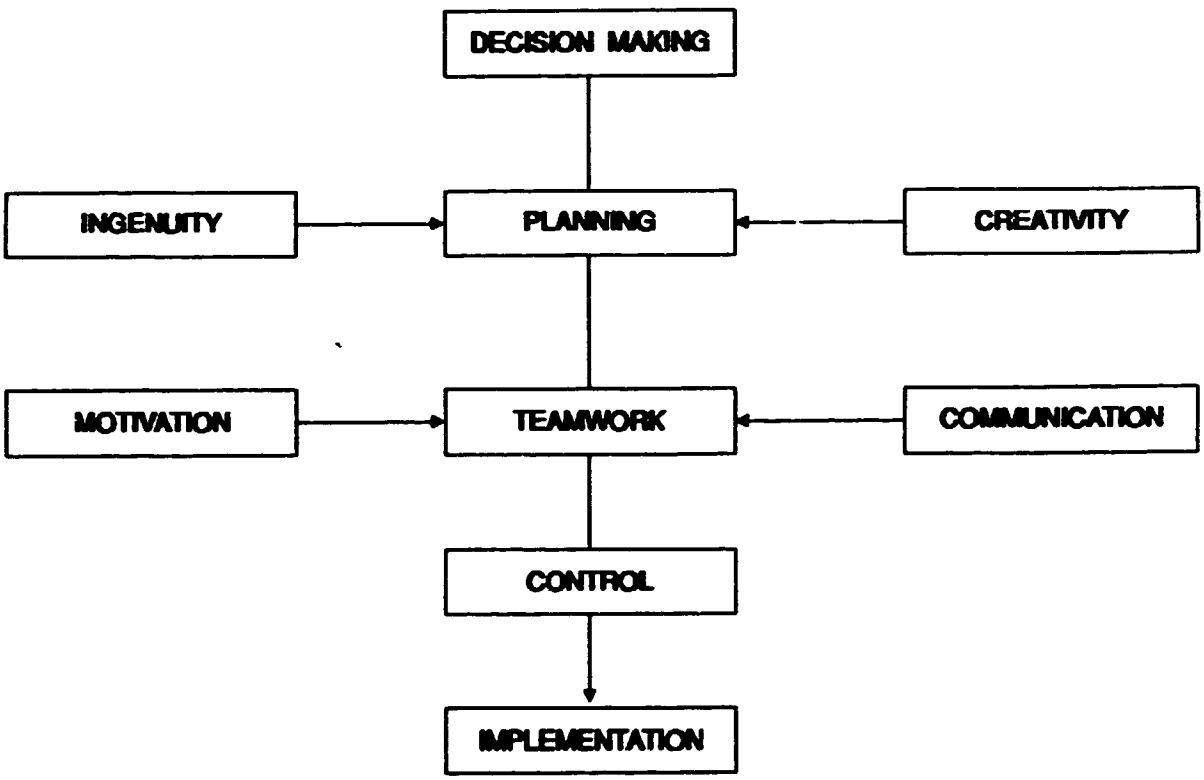
- A QUALITY ASSURANCE PROGRAM IS ESSENTIAL IN THE MANUFACTURE OF PHARMACEUTICALS.
- IMPLEMENTATION OF A COMPREHENSIVE QUALITY ASSURANCE PROGRAM IN A MANUFACTURING PROGRAM SHOULD BE STEP-BY-STEP.
- THE QUALITY ASSURANCE PROGRAM SHOULD BE PARTICIPATORY.
- DEVELOPMENT OF COMPANY HUMAN RESOURCES IS THE CORNER STONE OF A SUCCESSFUL IMPLEMENTATION.
- PROPER PRIORITIZATION IS ESSENTIAL FOR EFFECTIVE IMPLEMENTATION AND PROPER COST MANAGEMENT.
- SELECT PEOPLE THAT WANT TO LEARN IN YOUR COMPANY AND EDUCATE THEM.

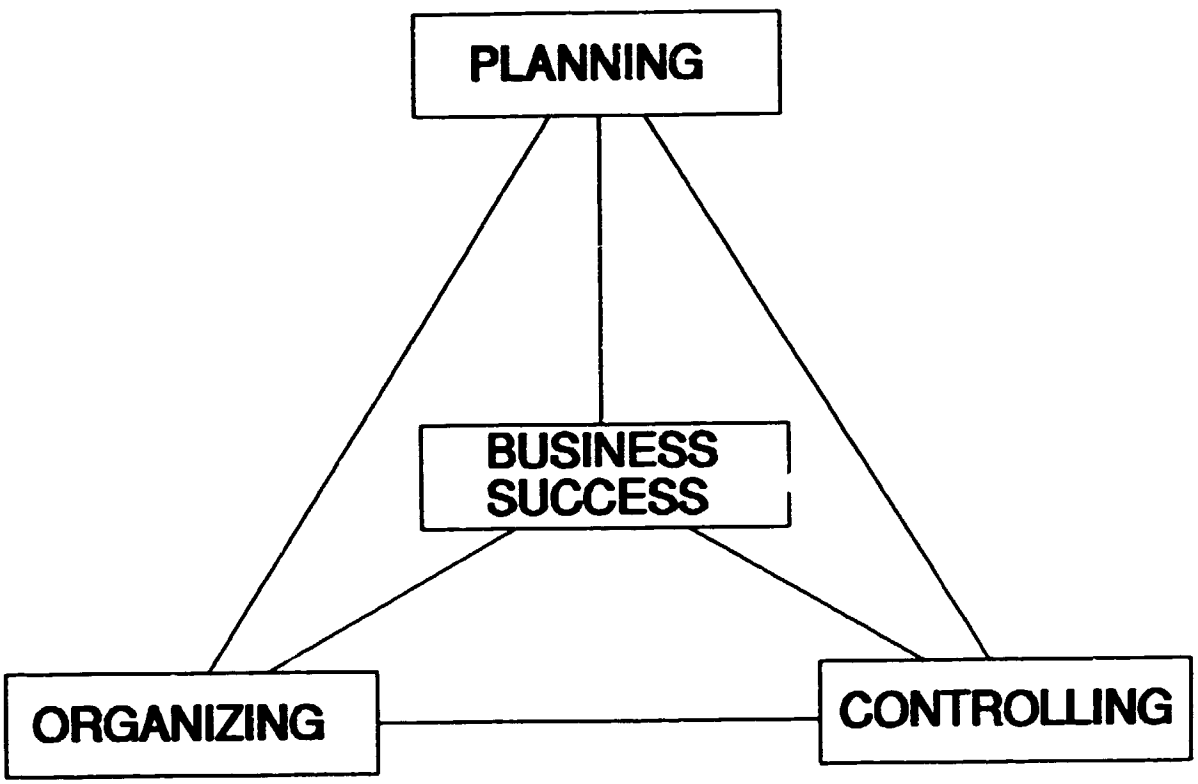
AN INVESTMENT IN QUALITY ASSURANCE WILL INSURE THE SUCCESS OF YOUR MANUFACTURING BUSINESS

DON'T JUST TRAIN YOUR PEOPLE - EDUCATE THEM


$
QUALITY ASSURANCE (GMP)
THE MOST SOLID INVESTMENT
FOR MANUFACTURING OPERATIONS
$
Profit
Quality

A REALISTIC WALK TO SUCCESSFUL MANAGEMENT




PLANNING
BUSINESS SUCCESS
ORGANIZING
CONTROLLING

STERILITY TESTING

ESTIMATED COST

STANDARD STERILITY TEST	=	**$ 100**
FIRST STERILITY RETEST	=	**$ 300**
SECOND STERILITY RETEST	=	**$1,000**

100 STERILITY TEST PER ANNUM (\$100 EACH)	=	\$10,000	
100 STERILITY TEST PER ANNUM	=	\$10,000	
+ 5% FIRST RETEST \$300 EA		\$ 1,500	
+ 5% SECOND RETEST \$1000 EA		\$ 5,000	
		\$16,500	(6,500)
100 STERILITY TEST PER ANNUM	=	\$10,000	
+10% FIRST RETEST \$300 EA		\$ 3,000	
+10% SECOND RETEST \$1000 EA		\$10,000	
		\$23,000	(13,000)

DEVELOPMENTS AND LIMITATIONS OF BIOTECHNOLOGY RESEARCH

Manuel M. Carpio
UNIDO Technical Consultant.

Unprecedented developments in the field of genetic engineering and biotechnology during the past decade have generated great expectations in the industrial application of the future products from these high-tech technological fields. The applications range from the agricultural, animal and human health, as well as the environment and the energy sector.

One of the current limitations in the fast development of new biotechnology products are the large number of patents and intellectual property issues involved on known procedures that are applicable to most leading-edge techniques, and know-how involved in the manufacture of new biotech products. Another limitation, is the huge gap that exist between the research and developments at bench level, and the required know-how for the industrial implementation of an industrial model on a cost effective basis. The latter also include the lack of sufficient biotechnology personnel with experience and knowledge of the biotechnology principles and enough experience in industrial technology including basic knowledge of the regulatory process that are essential for the registration for biotechnology products.

The current fields of biotechnology research could be differentiated in the following groups:

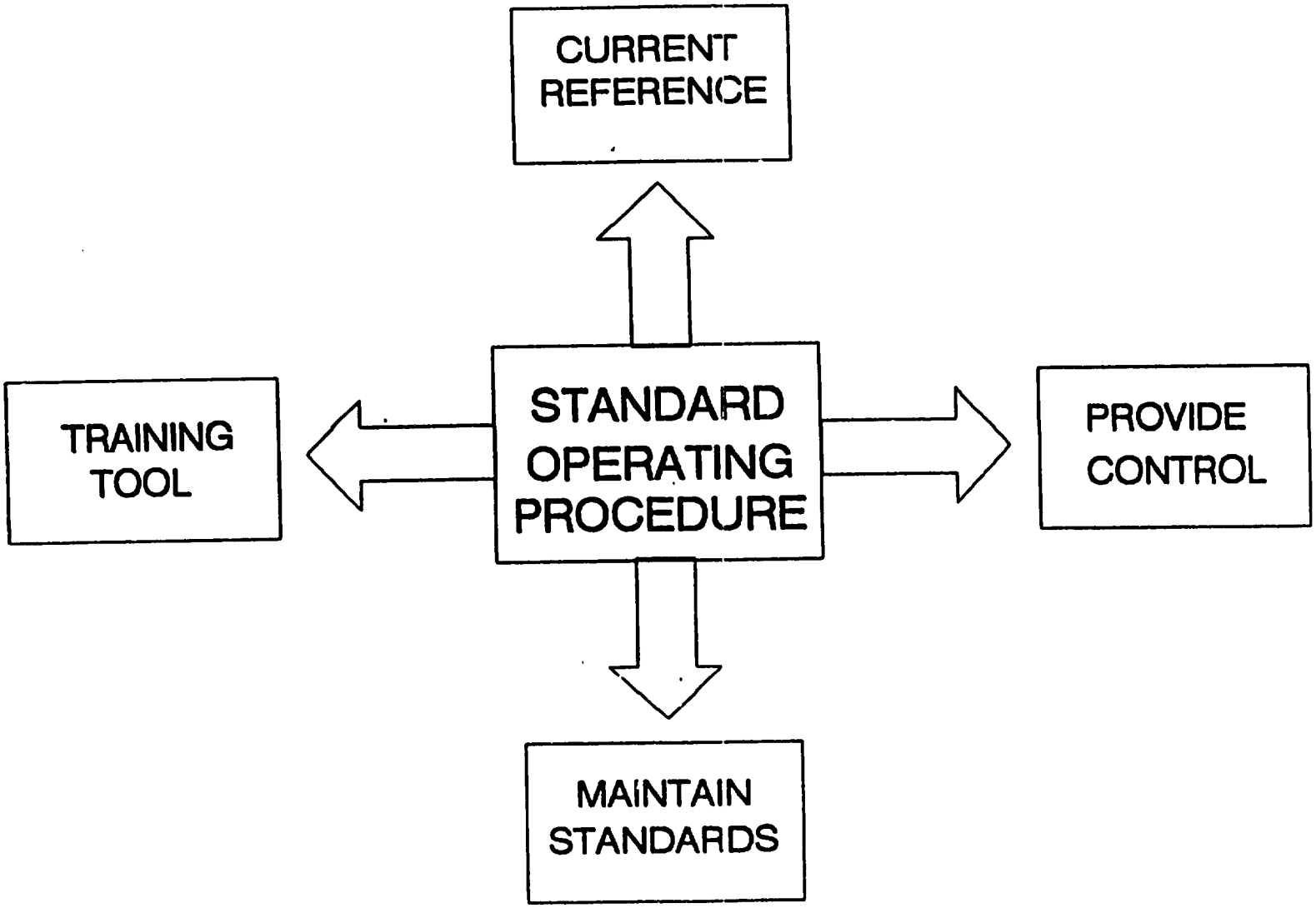
- Research in human genes
  - Oncology
  - Diagnostics
  - Therapeutics
- Research in animal genes
  - Animal Health
  - Diagnostics
  - Modification of development (Production)
- Research in plant genes
  - resistance (gene-transfer)
  - modification of development
- Research in microorganism genes
  - Expressions
  - Transformations
  - Carriers

It is very difficult to predict the impact that biotechnology will have in the major fields of influence such as agriculture, health and energy. However, we can be sure that biotechnology products will play a pivotal role in increasing the efficiency of current systems and creating new contemporary biotechnology procedures that will respond to new industrial needs with a significant global socio-economic impact.

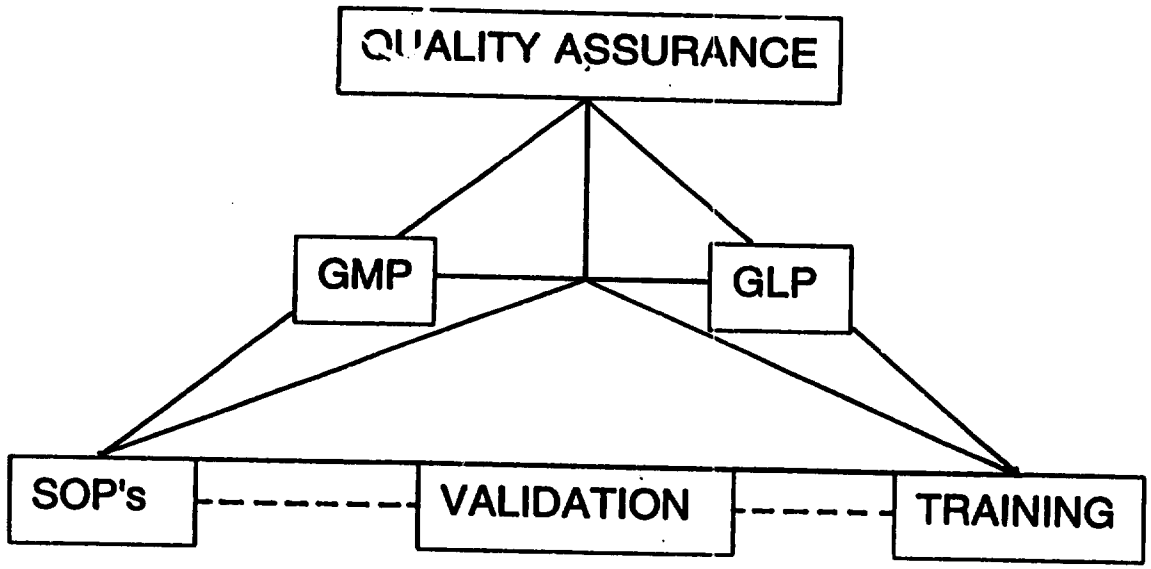
Appendix iii:

Audio-visuals and Handouts used in Process Validation Workshops

Standard Operating Procedures



The Quality Assurance Triangle



VALIDATION OF PHARMACEUTICAL OPERATIONS

PRESENTED BY

THE PHARMACEUTICAL TECHNOLOGY SERVICE CENTRE

Faculty of Pharmaceutical Sciences Chulalongkorn University

March 1993

INTRODUCTION

Validation is an important aspect of Good Manufacturing Practices. It means to ensure by systematic and documented procedures that the manufacturing process is reliable and reproducible and it consistently produces a product meeting specifications and other quality attributes. It is safe to say that the quality assurance concept is meaningless without validation.

The dictionary meaning of validation is "A PROCEDURE TO ENSURE THAT A PROCESS IS FIT FOR WORK".

In general all the supporting data collected by validation of a product and/or process helps to build in the overall quality and reduce defects, rejects and recalls, so that the end result is higher quality products.

WHY VALIDATION

The need to validate responds to the following reasons:

- To obtain proper documentation and technical evidence to give reasonable assurance that the equipment and/or process is performing to the required specifications.
- To identify critical process parameters and establish an acceptable range for these parameters, and provide a means by which to correct them.
- To reduce rework in the manufacturing operations.
- To reduce in-process losses.
- To minimize rejects and recalls.
- To increase process optimization.
- To upgrade manufacturing standards.
- To enhance equipment performance.

VALIDATION OVERVIEW

Validation plays an important role during the design of new facilities and/or the expansion of existing ones. In general there is a correlation between the quality of design and the

quality of manufacturing. Furthermore the validation of the design for a manufacturing process is an important element for license.

Validation of existing facilities requires a complete understanding of the manufacturing process,testing procedures and the regulations for the process and products manufactured in the facility.

There are many kinds of elements which influence the manufacturing process and manufacturing quality of the product, these elements are:

- Building and equipment.
- Laboratory services (water and air-systems).
- Materials and supplies.
- Personnel.
- Manufacturing method.
- Quality testing.
- Packaging.
- Storage conditions.

How to minimize and control the fluctuation of these elements is one of the objectives of validation.

In order to validate these elements the following points should be considered:

a) Determine the quality level of each of the elements.

b) Each element should be qualified in comparison with a predetermined standard.

c) Each element should be tested in its operational state and confirmed to be satisfactory in its function.

d) Each element should be challenged to assure performance in the worst case scenario.

e) Test results should be carefully recorded and analyzed.

The main purpose of validation is to prevent error, mix-up and prevent deterioration of an established quality assurance system in addition to achieving higher quality products and higher safety levels in the manufacturing process.

GLOSSARY

VALIDATION	Attaining sufficient evidence and documentation to give reasonable assurance that the process does what it is supposed to do.
QUALIFICATION	The approval that a particular component is suitable for the process.
CHALLANGE	Tests to determine the limits of capability for a component of the process.
CALIBRATION	Adjustment of the measuring device according to a recognized standard.
QUALITY ASSURANCE	The activity of providing the necessary evidence needed to establish confidence that the qualified function performed is adequate.
QUALITY CONTROL	The regulatory process through which actual quality performance is measured and compared with standards,and provides a mechanism to act on the difference.
QUALITY FUNCTION	The entire production activities related to product quality.
WORST CASE	The highest or lowest value of a given control parameter actually evaluated in a validation exercise.
PROVEN ACCEPTABLE RANGE (PAR)	All values of a given control parameter that fall between proven high and low worst case conditions.
EDGE OF FAILURE	A control parameter value which, if exceeded, means an adverse effect on the state of control and/or fitness for use of the product.
MONITORING	Carring out measurements and/or observations of one or more characteristics of any situation.
PROCESS VALIDATION	To prove that the process is doing what it is supposed to do.
PROCESS OPTIMIZATION	Achieving maximum efficiency while maintaining quality standards.

PROCESS VALIDATION	Establishing documented evidence that the process does what it is purported to do.
PROSPECTIVE VALIDATION	Establishing documented evidence prior to process implementation that a system does what it purports to do based on a preplanned protocol.
CONCURRENT VALIDATION	Establishing documented evidence that a process does what it purports to do based on information generated during actual implementation of the process.
RETROSPECTIVE VALIDATION	Establishing documented evidence that a system does what it purports to do based on review and analysis of historical information.
VALIDATION CHANGE CONTROL	A formal monitoring system by which qualified representatives of appropriate disciplines review the proposed or actual changes that may affect the validation status and cause corrective action to be taken which will ensure that the system retains its validated state of control.
REVALIDATION	The repetition of a validation process or a specific portion of it.
VALIDATION PROTOCOL	A document with experimental plans that when executed as intended to, produces documented evidence that the system has been validated.
CONTROL PARAMETERS	Those operating variables that can be assigned values that are used as control levels.
OPERATING VARIABLES	All factors including the control parameters, that may potentially affect the process state of control/or fitness of use of the end product.
STATE OF CONTROL	A condition in which all operating variables which can affect performance remain within such ranges, so that the system or process performs consistenly as intended.

INSTALLATION QUALIFICATION	Documented verification that all key aspects of the installation adheres to the appropriate codes and approved design, and that the manufacturer's recommendations are suitably considered.
OPERATIONAL QUALIFICATION	Documented verification that the system or sub-systems performs as intended throughout all of the anticipated operating ranges.
CHANGE REVALIDATION	Revalidation whenever a significant change is made which modifies the standard operating procedure (S.O.P.) and consequently affects the desired properties of the product.
PRODUCT CHANGE	Change in the physical characteristics of a raw material that may affect the mechanical properties of the product (i.e. density of the powder, viscosity of a liquid, etc.).
COMMODITY CHANGE	Change in the nature of the packaging component (production components) that can bring modification to the operation of the equipment and to the stability of the product.
PROCESS CHANGE	Changes in the process that may affect subsequent stages of manufacture and the quality of the product.
EQUIPMENT CHANGES	Changes in the equipment that are likely to have a major effect in the process and the product. Some part replacements can have a significant impact in modifying the characteristics of the equipment (i.e. belts from belt driven pumps etc).
PERIODIC REVALIDATION	Validations at regular intervals designed to detect the gradual drift of standard procedures.

A CHECKLIST FOR VALIDATION WORKING GROUP(S):

The following are required:

1.- A brief description of product processes.

2.- Product flow chart.

3.- Identification of critical steps(pass/failures).

4.- Do you have a SOP for the procedure.

5.- Review of SOP.

6.- Do you have regular preventive maintenance programs for the equipment involved in the process.

7.- Frequency of the process.

8.- What are the critical variables.

9.- What are the acceptable variables (quality acceptance criteria).

10.-How you presently control the critical variables.

11.-Qualifications of personnel involved in the operation.

12.-Capacity calculations.

13.-Equipment description.

14.-Current documentation.

VALIDATION OF SAMPLES

- To accept an individual SAMPLE
- To qualify authenticity of the sample
- To assure proper sampling procedures are followed
- To comply with GMP
- To minimize error

VALIDATION OF METHODOLOGY

- To assure acceptance of formalized procedure
- To standardize methodology
- To assure suitability of method
- To assure consistency in methods
- To minimize error

CALIBRATION

- To compare an instrument's measurement against another recognized standardized instrument
- To learn of possible deviations
- To qualify the instrument
- To eliminate or minimize bias in a measurement process

ALL ASPECTS OF THE MEASUREMENT PROCESS NEED TO BE CALIBRATED

REQUIREMENTS FOR CALIBRATION

- Proper procedures
- Proper accurate standards
- Trained personnel
- Proper documentation
- A certification and a calibration sticker

FREQUENCY OF CALIBRATION

- Manufacturer's recommendations
- Experience of the laboratory
- Q.A. established requirement

VALIDATION OF DATA

- Proper identification(comprehensive codification)
- Acceptance criteria
- Validation methodology
- Q.A. established requirement

HANDLING AND RECEIVING SAMPLES

RECEIPT AND RECORDING SAMPLES

- Labelling
- Receipt
- Recording

PROCESSING SAMPLES

- Distribution
- Identification throughout the distribution process
- Reconciliation
- Date and quantity
- Receiving

STORING SAMPLES

- The coding system
- Expiry dates
- Storage date or disposal
- Receiving initials

SAMPLES FOR VALIDATION

- Size
- Identification
- Representative samples
- Protection
- Preparation
- Suitable sub-sampling
- Retention
- Suitable processing
- Proper storage
- Proper distribution

PRECAUTIONS TO BE USED IN SAMPLING

- Prepare a written procedure for sampling
- Prepare a sampling program
- Evaluate quantity requirements
- Evaluate sampling uniformity and distribution
- Evaluate protection of integrity
- Evaluate an identification system
- Evaluate transportation systems and storage
- Evaluate distribution systems

KEY POINTS FOR PROCESSING

MATERIAL ORDERING

Proper work order
Supply plan for materials
Establishment of master batch card
Accuracy of bill of materials
Vendor approval program if possible

MATERIAL RECEIVING

Control receiving area (central warehouse)
Receiving protocol
Proper identification and storage
Traceability of vendor product identification

MATERIAL SAMPLING AND TESTING

Sampling responsibility of Q.A/Q.C.
Proper quarantine of materials on test
Proper release system
Comprehensive labeling

DISPENSATION

Proper dispensation system
Proper dispensation facility
Dispensation certification
Calibration of scales and balances
Proper identification and labeling

GRANULATION

Proper procedure
Proper inspection systems
Proper facilities
Proper equipment
Proper reconciliation system
Proper blending analysis

HISTORICAL DATA

ACTIVE DRUG DATA

1- PURITY

2- PARTICLE SIZE AVERAGE

3- PARTICLE SIZE DISTRIBUTION

4- MOISTURE CONTENT

TABLET CHARACTERISTICS

1- CONTENT UNIFORMITY

2- DISSOLUTION

3- TABLET WEIGHT

4- TABLET HARDNESS

5- TABLET GAUGE

PROCESS VARIABLES

1- FINISHED GRANULE WEIGHT

2- FINISHED COMPRESSING YIELD

3- COMPRESSING REJECTS

PACKAGING VARIABLES

1- PACKAGING YIELD

2- PACKAGING REJECTS

3- PACKAGING LINE

4- PACKAGING SIZE

NOTE: Use data from as long a production period as possible.
Try to include data from rejected batches if possible.
Try to evaluate variation within the batch.
Accompany the analysis with a process review, GMP compliance, product specification and an SOP.

ASSESSMENT OF DATA

1) DATA STORAGE

- Proper records.
- Proper storage.

2) PROCESS SPECIFICATIONS

- Criteria of assessment.
- Standard or specification.

3) SPECIFICATION LIMITS

4) ACHIEVABILITY

5) PROCESS CHALLENGE

6) DEVELOPMENT STAGE

7) FUNCTIONS INVOLVED

8) STATISTICAL ASSESSMENT OF HISTORICAL DATA

9) CERTIFICATION RESPONSIBILITY

10) REVALIDATION

RECORDING, HANDLING AND VALIDATING DATA

Data should be recorded accurately in a meaningful and accessible manner and in a reliable source. All data should be recorded in the official language.

DESIGN

The following points should be considered for the design of a comprehensive validation program:

- Using a schematic approach to validation
- Preparing a validation protocol covering:
    * Parameters
    * Method and methodology
    * Method of analysis
    * Standards
- The use of standard Operating procedures:
    * Forms
    * Documentation
    * Certification documents
    * Frequency
    * Criteria for acceptance

The protocol design should be :

- Clear
- Coherent in organization
- Easy to implement
- Easy to measure parameters
- Reviewed for compliance with the acceptable criteria.

ORGANIZATION

The establishment of a validation program within the company is recommended.

A validation team should be established with access to the following areas of expertise:

- Testing
  - Physical
  - Chemical
  - Biochemical
  - Microbiological
- Manufacturing
- Research and development
- Engineering and maintenance
- Statistical analysis
- Safety
- Materials management
- Regulatory affairs

There should be a designated officer responsible for quality assurance and/or the validation program. A comprehensive job-description should be developed which incorporates detailed duties and responsibilities.

A proper maintenance program should be established to monitor progress and achievements of the program.

A useful guideline W5 + H

WHO
WHAT
WHEN + HOW
WHERE
WHY

The company's responsibilities are:

Allocation of the necessary resources

VALIDATION OF STERILE PRODUCTS

- THE STERILIZATION PROCESS
  - EQUIPMENT
  - ACCESSORIES
  - PRODUCTION COMPONENTS

- STERILE PROCESS
  - WORKING ENVIRONMENT SANITATION
  - ASEPTIC OPERATIONS

- TECHNICAL PERSONNEL

"PERFECTION IS NOTHING MORE THAT THE COMPLETE ADAPTATION TO THE ENVIRONMENT".

INSPECTION AND REPORTING QUALITY ASSURANCE DEFICIENCIES

Q.A. AUDITS

MONITORING Q.A. DATA

REPORTING Q.A. PROBLEMS

TRAINING Q.A. AUDITORS

SCHEDULING AND FREQUENCY OF INSPECTIONS

- Random
- Upon request

INSPECTION STANDARDS

INSPECTION PREPARATION

INSPECTION PROCEDURE

GUIDE TO QUALITY ASSURANCE PROGRAMS

INTRODUCTION

This guide presents some basic elements of laboratory activities which will assist in the implementation of high quality laboratory practices.

The guide will present a series of check lists for the following aspects:

Data

Working environment

Equipment and instruments

Analytical methods

Glassware

Reagents and solutions

Media

Reference standards

Test Samples

Audits and inspections

DATA

Data should be recorded in the national language in a meaningful, accurate, accessible and reliable manner.

Special attention should be observed in the following aspects:

CONFIDENTIALITY

BOOKS, LOGS, NOTEBOOKS AND RECORDS

MINIMUM ACCEPTABLE PROCEDURES
(Laboratory notebook)

- Format
- Storage and distribution
- Data recording and corrections
- Procedure for data entries
- Data entry validation
  (signatures and initials)

WORKING ENVIRONMENT

The working environment should consider employee safety and suitability of the working activities.

Special attention should be observed in the following aspects:

LABORATORY ENVIRONMENT

- Layout
- Laboratory services
- Cleanliness
- Sanitation

ENVIRONMENTAL HYGIENE AND HEALTH

- Hygiene
- Policies (eating, drinking, smoking)
- Health

CLOTHING

SECURITY

SAFETY

ENVIRONMENTAL MONITORING

EQUIPMENT AND INSTRUMENTS

A comprehensive policy on equipment and instruments is required to ensure the integrity of the results produced by the laboratory.

Special attention should be placed on the following aspects:

DEFINITION OF EQUIPMENT, INSTRUMENTS AND POLICIES

INSTALLATION

PERFORMANCE CHECKS

MAINTENANCE

OPERATIONS

ANALYTICAL METHODS

The analytical method of choice must be selected with a view as to the purpose to which the method is to be put.

Special attention should be placed on the following aspects:

CRITERIA FOR SELECTING A METHOD

- Standard method
- New method

VALIDATING NEW METHODS

- Demonstrate that it is appropriate
- Obtain information on the precision and accuracy of the method (test).

MINIMUM ACCEPTABLE PROCEDURES FOR A NEW METHOD (All non-official methods must be tested and approved)

- Approval must be documented in a written report containing the following sections:
  - Introduction
  - Background
  - Objective
  - Statistical analysis
  - Discussion
  - Recommendations

KEY CONSIDERATIONS

The following attributes should be considered:

- **Reliability**
- **Applicability**
- **Specificity**
- **Detectability**
- **Sensitivity**
- **Accuracy**
- **Precision**
- **Cost**

APPROVAL OF A NEW METHOD

By the originating laboratory:

- **Recovery studies**
- **Authentic samples**

By one or more laboratories:

- **Method transfer (written documentation) for evaluation without further discussions**
- **Collaborative studies**

AUTHORIZATION OF NEW METHODS
(Formal approval from an authorized officer and incorporation into the methods manual)

DOCUMENTED NEW METHODS

(The written method must be clear and unambiguous and should provide sufficient information for the analysis to interpret the results obtained)

Suggested format for writing a new method:

- Title
- Date authorized
- Numbering
- Style (imperative with short sentences)
- References
- Abbreviations (defined)
- Scope
- Basic pinciples
- Apparatus and reagents
- Safety precautions
- Procedures
- Calculations
- Statistics
- Quality Assurance (sampling)
- Comments

MODIFICATION OF ANALYTICAL TESTING METHODS

Minor modifications:

Desirable quality improvements (e.g.sample size, slight pH adjustment)

Must be validated (running several samples and comparing results if considered necessary by the supervisor)

Major modifications:

Must be accompanied by full validation

Proper documentation must be implemented and incorporated into the original document as an addendum

Must be properly authorized

MANUALS

The Analytical method should be appropriately archived and be readily available to all laboratory personnel (Bulky manuals should be avoided)

NUMBERING OF NEW METHODS

Methods are to be identified by the Bureau and/or the division of origin (e.g. Bureau of Drug Research/ Pharmaceutical Chemical Division)

Followed by the a number which represents the date of the authorization, and the authorized signature

GLASSWARE
(Glassware is an integral part of the analytical method)

MINIMUM ACCEPTABLE PROCEDURES

- Class A volumetric glassware must be used for volumetric analysis
- The proper technique must be used in handling volumetric glassware
- Proper general cleaning procedures must be followed
- Special purpose glassware must be used when specified e.g. vitamin assay (light-protected etc)

GRADES OF GLASSWARE

- Storage and transfer
- Measurement of volumes
- Confinement of reactions

HANDLING VOLUMETRIC GLASSWARE

- Corrective reading (bottom of the meniscus should be tangential to the calibration mark)
- Changes in temperature can result in changes in the capacity (e.g. An ordinary glass flask of 1000 ml volume increases by 0.025 ml per degree rise in temperature).

- One litre of water or a 0.1 N solution increases in volume by approximately 0.20 ml per degree rise in temperature. On the average temperature should read 20 degrees Celsius.

- Calibration errors (calibrate the material to contain (TC) or to deliver (TD)). Flasks are calibrated to contain, while volumetric pippets are calibrated to deliver a fixed volume.

SPECIFICATIONS OF VOLUMETRIC GLASSWARE

Use standardized volumetric glassware "Class A". Class A glassware does not need to be calibrated before use.

CLEANING GLASS AND PORCELAIN

Standardize your procedures

Use low residue detergents

If you use organic solvents, wash and rinse the material(s) properly

Monitor your washing procedures

REAGENTS AND SOLUTIONS

(All reagents and reagent solutions must be of high quality. Water used in an analytical method is considered to be a reagent and must be purified to meet requirements).

MINIMUM ACCEPTABLE LABORATORY PROCEDURES FOR REAGENTS

- Reagents must be of an analytical grade
- Must meet the specifications of quality required by the method of regulation and GMP.
- Upon receipt reagents must be properly labelled in-house and contain the following information:
  - . date received
  - . expiry date
  - . date opened
  - . storage conditions
  - . safety precautions
- Reagent solutions must be dated as above when prepared, and bear the initials of the technician or operator who prepared them.
- The laboratory should have suitable equipment to produce, store and test all of the types of water used in the laboratory.
- Water quality should be in accordance with the American Chemical Society or any other recognized standard.
- A designated person should monitor the water quality in the laboratory.
- Comprehensive and up-to-date records are required.

REAGENT QUALITY

Reagents and solvents for metal analysis should be of spectrophotometric quality or an equivalent

Reagents for organic residue analysis should be of an analytical reagent grade (AR)

Reagents for Gas Chromatography needs to be of high quality

SPECIFICATIONS FOR WATER PURITY

General acceptance of high-purity water is water distillated and/or deionized and has a specific resistance in accordance with any recognized standard (e.g. conductivity).

MEDIA

A detailed procedures must be in place which describes the handling, and storage of media, and helps to ensure the quality of the media to be used in the laboratory.

MINIMUM ACCEPTABLE PROCEDURES

- There must be purchasing standards set for commercially prepared media
- Proper SOP's must exist for the preparation, handling and storage of media
- A program must be established to determine the sterility levels and growth-promoting qualities of prepared media
- Proper SOP's must be established for decontamination and disposal of media

QUALITY ASSURANCE

If pos ole ensure the quality of media by including an adequate number of positive and negative controls when using the media for analytical purposes

If quality failure is detected in the controls the test should be repeated

Criteria for Media Release:

- It must pass the proper test in accordance with the SOP
- All units should be incubated before use
- Media with indicators should be released as soon as all biological indicators are shown to be sterile
- During storage, precautions should be taken against leakage

REFERENCE STANDARDS FOR ANALYTICAL TESTING

A reference standard could be regarded as a model of the following essential properties which assures a level of confidence:

- Standard of identity
- Standard of purity
- Standard of potency

SPECIFICATIONS

A reference standard must be used in all determinations which require comparison. If the limits set in any test are based upon the behaviour of the reference standards then only that reference standard can be relied upon implicity for regulatory purposes.

STORAGE, HANDLING AND LABELLING

Proper storage handling and labelling should guarantee the integrity of the reference standard.

RECORDS

The records kept for each reference standard should include:

- Identity
- Activity and purity
- Date received
- Lot number
- Original source
- Storage and handling procedures
- Procedure for certification (Q.A.) of the Standard

SPECIAL ATTENTION FOR SUCCESSFUL TABLETING PROCESS

a) The formulation is key (detailed formulation procedure SOP).

b) The Equipment

Equipment selection,
maintenance,
adequate operators training.

c) The Facility

adequate space,
comprehensive layout,
proper construction materials,
proper housekeeping procedures,
proper ventilation and air system.

d) Personnel

properly trained,
motivated.

e) The Raw Materials

good quality,
reliable supplier.

TABLETS

FOR EACH VARIABLE:
- Record observations.
- Summarize statistics analysis.
  (average and standard deviation.
- CALCULATE THE SAMPLE SIZE.
- Compare results with specifications established in International standards i.e. USP, etc.
- Compare analysis results with internal standards.
- look for batch-to batch variation.

LIST OF VARIABLES AND ACTIVITIES NECESSARY TO BE MONITORED DURING PROCESS VALIDATION

It is necessary to select the minimum variables which have to be monitored and controlled as a minimum requirement.
All critical steps should have a proper SOP.

1) Characterize or define the process activity and/or step by identifying the SOP.

2) Identify the equipment employed in the activity and/or production step.

3) Describe the characteristics of the product that will be affected by 1 and 2.

4) Identify the variables of the process, enabling the manufacturer to monitor the performance of the process.

5) Control of the product variables assures the product quality.

SOME EXAMPLES OF VARIABLES AND/OR PARAMETERS

MIXING
Determine the agitation RPM,
the agitation time
the distribution of active ingredients in suspension.

BLENDING
Determine the blending time,
rotational speed of blender shell,
percentage of loading,
distribution of active ingredients,
uniformity of active ingredients,
particle size analysis,
density measures.

SCREENING
Determine chamber speed,
blade configuration,
feed rate,
screen size,
particle size
uniformity.

DRYING
Determine temperature distribution,
drying time,
vacuum level and time when applicable,
moisture.

COMPRESSSION
Determine type, make and size of the equipment,
maximun output,
dividing depth of upper punch,
pre-compression and compression force,
ejection force,
feeder speed,
filling high in hopper.

TABLET CHARACTERISTICS
Determine weight,
uniformity of weight,
crushing force,
friability
disintegration time,
dissolution rate,
content uniformity,
residual moisture,
colour, surface roughness,
breaking groove and diameter.

PROSPECTIVE VALIDATION

- Report from pilot plant experiments.
- Development of validation documents.
- Development of general manufacture directions.
- Development of product specification report(PER),to include the following:
  a) formula,
  b) manufacturing directions,
  c) packaging components,
  d) testing standards
  e) raw materials specifications.
  f) equipment specifications.

All this information should be contained in SOP's for the specific activities. The amount of validation and the groups involved vary from company to company. However all the critical activities should be validated in order to validate the process.

WET GRANULATION PROCESS

PARTICLE SIZE REDUCTION
(mills or grinders)

BLENDING

SCREENING

DRYING

IMPORTANT PARAMETERS

Cohesivenes and compressibility of powders

Suitable flow cohesion for compression

Uniformity and distribution

Dissolution rate

Humidity control

Solubility of powders

Relatively size and shape of powder particles

Viscosity of liquid binder

Type of agitation

TABLET PRESSES

STATION/S

Die(diameter and shape)

Punches(upper and lower = form)

Output(speed)

HOPPERS

FEED FRAME/S

CAMS

TABLET PROCESS VALIDATION

ACTIVE INGREDIENTS

Size of dose or quantity

Stability

Solubility

Density

Compressibility

SELECTION OF EXCIPIENTS
(Fillers, binders, desintegrants, lubricants glidants and antiadherents)

GRANULATION

Method

Character

TABLET CHARACTERISTICS

Press

Type

Size

Capacity

ENVIRONMENTAL CONDITIONS

Humidity control

PRODUCT STABILITY

BIOAVAILABILITY OF THE ACTIVE DRUG CONTENT

ASEPTIC AND STERILE OPERATIONS

PRODUCTION METHODS

CLEANLINESS

ORDERLINESS

PRECAUTIONS AGAINST CONTAMINATION

FILLING AND CONTAINERS

FILLING PROCEDURES

CONTAINERS

TESTS

RECORDS

SAMPLES

SAMPLE DISTRIBUTION

LABELLING

STERILE PRODUCTS

DESIGN OF VALIDATION PROTOCOL WILL VARY IN ACCORDANCE WITH TYPE OF SYSTEM AND/OR PRODUCT TO BE VALIDATED.

OBJECTIVE

To prove reproducibility within the approved written specifications.

- Certification of facility.
- Certification of equipment.
- Normal bioburden for:
    - raw materials.
    - production components.
- Certification of personnel.
- Certification of the procedure.

STERILE PRODUCT DESIGN MUST SHOW THAT IT GIVES STERILE PRODUCTS BY DESIGN (a challenge test for pre-sterilization is necessary).

- Aseptic filling.
- Final sterilization.

EQUIPMENT INSTALLATION PROTOCOL

1.0 Equipment description

1.1 Identification number 1.2 Serial number

1.3 Model number

2.0 Equipment location:

2.1 Department 2.2 Room number

3.0 Characteristics:

- 3.1 Electrical input
- 3.2 Utilities required
- 3.3 Environment required
- 3.4 Safety features
- 3.5 Special features

4.0 Operation

- 4.1 SOP for operation
- 4.2 SOP for sanitation
- 4.3 SOP for preventive maintenance
- 4.4 SOP for Log-book
- 4.5 SOP for validation

5.0 Maintenance

- 5.1 Material management information (purchasing department)
- 5.2 Installation drawings
- 5.3 Critical spare parts list
- 5.4 Installation and maintenance manuals

STERILIZING OVEN VALIDATION SHEET

1.0 Equipment description:

1.1 Identification number

1.2 Serial number

1.3 model number

1.4 installation date

1.5 last validation date

2.0 Equipment location:

2.1 department

2.2 room number

3.0 Process variables:

3.1 chamber temperature acceptable limits

3.2 setup time acceptable limits

4.0 Process description SOP:

5.0 Test functions:

5.1 calibration of recorders

5.2 indicator lamps

5.3 cycle timer test

5.4 set point

5.5 safety control test

5.5 thermocouples calibration

5.6 heat penetration test

6.0 Load pattern:

6.1 heat distribution maximum and minimum temperature

6.2 heat penetration

6.3 temperature differential

7.0 Oven cycle:

- 7.1 starting time
- 7.2 timer initiation
- 7.3 first and last thermocouple tc reach desired temperature time
- 7.4 end of cycle

8.0 Biological indicators:

- 8.1 identification
- 8.2 characteristics

9.0 Microbiological test

- 9.1 worst case bioburden
- 9.2 maximum D value of bioburden
- 9.3 biological challange(organism and D value)
- 9.4 minimum Fo calculation
- 9.5 biological challenge load determination

10 Analysis and conclusions

11 Validation officer

12 Date

13 Validation sticker

STEAM STERILIZER VALIDATION PROTOCOL

1.0 Date

2.0 Officer name

3.0 Identification number

4.0 Location

5.0 Process variables:

5.1	chamber temperature	acceptable limits
5.2	chamber pressure	acceptable limits
5.3	Chamber vacuum	acceptable limits
5.4	Steam pressure intake	acceptable limits
5.5	Time to achieve minimum chamber temperature	acceptable limits
5.6	Time to achieve minimum chamber pressure	acceptable limits
5.7	chamber leak test	acceptable limits

6.0 Process description SOP:

7.0 Test functions:

7.1 Calibration of recorders

7.1.1 temperature recorder
7.1.2 vacuum recorder
7.1.3 pressure recorder

7.2 Indicator lamps

7.3 Cycle timer test

7.4 Chamber temperature controller

7.5 Heat distribution test

7.6 Safety control test

7.7 Thermocouples calibration

7.9 Heat penetration test

8.0 Load pattern:

8.1 heat distribution

8.2 heat penetration

9.0 Biological indicators:

9.1 identification

9.2 characteristics

10. Microbiological test:

10.1 worst case bioburden

10.2 maximum D value of bioburden

10.3 biological challange(organism and D value)

10.4 minimum Fo calculation

10.5 biological challenge load determination

11.Analysis and conclusions

12.Validation officer

13.Date

14.Validation sticker number

MINIMAL INTERNAL ORGANIZATION FOR THE IMPLEMENTATION OF A BASIC VALIDATION PROGRAM

VALIDATION MANAGER
(RESPONSIBLE OFFICER FOR VALIDATION)

ORGANIZE VALIDATION PROJECTS

COORDINATE AND/OR SUPERVISE VALIDATION TEAMS

COORDINATE AND/OR SUPERVISE VALIDATION PROTOCOLS

COORDINATE AND/OR SUPERVISE VALIDATION PLAN

COORDINATE AND/OR SUPERVISE VALIDATION IMPLEMENTATION

RECOMMENDED STRATEGIC PLAN

SET VALIDATION PRIORITIES

DEVELOP A STRATEGIC PLAN

COORDINATE WITH OUTSIDE ASSISTANCE IF NECESSARY

DESIGN VALIDATION PROTOCOLS

PREPARE NECESSARY DOCUMENTATION (SOP'S)

ESTABLISH NECESSARY GUIDELINES

IMPLEMENT PILOT PROJECT

MONITOR IMPLEMENTATION

EVALUATE RESULTS

MAKE NECESSARY ADJUSTMENTS

REPLICATE THE PILOT PROJECT

ORGANIZE INTERNAL TRAINING

COORDINATE ACTIVITIES WITH MANAGEMENT

Appendix iv:

An Outline for Validation Workshops

Tableting Process Validation

Outlines :

a. **Process validation**
   1. Weighing and Blending
      - homogeneity
         - sampling and statistic of mixing
         - mixing problems
   2. Granulation, screen wet granulation
      - characterization of granulation
      - evaluation of tablets
      - use and care of the tools
      - preformulation testing
   3. Drying, screen dry granulation
      - size reduction
      - powder characterization
      - particle size analysis
      - compression
      - measurement of compression force
   4. Tablet compression
      - compressed tablet by wet granulation
      - manufacturing problems
      - compressed tablet by direct compression
      - tablet production design validation
   5. Process optimization

b. **In-process testing**
   - calibration of equipment
   - review of sampling procedures
   - review of testing procedures
   - validation of data recording

c. **Equipment validation**
   - balance
   - wet mixer
   - dry mixer
   - tableting machine
   - capsule filling machine
   - powder filling machine

d. **Environmental conditions**
   - removal of dust
   - removal of organic solvents
   - treatment of exhaust gases from coating processes

Validation of Sterile Product Process

a. Aseptic production process
b. Sterilization process

□Topics to consider for validation□

1. Environmental considerations
   - Air systems
   - temperature monitoring equipment
   - ventilation
   - filtration
   - sanitization
   - nonviable particles
   - viable particles
2. Utilities
   - gases
   - vacuum systems
   - electrical systems
   - steam systems
   - water systems
3. Facilities and Equipment
   - washing machine
   - sterilizing equipment
   - steam sterilization - autoclave
   - dry heat sterilization - hot air oven
   - ethylene oxide sterilization
   - aseptic processing filters
   - lyophilizer
   - filling machine
   - container sealing machine
4. Component Preparation Process
   - rubber closure
   - glass component
5. Operating personnel in aseptic area
   - well-trained
   - well-dressed
   - gowns materials and procedures

Water System Validation

Outlines :

1. Background of water purification
2. Distribution and utilization of water
3. Classification of impurities, characteristics types of water
4. Purification process
5. Disinfection and sterilization and pyrogen removal
6. Purified water practice and storage
7. Overview of water system validation
8. Types and classification of water system
9. Maintenance
10. Equipment of choice and maintenance

Quality Control Validation

□Topics to consider for validation□

1. Validation of Analytical Methodology
   - Method selection criteria
   - Reference standards
   - Reagents
   - Water specifications
   - Equipment
   - Analytical test procedures
   - Operators
   - Samples (Handling and receiving)
   - Critical support system
   - Working environment
   - SOP
   - Training
   - Documentation
   - Evalutation of the results
   - Method of evaluation
   - Validation of data
   - Criteria of acceptance
2. Equipment
   - Glassware
   - Instruments and accessories
   - Calibration
   - Performance checks
   - Preventive maintenance program
   - Critical support system
     - Electrical
     - Humidity
     - Temperature
   - Cleaning and Lubricating
   - History file
   - Personnel training
   - SOP
   - Documentation
3. Training
   - Topics
   - Target groups
   - Frequency
   - Methodology
   - Evaluation
4. Audit Functions
   - Objectives
   - Team
   - Methodology
   - Frequency
   - Problems solving
   - Documentation
   - Evaluation

□Validation of Analytical Methodology□

Purpose : - to determine the suitability of a measurement system for providing useful analytical dat
- to valuely judge the performance parameters of the method according to the requirements for the analytical data.

Criteria of Method Selection :

- simple, feasible, reliable and reproducible
- appropriate and suitable for use under conditions of the existing laboratory

- analyzing a sufficient number of reference samples and comparing the results to the expected or certified values.
- **approach II:** infer the appropriateness of methology from measurements on analogous reference materials.
- **approach III:** use spiked samples and surrogates as reference samples. This approach is less desirable and less satisfactory because of the difficulty in the reliable preparations of such samples and because artificially added materials such as spikes and surrogates may exhibit matrix effects differing from those of natural samples.

Numbers of tests required :

The test method should include atleast three levels of concentration - the extremes and the midrange of the compositions expected. Associated risk : a method that is valid in one situation could be invalid in another.

Statistical considerations :

At least six degrees of freedom (or seven measurements) should be involved at each decision point.

□Validation of Samples□

Purpose of sample validation :

- to accept an individual sample as a member of a population under study
- to admit samples to the measurement process
- to minimize later questions on sample authenticity
- to provide an opportunity for resampling when needed

Criteria for acceptance of a sample :

- positive identification
- conformance with physical/chemical specifications
- a valid chain of custody

Rejection of a sample can be based on

- knowledge that a sampling system was not in control at the time a sample was obtained
- erroneous or conflicting data on the identity or character of a sampler
- questions about a sample that cannot be resolved
- any information that would cast doubt on the status of a sample as a member of the population of interest.

□Validation of Data□

Purpose : To filter and accept or reject a data or a group of data based on a set of criteria.

Remark : Data validation can be facilitated if the analyst is fully informed on the nature of the problem, the end use of the data, and even the expected results.

Criteria of acceptance :

Statistically supported limits of uncertainty should be estimated.

Lists of possible checks :

The following checks should be made to eliminate blunders to the extent possible.

- checks for proper identification
- checks for transmittal errors
- checks for internal consistency
- checks for temporal and spatial consistency

Checking Techniques :

- intercomparisons with similar sample data
- checks for reasonableness of values with respect to a priori and/or a posteriori limits
- data plots
- regression analysis
- tests for outliers.

The checks may range from spot checks of randomly selected data to a total data analysis.

Appendix v:

A List of Participants in Validation Workshops

Validation of	University	Counterpart	Working group	Company's name
1. Tablet Processing	Poj Ampol Narong	Sureerat	Palsan Yodying Jurai Narumol	บ.ผูหรน Schering บ.เจริญภณัฑ G.D.H.
2. Sterile Product Processing	Rudee Parunee	Kajornrat Mantana	Sunee, Jurai Supattra	บ.เจริญภณัฑ General Drug House
3. Water System F.E.Zuellig	Parunee	Kasem	Nares Sanchai Sunanta Supasri Chukiet Surachet Surachai	บ.เจริญภณัฑ G.D.H. สิลปการแพทย์ ท่าศัก T.O ไทยพาน
4. Quality Control System	Sutathip Sirinart	Sumana	Sunanta Manee Sanhaluk Prompong Alongkot Ek-kasak Suban	บ.สิลปการแพทย์ บ.ผูหรน Schering T.O. L.P.Standard G.D.H บ.เจริญภณัฑ

List of Participants in Validation Program

Name		Company's Name	Working group on Validation of	Tel.	Fax.
1. สุนันทา Sununtha	ตันศิริเสริญกุล Tansirisernkul	Silom Medical Co., Ltd.	Water System	245-3391-3	
2. สันหลัก Sunhaluck	บัวสวย Buasuang	Schering	Q.C.	573-0053-5	573-1171
3. สุภาศรี Supasri	งามสันติกุล Ngamsantikul	F.E.Zuellig	Water System	579-3333 -9889	
4.สุรเชษฐ์ Surachade	ยุวถาวร Yoovathaworn	T.O.Chemical(1979) Ltd.	Water System	277-4141 -0187	277-7350
5. สุรีรัตน์ Sureerat	ประจักษ์ธรรม Pracharktam	General Drugs House	Tabletting	530-0590-4	530-1228
6. ภาวุณี Parunee	ธนอมเกียรติ Thanomkiat	Chulalongkorn University	Water System Sterile Product	251-1871-7	
7. อลงกต Alongkot	วิจารจักร์ Wijarajak	L.P.Standard Lab	Q.C	385-2116-8	385-2115
8. พรอมพงศ์ Prompong	อุกฤษพิมพันธ์ Ukakpimpan	T.O.Chemicals(1977) Ltd.	Q.C.	277-4141 275-5330	277-7350

Name	Company's Name	Working group on Validation of	Tel.	Fax.
9. สุมนา ชมวิลัย Sumana Khomvilai	Hoechst Pharma	Q.A.	463-0094	463-4929
10. เกษม กาญจนวงศ์ Kasem Kanchanavong	A.N.B.	Water System	510-0021	510-9945
11. ศิรินารถ วาสนะวัฒน Sirinart Vasanavathana	PTSC	Q.C.System	251-1871-7	
12.ดร.พรชัย กตวาณิช	Chulalongkorn University	Tablet Processing	2511871-7	2558227

Appendix vi:

A List of Individuals Interviewed during the Mission

INDIVIDUALS INTERVIEWED DURING THE MISSION

Dr. Pavich Thongroach
Dean Faculty of Pharmacy,
Chulalongkorn University.

Mr. Jaruronjna Dankietkong
President, of Thailand Pharmaceutical
Manufacturers Association,

Ms. Preeya Sibunruang
Vice Chairman of The Federation of Thai Industries,
Ex-president of TPMA.

Dr. Morakot Kornkasem
Secretary General,
Food and Drug Administration.

Dr. Suwit Wibulpolprasert
Director, Drug Control Division,
Food and Drug Administration.

Dr. Prasan Dhumma-upakorn
Director, Pharmaceutical Technology Service Centre.
Phaculty of Pharmacy,
Chulalongkorn University.

Mr. Nils Ramm-Ericson
UNIDO, Country Director.

Mr. Gerard R. Latortue
Director Area Program Division,
UNIDO.

Mr. Anders Paludan
UNIDO, Program Officer.

Mr. Nills Ellis
UNIDO, Program Officer.

Caroline de Bruijn
UNIDO, Technical Expert.
Pharmaceutical Technology Service Centre.

INDIVIDUALS INTERVIEWED DURING THE MISSION - CONT.

Cristina Cecchini
UNIDO, Associated Expert,
Pharmaceutical Technology Service Centre.

Mr. Sompong Panichpol
Director, Biolab

Mr. Virapatna Thakolsri
Deputy Managing Director
Biopharm

Mr. Nilsuwan Leelarasamee
National Expert,
Golden Cup Pharmaceutical Co, Ltd.

Ms. Rudee Saovakon
Professor, Faculty of Pharmacy,
Mahidol University.

Dr. Ampol Maitreevej
Professor, Faculty of Pharmacy,
Mahidol University.

Ms. Parunee Thanomkiet
Department of Manufacturing,
Faculty of Pharmacy,
Chulalongkorn University.

Dr. Poj Kulavanich
Department of Manufacturing,
faculty of Pharmacy,
Chulalongkorn University.

Dr. Sirinart Vasanavathana
Pharmaceutical Technology Service Centre
Laboratory Services.

Dr. Chamnan Patarapanich
Technical Advisor,
Quality Control and Quality Assurance.

Dr. Kaisiri Umprayan
Faculty of Pharmacy,
Chulalongkorn University.

INDIVIDUALS INTERVIEWED DURING THE MISSION - CONT.

Mr. Prepond Bandiyanond
National Expert
Quality Assurance.

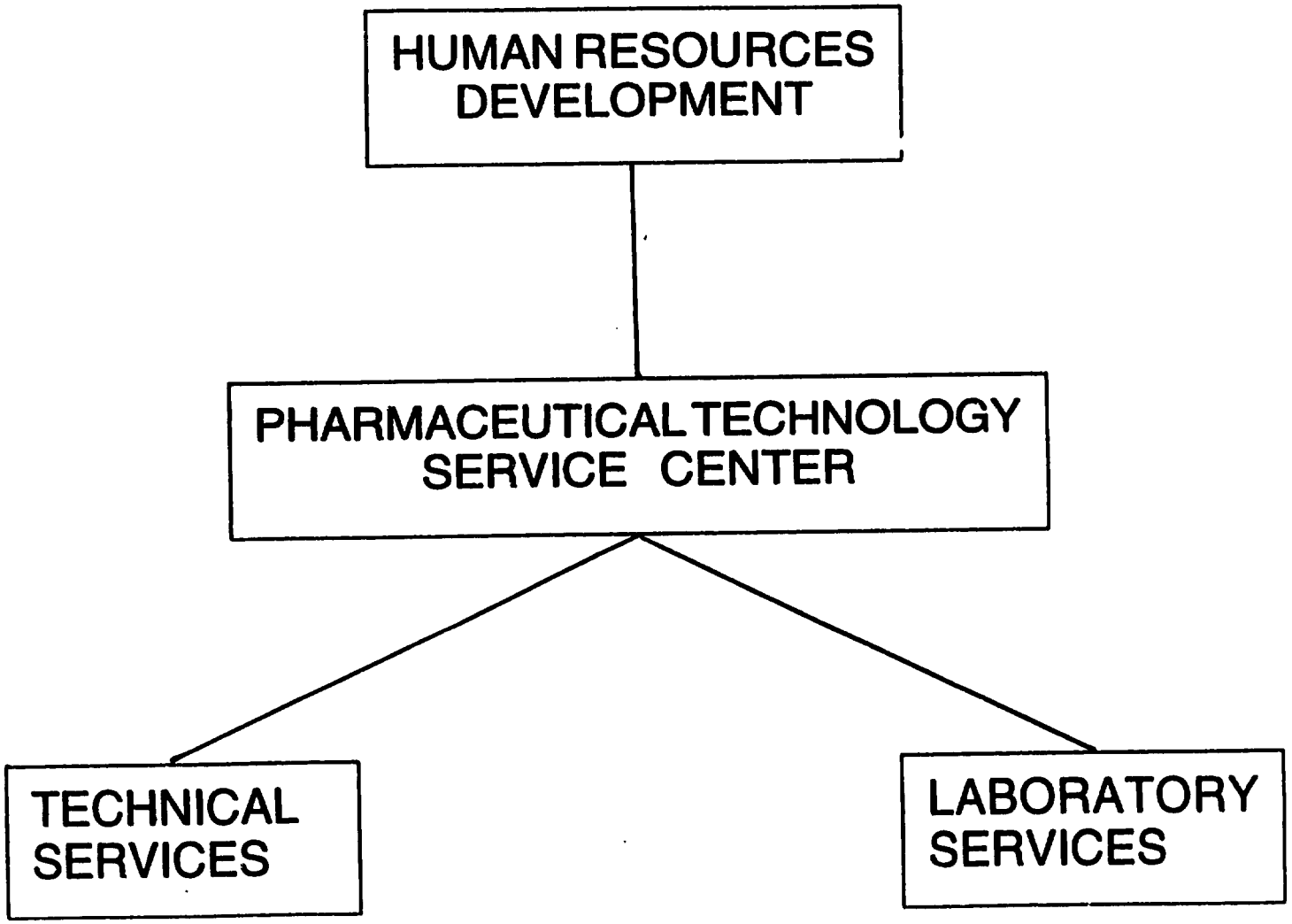
Mr. Varapot Vongsangah
Olan-Kemed Co, Ltd.
National Expert

Dr. Sureerat Prachuktam
General Drug House,
National Expert.

Mr. Ongart Xanthavanij
Palida C. Ltd.

Appendix vii:

The Pharmaceutical Technology Service Centre Activities Summary


HUMAN RESOURCES DEVELOPMENT
PHARMACEUTICAL TECHNOLOGY SERVICE CENTER
TECHNICAL SERVICES
LABORATORY SERVICES

HUMAN RESOURCES DEVELOPMENT

GMP TRAINING

- TRAINING THE TRAINERS
  - WORKING GROUPS
  - WORKSHOPS

- GMP SEMINARS
- PLANT VISITS AND GMP AUDITS

LABORATORY SERVICES

- ANALYTICAL TESTING
  - PHYSICAL TESTING
  - CHEMICAL TESTING

TECHNICAL SERVICES

- TESTING, RESEARCH AND DEVELOPMENT
- TROUBLE-SHOOTING
- TECHNICAL CONSULTANCY
- KNOW-HOW TRANSFER

Appendix viii:

Examples of Master SOP's produced by the PTSC
(setting up and organizing Validation
and
Raw Material Inventory Control)

A List of Master SOP's Prepared by the PTSC to-date March, 1993

1.	Receipt of Raw materials	65-0001
2.	Assignment of Receiving Control Numbers	65-0005
3.	Raw Material Inventory Control	65-0007
4.	Sampling of Raw Materials	60-0002
5.	Assignment of Product Code Number	60-0007
6.	Raw Material Specification Document	60-0001
7.	Dispensing and Weighing of Raw Materials	15-0001
SOP's under revision		
8	SOP Guidelines	60-0000
SOP's to be finalized		
9.	Preparation of Mater Formula and Method	60-0017
10.	Preparation and Use of Batch Manufacturing Record	15-0020
11.	Cleaning of Manufacturing Equipment	15-0003
12.	Calibration of Instruments	60-0028
13.	Stability Program	60-0013
14.	Returned Goods Policy	60-0012

STANDARD OPERATING PROCEDURE

TITLE	SOP # 75-0008/1		
	Effective	D	M Y
ORGANIZATION OF	date from	20	3 93
VALIDATION SET UP	to	20	3 95

Prepared by	Reviewed by	Approved by	Authorized by
Position	Position	Position	Position
Date	Date	Date	Date

1.PURPOSE

To establish a validation program to assure that all manufacturing and/or testing activities are performed in a reliable manner.

2. SCOPE

This SOP applies to validation of pharmaceutical products, processes, facilities, equipment and personnel working in Production and Quality Control.

3. RESPONSIBILITY

The validation task leader (VTL) is responsible for the implementation of the validation program in accordance with this SOP. The VTL is responsible for the organization of validation projects, the coordination and/or supervision of validation teams, validation plans, validation protocols and SOP's.

Please note that the VTL could have many other nominations in accordance with the organizational structure of each company.

4. GENERAL GUIDELINES

* Set up a validation program assisting the establishment of overall control over the entire operation.

  Additionally, validation
  - provides a high degree of Quality Assurance
  - optimizes inventory control
  - increases safety
  - reduces costs, due to
    . more efficient processes (less waste, less production time, less in process controls, less

failures, less breakdowns)
. reduced re-work
. reduced number of complaints
. reduced re-testing
. reduced number of recalls

5. FLOW CHART

	ACTIVITIES	RESPONSIBILITY
1. ESTABLISH	and ORGANIZE internal training program	plant management
2. SET UP	validation team	plant management
3. DEVELOP	strategic plan	VTL
4. PREPARE	documentation	VTL
5. CALIBRATE	instruments	VTL
6. IMPLEMENT	pilot project (*)	VTL
7. DOCUMENT	data	VTL
8. EVALUATE	test results	VTL
9. DOCUMENT	conclusions	VTL
10.CERTIFY	the validated process	VTL
11.TRAIN	key personnel	VTL
12.APPROVE	additional documentation	VTL, QA
13.REPLICATE	and EXTEND validation process to other areas	VTL
14.ASSESS	and PLAN validation program for the entire operation	VTL, QA
15.IMPLEMENT	process validation	VTL

(*) Pilot project is recommended for companies which are new in implementing validation processes ("first-timers")

6. DETAILED INSTRUCTIONS

6.1 ESTABLISH and ORGANIZE internal training program

* Establish and organize	an internal training program on QA in which the importance of validation, as part of Quality Assurance, is explained
* Point out	the importance of documentation and the responsibility of every person in the company to assist complying with this documentation
* Encourage	personnel to propose, adjust or generate documentation for critical processes, in accordance with company policies
* Prepare	an SOP, outlining the training program. State the responsible person(s) for the development and implementation of the training program.
* Train	personnel on the performance of validation activities

6.2 SET UP validation team

* Establish	the validation team, depending upon the company size and technical disciplines available, including representatives from Quality control (chemical, physical, microbiological testing), production, engineering, research & development, statistical analyis, safety, purchasing, regulatory affairs. The team will be coordinated and/or supervised by one person, the VTL, who has been recognized and officially appointed as responsible for the implementation of this task

6.3 DEVELOP strategic plan

* List	all critical manufacturing and testing processes and equipment to be considered for validation studies

* Set	validation priorities, in accordance with company policy and strategic objectives, based on e.g. product sells, needs (e.g. regulatory compliance), availability of resources

6.4 PREPARE documentation

* Provide	an SOP on Documentation Management for the validation process
* Prepare	a validation protocol, outlining in detail test procedures and acceptance criteria for each process. The protocol should include: - validation project number - introduction/purpose of the project - description of the system to be validated, including location - identification of process/specific equipment involved - characteristics to be investigated - test methods - test requirements - acceptance criteria - reference to SOP's or any other documentation - maintenance information, including purchasing order, drawings, service conditions, information on spare parts - signature for approval, including date The protocol should be signed for approval before initiating the validation activity.

6.5 CALIBRATE instruments

* Ensure	the instruments used for the validation process are calibrated. Calibrate the instruments in accordance with their SOP.

6.6 IMPLEMENT pilot project

* Decide	on a pilot project in accordance with the list of validation priorities

* Review	all documentation and adjust, as necessary, for this particular project
* Approve	the documentation
* Implement	the project. Fulfill all steps, laid down in the protocol.

6.7 DOCUMENT data

* File	all data directly in the protocol. Data should be clearly written, including units of measure. Changes must be reflected in the protocol.
* Summarize	test results in the validation report

6.8 EVALUATE test results

* Study	the data in combination with the acceptance limits, stated in the validation protocol
* Ensure	that all testing requirements were achieved

6.9 DOCUMENT conclusions

* State	in the validation report that the process has been validated, based on the test results

6.10 CERTIFY the validated process

* Identify	the validated system by a certificate (Exh.# 50), if possible

6.11 TRAIN key personnel

* Demonstrate	the validation method by using the necessary documentation
* Demonstrate	the way in which data should be collected, analyzed and interpreted
* State	the person to be contacted if clarification is required

6.12 APPROVE additional documentation

* Write and Approve	all necessary documentation before replicating the validation method to other areas

6.13 REPLICATE and EXTEND validation process to other areas

* Apply	the method of approach to other processes within the company's operations

6.14 ASSESS and PLAN validation program for the entire operation

* State	in an SOP the frequency and/or the situation for which the project has to be validated again, by using the same protocol.
* Revalidate	in case of a major change, e.g to any of the following parameters: - batch size - manufacturing equipment - manufacturing location - manufacturer of raw materials - method of formulation - formula - analytical method In case of processes for which visual inspection plays an important role, new inspection personnel has to be validated. For revalidation projects, new protocols have to be prepared.

6.15 IMPLEMENT process validation

* Validate	all processes in accordance with the validation program

7. GLOSSARY OF TERMS

* Validation	: establishing documented evidence that a process does what it purports to do
* Revalidation	: validation of a validated process, in which a major change has been implemented (will be revised)
* Validation report	: a final document on a validation project. It is recommended to use the following headings: - ABSTRACT - PLAN OF STUDY - EXPERIMENTS - RESULTS - CONCLUSION - LITERATURE OF REFERENCE - SIGNATURE/DATE for approval, by QA

8. EXHIBITS

EXHIBIT # 50	certificate for validated processes/equipment

Exhibit # 50/1

CERTIFICATE FOR VALIDATED PROCESSES/EQUIPMENT

VALIDATION CERTIFICATE

Validation project number :

Validated process/equipment:

Date of certification :
Effective to :

Authorized by:

ศูนย์บริการเทคโนโลยีเภสัชอุตสาหกรรม
PHARMACEUTICAL TECHNOLOGY SERVICE CENTRE
คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย ปทุมวัน กทม. 10330 โทร. 2511871-7
FACULTY OF PHARMACEUTICAL SCIENCES CHULALONGKORN UNIVERSITY BANGKOK 10330 THAILAND

SOP # 65-0007

STANDARD OPERATING PROCEDURE

FOR

RAW MATERIAL INVENTORY CONTROL

INDEX

STANDARD OPERATING PROCEDURE

TITLE	SOP # .....65-0007.....
RAW MATERIAL **INVENTORY CONTROL**	Effective Date D ..... M ..... Y .....
	Page .....1..... of .....9.....

1. PURPOSE

Establish a "FIFO" inventory control system which ensures the accountibility and traceability of inventory items in compliance with the GMP Regulations and Company Policy.

2. SCOPE

This procedure is applicable for all active and inactive materials used for the production of semi-finished or finished goods.

3. RESPONSIBILITY

The Production and the Quality Assurance Managers are be responsible that this procedure is being implemented.

Prepared by :	Reviewed by :	Approved by :	Authorized :
Date :	Date :	Date :	Date :
Position :	Position :	Position :	Position :

Form # _____
Date _____

STANDARD OPERATING PROCEDURE

TITLE	SOP # .....65-0007.....
RAW MATERIAL INVENTORY CONTROL	Effective Date D ..... M ..... Y .....
	Page .....2..... of .....9.....

4. GENERAL GMP GUIDELINES

DO

- Maintain raw material storage area in neat, orderly and clean condition.
- Check carefully the accuracy of the different reference documents obtained from the Receiving and Q.A. departments.
- Identify clearly the content of each container.
- Alert the supervisor and Q.A. department about any discrepancy or error observed during the material handling operations.
- Record the justification for any variance of raw material as applicable for each lot number and advise QA and Supervisor.
- Process only one raw material at the time of the same lot number in order to avoid errors during the transaction operations.

DO NOT

- Accept or store in the warehouse dirty containers.
- Erase or use white ink to correct written errors on the documents but cross out and initial the correction !!!

Prepared by :	Reviewed by :	Approved by :	Authorized :
Date :	Date :	Date :	Date :
Position :	Position :	Position :	Position :

Form # _____
Date _____

STANDARD OPERATING PROCEDURE

TITLE	SOP # .....65-0007.....
RAW MATERIAL INVENTORY CONTROL	Effective Date D ..... M ..... Y .....
	Page .....3..... of .....9.....

5. FLOW CHART

Activities	Responsibility
1. SET UP a Sequential Numerical Inventory Control system.	Material Storage
↓	
2. OBTAIN the reference documents for each lot of raw material.	Material Storage
↓	
3. RECORD the reference data on the Material Receipt Record.	Material Storage
↓	
4. TRANSFER the raw materials to the allocated storage area.	Material Storage
↓	
5. DISPENSE the raw materials on a FIFO basis.	Material Storage
↓	
6. MONITOR the inventory variances for each lot of raw material.	Material Storage
↓	
7. COORDINATE the resampling procedure of each lot of raw material.	Material Storage

Prepared by :	Reviewed by :	Approved by :	Authorized :
Date :	Date :	Date :	Date :
Position :	Position :	Position :	Position :

Form # _____
Date _____

STANDARD OPERATING PROCEDURE

TITLE	SOP # .....65-0007.....
RAW MATERIAL **INVENTORY CONTROL**	Effective Date D ..... M ..... Y .....
	Page .....4..... of .....9.....

6. DETAILED INSTRUCTIONS

6.1 SET UP a Sequential Numerical Control System.

- Set up a Standard Inventory Control System which summarizes all the required reference information regarding each raw material transaction to ensure the accountibility and traceability of each lot number.

- Complete the required reference information which must be recorded on the inventory record to comply with the GMP Regulations as illustrated in EXHIBIT # 6

- P.S. set up, if necessary, a separate sequential numerical filing system for the active and non active ingredients which is based upon the Product Code Number.

6.2 OBTAIN the reference documents for each lot of material.

- Obtain a copy of the Receiving Report (EXHIBIT #1) and the Q.A. Sampling Report (EXHIBIT # 3) which includes all the necessary reference information for each lot of raw material.

- Keep all the above documents "on file" to justify the accuracy of each inventory record.

Prepared by :	Reviewed by :	Approved by :	Authorized :
Date :	Date :	Date :	Date :
Position :	Position :	Position :	Position :

Form # _____
Date _____

STANDARD OPERATING PROCEDURE

TITLE	SOP # .....65-0007.....
RAW MATERIAL **INVENTORY CONTROL**	Effective Date D ..... M ..... Y .....
	Page .....5..... of .....9.....

6.3 RECORD the required reference information.

- Record all the required reference from the Receiving report (EXHIBIT # 1) and the Sampling Report (EXHIBIT # 3) on the Receipt of Material Record (EXHIBIT # 6) for each lot number.

- Indicate clearly the sequence in which each lot has been received on the Raw Material Record to facilitate the usage of raw materials on a FIFO basis or based upon the shortest expiry date (EXHIBIT # 1).

6.4 TRANSFER the Raw Materials to the allocated storage area.

- Proceed with the storage of the raw materials in accordance with the storage location system which has been established by the Company.

- Identify clearly each container and/or pallet regarding the "Q.A. Release Status" (e.g. Quarantine/Released) prior to storage and apply the appropriate sticker. (EXHIBIT # 4 and # 5)

- Segregate the active and non active ingredients within the storage area as deemed neccessary.

- Use a sequential numerical storage system to facilitate the location and retrieval of raw materials which is based upon the Product Code Number.

- Keep on file the most updated standard location layout for all raw materials.

Prepared by :	Reviewed by :	Approved by :	Authorized :
Date :	Date :	Date :	Date :
Position :	Position :	Position :	Position :

Form # _____
Date _____

STANDARD OPERATING PROCEDURE

TITLE	SOP # .....65-0007.....
RAW MATERIAL INVENTORY CONTROL	Effective Date D ..... M ..... Y .....
	Page .....6..... of .....9.....

6.5 DISPENSE the raw materials on a FIFO basis.

- Indicate on the "Material Usage Record" (EXHIBIT # 7) which specific lot number is being used for dispensing as illustrated on EXHIBIT # 7 (lot # 920017)
- Dispense the raw materials on a First in/ First out (FIFO) basis in order to comply with the GMP Regulations. Except, whenever a lot with the shortest expiry date is on hand.
- Record prior to start up of the weighing operations each lot number of the raw material which has been allocated for each Manufacturing order (EXHIBIT # 8). In the event that two different lot numbers are required clearly indicate on the Formula Sheet the "exact quantity" weighed for each lot.
- Indicate clearly the balance of the gross weight for each container partially filled. (EXHIBIT # 9)
- Attach the above record to the partially filled container.

Prepared by :	Reviewed by :	Approved by :	Authorized :
Date :	Date :	Date :	Date :
Position :	Position :	Position :	Position :

Form # _____
Date _____

STANDARD OPERATING PROCEDURE

TITLE	SOP # .....65-0007.....
RAW MATERIAL **INVENTORY CONTROL**	Effective Date D M Y ---- ....
	Page .....7..... of .....9.....

6.6 MONITOR the inventory variances for lot of raw materials.

- Calculate the inventory variance upon depletion of each lot number of raw material. (EXHIBIT # 7 : Usage of Materials Record)
- Investigate the cause of the variance and clearly indicate the justification on the "Usage of Materials Record" (EXHIBIT # 7).
- Report any inventory variances to the supervisor and the inventory control department in order to adjust the inventory and accounting records.

6.7 COORDINATE the resampling procedure of each lot of raw material.

- Set up an effective monitoring system to ensure the timely retesting of raw materials which must be completed at least 4 months prior to the expiry date (SOP # 60-0015)
- Contact the Q.A. department to initiate the resampling procedure in accordance with the existing SOP #60-0007 for Sampling of Raw Materials.

Prepared by :	Reviewed by :	Approved by :	Authorized :
Date :	Date :	Date :	Date :
Position :	Position :	Position :	Position :

Form # _____
Date _____

STANDARD OPERATING PROCEDURE

TITLE	SOP # .....65-0007.....
RAW MATERIAL INVENTORY CONTROL	Effective Date D M Y ....
	Page .....8..... of .....9.....

7. GLOSSARY OF TERMS

QUARANTINE :
Effective restriction of the availability of material for use until released by a designated authority.

LOT :
A quantity of any drug in dosage form, a raw material, or a packaging material, homogeneous within specified limits, constituting all or part of a single batch and identified by a distinctive lot number (Receiving Control Number)

RECEIVING CONTROL NUMBER (LOT NUMBER) :
Any combination of letters, figures, or both, by which any material can be traced prior, during or after the production cycle (e.g. Distribution).

SCOPE :
Range of action

Prepared by :	Reviewed by :	Approved by :	Authorized :
Date :	Date :	Date :	Date :
Position :	Position :	Position :	Position :

Form # _____
Date _____

STANDARD OPERATING PROCEDURE

TITLE	SOP # .....65-0007.....
RAW MATERIAL **INVENTORY CONTROL**	Effective Date D ..... M ..... Y .....
	Page .....9..... of .....9.....

8. EXHIBITS

Exhibit # 1	Receiving Report
Exhibit # 3	Sampling Report
Exhibit # 4	Quarantine Label
Exhibit # 5	Released Label
Exhibit # 6	Material Receipt Record
Exhibit # 7	Material Usage Record
Exhibit # 8	Master Formula Sheet
Exhibit # 9	Container Record

Prepared by :	Reviewed by :	Approved by :	Authorized :
Date :	Date :	Date :	Date :
Position :	Position :	Position :	Position :

Form # _____
Date _____

Appendix ix:

Recommended Additional Equipment and Spare Parts

ACCESSORIES FOR THE DISSOLUTION TEST STATION

A EIGHT-CHANNEL PERISTALTIC PUMP (230 volts)
Part No : 537092
A PUMP CONTROLLER BOARD
Part No : 537094
AN AUTO-7-SAMPLER
Part No : 537095
For equipment : Dissolution Test Station (HANSON®) model SR2
Manufacturer : Hanson Research Corporation
19727 Bahama Street
P.O.Box 35
Northridge, CA 91324
U.S.A.
To be attached to: UV-VIS Beckman Spectrophotometer
Model DU-68 Serials # PN 120680
Manufacturer : Beckman
A Smithkline Beckman Company
Scientific Instruments Division
2500 Harbor Boulevard
Fullerton, CA 92634
U.S.A.

A PAIR OF ELECTRODES
Conductivity cell
Part No. : 6.0908.110
Temperature probe (Pt 100)
Part No. : 6.1103.000
Cable connections
Part No.: 6.2112.050 (for titroprocessor)
6.2116.000 (for recorder)
6.2112.050 (for conductometric titration)

To be attached to : Conductometer METROHM model 660 Type 1.660.0010 ; Nr 1F6/198
Manufacturer : METROHM Ltd.
CH-9100 HERISAU
Switzerland
Tel. 071/531133
Telefax 071/521114

A SET OF STANDARD ORIFICE TUBES
Aperture nominal diameter 15, 30, 200, 400, and 800 microns
To be used with : COULTER MUTISIZER model II Part No. 6602716
Manufacturer : COULTER ELECTRONICS Ltd.
Northwell Drive,
Luton, Beds.,
LU3 3RH
England
Tel. Luton (0582) 491414
Fax (0582) 490390

AN ELECTROCHEMICAL DETECTOR

Model: Waters 464

AN A/D, D/A INTERFACE BOARD AND A SOFTWARE CONTROL

To be attached to: Waters High Performance Liquid Chromatography Model 510

Manufacturer:
Waters Chromatography Division
34 Maple Street
Milford, MA 01757
U.S.A.
Tel. (617) 478-2000
Telex 174166

DIFFUSION APPARATUS

POLAROGRAPHIC ANALYZER

Model: BAS 200 or the latest model

Manufacturer:
Bioanalytical Systems, Inc.,
2701 Kent Ave
West Lafayette
Indiana 47906
Tel. (317) 464-4527
Fax (317) 497-1102

GAS CHROMATOGRAPHY

Model: Hewlett 5890 series II or latest

Detector: Flame Ionization Detector

Autosampler: Model 7673 or latest

Manufacturer:
Hewlett - Packard Company
European Headquarters
Hewlett-Packard S.A.
150 Route du Nant-d'Avril
CH-1217 Meyrin 2
Geneva, Switzerland
Tel. (022)-780-8111

AUTOMATIC PURE WATER SYSTEM

Model: SA-27E

Manufacturer:
EYELA
Tokyo Rikakikai Co., Ltd.
Toei Bldg.,
4-3, 4-chome Muromachi Nihonbashi
Chuo-ku, Tokyo
Japan
Tel. (03) 245-0481
Fax (03) 241-0177 G2 or G3 mode

MOISTURE BALANCE

Model: MA 30

Manufacturer:
Sartorius, GmbH
P.O.Box 3243
D-3400 Goettingen
West Germany
Tel. 551-308-1
Fax 551-308-289

VACUUM ROTARY EVAPORATOR

Model	N-1 or latest
Manufacturer	EYELA Tokyo Rikakikai Co., Ltd. Toei Bldg., 4-3, 4-chome Muromachi Nihonbashi Chuo-ku, Tokyo Japan Tel. (03) 245-0481 Fax (03) 241-0177 G2 or G3 mode

MULTI SHAKER

Model	MMS-300
Manufacturer	EYELA Tokyo Rikakikai Co., Ltd. Toei Bldg., 4-3, 4-chome Muromachi Nihonbashi Chuo-ku, Tokyo Japan Tel. (03) 245-0481 Fax (03) 241-0177 G2 or G3 mode

MELTING POINT APPARATUS

Model	Griffin Serial No. PE 1158
Manufacturer	Griffin and George Ltd. London, England

MAGNETIC STIRRER WITH HEATING UNIT

Model	Monat F 21/1
Manufacturer	Sartorius, Germany

THIN LAYER CHROMATOGRAPHY KIT

Manufacturer	CAMAG Sonnenmattstrasse 11, CH-4132 Muttenz, Switzerland Tel. (061) 613-434 Fax (061) 610-702

REFERENCE SUBSTANCES

Manufacturer	United State Pharmacopoeia Ltd

EQUIPMENT	JUSTIFICATION
Accessories for existing instruments	
- eight-channel peristaltic pump	Simultaneous transfer of solution samples from the dissolution apparatus to be detected on the dedicated spectrophotometer
- a set of six-channel spectro-cell	To be used with the above described apparatus.
- a pair of electrodes for conductometer	To be used as electroprobes for the existing conductometer.
- a set of standard orifice tubes	To expand the application the COULTER COUNTER particle size analyzer.
- an electrochemical detector	To be attached to the existing HPLC and expanding its application capability, especially when combinations are necessary.
- an A/D and D/A interface board and associated software package for HPLC	To automate and increase the efficeincy of HPLC operation
Melting point apparatus	Necessary for primary identification of a compound.
Magnetic stirrer with heating facility	is needed for reagent and standard preparation in addition to titration tasks.
Automatic double distiller (4-8 litres/hr) with ion exchange and water purifier set	To purify water to standard quality for consumption in all analytical jobs.
Automatic flask shaker	To facilitate and increase efficeincy in routine solvent extraction and dissolution tasks.
A complete set of Thin Layer Chromatography with a UV detector	For primary identification of product samples
Gas Chromatography	To extend our analytical services to cover analytical determination of traditional medicines, volatile substances, and pesticide contamination.
Diffusion appartus	For the determination of diffusion rate of topical dosage form, an in-vitro study that is correlated to the bioavailability of the drug.
Polarographic analyzer	The instrument can be used as a relatively low cost substitution for an atomic adsorption spectrometer in the analytical determination of trace metal in raw materials or in product samples. In addition, the instrument can also be employed as another analytical tools in determination of electroactive components in any products.
Reference substances	To be used as standard for comparative and referenced purity with high accuracy.

Appendix x:

Thai Pharmaceutical Companies who have participated in PTSC Activities

A LIST OF THAI PHARMACEUTICAL COMPANIES WHO HAVE PARTICIPATED IN PTSC ACTIVITIES:

1. A.N.B. LABORATORIES CO., LTD.
   39/1 RAM INTRA ROAD, KM. 9
   BANGKOK 10230

2. ATLANTIC LABORATORIES CORP. LTD.
   2038 SUKHUMVIT ROAD, BANGCHAK
   BANGKOK 10250

3. B. B. PHARMA CO., LTD.
   22 SAMPRAYA ROAD, PRANAKORN
   BANGKOK 10200

4. BERLIN PHARMACEUTICAL INDUSTRY CO., LTD.
   63 ROMKLAO ROAD, LARDKRABUNG
   BANGKOK 10520

5. BIOLAB CO., LTD.
   38/5-6 SUKHMUMVIT 39 ROAD
   BANGKOK 10110

6. B. J. LIMITED PARTNERSHIP
   255 SUAN OY SOI 2, SAMSEN, BANGKOK
   BANGKOK 10300

7. B. L. HUA & CO., LTD.
   2 SOI SITHIKASEM, SOMDEJ CHAOPRAYA ROAD,
   BANGKOK 10600

8. THE BOOTS MANUFACTURING CO., (THAILAND) LTD.
   65 LARDRABANG-BANGPLEE ROAD, BANGPLEE
   SAMUTPRAKARN 10540

9. BRYWOOD PHARMACEUTICAL LTD. PART.
   313 SUKAWAT 7 ROAD, RASBURANA,
   BANGKOK 10140

10. BURAPHA DISPENSARY CO., LTD.
    19/19 SOI TIMALAND, NGARMVONGVARN ROAD,
    NONTHABURI 11000

11. CHAROEN BHAESAJ LAB CO., LTD.
209/56 PETCHKASEM ROAD, PHASEE CHAROEN,
BANGKOK 10160

12. CHEW BROTHERS & CO., LTD. PART.
1561/3 NEW PETCHBURI ROAD, MAKKASAN,
BANGKOK 10310

13. CHINTA TRADING CO., TLD.
420, 514 ASOKE-DINDAENG ROAD,
BANGKOK 10400

14. COMMUNITY PHARMACY PUBLIC COMPANY LIMITED
96/17 SOI WAT KHUBON, RAMINTRA ROAD,
BANGKOK 10230

15. COX LABORATORIES LTD. PART.
1014/3-4 SOI WATCHANNAI, SATHUPRADIT,
BANGPONGPANG, YANNAWA,
BANGKOK 10120

16. DUMEX LIMITED
359 THEPARAK RD., BANGPLEE INDUSTRIAL ESTATE,
SAMUTPRAKARN 10540

17. F. E. ZUELLIG (BANGKOK) LTD.
1899 SOI SIRISIAM (PHAHOLYOTHIN 39 ROAD),
BANGKOK 10501

18. THE FORTY-TWO LABORATORIES LTD.
77/37 SENANIKOM 1, PHAHOLYOTHIN ROAD,
BANGKOK 10900

19. GENERAL DRUGS HOUSE CO., TLD.
43/4-5 LARDPRAO ROAD, WANGTHONGLAND,
BANGKOK 10310

20. GLAXO-VIDHYASOM LTD.
6TH FLOOR, CHAOPRAYA TOWER,
89 SOI WAT SUAN PLU, BANGRAK,
BANGKOK 10501

21. THE GOLDEN CUP PHARMACEUTICAL CO., LTD.
289 CHARANSANITWONGSE ROAD, THAPHRA
BANGKOK 10600

22. GREATER PHARMA LTD. PART.
489/2 SOI BANGYEEKHAN,
CHARANSANITWONGSE ROAD,
BANGKOK 10700

23. HOECHT PHARMACEUTICAL INDUSTRIES LTD.
302 SILOM ROAD,
BANGKOK 10500

24. JACK CHIA INDUSTRIES (THAILAND) LTD.
144-144/1 SRI BAMPHEN ROAD,
BANGKOK 10120

25. THE JAWARAD CO., LTD.
1055/4 SUKHUMVIT 71 ROAD,
BANGKOK 10110

26. KENYAKU (THAILAND) LTD.
106/7 SOI KESORN (LADPRAO 91),
LADPRAO TOAD,
BANGKOK 10310

27. KRUNGDHEB PHARMACY LTD. PART.
611/1 NEAR CHAROEN NAKORN 8 BRIDGE,
CHAROEN NAKRON ROAD, BUKKALO,
BANGKOK 10600

28. L. P. STANDARD LABORATORIES LTD.
218/1 CHAROENKRUNG ROAD, SIPHRAYA,
BANGKOK 10500

29. LUPIN CHEMICALS (THAILAND) LIMITED
309 BANGPOO INDUSTRIAL ESTATE,
SUKHUMVIT ROAD, SAMUTPRAKAN 10280

30. M & H MANUFACTURING CO., LTD.
41 SUKHUMVIT ROAD, KM. 23, AMPHUR MUANG,
SAMUTPRAKARN 10270

31. MEDICAL SUPPLY CO., LTD.
101 SRIBAMPHEN ROAD, YANNAWA
BANGKOK 10120

32. MEDICAP LIMITED
384 SOI 6, PATTANA 3 ROAD,
BANGPOO INDUSTRIAL ESTATE,
SAMUTPRAKARN 10280

33. MODERN MANU CO., LTD.
54/1 SUKHAPHIBAL 1 ROAD,
KHLONGKOOM, BANGKAPI,
BANGKOK 10240

34. NAKORN PATANA PHARM CO., LTD.
495, 601/5-8 SOI SUTHIPORN,
DINDANG RD., HUAYKHWANG,
BANGKOK 10400

35. NAM KOK DISPENSARY CO., LTD.
59 MU 2, SRINAKARIN ROAD,
NONGBON, PRAVES,
BANGKOK 10260

36. NEOPLAST COMPANY LIMITED
298/144-145 PITSANULOKE ROAD, DUSIT,
BANGKOK 10300

37. OLAN-KEMED CO., LTD.
176-176/1-2 LARDPRAO ROAD,
LARDYAO, CHATUCHAK,
BANGKOK 10900

38. OLIC (THAILAND) LTD.
3223 SUKHUMVIT ROAD, BANGNA,
BANGKOK 10260

39. OSOTH INTER LABORATORIES CO., LTD.
600/9 SRIRACHA INDUSTRIAL GARDEN,
SUKHAPHIBAL 8, TAMBOL NONGKHAM,
SRIRACHA, CHOLBURI 20280

40. OSOTHSAPHA (TECK HENG YOO) CO., LTD.
2100 RAMKHAMHAENG ROAD, HUAMAK, BANGKAPI,
BANGKOK 10240

41. PHARMACARE CO., LTD.
120 MOO 4, LUM PLATEW, LARDKRABUNG,
BANGKOK 10520

42. POLIPHARM CO., LTD.
109 MOO 12, BANGA-TRAD RD.,
KM. 13, BANGPLEE,
SAMUTPRAKARN 10540

43. POND'S CHEMICAL (THAILAND) R.O.P.
79 MU 4, RAMINTRA ROAD, ANUSAVAREE, BANGKHEN,
BANGKOK 10220

44. P.P. LABORATORIES CO., LTD.
53/42-43 SOI AMORNPHAN 5,
VIBHAVADI RANGSIT RD., BANGKHEN,
BANGKOK 10900

45. PURE CHEM CO., LTD.
64/12 SUKHUMVIT SOI 20,
BANGKOK 10110

46. RHONE-POULENC THAI INUSTRIES LIMITED
BANGPOO INDUSTRIAL ESTATE
SAMUTPRAKARN 10280

47. SCHERING CHEMICALS LTD.
28/19 CHANGWATTANA ROAD
KM. 6, PAKKRED
NONTHABURI 11120

48. SENG THAI COMPANY LTD. PART.
148/5 NANGLINCHEE ROAD,
TUNGMAHAMEK, YANNAWA,
BANGKOK 10230

49. THE SERMMITR CO., LTD.
82-84 RAJDAMNERN AVENUE,
BANGKOK 10200

50. SIAM BHEASACH CO., LTD.
123 SOI CHOKECHAI RUAMMITR,
VIBHAVADI RANGSIT ROAD,
BANGKOK 10900

51. SIAMERICAN PHARMACEUTICALS CO., LTD.
THAI WAH TOWER, 18TH FLOOR,
21/52-54 SOUTH SATHORN ROD.,
BANGKOK 10120

52. SILOM MEDICAL CO., LTD.
27/2 PHYATHAI ROAD,
BANGKOK 10400

53. SOMCHITT DISPENSARY CO., LTD.
9/19 LARDPRAO 23 ROAD,
LARDYAO, CHATUCHAK,
BANGKOK 10900

54. SRIPRASIT PHARMA CO., LTD.
878/2 CHAROENRAT ROAD, KLONGSARN,
BANGKOK 10600

55. TAKEDA (THAILAND) LTD.
9/1 DEJO ROAD,
BANGKOK 10500

56. THAI MEIJI PHARMACEUTICAL CO., LTD.
GROUND FLOOR, REGENT HOUSE ANNEX,
183 RAJDAMRI RD.,
BANGKOK 10330

57. THAI NAKORN PATTANA CO., LTD.
94/7 NGARMVONGVARN ROAD,
NONTHABURI 11000

58. THAI OTSUKA PHARMACEUTICAL CO., LTD.
2ND FLOOR, BANGKOK CABLE BUILDING,
137/1 RAJDAMRI ROAD,
BANGKOK 10330

59. THAI P. D. CHEMICALS CO., LTD.
119 SOI CHOKECHAI RUAMMIT,
VIBHAVADI RANGSIT ROAD,
BANGKOK 10310

60. THAI PHARMED (1942) CO., LTD.
262 SUKSWAT ROAD, RASBURANA,
BANGKOK 10140

61. T.O. CHEMICALS (1979) LTD.
SOI SABAICHAI,
SUTHISARNVINITCHAI ROAD, HUAYKHWANG,
BANGKOK 10310

62. TOPDERM CO., LTD.
116/99 SOI PENSOOK,
PATTANAKARN ROAD,
BANGKOK 10250

63. T. P. DRUG LABORATORIES (1969) CO., LTD.
76 SUKHUMVIT SOI 62,
BANGKOK 10250

64. UDOMPHON (PHIHALAB) CO., LTD.
2282 SUKHAMVIT ROAD, BANGCHAK,
BANGKOK 10260

65. UNICHEM PHARMACEUTICALS CO., LTD.
101/85 PHAHOLYOTHIN ROAD, KM. 46,
KHLONGNUNG, KHLONGLUANG,
PATHUMTHANI 12120

66. UNION DRUG LABORATORIES LTD.
2601 SUKHUMVIT ROAD, BANGCHARK,
BANGKOK 10250

67. UNISON LABORATORIES CO., LTD.
160 SOI ONNUCH,
SUKHUMVIT ROAD, LADKRABUNG,
BANGKOK 10520

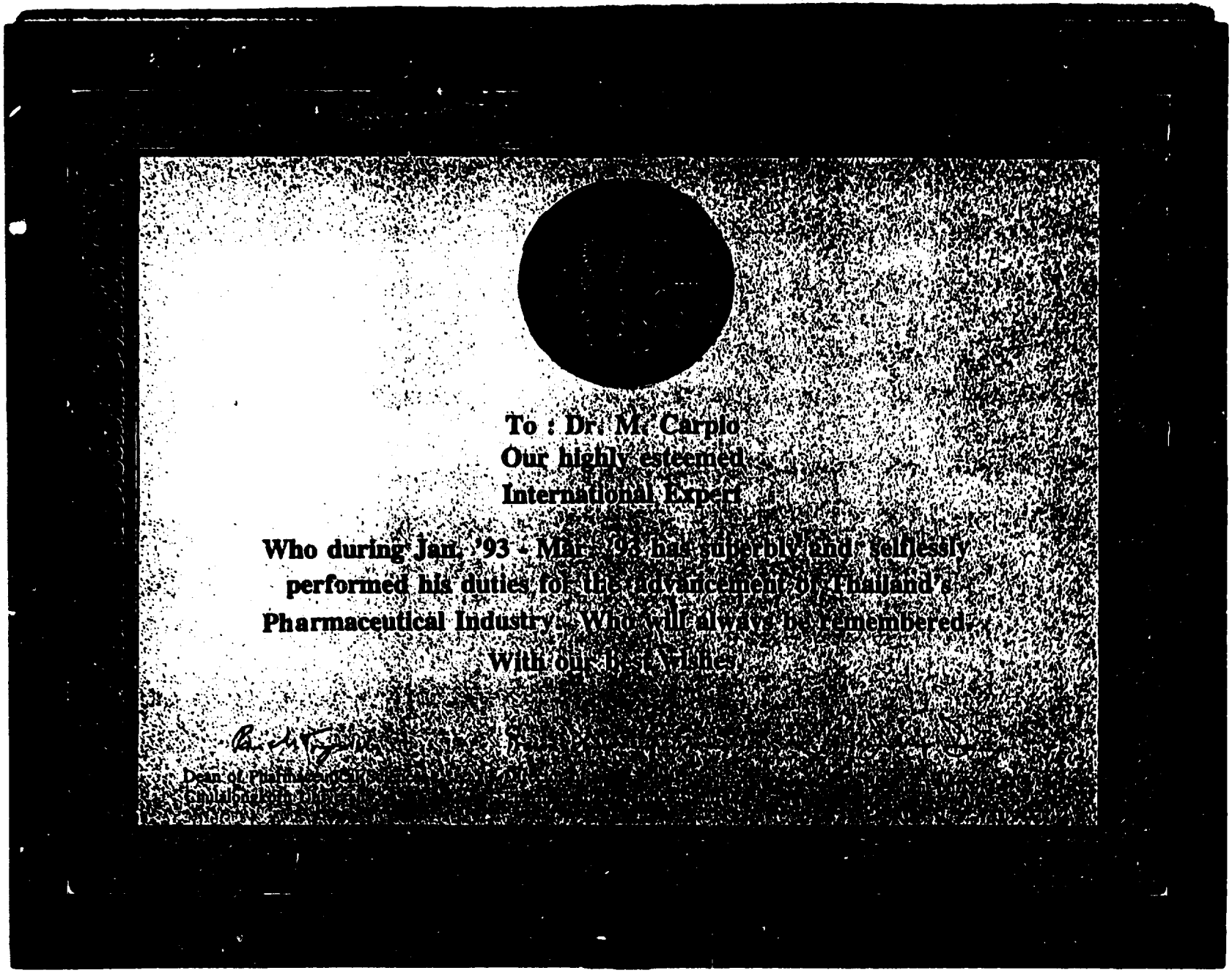
68. VIDHYASOM CO., LTD.
43, BLDG. NO. 8, RAJDAMNOEN AVENUE,
BANGKOK 10200

NOTE:

THE GOVERNMENT PHARMACEUTICAL ORGANIZATION (GPO) AND THE MILITARY PHARMACEUTICAL ORGANIZATION ARE ALSO PARTICIPATING IN TPSC ACTIVITIES.

Appendix xi:

A Diploma presented to the UNIDO Technical Expert



To : Dr. M. Carpio
Our highly esteemed
International Expert

Who during Jan. '93 - Mar. '93 has superbly and selflessly performed his duties for the advancement of Thailand's Pharmaceutical Industry. Who will always be remembered.

With our best wishes.

Dean of Pharmaceutical

1. UNIDO's Quality Criteria

"Development of the Pharmaceutical Industry in Thailand" is one of the high profile projects of UNDP/UNIDO since it is not only addressing successfully UNIDO's quality criteria (relevance, cost-effectiveness and sustainability), but it creates a new perception of UNIDO's technical assistance programme. It is an emerging consensus among all parties concerned, including WHO and multinational industry, to provide assistance to the Pharmaceutical Technology Service Center to achieve its sustainability. This project is the best example for the currently changing scope of UNIDO's technical assistance programme.

2. Backstopping Officer's technical comments on Mr. M.M. Carpio's report

The expert prepared a very concise report, but it became quite voluminous, illustrating the full scope of the extensive work programme of the project. The bulk of the report consists of outlines, samples and protocols of pharmaceutical quality assurance and particularly process validation documentation to comply with the current Good Manufacturing Practices.

Since the project in the last several months, according to the Director of PTSC's monthly reports, creates revenues, it seems to be very likely that the financial sustainability of the Center could be achieved even for long term. The financial sustainability of PTSC would be the base that potential areas of its expansion could positively be considered. It is our view that at least 3 areas seem to be good opportunities:

- regionalization of PTSC (Laos, Viet Nam),
- extend its scope to counterfeit drugs, and
- integration of women in pharmaceutical industry development.

Due to the central role of the quality in the pharmaceutical industry, the most recent UNIDO's views are very briefly discussed in the following chapters:

3. TOTAL QUALITY MANAGEMENT (TQM)

The size of economy can be achieved by improving productivity and efficiency. The adoption of the just-in-time (JIT) inventory approach, a manufacturing term referring to the achievement of excellence through the elimination of waste and excess inventory, could lead the consistent improvement of productivity. To achieve JIT, in addition to the computer integrated manufacturing (CIM) and business requirements planning (BRP) several new business practices should be introduced. The most important factor is the empowerment, that is the development and use of people's power to bring about business results. The most important elements for the empowerment are:

- Environment: leadership, trust, teamwork, communications, positive, support, etc.
- Individuals: choice, learn, change, grow, risk, supportive, energy, etc.
- Performance (customers): quality, value, timeliness, information, improvement, etc.

The plan of action to be taken should be as follows:

- Improvement forum,
- Strategy development,
- Identify initial opportunities,
- Develop improvement plans,
- Select initial teams,
- Select initial facilitators,
- Employee empowerment,
- Team training & Facilitation.

JIT is only one of the elements of the Total Quality Management (TQM), the most current trend in the industry, particularly in Japan and North America. TQM is a philosophy and methodology revolution in management that compels all employees to focus on meeting the customer's expectations and builds quality into every system and process within the company. TQM can successfully be implemented only with a collaborative empowered workforce having a shared vision. They should know and understand this "vision"; they should have the responsibility to improve the

status quo; and should have the authority to make relevant changes.

The vision, that is most commonly projected, is "zero defects". TQM necessitates the introduction of a new terminology: rejects per million or even rejects per billion items manufactured. The effects of shortcomings in quality at 99.9 % level (e.g. 1 defect per 1000 manufactured items) can be easily demonstrated in other areas of life with the following few North American examples:

- 20,000 wrong drug prescriptions per year,
- 15,000 new born babies accidentally dropped in hospitals per year,
- Unsafe drinking water for 1.5 hours per month,
- No telephone/television transmission for 8.6 hours per year,
- 2 short or long landing e.g. major airports at New York, Los Angeles per day,
- 500 incorrect surgical operations per week, and
- 2,000 lost articles of mail per hour.

At zero defects stage, the conventional wisdom that high levels of quality are prohibitively costly is not true. As an average, the total losses (that is, not only the defects) owing to sub-standard quality in manufacturing industry can amount to about 25 % of the total sales. The new, highly sophisticated technologies have paradoxically been developed by simplification and cycle time reduction of the manufacturing processes in addition to quality improvement, and consequently the manufacturing costs are relatively lower. As a result of this, a few European manufacturers of high quality generic drugs can successfully compete with the lowest prices for similar products from India and China.

TQM also changes the conventional criterion of quality, the "product only focus" perception. By novel definition, quality is "to meet the customer's expectations". Based on a North American survey in 1988, the following rank importance has been defined for competitiveness expressing the customer's expectations. It is interesting to note that low price ranked only the seventh, while consistent quality was the top-rated competitive priority on the list.

1. Conformance: Ability to offer consistent quality,
2. Dependability: Ability to make dependable delivery dates,

3. Performance: Ability to provide high performance products,

4. Speed: Ability to provide fast delivery,

5. Flexibility: Ability to make changes in design and introduce new products quickly,

6. Service: Ability to provide after-sales service,

7. Low price: Ability to offer low prices,

8. Product mix: Ability to offer a broad product mix,

9. Distribution: Ability to obtain broad distribution,

10. Volume: Ability to make rapid volume changes, and

11. Promotion: Ability to advertise/promote effectively.

Many strategic planners of the industry argue that TQM is only the beginning, what is needed is continuous quality improvement. To be globally competitive in the future, systems and processes must be more demanding than TQM.

4. QUALITY IMPROVEMENT TECHNIQUES

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 driving forces in shaping of 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 be cleared 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.

4.1. 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.

4.2 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 basis 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.

4.3. 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.

4.4. 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 lest 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.

4.5. ZERO DEFECTS PLANNING

Zero defects is a performance standard. It is the standard of a craftsperson 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.

5. COST OF QUALITY

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.

5.1 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.

5.2. 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.

5.3. 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.

5.4. 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.

6. REGULATORY AGENCY INSPECTION

Every pharmaceutical manufacturer knows that regulatory agencies, such as US FDA, have the right to inspect its facilities. These inspections, if one remains with the example of FDA, are intended to satisfy the inspectors that the manufacturer has

complied with applicable provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and regulations appearing in the Code of Federal Regulations (CFR). Many manufacturers may not know, however, that any information FDA acquires during and inspection becomes part of an FDA record, which may be disclosable to the public or used as evidence by the agency to support litigations. The message that the regulatory agency is sending to the industry is a warning that every manufacturer must be more cautious than ever before about the conduct and potential consequences of all FDA inspections.

In order to develop a policy for handling FDA inspections, it is helpful to know what FDA can - and cannot - do during an inspection. In general the following issues should be considered when developing a company policy:

- Company contact: Identify who is authorized to receive and accompany the FDA auditor and how oral inquiries and requests for documents are to be processed. Identify the notifiable persons when the inspection is commenced.

- Document production: Identify all documents that are disclosable and how requests for non-disclosable documents will be handled. If necessary, seek the advice of legal counsel.

- Document marking and duplication: Do not permit marking of documents by FDA inspectors. Maintain a copy of each document given to FDA inspectors. If documents contain confidential or trade secret information, mark documents accordingly before providing them to FDA.

- Photographs/videotapes: Establish whether it is permissible to take photographs and videotapes since FD&C Act is silent on this subject. Photograph and videotapes taken during the auditing have, however, been accepted by the courts as evidence.

- Tape recordings: In general, FDA does not seek to record conversations.

- Samples: When samples are provided, retain adequate samples from the same batch or lot for possible analysis. The FDA inspector will provide a receipt-for-samples form when obtaining samples.

- Affidavits: As a general rule, obtain a copy of any affidavit prepared by an FDA inspector, but neither acknowledge the content of nor sign the document.

- Internal memorandums: Consider whether a memorandum of any part of the inspection should be prepared internally

for future reference.

- Refusals and inspection warrant: Establish how disputes relating to refusals are to be identified and resolved. Develop procedures to ensure compliance with court-ordered inspection warrants.

- Employee contacts: Advise employees about their rights and about FDA authority to conduct inspections. Request than employees report any contact from FDA inspectors to the designated individual or legal counsel.

- Corrections during inspection: Consider what procedure the company will apply when and FDA inspector makes an observation for which a change is necessary.

- Use of counsel: Because information obtained by FDA can be used as evidence, it is advisable to identify all circumstances under which legal counsel is to be notified.

- Post-inspection conference: Identify who is to be present at the post-inspection conference with the FDA inspector and how the company will proceed with the review of any inspection observations.

- Issuance of a Form 483: It is a signal that objectionable conditions and practices have been observed by the FDA investigator. Because the form is a public document that is available on the request under the Freedom of Information Act (FOIA) and reflects the position of the FDA inspector(s), its significance to the inspected manufacturer cannot be overemphasized. This document is a permanent record that generally will not altered further. Therefore its revision should be attempted by the manufacturer during the post-inspection conference. Although there is no requirement to do so, it is generally advisable for the manufacturer to submit a timely written response commenting on the observations to the FDA in order to minimize possible damage associated with its public release.

- Establishment Inspection Report (EIR): In most cases, the FDA investigator will prepare and file an EIR after completing an inspection. In case of any errors, omissions, or inspector's statements that are not consistent with the manufacturer's record, the FDA should be requested that the manufacturer's comments should be made part of EIR.